HAEMODYNAMIC CHANGES DURING HUMAN PREGNANCY

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by

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Declaration

The investigations described in this thesis were performed by myself with the exception of the cardiac catheterization procedures and the estimations of cardiac output by the direct Fick technique which were performed by Dr. S. Hunter and Dr. R. Bexton.

Preface

The aim of this work was to investigate the physiological adaptations that occur in the maternal cardiovascular system during singleton and twin pregnancy. The cardiovascular system has been shown to undergo major adaptations during human pregnancy. Most investigators agreed that cardiac output increased during pregnancy however there was no unanimity regarding the extent and timing of this increase nor about the physiological mechanisms underlying it. Even less was known about the haemodynamic readjustments following delivery and about the alterations in multiple pregnancy.

Further study has been limited by the lack of an accurate noninvasive technique which is applicable and reproducible during pregnancy. Cross-sectional echocardiography combined with Doppler ultrasound measurement of blood velocity provides a noninvasive method for measuring cardiac output at a number of locations within the heart and great vessels. Preliminary investigations revealed that cardiac outputs determined by this method correlated closely with those measured by the direct Fick technique in non-pregnant subjects. In addition the method was highly reproducible in both pregnant and non-pregnant subjects. M-mode echocardiography allows accurate and noninvasive measurements of cardiac chamber size and ventricular function. These measurements were also found to be highly reproducible in pregnant and non-pregnant subjects. Using these techniques the aims of this thesis were to investigate the extent, timing and mechanisms of the changes in cardiac output during singleton and twin pregnancy.

Echocardiographic investigations were performed prior to and during singleton pregnancy, during the first 6 months after singleton pregnancy, and during and 6 months after twin pregnancy. All subjects were studied in the left semi-lateral position.The results suggested that;

(1) During singleton pregnancy cardiac output was increased early in the first trimester and continued to rise until 24 weeks gestation when values were 43-49% above pre-pregnant control values. Thereafter there was no further change. Heart rate and left ventricular function increased during the first trimester. Left atrial and left ventricular end-diastolic dimensions increased during the second trimester suggesting an increase in venous return. Cardiac valve cross-sectional areas and left ventricular wall thickness also increased during pregnancy. After delivery cardiac output had fallen to non-pregnant values by 2 weeks. This was associated with reductions in left ventricular performance and left atrial and left ventricular end-diastolic dimensions. The decrease in valve cross-sectional areas and left ventricular wall thickness was not evident until later in the puerperium.

(2) During twin pregnancy cardiac output was increased by 20 weeks gestation and thereafter showed no further change. Maximum cardiac output was 59-62% above postnatal control values. This increase was greater than that recorded during singleton pregnancy due to a relatively greater increase in heart rate. Twin pregnancy was also associated with a greater increase in left atrial dimension.

The results of these studies shed light on some of the the unanswered questions in the field of maternal haemodynamics. The noninvasive Doppler techniques used allowed accurate and reproducible measurements of cardiac output in pregnant subjects. This work has important implications for the future investigation of cardiac and hypertensive disorders during pregnancy.

Abbreviations

BP	Blood pressure
CI	Confidence interval
Circ	Circumferences
cm	Centimetres
CO	Cardiac output
CSA	Cross-sectional area
CW	Continuous wave
D	Diastolic
d	Days
dD/dt	Rate of change of dimension
EDD	End-diastolic dimension
ESD	End-systolic dimension
FS	Fractional shortening
g	Grams
Hg	Mercury
HR	Heart rate
Int	Intercept
kg	Kilograms
l	Litres
LAD	Left atrial dimension
LV	Left ventricular
LVID	Left ventricular internal dimension
LVPW	Left ventricular posterior wall
m	Metres
min	Minutes
ml	Millilitres
mm	Millimetres
mVcf	Mean velocity of circumferential fibre shortening
n	Number
PD	Pulsed Doppler
r	Correlation coefficient
S	Systolic
SD	Standard deviation
SEE	Standard error of the estimate
SEM	Standard error of the mean
sec	Seconds
SR	Studentized range
SV	Stroke volume

TWT	Total wall thickness
VI	Velocity integral
w	Weeks

CHAPTER 1

INTRODUCTION

1.1 Haemodynamics

1.1.1 Haemodynamics and the Circulation

The circulation is designed to provide the tissues with substrate for aerobic respiration and to remove metabolic waste. It is therefore a delivery system, which functions by pumping blood through the vascular system. The pumping action of the heart converts energy into pressure (P) which produces flow (Q). The translation of pressure waves into flow (CO) is impeded by the frictional resistance of the vasculature, the inertia of the blood, and the elastic properties of the vessel walls. In the peripheral systemic circulation the most important component of this impedance is resistance (R) which largely depends on vessel diameter.

The term haemodynamics refers to the relationship between the motion of blood and the forces affecting this motion. The relationship between pressure, flow, fluid properties and vascular dimensions is called Poiseuille's Law (1846). Poiseuille discovered that the relation between volume flow (Q) and the drop in pressure (P) along a tube of given length (L) and inner diameter (D) was;

$$Q = \frac{KPD^4}{L}$$

The coefficient (K) was independent of the tube diameter, length and flow but fell with decreasing temperature. It later became clear that K was related to viscosity (η). Thus Poiseuille's law states, in effect, that the ratio of pressure gradient to flow is a function of the dimensions of the tube and the viscosity of the moving fluid. The physical properties of the system determine how large a pressure gradient is required to produce a given flow. The ratio of mean pressure gradient (P) to mean flow (Q) is thus a measure of the extent to which the system opposes or resists flow; this ratio is called the vascular resistance (R);

$$R = \frac{P}{Q}$$

This equation is valid only for laminar flow in straight, rigid tubes and therefore represents a gross oversimplification of human haemodynamics. However it serves to illustrate the essential interrelationships of pressure, flow and resistance and highlights the important point that the key function of the circulatory system, that is to deliver flow, cannot be assessed by measuring blood pressure without knowing CO.

1.1.2 Cardiac Output

Cardiac output is determined by the product of HR and SV and it can be varied over an enormous range in normal man; from resting values of approximately 5 l/min to as much as 42 l/min during maximal exercise (Wade and Bishop 1962). An understanding of the principles governing changes in CO and cardiovascular responses is a prerequisite for interpreting the changes induced by pregnancy.

Cardiac output is influenced by four distinct although interrelated mechanisms (Schlant and Sonnenblick 1990);
(1) the **preload** (Starling's law of the heart), which is the passive load that establishes the initial muscle length of the cardiac fibres prior to contraction.
(2) the **afterload**, which is the sum of all the loads against which the myocardial fibres must shorten during systole, including the aortic impedance, the arterial resistance, the peripheral vascular resistance, and the end-diastolic volume through the LaPlace relation, as well as the mass of blood in the aorta and great arteries, and the viscosity of blood.
(3) the **inotropic** or **contractile state** of the heart, which is reflected in the speed and shortening capacity of the myocardium at a given instantaneous load.
(4) the **heart rate,** or frequency of contraction

The exact role of each of these factors in the maintenance of resting CO and the increase during exercise remains controversial. Their relative contribution to the changes in CO during pregnancy are even less clear. Whilst knowledge of the absolute changes in CO during pregnancy is important, to understand maternal cardiovascular adaptation it is necessary to identify the alterations in the four components described above.

This chapter reviews all previous studies that have measured CO during normal human pregnancy. The evolution of the understanding of CO changes has followed the development of measurement techniques; from the early procedures based on the Fick principle, to the more recent noninvasive techniques of echocardiography and impedance cardiography. It is important to appreciate that there is no direct method of measuring CO in the intact human. All the methods described are therefore indirect and as such are based on some assumptions. Clearly without understanding the assumptions and pitfalls of each technique, the reliability of the results cannot be determined. Therefore, before describing the results obtained in pregnant subjects using each method, an attempt has been made to briefly review the methodology, assumptions and limitations of each of the main measurement techniques.

1.2. Rebreathing (Indirect Fick) Studies

1.2.1 Measurement of Cardiac Output by Early Rebreathing Methods

In 1870 Adolph Fick, in a brief presentation to the Society of Physiology and Medicine of Wurzburg, expounded a theory for the measurement of blood flow: 'The total uptake or release of a substance by an organ is the product of the blood flow to the organ and the arteriovenous concentration of the substance'. Although the principle was probably first applied in dogs by Grehant and Quinquaud in 1886 (Wade and Bishop 1962), the application of the technique in man had to await the development of cardiac catheterization. During the intervening years a number of methods were devised which allowed the principle to be used without the need for direct sampling of mixed venous blood. The carbon dioxide rebreathing technique was the first practical method of measuring CO in man (Plesch 1909). Measurements were difficult to perform and the results were erroneous due to difficulty in obtaining a gas in true equilibrium with venous blood. The method was abandoned in favour of the far easier and apparently more accurate foreign gas methods.

Nitrous Oxide Rebreathing Method; Krogh and Lindhard (1912) developed the method from earlier work using nitrogen (Bornstein 1910). Nitrous oxide, being more soluble in blood, could be measured more accurately. Subjects rebreathed a mixture of 10-25% nitrous oxide in air. After a few minutes, to complete mixing of gas in the bag and the lung, the breath was held for 5-8 seconds. One litre was quickly expired and the last portion was sampled as alveolar gas. Ten seconds later, at full expiration, a second sample of alveolar gas was taken. The lung volume being known, analysis of the two samples allowed calculation of the mass of nitrous oxide carried from the lung by the blood in the interval between the two alveolar samples. Knowledge of the solubility of nitrous oxide in blood allowed calculation of CO. The rebreathing techniques could only be performed by carefully trained athletes.

Acetylene Rebreathing Method; This method was developed by Marshall and Grollman (1928). Subjects rebreathed a mixture of acetylene and air. Samples of alveolar gas were taken at 12-18 and 20-25 seconds after beginning the rebreathing procedure. Cardiac output could then be calculated from the gas tensions of the two samples, provided the solubility of acetylene in blood and the lung volumes were known. The acetylene method was simpler to perform than the nitrous oxide method and did not require trained athletes. As a result it gave more reproducible estimates of CO (Grollman 1930).

1.2.2 Assumptions and Errors of the Early Rebreathing Methods

Both methods assumed that the expired gas collected represented alveolar gas. This was subsequently shown to be invalid (Ernst and Weiss 1932). The rebreathing procedure, especially that used in the nitrous oxide method, also increased oxygen uptake (Wade and Bishop 1962). The measurement of nitrous oxide was technically very difficult and prone to large errors (Wade and Bishop 1962). The acetylene method assumed that there was negligible recirculation of acetylene by the time of the second sampling (20-25 seconds) Hamilton (1945) showed this assumption to be incorrect. Subsequent studies comparing CO measured by nitrous oxide and acetylene rebreathing with the direct Fick method clearly showed that, not only did the rebreathing methods underestimate CO, but individual values correlated poorly (Werko et al. 1949a, Chapman et al. 1950).

1.2.3 Early Rebreathing Studies during Pregnancy (Table 1.1)

Using the nitrous oxide rebreathing method, Lindhard (1915) reported the first measurement of CO in a pregnant subject. He measured CO before, during and after pregnancy and found that CO was increased in the last month of pregnancy and returned to pre-pregnant levels after delivery. The significance of these findings was clouded by the presence of anaemia at the time the CO was measured. Weiss (1924) measured CO in 8 pregnant women and compared the results with what he quoted as 'average' values from non-pregnant controls. He concluded that in late pregnancy CO was increased by 45-85 (mean 63)%. Gammeltoft (1926) made the first serial measurements of CO during normal pregnancy and in one woman he obtained 12 measurements between the 8th and 39th weeks of pregnancy. In this subject CO reached a peak of 5.65 l/min at 34 weeks and then fell to 4.9 l/min at 39 weeks. By 4 weeks after delivery CO was 4.4 l/min, representing a maximum rise during pregnancy of 28%. The maximum increase in other subjects ranged from 22-41% and occurred between the 20th and 38th weeks of pregnancy.

Stander and Cadden (1932) measured CO using the acetylene rebreathing method and concluded that CO rose from the fourth month of pregnancy until term and then fell immediately after labour, reaching normal values at the end of the third week. However this was based on only two measurements at ≤ 16 weeks gestation and 4 puerperal measurements. Burwell et al. (1938) measured CO using the same method every 2-6 weeks from the fourth month of pregnancy. Mean CO showed the greatest increase at 30-31 weeks although in individual subjects peak CO was recorded at 23, 24, 30 and 31 weeks. In late pregnancy each subject demonstrated a fall in CO. Burwell (1938) conceived the idea that the placenta was a form of systemic arterio-venous shunt and suggested that the fall in CO in late pregnancy was related to ageing of the placenta.

Author	n	Serial	Pos	Pregnancy Gestation	CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min^{-1})
Nitrous Oxide Rebreathing Method											
Lindhard (1915)	1	Yes	Sit	>36 w*	5.3 (43)			PC	3.7		
Weiss (1924)†	8	No	Sit	>36 w	6.2	81	75				
Liljestrand and Stenstrom (1926)	1	Yes	Sit	36 w#	6.0 (22)	68 (11)	88 (10)	PN (6 w)	4.9	61	80
Gammeltoft (1926)†	5	Yes	Sit	16-20 w#	5.2 (8)			PN (2-12 w)	4.8		
				36-40 w*	5.9 (23)						
Acetylene Rebreathing Method											
Schmidt (1932)†	5	Yes	?	12-20 w	4.83 (47)			NP$	3.29		
Stander and Cadden (1932)†	13	No	Sit	24-28 w (n=8)	4.67 (14)			PN (n=4)	4.08		
				36-40 w (n=10)	6.95 (70)						
Burwell et al. (1938)	4§	Yes	Sup	12-16 w#	4.0 (14)	47 (4)	85 (9)	PN (1-4 w)	3.5	45	78
				30-31 w*	6.0 (71)	62 (38)	93 (19)				
				38-40 w	4.1 (17)	48 (7)	84 (8)				

* Time of maximum increase in CO during pregnancy, † data calculated from tables, # time of first measurement during pregnancy, $ following abortion, § one subject had mitral valve disease. Figures in brackets are percentage changes relative to non-pregnant values.

Abbreviations: Pos, position of subjects; Sit, sitting; PC, pre-conception; PN, postnatal; Sup, supine; NP, non-pregnant

Table 1.1 Previous early studies of cardiac output during pregnancy using rebreathing methods.

1.2.4 Measurement of Cardiac Output by Recent Rebreathing Methods

Acetylene Rebreathing Method; Triebwasser et al. (1977) reported a modification of the acetylene rebreathing method in which acetylene gas concentrations were sampled continuously at the subject's mouth by a capillary tube connected to a mass spectrometer. Subjects exhaled to their residual volume and then rebreathed gas (containing 0.5% acetylene, 10% helium) for 15 seconds. The respired volume was measured by a pneumotachograph. Signals from the mass spectrometer and the pneumotachograph were analysed by an on-line computer.

A number of studies have reported a close correlation between CO measurements by the modified acetylene rebreathing and dye dilution or thermodilution methods with r values generally >0.90 (Triebwasser et al. 1977, Kallay et al. 1987). Significant errors occur when there is uneven distribution between ventilation and perfusion (Kallay et al. 1987). There is some evidence that during pregnancy a proportion of small airways close during tidal breathing (Bevan et al. 1974) suggesting some ventilation / perfusion imbalance. This could affect the accuracy of the technique during pregnancy although this has not been studied. The reproducibility of the method, expressed as the coefficient of variation of repeated measurements, has been reported to be between 7-10% (Kallay et al. 1987, Nielsen et al. 1990) although in the study of Kallay et al. (1987) the rebreathing method was less reproducible than dye dilution.

Carbon Dioxide Rebreathing Method; Renewed interest in this method stemmed from the development of rapid carbon dioxide analysers (Collier 1956, Defares 1958) and automated computer systems for respiratory analysis. Carbon dioxide output per minute was calculated from continuous measurements of expired minute volume and the concentration of carbon dioxide in expired gas. The arteriovenous content difference was derived from the partial pressures of carbon dioxide in venous and arterial blood using the whole blood carbon dioxide dissociation curve. This method assumes a haemoglobin concentration of 150 g/l and oxygen saturation of 95%. The partial pressure of carbon dioxide in arterial blood was estimated from the concentration of carbon dioxide in expired gas at the end of expiration. The carbon dioxide tension of mixed venous blood was estimated by the rebreathing procedure using either the equilibrium method of Collier (1956) or the exponential method of Defares (1958).

Small random errors in the estimation of arterial and mixed venous carbon dioxide concentrations from the end-tidal and the rebreathing equilibrium concentrations of carbon dioxide can result in relatively large errors in the estimation of the arterio-venous difference for carbon dioxide concentration (Wilmore et al. 1982). This problem is less important when the arteriovenous difference is large such as during exercise. Another important source of variation is that small deviations in ventilation and alveolar carbon dioxide tension

can result in large changes in carbon dioxide transfer and thus carbon dioxide production (Guyton 1963).

While the method appears to correlate reasonably closely with invasive measurements during exercise, the technique is of limited accuracy in resting subjects (Ferguson et al. 1968, Reybrouck and Fagard 1990, Russell et al. 1990). When compared with the direct Fick method, Reybrouck and Fagard (1990) reported that CO was overestimated by the carbon dioxide rebreathing method (mean difference -0.5 l/min, limits of agreement [± 2 SD] + 2.5, -1.5 l/min). Equally large limits of agreement were reported by Russell et al. (1990) with 28% of the differences being >20% of the mean value. The reproducibility of the method has also been shown to be poor at rest; Reybrouck and Fagard (1990) reported that the mean percentage difference between paired measurements was 25% and Russell et al. (1990) showed that only 50% of the differences between repeat measurements were within 20% of the mean value.

1.2.5 Recent Rebreathing Studies during Pregnancy

Sady et al. (1989) studied the cardiovascular response to exercise in 45 subjects during pregnancy (mean gestation 26 weeks) and then 5-15 weeks after delivery using the acetylene rebreathing method. Measurements were performed prior to and during exercise on a cycle ergometer. Reading from their graphs CO was 7.5 l/min during pregnancy compared with 5.1 l/min after delivery (an increase of 47%). Corresponding values for SV and HR were 73 and 58 ml and 103 and 87 beats/min respectively. The same group subsequently repeated studies in 9 of their original subjects at 7 months postpartum (Sady et al. (1990). From their graphs mean CO's appeared to be identical at 2 and 7 months postnatally.

Rees et al.(1988) measured CO by the carbon dioxide rebreathing technique in 21 subjects. Studies were performed 'where possible' every 4 weeks, within 72 hours after delivery and then at 6-12 weeks postpartum. No change in CO or SV was evident during pregnancy. The authors commented on the wide individual variability of CO measurements and the rather poor reproducibility of the method in their hands.

1.2.6 Limitations of Rebreathing Studies during Pregnancy

1. In view of the inaccuracies of the early rebreathing techniques, little can be concluded from these early studies except that CO was probably increased during pregnancy. The discrepant results of Rees et al. (1988) based on the carbon dioxide rebreathing technique almost certainly reflect the inaccuracies of this method, a point highlighted by the authors.
2. Sady et al. (1990) studied women only once during pregnancy. Subjects were studied immediately prior to exercise on a cycle ergometer when CO may have been elevated in anticipation of exercise (Wade and Bishop 1962). The high values of HR both during and after pregnancy would be consistent with this.

1.3 Direct Fick Studies

1.3.1 Measurement of Cardiac Output by the Direct Fick Method

The development of the cardiac catheter allowed application of the Fick principle to the lungs (Forssmann 1929, Cournand and Ranges 1941). The principle could be used with a number of soluble gases but oxygen was the commonest clinical marker. The difference between the arterial and mixed venous oxygen content reflected oxygen uptake per unit of blood as it passed through the lungs. Hence pulmonary blood flow could be determined by measuring the oxygen uptake and dividing by the difference in oxygen content of the blood entering and leaving the lungs. In the absence of a shunt within the heart or between the great vessels, mean flow through the pulmonary circulation was the same as CO, with a small error due to the presence of the bronchial circulation;

$$\text{CO (l/min)} = \frac{\text{Oxygen uptake (ml/min)}}{\text{Arterial - venous oxygen content (ml/l)}}$$

Oxygen Uptake was assessed by measurement of oxygen extracted by the lungs over a given period of time (usually 3 minutes). Subjects inspires room air and expired air was collected. The oxygen content of room air and expired air was then determined after correction for barometric pressure. the amount of oxygen consumed per litre of expired air was calculated as the difference between these two values. The minute ventilation (l/min) was calculated by dividing the total volume of air expired by the number of minutes of collection. Oxygen uptake (ml/min) was then calculated as;

(ml oxygen consumed/l expired air) x (litres expired air/min of collection)

Arteriovenous oxygen difference across the lungs was determined as the difference between the oxygen content of left ventricular or systemic arterial blood and that of pulmonary arterial blood. Samples were withdrawn during the period of gas collection. In most early studies arterial and venous oxygen content was measured directly by the method of Van Slyke and Neill (1924). This was time consuming and required considerable skill and experience. This method has now been generally superseded by less exact methods that measure oxygen saturation of haemoglobin by reflectance oximetry. Oxygen content (ml oxygen/l blood) is then calculated by multiplying the fraction of oxygen saturation by the theoretical oxygen-carrying capacity;

([Haemoglobin concentration (g/dl)] x 1.36 [ml oxygen/gm/haemoglobin]) x 10

1.3.2 Assumptions and Errors of the Direct Fick Method

The method assumes that there is no intracardiac shunt and that the lungs do not extract oxygen from the blood. Mitchell and Cournand (1955) confirmed that lung tissue is a negligible source of oxygen utilization. During the measurement of oxygen uptake it is assumed that the volume of oxygen taken up per minute from the expired gas is equal to the volume of oxygen per minute which passes from the alveolar gas to the blood in the pulmonary capillaries and that the volume of nitrogen in the lungs remains constant during the period of collection. This is not true when the composition of the inspired gas or the pattern of respiration changes or there is a change in the functional residual capacity of the lungs. Thus the accuracy of the measurement is dependent on a steady state in which oxygen consumption and CO remain constant over the period of measurement.

Since the oxygen uptake used in the Fick equation is the mean for the period of gas collection, it is necessary to obtain a mean value of the arterio-venous oxygen difference over the same period of time. This value should be a mean in relation to blood flow (volume average mean). This is not the same as a time average sample, derived by sampling at a steady state over a period of collection, which is generally used instead. When both CO and the arteriovenous oxygen difference are changing, the use of a time average sample will introduce error (Visscher and Johnston 1953). A small overestimation of CO also occurs when using systemic arterial blood because the oxygen content is 2-5 ml/l lower than the pulmonary venous blood due to bronchial venous drainage.

Despite these assumptions the direct Fick method probably gives the most accurate measurement of CO (Fagard and Conway 1990). If absolute steady-state conditions were achieved then the Fick principle would be infallible. However errors, especially in the measurement of oxygen uptake, can reduce the accuracy of the method. These errors can only be reduced by meticulous attention to technique. Comparison of other techniques with the Fick measurement is different from calibration and is essentially the comparison of a new method with an established reference technique rather than with the true quantity. Measurements of CO by the direct oxygen Fick method have been compared with direct measurements of pulmonary artery flow using an optical rotameter in dogs (Seely et al. 1950). The mean (SD) percentage difference between the two methods was 2.7 (7.0) %.

The reproducibility of CO measurements by the direct Fick oxygen method has been assessed by repeating measurements within a short period of time (usually 15 min) leaving the right heart catheter in place (Thomasson 1957, Selzer and Sudrann 1958, Fagard and Conway 1990). Reproducibility, expressed as the median percentage difference (absolute difference divided by the average of the two values, expressed as a percentage), varied between 4.4-7.6% for oxygen uptake and 5.2-7.2% for arterio-venous oxygen difference. The median percentage difference for CO measurements was 5.9-8.5%.

1.3.3 Direct Fick Studies during Pregnancy (Table 1.2)

Hamilton (1949) performed the first measurements of CO by the direct Fick method in pregnancy. He suggested that CO rose from the tenth week of gestation until 18-21 weeks. Thereafter there was little further change until 38-40 weeks when CO fell to values comparable to those recorded after delivery and in non-pregnant controls. Palmer and Walker (1949) confirmed that CO increased by the third gestational month. Statistical analysis was performed using analysis of variance and, with the exception of the seventh month, CO was elevated throughout pregnancy. Werko et al. (1950) reported an increase in CO at 13-20 weeks and a fall, back to non-pregnant values, at 33-38 weeks of pregnancy. Values of CO were consistently greater than those reported previously and their results disagreed with an earlier study (Werko et al. 1948) in which the authors reported no difference in CO between 6 non-pregnant and 10 pregnant women. Zimmerman (1950) reported the preliminary results of a catheterization study in 35 pregnant subjects. No values of CO were included but the author suggested that CO began to increase around the 12th week, reached a peak by the 32nd week, and then fell. Bader et al. (1955) suggested that maximum values of CO and SV were reached at 25-27 weeks gestation. Thereafter both fell, the decrease being statistically significant by the 'non-parametric test of unpaired replicates'. Non-pregnant measurements were not reported by either Bader et al. (1955) or Angelino et al. (1954).

In a recent study, Pivarnik et al. (1990) studied 7 women at 37 weeks gestation and then again 12 weeks after delivery as part of a larger study designed to compare noninvasive and invasive measures of maternal and fetal responses to positional change, exercise and volume loading. The ethical issues concerning such a study were discussed by Berkowitz and Berkowitz (1990). The authors suggested that CO, SV and HR were all significantly elevated during late pregnancy. The difference between these results and those of previous workers may reflect the fact that Pivarnik et al. studied subjects in the left lateral position. All the subjects subsequently went on to perform four sequential bouts of aerobic exercise and CO may also have been elevated in anticipation of this.

Author	n	Serial	Pos	Pregnancy Gestation	CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min^{-1})
Hamilton (1949)	75	No	Sup	6-9 w*	4.29 (-5)		78 (13)	NP (n=24)	4.51		68
				26-29 w†	5.73 (27)		78 (13)	PN (1-2 w, n=7)	4.44		
				38-40 w	4.60 (2)		82 (21)				
Palmer and Walker (1949)	84	No	Sup	9-12 w*	6.2 (35)			NP (n=8)	4.6		
				12-24 w†	6.4 (39)			PN# (n=4)	5.0		
				37-40 w	5.7 (24)						
Werko et al. (1950)	11	No	Sup	13-20 w*†	7.81 (19)	97 (-3)	80 (21)	NP (n=15)	6.54	100	66
				33-38 w	6.45 (-1)	71 (-29)	83 (26)				
Angelino et al. (1954)	15	No	Sup	25-28 w*	5.24						
				33-36 w†	6.44						
Bader et al. (1955)	47	No	Sup	14-24 w*	6.53	70	99				
				25-27 w†	6.96	75	93				
				36-40 w	5.53	58	96				
Pivarnik et al. (1990)	7	Yes	Lat	37 w	6.8 (58)	79 (27)	86 (23)	PN (12 w)	4.3	62	70

* Time of first measurement during pregnancy, † time of maximum increase in CO during pregnancy, # 'recently delivered'.

Abbreviations: Pos, position of subjects; Sup, supine; NP, non-pregnant; PN, postnatal; Lat, left lateral.

Table 1.2 Previous studies of cardiac output during pregnancy using the direct Fick method.

1.3.4 Limitations of Direct Fick Studies

1. The method employed by Palmer and Walker (1949) and Hamilton (1949) was inaccurate. venous blood was sampled from the right atrium where mixing is known to be incomplete (Warren et al. 1946). Furthermore arterial samples were not obtained and the arterial oxygen content was assumed to be 95% of the oxygen capacity. These deficiencies may explain the considerable variation in CO between individual subjects reported by Palmer and Walker (1949).

2. With the exception of the study of Pivarnik et al (1990) all other direct Fick studies were cross-sectional in design and investigated small numbers of subjects at each time point. Interpretation of the results is therefore limited by the wide variation in resting CO that exist between individuals (Wade and Bishop 1962). This is illustrated by the study of Palmer and Walker (1949) in which mean CO showed marked fluctuations between the 6th and 8th months of pregnancy. This is unlikely to represent true physiological variation and is more likely a reflection of the small numbers of measurements performed. Although Pivranik et al. (1990) studied the same small group of women after delivery, they only studied subjects once during pregnancy.

3. Measurement of CO by cardiac catheterization may falsely elevate resting CO due to the subjects' apprehension about the procedure (Stead et al. 1945). This may be more pronounced in pregnancy when the mother is concerned about the fetal risk. This problem was encountered by Palmer and Walker (1949) who found that initial measurements of CO were higher than those recorded later when 'any early anxiety had disappeared'. Apprehension may also explain the unusually high HR's reported by Bader et al. (1955).

4. In none of the studies were measurements performed during early pregnancy.

5. Some form of statistical analysis was performed in only three of the studies (Palmer and Walker 1949, Bader et al. 1955, Pivranik et al. 1990).

Thus cross-sectional catheterization studies, performed with subjects in the supine position, suggested that CO was elevated by the end of the first trimester, reached peak values during the second trimester and then fell, by a variable degree, during the third trimester due to a fall in SV. However one recent study, in which serial measurements were performed in the lateral position prior to exercise, suggested that CO was still substantially increased at 37 weeks gestation relative to postnatal values.

1.4 Pulse Pressure Studies

1.4.1 Measurement of Cardiac Output by Pulse Pressure

Frank (1899) first proposed that the area under the systolic portion of the aortic pressure pulse must bear some relationship to SV. Remington et al. (1948) subsequently derived a series of factors for the prediction of stroke index from the arterial pressure waveform. Warner et al. (1953) developed the theory and computer solution for a moderately complex pulse contour method based on a 'Windkessel' model. Stroke volume was calculated from the pressure as the driving force for flow during the ejection time;

$$SV = A_{SYS} / Z_{Ao}$$

where A_{SYS} = area under the systolic portion of the pressure wave and Z_{Ao} = characteristic impedance of the aorta (Jansen et al. 1990). The actual characteristic impedance is not known and therefore for quantitative measurement of SV, this term must be determined at least once for each subject by comparison with an absolute CO estimate (eg direct Fick or thermodilution). Furthermore Z_{Ao} changes as a function of HR and mean arterial pressure. The amount of change is predictable and has been built into a pulse pressure CO computer system (Wesseling et al. 1983).

The initial methods of calculating SV from pulse amplitude were based on numerous assumptions and were shown to be inaccurate (Warner et al. 1953). Hendricks and Quilligan (1955) compared measurements of CO using the method of Remington et al. (1948) with dye dilution methods during and after pregnancy. Although 90% of the CO determinations were within 25% of the dye measurements, individual measurements differed by up to 100%. Subsequent studies using computerized pulse wave analysis have shown that the method is reproducible and once calibrated against thermodilution provides a reasonably accurate measure of CO (SD of the difference 11%) (Jansen et al. 1990).

1.4.2 Pulse Pressure Studies during Pregnancy

Slemons and Goldsborough (1908) attempted to use the method during pregnancy but the recording techniques were not sufficiently accurate to yield useful results. Later Brehm and Kindling (1955) derived CO from pulse amplitude and frequency. They found no change in CO, relative to non-pregnant controls, until 5-8 months and thereafter CO fell. Hendricks and Quilligan (1956), using the method of Remington et al. (1948), suggested that CO increased during labour. Neither of these methods provided reliable measurements of CO and therefore pulse pressure studies added nothing to the existing literature.

1.5 Dye Dilution Studies

1.5.1 Measurement of Cardiac Output by Dye Dilution

In 1921 Stewart made the first measurements of CO using dye dilution in a dog. Subsequently Hamilton and his colleagues applied the method in man (Kinsman et al. 1929). A predetermined amount of dye was injected into the right atrium or a peripheral vein and its appearance and concentration in arterial blood were recorded from a peripheral systemic artery. A time-concentration curve was thus recorded that exhibited a rapid rise to a peak then a gradual decline in concentration that was interrupted by a secondary rise due to recirculation of the dye. The true first pass curve was obtained by plotting the concentration decline on semilogarithmic paper and extrapolating the early linear part of the plot (Kinsman et al. 1929). Cardiac output could then be calculated as:

$$CO\ (l/min) = I\ (mg) \times c\ (mg/l) \times t\ (min)$$

where I = quantity of dye injected, c = average concentration of the indicator during the first pass and t = duration of the curve. The product of c and t was easily measured as the area under the first pass curve. This area was first obtained by summing the concentration values at 1 sec intervals. Subsequently this method was replaced by planimetry and more recently by on-line computer methods (Lund-Johansen 1990).

Most of the early studies used 'blue' dyes (Evans Blue, Coomassie Blue, Indigo carmine) which had a peak spectral absorption between 600-700 μm wavelength. Indocyanine green, introduced in 1957, had a peak absorption at 805 μm, in the infrared region of the spectrum which is isobestic for both oxyhaemoglobin and reduced haemoglobin (Fox et al. 1957). Thus its photometric measurement was unaffected by changes in blood oxygen saturation and consequently it has gained widest acceptance in clinical practice.

The commonest form of photoelectric device used for detecting changes in dye concentration in blood was a cuvette densitometer. This measured the optical density of arterial blood as it was continuously withdrawn through a cuvette. An alternative and less invasive method of measuring dye concentration was a dichromatic earpiece densitometer (Beard and Wood 1951). This, when placed across the cartilage of the ear, measured maximal light transmission at 805 and 900 μm using two phototransistors. This configuration compensated for changes in the densitometer light path unrelated to dye concentration such as alterations in blood content, haematocrit and oxyhaemoglobin saturation (Beard and Wood 1951, Reed and Wood 1967).

1.5.2 Assumptions and Errors of the Dye Dilution Method

The method assumes that indicator is not added to or subtracted from the blood during one passage between the injection and sampling points; that the flow is constant during the period of the curve and that complete mixing of dye and blood occurs between injection and sampling points (Lund-Johansen 1990). To ensure complete mixing it is necessary to interpose a minimum of one atrium and one ventricle between the point of injection and sampling. However the further apart the injection and sampling points are the more the dye is distributed in time (Zierler 1962), and the dye curves tend to be of low amplitude and excessive width. Recirculation of blood containing dye then becomes a major problem.

The greatest source of error is dye recirculation, which makes extrapolation of the downslope of the time-concentration curve necessary (Daily and Schroeder 1981). Another source of error resulting in a distorted curve occurs when the arterial cannula is against the wall of the artery and blood is not withdrawn at a constant rate. Catheter and connector length can also introduce errors because the amount of dye and blood mixing increases with the length of the tubing. Mixing that occurs before density sensing at the cuvette does not give an accurate concentration reading (Daily and Schroeder 1981).

Most workers, but not all, have shown reasonable correlations between CO measurements by the dye dilution and Fick methods (Werko et al. 1949b, Taylor and Shillingford 1959, Miller et al. 1962, Reddy et al. 1972). However presentation of the data in this form conceals important information concerning the size of individual differences (Bland and Altman 1986). Eliasch et al. (1954) found that at resting outputs of 9-11 l/min the dye dilution method gave lower values than the Fick method. Taylor and Shillingford (1959) compared dye dilution and direct Fick measurements in 53 subjects. Twenty-three percent of measurements gave a >25% difference between the two methods (range +38% to -57%). Similar differences have been observed by other workers (Hamilton et al. 1948, Eliasch et al. 1954, Korner and Shillingford 1955). Paired measurements of CO by dye dilution and thermodilution have also shown large differences; mean difference -2.11 l/min, limits of agreement 1.41 to -5.63 l/min (de Leeuw and Birkenhager 1990).

The reproducibility of CO measurements using a cuvette densitometer, expressed as either the coefficient of variation or the mean percentage error, has been reported to be between 5-10% (Brandfonbrener et al. 1955, Robinson et al. 1979, de Leeuw and Birkenhager 1990). Taylor and Shillingford (1959) found the SD of a single observation was 0.71 l/min, compared with 0.59l/min for the Fick method. Twenty-one percent of these duplicated measurements differed by >15% but none differed by >25%. Greater variability has been reported for measurements using an ear densitometer (Robinson et al. 1979) and Powner et al. (1984) reported differences ranging from 0.33 to 2.8 l/min or 3-35% of the lowest value. A number of workers have also found the mean value of the first

determination to be consistently higher than that of the second and subsequent ones (Brandfonbrener et al. 1955, de Leeuw and Birkenhager 1990). When de Leeuw and Birkenhager (1990) systematically discarded the initial measurements, the variation of repeated determinations was within 8%. De Leeuw and Birkenhager (1990) are the only workers who have studied the temporal variability of dye dilution measurements. The mean difference between paired measurements performed 2 weeks apart was -0.42 l/min however the limits of agreement (± 2 SD) were wide (+ 2.08 to -2.92 l/min).

1.5.3 Dye Dilution Studies during Pregnancy (Table 1.3)

Adams (1954) injected Evans Blue dye into an antecubital vein and sampled from the femoral artery (19 samples over 6 minutes). No increase in CO or SV was noted until 24 weeks gestation. Maximum values of CO and SV occurred at 28 weeks and thereafter both fell, reaching postnatal values by 36 weeks gestation. Although Adams (1954) stated that the increase in CO was due primarily to an increase in SV, HR (calculated with figures derived from his graphs) showed a similar proportionate rise. No statistical analysis was performed. De Schwarcz et al. (1964) and Rovinsky and Jaffin (1966a) used similar methodology. In contrast to Adams, De Schwarcz et al. suggested that CO was increased by 8 weeks and reached maximum values by 16-19 weeks gestation. This was almost entirely due to an increase in SV. Little change in CO was evident between 20-35 weeks but by 40 weeks CO was only 24% above non-pregnant values. Rovinsky and Jaffin (1966a) found that CO was significantly greater than non-pregnant values between 21-40 weeks except for the 37-40 week interval. The decrease in CO during the third trimester was statistically significant and was due to a fall in SV.

Roy et al. (1966) injected Indigo Carmine dye into the right antecubital vein and sampled from the right femoral artery. No increase in CO was demonstrated until 21-27 weeks. Walters et al. (1966) injected Coomassie Blue into a peripheral vein and dilution curves were recorded by means of a photo-electric earpiece densitometer. Measurements were obtained from ≥ 27 subjects on each occasion apart from weeks 8-11 (n=20) and 40-43 (n=15). The highest recorded CO was obtained at 8-11 weeks of pregnancy. The authors suggested that part of this rise was due to the apprehension of the first measurement and that the 'true' maximum CO occurred between 24-32 weeks. They further suggested that this increase was due to an increase in SV rather than in HR. Inspection of their data however does not support this statement and an analysis of covariance showed that the overall difference between subject means was only significant for CO and HR and not SV.

Author	n	Serial	Pos	Pregnancy Gest	CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min^{-1})
Adams (1954)	31	No	?	14 w*	5.5 (-6)	60 (-29)	91 (32)	PN (4 w)	5.9	84	69
				28 w†	8.3 (41)	98 (17)	83 (20)				
				40 w	5.5 (-6)	67 (-20)	82 (19)				
De Schwarcz et al. (1964)	33	No	Sup	8-11 w*	7.8 (63)	98 (53)	79 (5)	NP (n=5)	4.8	64	75
				16-19 w†	8.9 (85)	113 (77)	78 (4)				
				40 w	6.0 (24)	72 (13)	83 (11)				
Roy et al. (1966)	29	No	Sup	<13 w†	5.9 (7)	70 (-9)	81 (13)	PN (?)	5.5	77	72
				28-34 w†	7.6 (38)	97 (26)	81 (13)				
				>35 w	5.8 (5)	73 (-5)	78 (8)				
Walters et al. (1966)	30	Yes	?	8-11 w*	7.0 (32)	91 (14)	78 (18)	PN (2-17 w)	5.3	80	66
				24-27 w†	6.6 (25)	82 (3)	81 (23)				
				36-39 w	5.6 (6)	71 (-11)	80 (21)				
				40-43 w	6.2 (17)	79 (-1)	79 (19)				
Rovinsky & Jaffin (1966a)	34	No	Sup	21-24 w*	8.1 (37)	94 (27)	87 (7)	NP (n=6)	5.9	74	81
				25-28 w†	8.5 (44)	96 (30)	89 (10)				
				37-40 w	5.9 (0)	63 (-15)	98 (21)				

* Time of first measurement during pregnancy, † time of maximum increase in CO during pregnancy. Figures in brackets are percentage changes relative to non-pregnant values.

Abbreviations: Pos, position of subjects; Gest, gestation; Sup, supine; ?, undefined; PN, postnatal; NP, non-pregnant.

Table 1.3 Previous studies of cardiac output during pregnancy using dye dilution.

1.5.4 The Effect of Posture on Measurement of Cardiac Output during Pregnancy

Prior to the publication of the work of Vorys et al (1961) little attention had been paid to the position of pregnant women during CO measurement. Most of the early investigators had carried out measurements with subjects in the sitting position (Lindhard 1915, Weiss 1926, Gammeltoft 1926, Stander and Cadden 1932). None of these workers reported a fall in CO in the last weeks of pregnancy with values at term still 36-70% above control values. The majority of later studies were performed with subjects in the supine position (Burwell et al. 1938, Hamilton 1949, Palmer and Walker 1949, Zimmerman 1950, Werko 1950, Brehm and Kindling 1955, Bader et al. 1955, de Schwarcz et al. 1964, Roy et al. 1966, Rovinsky and Jaffin 1966a). The position of subjects during CO measurements was not clearly stated by Adams (1954) and Walters et al. (1966), but from the discussions it seems likely the subjects were supine. All of these studies demonstrated a fall in CO and SV during the third trimester (usually evident from about 30 weeks gestation). Heart rate was generally found to increase during the same period (Hamilton 1949, Werko 1950, Bader et al. 1955, de Schwarcz et al. 1964, Rovinsky and Jaffin 1966a) although Burwell et al. (1938) and Roy et al. (1966) found a slight fall and Adams (1954) and Walters et al. (1966) reported no change. At term the mean percentage change in CO, relative to non-pregnant values, was +6% (range -10% to +24%) with only 2 studies reporting a lower CO at the end of pregnancy. Comparable figures for SV and HR were -9% (range -29% to +13%) and +17% (range +8% to +26%).

Vorys et al. (1961) were the first workers to compare CO in different positions during pregnancy using a reliable measurement technique. Quilligan and Tyler (1959) had found no systematic difference between CO in the supine and lateral positions. However CO was measured by pulse pressure and individual differences ranged from +23% to -17%. Vorys et al. obtained dilution curves in 31 pregnant women during the last month of pregnancy. The dye was injected into a peripheral vein and sampled via a cuvette from the brachial artery. In the supine position at term CO was 23% higher than in non-pregnant controls. In 6 women assumption of the left lateral position led to a increase in mean CO from 6.64 l/min to 7.68 l/min, a mean increase of 1.04 l/min (range 0.75 to 1.48 l/min). Lees et al. (1967a) studied 8 women at 36-40 weeks of pregnancy. Indocyanine green dye was injected into the right atrium and arterial blood was sampled from the aortic root by a constant speed withdrawal pump. In 3 subjects, in whom the fetal head was deeply engaged in the pelvis, there was little change in CO (mean change -7%, range +5% to -15%). Out of the 5 subjects in whom the fetal head was not engaged, 3 had a moderate fall (mean -20%, range -11% to -26%) and 2 a profound fall in CO (mean -48%, range -32% to -80%). This fall was related primarily to a reduction in SV. Mulholland and Boyle (1968), in a study using the direct Fick method, confirmed that a change of posture (supine to lateral) in late pregnancy was associated with an increase in CO. Such an increase was

not seen between 16-26 weeks.

Three groups studied CO in the left lateral position during pregnancy (Table 1.4). Pyorala (1966), using Evans Blue and a photoelectric earpiece, found no statistically significant fall in CO or SV during the last trimester. Lees et al. (1967b) injected Indocyanine green into right atrium and sampled from the aortic root. They found no significant change in CO, SV or HR during pregnancy. In a cross-sectional study, reported in the same paper, the mean values for CO at 11-13, 24-27 and 34-37 weeks gestation were 5.79, 6.13 and 5.74 l/min respectively. Stroke volume was 65 ml on each occasion. Thus these findings confirmed those of Pyorala (1966). Ueland et al. (1967) injected Indocyanine green into a peripheral vein and sampled from the brachial artery. Cardiac output was increased at 20-24 and 28-32 weeks but values obtained at 38-40 were not significantly different from postnatal values. No significant difference was demonstrated in SV at 28-32 and 38-40 weeks gestation. Both Lees et al. (1967b) and Ueland et al. (1969) confirmed that CO was lower in the supine position during late pregnancy.

Author	n	Serial	Pregnancy				Non-Pregnant			
			Gestation	CO (l/min)	SV (ml)	HR (min^{-1})	Time	CO (l/min)	SV (ml)	HR (min^{-1})
Pyorala* (1966)	48	No	20-24 w†	7.65 (42)	91 (26)	84 (12)	NP (n=12)	5.39	72	75
			28-32 w#	6.91 (28)	89 (24)	79 (6)				
			36-40 w	6.85 (27)	82 (14)	81 (8)				
Lees et al. (1967b)	5	Yes	11-13 w†	6.10	76	81				
			24-27 w#	6.18	75	84				
			34-37 w	6.26	76	84				
Ueland et al. (1969)	11	Yes	20-24 w†	6.9 (39)	95 (33)	73 (5)	PN (6-8 w)	5.0	71	70
			28-32 w#	7.0 (41)	88 (23)	82 (17)				
			38-40 w	5.7 (15)	69 (-3)	83 (20)				

* Figures are means (calculated from graphs) except heart rates which are medians; † Time of first measurement, # time of maximum increase in CO during pregnancy.
Figures in brackets are percentage changes from non-pregnant values.

Abbreviations: NP, non-pregnant; PN, postnatal.

Table 1.4. Previous studies of cardiac output in the lateral position during pregnancy using dye dilution.

1.5.5 Limitations of the Dye Dilution Studies

1. With the exception of Lees et al. (1967b), all dye dilution studies were performed by injection of dye into a peripheral vein. When compared to central injection, this method produces greater disturbance of the dye curve (due to recirculation) and consequently accurate measurement of the dye curve is more difficult. Peripheral dye injection is generally accepted to be a less accurate technique (Wade and Bishop 1962, Lund-Johansen 1990). Walters et al. (1966) recorded serial dye dilution curves using a earpiece densitometer. They calibrated the ear oximeter by determining the concentration of dye in samples of venous blood withdrawn during the tail of the dye dilution curve. Although this method obviated the need for serial sampling, the use of venous calibration is associated with large errors (Beard and Wood 1951). Measurements of CO obtained using ear oximetry have been shown to be less accurate than measurements obtained by either the cuvette densitometer (Beard and Wood 1951, Robinson et al. 1979) or by thermodilution (Powner et al. 1984).

2. Serial measurements were carried out in only three of the studies (Walters et al. 1966, Lees et al. 1967b, Ueland et al. 1969) of which only two included non-pregnant control values (Walters et al. 1966, Ueland et al. 1969). Walters et al. (1969) were the only group to perform measurements at less than 11 weeks gestation and on more than 3 occasions during pregnancy.

3. The use of postnatal measurements as 'non-pregnant control' values was limited by the uncertainty regarding the time at which CO returned to pre-pregnancy levels. Although Walters et al. (1966) reported serial measurements of CO during the first 17 weeks after delivery, investigations were performed at different time points in each subject and no pre-pregnant data or data from separate non-pregnant controls were included. Thus it was unknown if CO at 4 weeks after delivery (Adams et al. 1954, Ueland et al. 1969) was truly representative of the pre-pregnant state.

4. Adams (1954), de Schwarcz et al. (1964) and Roy et al. (1966) performed no statistical analysis. Although Lees et al. (1967b) and Ueland et al. (1969) quote p values, no mention is made of the method of statistical analysis. Walters et al. (1966) employed an appropriate method of analysis (analysis of variance) but they did not compare differences between time points either during or after pregnancy.

Thus dye dilution studies suggested CO increased from the end of the first trimester to a peak at between 20-28 weeks gestation. Whether this increase was due primarily to an increase in SV, HR or both was less clear. The importance of maternal posture during CO measurement became clear and certain studies suggested that the previously reported fall in CO and SV in late pregnancy was probably a postural artifact.

1.6 M-Mode Echocardiographic Studies

1.6.1. Measurement of Cardiac Output by M-mode echocardiography

Echocardiography utilizes pulsed ultrasound to visualize the heart. The principles of the technique are described in detail later (Chapter 3). Essentially an ultrasound beam is directed at the heart in the vicinity of the left ventricle. Some of the sound is reflected from the tissue interfaces along the beam and this reflected energy is converted into dots of which the brightness indicates the relative intensities (brightness or B-mode). An M-mode or motion mode recording is produced by adding the dimension of time to the B-mode display. This type of recording provides information about the axial movements and dimensions of the left ventricle.

Feigenbaum et al. (1969) first demonstrated that LV internal dimensions, measured from M-mode echocardiographic recordings, correlated with angiographically derived LV volume. This finding prompted investigators to derive several formulae for estimating LV volumes from a single M-mode measurement (Feigenbaum et al. 1969, Popp and Harrison 1970, Pombo et al. 1971a). The method which has been most widely used is that initially proposed by Feigenbaum et al. (1969);

$$SV = [(EDD)^3 - (ESD)^3] \div (EDD)^3$$

where EDD = LV end-diastolic dimension (cm) and ESD = LV end-systolic dimension (cm) measured from standard left ventricular M-mode echocardiographs.

1.6.2 Assumptions and Errors of the M-mode Echocardiographic Method

The method assumes that the left ventricle can be described as a prolate ellipse. The formula for the volume (V) of a prolate ellipse ie $V = \pi/6 \times D_1D_2L$ where D_1 and D_2 are the short axis diameters and L is the long axis diameter. If the short axis diameters are assumed to be equal and the long axis is assumed to be twice the short axis diameter the formula may be simplified to $V = \pi/6 \times D^2(2D)$. Accordingly the volume in both systole and diastole approximately equals the cube of the short diameter. However since the ventricle becomes more spherical as it dilates, the ratio of LV long-axis dimension to short-axis dimension decreases; conversely, when the LV is underfilled, it becomes more exaggeratedly elliptical (Hutchins et al. 1978). As a result the simple cube method tends to overestimate the volume of enlarged ventricles and to underestimate that of small chambers (Teichholz et al. 1976). In an attempt to correct for this tendency Teichholz et al. (1976) developed a modified formula (Volume = (7.0 / 2.4 + D) x D^3 where D = LV internal diameter). This was subsequently shown to yield a slightly higher correlation coefficient than the standard cubic

method when SV results were compared with those obtained by thermodilution (r=0.86 versus r=0.75) in patients with symmetrical or nearly symmetrical ventricular contraction (Kronik et al. 1979).

The method further assumes that global LV function is accurately reflected by contraction of the limited segment sampled for measurement of the LV minor-axis dimensions. Angiographic studies have shown that this assumption is not valid in many patients with cardiac disease and in these circumstances M-mode derived SV correlate poorly with invasively determined SV irrespective of which M-mode formula is used (Martin 1978, Antani et al. 1979, Kronik et al. 1979). A final conceptual limitation of extrapolating from a single linear dimension to three-dimensional measurements of SV and CO is that any error in primary measurements will be cubed in the calculation (Wallerson et al. 1990).

A number of previous studies have reported a reasonable correlation between SV's measured by M-mode echocardiography and angiography or thermodilution in subjects with symmetrically contracting ventricles (Pombo et al. 1971b, Teichholz et al. 1976, Kronik et al. 1979,). The correlation coefficients in these studies ranged from 0.83-0.96 and the SEE from 12-18 ml. However Kiowski et al. (1981) found a much poorer correlation (r = 0.55) in a group of normal subjects in which CO was determined by echocardiography and dye dilution. Equally low correlation coefficients were reported by Wallerson et al. (1990) when M-mode echocardiographic measurements were compared with Doppler and two-dimensional echocardiography. No study has investigated the agreement between M-mode and invasively determined SV using the more appropriate limits of agreement method of Bland and Altman (1986). Furthermore measurements of SV by M-mode echocardiography have not been validated in pregnant subjects.

Few workers have studied the reproducibility of CO measurements using M-mode echocardiography. Kiowski et al. (1981) reported that the coefficient of variation for repeated measurements was 8.4%. Kupari (1984) studied temporal variability of M-mode measurements. The coefficient of variation increased from 5.1% when repeat measurements were performed 3 hours apart to 15.5% when performed 14-18 months apart.

1.6.3 M-Mode Echocardiographic Studies during Pregnancy

Lateral Position: Rubler et al. (1977) were the first group to study maternal haemodynamics using M-mode echocardiography. Measurements were performed at 13-23 weeks gestation (n=13), 24-32 weeks gestation (n=15) and at 'term' (n=12). A group of 15 non-pregnant women were studied as controls. Heart rate, SV and CO were increased by 13-23 weeks (mean non-pregnant CO 3.93 l/min, mean at 13-23 weeks 6.05 l/min) and

thereafter no further changes were found. The results of subsequent serial echocardiographic studies in the left lateral position are shown in Table 1.4. All have confirmed the increases in CO and HR during the second trimester. Apart from Mashini et al. (1987), who found no significant change in SV at any time during pregnancy, all other workers have also demonstrated an increase in SV during the second trimester.

There is more disagreement about changes during the third trimester of pregnancy. Laird-Meeter et al.(1979) found no significant change in SV or CO during the third trimester although absolute values were not reported. Matsunaga (1984) also found no change in mean CO between 24-31 and 32-40 weeks gestation (values of SV were not reported). In contrast a number of studies have reported that CO increased further during the third trimester (Katz et al. 1978, Castillon et al. 1984, Hirata et al. 1984). Katz et al. (1978) suggested that this was due to a further increase in SV whereas Castillon et al. (1984) found no change in SV but an increase in HR. Hirata et al. (1984) reported an increase in HR and CO between 24 and 32 weeks and a further increase in SV between 32 and 36 weeks gestation. Arima (1982) is the only worker who has reported a fall in SV and CO during the third trimester. In this study it is unclear whether SV and CO remained elevated relative to control values because no non-pregnant data were reported.

Most of the echocardiographic studies that have included first trimester recordings have performed initial measurements at ≥ 10 weeks gestation and compared these with postnatal values (recorded between 3-12 weeks after delivery). One notable exception to this is the study of Capeless and Clapp (1989) who recruited 8 subjects prior to conception and studied them before pregnancy and at 8, 16 and 24 weeks of pregnancy. They reported an increases of 22% in both SV and CO by 8 weeks while HR was increased by 16 weeks. Castillon et al. (1984) also found an increase of CO of almost 20% between 9-16 weeks of pregnancy. Most other authors reported a small but statistically insignificant increase in CO.

Supine Position; Four studies have compared measurements of CO during pregnancy in the left lateral and supine positions. Rubler et al. (1977) studied women at term while Arima (1982) studied women between 20 and 37 weeks gestation. Katz et al. (1978) and Castillon et al. (1984) studied subjects during each trimester and after delivery. Heart rates were similar in the two positions and, with the exception of Arima (1982), no significant differences in CO were demonstrated. Arima (1982) reported a lower CO in the supine position at 20-21 weeks and 32-33 weeks gestation. This difference was not apparent at 24-25, 28-29 and 36-37 weeks of pregnancy. All groups found SV to be lower in the supine position during the third trimester. This reduction ranged from 6 ml (Castillon et al. 1984) to 22 ml (Rubler et al. (1977).

Author	n	Method	Gestation	Pregnancy CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min^{-1})
Katz et al. (1978)	19	F	End of 1st Trimester*	5.71 (6)	74 (-5)	85 (12)	PN (6-12 w)	5.40	79	69
			End of 2nd Trimester	7.41 (37)	86 (9)	85 (23)				
			End of 3rd Trimester†	8.56 (59)	97 (23)	88 (28)				
Arima (1982)	23	F	20-21 w*	6.3	77	85				
			32-33†	7.4	89	85				
			36-37 w	6.4	74	90				
Castillon et al. (1984)	10	F	9-16 w*	5.7 (19)	73 (6)	80 (11)	PN (10 w)	4.8	69	72
			33-39 w†	7.2 (50)	81 (17)	89 (24)				
Hirata et al. (1984)	25	F	10 w*	4.2 (5)	65 (3)	64 (3)	PN (3 w)	4.0	63	62
			36 w†	6.6 (65)	85 (40)	78 (26)				
Matsunaga (1984)	30	F	<1 5 w*	4.66 (-4)			PN (4 w)	4.84		
			24-31 w†	6.28 (30)						
			32-40 w	5.65 (17)						
Mashini et al. (1987)	7	T	10-14 w*	4.3 (2)	59 (-11)	75 (9)	PN (7-10 w)	4.2	66	66
			26-30 w†	5.5 (31)	68 (3)	88 (33)				
			34-38 w†	5.5 (31)	64 (-3)	88 (33)				
Capeless & Clapp(1989)#	8	T	8 w*	5.2 (24)	79 (22)	68 (4)	PC	4.2	65	65
			16 w†	5.9 (40)	83 (28)	72 (11)				
Steegers et al.(1990)¶	23	T	14 w*	5.3 (15)	70 (4)	76 (12)	PN (6 w)	4.6	67	68
			28 w†	6.6 (43)	76 (13)	85 (25)				
			38 w	5.7 (24)	72 (7)	80 (18)				

* Time of first measurement during pregnancy, † time of maximum increase in CO during pregnancy, # Last measurement at 24 weeks gestation, ¶ data taken from graphs.
Figures in brackets are percentage changes relative to non-pregnant values.

Abbreviations; F, LV volumes calculated according to formula of Feigenbaum et al. (1969) (F) or T, Teichholz et al. (1976); PN, postnatal; PC, pre-conception.

Table 1.4. Previous serial studies of cardiac output in the lateral position during pregnancy using M-mode echocardiography.

1.6.4 Limitations of M-mode Echocardiographic Studies

1. The stereometric assumptions inherent in the calculation of CO using M-mode echocardiography appear to be valid when ventricular volume is normal but do not hold true when pathological dilatation occurs (Fortuin et al. 1971). During pregnancy there is a progressive increase in heart volume (Ihrman et al. 1960b) and LV EDD (short axis) (Katz et al. 1978). Thus the assumptions regarding the shape of the left ventricle may no longer be valid. On theoretical grounds this could lead to an overestimation of SV. No study has validated the technique during pregnancy. Until this has been done the accuracy of the method must remain in question.

2. Arima (1982) reported no non-pregnant control data. In the remaining echocardiographic studies these data were derived from measurements performed after delivery. The timing of the postnatal measurement has varied from 3 weeks (Hirata et al. 1984) to 10 weeks (Castillon et al. 1984) after delivery. As discussed previously, data obtained during the early puerperium may not truly reflect pre-pregnant values. One exception to this was the study of Capeless and Clapp (1989) in which subjects were initially studied prior to conception. These workers were interested in the haemodynamic changes during early pregnancy and they reported no data after 24 weeks gestation.

3. The study of Capeless and Clapp (1989) was the only one to use appropriate statistical analysis (repeated measures analysis of variance with correction for multiple comparisons). All others have used Student's t-tests on paired differences, considering $p < 0.05$ as being statistically significant. This method of analysis was inappropriate because it involved multiple significance testing. Thus 1 in 20 comparisons will be 'statistically significant' due to chance alone and the overall significance of the analysis is likely to be considerably greater than 5% ($p > 0.05$).

In conclusion, M-mode echocardiographic studies confirmed that CO increased during the second trimester and that this increase was maintained or even augmented during the third trimester when measurements were performed in the lateral position. However there was a wide variation in peak values of CO (5.5-8.6 l/min). Although one group of workers studied women prior to conception, only one further study was performed during the first trimester and therefore the haemodynamic changes during this period remained poorly understood.

1.7. Impedance Cardiographic Studies

1.7.1 Measurement of Cardiac Output by Impedance Cardiography

The technique of impedance plethysmography was developed by Kubicek et al. (1966). Cardiac output was calculated by measuring transthoracic impedance and evaluating the changes in electrical conductivity associated with the ejection of blood into the pulmonary bed. Two band electrodes were placed around the subject's neck, a third around the thorax (at the level of the upper xiphisternal joint) and a fourth around the abdomen. An electrical current generator caused an interrogating current to enter and leave the body through the outer electrodes. The resultant voltage (impedance) changes occurring with the cardiac cycle were recorded from the inner two electrodes. By Ohm's law, the voltage across the inner bands was proportional to the impedance (Z) when the current applied was constant. Stroke volume was then calculated from a formula relating impedance change to volume change in a conducting medium (Kubicek et al. 1966);

$$SV = \rho\,(L/Z_0)^2 \text{ x } VET \text{ x } (dZ/dt)_{max}$$

where ρ = resistivity of blood at 100 kHz (ohm/sec), L = distance between the two inner electrodes (cm), Z_0 = thoracic base impedance (ohm), VET = ventricular ejection time (sec), $(dZ/dt)_{max}$ = maximum rate of change of impedance during systole (ohm/sec).

Granerus and Elg (1982) subsequently developed an alternative formula for calculating SV based on the impedance change (ΔZ);

$$SV = A \text{ x } L \text{ x } \Delta Z/Z_o$$

where A = cross-sectional area of the thorax (cm^2), ΔZ = maximum amplitude of the impedance change during systole (ohm), L and Z_0 are the same as in the above equation.

Sramek et al. (1983) reported a modification of the Kubicek formula;

$$SV = L^3 / 4.2 \text{ x } VET \text{ x } (dz/dt)_{max} / Z_o$$

where $(dz/dt)_{max}$ = maximum rate of change of impedance during systole (ohms/sec) and VET, L and Z_0 are the same as in the above equation. This equation was found to give more accurate estimates of SV (Bernstein 1986) and was incorporated in the computer software of the more modern impedance devices eg Noninvasive Continuous Cardiac Output Monitor (NCCOM-3).

1.7.2 Assumptions and Errors of the Impedance Cardiographic Method

The origin of the impedance changes associated with cardiac activity is poorly understood and the contribution of pulmonary blood flow, left ventricular output and expansion and contraction of the aorta to the recorded signals remains uncertain. The Kubicek technique considers the rib-cage to form a fairly rigid container surrounding a central core of solid or fluid-filled incompressible tissue, together with two columns of partially air-filled tissue. The method assumes that the resistance of the incompressible thoracic component does not change during the cardiac cycle and that the resistance of the compressible lung tissue varies as air is displaced by conducting blood injected into and flowing out of it during each cardiac cycle. If a fixed amount of blood could be injected into the pulmonary vascular bed and prevented from escaping, an increase in electrical current should occur corresponding to the proportional increase in conductive blood in relation to the existing non-variable conductive material between the electrodes in the thoracic cavity (de Swiet and Talbert 1986). Unfortunately, blood leaves the pulmonary vascular bed during systole and SV has to be estimated by extrapolation of the initial flow. This assumes that the ejection flow rate remains constant and equal to the initial flow rate as the pulmonary valve opens. This cannot be true since the pulmonary valve would not close unless flow reduced to zero at the end of systole.

Although the impedance changes recorded are thought to reflect right ventricular output there is some evidence that left ventricular output and expansion and contraction of the aorta contribute to the recorded signals (Geddes and Baker 1972). More recent studies have also shown that rheological properties of blood, phase of respiration, anatomical configuration and electrode location, as well as pulmonary blood flow, have substantial effects on the impedance cardiogram (Saito et al. 1983, Spinelli and Valentinuzzi 1983, White 1990).

Validatory studies in which impedance CO, determined by the Kubicek method, was compared with invasive measurements have shown conflicting results; correlation coefficients ranging from 0.63 (Donovan et al. 1986) to 0.93 (Nagger et al. 1975). More recent studies have used a more appropriate method of analysis and reported more consistent results. White et al. (1990) compared CO derived from the Kubicek equation with dye dilution. They found the limits of agreement (± 2 SD) were wide (± 2.66 l/min). Similar results were reported by Gotshall et al. (1989) when measurements were compared with thermodilution (± 2.01 l/min). Although Northridge et al. (1990) suggested that better agreement was obtained using the NCCOM-3 device incorporating the Sramek equation (± (± 1.27 l/min), this was not confirmed by Gotshall et al. (1989) (± 3.27 l/min). Interestingly this last group also compared impedance measurements using both equations. Measurements derived from the Sramek equation were on average 1.4 l/min lower than those derived from the Kubicek method (± 3.1 l/min).

Several studies have reported the correlation between impedance and thermodilution measurements of SV and CO during pregnancy (Table 1.5). Secher et al. (1979) and Milsom et al. (1983 a &b) included several data points from each subject in their analysis. Appropriate use of the correlation coefficient requires that each data point be independent of all others. Thus use of several data points from each subject is likely to falsely improve the r value. All 3 studies suggested that the impedance method systematically underestimated SV. Two more recent studies, both using the more modern NCOOM3 Cardiovascular Monitor which utilizes the modified Kubicek equation of Sramek et al. (1983), have reported markedly contrasting results. Easterling et al. (1989a) found no correlation between impedance and thermodilution measurements of CO ($r=0.17$ $p>0.05$), while Masaki et al. (1989) reported a close correlation ($r=0.91$, $p<0.001$). However 2 subjects were retrospectively excluded; one with tricuspid regurgitation in which the impedance estimate of CO was 53% greater than the thermodilution estimate; and one with septic shock in which the impedance estimate was 32% smaller than the thermodilution estimate. In the remaining 9 subjects the mean difference between impedance and thermodilution measurements was -11% (range -35.6% to +5.6%). Easterling et al.(1990a) subsequently analysed the data of Masaki et al. (1989) using the limits of agreement method and found a mean difference (±2 SD) of -0.73 (±1.97) l/min. Thus the agreement between impedance and thermodilution measurements of CO appears to be even poorer during pregnancy with the impedance method consistently underestimating CO.

Kubicek et al. (1966) reported that the confidence interval for a single measurement of CO by the impedance method was ± 12%. Subsequent studies have generally confirmed the reproducibility of the technique; coefficients of variation for consecutive measurements by the same observer ranging from 2.7% (Northridge et al. 1990) to 7.7% (Smith et al. 1988). Comparable values have been reported for inter-observer variability (White et al. 1990). White et al. (1990) studied temporal variability by comparing measurements performed on 2 consecutive days. The mean difference (±2 SD) was -0.05 (± 1.32) l/min.

Author	Subjects (n)	Measurements (n)	Method	Comparison	r	Slope	Int
Secher et al. 1979*	12	220	K	TD	0.69	0.84	10.7
Milsom et al. (1983a)*	10†	79	K	DD	0.87	0.75	11.2
Milsom et al. (1983b)*	10#	80	K	DD	0.83	0.65	-0.6
Easterling et al. (1989a)¶	10	10	S	TD	0.17		
Masaki et al. (1989)¶	9$	9	S	TD	0.91	1.04	-1.03

† 36-39 weeks gestation, # before and during Caesarean section, $ 2 additional subjects were retrospectively removed from the analysis

Abbreviations; K, SV determined by the equation of Kubicek et al (1966); S, SV determined by the equation of Sramek et al. (1983); TD, thermodilution; DD, dye dilution.

Table 1.6 Studies comparing stroke volume* and cardiac output¶ measured by impedance cardiography and thermodilution during pregnancy.

1.7.3 Impedance Cardiographic Studies during Pregnancy

Lateral position: The results of previous impedance studies in which CO has been measured serially during pregnancy in the left lateral position are summarized in Table 1.6. Atkins et al. (1981a) were the first group to use this technique serially during pregnancy. They studied 19 subjects at booking and thereafter at monthly intervals and again twice after delivery. In the same paper they reported a further study of 8 women recruited prior to conception and studied at monthly intervals during pregnancy and on three occasions after delivery. This was the first study in which women had acted as their own pre-pregnant controls. The results suggested that CO increased during the first trimester (the increase being statistically significant by 12 weeks gestation), plateaued between 12-20 weeks and thereafter fell until delivery when CO was below pre-pregnancy values. Heart rate rose during pregnancy, the increase being statistically significant by 28 weeks. Stroke volume apparently rose to about 12 weeks and then fell until delivery when values were significantly lower than those recorded prior to pregnancy.

Myhrman et al. (1982) calculated SV by both the dz/dt formula of Kubicek et al. (1966) and the ΔZ formula of Granerus and Elg (1982). Using the Kubicek formula, they found no significant change in SV or CO during pregnancy, relative to postnatal values. Stroke volumes calculated from the Granerus and Elg formula were significantly higher during pregnancy and significantly lower during the puerperium than those calculated from the Kubicek formula. Thus, using the ΔZ formula, CO increased from 6.2 l/min at 15-16 weeks to 7.2 l/min at 25-28 weeks. Thereafter CO fell and by 37-40 weeks CO was not significantly different from the postnatal value of 5.1.l/min.

Two more recent studies have reported quite different results. Milsom et al. 1988 measured CO during each trimester and then at 3-5 days and 12 weeks after delivery. They reported an increase in SV, measured by the Kubicek formula, HR and CO at 24 weeks gestation with further increases by 36 weeks. Zemel et al. (1990) measured cardiac index during each trimester. No non-pregnant control data were reported and values of body surface area were not included. Cardiac index was increased at 25 weeks (4.80 l/min/m^2) and 34-36 weeks gestation (4.93 l/min/m^2) relative to enrolment values.

Kagiya et al. (1984) performed cross-sectional measurements of CO, using impedance cardiography, at 16-23, 24-31 and 32-41 weeks gestation and 3-4 days after delivery. Mean values of CO were 7.88, 6.91, 6.32 and 5.47 l/min respectively. Corresponding values for SV were 109, 81, 83 and 79 ml respectively.

Author	n	Method	Pregnancy Gestation	CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min-1)
Atkins et al. (1981a)#	19	K	8-11 w*†	6.8 (21)	93 (-1)	73 (20)	PN (6 w)	5.6	94	61
			36 w	5.5 (0)	71 (-25)	77 (26)				
	8	K	4 w*	7.1 (9)	109 (9)	69 (3)	PC	6.5	100	68
			12 w†	7.7 (18)	110 (10)	75 (10)				
			36 w	5.9 (-9)	87 (-13)	74 (8)				
Myhrman et al. (1982)	14	K	15-16 w*	5.5 (0)	79 (-12)	70 (15)	PN (6-25 w)	5.5	90	61
			25-28 w†	6.2 (13)	87 (-3)	72 (18)				
			37-40 w	5.1 (-7)	83 (-8)	68 (12)				
	14	G	15-15 w*	6.2 (22)	89 (6)	70 (15)	PN (6-25 w)	5.1	84	61
			25-28 w†	7.2 (41)	101 (20)	72 (18)				
			37-40 w	5.3 (4)	78 (-7)	68 (11)				
Milsom et al. (1988)#	12	K	12 w*	5.8 (5)	80 (3)	73 (3)	PN (12 w)	5.5	78	71
			24 w	6.7 (22)	87 (12)	77 (8)				
			36 w†	7.8 (42)	96 (23)	82 (15)				
Zemel et al. (1990)¶	34	?	1st Tri*	6.1						
			2nd Tri	8.2						
			3rd Tri†	8.4						

* Time of first measurement during pregnancy, † time of maximum increase in CO during pregnancy, # data taken from graphs,¶ CO's calculated from reported cardiac indices (assuming body surface area = 1.7 m^2)
Figures in brackets are percentage changes relative to non-pregnant values.

Abbreviations; K, SV calculated from formula of Kubicek et al. (1966); G, SV calculated from formula of Granerus and Elg (1975); PN, postnatal; PC, pre-conception; Tri, trimester; ? undefined.

Table 1.7 Previous serial studies of cardiac output in the left lateral position during pregnancy using impedance cardiography.

Supine Position: In a separate paper, Atkins et al. (1981b) reported the influence of posture on the haemodynamic changes during pregnancy in the same 19 women studied between booking and term. Cardiac output in the left lateral position was consistently lower than CO in the supine position throughout pregnancy and the puerperium. This difference was not apparent when measurements were made in the left tilt position. Cardiac outputs in the right lateral and right tilt positions were consistently lower than those recorded in either the supine or left sided positions. These differences in CO primarily reflected differences in SV, posture having little effect in HR. Myhrman et al. (1982), calculating SV by the formula of Granerus and Elg, confirmed that SV and CO were consistently higher in the supine position compared with the left and right lateral positions throughout pregnancy and postnatally. However, two subsequent studies, both using the same method as Atkins et al. (1981) suggested that SV was higher in the left lateral position than in the supine position. Milsom et al. (1983a) found that SV was 15 ml lower in the supine position during the last trimester and comparable results were obtained between 32-41 weeks gestation by Kagiya et al. (1984). The latter group also found SV and CO to be higher in the left lateral position between 24-31 weeks but lower between 16-23 weeks and during the puerperium.

1.7.4 Limitations of Impedance Cardiographic Studies

1. Some of the physiological changes that occur during the course of pregnancy may be expected to influence the assumptions of the method and thus the outcome of the measurements. These assumptions and their validity during pregnancy have been critically reviewed by de Swiet and Talbert (1986). These authors pointed out that changes in blood viscosity, total blood volume, pulmonary vascular resistance and heart rate will all affect the time course of ejection of blood from the right ventricle. Davies et al. (1986) reassessed the data of Atkins et al. (1981a) in respect to the individual items of measurement. From this data it is apparent that the terminal fall in SV and CO reported by Atkins et al. was primarily related to the marked terminal fall in the term dz/dt. The physiological changes described above may well account for a large proportion of the change in the dz/dt term observed by Davies et al. (1986).

2. Validatory studies of impedance cardiography during late pregnancy have suggested that the technique is of limited accuracy (Table 1.5). The consistent underestimation of CO may explain why most impedance studies have suggested that SV at term is less than or comparable with non-pregnant values.

3. Studies during pregnancy using the dz/dt formula of Kubicek et al. (1966) have shown very inconsistent results, both in terms of the absolute values of SV and CO and the effect of posture. Furthermore the results of SV calculated by the dz/dt formula are completely different from those using the ΔZ formula. These inconsistencies cast further doubt on the

validity of the technique.

4. With the exception of the study of Zemel et al. 1990, all results from serial studies were analysed using Student's t-test on paired differences. In all cases the differences were considered statistically significant when p was less than 0.05. This method of analysis is inappropriate (see section 1.6.4).

In conclusion, impedance cardiography initially appeared to be the ideal method for studying CO during pregnancy. Atkins et al. (1981a) carried out a study of optimal design in which each subject acted as their own pre-pregnant control. Their data appeared to confirm what had been suspected previously that CO increased early in pregnancy. Most impedance studies suggested that CO fell during the third trimester, in some cases to values below those recorded in the non-pregnant state. The subsequent demonstration of the inaccuracy of this method in pregnant subjects has, however cast doubt on the validity of these results.

1.8 Thermodilution Studies

1.8.1 Measurement of Cardiac Output by Thermodilution

The technique was introduced by Fegler (1953) but did not gain popular acceptance until 1971, when Swan and Ganz developed a multi-lumen, flow directed, thermal sensitive measurement catheter (Ganz et al. 1971). The principle of measuring CO by thermodilution is similar to that of other indication dilution techniques. A bolus of sterile fluid (usually ice-cold saline) is injected into the right atrium and the resultant temperature change is measured at a point downstream (pulmonary artery). The blood temperature change is recorded as a resistance change in a thermistor balanced through a Wheatstone bridge attached to a CO computer. The area under the temperature-time curve represents the integral of the instantaneous mixture temperature at the sensing point. Cardiac output is calculated by the modified Stewart-Hamiltom method;

$$CO\ (L/min) = \frac{V_1\ (T_B - T_I)\ K_1\ K_2}{\int T_b(t)\ dt}$$

where V1 = injectate volume (l), TB = initial blood temperature (°C), TI = initial injectate temperature (°C), K1 = density factor [1.08] (ratio of the specific heat and specific gravity of injectate and blood), K2 = computation constant or conversion factor [60], $\int Tb(t)dt$ = change in temperature as a function of time (area under the thermodilution curve, °C/sec). A critical analysis of each of these factors was presented by Levett and Replogle (1979).

While there many similarities between the thermodilution and dye dilution methods, the former is more convenient because; only one invasive procedure is required; the detection system is entirely internal and therefore withdrawal of blood is not required; measurements are minimally affected by recirculation of the indicator and therefore can be repeated in rapid succession; and proper operation of the system can be checked by calibration of the thermistors using fixed resistors. Conversely there are small but definite risks associated with placement of pulmonary artery catheters (Damen and Bolton 1986).

1.8.2 Assumptions and Errors of the Thermodilution Method.

The method assumes that firstly there is adequate mixing of the injectate with the volume flow. Vliers et al. (1973) have established that adequate mixing occurs between the right atrium and the pulmonary artery. Secondly there is no additional blood leaving or entering the circulation beyond the site of mixing and before the site of detection. Thus the method cannot be used in the presence of circulatory shunts or significant disease of the tricuspid or pulmonary valves. Thirdly, steady state conditions apply. Acute changes in cardiovascular status can therefore invalidate the method. Fourthly the injection is instantaneous and

finally the amount of indicator injected is accurately measured and there is no loss of indicator between the sites of injection and detection. These last two points are the greatest source of imprecision (Conway and Lund-Johansen 1990). Apart from the difficulties of accurately measuring the volume in the syringe and ensuring the temperature of the injectate does not change as it is drawn into the syringe and injected, there are also the problems of transfer of 'cold' from the injectate to the catheter wall and surrounding blood and the transfer of 'heat' from the blood to the injectate within the catheter after injection (Nadeau and Noble 1986). An additional problem is that there are distinct fluctuations in pulmonary artery temperature, related to cardiac and respiratory cycling, leading to a fluctuating thermal baseline. In some patients, these fluctuations approach the magnitude of the temperature change that follows 'cold' injection (Weisel et al. 1975). The potential for error in thermodilution measurements is most evident at low CO's because of the loss of thermal indicator and the recirculation of indicator before the computed analysis is complete (Nadeau and Noble 1986).

The thermodilution method has shown no systematic difference in estimation of continuous flow compared with absolute measurement (timed collection of fluid), the mean difference between the two methods being about 4-5% (Bilfinger et al. 1982). However MacKenzie et al. (1986) found a deterioration in performance with pulsatile flow; they studied 3 thermodilution computer systems and found the confidence limits varied from 30-62% of actual flow. Studies comparing thermodilution and the direct Fick method have reported correlation coefficients ranging from 0.70 to 0.93 (Hodges et al. 1975, Wyse et al. 1975). Thermodilution was less accurate al low CO with errors of ≥ 20% (Runciman et al. 1981). Slightly closer correlation has generally been reported between thermodilution and dye dilution measurements (r = 0.85-0.99) (Ganz et al. 1971,Weisel et al. 1975) although some workers have reported mean thermodilution values to be 5-31% greater than those obtained with dye dilution (Vliers et al. 1973, Russell et al. 1990).

Stetz et al. (1982) reviewed studies of the reproducibility of thermodilution measurements. They reported a SEM% (standard error of the mean/average CO) of between 2-5% when 3 measurements were used for each determination and 3.5-8.7% when one measurement was used. The authors concluded that differences of more than 12-15% between repeat measurements were likely to be of 'clinical significance'. Russell et al. (1990) assessed the reproducibility of repeat thermodilution measurements using the limits of agreement method of Bland and Altman (1986). The mean difference between measurements was -0.31 l/min, however the SD of the difference was large (1.11 l/min)

1.8.3 Thermodilution Studies during Pregnancy

Benedetti et al. (1980) first reported the use of this technique during pregnancy in women with severe pre-eclampsia. Because of the small but definite risk of cannulating the central circulation, subsequent studies have been primarily limited to critically ill obstetric patients. However two groups have reported the results of pulmonary artery catheterization studies during normal pregnancy. Wallenburg (1988) studied 7 subjects at 28-34 weeks gestation. The median cardiac index, stroke index and HR were 4.0 (range 3.9-5.0) l/min/m^2, 55 (range 43-61) ml/m^2 and 80 (range 67-93) beats/min respectively. Clark et al. (1989) studied 10 subjects at 36-38 weeks gestation and 11-13 weeks postpartum. Mean CO decreased from 6.2 l/min during pregnancy to 4.3 l/min after delivery. Mean SV and HR decreased from 75 ml to 61 ml and 83 beats/min to 71 beats/min respectively.

Whether such invasive studies are ethically justifiable is a matter of considerable debate (Berkowitz and Berkowitz 1990). Because central monitoring is often used in the management of critically ill pregnant patients, the investigators argued that a knowledge of normal baseline values was essential for the optimal management of women requiring this type of surveillance. It is certainly true that some of the haemodynamic data reported in these studies (eg. pulmonary arterial pressure, pulmonary capillary wedge pressure and left ventricular stroke work index) cannot be accurately obtained by noninvasive means. Much of this information was however available from earlier studies. Ethical issues aside, these small studies have provided valuable normal data against which the results of noninvasive studies can be compared. However they provide no information regarding the pattern of haemodynamic changes during and after normal pregnancy. These issues can only be resolved by studies using reliable noninvasive methodology.

1.9 Doppler Echocardiographic Studies

1.9.1 Measurement of Cardiac Output by Doppler Echocardiography

Cardiac output can be calculated from Doppler ultrasound measurement of blood velocity combined with echocardiographic measurement of flow area. The method was first used to measure CO in man by Magnin et al.(1981). Velocities can be measured from a number of sites within the heart and great vessels using CW or PD. The corresponding cross-sectional areas can be measured by A-mode, M-mode or cross-sectional echocardiography. The techniques of measurement and the limitations and assumptions of the method will be discussed in detail in the subsequent chapters.

Three studies have validated the method in critically ill pregnant women (Table 1.7). Cardiac outputs determined by the Doppler technique correlated closely with those obtained by thermodilution and the SEE's were small. Easterling et al. (1990b) also reported the regression equation obtained when both their studies were combined (r=0.93, y = 1.07x - 0.58). Both groups found that the Doppler method slightly underestimated CO compared with the thermodilution method. Although Lee et al. (1988) suggested that their method (using PD from the left ventricular outflow tract) was theoretically superior to that used by Easterling et al. (1987, 1990b), Easterling and Benedetti (1989b) subsequently showed that the difference between thermodilution measurements and those obtained by CW Doppler were actually smaller than those obtained using PD.

Author	n	Comparison	Site	Method	r	SEE	Slope	Int
Easterling et al. (1987)	12*	TD	AA	CW, A	0.91	0.3	1.11	-0.98
Lee et al. (1988)	16†	TD	LVOT	PD-X	0.94	0.64	0.74	1.91
Easterling et al. (1990b)	11#	TD	AA	CW, A	0.95		1.05	-0.35

* Pre-eclampsia (11) pneumonia (1); † pre-eclampsia, eclampsia, shock, renal failure; # pre-eclampsia (8), cardiomyopathy (2), haemorrhage (1).

Abbreviations: AA, ascending aorta; LVOT, left ventricular outflow tract; A-M, A-mode echocardiography; X, cross-sectional echocardiography.

Table 1.7 Combined cross-sectional and Doppler echocardiographic measurement of cardiac output: validatory studies in pregnant subjects.

1.9.2. Doppler Echocardiographic Studies during Pregnancy

Newman (1982) first used the Doppler technique to measure changes in mean aortic velocity during caesarean section. Haites et al. (1985) and McLennan et al. (1987) subsequently reported changes in velocity integral during pregnancy. None of these workers measured vessel cross-sectional area and therefore calculation of CO was not possible. Studies that have reported measurements of CO using the combined technique are shown in Table 1.8. James et al. (1985) reported the first serial study of CO during pregnancy using this technique. Following their initial abstract, which included the results from 7 women, they subsequently reported results from 20 women (Caton and Banner 1987). Although CO results were grouped in 2-3 week intervals, each subject was not studied during every gestation interval. Mean CO's were not reported and no statistical analysis was performed. The same group also studied the effect on CO of prostaglandin-induced termination at 17-23 weeks gestation (Willis et al. 1987).

Easterling et al. (1988) reported a cross-sectional study designed to determine the effects of orthostatic stress in pregnancy. Adoption of the sitting position during the first trimester induced a fall in CO, relative to values in the lateral recumbent position. Standing produced a further fall in CO. Comparable changes were evident during the third trimester and in non-pregnant controls. The same group subsequently published the largest serial study of CO during pregnancy (Easterling et al. 1990c). One hundred and seventy-nine primigravidae were recruited prior to 22 weeks gestation. Doppler and A-mode echocardiographic measurements were performed during pregnancy, at intervals corresponding to the routine antenatal clinic visits, and at 6 weeks postpartum. They studied 19 subjects at 10-13 weeks and thereafter 50-83 subjects during each 3-week epoch. Mean values of CO were not reported and therefore the data shown in Table 1.9 are taken from their graph. The authors commented that CO rose steadily until 34 weeks gestation. From 34 weeks until the last measurement before delivery CO fell by 0.5 ± 1.3 l/min, although the performance of individual subjects was variable (29% of subjects had a fall in CO of ≥ 1.0 l/min while in 9% CO increased by ≥ 1.0 l/min). No data regarding SV or HR were reported although the authors stated that SV rose steadily to 96 ml at 31 weeks and then fell while HR climbed steadily throughout pregnancy.

Author	n	Method	Pos	Pregnancy Gestation	CO (l/min)	SV (ml)	HR (min^{-1})	Non-Pregnant Time	CO (l/min)	SV (ml)	HR (min-1)
Caton & Banner (1987)#	20	AA, CW A	LL	< 12 w* (n=10)	5.5 (2)			PN (>6 w, n=14)	5.4		
				25-28 w† (n=20)	7.0 (30)						
				39-40 w (n=10)	6.0 (11)						
Willis et al. (1987)¶	13	AA, CW A	S/R	17-23 w	7.7	97	82				
Easterling et al. (1988)	14	AA, CW A	LL	1st Tri	5.6 (2)	78 (-11)	71 (13)	N-P	5.5	88	63
	16			3rd Tri	6.7 (22)	82 (-7)	84 (33)				
Easterling et al. (1990)#	89	AA, CW A	LL	11 w*	6.2 (15)			PN	5.4		
				34 w†	7.7 (43)						
				40 w	7.4 (37)						

* Time of first measurement during pregnancy, † time of maximum increase in CO during pregnancy, # data taken from graphs, ¶ prior to prostaglandin termination of pregnancy.

Abbreviations: Pos, position; AA, ascending aorta; A, A-mode echocardiography; S/R, semi-recumbent; LL, left lateral; PN, postnatal; N-P, non-pregnant.

Table 1.9 Previous studies of cardiac output during pregnancy using combined cross-sectional and Doppler echocardiography.

1.9.2 Limitations of Doppler Echocardiographic Studies

1. Caton and Banner (1987) and Easterling et al. (1990c) were the only workers to perform serial measurements although in neither study were all subjects investigated at each time point. Both groups only presented their results graphically and no SV or HR data were reported. In addition neither group studied women prior to conception or during the early part of the first trimester.

2. Aortic diameters were measured using A-mode echocardiography. This method is less accurate than cross-sectional echocardiography.

3. Caton and Banner (1987) performed no statistical analysis. Easterling et al. (1990c) compared the CO curves obtained in normotensive and hypertensive subjects using the technique of restricted maximum likelihood. Very limited statistical analysis was performed within the normotensive group.

In conclusion, validatory studies suggested that the Doppler technique was accurate during pregnancy. The results of serial studies during pregnancy suggested that CO increased to ≥ 7 l/min by the beginning of the third trimester and thereafter fell by 0.5-1.0 l/min. Thus although the technique appeared to be ideally suited to haemodynamic studies during pregnancy, the reported data added little to the existing literature.

CHAPTER 2

FACTORS INFLUENCING STUDY DESIGN

2.1 Need for Further Study

2.1.1 Cardiac Output during Normal Pregnancy

It will be apparent from the preceding chapter that there was uncertainty in the literature concerning the extent and timing of the changes in CO during normal human pregnancy. Much of the conflict may be explained by differences in investigative technique and study design. Most early studies were not longitudinal in design and were therefore of limited value because of the wide variations between individual subjects. Lees et al. (1967b) and Ueland et al. (1969) did perform serial dye dilution studies, but their investigations were limited to small numbers of patients at infrequent intervals during pregnancy.

The development of more non-invasive methods has allowed serial measurements to be performed at frequent intervals during pregnancy. Furthermore, because subjects are investigated at rest and without sedation, these investigations provide information about haemodynamics in a basal state which may be altered by invasive procedures. However, measurement of CO by M-mode echocardiography has never been validated in pregnancy. Furthermore, the accuracy of this technique in non-pregnant subjects has been questioned and the geometric assumptions inherent in the method may not be valid in pregnancy. Measurements of CO by impedance cardiography have been compared with invasive measurements in pregnant subjects. The correlation however, has been poor and the validity of the assumptions of the Kubicek method during pregnancy have been questioned.

There was a need for a well designed study of CO during pregnancy. Such a study required a non-invasive method that would allow simple, accurate and reproducible measurements of CO on repeated occasions throughout pregnancy. The combined technique of cross-sectional and Doppler echocardiography appeared to fulfil these requirements. In view of the uncertainties as to when CO returned to 'non-pregnant' values after delivery, such a study also required control investigations to be carried out prior to conception. At the time of starting the present investigations, no group had reported serial measurements of CO during pregnancy using the Doppler technique. Since then a number of studies have been reported. However the present study is the first to investigate serial changes in CO, using each subject as her own pre-pregnant control.

2.1.2 Factors Influencing Changes in Cardiac Output during Normal Pregnancy

Despite the extensive literature concerning changes in CO, relatively little was known about the mechanisms underlying these changes. With the exception of M-mode echocardiography, none of the techniques used to measure CO provided information on cardiac chamber size, preload or the inotropic state of the heart. Although many of the serial CO studies also reported blood pressure measurements, few had calculated peripheral vascular resistance (one component of afterload).

Some M-mode echocardiographic studies had suggested that pregnancy was associated with an increase in myocardial contractility and left ventricular cavity and wall dimensions (Katz et al. 1978, Laird-Meeter et al. 1979). Others had failed to confirm these findings (Thompson et al. 1986, Mashini et al. 1987). Studies of myocardial contractility using systolic time intervals had also reported conflicting results (Lim et al. 1976, Cellina et al. 1981). In none of these studies had measurements been performed prior to conception.

In view of these uncertainties it was decided to investigate changes in blood pressure (and therefore vascular resistance), left atrial and ventricular dimensions, and left ventricular thickness and function, in addition to measuring CO.

2.1.3 Changes in Cardiac Output During the Puerperium

Very little was known about the reversal of cardiovascular adaptations during the puerperium. The majority of workers who studied CO during pregnancy had reported isolated measurements during the puerperium. Walters et al. (1966) studied women at 0-11 days and then 2-17 weeks after delivery, but the exact timing of the measurements varied in each subject. Atkins et al. (1981a) measured CO by impedance cardiography at 6 weeks and then 4-16 months after normal delivery. The limitations of this technique have been discussed previously (Section 1.7.2). Two M-mode echocardiographic studies had reported measurements of CO during the early puerperium; Matsunaga (1984) at 5 days and 4 weeks after normal delivery and Maruta (1982) at 1 hour and 1-2 weeks after Caesarean section and after normal delivery. Thus no study had investigated serially the changes in CO during the puerperium. It was therefore decided that a further study should be undertaken. Since completing this study three groups have reported studies in which serial measurements were performed on two occasions during the first 12 weeks after delivery (Milsom et al. 1988, Sady et al. 1990, Capeless and Clapp 1991).

Because of the temporal constraints of completing the pregnancy studies within a two year period it was not possible to continue serial investigations in this group of women

throughout the puerperium. A separate group of women were therefore recruited at 38-39 weeks of pregnancy and investigations carried out during the first 6 months after delivery. To try and elucidate the mechanisms underlying the changes in CO, serial measurements of BP, left atrial and ventricular dimensions, and left ventricular thickness and function were also recorded. Subjects involved in the pregnancy study were however studied again at 6 months after delivery to confirm that values obtained at this stage of the puerperium were truly representative of the pre-pregnant state.

2.1.4. Cardiac Output during Twin Pregnancy

Although numerous workers had studied the haemodynamic alterations during singleton pregnancy, few had extended these observations to twin gestation. MacGillivray et al. (1971) reported that plasma volume was greater in twin compared with singleton pregnancy. Thus one might anticipate that CO would be greater during twin pregnancy due to a greater SV consequent upon an increased cardiac preload. Two cross-sectional studies had indeed suggested that CO was higher during twin gestation. Rovinsky and Jaffin (1966a) measured CO by dye dilution but the subjects were studied in the supine position. Veille et al. (1985) performed M-mode echocardiographic studies and suggested that SV was higher in twin pregnancy although this was only evident during the third trimester. Perhaps surprisingly the increased SV was not due to an increase in LV diastolic chamber size but to a increase in ventricular function (as suggested by a difference in percent fractional shortening). Values for left atrial dimension were not reported. No longitudinal study of the haemodynamic changes during twin pregnancy had been reported.

Therefore, in an attempt to understand further the factors underlying alterations in CO during pregnancy and specifically the importance of increased cardiac preload, it was decided to study serially changes in CO, BP, left atrial and left ventricular dimensions and left ventricular thickness and function in a group of women with twin pregnancy.

2.2 Choice of Posture for Serial Studies

Bieniarz et al. (1968) demonstrated angiographically that assumption of the supine position during late pregnancy led to aortocaval compression. Earlier dye dilution studies had shown that caval compression during late pregnancy led to a reduction in SV and CO due to a fall in venous return (Kerr et al. 1964, Lees et al. 1967a). However later studies using M-mode echocardiography suggested that although SV was consistently reduced in the supine position in late pregnancy, this was not invariably associated with a fall in CO (Section 1.6.3). In a comprehensive study of the effects of posture on haemodynamic changes during pregnancy, Atkins et al. (1981b) suggested that CO was consistently lower in the left lateral position, compared with the supine position. This difference was evident throughout pregnancy and the puerperium. Cardiac output was measured by impedance cardiography and inspection of their graphs suggests this difference in CO was primarily due to a higher HR in the supine position. These results were not confirmed by two later reports using the same methodology (Milsom et al. 1983a, Kagiya et al. 1984). Thus, apart from the study of Atkins et al. (1981b) virtually all other studies had shown a lower SV during the third trimester in the supine position when compared with the left lateral position.

It was therefore apparent that to avoid postural artifacts, studies would have to be performed in the lateral position. Preliminary observations revealed that access to the cardiac apex and suprasternal notch with echocardiographic transducers was difficult and uncomfortable for both subject and observer when investigations were performed with the subject in a full left lateral position (90° to the horizontal). All studies were therefore conducted with subjects in a left semi-lateral position (45° to the horizontal).

2.3. Use of Cardiac Index in Pregnancy

To allow individual subjects of different body size to be compared, it has been conventional cardiological practice to express CO in terms of body surface area. In contrast few workers studying haemodynamics during pregnancy have calculated CO per square metre of body surface area (cardiac index). The value of this correction in pregnant women has been doubted, especially when the same adult subjects are studied longitudinally (Hytten and Leitch 1971), and many of those who have quoted cardiac indices have themselves questioned its validity in pregnancy (Bader et al. 1955, Walters et al. 1966). Body surface area has been determined from the subject's height and weight using standard tables. The accuracy of these tables depends on the subjects possessing a normal body shape (Du Bois and Du Bois 1916) and their use during pregnancy takes no account of the change in body contour. Also, if mother's total weight is used, an error is introduced by the contribution of the fetus and liquor to this weight (Walters et al. 1966). Finally, Easterling et al. (1987) found a very poor correlation between CO and body surface area in women during the third trimester of pregnancy. They concluded that use of cardiac index was inappropriate during pregnancy. In view of these limitations cardiac indices were not calculated.

2.4 Outline of Studies to be Described

2.4.1 Studies

1. Validation of CO measurement by the Doppler method.

2. Reproducibility of cross-sectional, Doppler and M-mode echocardiographic measurements.

3. Haemodynamic changes during singleton pregnancy.

4. Haemodynamic changes during the puerperium.

5. Haemodynamic changes during twin pregnancy.

2.4.2 History of Investigations

It will be apparent that each subject in Study 3 would be under investigation for at least 18 months; those in Study 4 for at least 7 months; those in Study 5 for at least 11 months. Thus not all questions could be answered in the precise order in which they have been listed in the preceding section.

The work was commenced in August 1985. The first year was funded by Newcastle Health Authority and the second year by Birthright. Recruitment of women for Studies 3 and 4 was begun immediately. Some of the 'preconception' subjects were enrolled from a special register at the MRC Human Reproduction Group, Princess Mary Maternity Hospital, Newcastle upon Tyne. Others were members or friends of the midwifery staff at this hospital. Subjects for Studies 4 and 5 were recruited from the antenatal clinics at the Princess Mary Hospital. While recruitment and baseline investigations were continuing for Studies 3 and 4, the validatory and reproducibility studies were carried out. Studies 1 and 2 were completed by February 1986 and Study 4 was completed by May 1986, by which time all the women for Study 3 had been recruited. Recruitment for Study 5 was begun in May 1986 and was completed by August 1987. Investigations during pregnancy in Studies 3 and 5 were completed by the end of the period of funding (July 1987). Postnatal investigations were completed by January 1988.

All the echocardiographic studies were performed by the author in the Department of Cardiology, Freeman Hospital, Newcastle upon Tyne.

Five publications have resulted from this work:

(1) Robson, S.C., Dunlop, W., Moore, M., and Hunter, S. (1987) Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. Br J Obstet Gynaecol 94: 1014-1027

(2) Robson, S.C., Hunter, S., Moore, M., and Dunlop, W. (1987) Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol 94: 1028-1039.

(3) Robson, S.C., Boys, R.J., and Hunter, S. (1988) Doppler echocardiographic estimation of cardiac output; analysis of temporal variability. Eur Heart J 9: 313-318.

(4) Robson, S.C., Hunter, S., Boys, R.J., and Dunlop, W. (1989) Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol 256: H1060-H1065.

(5) Robson S.C., Hunter, S., Boys, R.J., and Dunlop, W. (1989) Hemodynamic changes during twin pregnancy. A Doppler and M-mode echocardiograph study. Am J Obstet Gynecol 161: 1273-1278.

In addition, parts of the material have been published as letters or abstracts and presented at research meetings, both national and international.

2.5 Ethical Permission

Permission for all the investigations was obtained from the Joint Ethical Committees of Newcastle Health Authority and the University of Newcastle upon Tyne. Informed consent was obtained from each subject.

CHAPTER 3

ECHOCARDIOGRAPHY: PRINCIPLES, EQUIPMENT AND EXAMINATION TECHNIQUES

3.1 Ultrasound

3.1.1 Physical Properties

A sound wave is a series of compressions and rarefactions. The combination of one compression and one rarefaction is one cycle and the distance between one cycle to the next is the wavelength (λ). The velocity (v) represents the speed with which sound waves travel through a particular medium and it is equal to the product of frequency (f) and wavelength ($v = f \times \lambda$). Thus frequency and wavelength are inversely related. Ultrasound is sound with a frequency greater than 20,000 cycles/second or Hertz (Hz) which is above the audible range. Most ultrasound instruments in clinical use employ frequencies in the range of 1-10 MHz.

Sound waves travel in tissue at a speed which depends on the physical properties of the tissue. The velocity of sound is fairly constant for human soft tissue, being approximately 1,540 m/sec (Eldridge et al. 1983). However there is a significant difference in velocity if sound passes through a solid structure such as bone. When an ultrasound beam reaches an interface between two tissues of different acoustic properties (impedances), the beam undergoes reflection and refraction. The amount of sound that is reflected depends on the degree of acoustic mismatch between the two tissues, the angle the beam strikes the interface and the relative size of the mismatched tissue and the wavelength. The total thickness presented to the ultrasound beam must be at least one quarter of the wavelength for ultrasound to be reflected. Ultrasound with a high frequency can reflect sound from smaller objects and therefore has a high resolving power. Sound with a frequency of 2 MHz permits the recording of distinct echoes from interfaces that are approximately 1 mm apart.

The amplitude (intensity) of an ultrasound wave is reduced (attenuated) as the distance of travel increases. The extent of this depends on the transmitted frequency, energy absorption by the tissues and the amount of reflection by the tissue interfaces. Very high frequency ultrasound is reflected by many small interfaces and therefore less energy is available to penetrate deeply into the body. Thus, the penetration of the beam decreases as frequency increases.

3.1.2 Transducers

Ultrasound energy is generated by a piezoelectric transducer which is in contact with the tissue being examined. When an electric current is applied to piezoelectric crystal the shape of the crystal varies with the polarity. As the crystal expands and contracts it produces

compressions and rarefactions or sound waves. The crystal also acts as a receiver and when it is struck by a sound wave it produces an electrical impulse. The duration of each ultrasonic impulse may be as short as one microsecond and the rate with which the bursts of ultrasound are emitted is the pulse repetition frequency (200 - 5,000 pulses/sec). The remainder of the time (approximately 99%) the transducer functions as an extremely sensitive receiver, being able to detect a signal even if less than 1% of the ultrasound energy is reflected.

3.1.3. Biological Effects

There are two mechanisms by which ultrasound is known to induce biological effects;
1. **Heat**; The amount of heat generated is related to the time-average intensity (power per unit area) of the applied sound field, the dwell time, the centre frequency of the source and the absorption coefficient of the medium. The intensities used in diagnostic echocardiography are too low to cause measurable temperature elevation in tissues, even disregarding thermal convection by the circulation (Ter Haar and Williams 1981). Furthermore, as the beam is constantly moving, any particular part of the heart receives little ultrasonic energy. Even the higher average intensities used with continuous wave Doppler, are too low to produce significant temperature elevations in tissues in-vivo (Miller et al. 1987).

2. **Cavitation**; In order for acoustic cavitation to exist there must be stabilized bubbles (or gas nuclei) present. Under appropriate ultrasonic conditions dissolved gas will be driven into the existing gas bodies and 'cavities' will be detected. There are two types of acoustic cavitation, both of which have the potential to cause biological effects;
Stable cavitation; this involves the oscillation of existing bubbles. The effect requires very little energy and is probably of little relevance to the issue of human safety because stabilized bubbles do not appear to exist within the intercellular fluids of the body (Miller et al. 1987).
Transient cavitation; this involves rapid growth, high frequency oscillation and the eventual implosion of bubbles. This form of cavitation requires much more energy and there is some evidence that it can cause cell lysis in-vitro (Clarke and Hill 1970). Ter Haar et al. (1982) reported the induction of stable bubbles in the hind limb of a mammal with a continuous wave device. This report is unconfirmed and so far attempts at detecting ultrasonically generated bubbles in blood in-vivo have not been successful (Gross et al. 1985).

Finally a large percentage of the total ultrasonic energy is absorbed by the chest wall and only a small percentage of the energy leaving the transducer ever enters the heart. Thus the evidence that exists to-date suggests that diagnostic ultrasound, as used in echocardiography, is safe (Feigenbaum 1986).

3.2 Cross-sectional and M-Mode Echocardiography

3.2.1 History of Echocardiography

Echocardiography is a procedure that utilizes ultrasound to visualize the heart non-invasively. The use of ultrasound as a diagnostic tool in medicine began after the end of the Second World War. Edler and Hertz (1954) were the first to use pulsed reflected ultrasound to examine the heart. Initially they could only record echoes from the back wall of the heart but they subsequently reported the detection of mitral stenosis, left atrial tumours and anterior pericardial effusions (Edler et al. 1961). Development of real time cross-sectional echocardiography began in the late 1960's. Interest greatly increased with the development of a multi-element cardiac scanner (Bom et al. 1971) and it soon became clear that this technique, with its correct spatial orientation of the echoes, provided useful supplemental information to standard M-mode echocardiography.

3.2.2 Principles of Cross-sectional and M-ModeEchocardiography

Ultrasound can be recorded in A, B or M-mode displays. 'A' refers to amplitude mode in which returning signals are displayed as representative amplitude spikes along a baseline. The distance along the baseline is equivalent to the distance the signal must travel from the target to the transducer. B-mode refers to brightness display. Instead of amplitude spikes, the reflected sound energy is converted to dots of varying brightness. If the spatial orientation of the transducer is tracked electronically, then a two-dimensional image can be created. If time is introduced as the second dimension, instead of another distance measurement as in B-mode scanning, then motion can be recorded. This type of presentation is called M-mode or motion mode and provides accurate information about axial movements and dimensions.

Cross-sectional echocardiography or real-time B-mode scanning describes the technique of creating a spatially correct image of the heart using ultrasound. The image does in fact resemble a cross-section and the term cross-sectional echocardiography is less confusing than two-dimensional echocardiography since M-mode echocardiography is also two-dimensional, one dimension being time, the other distance. Cross-sectional echocardiography allows accurate assessment of anatomical relationships and shape and unlike M-mode echocardiography, it can be used to investigate lateral vectors of motion. Thus the two techniques provide complementary information.

Cardiological imaging is generally performed using an electronic phased-array sector scanner. This system uses a multielement transducer to emit a single ultrasound beam, the direction of which can be altered by electronically controlling the time at which each

element is fired (phased array excitation). The beam can therefore be steered through a desired sector arc and can also be focused. Good quality images can therefore be obtained from the limited echocardiographic window that is available for cardiac scanning. Linear array systems are unsuitable for cardiac scanning because the larger transducer head overlies several interspaces and ribs. Some of the signals are consequently attenuated as they pass through bone, distorting the image. A second advantage of the phased array system is that simultaneous M-mode and cross-sectional echocardiograms can be obtained. This is possible because the system can time-share between the M-mode and cross-sectional sector examination. An electronically generated cursor line is directed through the desired part of the cross-sectional examination to obtain the appropriate M-mode examination.

3.2.3 Transducer Positions and Basic Planes of Imaging

Cross-sectional examination; The heart has a long axis, formed by a line between the base and the apex, and a short axis, formed by a line at right angles to the long axis, about which the left ventricle is supposed to rotate. Using this framework, three families of orthogonal planes may be defined to describe all tomographic views of the heart (Figure 3.1).

There are four transducer positions from which the heart can be imaged using cross-sectional echocardiography; suprasternal, parasternal, apical and subcostal (Roelandt 1983). Two of these were used during the present investigations;

1. Parasternal position; The transducer is placed along the left sternal border in the third or fourth intercostal space over the anterior precordium. From this position an image of the heart is obtained in the long and short axis planes (Figure 3.1). The long axis view of the left ventricle is obtained in a plane extending from the right shoulder towards the apex. The short axis view is obtained by rotating the transducer clockwise, approximately 90°, so that the plane of scanning is perpendicular to the long axis view. The interrogation plane can be swept from the base of the heart to the apex to allow examination at the level of the great arteries, the mitral valve, the papillary muscles and the apex.

2. Apical position; The transducer is placed directly upon or just medial to the palpable apical impulse. From this position a sector image of the heart is obtained in the four chamber plane. The apical four chamber plane is obtained by directing the scanning plane superiorly and medially towards the right scapula in a plane parallel to the dorsal and ventral surfaces of the heart. The plane transects and is perpendicular to the mitral and tricuspid valve orifices, and both the atrial and ventricular septa.

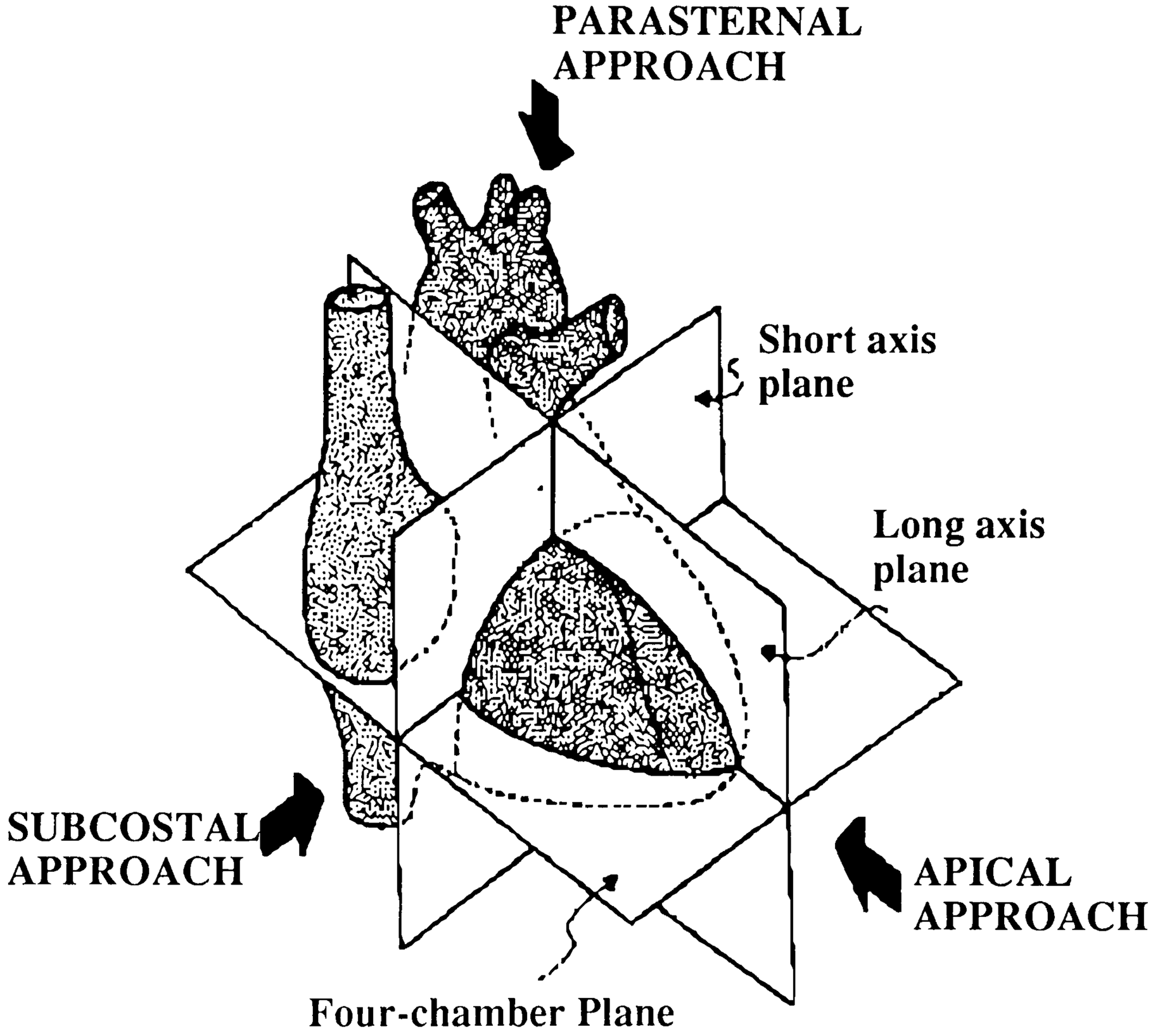


Figure 3.1 Diagram of the three orthogonal planes used to visualize the heart with cross-sectional echocardiography

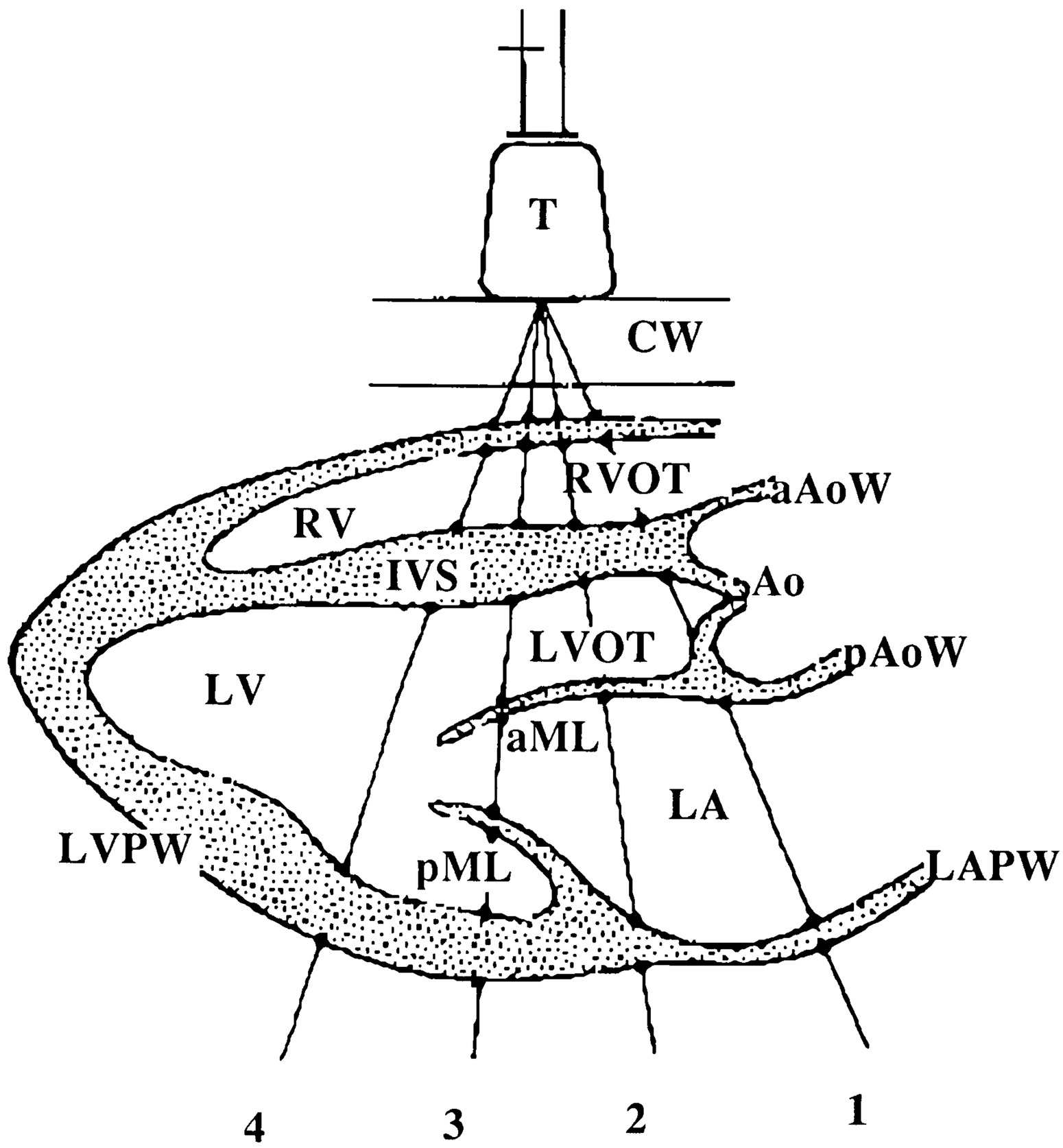
M-mode examination; Although M-mode examination of the heart can be performed with the transducer located at the same four positions as for cross-sectional imaging, useful haemodynamic information is mainly recorded from the parasternal location, scanning in the long axis plane. Scanning from aorta to apex, four anatomical areas with specific cardiac structures and motion patterns can be distinguished (Roelandt 1983) (Figure 3.2).

Of these four areas, only two have been used during the present investigations;
1. Mitral leaflet level; The ultrasound beam passes through the anterior chest wall, anterior heart wall, right ventricular cavity, interventricular septum, left ventricular cavity with the tips of anterior and posterior mitral leaflets and the left ventricular posterior wall.
2. Aortic valve level; The ultrasound beam passes through the anterior chest wall, anterior heart wall, right ventricular outflow tract, anterior aortic wall, aortic valve cusps, posterior aortic wall, left ventricular cavity and left atrial posterior wall.

3.2.4 Echocardiographic Recordings and Measurements

Each M-mode echo has a finite width; the leading edge of the echo closest to the transducer is the leading edge (LE) and the edge away from the transducer is the trailing edge (TE). Measurements can either be made from the TE of the initial echo to the LE of the more distant echo (TE-LE) or from the LE of the initial echo to the LE of the distal echo (LE-LE). The location of the TE echoes may vary from one instrument to another and with the gain setting of the echocardiograph. The location of the LE echoes is independent of these factors and therefore measurements from LE to LE are theoretically more accurate (Feigenbaum 1986). M-mode measurements can be made on-line using computer facilities. Alternatively the M-mode image can be stored on a strip chart recording and measurements made from this using either a computer or more commonly simple calipers.

There is some evidence that the LE-LE technique is also a more accurate method of obtaining measurements from cross-sectional echocardiographs (Feigenbaum 1986). Any area or lateral dimension measurement from a cross-sectional image is highly gain dependent and because axial resolution is better than lateral resolution, thesemeasurements are less accurate. When measuring lateral dimensions, it is unclear whether it is more accurate to measure between the inner, central or outer echoes. Although many instruments have on-line freeze-frame facilities, it is easier to make cross-sectional measurements off-line using tape recorders that can go backward and forward in real-time or frame-by-frame. The ability to analyse a videotape, either on the instrument or on an off-line analyser, provides a greater possibility of finding satisfactory cardiac cycles for measurement. Measuring is also facilitated by electronic devices such as a joystick and callipers or a tracker ball.



Abbreviations; T, transducer; CW, chest wall; aHW; RV, right ventricle; RVOT, right ventricular outflow tract; IVS, interventricular septum; aAoW and pAoW, anterior and posterior aortic walls; Ao, aorta; LV, left ventricle; LVOT, left ventricular outflow tract; aML and pML, anterior and posterior mitral leaflets; LV PW, left ventricular posterior wall; LA, left atrium; LAPW, left atrial posterior wall.

Figure 3.2 Schematic cross-section of the heart showing anatomical areas visualized during M-Mode echocadiography

3.3 Doppler Echocardiography

3.3.1. History of Doppler Echocardiography

Johann Christian Doppler is generally credited with the first description of what has become known as the 'Doppler effect'. His article, published in 1842, established the relationship between of frequency shift to velocity. Doppler applied the principle to light, but not directly to sound. Development of the principle for medical investigation began following the Second World War and Satomura (1956) first reported cardiac evaluation using the Doppler principle.

Edler and Lindstorm (1969) and Kalmanson et al. (1971) studied the use of the technique for non-invasive cardiac investigation but introduction of Doppler as a major diagnostic modality had to await the development of the first commercial pulsed Doppler instrument in 1975-76 (Goldberg et al. 1988). Frequency shift was analysed by time interval histography and although information could be gained regarding direction and, to some extent, flow disturbance, most signals could not be recorded accurately. Between 1976-78 numerous studies were published reporting the use of Doppler to qualitatively assess cardiac defects and to measure pressure drop (Holen et al. 1976, Hatle et al. 1978, Goldberg et al. 1978). In 1978 a method of combining cross-sectional echocardiography with fast Fourier analysis of the pulsed Doppler signal was developed (Goldberg et al. 1988). This combination provided linear signal analysis and a convenient method for pulsed Doppler sample volume placement by cross-sectional echocardiographic guidance.

The development of Doppler for non-invasive estimation of CO began with Light (1969) who used continuous wave Doppler to interrogate the aorta. He calculated a VI and found this was proportional to blood flow. Subsequently Magnin et al. (1981) compared measurements of CO, using pulsed Doppler, analysed by a non-linear zero crossing detector, with those obtained using the direct Fick method. Although they reported a reasonable correlation, the Doppler method consistently underestimated flow. Subsequently Goldberg et al. (1982) found a closer agreement with dye CO when fast Fourier transform was used to analyse the pulsed Doppler signals. Since these early reports of Doppler aortic flow, numerous studies have validated the flow distal to the other intracardiac valves.

3.3.2 The Doppler Principle

The measurement of blood flow velocity using Doppler ultrasound depends on the Doppler effect. This describes the apparent shift in the transmitted frequency of ultrasound whenever there is relative motion between the sound source and the reflector. If the target reflecting ultrasound is moving towards the source then the received frequency is increased

whereas if it is moving away, the received frequency is decreased. The difference between the transmitted and received frequencies is termed the Doppler shift (f_d) and is related to the velocity (v) of the reflector by the following equation;

$$f_d = \frac{2 f v \cos\theta}{c}$$

where f = frequency of the transmitted ultrasound,

c = velocity of sound in the medium being examined and

θ = angle between the ultrasound beam and the moving target.

As f and c are constants in any given situation, the Doppler shift is directly proportional to the velocity of the reflector and the cosine of the intercept angle.

When Doppler ultrasound is used to detect blood flow, the target reflecting sound is the red blood cells. These act as moving interfaces which scatter ultrasound. By convention ultrasound beam direction refers to the reflected beam. Accordingly, if the reflected beam and blood flow travel in the same direction, the intercept angle is 0°, the cosine is 1, and the maximum Doppler-shifted frequencies, reflecting the true velocity, will be detected. In these circumstances the waveform will be displayed above the baseline. If the reflected beam and the direction of blood flow are in opposite directions, the intercept angle will be 180° and the cosine is -1, but again the maximum Doppler -shifted frequencies will be detected. In this case the waveform will be displayed below the baseline. However, if θ is other than 0° or 180°, the cosine deviates from 1 and the detected Doppler frequency shift is reduced according to the cosine. The magnitude of the measured velocity is therefore less than the true velocity. At $\theta = 90°$ there is no detectable Doppler shift. The intercept angle is therefore of crucial importance when Doppler ultrasound is used to quantitate velocity. Fortunately, the relationship between cosine and angle is not linear. As long as the angle is within 20° of either 0° or 180°, the cosine is close to 1 and the magnitude of the velocity will be reduced only be $\leq 6\%$ (Goldberg et al. 1988). Once θ becomes greater than 20°, the cosine becomes significantly less than 1 and the magnitude of recorded velocity drops rapidly.

3.3.3 Doppler Modes

Continuous wave Doppler; Continuous wave Doppler uses two crystals, one continuously sending and the other continuously receiving ultrasound. Since the Doppler beam is constant, all the moving targets within the beam produce Doppler signals. Accordingly, information is received from all along the length of the beam and it is not possible to determine the depth at which the frequency shift occurs (range ambiguity). Continuous wave Doppler however permits analysis of high velocities (Hatle and

Angelsen 1985) .

Pulsed Doppler; In this system the crystal emits a short pulse of ultrasound and then 'listens' for reflected signals. In this way the same crystal acts as both a transmitter and receiver. The transmitting time (approximately 1μsec) occupies only a very small fraction of the cycle (approximately 1 msec). Interrogation of one small area along the beam (range gating) is possible because the speed of ultrasound through tissue is approximately 1540 m/sec and it is therefore possible to determine when information from a chosen depth returns to the crystal. Analysis of the reflected signal for frequency change at a given depth is accomplished by analysing only for that time interval and disregarding reflections from other depths (Hatle and Angelsen 1985). The area in which range gating is accomplished is conventionally known as the sample volume. The dimensions of the sample volume are determined by the beam area and the duration of time the receiver gate is open. Alteration of this interval by the operator allows the length of the sample volume to be altered.

The advantage of PD is that it can be combined with a cross-sectional image. This allows the operator to set the sample volume at various depths along the cursor line within the heart and to move it freely from one side of the sector to the other thus obtaining Doppler signals from a specific site. Pulsed Doppler however has velocity measurement limitations. The pulsed system has a pulse repetition frequency (PRF) and this determines the maximum frequency shift that can be detected. The upper limit of this is known as the Nyquist limit or number. This is defined as one half of the PRF. If the Doppler frequency shift exceeds this limit aliasing, or frequency ambiguity, occurs regardless of the method of signal processing that occurs (Goldberg et al. 1988). The high frequency part of the waveform is cut off and reinserted into the display but in the opposite direction channel. This phenomenon is called 'wrap around'. The PRF also limits the maximum depth of sampling, since all the echoes from the region of interest must have time to return to the transducer before the next transmission phase. The maximum range or depth of sampling (R_{max}) for a given PRF is calculated as follows;

$$R_{max}\ (cm) = \frac{c}{20\ PRF}$$

where c = velocity of sound in tissue. Therefore the PRF of the instrument places limits on the measurable velocity and the maximum depth of penetration. Higher PRF's permit greater measurable velocities but at the expense of penetration.

3.3.4 Frequency Analysis

The Doppler frequency shift that occurs in the heart and blood vessels is relatively small and within the audible range. For some clinical applications, the presence of the audible signal may be adequate. For Doppler echocardiography however, precise quantitation of the frequency shift is required. This means that at each instant in time the received frequencies must be compared with the transmitted frequency. The situation is further complicated by the fact that the red cells within the sample volume may be moving at different velocities. The instrument which processes and quantitates these different Doppler shift frequencies is the frequency (spectrum) analyser.

A frequency analyser is capable of determining the relative powers of the various frequency components that are present in the signal at a given time. Prior to 1978, most echocardiographic spatial analyses were performed by a zero-crossing frequency detector and the output was displayed as a time interval histogram. This method however did not allow simultaneous analysis of more than one sine wave. The development of linear frequency analysis devices provided a means of separating and quantifying all the Doppler frequencies within the sample volume and presenting them in real-time on a visual display (Goldberg et al. 1988). The most commonly used linear method for performing frequency analysis is fast Fourier transform (FFT). This method involves sampling of the Doppler signal over a short time (eg 5 msec). The Doppler signal is digitized and the FFT analysis carried out on the digitized signal segment. The frequency spectrum is then displayed virtually in real-time and this process is continually repeated during the Doppler examination. The power at any given frequency relates the quantity of blood flowing at the corresponding velocity. The spectrum is usually displayed as a sonogram, in which a single spectrum is depicted as a vertical line on whose axis lies frequency, with brightness modulated at each point to represent power. Subsequent spectra are displayed as vertical lines at a fixed distance apart, creating an image that scrolls from left to right with time. The three variables of time, frequency and power are thus shown in real time as the signal is heard.

3.4 Doppler Echocardiographic Measurement of CO

3.4.1 Mathematical Considerations

The flow of fluid (Q) through a tube of constant diameter is equal to the product of the CSA and the linear flow velocity when the CSA is fixed and the velocity is constant. Flow through a blood vessel or across a valve orifice is rather more complex because velocity is changing and flow is pulsatile. In these circumstances flow may be calculated as;

$$Q_{(t)} = V_{(t)} \times CSA_{(t)}$$

where V = spatial mean velocity and (t) denotes that the variables are functions of time.

Measurement of blood velocity by Doppler varies inversely with the cosine of the angle between the ultrasound beam and flow (θ). If cosine θ is close to 1 (θ = 0-20°) and if one assumes a constant CSA of flow during the cardiac cycle, SV can be calculated as;

$$SV = CSA \times \int v_{(t)}\, dt$$

where $\int v_{(t)}\, dt$ = time velocity integral (the integral of the instantaneous velocities over the period within the cardiac cycle during which flow occurs). This VI is equal to the distance that a column of blood moves during the ejection period. Cardiac output may then be calculated as;

$$CO\ (ml/min) = SV\ (ml) \times HR\ (beats/min)$$ where

$$SV\ (ml) = CSA\ (cm^2) \times VI\ (cm)$$

3.4.2 General Principles

For a constant flow, velocity is inversely proportional to CSA. Small alterations in vessel or orifice diameter produce significant changes in velocity, since CSA is related to the square of the vessel or orifice radius. Consequently, measurements of flow are theoretically more accurate when flow velocity is measured at the same site as CSA is measured. This can only be done by combining PD with imaging by cross-sectional echocardiography. In practice, the Doppler sample volume is positioned within the annulus of the valve or in one of the great vessels utilizing an appropriate window that places the ultrasound beam in an orientation nearly parallel with blood flow. Blood velocities are recorded and the respective CSA derived from cross-sectional echocardiography. Determination of flow using CW Doppler is theoretically less accurate because;

1. Information is received from the entire length of the ultrasound beam and consequently it is not possible to determine the depth at which the frequency shift occurred and
2. CW transducers are not usually combined with imaging transducers. Thus the sampling

site cannot be seen and the beam-flow angle cannot be estimated.

Using the CW Doppler technique, the spatial mean velocity could be obtained from the mean Doppler shift if the ultrasound beam insonates all the vessel area. However, since the ultrasound beam is narrow and insonates only a part of the CSA of flow, it is important to define the flow profile through a given vessel or orifice. For a perfectly flat profile, the spatial mean velocity, the modal velocity (ie the velocity of the majority of the blood cells), and the maximal velocity are similar. However, as the profile becomes more parabolic, the modal and maximal velocities may vary from the mean spatial velocity. Since the ultrasound beam insonates only a part of the flow area, the mean spatial velocity is frequently not equal to the mean spatial velocity.

Measurement of systolic or diastolic VI can be done on-line using a computer within the Doppler instrument, or off-line by planimetry of the area under the velocity recording using a computer and digitizer. Some workers use the modal velocity, represented by the darkest contour on the spectral velocity display, others have favoured velocities closer to the maximal velocity (ie around the external contour of the spectral display (Goldberg et al. 1988).

Absolute measurement of CSA requires imaging the vessel or valve annulus in a transverse plane. While this is possible for some sites (eg mitral valve, aorta), it is not feasible for all. Thus CSA is often derived from a diameter measurement utilizing a geometric model. Diameter is generally measured from a stop-frame during the portion of the cardiac cycle corresponding to flow.

CHAPTER 4

ECHOCARDIOGRAPHIC METHODS

4.1. Plan of Investigation

All investigations, with the exception of those performed as part of the validation study, were performed in a warm, quiet room in the Echocardiographic Department, Freeman Hospital, Newcastle Upon Tyne. Subjects were asked to refrain from smoking and eating for 4 hours prior to attendance. On arrival the subjects were positioned on a couch in the left semi-lateral position (approximately 45° from supine). Electrocardiographic leads were applied to the subject's chest and connected to the echocardiographic system.

Measurements of heart rate (by palpation of the radial pulse over 60 seconds) were recorded every 5 minutes. Echocardiographic investigations were started when the subjects were considered haemodynamically stable (3 consecutive measurements of heart rate within 5%). Only rarely did this require more than 15 minutes rest.

All investigations were performed by the author with the subjects in the left semi-lateral position. The order of obtaining cross-sectional, M-mode and Doppler echocardiographic recordings was varied at each successive investigation. Investigations took approximately 30 minutes to complete.

4.2. Echocardiographic Equipment

All echocardiographic investigations were performed using a Hewlett-Packard 77020A echocardiographic system. This is a cross-sectional phased array Doppler echocardiographic system which can present information in real-time, M-mode, pulsed Doppler and continuous wave Doppler modes. The system is linked to a strip chart recorder and a video recorder and a simultaneous electrocardiograph is available with all operating modes. This system was chosen because it provided the highest quality cardiological imaging and Doppler facilities.

Cross-sectional, M-mode and pulsed Doppler examinations were performed using either a 3.5 MHz or a 5 MHz phased array transducer. The 5 MHZ transducer was used whenever possible because this gave better image quality. However in some cases, especially when scanning from the cardiac apex towards the end of pregnancy, this did not give adequate depth of penetration and it was necessary to use the 3.5 MHz transducer. Continuous wave Doppler examinations were performed with a dedicated independent 2.5 MHz continuous wave transducer. The Hewlett-Packard system performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity of flow according to the Doppler equation (Section 3.3.2).

4.3 M-Mode Echocardiographic Methods

4.3.1 Left Ventricular Dimensions

Standard LV M-mode echocardiographs were obtained from the parasternal long axis view (Figure 4.1). The M-mode cursor was positioned perpendicular to the left ventricular cavity, at the level of the tips of the mitral leaflets (Section 3.2.3). Echocardiographs were recorded on a strip chart with an electrocardiogram at a paper speed of 100 mm/sec. Each recording contained a minimum of ten consecutive cardiac cycles. The recordings were assessed for quality and the four consecutive cycles with the best visualization of the right and left septal surfaces as well as the endocardial and epicardial surfaces of the posterior wall were chosen for analysis.

The following measurements were made (Figure 4.1);

Left ventricular internal dimensions; Measurements were made following the recommendations of the ISFC/WHO Task Force (O'Rourke et al. 1985);

a. Left ventricular end-diastolic dimension was measured as the distance from the leading edge of the left septal echo to the leading edge of the posterior LV endocardium at the time of the onset of the Q wave of the electrocardiograph.

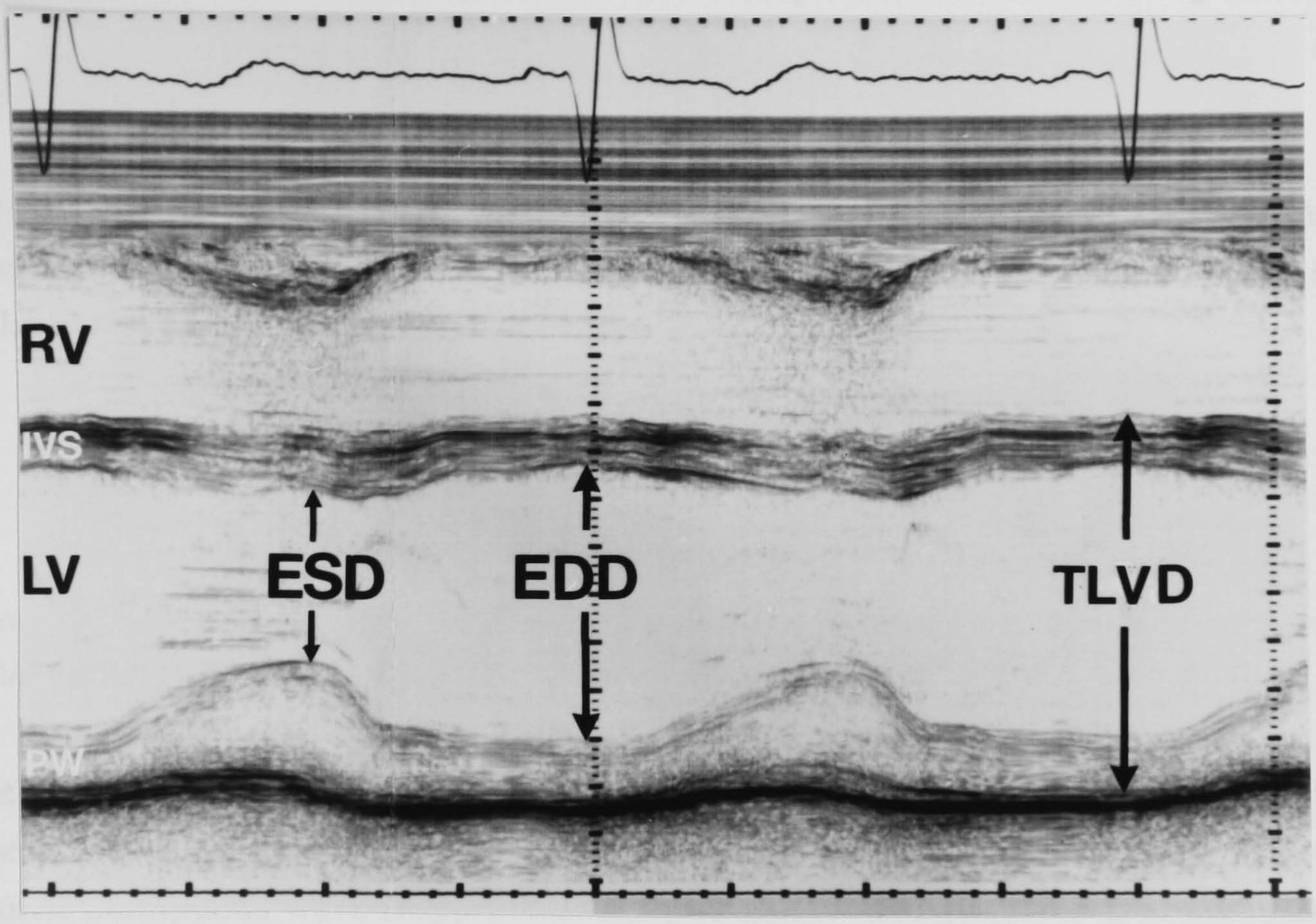
b. Left ventricular end-systolic dimension was measured from the leading edge of the left side of the septum to the leading edge of the posterior LV endocardium. End-systole was defined as the smallest LV dimension which generally coincided with the peak downward motion of the interventricular septum.

Total left ventricular dimension (TLVD) was measured from the leading edge of the endocardial echoes of the right side of the septum to the leading edge of the epicardial echoes of the posterior LV wall. Measurements were made at end-diastole at the time of onset of the Q wave of the electrocardiograph.

4.3.2 Left Atrial Dimension

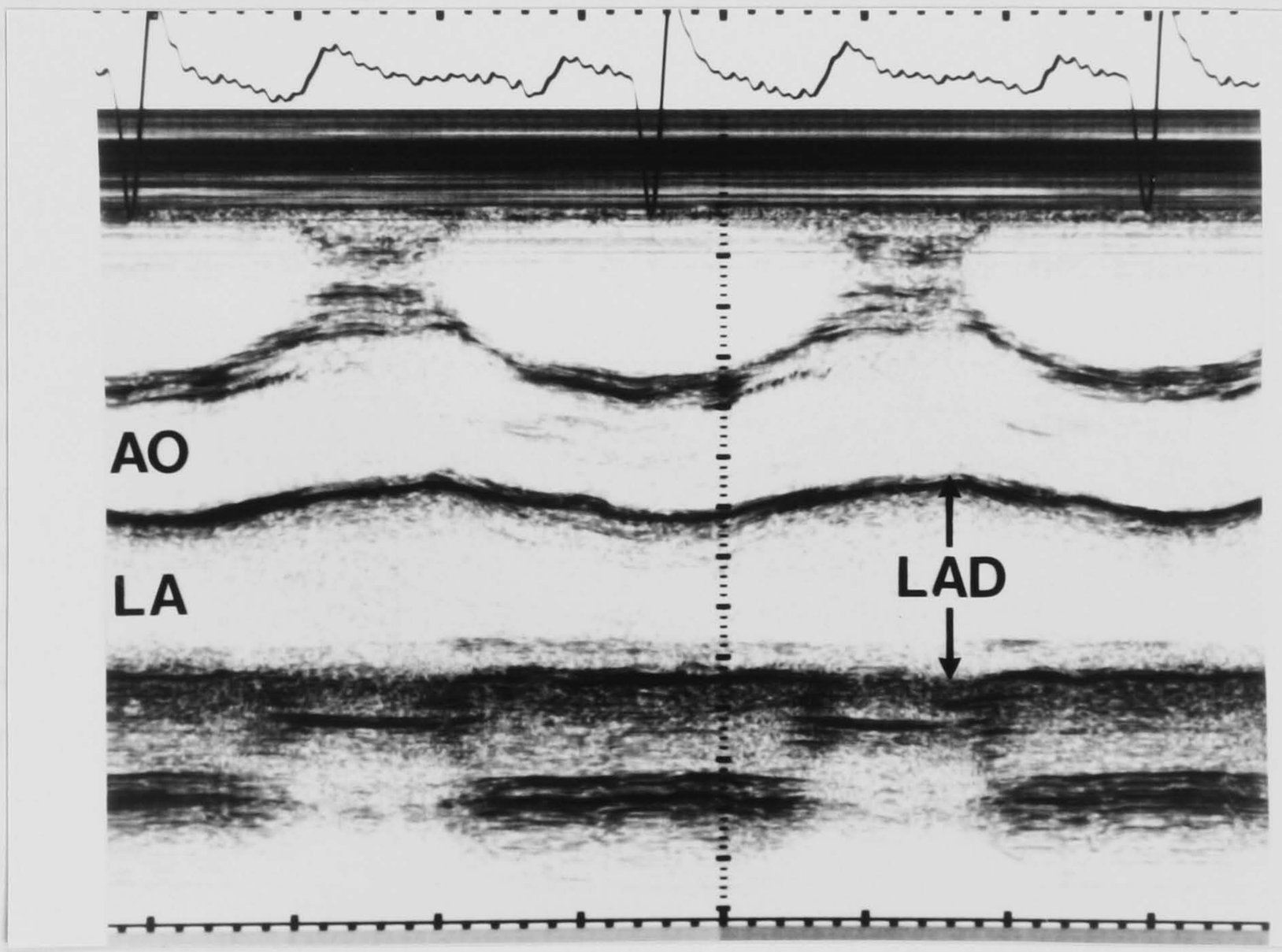
Standard aortic/left atrial M-mode echocardiographs were obtained from the parasternal long axis view (Figure 4.2). The M-mode cursor was positioned at the level of the aortic cusps such that both cusps were visualized on the M-mode echocardiograph (Section 3.2.3). Recordings were made of a minimum of ten consecutive cycles on a strip chart at a paper speed of 100 mm/sec. The recordings were again assessed for quality and the four consecutive cycles with the best visualization of the posterior aortic and left atrial walls were chosen for analysis.

Left atrial dimension was measured from the anterior edge of the posterior aortic wall to



Abbreviations: RV, right ventricle; IVS, interventricular septum; LV, left ventricle; PW, left ventricular posterior wall; ESD, end-systolic dimension; EDD, end-diastolic dimension; TLVD, total left ventricular dimension

Figure 4.1 Left ventricular M-mode echocardiograph



Abbreviations: AO, aorta; LA, left atrium; LAD, left atrial dimension

Figure 4.2 Aortic/left atrial M-mode echocardiograph

the leading edge of the left atrial posterior wall at the point of the maximum upward motion of the aortic wall (Figure 4.2) according to the the recommendations of the ISFC/WHO Task Force (O'Rourke et al. 1985).

M-mode measurements were made using callipers. The actual chamber dimensions were determined from the centimetre scale on the vertical axis of the recording by a simple calculation. Four consecutive cycles were averaged for each determination.

4.3.3 M-Mode Indices of Left Ventricular Function

Several indices of left ventricular function (ejection phase indices) were determined from the LV M-mode recording:

Mean Rate of Circumferential Fibre Shortening (Mean Vcf) was calculated using the mean LV internal dimensions and left ventricular ejection time (LVET) determined from the aortic continuous wave Doppler recording (Section 4.5.1), according to the formula of Fortuin et al. (1972);

$$\textbf{Mean Vcf}\ (\text{circumferences/sec}) = \frac{\text{EDD (cm)} - \text{ESD (cm)}}{\text{EDD (cm)} \times \text{LVET (sec)}}$$

Fractional Shortening (FS) was calculated using the mean LV internal dimensions according to the formula of Fortuin et al. (1972);

$$\textbf{FS}\ (\%) = \frac{\text{EDD (cm)} - \text{ESD (cm)}}{\text{EDD (cm)}} \times 100$$

Peak Systolic and Diastolic Rates of Change of Left Ventricular Internal Dimension were determined using a digitizing tablet linked to a microcomputer (Apple II). The principles of this procedure have been described by Gibson and Brown (1973) and the digitizing programme used was one developed in Newcastle (Griffiths et al. 1982). The outline of the LV cavity was digitised throughout one cardiac cycle. The computer then displayed the rate of change of dimension (dD/dt) during the cardiac cycle (Figure 4.3) together with the peak rate of change of dimension during systole and diastole. Four consecutive cycles were averaged for each determination.

Peak Systolic and Diastolic Rates of Change of Posterior Wall Thickness were determined using the same methodology by digitizing the outline of the left ventricular posterior wall throughout one cardiac cycle (Griffiths et al. 1982). Four consecutive cycles were used for each determination.

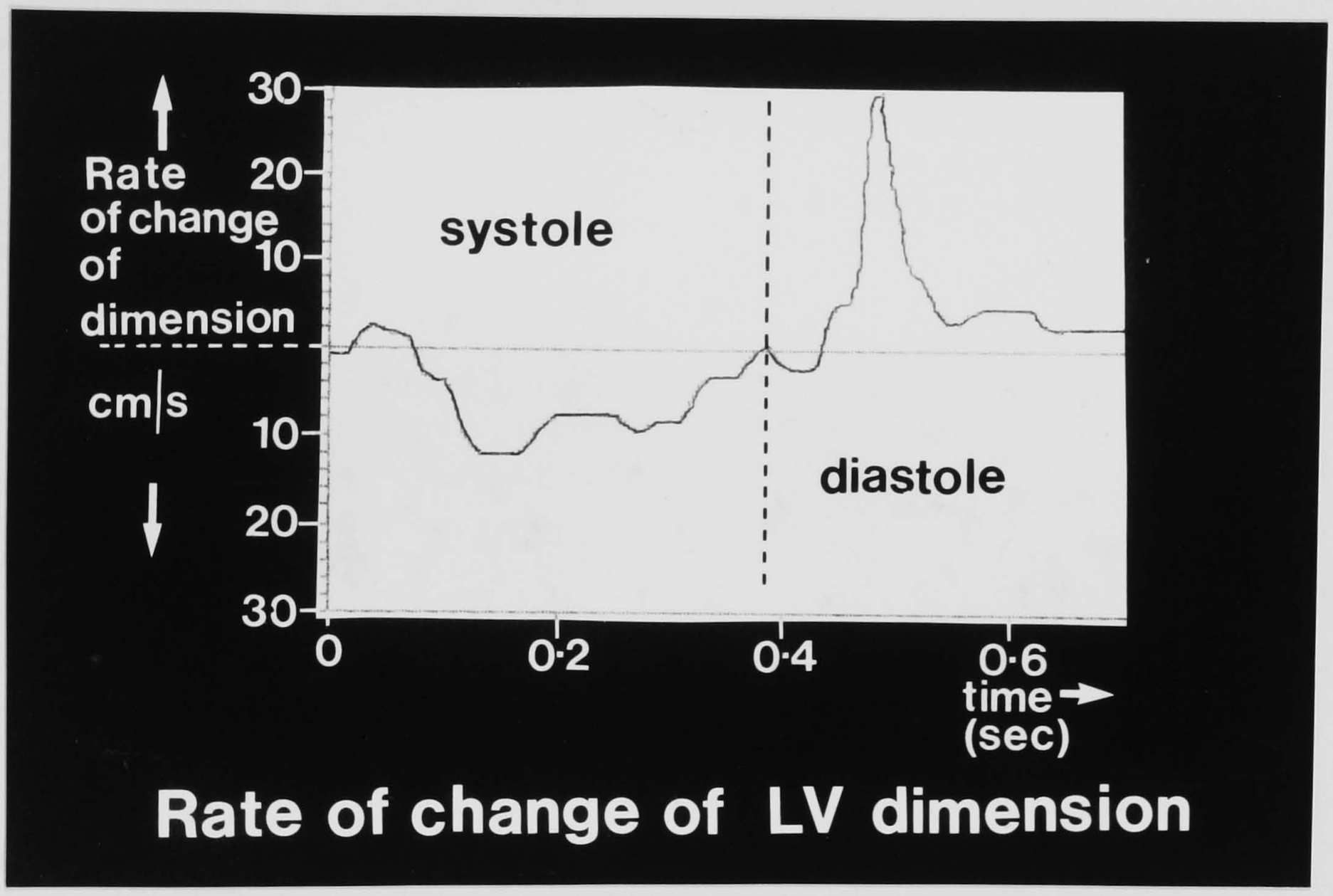


Figure 4.3 Computer plot of systolic and diastolic rates of change of left ventricular internal dimension.

4.3.4 Left Ventricular Wall Thickness and Mass

Total Left Ventricular Wall Thickness (TWT) was calculated as follows;

$$\textbf{TWT}\ (\text{cm}) = \text{LVTD}\ (\text{cm}) - \text{EDD}\ (\text{cm}).$$

Left Ventricular Mass (LV Mass) was calculated according to the formula of Devereux and Reichek (1977);

$$\textbf{LV Mass}\ (\text{g}) = 1.04\ (\text{TWT}^3 - \text{EDD}^3) - 13.6$$

where TWT and EDD are in centimetres.

4.4 Cross-sectional Echocardiographic Methods

4.4.1 Aortic and Pulmonary Artery Diameter.

Measurements were made from cross-sectional echocardiographs recorded on videotape, using a freeze-fame facility and calliper markers.

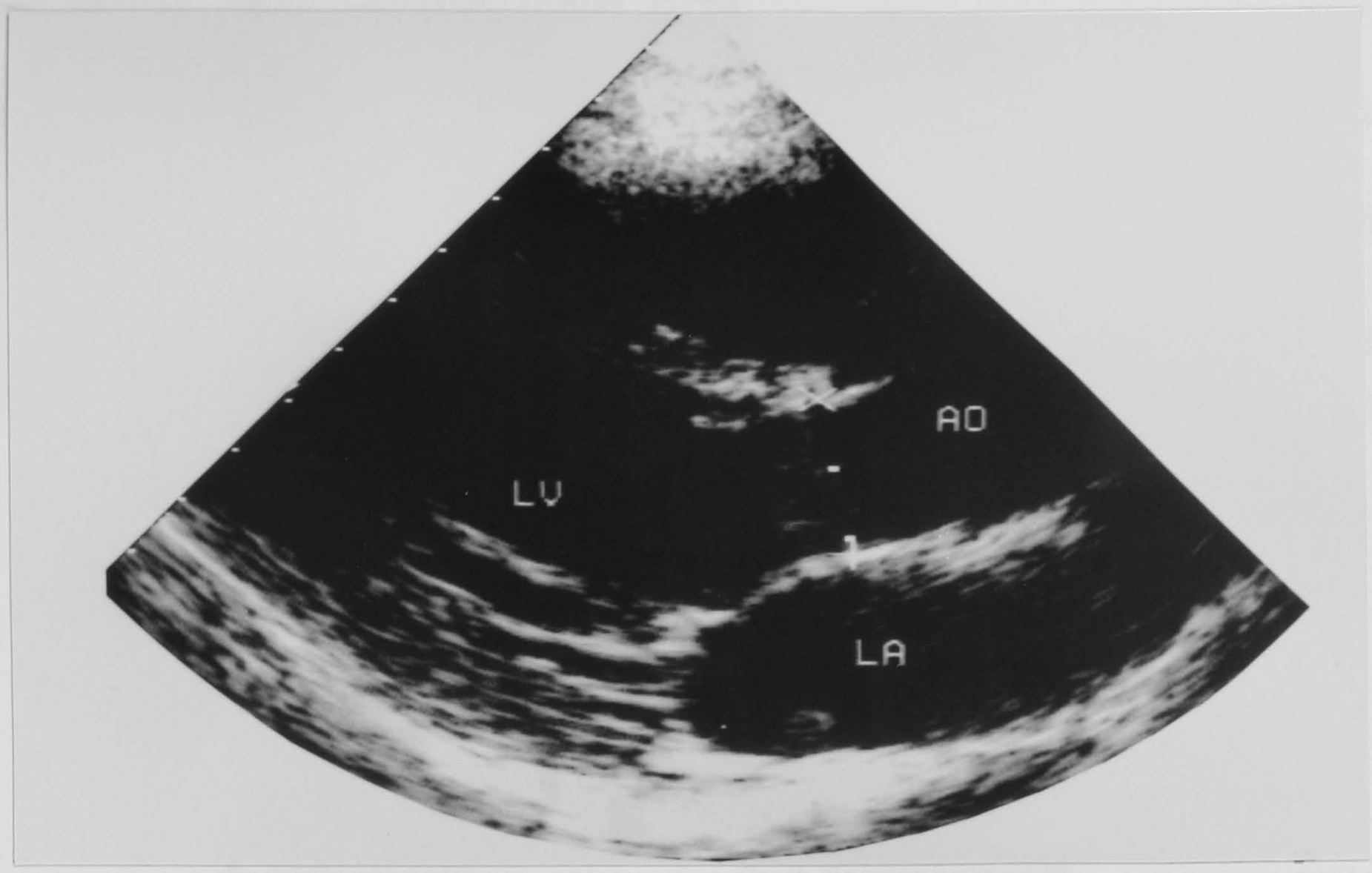
Aortic diameter was measured during systole from the parasternal long axis view at the level of the aortic annulus (Ihlen et al. 1984). Measurements were made from the leading edge of the anterior wall to the leading edge of the posterior wall (Figure 4.4).

Pulmonary artery diameter was measured during systole from the parasternal short axis view at the level of the great arteries (Goldberg et al. 1982). Measurements were made from the centre of the medial wall echoes to the centre of the lateral wall echoes (Figure 4.5A). It was often necessary to rotate the subject to the left in order to image the lateral pulmonary artery wall separate from lung echoes. Diameter measurements were made at the level of the pulmonary annulus.

The diameters from five consecutive beats were averaged and the CSA was calculated as follows;

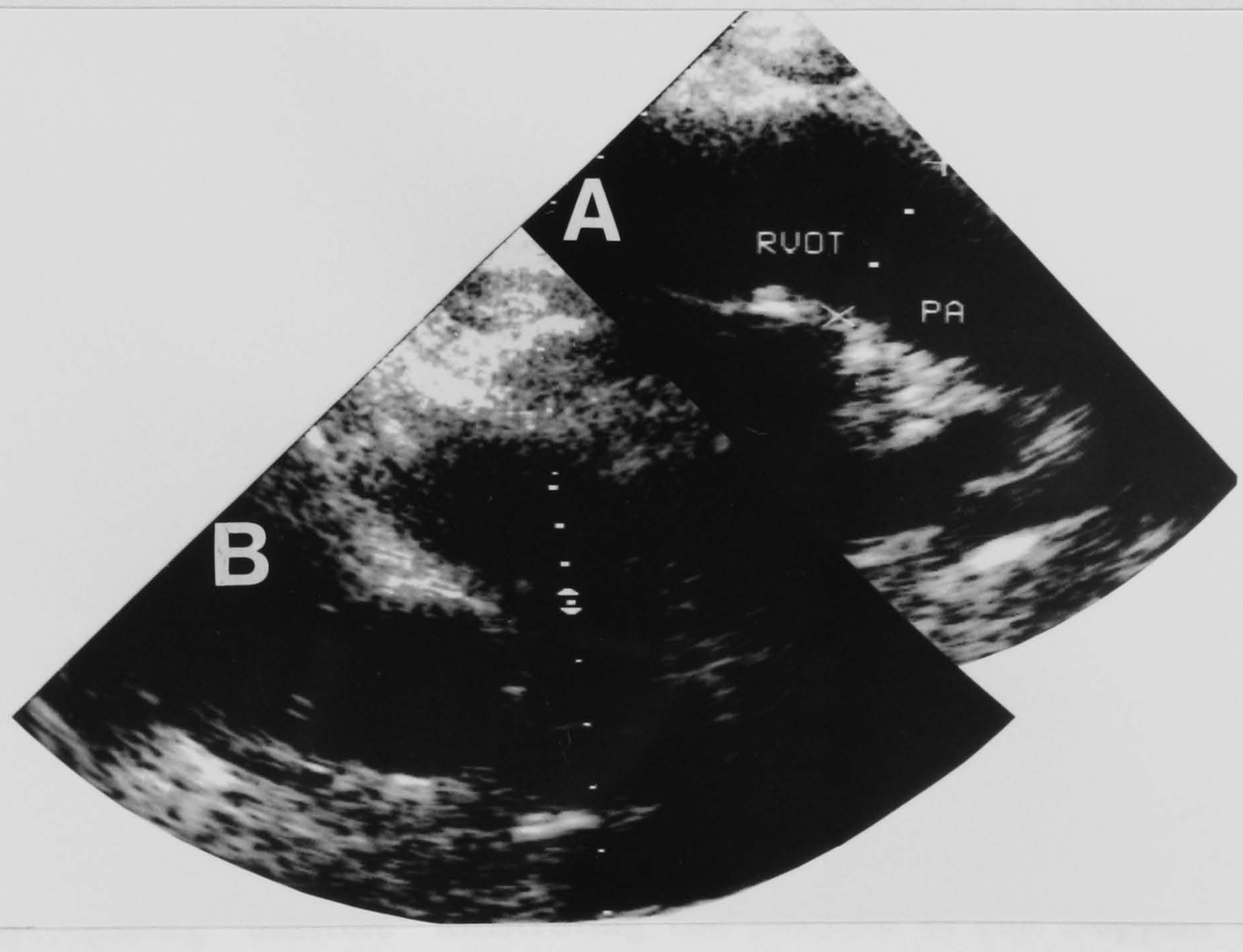
$$\mathbf{CSA}\ (cm^2) = \Pi \times (D/2)^2$$

where D = mean diameter of the aorta or pulmonary artery.



Abbreviations: LV, left ventricle; AO, aorta; LA, left atrium

Figure 4.4 Parasternal long axis view during systole illustrating the site of measurement of aortic annular diameter

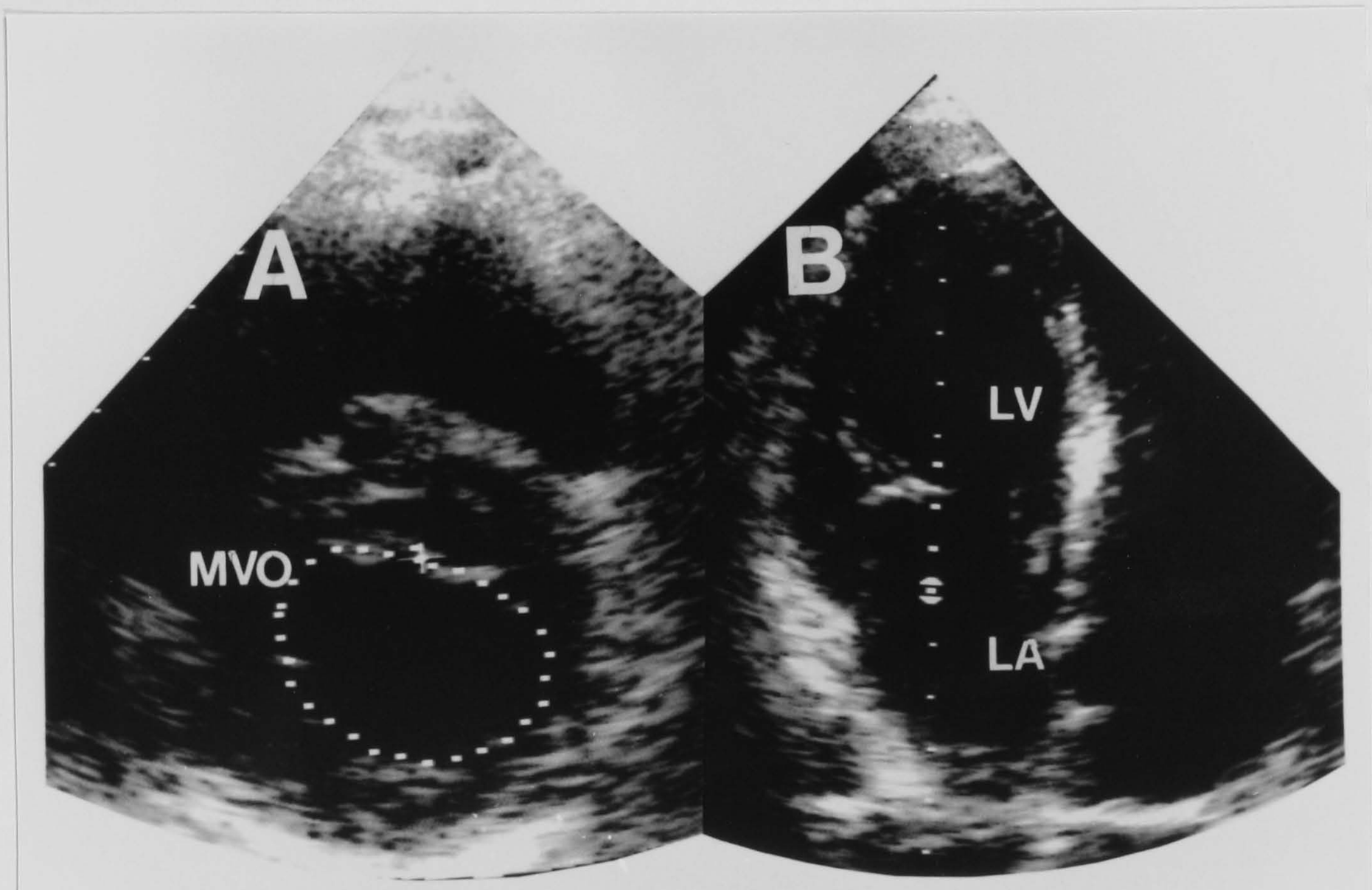


Abbreviations: RVOT, right ventricular outflow tract; PA, pulmonary artery

Figure 4.5 Parasternal short axis view during systole at the level of the great arteries illustrating A) the site of measurement of pulmonary annular diameter and B) the Doppler cursor and the sample volume placed just distal to the pulmonary annulus.

4.4.2 Mitral Valve Cross-sectional Area

Mitral valve CSA was measured directly from cross-sectional echocardiographs using a freeze frame facility and a tracker ball technique. The maximum diastolic area was measured from the parasternal short axis view at the level of the mitral annulus (Goldberg et al. 1985). In this view the annulus was generally ellipsoid in shape and the area was measured using the leading edges of the anterior and posterior annular edges and the centres of the lateral edges (Figure 4.6). Areas from five consecutive beats were averaged.



Abbreviations: MVO, mitral valve orifice; LV, left ventricle; LA, left atrium

Figure 4.6 A) Parasternal short axis view during diastole at the level of the mitral valve orifice illustrating the site of mitral valve annular cross-sectional area measurement B) Apical four chamber view during diastole illustrating the position of the Doppler cursor and the sample volume placed just distal to the mitral annulus.

4.5 Doppler Echocardiographic Methods

4.5.1 Aortic Velocities

Ascending aortic velocities were recorded from the suprasternal notch. During preliminary investigations velocities were recorded using pulsed Doppler. However because of the size of the transducer, great difficulty was encountered aligning the ultrasound beam with the ascending aorta. Consequently satisfactory velocity traces were obtainable in only 30-40% of subjects. The smaller off-axis CW Doppler transducer allowed easier interrogation of the ascending aorta from the suprasternal notch and good quality velocity traces were recorded from virtually all subjects. Therefore all aortic velocities were recorded using CW Doppler.

The ultrasound beam was directed behind the sternum and adjusted until the highest velocities with the 'cleanest' velocity envelope (least spectral dispersion) were obtained (Figure 4.6C). Whenever possible, echoes from closure of the aortic valve were obtained. Fifteen to 20 cycles were then recorded, together with a simultaneous electrocardiograph, on a strip chart at a paper speed of 100 mm/sec. It was assumed that these velocities represented the velocities at the aortic orifice and that the beam was parallel with flow. Aortic ejection time was measured from the chart recording, using callipers. The distance between the start and finish of forward flow velocities was measured and then converted to milliseconds.

4.5.2 Pulmonary and Mitral Velocities

Pulmonary velocities (Figure 4.7A) were recorded from the parasternal short axis view, using pulsed Doppler ultrasound. The Doppler cursor was aligned parallel with the pulmonary artery walls and the sample volume was placed just distal to the valve annulus (Figure 4.5B). Whenever possible echoes from closure of the pulmonary valve were obtained. Fifteen to 20 cycles were then recorded, with a simultaneous electrocardiograph, on a strip chart at a paper speed of 100 mm/sec.

Mitral velocities (Figure 4.7B) were recorded from the apical four chamber view using pulsed Doppler ultrasound. The Doppler cursor was aligned parallel with the interventricular septum and the sample volume was placed just distal to the valve annulus (Figure 4.6B) (Goldberg et al. 1985). Fifteen to 20 cycles were then recorded, together with a simultaneous electrocardiograph, on a strip chart at a paper speed of 100 mm/sec.

For flow calculation the angle between the ultrasound beam and the direction of flow (θ) should be zero or should be accurately determined. In practice this angle cannot be

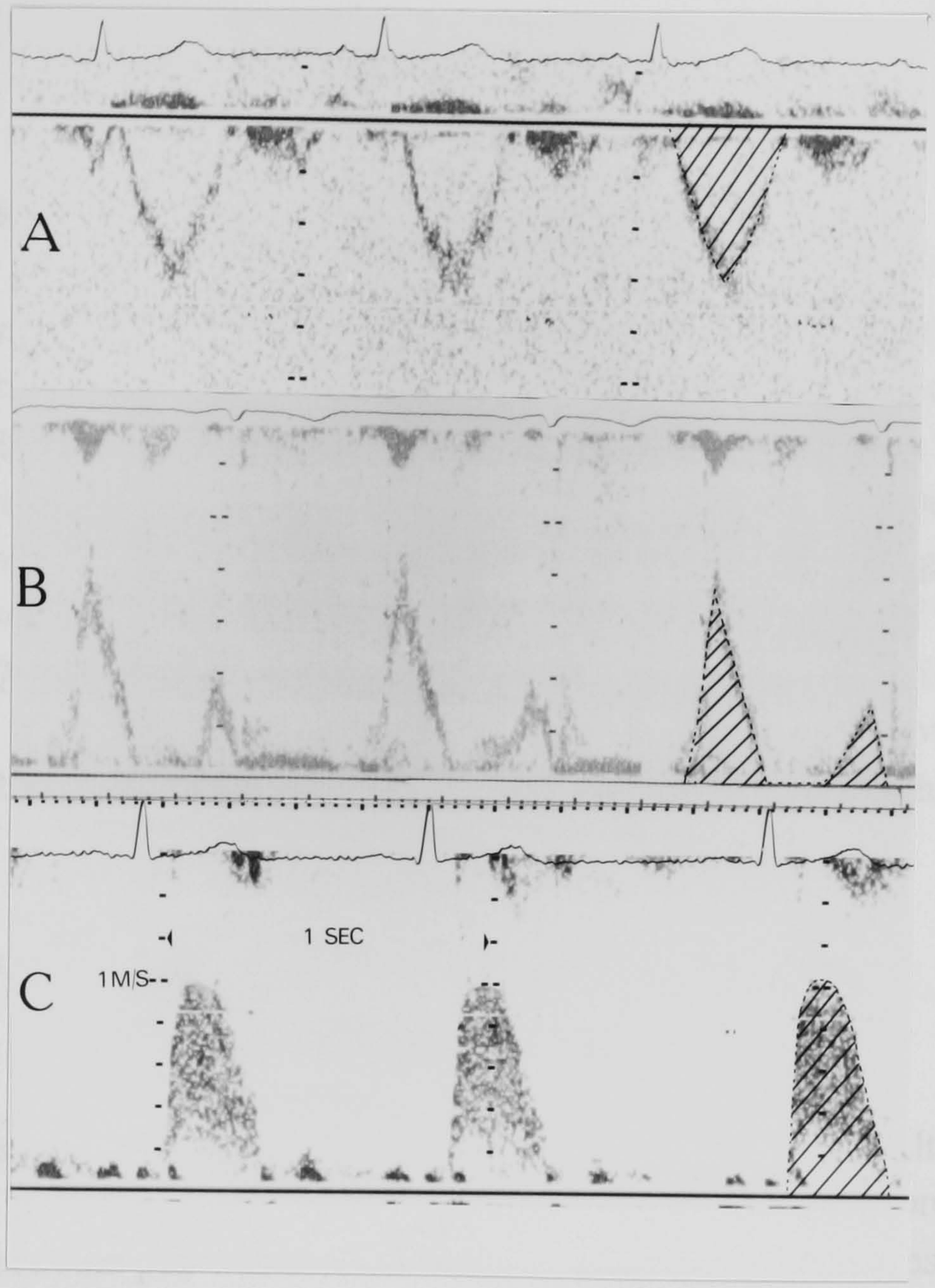


Figure 4.6. Doppler flow velocities recorded from A) pulmonary artery and B) mitral valve using pulsed Doppler and C) ascending aorta using continuous wave Doppler. The cross-hatched area indicates the velocity integral.

accurately measured from a two-dimensional image. During the present investigations, every attempt was made to align the ultrasound beam parallel to flow in two planes and then tilt the transducer slightly in the third (elevational) plane until the highest velocities were obtained. At this point spatial alignment in all three planes was assumed i.e. $\theta = 0°$ and cosine $\theta = 1$).

4.5.3 Calculation of Cardiac Output

From the 15 to 20 cardiac cycles recorded on the velocity trace, the 10 beats with the least spectral dispersion were selected for analysis. The area under the velocity curve (VI) was determined using a digitizing tablet linked to a microcomputer (Apple II) (Goldberg et al. 1985). The computer programme was written by the Medical Physics Department, Freeman Hospital. Using an electronic pen, the VI was determined by tracing from the baseline around the maximum velocity curve i.e. around the external contour of the spectral display (Zoghbi and Quinones 1986). Only velocities recorded during the period of flow (systole for the aortic and pulmonary flows and diastole for the mitral flow) were digitized. Determining the end point of flow was facilitated by valve closure echoes on the velocity trace.

Stroke volume across each valve was then calculated as follows:

$$\mathbf{SV}\ (\text{ml}) = \text{VI}\ (\text{cm}) \times \text{CSA}\ (\text{cm}^2)$$

Heart rate was determined from the electrocardiograph recorded simultaneously with each velocity trace. This was done using the digitising tablet and computer programme described above. The electronic pen was used to mark the R-R interval of successive cardiac cycles and the computer calculated the mean HR over the ten cycles.

Cardiac output across each valve was then calculated as follows:

$$\mathbf{CO}\ (\text{ml/min}) = \text{SV}\ (\text{ml}) \times \text{HR}\ (\text{beats/min})$$

Mean Doppler CO and HR were calculated as the average of the three measurement sites.

4.6. Measurement of Blood Pressure and Calculation of Systemic Vascular Resistance

Arterial BP was measured in the right brachial artery using an inflatable cuff attached to a standard mercury sphygmomanometer. A standard cuff (12 x 23 cm.) was used throughout. Systolic BP was defined as the first phase of the Korotkoff sounds. Diastolic BP was taken as the fourth phase (muffling) of the Korotkoff sounds (Petrie et al. 1990). Measurements were commenced after the subject had rested for 5 minutes and were repeated every 5 minutes for three measurements. These three measurements were then averaged.

Mean arterial blood pressure (MAP) was calculated as follows:

$$\textbf{MAP}\ (\text{mm Hg}) = \text{Diastolic BP} + \frac{\text{Systolic BP - Diastolic DBP}}{3}$$

Total Systemic Resistance (TSR) was calculated from MAP and cardiac output according to the formula (Yang et al. 1978):

$$\textbf{TSR}\ (\text{dyne sec cm-5}) = \frac{\text{MAP (mm Hg) x 80}}{\text{CO (l/min)}}$$

where CO = Mean Doppler CO calculated as the average of the flows across the aortic, mitral and pulmonary valves.

4.7 Discussion of M-Mode Echocardiographic Methods

4.7.1 Number of Replicates

A degree of cycle-to-cycle variation exists in M-mode echocardiographic measurements of LV dimension and function (Bett and Dryburgh 1981). However the size of this cycle variability is small relative to the overall variability of the measurements and is consistently less than the replication variability (when the same investigator analyses the same cycle on a separate occasion) (Bullock et al. 1984). There is therefore a balance between increasing the number of replicates or cycles to increase the precision of the measurement and the extra time each additional measurement adds to the analysis time.

Previous workers have usually averaged between three and five cycles (Bett and Dryburgh 1981). Bullock et al. (1984) recommended measuring 4 cycles and this number was used for all the present studies. Bett and Dryburgh (1981) actually recommended measuring 5 or more cycles. Close inspection of their data however shows that the percentage of samples whose means differed by more than one standard deviation from the mean value of all cycles measured for each subject was only marginally less when 5 cycles were analysed as compared with 4 cycles.

4.7.2 Left Ventricular and Left Atrial Measurements

Left ventricular internal dimensions were used as estimates of the size of the left ventricle. Previous studies have confirmed that M-mode internal dimensions correlate closely with angiographic long and short left ventricular axes (Feigenbaum et al. 1969, Fortuin et al. 1971, Feigenbaum 1972, Murray et al. 1972). No attempt was made to convert these measurements to volumes because the assumptions on which this conversion are based are frequently erroneous (Teichholz et al. 1976) and measurement of left ventricular volume from a single M-mode dimension is unreliable and prone to error (Martin 1978, Antani et al. 1979, Kronik et al. 1979).

Left atrial antero-posterior dimension has also been shown to correlate closely with angiographic dimension (Hirata et al. 1969, Lundstom and Mortensson 1974). Some workers have recommended determining the aorta-left-atrium ratio to correct for variations in subject size (Brown et al. 1973). This method was not adopted in the present study because it does not reduce inter subject variability in adult subjects and because the present investigations were concerned with intra-subject comparisons. Correction for variation in body size was not therefore necessary.

Left ventricular EDD and LAD may provide non-invasive measurements of cardiac preload. Left ventricular EDD is increased in conditions associated with compensated volume overload (Fortuin et al. 1972) and acute increases in preload (induced by infusion of Dextran or saline) produce increases in LV end-diastolic pressure and dimension (Quinones et al. 1976). Maximal M-mode LAD has proved useful as a semiquantitative method of assessing left-to-right shunts in children (Laird and Fixler 1974). It has been shown to correlate with left atrial volume (Wade et al. 1987) and LV filling pressure (Haendchen et al. 1982). Furthermore acute volume loading has been shown to increase echocardiographic LAD (Okamato et al. 1991). Thus changes in these two echocardiographic dimensions may reflect changes in left sided cardiac filling pressure and venous return.

4.7.3 Indices of Left Ventricular Function

Numerous M-mode echocardiographic parameters have been used to evaluate left ventricular performance (Feigenbaum 1986). One of the earliest measurements to be studied was the velocity of circumferential shortening or Vcf (Cooper et al. 1972), derived by measuring the change in circumference of the ventricle (Π x D, where D = diameter). If this is then divided by ejection time, the mean Vcf can be obtained. This assumes the short-axis cross-sectional configuration of the left ventricle is a circle and the left ventricle M-mode dimension is a diameter of this circle. Cineangiographic mean Vcf has been shown to correlate closely with the instantaneous force-velocity relationship (the relation between the instantaneous velocity of fibre shortening of the minor equator of the left ventricle to the maximum wall tension during ejection) (Karliner et al. 1971) and M-mode echocardiographic estimation of mean Vcf correlates closely with angiographic mean Vcf (Quinones et al. 1974) and ejection fraction (Cooper et al. 1972).

Fractional shortening is the percent shortening of the LV dimension. It was used in preference to the M-mode derived ejection fraction ($[EDD^3 - ESD^3] \times EDD^3$) because no assumptions are made concerning ventricular volumes. M-mode fractional shortening has been shown to correlate closely with angiographic ejection fraction (Fortuin et al. 1971, Quinones et al. 1978).

Digitization allows a more sophisticated assessment of changes in cavity dimension and wall thickness (Traill et al.1978, Hanrath 1983). The peak systolic rates of change of dimension (dD/dt) measured from the echocardiograph have shown a close correlation with similar measurements made from left ventricular cineangiograms (Gibson and Brown 1974). However, there is no evidence that these computer-derived parameters are superior to more conventional indices (mean Vcf, fractional shortening) in differentiating patients

with heart disease from normal subjects (Kugler et al. 1980). The clinical relevance of changes in peak diastolic rates of change of cavity dimension and wall thickness are less clear. There is some evidence that they may reflect ventricular distensibility (Sanderson et al. 1978, Siegert et al. 1978). As LV cavity and wall dD/dt had not been previously studied during pregnancy it was decided to include these parameters in addition to mean Vcf and fractional shortening.

Mean Vcf, fractional shortening and the LV peak systolic dD/dt are all ejection phase indices. It is important to realize that while changes in these indices reflect changes in global left ventricular performance they do not necessarily represent alterations in inherent left ventricular contractility. Changes in heart rate, preload and afterload may all potentially alter these parameters independently of inotropic state (Davidson et al. 1974). In actual fact a number of studies have shown that ejection phase indices are relatively independent of preload (Quinones et al. 1976, Kass et al. 1987) and only mean Vcf is significantly altered by changes in HR (DeMaria et al. 1979). However all these measurements must display some afterload dependence, since they return to zero at infinite afterload (isovolumetric contraction) independent of contractile state (Kass et al. 1987). This must be borne in mind when interpreting changes in all M-mode indices of ventricular function.

4.7.4 Left Ventricular Wall thickness and Mass

All previous M-mode echocardiographic studies of LV wall thickness have measured the septal and posterior walls separately. While this method has proved to be more accurate than either electrocardiography or cross-sectional echocardiography in detecting left ventricular hypertrophy (Woythaler et al. 1983, Dancy 1986, Kristensen 1989) the ability of these measurements to detect smaller changes within an individual has been questioned (Monoson et al. 1978). The relatively large percentage error in each of these measurements is partly due to the small distances being measured (Monoson et al. 1978). To try and reduce this, the total LV wall thickness was determined during the present studies by simply subtracting the end-diastolic cavity dimension from the total LV thickness.

Calculation of LV mass from LV cavity and wall dimensions is based on estimating the volume bounded by the epicardial surface of the ventricle and then subtracting the volume of the cavity. This difference represents the volume of the ventricular wall and multiplication by the specific gravity of cardiac muscle gives LV mass. Unfortunately these calculations suffer from the inaccuracies of the echocardiographic determination of volume. Nevertheless measurements of LV mass obtained by M-mode echocardiography have correlated closely with angiographic measurements (Troy et al. 1972) and postmortem anatomic mass (Devereux and Reichek 1976). Left ventricular mass can also be calculated from cross-sectional echocardiographs. However this method is more complicated and has

not been shown to be more accurate than M-mode estimations (Reichek et al. 1983, Woythaler et al. 1983, Collins et al. 1989).

4.8 Discussion of Cross-sectional and Doppler Methods

4.8.1 Number of Replicates

Velocity Integral; Most previous workers have averaged between 5 and 12 consecutive cardiac cycles for each determination of VI (Ihlen et al. 1984, Lewis et al. 1984, Nishimura et al. 1984, Kolev et al. 1986, Bouchard et al. 1987). The rationale for this is that velocities vary with respiration and rhythm (Goldberg et al. 1988). At the commencement of the present work no study had addressed the issue of the optimal number of beats to digitize. Consequently ten consecutive beats were chosen to ensure one respiratory cycle was included. Subsequently Kristensen and Goldberg (1987) estimated the magnitude of error associated with digitizing 1-5 beats in the determination of VI in the ascending aorta and pulmonary artery. They suggested that there was little advantage, in terms of reducing error, in digitizing more than 3 beats for pulmonary velocity, whereas inclusion of 5 beats provided improved accuracy for ascending aortic velocity measurements. It remains uncertain whether digitization of more than 5 beats would reduce the error even further.

Diameter and Cross-sectional Area; Previous studies have averaged between 3 and 6 measurements for each determination of diameter or CSA (Lewis et al. 1984, Labovitz et al. 1985, Goldberg et al. 1985, Gardin et al. 1985, Christie et al. 1987). To date no study has reported the optimum number of replicates and therefore five consecutive cycles were chosen in line with previous reports.

4.8.2 Assumptions and Sources of Error in Flow Measurement

Velocity Measurement; Blood flow calculation using CW Doppler assumes that the maximum velocity recorded corresponds to the velocity at the level at which CSA is measured. The highest velocities are assumed to come from the narrowest part of the insonated vessel which in the aorta is the valve annulus (Ihlen et al. 1984). Measurements of diameter were made at this level throughout the present studies. With pulsed Doppler, where the sample volume can be placed at a specific depth, velocity and CSA can be sampled at the same level.

The velocity profile recorded within the sample volume is assumed to represent the velocity across the entire CSA of the vessel or valve orifice (mean spatial velocity or spatial average velocity). The relative accuracy of this assumption depends on the spatial variability of blood flow at the level sampled. The assumption is acceptable if the spatial velocity profile is flat. In this circumstance the maximum velocity recorded at any point across the vessel will be very similar to the mean spatial velocity. The flow profile is dependent on flow acceleration, viscous forces and geometric factors (Skjaerpe et al.

1985). Acceleration and convergence of flow, such as occurs in the ventricular outflow tracts and in the immediate proximity of the semilunar valves, flattens the velocity profile. On the other hand divergence of the flow stream, which occurs within a ventricular chamber or in a dilated aortic root, results in a more parabolic flow profile. Alterations in vessel geometry, such as the curvature of the aorta and asymmetry of the outflow tract, may cause the location of peak flow velocities to shift from the centre of the flow stream. Studies of flow profiles in animals have suggested that the velocity profile in the proximal aorta and at the mitral annulus are relatively flat (Lynch and Bove 1969, Schultz et al. 1969, Seed and Wood 1971, Clark and Schultz 1973, Lucas et al. 1984). Magnetic resonance studies in humans have shown a flat profile during most of systole in the regions just distal to the aortic and pulmonary valves (Klipstein et al. 1987, Bogren et al. 1988). Studies of mitral flow velocity profiles in humans have shown conflicting results. Taylor and Whamond (1976) reported that the velocity profile at the level of the mitral annulus was relatively flat while Samsted et al. (1989) reported a variable skew at this site. Thus while a flat velocity profile may be reasonable assumption at the aortic and pulmonary artery annulus this may not be valid at the mitral annulus.

The effect of viscosity on velocity measurements is complex and poorly understood. Daniel et al. (1986) reported a weak but significant negative correlation between aortic velocity integral and haemoglobin concentration ($r = -0.38$, $p < 0.05$). Their data would suggest that for a fall in haemoglobin concentration of 1 g/dl, the aortic velocity integral will change by 0.5 cm. During human pregnancy the haemoglobin concentration may fall by 2 g/dl (Hytten and Lind 1973). The resulting decline in blood velocity will lead to an overestimation of Doppler-determined velocity but failure to correct for these viscosity changes would lead to an overestimation of cardiac output of only 5%.

Blood velocity estimated by the Doppler technique is inversely proportional to the cosine of the angle between the ultrasound beam and the direction of flow. The cosine of the angle 20° is 0.94, but as the angle of interrogation increases above this, the degree of underestimation of velocity becomes more significant. Some investigators have attempted to correct this error by measuring, from the cross-sectional image, the angle between the Doppler beam and the direction of flow (taken as the centre line of the vessel or chamber). Blood flow, however, is a three-dimensional vector and correcting for an imaginary angle in two dimensions does not account for the third (elevational) plane. During these investigations the beam-flow angle was not measured. The beam was aligned approximately parallel with flow and the Doppler signal was maximized by changing transducer angulation (Zoghbi and Quinones 1986). It was then assumed that the beam was parallel with flow and therefore that $\cos \theta$ was equal to 1. Provided that the intercept angle was within 20° of the flow axis the velocity would have been underestimated by less than 6% (Goldberg et al. 1988).

Cross-sectional area measurement; The major source of error in the determination of CO by the Doppler method lies in echocardiographic measurements of the area through which flow occurs. Most estimates of valve or vessel area used for flow calculations are derived from vessel diameter. It is assumed that the area through which blood flows can be truly represented by a geometric figure of constant shape and the measured dimensions represent reproducible diameters of that figure. Deviations from a circular shape increase with age and the presence of focal calcification. However in the case of the aorta and pulmonary artery, the assumption of circular geometry appears reasonable and diameter taken from a plane that includes the long axis of the vessel should permit calculation of vessel area (Ascah et al. 1985). For the mitral valve, on the other hand, the assumption of circular geometry, although applied widely and validated clinically (Lewis et al. 1984), does not appear to be anatomically correct. During the present studies mitral valve area was planimetered directly from the short axis view. Thus no geometrical assumptions were made. However, the accuracy of area measurements from this view is limited by rotational errors in plane alignment, imprecision in plane positioning relative to the limiting orifice, and the potential for the heart to shift relative to the short axis plane of view during diastole.

When using any linear dimension to derive an area, the percentage error in measurement of the area equals twice the percentage error in the measurement of the linear dimension because the area is proportional to the square of the linear dimension. For a 1 mm measurement error, the difference between the maximum and minimum possible calculated areas can be as much as 12% of the maximum calculated area (Ascah et al. 1985). This is especially important in small vessels. For a 10 mm vessel, the same 1 mm error would result in up to a 33% difference in the calculated area (Ascah et al. 1985). In a very small child the potential measurement error may be so large as to limit the validity of the method whereas in an adult these measurements can almost certainly assess the CSA with reasonable accuracy.

During flow calculations it is also assumed that the area through which blood flows is of constant size throughout the period of flow. This assumption is unlikely to be true; Loeber et al. (1987b) demonstrated in a canine preparation that aortic and pulmonary artery area varied by a mean of 6% and 12% respectively during the cardiac cycle under conditions of marked changes in preload and afterload. At baseline flow, maximal variation in vessel area was approximately half this value. Studies in humans have suggested that the mean changes in CSA during systole are larger in the pulmonary artery (23%) (Greenfield and Griggs 1963) than in the proximal aorta (11%) (Greenfield and Patel 1962). Such large changes in CSA are unlikely to occur at the level of the fibromuscular valve annulus and Ihlen et al. (1984) reported no change in aortic orifice CSA during systole. Mitral valve area has also been shown to vary during the cardiac cycle (Ormiston et al. 1981). This change is much larger at the leaflet tips than at the valve annulus and Ormiston et al. (1981) found a 10% increase in annular area during diastole.

Other assumptions; One further assumption is that forward flow during the opposite part of the cardiac cycle is negligible. This proposition has not been adequately studied. Goldberg et al. (1988) have suggested that there is some diastolic forward flow in the pulmonary artery and this is not taken into account by present Doppler flow methods. However this flow appears to be very small in volume (Goldberg et al. 1988). Forward flow through other valves during the opposite part of the cardiac cycle has not been reported.

4.8.2 Sites and Techniques of Flow Measurement

Blood flow across the four cardiac valves is equal in the adult heart and therefore cardiac output can be measured at any of these sites. During the present studies flow was measured across the aortic, mitral and pulmonary valves, thereby allowing three independent estimates of cardiac output. No attempt was made to measure flow across the tricuspid valve because at the onset of these studies no satisfactory validatory study of this method had been reported. Subsequently some workers have reported a high correlation between Doppler flow across the tricuspid valve and invasively determined flow (Meijboom et al. 1985, Kolev et al. 1986) while others have found this method to be very inaccurate (MacLennan et al. 1986). Sahn and Valdez-Cruz (1986) have suggested that averaging flow from several sites may provide a more accurate estimate of CO. No study has confirmed this suggestion and therefore it was decided to present flow measurements from each site separately. Subsequent analysis showed there was no systematic difference between flow measurements at any of the three sites and therefore statistically it would have been acceptable to average these values.

Aortic Flow; Parallel interrogation of the ascending aorta proved difficult with the pulsed Doppler transducer. Consequently good quality images of the ascending aorta and good quality velocity envelopes could not be consistently recorded. This was because the transducer was physically large and the crystals were in-line with the transducer handle. This problem has been reported by other workers and can be overcome by using a 25° off-axis cross-sectional transducer (Goldberg et al. 1988). Unfortunately such a transducer was not available for the Hewlett-Packard system.

Aortic flow can also be measured using pulsed Doppler from the descending aorta (Goldberg et al. 1988) and left ventricular outflow tract (Lewis et al. 1984). Calculation of flow from the descending aorta theoretically underestimates cardiac output because it does not include head and neck blood flow. The velocity profile may also be skewed (Skjaerpe et al. 1985). This results in marked spectral dispersion of the velocity envelope, making digitization difficult (Goldberg and Loeber 1983). Velocity measurements have been found to differ quite substantially from ascending aortic measurements in a significant number of

subjects (Wilson et al. 1987). Labovitz et al. (1985) reported a reasonable correlation between descending aortic flow and invasively determined CO (r = 0.83) however the standard error of the estimate was large (1.10 l/min) and satisfactory velocity and cross-sectional recordings were obtainable from the suprasternal notch in only 42% of subjects. No other workers have validated this method. In view of these limitations it was decided not to measure flow from the descending aorta.

Lewis et al. (1984) were the first group to report flow measurements from the left ventricular outflow tract. Velocity recordings were made from the cardiac apex and aortic annular diameter was measured from the parasternal long axis view. Although velocities and diameter were not measured from the same site, they reported a close correlation between Doppler and invasive flows (r = 0.91). Subsequent validatory studies, including one carried out in pre-eclamptic pregnant women, have confirmed these findings (Labovitz et al. 1985, Lee et al. 1988). When the present investigations were started only Lewis et al. (1984) had validated this method. In contrast a number of validatory studies had reported a close correlation between aortic flow measured by CW Doppler and invasive flows (Darsee et al. 1980, Distante et al. 1980, Huntsman et al. 1983, Rose et al. 1984, Nishimura et al. 1984, Chandraratna et al. 1984). Consequently, despite the potential advantages of measuring flow using pulsed Doppler (Section 3.4.2), it was decided to measure aortic flow using CW Doppler.

Aortic diameter can be measured using A-mode, M-mode and cross-sectional echocardiography. Measurements can also be made at different anatomical sites from the aortic annulus (or orifice) proximally, to the ascending aorta above the sinus of Valsalva. Cross-sectional echocardiography has the theoretical advantage that diameter can be measured perpendicular to the long axis of the aorta at a particular site. Such is not the case with A-mode and M-mode. Studies comparing different measurement techniques have confirmed that Doppler flows calculated using cross-sectional measurements correlate the closest with invasive measurements (Ihlen et al. 1984, Gardin et al. 1985, Christie et al. 1987). Studies comparing different measurement sites have shown less consistent results. Gardin et al (1985) found flows calculated from diameters measured distal to the sinus of Valsalva correlated the closest with invasive flows. However Ihlen et al. (1984) found this method systematically overestimated flow and suggested that flow calculated using aortic annular diameter was the most accurate. These findings were confirmed by Christie et al. (1987). Diameters measured at the aortic annulus do not change significantly during the cardiac cycle (Ihlen et al. 1984) and they have also been shown to be the most reproducible measurements (Ihlen et al. 1984, Skjaerpe et al. 1985). Thus all measurements of aortic diameter during the present studies were performed at the level of the valve annulus.

Mitral Flow; All previous studies of mitral flow have recorded mitral velocities from the the apical four chamber view because this provides the most parallel orientation between the

sound beam and flow. Transmitral flow has been measured at the level of the valve leaflets (outflow orifice) and at the level of the valve annulus (inflow orifice). Some methods have taken account of the phasic changes in orifice area (dynamic estimates) while others have not (static estimates). There is no unanimity as to which technique is better. However it is clear that paired measurements of transmitral velocities and mitral CSA must be made at a consistent site as VI and CSA are significantly different at the inflow and outflow orifice (Ormiston et al. 1981, Delemarre et al. 1987).

Fisher et al. (1983) developed and validated the 'effective mean mitral orifice area' method in animals. Measurements of maximal diastolic orifice area were made at the level of the mitral leaflets (from the parasternal short axis view). The area was then corrected for changes during diastole by an index (the ratio of mean-to-maximal mitral leaflet separation) derived from a mitral M-mode echocardiographic recording. Touche et al. (1985) subsequently developed an elliptical method that used mitral annulus diameter (from the apical four chamber view) for the long axis of the ellipse and a dynamic estimate for the short axis derived from M-mode leaflet separation. Although accurate results have been reported with these methods in the experimental setting and in early clinical studies (Fisher et al. 1983, Zhang et al. 1985, Ascah et al. 1989), subsequent reports have called these studies into question (De Zuttere et al. 1988, Miller et al. 1990). Furthermore the methods are time consuming and may not be feasible in a significant number of adult subjects because of the difficulty recording good quality echocardiographs of the maximal valve outflow orifice (Zoghbi et al. 1986, De Zuttere et al. 1988).

Valdes-Cruz et al. (1983) reported the first method of measuring transmitral flow at the level of the valve annulus. The sample volume was placed between the corners of the annulus and area was calculated from the mid-diastolic annular diameter, measured from the apical four chamber view, assuming a circular fixed flow area. Despite the fact that the annular area does change during diastole (Ormiston et al. 1981) they reported a close correlation with invasively determined flow. This was confirmed by subsequent studies (Lewis et al. 1984, Gillam et al. 1985, Meijboom et al. 1987a). However, other workers found this simple static method inaccurate; Doppler overestimating invasively determined flow (Touche et al. 1985, Goldberg et al. 1985, Dittman et al. 1987). Goldberg et al. (1985) measured diastolic mitral annular area by planimetry directly from echocardiographs recorded from the parasternal short axis plane. They compared this with area calculated from annular diameters, measured from the same echocardiographic recordings, using a formula assuming elliptical geometry. In 92% of subjects the annulus appeared elliptical in shape and results of the area calculation were within 8% of the planimetered area. In the remaining subjects the annulus was either scalloped or circular and in these cases calculated and planimetered areas differed by 10-20%. In the subsequent validation study they used calculated area in subjects where the area appeared elliptical in shape and planimetered area in the remainder. Using this technique Doppler flows

correlated closely with Fick flows and were more accurate than flows calculated from mitral annular diameter (assuming circular geometry). This finding is perhaps not surprising since the annular area was circular in only one subject. As this method appeared to be as accurate as earlier more complicated dynamic estimates it was used throughout the present studies. However rather than assume that annular area was always elliptical in shape, it was measured by planimetry in each subject.

Pulmonary Flow; The parasternal short axis view provides the best parallel orientation of the ultrasound beam with flow. Initial studies in children reported a reasonable correlation between Doppler flow measurements from the distal pulmonary artery and invasive flow measurements (Goldberg et al. 1982, Sanders et al. 1983, Barron et al. 1984). Unfortunately, in the average adult the lateral wall of the main pulmonary artery is often obscured by overlying lung echoes, making diameter measurement difficult. The right ventricular outflow tract and pulmonary annulus however are easier to image in adults and flow measurements at the level of the pulmonary annulus have been shown to correlate closely with invasive flows (Gillam et al. 1985, Labovitz et al. 1985, Zoghbi and Quinones 1986, Kolev et al. 1986). In the short axis view, the annulus and proximal pulmonary artery are imaged in lateral resolution. Some workers have measured diameter from the centre of the medial wall echoes to the centre of the lateral wall echoes (Loeber et al.1984, Goldberg et al. 1988) which was the method used throughout the present studies. Subsequent studies have measured from inner edge to inner edge (Labovitz et al. 1985, Kolev et al. 1986) and reported equally good results.

4.9 Statistical Methods

4.9.1 Comparison between Flows

In Study 1, Fick and Doppler CO's were compared by correlation and linear regression analysis using the statistical package SPSS-X. The difference between Fick and Doppler CO values was divided by the Fick CO to determine the percentage difference. In addition the mean differences and the SD's of the differences between CO measured by the Fick and 3 Doppler methods were determined (Bland and Altman 1986).

In Studies 3,4 and 5 the results of flows measured at the aortic, mitral and pulmonary valves were compared by correlation and linear regression analysis.

4.9.2 Reproducibility of Echocardiographic Measurements

In Study 2 an analysis of variance was used to determine the contribution of various factors (variance components) to overall variability. In the non-pregnant group, 2 separate analyses were performed to estimate the short term variance and the long term variance. For each analysis the total variance consists of;

1. a component due to differences between subjects (σ_S^2) and
2. a component due to differences within subjects (σ_W^2)

Two values of (σ_S^2) were therefore obtained and the average calculated (σ_S^2). The within subject variance consists of;

1. a temporal component (σ_{ST}^2 or $\sigma_{ST}^2 + \sigma_{LT}^2$) and
2. a component representing the residual variability (σ_R^2).

The quantity of σ_{LT}^2 represents the additional variability that a subject experiences in the long term over that already experienced in the short term (σ_{ST}^2). The intraobserver variance, calculated by reanalysing the initial recordings, gave an estimate of σ_R^2 which was then used to calculate σ_{ST}^2 and σ_{LT}^2.

For serial studies on individual subjects, only the within subject variability is of interest. This variability can be expressed in terms of variance components as;

$$\sigma_W^2 = \sigma_{ST}^2 + \sigma_{LT}^2 + \sigma_R^2$$

An approximate 95% CI for a particular measurement on a typical subject was calculated as follows; mean $\pm$ 2 σ_W. This is probably the most clinically useful measurement of variability because it gives a guide to the size of change which is likely to represent a

genuine alteration in a particular haemodynamic parameter. The CI's calculated in this way only relate to means determined from the number of replicated measurements quoted eg 5 for aortic diameter.

In the pregnant group, one analysis of variance was performed to determine the short term variance. In this case the within subject variance can be expressed as;

$$\sigma_W^2 = \sigma_{ST}^2 + \sigma_R^2$$

An approximate 95% CI was then calculated as described above. No attempt was made to measure long term variability because of the potential confounding effects of pregnancy-related haemodynamic changes.

To allow comparison with previous studies, the percentage errors of paired differences made 30-60 minutes and 1-3 months apart were also calculated as the difference between the greater and lesser measurement expressed as a percentage of the mean of the pair.

4.9.3 Sample Size

Where possible the sample size required to demonstrate a significant difference was estimated approximately from the formula;

$$n > 2 (Z_{2\alpha} + Z_{\beta})^2 \times (s / \delta)^2$$

where; n = number of paired observations, $Z_{2\alpha}$ = value of t representing Type 1 error (ie corresponding to significance of difference) eg at the 5% level, $2\alpha = 0.05$), Z_{β} = value of t representing Type 2 error (ie corresponding to power of test) eg 95% chance, $\beta = 0.05$, s = SD, δ = mean difference between values.

4.9.4 Significance of Mean Differences

Studies 3,4 and 5 were designed so that paired comparisons could be made within subjects, each of whom would therefore act as her own control.

A repeated measures analysis of variance (ANOVA) was used for each haemodynamic variable using the statistical package BMDP. This method allowed analysis of the way the mean value of each variable was affected by various classifications of the data. Thus the significance of temporal effects could be assessed using one overall test. Using a repeated measures ANOVA allowed for the fact that observations over time in any individual were likely to be correlated.

To overcome the problem of multiple significance testing, the differences between time

points were compared with the use of the studentized range at the 1% level (Pearson and Hartley 1966);

$$\text{Range} = q_{(v)} \times (s / \sqrt{n})$$

where; $q_{(v)}$ = critical value for comparing two time points, s2 = residual mean square (from ANOVA) with v degrees of freedom, n = number of subjects. Thus any change greater than the studentized range was considered statistically significant.

In Study 5, the difference between the twin and singleton groups were compared by calculating the change in each haemodynamic variable at each gestation relative to the postnatal control value. The relative changes during pregnancy in each variable between the two groups were then compared using an analysis of variance.

CHAPTER 5

VALIDATION OF CARDIAC OUTPUT MEASUREMENT BY THE DOPPLER METHOD

5.1 Introduction

In recent years a large number of animal and human studies have validated flow measurements using the Doppler technique. Despite this wealth of published work there is no unanimity about the best measurement site or technique. It was therefore felt that, although the Doppler methods used throughout the present study had been validated previously by others, it was important to establish the accuracy of the techniques in the authors hands. Aortic, pulmonary and mitral flows, determined by Doppler and cross-sectional echocardiography, were therefore compared with flow measured by the direct Fick method. The direct Fick method has been validated in animals (Seely et al. 1950) and is probably the most accurate reference method currently available being dependent on the least number of assumptions (Fagard and Conway 1990). Because of the need for right and left heart catheterization it was not ethically acceptable to perform such a validatory study in pregnant subjects and therefore cardiac patients, undergoing diagnostic catheterization, were studied.

5.2 Subjects and Methods

Eighteen patients, admitted to the Regional Cardiothoracic Centre for routine diagnostic cardiac catheterization, were recruited. The details of the group are shown in Table 5.1.

	Number	
Age (years)	47 (13-67)*	
Sex	Male	12
	Female	6
Clinical Diagnoses	Aortic Coarctation	2
Cardiomyopathy	3	
	Mitral Valve Disease	2
	Coronary Artery Disease	11

* Mean (Range)

Table 5.1. Subject Details

Three patients, all over 65 years, were subsequently excluded because preliminary cross-sectional echocardiographs were of such poor quality that diameter measurements were not possible. No attempt was made to measure mitral flow in the 2 patients with mitral valve disease.

Subjects underwent routine diagnostic right and left heart catheterization. Following percutaneous puncture of the femoral vein an 8 French size catheter was advanced across the tricuspid valve and then into the pulmonary artery. Following percutaneous puncture of the femoral artery a 7 French catheter was advanced to the ascending aorta. After insertion of the catheters the patients were tilted into the left semi-lateral position. Oxygen (O_2) consumption was measured using a Walters MRM-2 Oxygen Consumption Monitor. The patient's nose was firmly clipped. Expired air, collected via a headbox, and room air were mixed and the mixture was analysed for oxygen by a polarographic oxygen sensor. Oxygen consumption, averaged over 20 seconds, was then displayed digitally. The mean of ten consecutive readings was used to calculate cardiac output. On two occasions during the gas collection, blood samples were withdrawn from the pulmonary artery and aorta. The average pulmonary arterial and aortic oxygen saturation were determined using a reflection oximeter (American Optical Unistat Oximeter). At the same time, a sample of blood was obtained for measurement of haemoglobin concentration. Systemic arterial and mixed

venous blood oxygen content (ml O_2/litre blood) was calculated by multiplying the fraction of oxygen saturation by the theoretical oxygen carrying capacity:

([Haemoglobin concentration, g/100 ml] x 1.36 [ml O_2/g Haemoglobin]) x 10

Cardiac output was calculated using the standard formula:

$$CO\ (l/min) = \frac{O_2 \text{ consumption (ml/min)}}{\text{Arterial } O_2 \text{ content - mixed venous } O_2 \text{ content (ml/l)}}$$

In each patient an attempt was made to measure flow across the aortic, pulmonary and mitral valves. In 2 subjects it was not possible to visualize the lateral wall of the pulmonary artery and therefore pulmonary flow measurements were only available in 13 subjects. Cross-sectional echocardiographs and Doppler velocities wee recorded immediately after completion of the direct Fick procedure and before angiography. On each occasion echocardiographic measurements were completed within 15 minutes of finishing the gas collection. Doppler flows were calculated by the author without knowledge of the Fick measurements.

5.3 Results

The correlations between Fick cardiac output and aortic, mitral and pulmonary flows determined by Doppler are shown in Fig. 5.1. There was a high correlation at all three sites. None of the slopes were significantly different from unity and none of the intercepts was significantly different from zero. The large standard errors for the intercept are due to the lack of data points at low cardiac outputs.

The mean absolute and percentage differences between measurements of cardiac output by the Fick method and the three Doppler methods are shown in Table 5.2. The plots of difference against mean of CO determined by the Fick and Doppler methods are shown in Figure 5.2.

Doppler Site	**n**	**Mean (SD) CO (l/min)**		**Mean (SD) Difference* (l/min)**	**Mean (Range) % Difference**
		FICK	DOPPLER		
Aortic	15	4.96 (1.02)	4.96 (0.93)	-0.01 (0.35)	0 (-14 - +16)
Mitral	13	5.01 (1.08)	5.04 (0.91)	-0.04 (0.43)	0 (-9 - +21)
Pulmonary	13	4.92 (1.09)	4.70 (0.87)	-0.23 (0.40)	-5 (-19 - +9)

* Fick CO versus Doppler CO.

Table 5.2. Comparison of cardiac output measured by direct Fick and Doppler methods.

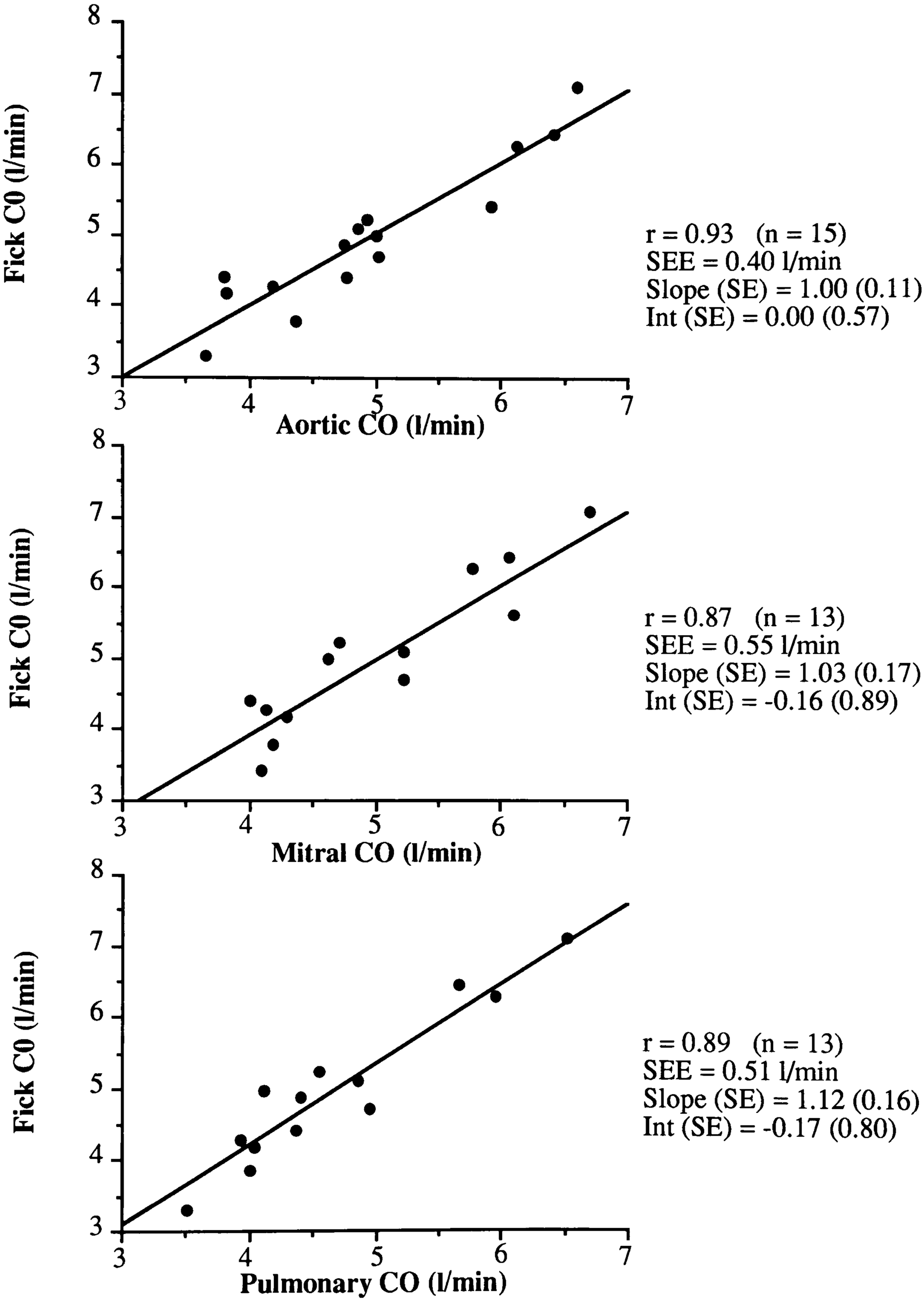


Figure 5.1 Correlations between Fick CO and aortic, mitral and pulmonary flows determined by Doppler.

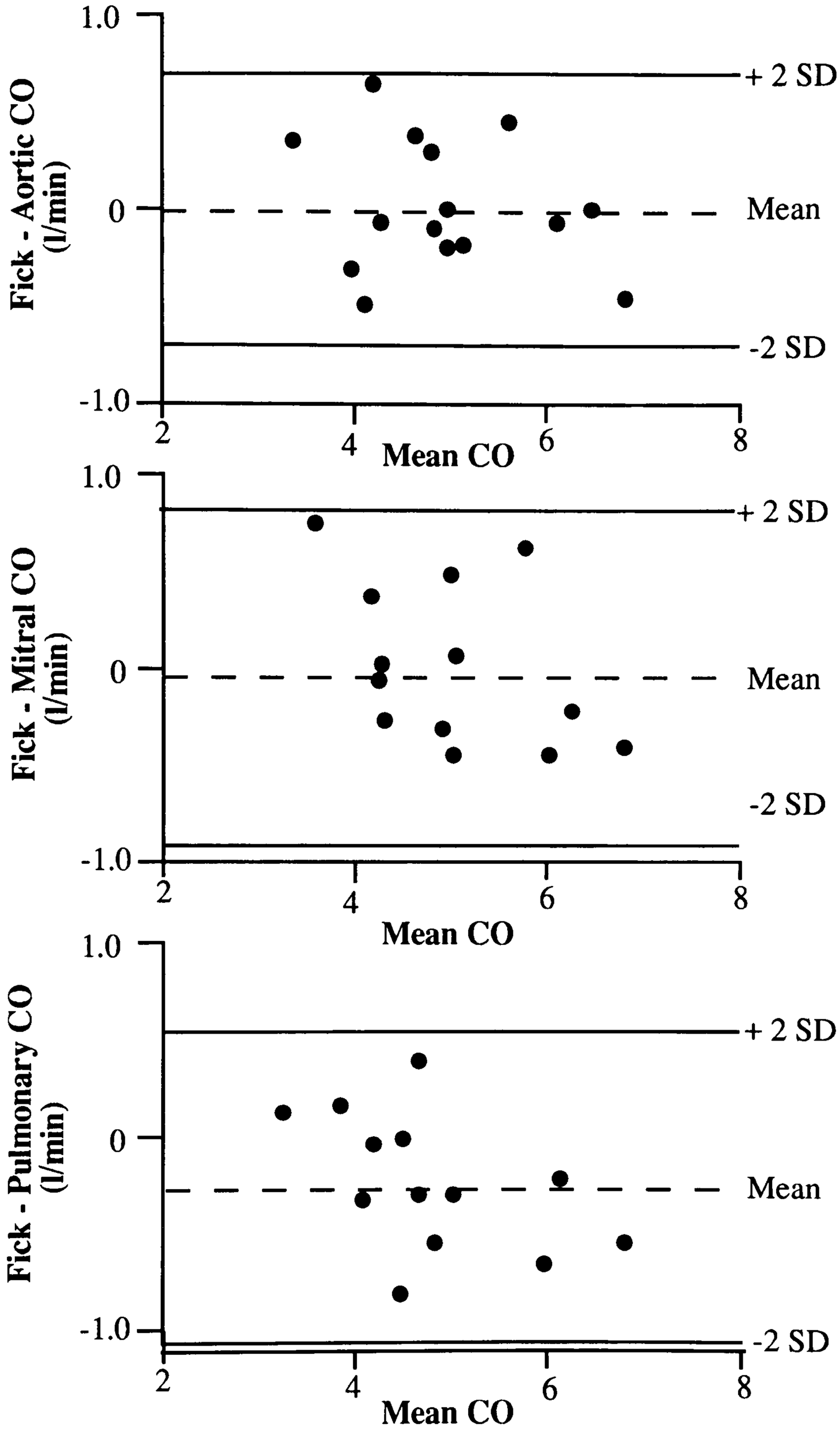


Figure 5.2 Plots of difference against mean value of CO determined by the Fick and Doppler methods

5.4 Discussion

Despite the assumptions of flow estimation by the Doppler method there was a close correlation between Fick CO and Doppler CO calculated at the aortic, pulmonary and mitral valves. Previous studies that have compared flow across the aortic valve, measured by CW Doppler, with CO measured invasively in adults are shown in Table 5.3. The results of the present study compare favourably; the SEE (or residual SD) being smaller than most previously reported. Two studies in which the Doppler method has been compared with thermodilution during pregnancy have also shown close agreement (Easterling et al. 1987, Easterling et al. 1990b). Comparable results have been obtained using PD to measure ascending aortic velocities from the suprasternal notch (Ihlen et al. 1984, Goldberg et al. 1985, Hinderliter et al. 1986, Innes et al. 1987, Dubin et al. 1990) and to measure left ventricular outflow tract velocities from the cardiac apex (Lewis et al. 1984, Labovitz et al. 1985, Dittmann et al. 1987, Niederle et al. 1988, Kurokawa et al. 1988, Dericbourg et al. 1990). Thus, despite the theoretical advantages of velocity measurement using PD, consistently closer agreement with invasive CO has not been demonstrated. However, few studies have compared aortic flow measured by both Doppler methods. Ihlen et al. (1984) found no significant difference in CO when aortic velocities were measured by CW and PD and CSA was calculated from distal aortic root diameter. Both methods however overestimated flow compared with the Fick method. Waters et al. (1982) compared CO measured by both Doppler modes with thermodilution. There was no difference in the correlation coefficient between the two Doppler methods.

All but one of the previous validatory studies have investigated the agreement between Doppler and invasive results solely by using the correlation coefficient. This is not a good method of comparing the accuracy of a test or comparing the results of one study with another (Bland and Altman 1986). Only Northridge et al. (1990) have compared Doppler flow estimates with CO measured by thermodilution using the limits of agreement method (Bland and Altman 1986). They recorded aortic velocities from the suprasternal notch using CW Doppler and LV outflow tract diameters (immediately proximal to the aortic leaflets) from the parasternal long axis plane. Diameters were measured using the trailing edge-leading edge method. Their 95% limits of agreement were -1.23 to +1.32 l/min. These values are almost twice those reported in the present study and may reflect the subjects studied (unselected subjects within 24 hours of myocardial infarction) or their method of measuring aortic diameter.

Previous studies that have compared flow across the mitral valve, measured by PD, with invasively determined CO are shown in Table 5.4. The results of the present study show a comparable agreement with invasive flow. Despite the varied methods of calculating mitral CSA, the majority of studies have reported a close correlation with invasive flow. There does not appear to be any clear advantage in using the more complex

Author	n	Diameter*	r	SEE	Slope	Int
Darsee et al. (1980)†	14	M, AR	0.96	0.23	1.02	+0.76
Waters et al.(1982)#	29	M, Ao	0.60	1.75		
	12¶	M, Ao	0.84	1.10		
Huntsman et al.(1983)#	45	A, Ao	0.94	0.58	0.95	+0.38
Chandraratna et al.(1982)#	39	A, AR	0.97	0.42	0.93	+0.41
Nishimura et al.(1984)#	54$	A, Ao	0.94	0.78	1.00	-0.13
	26§	A, Ao	0.85	0.78	0.70	+1.50
Rose et al. (1984)#	16	X, AR	0.92	0.48	1.04	-0.15
Mehta et al. (1985)#	21	M, AR	0.97	0.48	0.95	+0.11
Vandenbogaerde et al.(1986)#	41	A, AR	0.97			
Bouchard et al. (1987)#	13	M, AVO	0.97	0.4	0.89	+0.40
Christie et al. (1987)†	15¢	M, An	0.91		1.1	-2.4
Christie et al. (1987)#	15¢	M, An	0.86		1.0	+0.7
Easterling et al. (1987)	12@	A, AR	0.91	0.3	1.11	-0.98
Maeda et al. (1989)#	34¢	X, Ao	0.85	0.59	1.37	+0.67
Easterling et al. (1990b)	11@	A, AR	0.95		1.05	-0.35
Present Study†	15	X, An	0.93	0.40	1.00	+0.0

* Quoted echocardiographic method and site of aortic diameter measurement; † compared with Fick method; # compared with thermodilution method; ¶ subgroup with high quality ultrasonic recordings; $ medical patients; § surgical patients; ¢ during exercise; @ pregnant patients.

Abbreviations; M, M-mode; A, A-mode; X, cross-sectional; Ao, ascending aorta (above sinus of Valsalva); AR, aortic root; AVO, aortic valve opening; An, aortic annulus.

Table 5.3. Previous studies comparing aortic flow, measured by continuous wave Doppler, with invasively determined CO in adult subjects.

Author	n	Flow Method	Area Site/Shape	r	SEE	Slope	Int
Lewis et al. (1984)*	24	X(4C),S	An/C	0.87	0.59	0.80	+0.94
Goldberg et al.(1985)#	35	X(PS),S	An/E(T)	0.96	0.52	0.9	+0.30
	35	X(PS),S	An/C	0.91	1.00	1.13	+0.87
Zhang et al.(1985)#	20	X(PS),D	L/E(T)	0.89	0.71	0.90	+0.80
Gillam et al.(1985)*	18	X(4C),S	An/C	0.94		1.03	-0.19
Dittmann et al.(1987)*	40	X(4C),S	An/C(T)	0.86	0.80	0.88	+1.75
	40	X(PS),D	L/E(T)¶	0.91	0.53	0.79	+0.63
	40	X(PS),D	An/E(T)	0.81	0.73	0.67	+1.29
De Zuttere et al.(1988)*	30	X(4C),D	An/E	0.89	0.55	0.84	+0.56
	30	X(4C),D	An/E$	0.80	0.74	0.79	-0.14
Hoit et al. (1988)*	48	M(PS),D	L/C	0.93	0.36	1.1	-0.45
Kurokawa et al. (1988)*	20	M (PS),D	L	0.85	1.03	1.18	-0.24
Miller et al. (1990)*	17	X(PS),D	L/E(T)¶	0.91	0.51	0.75	+0.01
	17	X(PS),D	L/E(T)§	0.91	0.58	0.86	+0.09
Present Study#	13	X(PS),S	An/E(T)	0.87	0.56	1.03	-0.16

* Compared with thermodilution method, # compared with Fick method, ¶ uses ratio of mean to maximal mitral leaflet separation (Fisher et al. 1983) $ uses leaflet separation-velocity integral obtained by integration, § excludes period of diastasis in calculation of average leaflet separation.

Abbreviations: X, cross-sectional; M, M-mode; 4C, apical 4 chamber; PS, parasternal short axis; S, static; D, dynamic (i.e. takes account of changes in mitral valve area over cardiac cycle; An, annulus; L, leaflet tips; C, circle; E, ellipse; T, traced.

Table 5.4 Previous studies comparing mitral flow, measured by pulsed Doppler, with invasively determined cardiac output in resting subjects.

dynamic or corrected formulas for flow area which adjust for diastolic variation in mitral CSA.

Previous studies that have compared flow across the pulmonary valve, using PD, with invasively determined CO are shown in Table 5.5. There have been relatively few validatory studies in adults but all have shown a reasonable correlation with invasive flow. The results of the present study are in agreement with these.

Author	n	Diameter*	r	SEE	Slope	Int
Gillam (1985)#	18	X, An	0.97		0.99	-0.03
Labovitz (1985)#	12	X, An	0.81	0.82		
Kolev (1986)#	29	X, PPA	0.93			
Present Study¶	13	X, An	0.89	0.51	1.12	-0.17

* Quoted echocardiographic method and site of pulmonary artery diameter measurement,
# Compared with thermodilution method, ¶ Compared with Fick method.
Abbreviations: X, cross-sectional; An, annulus, PPA, proximal pulmonary artery.

Table 5.5 Previous studies comparing pulmonary flow, measured by pulsed Doppler, with invasively determined cardiac output in adult subjects.

One problem encountered during the present study was the difficulty in visualizing the lateral pulmonary artery wall. Out of the 18 patients originally recruited it was not possible to measure pulmonary artery diameter, because of overlying lung echoes, in 5/18 (28%) subjects. Similar problems were encountered by Labovitz et al. (1985) who recorded pulmonary flow in only 12/55 (22%) adults studied. They ascribed this not only to the difficulty in measuring pulmonary diameter but also to the study design, which designated pulmonary flow studies as the last of the four sites examined. In contrast Gillam et al. (1985) and Kolev et al. (1986) obtained pulmonary flow measurements in all of the adult subjects they studied. However it is not clear from these reports whether the patients were selected because they were good echocardiographic subjects. Visualization of the lateral pulmonary artery wall may be easier in young thin people as successful flow measurements have been reported in 88-100% of children (Goldberg et al. 1982, Sanders et al. 1983) and it is interesting that, in the present study, satisfactory pulmonary artery

measurements were recorded in all subjects less than 50 years of age. A recent report has suggested that the left and right oblique subcostal views may improve the visualization of the pulmonary artery in adults (Ferrazza et al. 1990). In this study pulmonary artery diameters were recorded from 88% of subjects with chronic obstructive pulmonary disease. These views may well prove valuable when adequate visualization is not possible in the parasternal plane.

The present results suggest that measurements of CO from the aortic valve give the closest agreement with invasive flow. This confirms previous reports that have compared aortic and mitral flow (Lewis et al. 1984, Goldberg et al. 1985, Gillam et al. 1985, Kurokawa et al. 1988) or aortic and pulmonary flow (Goldberg et al. 1982, Labovitz et al. 1985, Gillam et al. 1985).

Although there was no systematic difference between results obtained using the Fick and Doppler methods there were significant individual differences in a number of paired measurements. However in all but one comparison, the difference between CO measured by the two methods was less than 20%. While there appears to be no systematic bias between direct Fick and dye dilution estimates of CO (Hamilton et al. 1948, Reddy et al. 1976) large individual differences have been reported. Thus 25% of paired comparisons differed by more than 25% and individual variation ranged from +58% to -57% (Taylor and Shillingford 1959, Reddy et al. 1976). Studies comparing CO measurements by dye dilution and thermodilution have shown conflicting results. Ganz et al. (1971) found no systematic bias between the two methods and individual differences ranged from +16% to -17%. However, in a more recent comparison, Russell et al. (1990) found that thermodilution overestimated CO relative to dye dilution by a mean of 1.85 (95% CI 1.24-2.47) l/min (+31%). Few studies have compared the Fick and thermodilution techniques in a large number of subjects. Hillis et al. (1985) found that in 96% of 207 subjects the difference between the two methods was $\leq$ 20% but individual differences varied by as much as 69%. The major problem in assessing any study that compares CO measurement techniques is to decide which measurement is the most accurate. There is no gold standard in the intact human subject. We may only measure how reproducible a technique is and how well it compares with other methods.

5.5 Summary

Flow across the aortic, mitral and pulmonary valves, measured by Doppler and cross-sectional echocardiography, was compared with cardiac output measured by the Fick oxygen method in 15 non-pregnant subjects. In agreement with previous studies, there was a close correlation at all three sites, indicating there was no systematic difference between results obtained using the Fick and Doppler methods. Absolute values of cardiac output agreed closely suggesting that the Doppler methods described provide an accurate non-invasive technique for measurement of flow.

CHAPTER 6

REPRODUCIBILITY OF DOPPLER, CROSS-SECTIONAL AND M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS

6.1 Introduction

The major advantage of studying haemodynamics using echocardiography is that measurements may be repeated as often as necessary without discomfort or risk to the subject. Before these techniques are applied to serial studies, the variability of the measurements must be known. The studies in this chapter were carried out to examine the intraobserver and temporal variability of the echocardiographic measurements used in the serial study of haemodynamics during pregnancy. As all the echocardiographic recordings were to be recorded and analysed by the author only intraobserver and not interobserver variability was examined. Furthermore because serial investigations were to extend over many months it was also felt necessary to examine long term temporal variability. Because of the likely temporal changes in haemodynamics during pregnancy, investigations were performed on non-pregnant subjects. In addition, as no previous study had reported whether pregnancy itself affects the variability of echocardiographic measurements, a smaller study was undertaken on pregnant subjects to answer this question.

6.2 Subjects and Methods

Fourteen healthy non-pregnant women (mean age 27, range 23-31 years) were studied. The subjects were recruited to take part in the serial study of haemodynamics during pregnancy. Ten of the women subsequently became pregnant and were studied again at 16 weeks gestation.

Investigations were performed between days 21 and 24 of the menstrual cycle in the non-pregnant group and during the sixteenth week of normal pregnancy in the pregnant group. Fasted subjects were studied in a warm quiet room. All investigations were performed in the left semi-lateral position after haemodynamic stability had been achieved (see Section 4.1). Cross-sectional echocardiographs, Doppler velocities, M-mode echocardiographs and blood pressure were recorded by the author as described previously. In each subject initial recordings were made and then repeated after 30-60 minutes. The subjects remained recumbent between each series of recordings. In the non-pregnant group a further set of recordings were made 1-3 months after the initial investigations.

All the echocardiographic recordings were analysed by the author. Doppler velocity and M-mode recordings were numbered and analysed blindly in random order. Cross-sectional echocardiographs were stored on videotape and therefore could not be analysed in random order. To try and eliminate bias, echocardiographic recordings from each period of investigation were analysed several weeks apart. Intraobserver variability was evaluated by re-analysis of the Doppler velocity traces together with the cross-sectional and M-mode echocardiographic recordings obtained at the initial investigation. The repeat analysis was performed several weeks after the initial analysis.

To allow comparison with previous studies, the percentage errors of paired measurements made 30-60 minutes and 1-3 months apart were also calculated as the difference between the greater and lesser measurement expressed as a percentage of the mean of the pair.

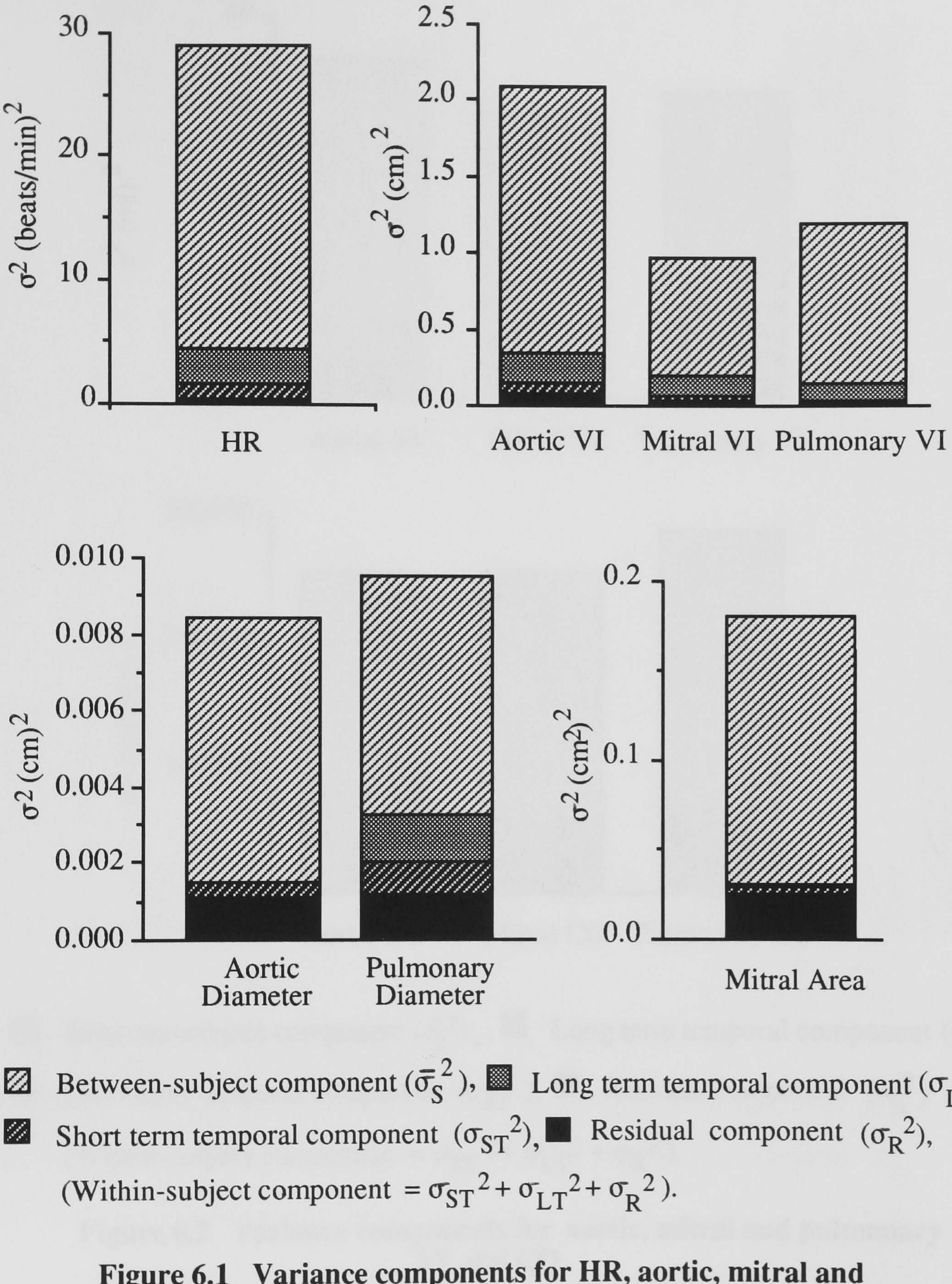
6.3 Results

Satisfactory velocity, cross-sectional and M-mode measurements were obtained from the aorta and mitral valve in all subjects. It was not possible to measure the pulmonary artery diameter in two of the non-pregnant subjects (14%) and one of the pregnant subjects (10%) because overlying lung echoes obscured the lateral pulmonary arterial wall.

Non-pregnant subjects: The variance components for all the Doppler, cross-sectional and M-mode echocardiographic measurements and calculated variables are shown in Figures 6.1.- 6.4. The within-subject variances were much smaller than the variances between subjects: $\sigma_S 2$ were significantly greater than zero ($p<0.001$) for all variables whereas $\sigma_W 2$ was never significantly different from zero. The additional long term variability was generally larger than short term variability.

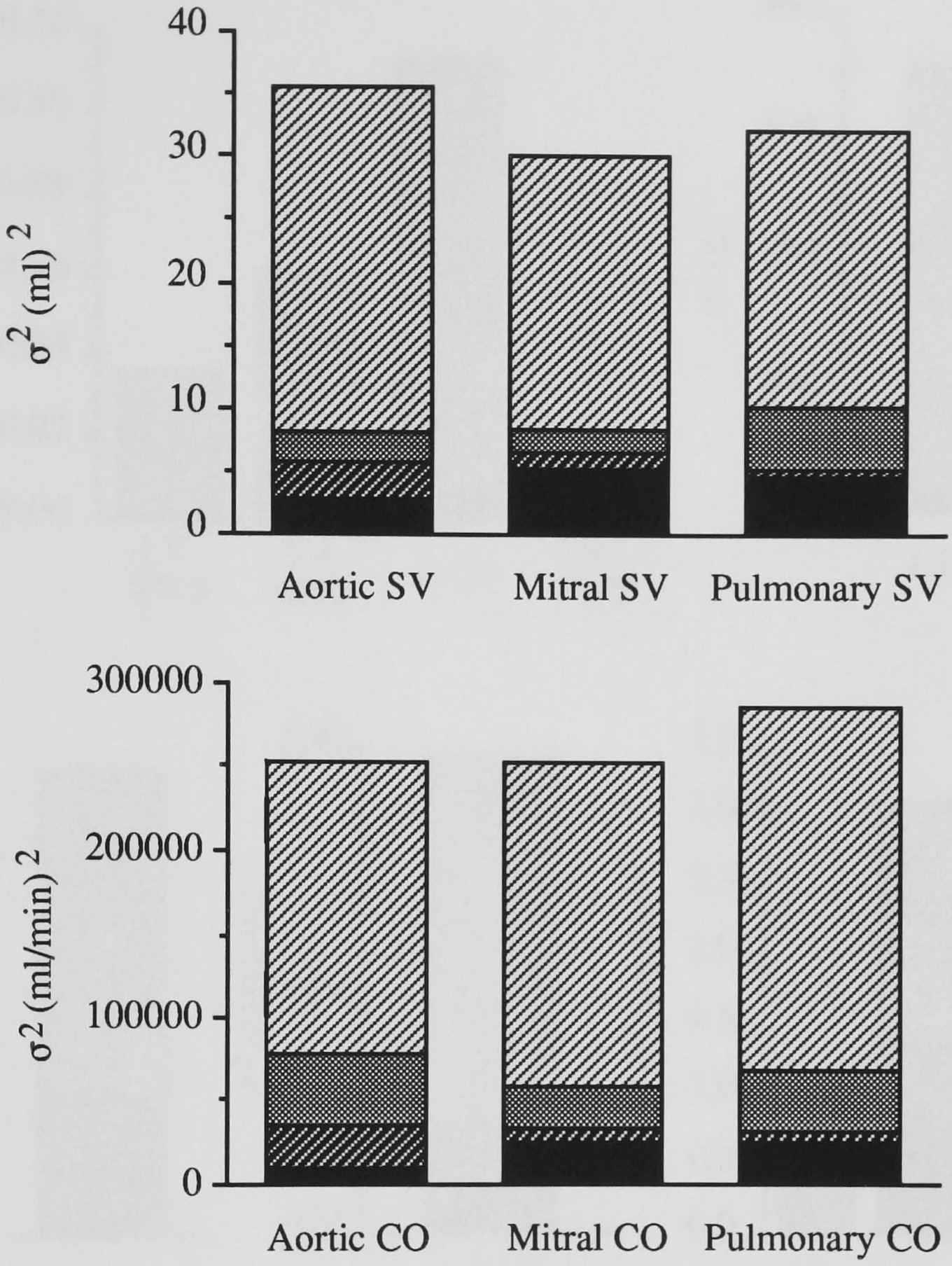
The mean and estimated 95% confidence interval together with the mean percentage errors for each Doppler and cross-sectional echocardiographic variable are shown in Table 6.1. Measurements of HR and VI from the Doppler recordings and measurements of valve diameter and CSA from the cross-sectional echocardiographic recordings were highly reproducible (mean percentage errors <5%). The errors for the derived variables SV and CO were slightly greater but still acceptable (mean percentage errors <8%). There was no significant differences in the errors of measurements performed at the aortic, mitral and pulmonary valves, suggesting that flow measurements from these three sites are equally reproducible.

The corresponding means and 95% confidence intervals for the M-mode echocardiographic and BP measurements are shown in Table 6.2. Left atrial and ventricular measurements were highly reproducible (mean percentage errors <5%). Variables calculated using these measurements had slightly greater percentage errors but again these remained acceptable. Measurements of left ventricular and posterior wall rates of change of dimension were less reproducible.



▨ Between-subject component ($\bar{\sigma}_S^2$), ■ Long term temporal component (σ_{LT}^2),
▨ Short term temporal component (σ_{ST}^2), ■ Residual component (σ_R^2),
(Within-subject component = $\sigma_{ST}^2 + \sigma_{LT}^2 + \sigma_R^2$).

Figure 6.1 Variance components for HR, aortic, mitral and pulmonary VI's, aortic and pulmonary artery diamteter and mitral valve area.

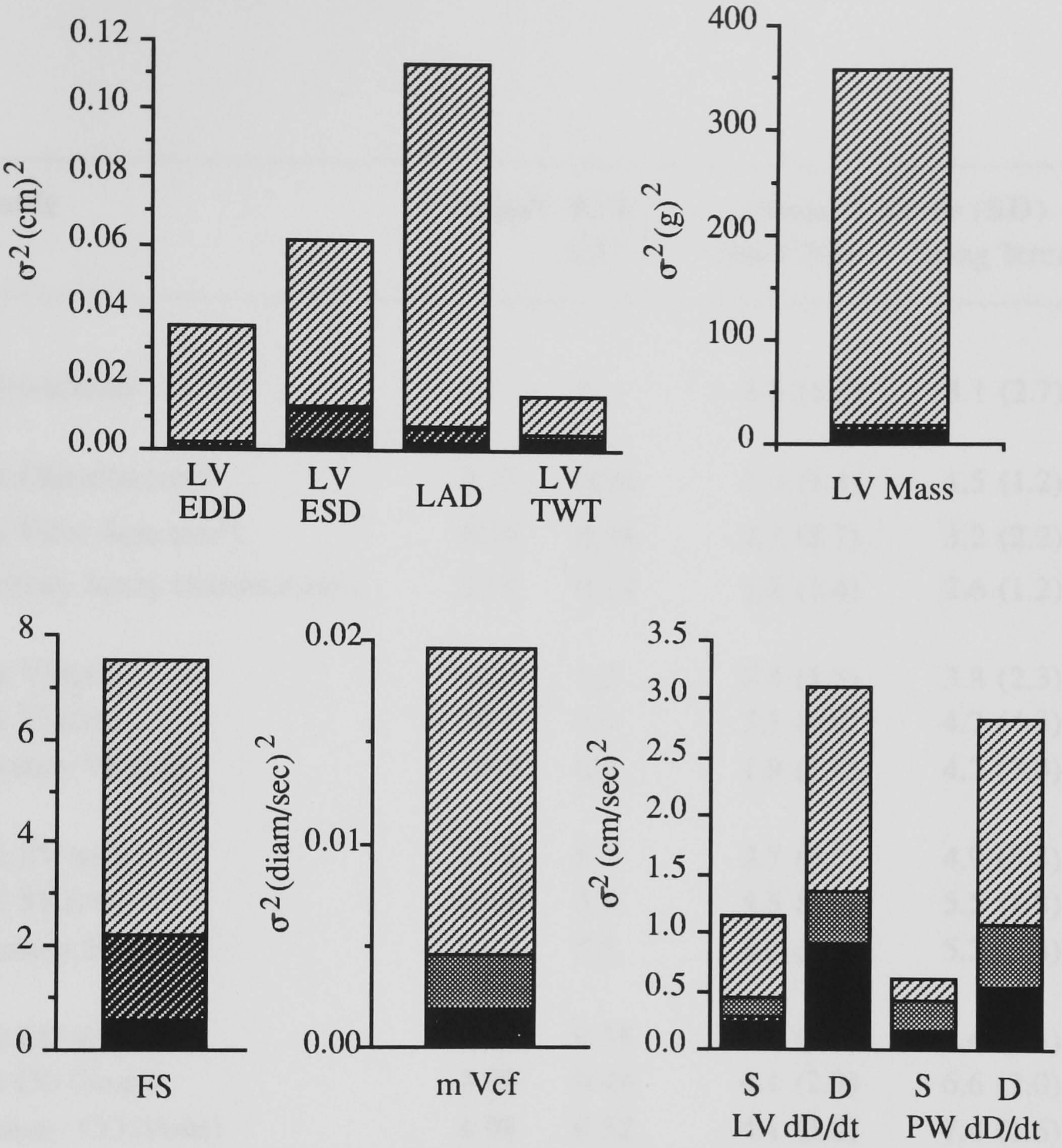


Between-subject component ($\bar{\sigma}_S^2$), Long term temporal component (σ_{LT}^2),

Short term temporal component (σ_{ST}^2), Residual component (σ_R^2)

(Within-subject component $= \sigma_{ST}^2 + \sigma_{LT}^2 + \sigma_R^2$).

Figure 6.2 Variance components for aortic, mitral and pulmonary SV and CO



Abbreviations; S, systole; D, Diastole

Between-subject component ($\bar{\sigma}_S^2$), Long term temporal component (σ_{LT}^2),

Short term temporal component (σ_{ST}^2), Residual component (σ_R^2)

(Within-subject component $= \sigma_{ST}^2 + \sigma_{LT}^2 + \sigma_R^2$).

Figure 6.3 Variance components for M-mode LV dimensions, LAD, LV Mass and indices of LV function.

Variable	Mean*	95% CI	Mean % Error (SD)	
			Short Term	Long Term
HR (beats/min)	75	4	1.6 (1.8)	3.1 (2.7)
Aortic Diameter (cm)	2.17	0.06	1.3 (1.4)	1.5 (1.2)
Mitral Valve Area (cm^2)	6.39	0.34	2.7 (2.7)	3.2 (2.2)
Pulmonary Artery Diameter (cm)	2.79	0.11	1.8 (1.4)	2.6 (1.2)
Aortic VI (cm)	18.2	1.2	2.4 (1.8)	3.8 (2.3)
Mitral VI (cm)	10.4	0.9	3.1 (2.0)	4.7 (4.3)
Pulmonary VI (cm)	10.8	0.8	1.9 (1.3)	4.2 (3.0)
Aortic SV (ml)	67.2	5.7	3.7 (3.7)	4.9 (3.4)
Mitral SV (ml)	66.4	5.8	4.5 (3.1)	5.5 (2.8)
Pulmonary SV (ml)	66.1	5.8	3.0 (2.9)	5.2 (3.4)
Aortic CO (l/min)	5.03	0.56	4.8 (3.4)	6.4 (4.3)
Mitral CO (l/min)	4.99	0.49	4.1 (2.9)	6.6 (2.0)
Pulmonary CO (l/min)	4.98	0.52	4.1 (3.0)	7.4 (1.6)

*Average of values at first investigation (initial and reanalysis).

Table 6.1. Reproducibility of Doppler and cross-sectional echocardiographic measurements in non-pregnant subjects.

Variable	Mean*	95% CI	Mean % Error (SD) Short Term	Long Term
LV EDD (cm)	4.52	0.10	1.2 (1.0)	1.4 (0.9)
LV ESD (cm)	2.93	0.23	3.6 (4.5)	4.5 (3.6)
LAD (cm)	3.17	0.16	3.0 (1.7)	3.2 (2.7)
LV TWT (cm)	1.50	0.12	2.4 (1.8)	4.1 (2.5)
LV Mass (g)	120	10	4.7 (2.3)	4.9 (3.9)
FS (%) 35.0	2.2	3.2 (3.0)	4.2 (2.9)	
Mean Vcf (Circ/sec)	1.27	0.13	3.9 (2.2)	6.6 (2.7)
LV dD/dt - Systole (cm/sec)	8.0	1.4	7.8 (6.1)	8.2 (7.8)
LV dD/dt - Diastole (cm/sec)	12.1	2.4	10.0 (5.3)	12.0 (6.8)
PW dD/dt - Systole (cm/sec)	4.2	1.3	8.0 (9.3)	12.5 (13.5)
PW dD/dt - Diastole (cm/sec)	8.6	1.9	8.4 (6.1)	12.8 (9.7)
Systolic BP† (mm Hg)	104	3	1.1 (0.8)	1.8 (1.4)
Diastolic BP† (mm Hg)	64	5	2.4 (2.6)	5.0 (2.5)

* Average of values at first investigation (initial and reanalysis), except † initial only.

Table 6.2. Reproducibility of M-mode echocardiographic and blood pressure measurements in non-pregnant subjects.

Pregnant Subjects: The means, 95% confidence intervals and percentage errors for each variable are shown in Table 6.3. and Table 6.4. Doppler flow measurements from the three sites were again equally reproducible. The 95% confidence intervals for all the variables were similar to those obtained in the non-pregnant subjects and there was no significant difference in the short term mean percentage errors in pregnant and non-pregnant subjects. Although these results suggest that echocardiographic measurements are equally reproducible when carried out during pregnancy, it should be noted that the 95% confidence interval calculated for measurements obtained during pregnancy does not include error due to long term temporal variability. The importance of this cannot be determined because of the temporal haemodynamic changes associated with pregnancy itself. However, judging by the results in the non-pregnant group, this additional variability is of little clinical importance.

Variable	**Mean***	**95% CI**	**Mean % Error (SD)** Short Term
HR (beats/min)	85	4	1.5 (1.9)
Aortic Diameter (cm)	2.24	0.07	1.4 (1.0)
Mitral Valve Area (cm2)	6.73	0.50	2.6 (1.7)
Pulmonary Artery Diameter (cm)	2.89	0.16	2.7 (1.2)
Aortic VI (cm)	21.6	1.2	2.7 (1.2)
Mitral VI (cm)	12.1	0.9	3.1 (2.0)
Pulmonary VI (cm)	12.1	1.0	2.7 (1.2)
Aortic SV (ml)	84.3	5.4	4.3 (2.6)
Mitral SV (ml)	81.8	5.0	3.5 (2.4)
Pulmonary SV (ml)	79.8	4.7	4.3 (3.3)
Aortic CO (l/min)	7.02	0.58	3.7 (2.8)
Mitral CO (l/min)	7.01	0.54	3.6 (2.4)
Pulmonary CO (l/min)	6.76	0.66	4.8 (3.5)

* Average of values at first investigation (initial and reanalysis).

Table 6.3. Reproducibility of Doppler and cross-sectional echocardiographic measurements in pregnant subjects.

Variable	Mean*	95% CI	Mean % Error (SD) Short Term
LV EDD (cm)	4.70	0.12	1.3 (1.6)
LV ESD (cm)	2.90	0.26	3.8 (4.0)
LAD (cm)	3.35	0.23	4.5 (2.4)
LV TWT (cm)	1.61	0.12	2.2 (1.6)
LV Mass (g)	140	15	4.9 (3.9)
FS (%)	38.4	2.0	3.4 (2.3)
Mean Vcf (Circ/sec)	1.41	0.15	3.7 (2.2)
LV dD/dt - Systole (cm/sec)	9.3	2.0	10.5 (6.6)
LV dD/dt - Diastole (cm/sec)	14.5	2.3	10.3 (6.0)
PW dD/dt - Systolie (cm/sec)	5.5	1.7	10.4 (7.8)
PW dD/dt - Diastole (cm/sec)	10.8	1.9	8.0 (5.5)
Systolic BP† (mm Hg)	105	3	1.7 (1.7)
Diastolic BP† (mm Hg)	61	5	2.6 (2.0)

* Average of values at first investigation (initial and reanalysis) except † initial only.

Table 6.4. Reproducibility of M-mode echocardiographic and blood pressure measurements in pregnant subjects (n=10).

6.4 Discussion

This study reports the variability of echocardiographic measurements in a group of healthy young women. Echocardiographs were recorded by one skilled echocardiographer from women who were good echocardiographic subjects and therefore the recordings for analysis were of high quality. In contrast as few as 20% of clinical echocardiographic recordings may be of equivalent quality (Bullock et al. 1984). Thus these results are likely to represent the optimum reproducibility obtainable using the methods described. Introduction of other echocardiographers and older subjects will undoubtedly increase the variability of these measurements.

Most previous studies of echocardiographic reproducibility have investigated intra and inter observer variability and much less is known about the temporal variability of echocardiographic measurements.One component of this is beat-to-beat variability which exists for both M-mode (Bett and Dryburgh 1981) and Doppler (McLennan et al. 1986) measurements. As the present study was designed primarily to investigate long term temporal variability no attempt was made to assess beat-to-beat changes. Measurements from a constant number of consecutive cardiac cycles were averaged and this mean value was used in the analysis for each variable. Temporal variability also includes an intraobserver component. This was was estimated by reanalysing one set of recordings. No attempt was made to measure interobserver variability in this study as all future measurements were to be performed by the author. However the results of interobserver variability studies of aortic flow measurement have been published by the author (Robson et al. 1988). When comparing the present results with those of previous workers it is important to bear in mind that the methods used have not been consistent: the selection of subjects has varied; the method of measuring certain variables has varied (this is especially true for valve CSA); the number of replicate measurements made in each subject has varied; and finally but perhaps most importantly, the method of expressing variability has varied (most studies have reported either a mean percentage error between paired measurements or a coefficient of variation [standard deviation/mean, expressed as a percentage]). The reported differences in variability may be partly explained by the inconsistencies in methodology.

Doppler and cross-sectional echocardiographic measurements: Previous studies that have reported the variability of Doppler aortic flow measurements are shown in Table 6.5. Ihlen et al. (1987a) and Bouchard et al. (1987) reported the variability of aortic SV measurements using continuous wave Doppler. In comparison with the present results, the greater variability reported in these two studies may reflect the fact that the subjects investigated were older and unselected. Loeber et al. (1987a) are the only other group who have studied longer term temporal variability. They used pulsed Doppler to investigate investigate 16 selected subjects (mean age 24 years) on 6 occasions (before breakfast,

Author	Method	Variable	Variability			
			Inter-Observer	Intra-Observer	Temporal	Total
Lewis et al.(1984)	PD, X	SV,CO	6.8*			
Ihlen et al.(1987a)	CW, X	SV	0.9†		0.3†	6.2#
Ihlen et al.(1987b)	PD, X¶	SV	0.1†		0.9†	9.2#
Bouchard et al.(1987)	CW, M-M	SV	8.6*	11.1*		
Loeber et al.(1987a)	PD, X	SV,CO			13†	
Claflin et al. (1988)	PD, M-M	SV	3.4†	7.4†		
	PD, M-M	CO	3.1†	7.0†		
Nicolosi et al.(1988)	PD, X	CO	4.7†	5.8†		7.8$
	PD, X§	CO	2.5†	6.9†		7.4$
Looyenga et al.(1989)	DBPD	CO			9.9†	
Wong et al. (1989)	CW, Nom	CO	<10†	<10†		
Present Study	CW, X	SV			4.9*	
		CO			6.4*	

* Mean percentage error, † coefficient of variation, # coefficient of variation between any pair of measurements in each subject, ¶ during exercise, $ total interpretive variability expressed as coefficient of variation, § Doppler velocities recorded from apex.

Abbreviations; X, cross-sectional echocardiography; M-M, M-mode echocardiography; DBPD, Dual beam pulsed Doppler; Nom, aortic diameter derived from nomogram.

Table 6.5 Previous studies of the variability of aortic cardiac output and stroke volume measurements using Doppler echocardiography.

after breakfast, after lunch, after exercise, and twice at random) over a 6 week period. The differences between their results and those reported here may be due to the different circumstances in which Loeber et al. measured 'resting' CO. Some of the additional variability may be due to the variation in prandial state of their subjects, CO being found to increase after a meal. Only one study, performed on newborn infants, has investigated the reproducibility of aortic flow measurements using various echocardiographic techniques (ie PD versus CW Doppler, cross-sectional versus M-mode echocardiography) (Hudson et al. 1990). While it would be dangerous to extrapolate the results directly to adult studies some of the results are of interest. They found that the most reproducible method of measuring aortic flow was by using velocities recorded by CW Doppler from the suprasternal notch combined with aortic diameters measured from M-mode echocardiographs. Using this technique the estimated standard deviation for interobserver comparisons was nearly twice that for intraobserver comparisons (16.5 vs. 29.0 ml/kg/min).

Several previous studies have investigated the reproducibility of measurements of VI obtained from aortic CW Doppler recordings. Most studies have reported interobserver, intraobserver and day to day variability, whether expressed as mean percentage error or as a coefficient of variation, to be less than 6% (Fraser et al. 1976, Gardin et al. 1984, McLennan et al. 1986, Northridge et al. 1990). Comparable figures have been reported for heart rate measurements (Felner et al. 1980, Kupari 1984, McLennan et al. 1986). The results of the present study are consistent with these findings. Although several workers have investigated the change in aortic diameter during the cardiac cycle (Greenfield and Patel 1962, Gardin et al. 1985), this is the first study to report the temporal variability of cross-sectional echocardiographic measurements of aortic annular diameter. Northridge et al. (1990) investigated the intraobserver variability of aortic root diameter measurements. They reported a coefficient of variation of 1.5%. Interestingly, in the study reported by Hudson et al. (1990) discussed above, although aortic diameters measured from M-mode echocardiography had the lowest intra and inter observer variability the lowest overall variability, as expressed as the standard deviation of a single measurement, was found with cross-sectional measurements.

Previous studies that have investigated the variability of pulsed Doppler mitral flow measurements are shown in Table 6.6. Intraobserver variability has consistently been reported to be less than 7%. Results of interobserver variability have been less consistent, ranging from 0.1 to 16%. (Nicolosi et al. 1988). In all these studies the measurement of mitral VI has been highly reproducible (variability less than 5%) and this has been confirmed in patients with mitral stenosis and prosthetic mitral valves (Rijsterborgh et al. 1990). In contrast cross-sectional area measurements have been more variable, probably reflecting the different methods used to measure flow area. Two of the studies calculated area from mitral annular diameter. Lewis et al. (1984) measured diameter at mid-diastole (static estimate) and reported an interobserver variability, expressed as mean

Author	Method	Variable	Variability			
			Inter-Observer	Intra-Observer	Temporal	Total
Lewis et al. (1984)	PD, X	SV,CO	16.4*			
Nicolosi et al. (1986)	PD, X(D)	CO	5.8†	6.2†		
Meijboom et al. (1987)	PD, X(S)	CO	5.6†			
Hoit et al. (1988)	PD, M-M(D)	CO	5.1*	4.9*		
Nicolosi et al. (1988)	PD, X(S)	CO	16.0†	6.8†		20.0#
	PD, X(D)	CO	0.1†	5.3†		7.7#
Present Study	PD, X(S)	SV			5.5*	
		CO			6.6*	

* Mean percentage error, † coefficient of variation, # total interpretive variability expressed as coefficient of variation.

Abbreviations; PD, pulsed Doppler; X, cross-sectional echocardiography; M-M, M-mode echocardiography; S, static estimate of CSA; D, dynamic estimate of CSA.

Table 6.6 Previous studies of the variability of mitral cardiac output and stroke volume measurements using Doppler echocardiography.

percentage error, of 14.8%. Nicolosi et al. (1988) found comparable results using the same method. In contrast Meijboom et al. (1987b), using an average annular diameter calculated from measurements made at four time points during the cardiac cycle, found intraobserver variability to be only 3.4%. Other studies have measured mitral area directly from parasternal short axis views, taking into account phasic changes in flow area during the cardiac cycle (dynamic estimates). In all cases the reported variability was less than 8% (Marino et al. 1983, Nicolosi et al. 1986, De Zuttere et al. 1988, Nicolosi et al. 1988). Comparable results were obtained in the present study using a static method of area measurement.

Previous studies that have investigated the variability of PD pulmonary flow measurements are shown in Table 6.7. Variabilities have been consistently less than 8%. Nicolosi et al. (1988) reported the variability of pulmonary Doppler and cross-sectional area measurements, expressed as coefficients of variation, to be 4.2% and 5.4% respectively. The present results are comparable with these results.

Author	Method	Variable	Variability			
			Inter-Observer	Intra-Observer	Temporal	Total
Barron et al. (1984)	PD, X	CO	<5*	<5*		
Nicolosi et al. (1988)	PD, X	CO	5.6†	4.3†		7.9#
Present Study	PD, X	SV				5.2¶
		CO				7.4¶

* 'Standard errors of the means of repeated measurements', † coefficient of variation, # total interpretive variability expressed as coefficient of variation, ¶ mean percentage error.

Abbreviations; PD, pulsed Doppler; X, cross-sectional echocardiography.

Table 6.7 Previous studies of the variability of pulmonary cardiac output and stroke volume measurements using Doppler echocardiography.

M-mode echocardiographic measurements: The present results suggest that dimensional measurements from M-mode echocardiographs are highly reproducible. The size of the 95% confidence intervals for some of these measurements is actually close to the axial resolution of most modern imaging systems. Previous studies of the inter and intra observer variability of M-mode measurements have generally reported values of less than 5% (Clark et al. 1980, Ladipo et al. 1980, de Leonardis and Cinelli 1986, Szalachcic et al. 1986). Bullock et al. (1984) calculated the 95% confidence interval for a single measurement of left ventricular end-diastolic and end-systolic dimension to be ± 0.32 cm and ± 0.27 cm respectively. Half the within-subject variance was due to replication error while the other half was divided equally between cycle variation and interobserver variation. The smaller confidence interval reported in the present study may therefore be partly explained by the single observer and the measurement of 4 cycles. Kupari (1984) studied temporal variability by performing duplicate M-mode recordings at intervals ranging from 3 hours to 14-18 months. In all cases the variability of left ventricular cavity measurements, expressed as a coefficient of variation, was less than 4%. These results and those of Felner et al. (1980) and Clark et al. (1980) confirm the results of the present study suggesting that temporal variability contributes little to the overall variability of left ventricular cavity measurements. In contrast, Szalachcic et al. (1986) suggested that the

interstudy coefficient of variation of LAD was 20%. However these results were obtained in patients with aortic regurgitation and no other study has reported temporal variability in normal subjects.

The data concerning the variability of LV wall measurements are more conflicting. Interobserver variability of interventricular septal or LV posterior wall measurement, expressed as a coefficient of variation, has varied from 4.8% to 16.4% (Vignola et al. 1977, de Leonardis and Cinelli 1986). Kupari (1984) found the coefficient of variation for temporal variability to be <8% even when recordings were not repeated for 14-18 months. However, Monoson et al. (1978) reported that the interobserver difference for individual measurements of septal thickness may be as high as 4 mm and Bullock et al (1984) found the 95% confidence interval for a single measurement of LV posterior wall thickness was ± 0.23 cm. Measuring small dimensions does pose problems in terms of resolution and definition (Monoson et al. 1978). Estimation of TWT, by subtracting the diastolic cavity dimension from total LV dimension, overcomes some of these difficulties. This was reflected in the lower variability reported in the present study. Collins et al. (1989) studied the temporal variability of LV mass measurements in normal subjects on 3 occasions over a 5 month period. The 95% CI for the differences within an individual were 25 g. This compares with the present figure of 15 g for 2 measurements performed 1-3 months apart.

Fractional shortening and mean Vcf were found to be more reproducible than the peak rates of change of dimension. The percentage errors for FS and mean Vcf reported here are very similar to the temporal coefficients of variation reported by Kupari (1984). Clark et al. (1980) found temporal variability to be slightly higher (coefficient of variation 9.7%) but of similar magnitude to measurement variability (11.6%). Bullock et al. (1984) also noted the poor reproducibility of digitized measurements of left ventricular peak rates of dimensional change. Their 95% confidence interval for a single measurement was ± 2.6 cm/sec in systole and ± 6.5 cm/sec in diastole. They found the largest variance component was related to replication and this probably accounts for the large residual component found in the present study. Performing more replicates would have reduced this component of variability but obviously would have increased the analysis time.

6.5 Summary

The temporal variability of Doppler, cross-sectional and M-mode echocardiographic measurements was studied in 14 non-pregnant and 10 pregnant women. For all variables the between subject variability was significantly greater than the within subject variability and there was no significant difference between the variability of measurements performed 30-60 minutes and 1-3 months apart. With the exception of peak rates of change of LV and posterior wall dimension, the mean percentage error for all other variables was less than 8%. Comparable values were obtained in pregnant subjects. Measurements of flow from the aortic, mitral and pulmonary valves were equally reproducible and temporal variability was comparable to the inter and intra observer variabilities reported by previous workers. These results suggest that when recordings are made by one skilled echocardiographer, from women who are good echocardiographic subjects, the majority of echocardiographic measurements are highly reproducible. For a particular variable, changes greater than the 95% confidence interval cannot be explained by measurement variability and they are therefore likely to represent a true haemodynamic change.

CHAPTER 7

HAEMODYNAMIC CHANGES DURING SINGLETON PREGNANCY

7.1 Introduction

Having demonstrated that accurate and reproducible measurements of CO could be obtained using cross-sectional and Doppler echocardiography, these methods were systematically applied to women prior to and throughout normal pregnancy. Furthermore, as M-mode echocardiography appeared to provide reproducible measurements of cardiac chamber dimensions and left ventricular thickness and function, it was planned to record simultaneous M-mode echocardiographs in the same group of women to try and elucidate some of the structural and functional adaptations that may underlie changes in CO during pregnancy.

7.2 Subjects

Using the variance obtained from measurements performed during Study 4 (Chapter 8) it was calculated that 10 subjects would be necessary to be sure (probability = 0.95, β = 0.05) of determining a difference in CO of 1 l/min as being significant at the 5% level (2α = 0.05). To allow for conception and abortion rates, seventeen healthy women with regular menstrual cycles were recruited prior to conception. None of the subjects had used a hormonal method of contraception for at least 2 months and none smoked. One of the women was excluded because she was a poor echocardiographic subject and 2 others failed to conceive. Thirteen of the remaining fourteen had an uneventful pregnancy and delivered a liveborn infant of normal birthweight at term. The details of this group are shown in Table 7.1. Serial haemodynamic changes were investigated in these thirteen subjects.

Investigations were performed on the 21st day of 2 consecutive menstrual cycles and the mean value used as the pre-pregnant control value for future comparison. Women were asked to provide a specimen of urine for human chorionic gonadotrophin estimation (β Stat, Alpha Laboratories) if their menstrual periods were delayed by 3 days. Investigations were repeated as soon as possible after conception was confirmed (mean 35, range 31-40 days after the last menstrual period) and then monthly from 8 weeks till 36 weeks of pregnancy. The final investigation during pregnancy was performed at 38 weeks of pregnancy. Investigations were repeated 6 months after delivery. Ultrasonic measurement of biparietal diameter at 16-18 weeks of pregnancy confirmed the menstrual dates in all cases.

Age (years)		28 (3)
Height (m)		1.62 (0.06)
Weight (Kg)		59.6 (7.9)
Parity;	Nulliparous	6
	Multiparous	7
Gestation at Delivery (w)		40.3 (1.0)
Mode of Delivery;	Normal	11
	Caesarean section	2
Birthweight (Kg)		3.67 (0.28)
Mode of Feeding;	Breast	9
	Bottle	4
Contraception;	Combined pill	5
	Progestogen-only pill	3
	IUCD	2
	None	3

Figures are mean (SD)

Table 7.1 Subject details.

7.3 Results

7.3.1 Cross-sectional and Doppler Echocardiographic Results

Serial cross-sectional and Doppler echocardiographic measurements were obtained from all 3 sites in all subjects. Measurements of CO from the aortic, mitral and pulmonary sites correlated closely (r = 0.91-0.93, residual standard deviation 409-454 ml/min).

Cross-sectional and Doppler echocardiographic results are shown in Table 7.2. Aortic, mitral and pulmonary valve CSA's increased during pregnancy. The increases were statistically significant by 12 weeks gestation and maximum values were attained between 32 and 38 weeks. These changes represent increases above pre-pregnant values of 12 to 14%. There was no statistically significant change in any of the valve areas between 28 and 38 weeks. Aortic, mitral and pulmonary VI's increased during the first half of pregnancy, the increases being statistically significant by 8 weeks. Maximum values were attained between 16 and 20 weeks. These changes represent increases above pre-pregnant values of 21 to 22%. Following this the VI's all decreased and the differences between the peak values and those obtained at 38 weeks of pregnancy were statistically significant for all 3 sites. However the values obtained at the end of pregnancy remained statistically greater than the respective pre-pregnant values.

The results of HR and calculated Doppler SV and CO are shown in Table 7.3. Heart rate was increased by 5 weeks of pregnancy. The increase continued till 32 weeks and thereafter there was no further statistically significant change. This represents an increase above pre-pregnant values of 17%. The pattern of change in SV and CO was consistent for the 3 measurement sites. Stroke volumes were increased by 8 weeks and maximal values were attained by 20 weeks of pregnancy. This increase was then maintained till 38 weeks; the slight fall recorded during this period was not statistically significant for any of the measurement sites. Cardiac outputs were increased by 5 weeks after the last menstrual period and by 12 weeks gestation CO was 34 to 39% above pre-pregnant values. The increase continued to 24 weeks by which time CO was increased by 43 to 48%. This augmented CO was then maintained till 38 weeks. Maximum values for CO were obtained after the 24th week at each site, representing maximal increases of 48 to 50%. The maximum difference (0.25 l/min) between any two time points during the period 24 to 38 weeks for any of the measurement sites was not statistically significant. Individual values of CO for the 13 subjects are shown in Figure 7.1.

	Aortic		Mitral		Pulmonary	
	CSA (cm^2)	VI (cm)	CSA (cm^2)	VI (cm)	CSA (cm^2)	VI (cm)
Pre-pregnancy	3.66	18.1	6.44	10.2	6.21	10.5
Pregnancy (w)						
5	3.69	18.7	6.49	10.6	6.26	10.7
8	3.79	20.3	6.62	11.6	6.38	11.8
12	3.89	21.2	6.73	11.9	6.50	12.0
16	3.90	22.1	6.79	12.3	6.58	12.5
20	4.00	21.9	6.95	12.3	6.55	12.7
24	4.05	21.4	7.13	12.0	6.67	12.4
28	4.05	21.0	7.18	11.8	6.74	12.2
32	4.16	20.4	7.21	11.5	6.89	11.9
36	4.16	20.2	7.22	11.4	6.96	11.7
38	4.15	20.2	7.18	11.5	6.97	11.7
Postnatal	3.58	19.2	6.33	10.3	6.03	10.9
SEM	0.04	0.4	0.07	0.1	0.07	0.1
SR	0.17	1.2	0.28	0.5	0.29	0.6

Table 7.2 Cross-sectional and Doppler echocardiographic results; flow area and velocity integral.

		Aortic		Mitral		Pulmonary	
	HR (beats/min)	SV (ml)	CO (l/min)	SV (ml)	CO (l/min)	SV (ml)	CO (l/min)
Pre-pregnancy	75	65.8	4.88	65.1	4.89	65.4	4.88
Pregnancy (w)							
5	79	68.6	5.40	68.6	5.44	67.0	5.31
8	80	76.9	6.12	76.6	6.15	75.4	6.16
12	83	82.8	6.72	80.0	6.66	78.1	6.52
16	83	86.3	7.09	83.4	7.01	82.6	6.91
20	83	87.2	7.11	85.4	7.11	83.3	6.98
24	84	86.5	7.21	84.0	7.22	83.0	6.95
28	85	85.1	7.18	84.7	7.15	82.2	7.00
32	88	84.7	7.33	82.5	7.19	81.7	7.12
36	88	84.0	7.34	82.1	7.17	81.4	7.13
38	87	83.6	7.22	82.7	7.14	82.2	7.19
Postnatal	73	68.4	5.00	65.4	4.87	65.5	4.81
SEM	1	1.3	0.11	1.3	0.10	1.3	0.11
SR	5	5.3	0.46	5.7	0.44	5.3	0.47

Table 7.3 Cross-sectional and Doppler echocardiographic results; heart rate, stroke volume and cardiac output.

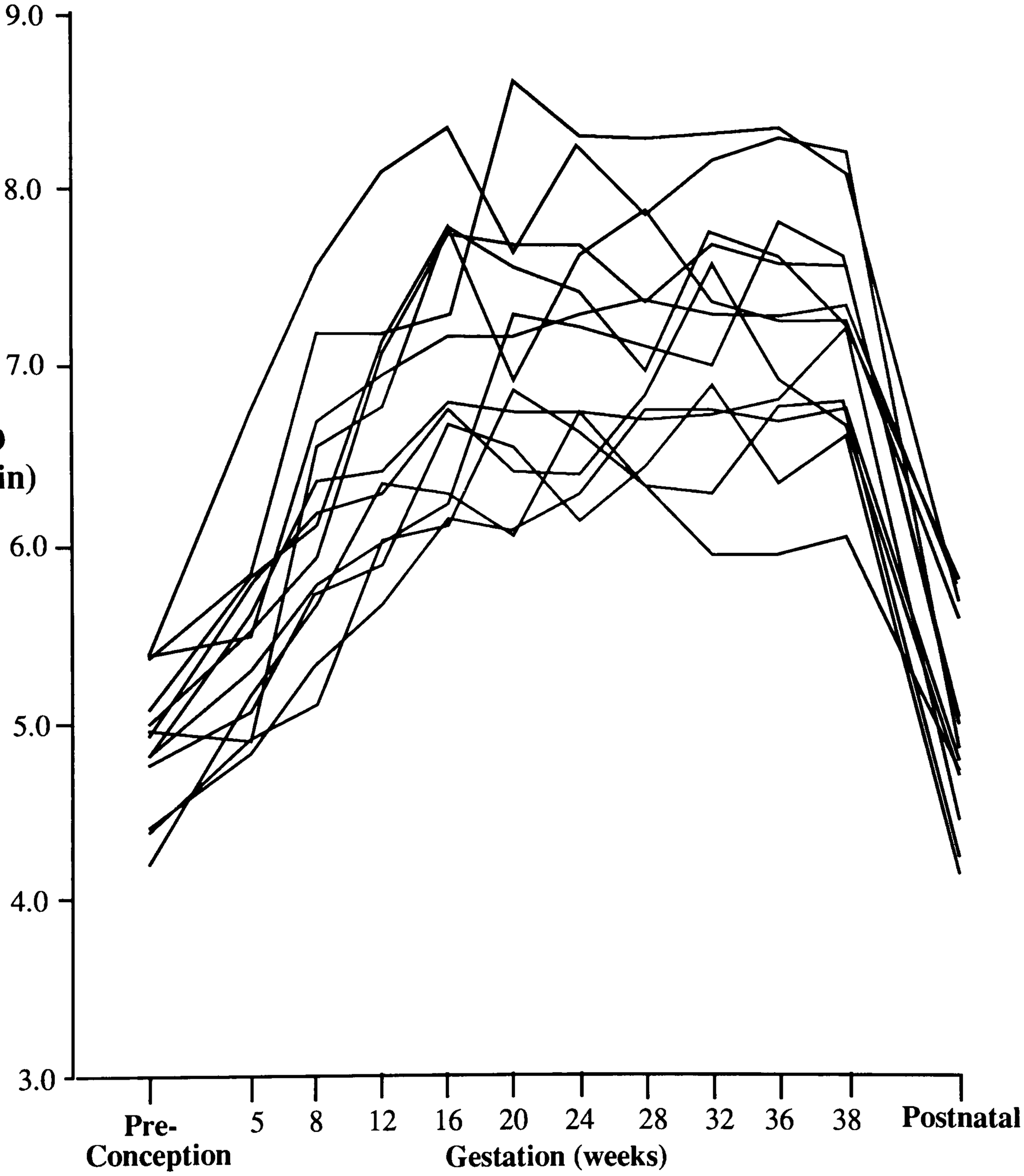


Figure 7.1 Changes in mean Doppler cardiac output in 13 subjects studied serially from prior to conception throughout pregnancy to 6 months postnatally

7.3.2 M-mode Echocardiographic Results

Satisfactory M-mode echocardiographs were obtained in all subjects throughout pregnancy. The results of left atrial and LV dimensions and LV mass are shown Table 7.4. Left ventricular ESD remained relatively unchanged till 38 weeks of pregnancy when there was a small but statistically significant increase relative to pre-pregnant values. Left ventricular EDD was increased above pre-pregnancy values by 12 weeks. The increase continued till 24 weeks and thereafter EDD remained relatively constant till term. This represents an increase of 7% above pre-pregnancy values. Left atrial dimension was increased by 12 weeks of pregnancy. Maximal values were reached at 28 weeks and thereafter there was no further change. This represents an increase during pregnancy of 16%. Left ventricular TWT and mass were both increased by 12 weeks. Thereafter there was a progressive increase in both parameters throughout pregnancy. At 38 weeks TWT was increased by 28% and LV mass by 52% above pre-pregnant values.

The changes in M-mode indices of LV function are shown in Table 7.5. The pattern of change was consistent for all the indices measured. Fractional shortening, mean Vcf and LVID and LVPW peak systolic dD/dt were all increased by 8 weeks. There was no statistically significant change in any of these parameters between 12 weeks and 28 to 32 weeks but thereafter all measurements fell. The decrease from maximum values was statistically significant for each index of ventricular performance except mean Vcf. However the values at 38 weeks remained statistically significantly above those found prior to pregnancy. The LVID and LVPW peak diastolic dD/dt were increased by 12 weeks. Maximum values were attained at 24 weeks and unlike peak systolic rates there was no subsequent fall.

There was no statistically significant difference between the pre-pregnancy and postnatal values for any of the echocardiographic variables studied.

	ESD (cm)	EDD (cm)	LAD (cm)	TWT (cm)	LV mass (g)
Pre-Pregnancy	2.90	4.49	3.12	1.48	120
Pregnancy (w)					
5	2.86	4.51	3.13	1.52	124
8	2.84	4.60	3.29	1.54	127
12	2.88	4.66	3.31	1.59	137
16	2.87	4.69	3.32	1.61	141
20	2.87	4.72	3.43	1.66	149
24	2.93	4.77	3.49	1.69	157
28	2.95	4.79	3.56	1.74	165
32	2.94	4.76	3.62	1.78	166
36	3.02	4.79	3.63	1.85	179
38	3.04	4.78	3.63	1.89	183
Postnatal	2.88	4.52	3.28	1.55	126
SEM	0.03	0.03	0.05	0.03	3
SR	0.14	0.12	0.20	0.10	15

Table 7.4 M-mode echocardiographic results; left atrial dimension and left ventricular dimensions and mass.

	FS (%)	Mean Vcf (Circ/sec)	dD/dt (cm/sec)			
			LVID		LVPW	
			Systole	Diastole	Systole	Diastole
Pre-Pregnancy	35.4	1.22	7.8	12.2	4.0	8.9
Pregnancy (w)						
5	36.6	1.32	8.3	13.3	4.4	9.3
8	38.0	1.39	9.4	13.8	4.8	10.0
12	38.2	1.40	9.6	14.4	5.2	10.5
16	38.8	1.40	9.5	14.8	5.3	10.8
20	39.2	1.39	10.1	17.0	5.3	11.5
24	38.6	1.40	10.7	17.7	5.5	11.8
28	38.4	1.39	10.3	17.2	5.3	11.9
32	38.2	1.41	10.3	17.5	5.2	11.7
36	37.0	1.36	9.6	16.1	4.8	10.8
38	36.4	1.35	9.7	15.8	4.7	10.8
Postnatal	36.2	1.28	7.9	12.8	4.0	8.0
SEM	0.3	0.04	0.4	0.5	0.2	0.4
SR	1.0	0.10	1.0	2.1	0.6	1.7

Figure 7.5 M-mode echocardiographic results; Indices of left ventricular function.

7.3.3 Blood Pressure and Total Systemic Resistance Results

Blood pressure and TSR results are shown in Table 7.6. The values of mean Doppler CO used to calculate TSR are also shown. Systolic BP remained relatively constant until 36 weeks gestation when there was a slight rise. This was maintained at 38 weeks gestation. Diastolic BP fell during the first half of pregnancy, reaching statistical significance at 20 weeks. Thereafter, there was a progressive increase, and by 38 weeks diastolic BP was significantly higher than preconception values. The net effect on TSR was a progressive fall until 20 weeks of pregnancy. This decrease was statistically significant by 5 weeks gestation. During the second half of pregnancy, TSR showed a small but statistically significant increase. There was no statistically significant difference between the pre-pregnancy and postnatal values for BP or TSR.

	Mean Doppler CO (l/min)	**BP** (mm Hg) Systolic	Diastolic	**TSR** (Dyne sec-1 cm-5)
Pre-Pregnancy	4.88	108	67	1326
Pregnancy (w)				
5	5.38	109	66	1213
8	6.15	107	63	1052
12	6.61	106	64	943
16	7.01	107	63	893
20	7.06	105	62	875
24	7.13	108	65	902
28	7.11	109	65	904
32	7.21	110	67	908
36	7.21	114	71	966
38	7.19	114	72	966
Postnatal	4.89	108	64	1295
SEM	2	1		22
SR	7	5		95

Table 7.6 Mean Doppler cardiac output, blood pressure and total systemic resistance results.

7.4 Discussion

The changes demonstrated in each variable during this study are greater than the corresponding 95% confidence intervals reported in Study 2. Thus the changes are unlikely to be due to measurement variability and are likely to represent genuine haemodynamic alterations during pregnancy.

The value of mean non-pregnant CO (4.9 l/min) is within previously published normal ranges for resting CO derived from invasive measurements (Barratt-Boyes et al. 1958, Spiller and Webb-Peploe 1985). Clark et al. (1989) reported a mean non-pregnant CO (measured by thermodilution at 11-13 weeks postpartum) of 4.3 l/min. This value is less than the mean reported in the present study and indeed is below most published normal ranges (Wade and Bishop 1962). Few studies using reliable invasive methodology have reported CO measurements in the lateral position in resting pregnant women. Wallenburg (1988) reported thermodilution measurements in 7 healthy women at between 28-34 weeks gestation. The mean cardiac index was 4.0 l/min/m^2 (stroke index 55 ml/m^2, HR 80 beats/min). Assuming a body surface area of 1.74 m^2 in the third trimester (Katz et al. 1978), this is equivalent to a CO of 7.0 l/min and SV of 96 ml. Clark et al. (1989), using similar methodology, reported a lower mean CO of 6.2 l/min (SV 75 ml, HR 83 beats/min) in 10 women between 36-38 weeks gestation. Pivarnik et al. (1990) measured CO using the direct Fick method in 7 primigravidae at 37 weeks gestation. The mean CO in this study was 6.8 l/min (SV 79 ml, HR 86 beats/min). The results from the present study are comparable with those of Wallenberg (1988) and Pivarnik et al. (1990) and slightly higher, but not statistically different from, those of Clark et al. (1989). Thus CO measured by the Doppler method appears to give results consistent with previous invasive studies. The values of Doppler CO recorded at the end of pregnancy are also in close agreement with those reported in other studies by the author (Robson et al. 1987, Robson et al. 1989a&b, Robson et al. 1990).

The present results suggest that haemodynamic changes begin very early in pregnancy. Cardiac output was increased by 5 weeks after the last menstrual period and this increase continued throughout the first trimester, such that by 12 weeks gestation CO was 1.6-1.8 l/min (34-39%) above pre-pregnant values. This is the earliest reported change in CO. Atkins et al. (1981a) demonstrated a statistically significant increase in CO by 12 weeks gestation when CO was 18% above the pre-pregnant mean. This change was entirely due to an increase in HR. In their study pre-pregnant CO was 6.5 l/min. This is substantially higher than the corresponding value found in the present study and also considerably higher than the non-pregnant values reported in non-pregnant women using the direct Fick and dye dilution methods (Wade and Bishop 1962). This suggests that either their first measurement may have been falsely elevated by apprehension or perhaps more likely, in

view of the comparable values of non-pregnant HR, the impedance method systematically overestimated SV. Walters et al. (1966) reported an increase in CO, relative to postnatal values, of 32% at 8-11 weeks gestation. The statistical significance of this difference was not reported. In contrast to Atkins et al. (1981b), they found an increase in both HR and SV over this period. The present results would confirm their findings. Serial studies in which CO has been measured by M-mode echocardiography during the first trimester have reported conflicting results. Castillon et al. (1984) reported a 19% increase in CO, relative to postnatal values, at 9-16 weeks. Capeless and Clapp (1989) reported a significant increase in CO by 8 weeks gestation (pre-pregnancy 4.2 l/min, 8 weeks gestation 5.2 l/min). This change was due to an increase in SV, there being no significant change in HR. Other workers have found little change in CO during early pregnancy (Katz et al. 1978, Hirata et al. 1984, Matsunaga 1984, Mashini et al. 1987). A number of dye dilution studies have reported cross-sectional measurements of CO during the first trimester (Adams 1954, de Schwarcz et al. 1964, Roy et al. 1966). The change in CO ranged from -6% to +63% and similar inconsistencies were found for HR and SV.

Clapp (1985) serially studied morning heart rate in 10 women over conception. The mean increase was 7 beats/min at 4 weeks menstrual age and 8 beats/min at 8 and 12 weeks menstrual age. Interestingly, two studies have shown that HR changes during the menstrual cycle (Brehm 1953, Kelleher et al. 1986). Maximum values were recorded around Day 21 and this was followed by a decrease of around 5 beats/min in the days prior to menstruation (Brehm 1953, Kelleher et al. 1986). This fall in HR does not apparently occur if fertilisation occurs. Furthermore a continued increase in HR appears to be earliest haemodynamic change associated with pregnancy.

A number of investigators have measured CO, using techniques other than Doppler echocardiography, at monthly intervals from the beginning of pregnancy (Burwell et al. 1938, Adams 1954, Walters et al. 1966, Atkins et al. 1981a). The results of the present study agree with those reported by Burwell et al. (1938) and Adams (1954) who suggested CO attained its maximum by the beginning of the third trimester. This is also in agreement with other studies where investigations have been performed at less frequent intervals (Ueland et al. 1969, Mashini et al. 1987, Steegers et al. 1990). However, the results of two studies have suggested that maximal haemodynamic changes are found at the end of the first trimester (Walters et al. 1966, Atkins et al. 1981a). Walters et al. (1966) suggested that the increase found early in pregnancy may have been artefactual and that otherwise peak values for CO would have been attained later in the second trimester. Atkins et al.(1981a) were the only group to report an early peak in CO and a fall from 20 weeks of pregnancy.

Eleven previous studies have investigated serial changes in CO in the lateral position during pregnancy and the puerperium (Ueland et al.1969, Katz et al. 1978, Atkins et al.

1981a, Myhrman et al. 1982, Castillon et al. 1984, Hirata et al. 1984, Matsunaga 1984, Mashini et al. 1987, Milsom et al. 1988, Steegers et al. 1990). The time of maximum increase in CO ranged from 8-11 weeks to 33-39 weeks gestation. With the exception of the study of Milsom et al. (1988), impedance cardiographic studies have reported maximum CO values earlier in pregnancy (<28 weeks) than dye dilution (28-32 weeks) and M-mode echocardiographic studies (>34 weeks). The mean peak increases in CO, SV and HR during pregnancy, expressed as absolute and percentage changes from postnatal values, are shown in Table 7.7. Although the magnitude of these increases has varied considerably the mean values are comparable to those reported in the present study.

	Previous Studies		**Present Study**	
	Absolute	Percentage	Absolute	Percentage
CO (l/min)	2.0 (0.7 - 3.2)	40 (13 - 65)	2.3	46
SV (ml)	14 (-3 - 30)	20 (-3 - 40)	17	27
HR (beats/min)	13 (7 - 22)	20 (10 - 33)	12	17

Figures are mean (range) absolute and percentage differences from non-pregnant values.

Table 7.7 Average peak increase in cardiac output, stroke volume and heart rate during pregnancy: Comparison of the present results with those from 11 previous serial studies in which CO was measured in the left lateral position (Doppler echocardiographic studies are not included).

No significant changes were demonstrated in CO, SV or HR during the third trimester. This confirms the findings of a number of dye dilution (Pyorala 1966, Lees et al. 1967b), M-mode (Rubler et al. 1977, Matsunaga 1984, Mashini et al. 1987, Steegers et al. 1990) and impedance (Zemel et al. 1990) studies performed in the lateral position. Katz et al. (1978) and Milsom et al. (1988) are the only 2 groups who have reported a statistically significant increase in CO during the third trimester. In both studies this was primarily due to an increase in SV. However 4 studies have suggested that CO in the lateral position may fall during the third trimester, due primarily to a reduction in SV. In three of these studies SV was measured by impedance cardiography (Atkins et al. 1981a, Myhrmam et al.

1982, Kagiya et al. 1984). The limitations of this method have been discussed in Chapter 1. In the fourth study (Ueland et al. 1969) SV, measured by dye dilution, fell from 88 ml at 28-32 weeks to 69 ml at 38-40 weeks. This last value was actually less than the non-pregnant SV. Why these results should be so different from other dye dilution studies is unclear.

Two previous studies have reported serial Doppler measurements of CO during pregnancy (Caton et al. 1987, Easterling et al. 1990c). Caton et al. (1987) studied 10 women at different intervals during pregnancy. Results were compared with 14 non-pregnant measurements (10 from non-pregnant controls and 4 postnatal measurements). Mean CO (estimated from their graph) increased from 5.3 l/min to a peak of 7.0 l/min at 30 weeks gestation. Thereafter CO appeared to fall slightly to approximately 6 l/min at term however no statistical analysis was carried out. Data on SV and HR were not reported. Easterling et al. (1990c) studied 89 normal pregnant women at 1-4 weekly intervals during pregnancy and then again at 6 weeks after delivery. The first investigations were performed at 10-13 weeks gestation but all subjects were not studied at each time point (numbers varied from 19 subjects at 10-13 weeks to 83 subjects at 30-33 weeks). Mean CO (estimated from their graph) increased from 5.5 l/min to a peak of 7.7 l/min at 34 weeks. This represents an increase above non-pregnant values of 40% which is similar to that reported in the present study. Values for SV and HR were not reported although the authors comment that SV rose steadily to a maximum of 96 ml at 31 weeks gestation. From 34 weeks until the last measurement prior to delivery CO fell by 0.5 ± 1.3 l/min. During this period 29% of subjects showed a fall in CO of at least 1.0 l/min while 9% showed an increase of at least 1.0 l/min. The fall in CO was apparently related to a reduction in SV although mean values during late pregnancy were not reported. In an earlier cross-sectional study designed to investigate the haemodynamic effects of orthostatic stress (Easterling et al. 1988), the same group reported a mean SV at 37 weeks gestation (range 35-40) of 82 ml (corresponding values of CO and HR were 6.7 l/min and 84 beats/min respectively). These values are very similar to those recorded at 38 weeks gestation in the present study. Thus the only difference between the present results and those of Easterling et al. (1990c) appears to be that their values of SV at the beginning of the third trimester are approximately 10 ml higher.

While a consistent fall in SV during the second half of pregnancy was evident in the present study, this did not reach statistical significance at any of the measurement sites. However the study was not designed to investigate small changes in SV and CO during the third trimester. The much larger study of Easterling et al. (1990c) would however suggest that SV does fall during the latter part of the third trimester. This fall appears to be at least partly countered by an increase in HR such that while CO may fall slightly during late pregnancy, this is unlikely to be of haemodynamic significance.

McLennan et al. (1987) reported a serial study of Doppler aortic VI during pregnancy. The results from 45 normal pregnancies were compared with 42 non-pregnant controls. Velocity integral increased from a non-pregnant mean of 29 cm (estimated from their graph) to a maximum of about 34 cm at 16 weeks gestation. Thereafter VI fell and by term there was no significant difference compared with non-pregnant values. Although the pattern of change in VI during pregnancy is very similar to that reported here, the absolute values are widely disparate. Relatively few studies have reported data on the normal non-pregnant aortic VI, measured by CW Doppler. Gisvold and Brubakk (1982) reported the mean VI in a group of women aged 20-40 years to be 19.2 cm. Gardin et al. (1984) studied men and women, between 20-33 years of age, and reported a mean of 19 cm. Salamasi et al. (1987) measured VI in a large group of men and women between 18-67 years of age. Mean VI was 21.9 (SD 4.8) cm. The slightly greater values of VI obtained by Salmasi et al. are due to the fact that they used a triangular approximation method for determining VI. This has been shown to overestimate the area of the waveform by 10-25% (Sequeira et al. 1976). Thus the non-pregnant data on VI from the present study are comparable with these results and suggest the possibility of a systemic overestimation of VI by McLennan et al. (1987).

The changes in CO described in the present study were associated with a number of structural and functional changes in the heart. The increase in valve orifice areas reported here are consistent with previous studies of the aortic (Katz et al. 1978, Hart et al. 1987) and tricuspid (Limacher et al. 1985) valves. This is an important finding in view of the recent interest in Doppler aortic minute distance (velocity integral x heart rate) which has been reported to reflect changes in CO in the non-pregnant state (Haites et al. 1985). Using this parameter in pregnancy (McLennan et al. 1987) is likely to underestimate changes in CO because no account is made of the changes in valve orifice area.

The non-pregnant M-mode echocardiographic measurements were comparable to previously reported normal values (Quinones et al. 1974, Henry et al. 1980, Voogd et al. 1984). Left atrial dimension and LV EDD increased during the first and second trimesters and thereafter remained relatively constant. Similar increases in LAD and EDD have been reported by other workers (Rubler et al. 1977, Katz et al. 1978, Laird-Meeter et al. 1979, Arima 1982, Hirata et al. 1984, Castillon et al. 1984, Steegers et al. 1990) although in these studies the increase in EDD was not evident till the second trimester. Capeless and Clapp (1989) in the only other study in which women were recruited prior to conception, also reported a progressive increase in EDD during the first 24 weeks (no measurements were performed after this). Interestingly they reported an increase in end-diastolic volume (calculated from EDD) by 8 weeks gestation. In the present study LV ESD was increased at term. This confirms the findings of Katz et al.(1978) and Arima (1982) but not those of other workers who reported no significant change in ESD during pregnancy (Rubler et al. 1977, Laird-Meeter et al. 1979, Hirata et al. 1984, Castillon et al. 1984). However in all of these latter studies measurements were performed before 38 weeks gestation. The

significant increase in ESD, relative to pre-pregnant values, was only evident at 38 weeks in the present study.

Measurements of LV TWT and mass suggest the possibility that pregnancy is associated with myocardial hypertrophy. Electrocardiographic studies have failed to demonstrate electrical evidence of this (Carruth et al. 1981) but M-mode echocardiography is a more sensitive method of detecting left ventricular hypertrophy (Woythaler et al. 1983). Previous echocardiographic studies have shown conflicting results. Some have reported increases in left ventricular wall thickness or mass in pregnancy (Katz et al. 1978, Laird-Meeter et al. 1979) . Others have failed to confirm these findings (Rubler et al. 1977, Thompson et al. 1986). However Rubler et al. (1977) studied a different group of non-pregnant controls and Thompson et al. (1986) included no non-pregnant data.

All indices of ventricular systolic performance were found to increase early in pregnancy and thereafter remained relatively constant till the beginning of the third trimester when there was a small but significant decline. The present findings confirm a number of previous M-mode echocardiographic studies, performed with the subject in the lateral position, which have suggested that there is an increase in ventricular performance during the first two trimesters and a fall towards term (Laird-Meeter et al. 1979, Castillon et al. 1984). However some workers, using the same methodology, have suggested that the increased systolic performance is maintained throughout the third trimester (Rubler et al. 1977) while others have failed to demonstrate any significant change in M-mode ejection phase indices (Katz et al. 1978, Hirata et al. 1984, Thompson et al. 1986, Mashini et al. 1987). As discussed in Chapter 4, M-mode measurements of ventricular performance may not provide a reliable index of inherent myocardial contractility. Interpretation of these results is particularly difficult during pregnancy because changes in ventricular mass, heart rate, venous return (pre-load) and peripheral resistance (afterload) affect ejection phase indices. Fractional shortening (FS) and peak systolic rates of change of dimension are considerably less dependent on HR than mean rate of circumferential fibre shortening (mean Vcf) (DeMaria et al. 1979). The changes in mean Vcf demonstrated here however were considerably greater than could be accounted for by changes in HR alone (DeMaria et al. 1979). Fractional shortening and Vcf are relatively pre-load independent but are very sensitive to changes in afterload (Kass et al. 1987). Consequently the changes in ventricular performance during late pregnancy could simply reflect the changes in blood pressure.

Studies of systolic time intervals have also lent support to an increased inotropic state during pregnancy. Reductions in pre-ejection period and isovolumic contraction time have been reported during the first and second trimesters (Rubler et al. 1973, Burg et al. 1974, Cellina et al. 1983, Kagiya et al. 1984). Furthermore Burg et al. (1974) and Cellina et al. (1983) showed that, when serial measurements were performed in the lateral position, pre-

ejection period subsequently increased during the third trimester. These findings are in agreement with the present M-mode results. Clark et al. (1989) are the only group to have studied intrinsic left ventricular contractility during normal pregnancy. A small but statistically insignificant increase in left ventricular stroke work index was found in 10 normal women at 36-38 weeks pregnant. Meaningful comparisons of myocardial contractile state during pregnancy, requires that measurements are performed under constant loading conditions. These conditions cannot be achieved in the human during pregnancy.

The alterations in diastolic rates of change of dimension are more difficult to interpret. They may reflect increased diastolic filling due to an increase in venous return. This is supported by the close temporal relationship between changes in diastolic rates of change of dimension and EDD and LAD.

Blood pressure fell during the first half of pregnancy, reaching a nadir around 20 weeks gestation, and then progressively increased to term. This pattern confirms the findings of a number of previous serial studies (Schwarz 1964, MacGillivray et al. 1969, Katz et al. 1978, Atkins et al. 1981a, Mountquin et al. 1985, Mooney et al. 1990, Easterling et al. 1990c), all of which documented a nadir in both SBP and DBP between 16-20 weeks. Consistent with the present results the decrease in DBP has generally been greater than that recorded for SBP. With the exception of Atkins et al. (1981a) and Easterling et al. (1990c) both of whom reported an increase in SBP at term relative to postnatal values, all other studies have shown little difference between BP values at term and those in non-pregnant controls.

Substantial reductions in calculated TSR were evident during the first half of pregnancy and thereafter there was a small increase till term. Few of the serial studies of CO during pregnancy have reported resistance measurements. Capeless and Clapp (1989) reported a comparable reduction in TSR during the first half of pregnancy, the decrease being significant by 8 weeks. In the study of Easterling et al. (1990c) TSR fell to about 20 weeks gestation Values at this time were approximately 23% below those recorded postnatally. Thereafter TSR remained essentially constant until 32 weeks gestation when it increased towards non-pregnant values. Atkins et al. (1981a) reported a nadir in TSR at 16 weeks and then a return to non-pregnant values by term, This substantial increase in the second half of pregnancy reflects the marked reduction in CO during this time. Mashini et al. (1987) suggested that TSR fell up till 30 weeks gestation but they also confirmed the terminal increase. Similar findings were reported two cross-sectional dye dilution studies (Bader et al. 1955, Roy et al. 1966).

7.5 Summary

Cardiac output, measured in the left semi-lateral position, increased during the first half of human pregnancy. This increase was evident by 5 weeks after the last menstrual period and by 20 weeks gestation CO was 45% higher than pre-pregnancy values. The increase in CO was due to increases in both HR and SV. The changes in HR occurred slightly earlier than those in SV. However the magnitude of the increase in SV was proportionally greater. Associated with a reduction in BP, TSR decreased, reaching a nadir at 20 weeks gestation. During the second half of pregnancy CO remained relatively constant. This was associated with a further small increase in HR and a trend suggesting a possible small (and probably haemodynamically insignificant) reduction in SV. After 20 weeks gestation BP and hence TSR increased.

The changes in CO and TSR were associated with a number of structural and functional changes in the heart. Valve orifice areas together with LV wall thickness and mass increased throughout pregnancy. This latter finding suggests that pregnancy is associated with a degree of myocardial hypertrophy. Left atrial and left ventricular EDD's increased during the second trimester. These findings suggest that part of the increase in SV is related to increased diastolic filling. However the increase in ventricular systolic performance, evident from early in the first trimester, may also contribute to the increase in SV. Ventricular performance declined during the third trimester, possibly in response to the increased TSR.

CHAPTER 8

HAEMODYNAMIC CHANGES DURING THE PUERPERIUM

8.1 Introduction

The results of the previous study suggest that pregnancy is associated with dramatic structural and functional changes in the cardiovascular system. Furthermore all these adaptations appear to have regressed by 6 months after delivery. This study was designed to investigate the haemodynamic readjustments after delivery.

8.2 Subjects

Eighteen healthy women with uncomplicated singleton pregnancies were recruited at 38 weeks gestation from the antenatal clinic. One of the subjects was excluded because she was a poor echocardiographic subject and two subjects failed to attend for at least one postnatal investigation. The details of the remaining fifteen women who comprised the study group are shown in Table 8.1.

Investigations were performed during the 38th week of pregnancy and then 2, 6, 12 and 24 weeks after delivery. Women who had had a normal delivery were also studied on the second postnatal day. All of the women had an uncomplicated puerperium.

Age (years)		26 (3)
Height (m)		1.69 (0.07)
Weight* (Kg)		66.2 (6.3)
Parity;	Primigravidae	11
	Multigravidae	4
Gestation at Delivery (w)		40.6 (0.8)
Mode of Delivery;	Normal	10
	EBL (ml)	210 (75)
	Forceps	3
	EBL (ml)	366 (57)
	Caesarean section	2
	EBL (ml)	500 (70)
Birthweight (Kg)		3.48 (0.33)
Mode of Feeding;	Breast	11†
	Bottle	4
Contraception;	Combined pill	3
	Progestogen-only pill	7
	IUCD	3
	None	2

Figures are mean (SD)
* Weight at 6 months postpartum, † 7 still breast feeding at 24 weeks.
Abbreviations; EBL, estimated blood loss

Figure 8.1 Subject details.

8.3. Results

There were no statistically significant differences in any of the variables between the normal and 'abnormal' delivery groups at 38 weeks of pregnancy and 2,6,12 and 24 weeks after delivery. The results for the whole group are therefore presented together. The results from the second postnatal day in the normal delivery group are presented separately.

8.3.1. Cross-sectional and Doppler Echocardiographic Results

Serial cross-sectional and Doppler echocardiographic measurements from the aortic and pulmonary valves were obtained in all subjects. Good quality mitral velocities could not be obtained in 4 subjects. Measurements of CO from the aortic, mitral and pulmonary sites correlated closely (r = 0.91-0.92, residual standard deviation 419-502 ml/min).

Cross-sectional and Doppler echocardiographic results are shown in Tables 8.2 and 8.3. Aortic, mitral and pulmonary CSAs decreased after delivery. The decreases were all statistically significant by the 12th puerperal week. These changes represent decreases below pregnant values of 9 to 12%. There was no statistically significant change in any of the valve areas between 12 and 24 weeks.

Aortic, mitral and pulmonary VI's decreased after delivery. These decreases were statistically significant by 12 weeks for the mitral and pulmonary valves and by 24 weeks for the aortic valve. The changes at 24 weeks after delivery represent decreases below pregnant values of 8 to 13%.

The results of HR and calculated Doppler SV and CO are shown in Table 8.3. Heart rate was decreased by 2 weeks after delivery. Thereafter there was no further change. This represents a decrease below pregnant values of 21%.

The pattern of change in SV and CO was consistent for the 3 measurement sites. Stroke volumes were decreased by 2 weeks after delivery and a further fall was evident between the second and 24th weeks. Values at 24 weeks were 17 to 19% below those obtained in late pregnancy. Cardiac outputs decreased by between 27 and 29% during the first 2 weeks after delivery. Thereafter there was a more gradual decline to minimum values at 24 weeks of between 32 and 34%. The decrease between 2 and 24 weeks was statistically significant for the aortic valve only. Individual values of CO for the 15 subjects are shown in Figure 8.1.

	Aortic		Mitral		Pulmonary	
	CSA (cm^2)	**VI** (cm)	**CSA** (cm^2)	**VI** (cm)	**CSA** (cm^2)	**VI** (cm)
Pregnancy (w)						
38	4.44	20.0	7.58	11.7	7.16	12.2
Postnatal (w)						
2	4.33	18.7	7.26	11.0	7.19	11.2
6	4.22	19.0	7.22	11.2	6.96	11.6
12	4.05	19.4	6.89	11.0	6.68	11.1
24	3.97	18.4	6.69	10.8	6.61	10.6
SEM	0.05	0.4	0.08	0.2	0.08	0.2
SR	0.21	1.5	0.30	0.7	0.30	0.8

Table 8.2 Cross-sectional and Doppler echocardiographic results; flow area and velocity integral.

		Aortic		Mitral		Pulmonary	
	HR	**SV**	**CO**	**SV**	**CO**	**SV**	**CO**
	(beats/min)	(ml)	(l/min)	(ml)	(l/min)	(ml)	(l/min)
Pregnancy (w)							
38	87	88.3	7.60	88.5	7.21	87.1	7.44
Postnatal (w)							
2	69	80.7	5.56	79.9	5.13	80.0	5.43
6	67	80.3	5.35	80.1	5.27	81.4	5.36
12	67	78.4	5.21	76.6	5.03	74.1	5.00
24	69	73.4	5.02	72.5	4.93	70.3	4.93
SEM	2	1.7	0.13	1.9	0.14	1.7	0.15
SR	6	6.5	0.50	7.4	0.54	6.4	0.56

Table 8.3 Cross-sectional and Doppler echocardiographic results; heart rate, stroke volume and cardiac output.

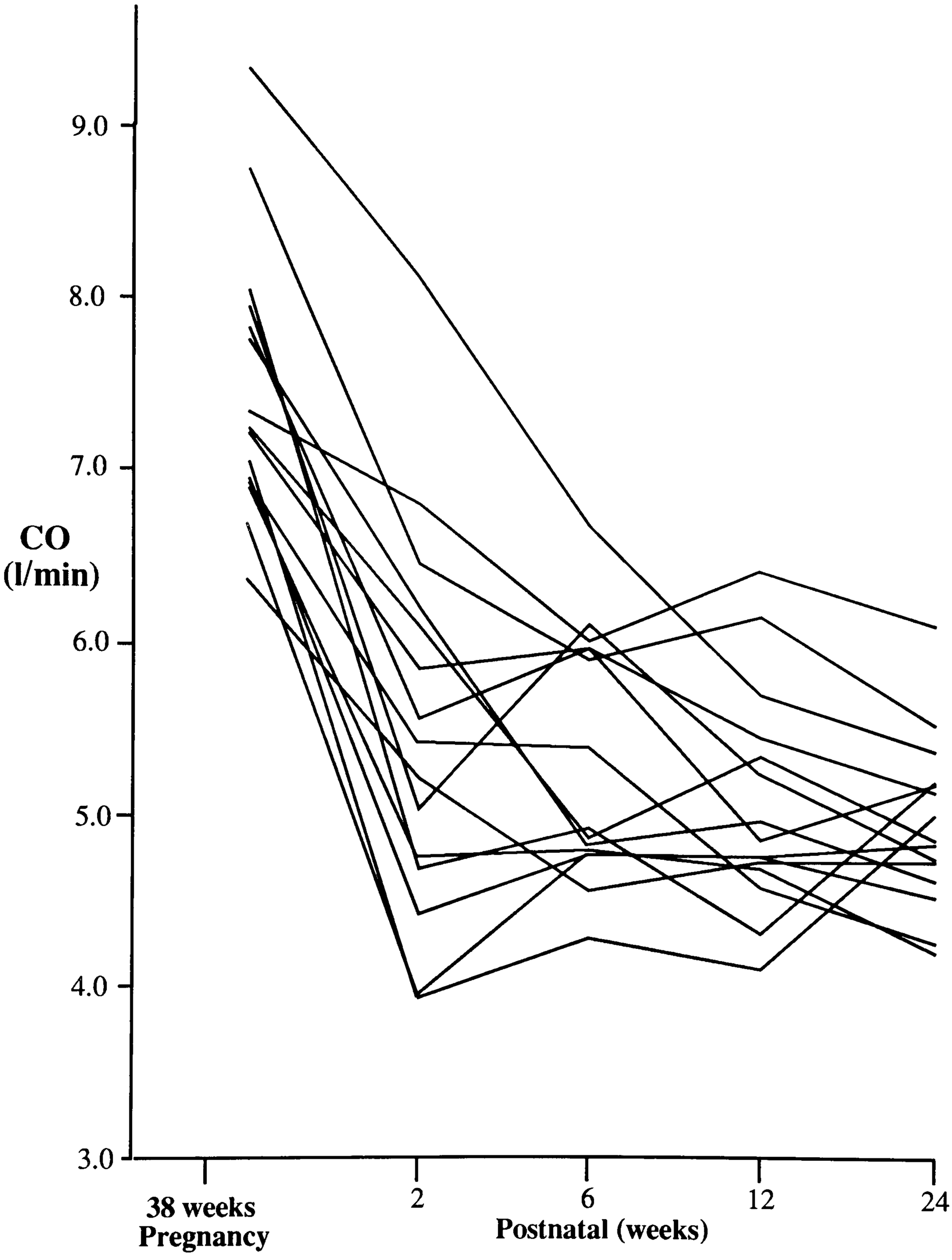


Figure 8.1 Changes in mean Doppler cardiac output in 15 subjects studied serially throughout the puerperium

8.3.2 M-mode Echocardiographic Results

Serial M-mode echocardiographic measurements were obtained in all subjects. The results of left atrial and LV dimensions and LV mass are shown in Table 8.4. Left ventricular ESD remained unchanged after delivery. Left ventricular EDD was significantly decreased by the sixth puerperal week. Thereafter no further statistically significant change was seen. The values at 24 weeks represent a decrease of 4% below pregnancy values. Left atrial dimension also declined after delivery, the difference being statistically significant by 2 weeks. By 24 weeks after delivery values were 11% below pregnancy values. Left ventricular TWT and mass both declined after delivery. The differences were statistically significant by 12 weeks for TWT and 6 weeks for LV Mass. Thereafter both showed a further decline to 24 weeks. These changes represent a reduction, relative to the end of pregnancy, of 16% and 23% respectively.

The changes in M-mode indices of LV function are shown in Table 8.5. The pattern of change during the puerperium was consistent for all the indices measured. Fractional shortening, mean Vcf, and LVID and LVPW peak systolic dD/dt were all decreased by 2w weeks after delivery. There was no statistically significant change in any of these parameters thereafter. The LVID and LVPW peak diastolic dD/dt showed a similar pattern of decline during the puerperium.

	ESD (cm)	EDD (cm)	LAD (cm)	TWT (cm)	LV Mass (g)
Pregnancy (w)					
8	3.22	4.86	3.74	2.01	203
Postnatal (w)					
2	3.30	4.75	3.42	1.97	191
6	3.23	4.72	3.45	1.94	182
12	3.22	4.68	3.36	1.81	167
24	3.17	4.67	3.33	1.69	157
SEM	0.03	0.03	0.06	0.03	4
SR	0.12	0.13	0.21	0.12	14

Table 8.4 M-mode echocardiographic results; left atrial dimension and left ventricular dimensions and mass.

FS	Mean Vcf		dD/dt (cm/sec)			
	(%)	(Circ/sec)	LVID		LVPW	
			Systole	Diastole	Systole	Diastole
Pregnancy (w)						
38	34.1	1.27	9.3	14.7	4.8	10.5
Postnatal (w)						
2	30.8	1.09	7.2	11.3	3.9	8.3
6	31.4	1.08	7.0	12.0	3.8	7.7
12	31.0	1.05	6.8	11.5	3.7	8.3
24	31.5	1.07	6.7	11.3	3.7	7.7
SEM	0.4	0.02	0.3	0.8	0.2	0.5
SR	1.4	0.08	1.1	2.8	0.7	2.0

Table 8.5 M-mode echocardiographic results; indices of left ventricular function.

8.3.3 Blood Pressure and Total Systemic Resistance Results

Blood pressure and TSR results are shown in Table 8.6. The values of mean Doppler CO used to calculate TSR are also shown. Systolic and diastolic BP remained unchanged during the first 12 postnatal weeks. Thereafter both values increased and at 24 weeks diastolic BP was significantly higher than values recorded at the end of pregnancy. Calculated TSR was increased by 2 weeks after delivery and there was a further statistically significant increase between 2 and 24 weeks.

Comparisons of the haemodynamic measurements between lactating and non-lactating women and between hormonal contraceptive users and non-users revealed no statistically significant differences in any of the variables.

	Mean Doppler CO (l/min)	**BP** (mm Hg) Systolic	Diastolic	**TSR** (Dyne sec-1 cm-5)
Pregnancy (w)				
38	7.42	102	63	831
Postnatal (w)				
2	5.42	101	65	1138
6	5.33	100	63	1135
12	5.09	98	64	1190
24	4.95	109	69	1325
SEM		2	1	30
SR		7	5	114

Table 8.6 Mean Doppler cardiac output, blood pressure and total systemic resistance results.

8.3.4. Early Haemodynamic Changes in the Normal delivery Group

With the exception of mitral velocities, which could not be recorded in 2 women, serial echocardiographic measurements were obtained in all 10 subjects. Cross-sectional and Doppler echocardiographic results together with BP and TPR results are shown in Table 8.7. No significant changes were found in valve CSA's 48 hours after delivery. Aortic VI was increased at this time, however no statistically significant change was found for mitral VI and pulmonary VI. Heart rate had decreased by the second day and although SV's showed a slight increase, these changes were not statistically significant. Cardiac output thus remained unchanged, relative to pregnancy values, 2 days after delivery. Blood pressure and TSR also remained unchanged.

M-mode echocardiographic results are shown in Table 8.8. The only statistically significant change at 48 hours after delivery was an increase in EDD.

	Pregnancy	Postnatal		SE	SR
	38 w	48 h	2 w		
Aortic CSA (cm^2)	4.45	4.35	4.26	0.06	0.24
Mitral CSA (cm^2)	7.58	7.43	7.22	0.09	0.35
Pulmonary CSA (cm^2)	7.02	7.04	7.03	0.09	0.35
Aortic VI (cm)	19.6	22.1	18.9	0.6	2.3
Mitral VI (cm)	11.5	12.1	10.8	0.2	0.9
Pulmonary VI (cm)	12.1	12.7	11.4	0.2	0.9
Heart Rate (beats/min)	86	75	64	2	8
Aortic SV (ml)	87.4	96.1	81.1	3.3	13.1
Mitral SV (ml)	87.5	90.0	79.0	2.2	8.9
Pulmonary SV (ml)	84.8	89.2	80.2	2.1	8.6
Aortic CO (l/min)	7.46	7.22	5.16	0.21	0.85
Mitral CO (l/min)	7.22	6.84	4.98	0.22	0.88
Pulmonary CO (l/min)	7.26	6.74	5.03	0.18	0.75
Systolic BP (mm Hg)	103	104	100	2	10
Diastolic BP (mm Hg)	63	60	66	2	8
TSR (Dyne sec-1 cm-5)	838	865	1215	35	140

Table 8.7 Cross-sectional, Doppler, blood pressure and total systemic resistance results in normal delivery group.

	Pregnancy	Postnatal		SE	SR
	38 w	48 h	2 w		
ESD (cm)	3.19	3.26	3.24	0.04	0.16
EDD (cm)	4.79	4.95	4.70	0.04	0.14
LAD (cm)	3.72	3.92	3.46	0.07	0.28
TWT (cm)	2.02	2.05	1.97	0.04	0.16
LV Mass (g)	203	214	192	6	23
FS (%)	33.6	34.1	30.8	0.6	0.23
Mean Vcf (Circ/sec)	1.26	1.19	1.08	0.08	0.30
LVID dD/dt (cm/sec)					
Systole	9.2	8.5	7.5	0.4	1.5
Diastole	13.9	12.1	11.5	0.8	3.3
LVPW dD/dt (cm/sec)					
Systole	4.8	4.4	3.9	0.2	0.9
Diastole	9.2	7.7	7.8	0.6	2.5

Table 8.8 M-mode echocardiographic results in normal delivery group.

8.4 Discussion

The values of CO at 38 weeks gestation and 6 months postpartum are comparable to those reported in Study 3 and in other studies reported by the author (Robson et al. 1987, Robson et al. 1989a&b). Stroke volumes were slightly higher in the present study ($p<0.05$) due to consistently greater valve CSA's. The absolute differences between CSA measurements obtained at the end of pregnancy and 6 months postnatally in Studies 3 and 4 were however comparable. Furthermore, all postnatal CSA measurements were within previously reported normal ranges for aortic CSA (Francis et al. 1975) and mitral CSA (Ormiston et al. 1981). Kolev et al. (1986) are the only other group who have reported pulmonary CSA in normal adults measured by cross-sectional echocardiography. Their mean CSA was lower than the values reported in the present studies. However pulmonary artery diameter was measured from a more distal site using an inner edge to inner edge technique. Values of pulmonary artery diameter, measured by an electrical stain-guage calliper at the time of open-heart surgery, are comparable with the present diameters (Greenfield and Griggs 1963). One possible explanation for the slightly higher CSA's of the women in Study 4, as compared to those in Study 3, is their increased height and weight (and therefore body surface area). Aortic CSA, measured by echocardiography, has been shown to correlate, albeit loosely, with body surface area (Henry et al. 1980).

The results of the present study suggest that the decrease in CO to non-pregnant values is virtually complete by the end of the second puerperal week. Previous studies in which CO was measured at the end of pregnancy and after delivery are shown in Table 8.9. Most workers have carried out postnatal measurements between the sixth and twelfth postnatal week. All have reported a decrease in CO (mean percentage change -25%, range -8% to -37%) and HR (mean percentage change -17%, range -10% to -25%) relative to measurements at the end of pregnancy. The changes in SV have been far more variable. Most studies in which CO was measured by dye dilution and impedance cardiography have shown no statistically significant change in SV (Ueland et al. 1969, Atkins et al. 1981a, Myhrman et al. 1982). In contrast most M-mode echocardiographic studies have reported a significant decrease in SV at 6-12 weeks (Katz et al. 1978, Maruta 1982, Hirata et al. 1984). Two groups of workers have performed serial measurements at the end of pregnancy and after delivery using reliable invasive methodology (Clark et al. 1989, Pivarnik et al. 1990). It is unclear from these reports whether some of the subjects were included in both studies. Significant reductions in CO, SV and HR were reported at 12 weeks after delivery (Table 8.9). Although CO's was slightly lower, the percentage reductions in CO, SV and HR were similar to those reported in the present study.

Six groups have performed serial measurements during the puerperium. (Walters et al. 1966, Atkins et al. 1981a, Matsunaga 1984, Milsom et al. 1988, Sady et al. 1990,

Author	n	Method	Pregnancy*			Postnatal			
			CO	SV	HR	Time	CO	SV	HR
Walters et al. (1966)†	30	Dye	6.2	79	79	0-11 d 2-17 w	5.7 (-8) 5.3 (-15)	81 (+3) 80 (+1)	72 (-8) 66 (-16)
Ueland et al. (1969)	11	Dye	5.7	69	83	6-8 w	5.0 (-12)	71 (+3)	70 (-16)
Katz et al. (1978)	19	M-M	8.6	97	88	6-12 w	5.4 (-37)	79 (-19)	69 (-22)
Castillon et al. (1984)	10	M-M	5.7	73	80	10 w	4.8 (-16)	69 (-5)	72 (-10)
Hirata et al. (1984)#	25	M-M	6.6	85	78	3 w	4.0 (-39)	63 (-26)	62 (-21)
Matsunaga (1984)	30	M-M	5.8			5 d 4 w	5.7 (-2) 4.8 (-17)		
Mashini et al. (1987)	7	M-M	5.5	64	88	7-10 w	4.2 (-24)	66 (+3)	66 (-25)
Steegers et al. (1990)#	23	M-M	5.7	72	80	6w	4.6 (-19)	67 (-7)	68 (-15)
Atkins et al. (1981a)#	8	IC	5.9	81	74	6 w 16-64w	5.4 (-8) 6.5 (+10)	93 (+15) 100(+23)	57 (-23) 68 (-8)
Myhrman et al. (1982)	14	IC	5.1	83	68	6-25 w	5.5 (+8)	90 (+8)	61 (-10)
Milsom et al. (1988)#	12	IC	7.9	96	82	3-5 d 12 w	6.6 (-16) 5.8 (-36)	86 (-10) 80 (-20)	78 (--5) 73 (-12)
Easterling et al. (1990c)#	89	Dopp	7.4			6 w	5.4 (-27)		
Sady et al. (1990)#	9	Acet	7.0	70	100	8 w 28 w	5.0 (-29) 4.8 (-31)	60 (-14) 56 (-20)	82 (-18) 88 (-12)
Clark et al. (1989)	10¶	TD	6.2	75	83	12 w	4.3 (-31)	60 (-20)	71 (-14)
Pivarnik et al. (1990)	7	Fick	6.8	79	86	12 w	4.3 (-37)	62 (-22)	70 (-19)
Present Study	15	Dopp	7.4	88	87	2 w 6 w 24 w	5.4 (-27) 5.3 (-28) 5.0 (-32)	80 (-8) 80 (-8) 72 (-18)	69 (-20) 67 (-23) 69 (-20)

* Last measurement during pregnancy, † position not defined & same subjects not investigated at each time point, # data taken from graphs, ¶ may contain 7 subjects studied by Pivarnik et al. (1990).
Figures in brackets are percentage changes relative to pregnancy values.

Abbreviations: Dye, dye dilution; M-M, M-mode echocardiography; IC, impedance cardiography; Dopp, Doppler; Acet, acetylene rebreathing; TD, thermodilution

Table 8.9 Previous serial studies of cardiac output in the lateral position during the puerperium.

Capeless and Clapp 1991). Walters et al. (1966) studied different women at varying times after delivery (ranging from 0-3 days to 14-17 weeks) and the results are therefore not truly serial. Atkins et al. (1981a) suggested that CO, SV and HR all increased between 6 weeks and 4-16 months after delivery although none of these changes appeared statistically significant. The authors commented that pre-pregnancy values of CO were attained by the last postnatal visit. The pattern of puerperal haemodynamic change reported by this group are markedly different from those reported in the present study. Furthermore the values of SV and CO recorded at 4-16 months after delivery are considerably higher than accepted normal values (Wade and Bishop 1962, Kennedy et al. 1966). Sady et al. (1990) performed acetylene rebreathing measurements before and during cycle exercise. Although mean CO's were very similar to those reported in the present study, the values of SV and HR were quite different (Table 8.9). Their results suggest that the acetylene technique systematically underestimated SV while resting HR was elevated, possibly in anticipation of exercise (Wade and Bishop 1962). Matsunaga (1984) and Milsom et al. (1988) both reported serial reductions in CO between 3-5 days and 12-24 weeks after delivery.

Capeless and Clapp (1991) recently reported an M-mode echocardiographic study in which 13 subjects were studied prior to conception and then 6 and 12 weeks after pregnancy. Breast feeding was continued throughout the puerperium in all subjects. Cardiac output was 4.3 l/min prior to conception, 4.6 l/min at 6 weeks and 4.9 l/min at 12 weeks after delivery. The value at 12 weeks was significantly greater than that recorded prior to pregnancy. Heart rate was unchanged throughout the study while SV was higher after delivery (68, 81 and 79 ml respectively). The values of puerperal SV were very similar to those reported in the present study. Based on these results and those of Study 3 it would appear that there may be a small decrease in SV between 12 and 24 weeks after delivery. It seems unlikely that this fall is related to the discontinuation of breast feeding since breast feeding does not affect puerperal CO (Robson et al. 1989c). The combined oral contraceptive has been shown to increase SV and CO (Walters and Lim 1969). The importance of this in relation to puerperal CO is uncertain. The number of women taking the combined pill was small in the present study and Capeless and Clapp (1991) did not report the contraceptive practices of their subjects.

Little data exist regarding haemodynamic measurements during the early puerperium. Walters et al. (1966) grouped their results from days 0-11 and reported an 8% fall in CO, due to a decline in HR. Inspection of their raw data shows that the mean CO's at 0-3, 4-7 and 8-11 days were 6.0, 5.7 and 5.5 l/min respectively. This would suggest that CO remains elevated for up to 72 hours after delivery. In a previous study investigating CO (measured at the pulmonary valve) during and after labour (Robson et al. 1987), the author found that CO at 24 hours after delivery was unchanged from that recorded prior to labour (7.08 vs. 6.99 l/min respectively). Matsunaga (1984) performed their first puerperal measurement on the 5th day and found values similar to those recorded at the end of

pregnancy suggesting that the elevation of CO is sustained for most of the first puerperal week. In order to ascertain the pattern of change during the early puerperium, the author conducted a further study in 30 women who had had a normal uncomplicated delivery (Robson et al. 1989a). Aortic CO was measured in the lateral position using CW Doppler. The results are summarized in Table 8.10. Values of CO, SV and HR at 38 weeks gestation and 2 weeks postnatally are comparable to those reported in the present study. The results suggest that CO starts to fall on the second puerperal day and this decline continues until middle of the second week.

	Pregnancy	Postnatal Day				
	(38 w)	1	2	6	10	14
HR (beats/min)	82	80	76	73	69	68
SV (ml)	87.5	90.7	88.8	82.4	79.4	78.5
CO (l/min)	7.20	7.15	6.74	6.00	5.39	5.30

Table 8.10 Serial measurements of cardiac output during the early puerperium (Robson et al. 1989a).

Coexistent with the reduction in CO, the structural and functional adaptations of the heart all regressed after delivery, confirming the results of Study 3. Valve orifice CSA's had all decreased by 12 weeks after delivery. Katz et al. (1978) measured aortic root diameter using M-mode echocardiography at 6-12 weeks postpartum. Their values were consistently larger but the change in aortic area after delivery was of similar order to that found in the present study (-14% versus -11%). The discrepancy in absolute size may be due to the measurement of aortic diameter at different sites. Diameters measured at the aortic root are considerably larger than those measured at the aortic orifice (Ihlen et al. 1984). More recently Hart et al. (1986), using a similar technique to Katz et al. (1978) reported a change in aortic area from 4.56 cm^2m^{-2} at the end of pregnancy to 3.49 cm^2m^{-2} at 3-6 months postpartum, a decrease of 23%. It is interesting to note that these authors found a smaller decrease in aortic area in primigravidae (8%), who made up the majority of the present study population. No data are available regarding changes in pulmonary artery and mitral orifice areas during and after pregnancy.

Interestingly the time course of the puerperal M-mode echocardiographic changes varied. The functional changes (LV EDD, LAD and the indices of ventricular function) regressed over a shorter period of time than the structural changes (LV TWT and mass). The values

of LV cavity dimensions and LAD were not significantly different from those reported in Study 3. Left ventricular EDD and LAD decreased during the first 6 postnatal weeks. Previous studies have only reported isolated puerperal measurements (3-12 weeks after delivery). All demonstrated a similar decrease in EDD and LAD (3-7% for EDD and 8-11% for LAD), consistent with the present results (Rubler et al. 1977, Katz et al. 1978, Hirata et al. 1984, Castillon et al. 1984, Steegers et al. 1990). None of these studies found a statistically significant change in ESD after delivery. Capeless and Clapp (1991) recorded left ventricular M-mode echocardiographs in a group of subjects prior to and then 6 and 12 weeks after pregnancy. Left ventricular EDD was not reported but LV end-diastolic volume, derived from the equation of Teichholz et al. (1976), was significantly increased at both 6 and 12 weeks postpartum. These findings suggest that EDD had not returned to non-pregnant values by 12 weeks after delivery. While these findings may not be consistent with those of the present study, a direct comparison cannot be made. The results of Study 3 however suggest that EDD had returned to pre-conception values by 24 weeks after delivery.

Left ventricular wall thickness and mass continued to decrease throughout the period of study. Both measurements were slightly higher in this study than in Study 3. This difference was evident at 38 weeks gestation ($p<0.05$) and at 6 months postnatally ($p<0.01$). The percentage decrease after delivery was however similar in the two studies. Smaller postnatal reductions in LV mass and posterior wall thickness have been reported previously (Katz et al. 1978, Laird-Meeter et al. 1979). However in both studies measurements were performed at between 6-12 weeks when the reversal of pregnancy-induced changes may not have been complete.

Fractional shortening and mean Vcf at 24 weeks postpartum were also slightly lower compared with the corresponding measurements in Study 3. While these differences are difficult to explain they are probably of little clinical significance. Certainly all late postnatal measurements were within previously reported normal ranges for healthy women (Quinones et al. 1974, Henry et al. 1980, Voogd et al. 1984). The reduction in ventricular performance reported in the present study confirms previous M-mode echocardiographic (Katz et al. 1978, Maruta 1982, Hirata et al.1984, Castillon et al. 1984) and systolic time interval (Rubler et al. 1973, Cellina et al. 1983, Kagiya et al. 1984) studies. Maruta (1982) reported a 6% fall in ejection fraction and a 13% fall in mean Vcf at 2 weeks after delivery. These changes are similar to those reported in the present study (4% and 14% respectively).

Serial data on BP changes during the puerperium are surprisingly sparse. Most of the work has been done on small numbers of subjects and isolated postnatal measurements have been made at 6-12 weeks. Some authors have found a slight increase in systolic BP relative to the end of pregnancy (MacGillivray et al. 1969, Katz et al. 1978), others have

found a slight decrease (Ihrman 1960a, Schwarz 1964, Atkins et al. 1981a, Myhrman et al. 1982). Only Atkins et al. (1981a) reported a statistically significant difference. Diastolic BP has generally been reported to fall slightly (Ihrman 1960a, Schwarz 1964, MacGillivray et al. 1969, Myhrman et al. 1984) although Katz et al. (1978) demonstrated a significant elevation at 6-12 weeks. No significant differences in BP were found between 38 weeks and 12 weeks post delivery in the present study. The increase in DBP between 12 and 24 weeks is unexplained. The increase did not appear to be related to lactation nor to the type of contraception used. The largest serial study of early puerperal BP was reported by the author (Robson et al. 1989a). Although a reduction in BP was found on the first and second postnatal days, values on days 6,10 and 14 were similar to values recorded at the end of pregnancy.

8.5 Summary

Cardiac output, measured in the left semi-lateral position, remained elevated 48 hours after normal delivery. Between 48 hours and 2 weeks CO fell substantially due to reductions in both HR and SV. Thereafter there was a further fall in SV such that by the 24th postnatal week CO was 32-34% below pregnancy values. Blood pressure remained essentially unchanged during the puerperium, apart from an increase in DBP between 12 and 24 weeks. As a result TSR was increased by 2 weeks after delivery and there was a further slight increase at 24 weeks.

The structural and functional changes in the heart also regressed after delivery. Left atrial and LV EDD's together with indices of ventricular systolic performance decreased during the first 6 postnatal weeks. The return of valve CSA's and LV wall thickness and mass to non-pregnant values took rather longer, being complete by 12-24 weeks. These changes suggest that the early reduction in SV may be related to a decrease in ventricular filling together with a decline in ventricular performance.

CHAPTER 9

HAEMODYNAMIC CHANGES DURING TWIN PREGNANCY

9.1 Introduction

Pregnancy is associated with profound alterations in maternal physiology. These alterations may be even more marked in twin pregnancy. The preceding two studies have shown the maternal cardiovascular adaptations during and after normal singleton pregnancy. This study was designed to determine the extent and timing of the cardiovascular changes during twin pregnancy.

9.2 Subjects

Using the variance obtained from measurements performed during Study 4 (chapter 8) it was calculated that 10 subjects would be necessary to be sure (probability = 0.95, β = 0.05) of determining a difference in CO of 1 l/min as being significant at the 5% level (2α = 0.05). Fifteen healthy women were recruited at 16-18 weeks gestation when twin pregnancy was identified on a routine ultrasound scan. Two women were excluded because they were poor echocardiographic subjects. Two other women were excluded because of complications during pregnancy; one developed proteinuric hypertension and the other developed polyhydramnios of one sac leading to delivery at 33 weeks gestation. One further subject failed to attend after delivery; thus 10 subjects were available for the complete study. The details of this group are shown in Table 9.1.

Age (years)		28 (4)
Height (m)		1.67 (0.07)
Weight (Kg)		62.6 (7.0)
Parity;	Nulliparous	6
	Multiparous	4
Gestation at Delivery (w)		37.6 (1.1)
Mode of Delivery;	Normal	6
	Caesarean section	4
Birthweight (Kg);	Twin I	3.12 (0.29)
	Twin II	3.02 (0.37)
Mode of feeding;	Breast	5
	Bottle	5
Contraception;	Combined pill	3
	Progestogen-only pill	2
	IUCD	1
	None	4

Figures are mean (SD)

Table 9.1 Subjects details.

Investigations were performed at 20 weeks gestation and then every 4 weeks until 36 weeks. The final measurements were carried out 6 months after delivery.

The data from the ten women with twin pregnancy were compared with the data from the 13 women with normal singleton pregnancy reported in Study 3.

9.3 Results

9.3.1 Cross-sectional and Doppler Echocardiographic Results

Serial cross-sectional and Doppler echocardiographic measurements were obtained from all 3 sites in all subjects. Measurements of CO from the aortic, mitral and pulmonary sites correlated closely (r = 0.87-0.95, residual standard deviation 368-477 ml/min).

Cross-sectional and Doppler echocardiographic results are shown in Table 9.2. Aortic, mitral and pulmonary CSA's were increased, relative to postnatal values, by 20 weeks gestation. There was a further increase in all CSA's between 20 and 36 weeks of pregnancy. These changes represent increases above postnatal values of 12 to 17%.

Aortic, mitral and pulmonary VI's were increased by 20 weeks gestation. Thereafter there was no further change in aortic and pulmonary VI. Mitral VI decreased between 20 weeks and 28-32 weeks gestation however the difference between 20 weeks and 36 weeks was not statistically significant. Maximum values of VI were attained between 20 and 28 weeks. These changes represent increases above postnatal values of 14-19%.

The results of HR and calculated Doppler SV and CO are shown in Table 9.3. Heart rate was increased by 20 weeks of pregnancy and thereafter there was no further change. Maximum values were recorded at 28-32 weeks gestation and represent an increase of 31% above postnatal values. The pattern of change in SV and CO was consistent for the 3 measurement sites. Stroke volumes and CO's were increased by 20 weeks gestation and thereafter there was no further statistically significant change. Maximum SV's were attained at 24 weeks gestation when the increase was 24-27% above postnatal values. Maximum CO's were attained at 24-28 weeks gestation when the increase was 59-62% above postnatal values. Individual values of CO in the 10 subjects are shown in Figure 9.1.

	Aortic		Mitral		Pulmonary	
	CSA (cm^2)	**VI** (cm)	**CSA** (cm^2)	**VI** (cm)	**CSA** (cm^2)	**VI** (cm)
Pregnancy (w)						
20	3.87	23.2	6.86	13.1	6.44	13.3
24	3.99	23.1	6.97	12.9	6.65	13.2
28	4.04	23.5	6.94	12.3	6.70	13.0
32	4.09	21.5	7.04	12.1	6.86	12.6
36	4.14	22.0	7.13	12.5	7.00	12.6
Postnatal	3.61	20.7	6.37	11.0	5.96	11.8
SEM	0.04	0.5	0.05	0.1	0.06	0.2
SR	0.15	1.8	0.19	0.5	0.22	0.8

Table 9.2 Cross-sectional and Doppler echocardiographic results; flow area and velocity integral.

	HR	Aortic		Mitral		Pulmonary	
		SV	CO	SV	CO	SV	CO
	(beats/min)	(ml)	(l/min)	(ml)	(l/min)	(ml)	(l/min)
Pregnancy (w)							
20	88	88.8	7.63	89.5	7.85	85.1	7.51
24	90	91.8	8.14	89.9	8.08	87.9	7.96
28	92	90.7	8.27	85.5	7.82	87.3	8.07
32	92	87.5	8.04	85.3	7.94	86.3	8.00
36	88	90.4	7.84	88.1	7.86	87.6	7.69
Postnatal	70	74.3	5.14	70.6	5.09	70.8	4.97
SEM	1	1.2	0.14	1.2	0.14	1.4	0.14
SR	5	4.9	0.55	4.6	0.53	5.5	0.54

Table 9.3 Cross-sectional and Doppler echocardiographic results; heart rate, stroke volume and cardiac output.

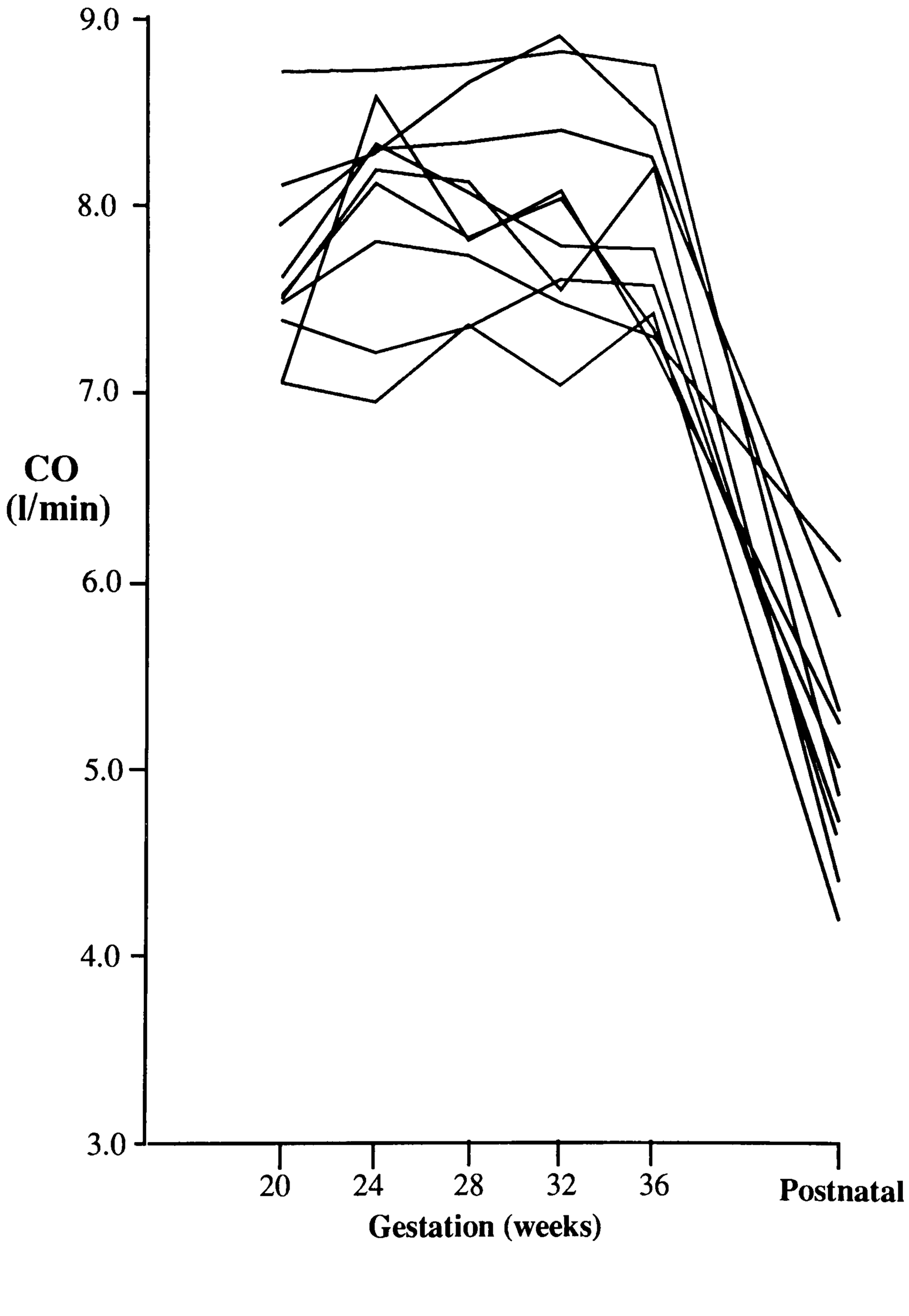


Figure 9.1 Changes in mean Doppler cardiac output in 10 subjects with twin pregnancy studied serially throughout pregnancy and 6 months postnatally

9.3.2 M-mode Echocardiographic Results

Serial M-mode echocardiographic measurements were obtained in all subjects. The results of left atrial and LV dimensions and LV mass are shown in Table 9.4. Left ventricular ESD had not increased, compared with postnatal values, by 20 weeks gestation. There was a significant increase in ESD between 20 and 36 weeks gestation. Left ventricular EDD and LAD were increased throughout pregnancy. The increment in LAD between 20 weeks and 28 weeks was also statistically significant. Left ventricular TWT was increased, compared with postnatal values, by 24 weeks gestation. There was a further increase between 24 and 32 weeks of pregnancy. Left ventricular mass was increased throughout pregnancy; the increase was statistically significant by 20 weeks and were further increases between 20 and 28 weeks and 28 and 36 weeks gestation.

The changes in M-mode indices of LV function are shown in Table 9.5. Fractional shortening, mean Vcf and LVID and LVPW peak systolic dD/dt were all increased by 20 weeks gestation. Thereafter there were no further changes except FS which decreased between 20 and 28 weeks gestation. The LVID and LVPW diastolic dD/dt were increased by 20 weeks and thereafter showed no further change.

	ESD (cm)	EDD (cm)	LAD (cm)	TWT (cm)	LV Mass (g)
Pregnancy (w)					
20	3.05	5.00	3.77	1.66	165
24	3.13	5.02	3.87	1.72	176
28	3.21	5.04	4.08	1.83	193
32	3.20	5.07	4.04	1.87	200
36	3.25	5.13	4.15	1.95	215
Postnatal	3.09	4.70	3.29	1.57	138
SEM	0.04	0.04	0.07	0.03	4
SR	0.15	0.15	0.27	0.12	16

Table 9.4 M-mode echocardiographic results; left atrial dimension and left ventricular dimensions and mass.

	FS (%)	Mean Vcf (Circ/sec)	dD/dt (cm/sec) LVID		dD/dt (cm/sec) LVPW	
			Systole	Diastole	Systole	Diastole
Pregnancy (w)						
20	39.1	1.43	9.8	18.8	6.0	11.6
24	37.8	1.39	10.9	18.5	5.8	11.8
28	36.6	1.39	10.5	17.7	5.7	10.7
32	36.5	1.41	10.5	17.4	5.3	10.4
36	36.4	1.39	10.0	17.5	5.6	10.6
Postnatal	34.3	1.20	7.2	12.0	4.2	7.7
SEM	0.4	0.03	0.4	0.8	0.3	0.4
SR	1.6	0.13	1.4	2.9	1.0	1.6

Table 9.5. M-mode echocardiographic results; Indices of left ventricular function

9.3.3 Blood Pressure and Total Systemic Resistance Results

Blood pressure and TSR results are shown in Table 9.6. Systolic BP increased between 28 and 36 weeks of pregnancy and diastolic BP increased between 24 and 36 weeks. Values of SBP and DBP at 36 weeks gestation were not statistically significantly different from postnatal values. Total systemic resistance was reduced in relation to postnatal values at 20 weeks gestation; thereafter no further change was apparent.

	Mean Doppler	**BP** (mm Hg)		**TSR**
	CO (l/min)	Systolic	Diastolic	(Dyne sec-1 cm-5)
Pregnancy (w)				
20	7.63	111	65	856
24	8.06	112	64	797
28	8.04	110	66	812
32	7.98	115	71	862
36	7.76	120	73	918
Postnatal	5.07	111	70	1330
SEM	0.12	2	2	32
SR	0.45	9	8	124

Table 9.6 Mean Doppler cardiac output, blood pressure and total systemic resistance results.

9.3.4 Comparison of Haemodynamic Changes during Singleton and Twin Pregnancy

Comparisons of echocardiographic and BP changes during twin and singleton pregnancy are presented in Table 9.7. Heart rate, CO, LAD and mean Vcf were significantly higher during twin pregnancy. Changes in mean Doppler SV and CO were comparable to those found at each of the 3 measurement sites and therefore the mean values are presented. None of the differences in other variables was statistically significant and the figures for CSA, VI and dD/dt have been omitted for brevity.

	Group	Pregnancy (w)					p value
		20	24	28	32	36	
HR (beats/min)	T	+18	+20	+22	+22	+18	0.004
	S	+10	+11	+12	+15	+15	
Mean Doppler SV (ml)	T	+16	+18	+17	+14	+17	0.54
	S	+18	+18	+17	+16	+16	
Mean Doppler CO (l/min)	T	+2.56	+2.99	+2.97	+2.91	+2.69	0.02
	S	+2.17	+2.24	+2.22	+2.32	+2.32	
ESD (cm)	T	-0.04	+0.04	+0.12	+0.11	+0.16	0.59
	S	-0.01	+0.05	+0.07	+0.06	+0.14	
EDD (cm)	T	+0.30	+0.32	+0.34	+0.37	+0.43	0.10
	S	+0.20	+0.25	+0.27	+0.24	+0.27	
LAD (cm)	T	+0.48	+0.58	+0.79	+0.75	+0.86	0.01
	S	+0.15	+0.21	+0.28	+0.34	+0.35	
TWT (cm)	T	+0.09	+0.15	+0.26	+0.30	+0.38	0.71
	S	+0.11	+0.14	+0.19	+0.23	+0.30	
LV Mass (g)	T	+27	+38	+55	+61	+77	0.15
	S	+23	+31	+39	+40	+54	
FS (%)	T	+4.8	+3.5	+2.3	+2.2	+2.1	0.56
	S	+3.0	+2.4	+2.2	+2.0	+0.8	
Mean Vcf (Circ/sec)	T	+0.23	+0.19	+0.19	+0.21	+0.19	0.02
	S	+0.11	+0.12	+0.11	+0.08	+0.08	
Systolic BP (mm Hg)	T	0	+1	-1	+4	+9	0.84
	S	-3	0	+1	+2	+6	
Diastolic BP (mm Hg)	T	-5	-6	-4	+1	+3	0.39
	S	-2	+1	+1	+3	+7	
TSR (Dyne cm-5 sec-1)	T	-474	-533	-518	-468	-412	0.20
	S	-420	-393	-391	-387	-329	

Table 9.7 Haemodynamic changes, relative to postnatal values, in twin (T) pregnancy and singleton (S) pregnancy.

9.4 Discussion

The values of CSA, HR, SV and CO at 6 months postpartum are comparable to those reported in Study 3. Values of aortic and pulmonary VI at 6 months postpartum were slightly higher in the present study compared with those reported in Study 3 ($p<0.05$). The reason for these small differences is unclear.

This study is the first to report longitudinal haemodynamic measurements during twin pregnancy. The results suggest that CO is increased by 20 weeks gestation and thereafter remains relatively constant until 36 weeks. The results of two previous cross-sectional studies are shown in Table 9.10. Veille et al. (1985) reported cardiac index during the second and third trimesters of twin pregnancy. Cardiac output, calculated from their values of mean cardiac index and body surface area, was 7.22 l/min in the second trimester and 7.69 l/min in the third trimester. These values are comparable to those reported in the present study. Rovinsky and Jaffin (1966a&b) studied 20 women with twin pregnancies between 21 and 40 weeks gestation. Peak values of CO were recorded at 21-24 weeks gestation (the time of the first measurement) when CO was 53% higher than non-pregnant controls. Thereafter CO fell so that values at 37-40 weeks were only 18% above control values. This difference is likely to reflect differences in posture. These workers performed measurements with the subjects in the supine position in which caval compression by the gravid uterus may have reduced CO (Bieniarz et al. 1968, Lees et al. 1967).

Author	Method	Time of Measurement	Twin pregnancy N	CO	SV	HR	Singleton Pregnancy N	CO	SV	HR
Rovinsky & Jaffin (1966 a&b)	Dye	21-24 w	20*	9.01	108	84	34*	8.10	94	87
		25-28 w		8.52	100	86		8.56	96	89
		29-32 w		7.97	90	90		7.71	85	91
		33-36 w		7.83	84	94		6.52	71	92
		37-40 w		6.93	61	115		5.94	63	98
Veille et al. (1985)	M-M	II trimester	6	7.22	85	86	16	5.77	76	75
		III trimester	14	7.69	93	83	17	5.14	71	74

* Total number (number of subjects studied at each time point not stated)

Table 9.8 Previous cross-sectional studies of cardiac output during twin and singleton pregnancy.

Twin pregnancy was associated with a significantly higher CO than singleton pregnancy, confirming previous reports (Rovinsky and Jaffin 1966a, Veille et al. 1985). The results of the present study suggest that this increase is caused by a higher HR in twin pregnancy. These findings agree with those of Veille et al. (1985) and Rovinsky and Jaffin (1966b), although in the latter study the increase in HR only reached statistical significance at 37-40 weeks of pregnancy. Veille et al. (1985) also reported that SV was higher during the third trimester. This finding is in disagreement with the present results and those of Rovinsky and Jaffin (1966b). Campbell et al. (1985) reported longitudinal measurements of aortic VI and minute distance (VI x HR) during twin pregnancy. The authors commented that the majority of women with twin pregnancy, when studied in the lateral position, had VI's and minute distances within the singleton range, but no statistical analysis was performed. As discussed previously (Chapter 7), measurements of stroke distance and minute distance are unlikely to closely reflect changes in SV and CO because of the increase in aortic CSA.

The M-mode echocardiographic results at 6 months postpartum are comparable to those reported in Study 3. The findings confirm that, as in singleton pregnancy, there is an increase in left atrial and LV EDD's. Interestingly, the increase in LAD was greater during twin pregnancy. This may reflect a higher venous return associated with the larger increase in plasma volume that is known to occur during twin pregnancy (MacGillivray et al. 1971). Under these circumstances a comparable increase in left ventricular EDD might have been expected. This was not demonstrated in the present study, a finding which confirms the results of Veille et al. (1985).

The results of this study also suggest that left ventricular function and mass are increased during twin pregnancy. The increases were comparable to those in singleton pregnancy except for a greater increase in mean Vcf during twin gestation. However mean Vcf is influenced by HR (Mangiarotti et al. 1985), and the differences between the two groups almost certainly reflect the higher HR during twin pregnancy. If mean Vcf is corrected for HR (Mangiarotti et al. 1985), there is no longer a statistically significant difference in mean Vcf between the two groups. Veille et al. (1985) suggested that the higher SV that they recorded during the third trimester of twin pregnancy was caused by an increase ventricular contractility. This suggestion was based on the greater fractional shortening during the third trimester in the twin pregnancy group. This finding was not confirmed in the present study. As discussed in Chapter 4, M-mode ejection phase indices do not accurately reflect inherent left ventricular contractility. Nevertheless there is no obvious explanation for the discrepancy between the two studies.

Campbell and Campbell (1985), reporting a longitudinal study of BP in primigravid subjects with twin pregnancy, postulated that there might be more "vasodilator substance" from the fetoplacental unit present during twin pregnancy. This, they suggested, might lead to a greater drop in peripheral resistance and therefore lower BP. They found that a

significantly greater percentage of primigravid women with twins than with singletons had a diastolic BP < 80 mm Hg at 20 weeks gestation. There was no difference at the same gestation in systolic BP. Mean values for BP were not reported by these workers. The present data suggest that diastolic BP and TSR are lower during the late second trimester in twin pregnancy, but the differences between twin and singleton groups for the whole study were not statistically significant. Veille et al. (1985) reported values of mean arterial pressure (calculated as ([systolic BP + 2 Diastolic BP]/3) during the second and third trimester. They found no significant differences between twin and singleton pregnancies.

9.5 Summary

Cardiac output, measured in the left semi-lateral position, increased during twin pregnancy. The increase was evident at 20 weeks gestation, the time of the first measurement, and thereafter values remained essentially unchanged till 36 weeks. The increase in CO was due to increases in SV and HR. Throughout much of twin pregnancy, CO was maintained at levels approximately 60% above non-pregnant values and 15% above those found during singleton pregnancy. The greater increase in CO during twin pregnancy compared with singleton pregnancy was due to a higher HR. The changes in BP and TSR were comparable to those found during singleton pregnancy.

Twin pregnancy was associated with increases in left atrial and LV dimensions and LV function. The size of these increases was comparable to those found in singleton pregnancy with the exception of left atrial dimension which was greater in twin pregnancy. This may reflect the higher blood volume found in twin pregnancy.

CHAPTER 10

DISCUSSION

10.1 Introduction

In 1971 Hytten and Leitch wrote regarding previous studies of CO during pregnancy; " ..A wholly satisfactory study has yet to be made: we can but record that Walters et al. were not aware of the supine effect, that Pyorala and Ueland et al. made no measurements in early pregnancy and that Lees et al. had no matching non-pregnant value. Yet the circumstantial evidence is strong that for normal pregnant women at rest, but not lying on their back, cardiac output rises within the first ten weeks of pregnancy by about 1.5 litre per minute and the rise is maintained for the remainder of the pregnancy."

Following this review a number of non-invasive methods were developed which allowed serial measurements of CO. Impedance cardiography and M-mode echocardiography, were extensively applied to pregnant subjects during the 1970's and 1980's. Rather than clarifying the uncertainties, these studies added more confusion to the literature; not only did many of them disagree with earlier invasive studies but there were marked differences even between studies using the same methodology. Thus at the time of conceiving the present studies, a wholly satisfactory study of CO during pregnancy had still not yet been performed and the conclusions of Hytten and Leitch (1971) remained based on circumstantial and rather unconvincing evidence.

The most recent non-invasive technique for measuring CO, that of combined cross-sectional and Doppler echocardiography, was developed and extensively studied in the early 1980's. Although a few workers had used the method in small numbers of pregnant subjects, no-one had systematically applied the method to the study of haemodynamic changes during pregnancy. Thus the aim of the present studies was to investigate the accuracy and reproducibility of the method and then, having determined the reliability of measurements in the authors hands, to systematically study CO during pregnancy. In addition M-mode echocardiographic studies were performed to determine the functional and structural adaptations responsible for the changes in CO.

The originality of this work can be summarized as follows;

(1) Study 3 remains the only study of maternal haemodynamics in which women have been investigated prior to conception and then at frequent intervals throughout pregnancy using accurate and reproducible methodology.

(2) Study 4 was the first to report serial haemodynamic investigations throughout the puerperium. It remains the most extensive study of puerperal haemodynamics.

(3) Study 5 is the only serial study of maternal haemodynamics during twin pregnancy.

10.2 Factors Influencing Changes in Cardiac Output during Pregnancy and the Puerperium

Cardiac output is influenced by four distinct although interrelated mechanisms (Schlant and Sonnenblick 1990), all of which appear to contribute to the changes in CO during in pregnancy.

10.2.1 Preload

The term preload represents the degree to which the myocardium is stretched before it contracts. Frank (1895) first described the importance of end-diastolic myocardial fibre length in determining SV in isolated frog hearts. The principle, which has become known as the Frank-Starling law of the heart, was extended by Patterson and Staling (1914) to an isolated canine heart-lung preparation. They noted that, provided the functional condition of the heart is unchanged, SV varied directly with initial end-diastolic fibre length and thus with diastolic filling. Subsequent studies confirmed that initial fibre length, rather than intraventricular pressure, was primarily important in determining the strength of contraction. Although these two factors are usually related, the relation may vary considerably because of changes in ventricular distensibility or compliance. The length of the muscle fibres (ie the extent of the preload) is proportionate to the end-diastolic volume.

M-mode and cross-sectional echocardiography studies during pregnancy, have shown consistent increases in left and right sided end-diastolic chamber dimensions (Rubler et al. 1977, Katz et al. 1978, Laird-Meeter et al. 1979, Arima 1982, Hirata et al. 1984, Castillon et all. 1984, Limacher et al. 1985). Immediately after delivery these dimensions increase and then return to non-pregnant values by 6 weeks postpartum. Changes in EDD have been shown to correlate reasonably closely with end-diastolic volume, as measured by angiography, in non-pregnant subjects (Fortuin et al. 1971, Murray et al. 1972). Thus the changes in EDD are likely to represent changes in end-diastolic volume. These findings therefore suggest that preload is increased during pregnancy, increases further immediately after delivery and declines during the puerperium.

End-diastolic volume is influenced by total blood volume, venous tone and the pumping action of skeletal muscles, intrathoracic and intrapericardial pressure, the atrial contribution to ventricular filling, ventricular distensibility, and the time available for cardiac filling (Braunwald 1988).

1. **Total blood volume**: Both plasma volume and red cell mass increase during pregnancy such that total blood volume increases by approximately 1250 ml. (Hytten 1985). This represents an increase of just under 50% relative to non-pregnant values.

Although some workers have suggested that the changes in plasma volume begins early in the first trimester (Lund 1951, Clapp et al. 1988), the bulk of the increase appears to occur during the second trimester with little further increase beyond 30 weeks gestation (Pirani et al. 1973). The timing of the plasma volume increase coincides approximately with the changes in left atrial and LV EDD reported here. This may suggest that the former is responsible for changes in cardiac dimensions. Under such circumstances it might have been anticipated that both left atrial and LV EDD's would be greater in twin pregnancy, where the increase in plasma volume is even greater (MacGillivray et al. 1971). However only the former was increased above singleton values. Acute increases in central blood volume and venous return, induced by whole body immersion, also induce an increase in cardiac chamber dimensions which is most marked in the atria (Gauer and Henry 1976, Kinney et al. 1987). This phenomenon is likely to reflect the thinner walls and greater compliance of the atrial chambers. It is also noteworthy that the increases in cardiac chamber size do not appear to result in an elevation of right heart or pulmonary capillary wedge pressures (Rose et al. 1956, Clark et al. 1989).

Immediately after delivery there is an increase in pulmonary blood volume (Adams and Alexander 1958) and central venous pressure (Kjeldsen 1979). This probably reflects an increase in venous return (due to a shift of blood from the choriodecidual space into the central circulation as the uterus contracts after delivery) and is likely to be responsible for the increase in left atrial and LV EDD's at this time. Subsequent puerperal changes in blood volume are less clear, and no study has performed serial measurements in the lateral position to avoid postural artifacts. Most studies have reported a 16-20% reduction in blood volume during the first puerperal week (Pritchard et al. 1962, Ueland 1976). The reduction in EDD's during the early puerperium may therefore reflect a reduction in venous return secondary to a fall in blood volume. Thus a reduction in preload is likely to be at least partly responsible for the fall in SV during the first two weeks of the puerperium. Interestingly, most of the early reduction in stroke volume occurs between the second and sixth days after delivery (Robson et al. 1989a), corresponding to the time of the puerperal diuresis (Davison and Dunlop 1984) and the period of maximal reduction in blood volume (Pritchard et al. 1962).

2. **Venous tone and the pumping action of skeletal muscle**: Plethysmographic studies in the calf and forearm suggest that venous distensibility and capacitance are increased during pregnancy (Barwin and Roddie 1976). These changes are most noticeable during the second trimester (Clarke-Pearson and Jelovsek 1981) and presumably occur to accommodate the augmented blood volume of pregnancy. Although femoral venous pressure has been reported to be elevated in late pregnancy (McLennan 1943), this reflects obstruction by the gravid uterus and there is no evidence that other venous pressures are elevated in pregnancy (Thompson et al. 1938). There is no reason to suppose that the pumping action of skeletal muscle is materially altered in pregnancy and therefore changes

in end-diastolic volume are unlikely to be related to alterations in venous tone.

3. **Intrathoracic and intrapericardial pressure**: No data exist regarding changes in intrathoracic pressure during pregnancy. Enein et al. (1987) reported that 43% of pregnant women had echocardiographic evidence of pericardial effusions during the third trimester. While this may suggest that intrapericardial pressure is increased in late pregnancy this has not been directly measured.

4. **Atrial contribution to ventricular filling**: Recent studies have suggested that transmitral Doppler flow velocities can be used to study left ventricular diastolic filling (Rokey et al. 1985). One such measurement, the ratio between the heights of the early diastolic flow-velocity peak and the late atrial diastolic flow-velocity peak (E/A ratio), represents a Doppler measure of the relative contribution of early diastolic filling and atrial systole to overall left ventricular filling. Retrospective analysis of the data from Study 3 showed that the mean E/A ratio prior to pregnancy was 1.62 and although there was a tendency for this to decrease in late pregnancy (mean E/A at 38 weeks gestation = 1.40) this was not statistically significant (Studentized range at 1% level = 0.24). The difference between the means at 5, 8 and 12 weeks of pregnancy (1.66, 1.68 and 1.71 respectively) and the mean at 38 weeks was however significant ($p<0.01$) suggesting that relative contribution of atrial systole to ventricular filling increases in late pregnancy. No other studies of transmitral flow velocities during pregnancy have been reported.

5. **Ventricular distensibility**: Little is known about the factors which affect ventricular distensibility. The rate of change of LV dimension, as measured by angiography and M-mode echocardiography, has been suggested as a measure of distensibility (Sanderson et al. 1978, Siegert et al. 1978). During pregnancy, when the diastolic filling pressure appears to be unchanged, the increase in the peak rate of change of left ventricular cavity and posterior wall dimension reported in Chapter 7, may suggest that ventricular distensibility is increased.

6. **Heart Rate**: Heart rate affects the time available for cardiac filling. Increases in HR are usually accompanied by a decrease in ventricular SV secondary to a reduction in end-diastolic muscle fibre length. The reduction in end-diastolic size is difficult to explain solely on the basis of a temporal limitation in filling since the greater part of ventricular filling occurs early in diastole; increases in HR of up to 100 beats/min would be expected to primarily reduce the period of diastasis, and therefore have little direct influence on filling (Bishop et al. 1976). It is possible, however, that shortening of ventricular diastole could influence atrial systole and the rate of myocardial relaxation. DeMaria et al. (1979) showed a close inverse correlation between LV EDD and HR over a range of 50-150 beats/min. From their figures, EDD would be expected to decline from 4.82 cm at a heart rate of 70 beats per minute to 4.64 cm at 85 beats/min. Clearly such a reduction in EDD does not

occur during pregnancy, suggesting that other factors which increase diastolic filling predominate.

Thus, there is convincing evidence that end-diastolic volume and preload are increased during pregnancy and immediately after delivery. The increased stretching of the myocardium leads to an increase in ventricular performance and an augmentation of SV. These changes are reversed during the early weeks of the puerperium. While a number of factors may contribute to this, the changes in blood volume are likely to be the predominant mechanism.

10.2.2 Afterload

Ventricular ejection and performance are also influenced by the resistance against which the ventricle contracts (afterload). The effects of afterload continuously influence the length-tension relationship of cardiac muscle; when the afterload is increased, a larger amount of energy is expended in the development of contractile tension. Consequently the extent of shortening decreases. Since afterload influences the rate and extent of systolic emptying of the ventricles, it directly influences the ventricular end-systolic volume and indirectly influences the diastolic characteristics (filling pressure and volume) of the next beat of the ventricle. In intact conscious animals with a constant HR, an increase in arterial pressure above 120-150 mm Hg severely limited the extent of shortening as a result of the elevated end-systolic ventricular size (Bishop et al. 1976). However over the normal physiological range (80-120 mm Hg) SV was almost independent of arterial pressure.

The major factors determining LV afterload are systemic vascular resistance, aortic impedance, and the mass and viscosity of blood. The corresponding factors for the right ventricle are the pulmonary impedance and pulmonary vascular resistance (Schlant and Sonnenblick 1990).

1. **Systemic vascular resistance**: Vascular resistance cannot be measured directly and must be calculated from mean arterial pressure and CO. All studies in which measurements of CO and arterial pressure have been made have shown a dramatic decrease in TSR during the first half of pregnancy (Bader et al. 1955, de Schwarcz et al. 1964, Atkins et al. 1981a, Myhrman et al. 1982, Castillon et al. 1984, Capeless and Clapp 1989). Thereafter BP increases to term (Schwarz 1964, MacGillivray et al. 1969). Most studies have shown a corresponding increase in TSR, although the extent of this increase has varied dramatically, reflecting the variability of CO measurements during the third trimester (Bader et al. 1955, de Schwarcz et al. 1964, Atkins et al. 1981a, Myhrman et al. 1982, Easterling et al. 1990c). The results from the present study confirm this pattern of change and also show an increase in ESD at term. Since afterload is the principle factor affecting end-

systolic volume, this increase in ESD may be partly accounted for by the increase in TSR.

In contrast to pregnancy, there are relatively few serial studies of BP during the puerperium. The available evidence suggests that both systolic and diastolic BP fall during the first 48 hours after delivery and then increase such that by the end of the first postnatal week values are similar to those recorded at the end of pregnancy (MacGillivray et al. 1969, Walters et al. 1986, Robson et al. 1989a). Total systemic resistance should therefore fall during the first two days and then increase. Only one study has reported serial measurements of TSR during the early puerperium (Robson et al. 1989) and although this pattern was confirmed, the initial decrease was not statistically significant. Alterations in afterload may therefore contribute to the reduction in SV after delivery.

Considerably less is known about pulmonary vascular resistance during pregnancy. Cardiac catheter studies have reported normal mean pulmonary artery pressures during pregnancy but no non-pregnant data were reported from the same subjects (Werko 1954, Bader et al. 1955, Wallenburg 1988). Recently pulmonary blood flow velocities, recorded using pulsed Doppler, have been used to estimate pulmonary artery pressure. The ratio between pulmonary artery acceleration time and right ventricular ejection time correlates quite closely with mean pulmonary artery pressure (Kitabatake et al. 1983, Debestani et al. 1987). In a recent study, in which these parameters were calculated from the pulmonary velocity traces of the subjects in Study 3, the author reported no significant changes in mean pulmonary artery pressure during pregnancy (Robson et al. 1991). Total pulmonary resistance, calculated from mean pulmonary artery pressure and right ventricular CO, fell during early pregnancy and thereafter showed no further change (Robson et al. 1991). The size of fall (29%) was comparable to that reported by Clark et al. (1989) who studied a group of normal women at 36-38 weeks gestation and again at 11-13 weeks postpartum using a pulmonary artery catheter.

2. **Aortic Impedance**: A number of studies have demonstrated an increase in aortic area during pregnancy (Katz et al. 1978, Hart et al. 1987). The results of the present studies confirm these findings. Hart et al. (1987) also studied aortic compliance by examining the relationships between aortic area and pressure. They demonstrated that the slope of the aortic pressure-area relation was significantly lower in late gestation compared with postpartum. Since the slope is the inverse of compliance, they concluded that the aorta was more compliant during pregnancy. These functional alterations may be related to the marked histological changes seen in the reticulin and elastin fibres of the aortic media during pregnancy (Manalo-Estrella et al. 1967). These findings suggest that aortic impedance is reduced during pregnancy.

3. **Blood viscosity**: Haemorheological studies have demonstrated significant changes in blood viscosity during pregnancy. Plasma viscosity is elevated throughout pregnancy,

primarily reflecting the increase in fibrinogen levels (Eastham 1965, Buchan 1984). Whole blood viscosity falls during the first 24 weeks and then remains stable until the last 6-8 weeks of pregnancy when it increases (Hamilton 1950, Buchan 1984). Serial changes in viscosity have not been reported after delivery. Thus changes in viscosity will tend to reduce afterload during the first half of pregnancy and increase it near term.

The available evidence therefore suggests that afterload is dramatically decreased during the first half of pregnancy secondary to reductions in vascular resistance, aortic impedance and blood viscosity. These changes will tend to increase the extent of myocardial shortening, for any given preload, and thereby increase SV. Towards the end of gestation vascular resistance, at least on the systemic side of the circulation, and blood viscosity increase, although probably neither returns to non-pregnant levels. Consequently afterload may increase slightly near term. The decrease in SV reported by Ueland et al. (1969) and Easterling et al. (1990c) during the third trimester may be at least partly related to the increase in afterload during this time. Systemic vascular resistance increases further after delivery although this change is not apparent until the end of the first postnatal week. Presumably blood viscosity and aortic impedance also increase during the puerperium although the timing of this is unknown. These changes suggest that afterload increases after delivery and this is likely to contribute to the reduction in SV.

10.2.3 Myocardial Contractility

For any given preload or afterload, the extent of myocardial shortening is a function of the contractile (inotropic) state of the heart. At any given end-diastolic volume and afterload, an inotropic stimulus causes a greater shortening, as reflected by a smaller end-systolic size. When sympathetic stimulation causes the heart to beat with increased contractility and with a faster rate, not only is the contraction more forceful and more rapid, but the relaxation and elastic recoil of the ventricular musculature is more rapid. Both these effects tend to increase SV. The increased emptying also means that, at the beginning of the next diastole, the fibre length will be shorter. This tends to increase the distensibility of the ventricle and to allow greater filling at a lower pressure. While these effects are readily demonstrable in isolated heart preparations, the extent to which alterations in contractility influence SV in the normal heart are not clear (Bishop et al. 1974).

Assessment of myocardial contractility in-vivo has long been hampered by the fact that ventricular performance, while readily measurable, is dependent not only on contractility, but on ventricular end-diastolic volume (preload) and on the tension generated during systole (afterload). Traditional indices of contractility have fallen into three categories all of which have been applied to pregnant subjects:

1. **Ejection phase indices**: These include ejection fraction, FS, mean systolic ejection rate, peak systolic rates of change of dimension, and mean and peak Vcf. Studies in pregnancy have used M-mode echocardiographic measurements to derive these indices. The results, even in women studied in the left lateral position, have been conflicting. Data from the present studies and those of Laird-Meeter et al. (1979) and Castillon et al. (1984) suggest that there is an increase in ejection phase indices during the first two trimesters and a fall towards term. In contrast Rubler et al. (1977) found that the increased ventricular performance was maintained throughout the third trimester while others have failed to show any significant change in ejection phase indices during pregnancy (Katz et al. 1978, Hirata et al. 1984, Thompson et al. 1986, Mashini et al. 1987).

Ejection phase indices are affected by HR, preload, and afterload all of which change during pregnancy (Fifer and Braunwald 1985). Fractional shortening and peak systolic rates of change of dimension are considerably less dependent on HR than mean Vcf (DeMaria et al. 1979). The changes in mean Vcf reported in the present study are however considerably greater than could be accounted for by changes in HR alone (DeMaria et al. 1979). Fractional shortening and mean Vcf are relatively preload independent but very sensitive to changes in afterload (Kass et al. 1987). Consequently the changes in ejection phase indices may, at least in part, reflect alterations in afterload.

2. **Ventricular function curves**: These relate preload (or some index thereof, such as ventricular end-diastolic volume / pressure) to some index of pump performance (such as SV). Movement along a curve relating these variables reflects operation of the Frank-Starling mechanism; upward or downward displacement of the curve reflects changes in contractility. Ventricular function curves take account of the effects of alterations in preload on ventricular performance, but are influenced by afterload (Fifer and Braunwald 1985). Therefore, for ventricular function curves to provide meaningful information regarding changes in contractility during pregnancy, serial measurements must be made and afterload must be held constant, or controlled. Not surprisingly, serial data of this kind have not been reported during pregnancy. Clark et al. (1989) studied left ventricular function in 10 women at 36-38 weeks of normal pregnancy using a pulmonary artery catheter. They plotted left ventricular stroke work against pulmonary capillary wedge pressure and found that 8 women had normal ventricular function and 2 had hyperdynamic function when compared to standard ventricular function curves. Measurements were repeated at 11-13 weeks postnatally but individual ventricular function curves were not plotted.

3. **Isovolumic phase indices**: By definition these indices are derived from measurements made prior to opening of the aortic valve; therefore they are less sensitive to afterload than ejection phase indices or ventricular function curves. These indices, the simplest of which is the peak rate of left ventricular pressure development (peak dP/dt), require ventricular pressure measurement and no studies have been performed in pregnant

subjects. A non-invasive measure of the isovolumic phase of cardiac contraction can be derived from the study of systolic time intervals. Simultaneous recording of a phonocardiogram, indirect carotid pulse tracing, and an electrocardiogram allows determination of the pre-ejection period (PEP) which comprises the electro mechanical delay (Q wave to onset of pressure rise in the left ventricle) and the isovolumic contraction period. Studies during pregnancy have reported a reduction in the PEP, corrected for changes in HR, during the first and second trimesters (Rubler et al. 1977, Burg et al. 1974, Cellina et al. 1983, Kagiya et al. 1984). Burg et al. (1974) and Cellina et al. (1983) also suggested that, when serial measurements were performed in the lateral position, PEP subsequently increased during the third trimester. However PEP is influenced by preload (Lewis et al. 1977) and the reduction in PEP during the first two trimesters may partly reflect the increased preload.

More recently end-systolic indices have been used to study ventricular contractility. The slope of the end-systolic pressure-volume relation obtained at various afterloads is sensitive to contractile state and is insensitive to alterations in preload (Carabello and Spann 1984, Fifer and Braunwald 1985). Use of M-mode echocardiography and calibrated carotid pulse recording allows the non-invasive assessment of the load independent end-systolic stress-rate corrected velocity of shortening relationship (Hausdorf et al. 1987). The preliminary results of one small study in which measurements were performed in early labour and 6 weeks after delivery suggested that there was little alteration in contractility over this period (Pridjian et al. 1988). No serial data during pregnancy have been reported.

Thus the effect of pregnancy on myocardial contractility has yet to be clearly defined. Most of the available data suggest that ventricular performance is augmented during the first two trimesters and then declines near term. However the extent to which these changes reflect alterations in loading remains to be determined. Studies in pregnant rats using an isolated, perfused working heart model have allowed investigation of cardiac function under fixed loading conditions and in the absence of local neurohumoral influences. Under these circumstances Buttrick et al. (1987) reported an increase in mean Vcf and fractional shortening during late pregnancy. In addition, the slope of the force-velocity relationship at varying afterloads was shifted upwards in pregnant animals. This strongly suggests that, at least in the pregnant rat, myocardial contractility in increased in pregnancy.

10.2.4 Heart Rate

The fourth major determinant of cardiac function is HR. Neural influences produce the most dramatic and important alterations in HR with sympathetic stimulation increasing the rate and parasympathetic influences producing bradycardia. Other factors, including chemical, humoral, or mechanical alterations, and changes in body temperature or osmotic

pressure also modify pacemaker activity. The actual HR is due to the net effect of all these influences superimposed upon the spontaneous pacemaker rate. As discussed above, changes in HR also effect SV by reducing end-diastolic fibre length. However, this effect is probably small at heart rates below 90 beats/min (Rushmer 1959).

Studies during pregnancy have consistently shown that HR increases.The present results, and those from another study in which HR was measured over conception (Clapp 1985), suggest that this increase begins very early in the first trimester. Thereafter, most serial studies have shown a further rise between the second and third trimesters with a small, but statistically insignificant, increase during the third trimester (Atkins et al. 1981a, Arima 1982, Castillon et al. 1984, Hirata et al. 1984, Mashini et al. 1987, Milsom et al. 1988). Heart rate falls within one hour of delivery (Maruta 1982, Robson et al. 1987). This relative bradycardia may be a reflex response mediated by receptors in the pulmonary bed in response to the increase in pulmonary blood volume which occurs at delivery (Ganong 1977). This effect is relatively shortlived and by 24 hours after delivery HR has returned to values comparable to those found at the end of pregnancy (Robson et al. 1987). Thereafter HR falls, reaching non-pregnant values by the second postnatal week (Walters et al. 1966, Maruta 1982, Robson et al. 1989).

10.2.5 Summary

From the evidence discussed above, the following sequence of haemodynamic alterations may be proposed;

First trimester; There is a progressive increase in CO secondary to increases in both HR and SV. The changes in HR are evident earlier than those in SV. The increase in SV is probably secondary to a reduction in peripheral resistance (and therefore cardiac afterload) although myocardial contractility may also be augmented. The reduction in peripheral resistance is greater than the increase in CO with the result that BP falls.

Second trimester; CO continues to increase due to further elevations in HR and SV. The increase in SV at this time is probably due primarily to an increase in cardiac preload although further alterations in afterload and contractility, at least up until the twentieth week, may also contribute. Peripheral resistance and BP continue to fall, reaching a nadir at 20 weeks.

Third trimester; CO reaches a peak at the beginning of the third trimester and thereafter remains essentially unchanged. During this period, HR increases slightly and SV probably falls near term although values remain elevated relative to those recorded prior to pregnancy. Preload continues to increase up until around 34 weeks and then remains constant while BP and afterload increase throughout the third trimester. A reduction in contractility may also contribute to the changes in SV.

CO is increased in twin pregnancy from at least 20 weeks gestation. Thereafter CO shows little further change and remains consistently higher than singleton values for the remainder of gestation. This difference appears to be due to a higher HR, although preload may also be elevated.

Postpartum; Immediately after delivery SV increases, due to an increase in preload, and HR falls. By 24 hours HR and SV have returned to values comparable to those recorded at the end of pregnancy. Over the next 24 hours, HR starts to fall while SV remains elevated, possibly reflecting a reduction in cardiac afterload. The net result is that CO remains essentially unchanged during the first 48 hours after delivery. Over the next week HR and SV fall quite dramatically. The reduction in SV is related to decreases in preload and contractility, together with an increase in afterload. By 2 weeks after delivery HR and CO have returned to non-pregnant values. There appears to be a further small reduction in SV after this time which may reflect alterations in afterload.

10.3 Factors Influencing Structural Changes in the Heart during Pregnancy and the Puerperium

10.3.1 Ventricular Wall Thickness

Previous M-mode echocardiographic studies have suggested that left ventricular wall thickness may be increased during pregnancy (Katz et al. 1978, Laird-Meeter et al. 1979) and the results of the present studies would confirm these findings. The development and regression of these changes appears somewhat slower than the functional alterations discussed above. While the increase in wall thickness could be related to interstitial oedema, it seems more likely this change represents myocardial hypertrophy. Histological studies of pregnant myocardium have been limited to women with cardiac disease, particularly peripartum cardiomyopathy. While myocardial muscle fibre hypertrophy is a common finding in this condition (O'Connell et al. 1986), the changes may simply reflect the underlying disease rather than a structural alteration associated with pregnancy.

More interesting information comes from echocardiographic studies of female athletes. Women engaged in regular isotonic (endurance) exercise, such as running and swimming, have been shown to have an increase in left ventricular EDD and wall thickness (Lusiani et al. 1986, Fagard et al. 1987). The development of such changes does not require prolonged training and changes comparable to those seen during pregnancy have been reported in subjects after only 12 weeks of training (DeMaria et al. 1978, Lusiani et al. 1986) The unchanged ratio of wall thickness to internal radius suggests that female athletes and pregnant women develop eccentric left ventricular hypertrophy. This type of hypertrophy is also seen in volume overload states (Dodge and Baxley 1969). It is thought that, in analogy with the volume load in pathological conditions, the increase in CO during training, leads to an increase of end-diastolic wall stress, which enlarges the internal diameter and consequently augments systolic wall stress (Fagard et al. 1987). The increase in wall thickness serves to normalize systolic wall stress (Grossman et al. 1975). The same sequence of events may operate during pregnancy.

10.3.2 Valve Orifice Areas

During the present studies, valve areas were found to progressively increase during pregnancy and then return to non-pregnant values after delivery. The time scale of these changes was more in keeping with the increase in wall thickness rather than the changes in SV and CO. Other M-mode and cross-sectional echocardiographic studies have reported increases in cardiac valve diameters and areas during pregnancy (Katz et al. 1978, Limacher et al. 1985, Hart et al. 1987). Roller-pump studies in animals, in which HR was

held constant, have shown that an increase in forward flow through the aortic, pulmonary and mitral valves was associated with increases in valveCSA (Stewart et al. 1985). Whether this flow-related increase in area is associated with any morphological changes in the valve rings during pregnancy is unknown. It is likely that valvular dilatation is responsible for the increased incidence of regurgitant flow velocities seen during pregnancy (Limacher et al. 1985, Robson et al. 1992).

10.4. Regional Distribution of Increased Cardiac Output during Pregnancy

An extensive review of the distribution of resting CO in non-pregnant subjects was presented by Wade and Bishop (1962). It is apparent from their review that published values for individual organ blood flow have varied considerably. Average values of regional blood flow (ml/min) in a 70 Kg man (surface area 1.7 /m^2) were; renal 1100, skeletal muscle 1200, skin 500, splanchnic 1400, cerebral 750, coronary 250, other organs 600. During pregnancy CO increases by approximately 2000 ml/min. The distribution of this increased flow may be summarized as follows:

Renal blood flow: Dunlop (1981) performed serial measurements of effective renal plasma flow (ERPF) using para-aminohippurate clearance. During early pregnancy ERPF increased by 80%. Maximum flows were recorded at 26 weeks gestation when ERPF was 400 ml/min greater than non-pregnant values.

Peripheral blood flow (PBF): Virtually all studies of PBF during pregnancy have been performed using venous occlusion plethysmography. Ginsburg and Duncan (1967) reported a serial increase in mean hand blood flow from 2.7 to 18.1 ml/100 ml/min at term and an increase in mean foot blood flow from 1.7 to 5.6 ml/100 ml/min at term. Cross-sectional studies have reported an increase in forearm and calf blood flow during pregnancy (Goodrich and Wood 1964, Weinstein et al. 1981) however this was not confirmed by the serial studies of Ginsburg and Duncan (1967). By term PBF has probably increased by 500 ml/min (Hytten and Leitch 1971).

Uterine blood flow (UBF): Assali et al. (1960) measured UBF using an electromagnetic flowmeter. Flow increased from around 60 ml/min during the first trimester to 180 ml/min at 28 weeks, with most of this change occurring after 16 weeks. Studies using the Fick principle (with nitrous oxide) have reported mean values of UBF at term of around 500 ml/min but with a wide individual range (Assali et al. 1953, Romney et al. 1955). A recent serial study using transvaginal Doppler reported a steady increase in left uterine blood flow from 95 ml/min before pregnancy to 340 ml/min at term (Thaler et al. 1990).

Liver blood flow: In a serial study using indocyanine green clearance the author found no change in apparent liver blood flow during pregnancy (Robson et al. 1990).

Cerebral blood flow: McCall (1949) measured cerebral blood flow by the Fick principle with nitrous oxide. He found no difference between men and pregnant women.

Mammary blood flow: No quantitative measurements of mammary blood flow have been performed during pregnancy. Using a thermometric technique Pickles (1953) suggested that flow increased markedly during pregnancy. Doppler flow velocities have also been shown to increase 2.5 fold during mid-pregnancy (Thoresen and Wesche 1988).

Other sites: No data exist regarding changes in coronary, gut, pancreatic, splenic, ovarian and adrenal blood flow during human pregnancy. Animal studies using radioactive microspheres have reported increases in blood flow to the gut, pancreas, spleen and ovaries during pregnancy (Rosenfeld 1977, Peeters et al. 1980, Johnson et al. 1985).

Thus the majority of the early increase in CO appears to be directed to the kidney and the skin with uterine blood flow increasing later in the second and third trimesters. The distribution of the remaining 500 or so ml/min remains unclear although at least a part of this is likely to be directed to the mammary, coronary and gut circulations.

10.5 Relationship of the Haemodynamic Changes to Sodium and Water Retention in Pregnancy: A hypothesis of circulatory control

The results of the present studies clearly suggest that elevation of CO and reduction of vascular resistance begin very early during normal pregnancy. How then do these changes fit into a hypothesis of circulatory control and fluid volume regulation during pregnancy ?

The increase in plasma and extracellular fluid volume, glomerular filtration rate and renal plasma flow have led some workers to suggest that pregnancy is a state of volume overload; the so called 'overfill' hypothesis. This theory proposed that primary hypersecretion of aldosterone led to sodium and water retention in excess of the amounts attributable to the conceptus and placental circulation (Katz et al. 1978, Bay and Ferris 1980). A more attractive hypothesis proposes that pregnancy is a state of reduced effective blood volume which is accompanied by secondary aldosteronism; the underfill' hypothesis (Nolton and Ehrlich 1980, Schrier 1988). According to this hypothesis, peripheral arterial vasodilation is the primary circulatory change which leads to undefilling of the circulation. The consequences of this include decreased BP, increased CO secondary to afterload reduction, stimulation of the renin-angiotensin-aldosterone axis, nonosmotic stimulation of thirst and vasopressin release, and renal sodium and water retention with expansion of the extracellular fluid and plasma volume compartments (Schrier and Briner 1991). What is the evidence that supports the underfill hypothesis ?

During pregnancy glomerular filtration rate (GFR), renal blood flow and total extracellular fluid (ECF) and blood volumes all increase by 30-50% (Davison and Dunlop 1980, Hytten 1985). If total ECF and blood volumes were expanded to this degree in a normal subject, the kidney would respond by excreting sodium and water. However pregnancy appears to be the only circumstance where total ECF and blood volumes expand by 30-50% secondary to sodium and water retention, in spite of a markedly increased GFR (Schrier 1988). The increase in GFR has been attributed to the increase in blood volume. However, GFR is increased by the fourth week of pregnancy (Davison and Noble 1981), long before any documented change in blood volume. In addition, Reckelhoff et al. (1989) have shown that comparable volume expansion, as observed in the pregnant rat, is not associated with a comparable rise in GFR in the non-pregnant rat.

The increase in CO during pregnancy has also been attributed to increase in blood volume (Katz et al. 1978). However the present results and those of Capeless and Clapp (1989) clearly suggest that the increase in CO occurs before any demonstrable change in blood volume. This is supported by serial haemodynamic studies in the baboon (Phippard et al. 1986). This group measured CO by thermodilution in 8 animals prior to and throughout

gestation. Simultaneous measurements of red cell volume (using ^{32}P-labelled red cells) and plasma volume (using ^{125}I-labelled albumin) were also performed. The results showed a significant increase in CO by 4 weeks gestation (the average length of baboon gestation being 26 weeks) due primarily to an increase in SV. These changes occurred some 8 weeks before any demonstrable change in plasma volume and total blood volume. The same group also demonstrated a significant fall in systemic and pulmonary vascular resistance by 4 weeks of pregnancy. This is in agreement with the authors results (Robson et al. 1991). Interestingly Phippard et al. (1986) also reported a significant reduction in right atrial pressure by 4 weeks gestation. It is unknown whether a comparable fall occurs during early human pregnancy as no serial measurements have been performed. Results from later cross-sectional studies have reported RAP to be decreased (Colditz and Josey 1970) or unchanged (Bader et al. 1955).

Because vascular resistance cannot be measured directly, it is not possible to separate the temporal changes in vascular resistance and CO. Schrier and Briner (1991) have argued that the primary event is peripheral vasodilation leading to a reduction in renal, pulmonary and systemic vascular resistance. As a result of these changes BP falls and CO increases secondary to afterload reduction. If this were the case then the elevation of CO must not completely compensate for the fall in resistance as BP falls during the first trimester. This hypothesis does not readily explain the very early increase in HR although this could represent an extension of the luteal phase elevation in HR (Brehm 1953, Kelleher et al. 1986). The profound early reduction in systemic vascular resistance cannot be attributed to a reduction in uteroplacental vascular resistance as uterine blood flow does not increase until later in pregnancy (Assali et al. 1960). Therefore it seems likely that either a circulating or an autocrine vasodilator is the common mediator of the early decrease in renal, pulmonary and systemic vascular resistances.

The activity of the renin-angiotensin-aldosterone system is increased during pregnancy (Bay and Ferris 1979), despite the increase in blood volume and ECF volume, a circumstance in which this hormonal system is generally depressed. Human studies have shown that the activation of the renin-angiotensin-aldosterone system occurs during the first trimester (Symonds 1983) and Phippard et al. (1986) have shown that this increased activity occurs in association with the fall in systemic vascular resistance and before the increase in blood volume. It is well established that arterial vasodilation is associated with a compensatory activation of the renin-angiotensin-aldosterone system (McDonald et al. 1975). This hormonal response appears to constitute a compensatory reflex to maintain arterial circulatory integrity. The finding that converting-enzyme inhibitors significantly lower mean arterial pressure in anaesthetized pregnant but not non-pregnant rats, despite a lower baseline pressure during pregnancy, supports such a compensatory response (Bayliss and Collins 1986). Thus in a state of peripheral vasodilation, angiotensin could

contribute along with the rise in CO, to the maintenance of BP.

Under steady-state conditions the renal excretion of a sodium load has been shown to be normal in pregnancy suggesting that escape from the sodium-retaining effects of aldosterone occurs (Barron 1987). In most states of arterial undefilling secondary to peripheral arterial vasodilation, aldosterone escape does not occur (Schrier 1988). The increase in progesterone, which is known to counteract the tubular sodium transport properties of aldosterone, may account for the aldosterone escape in pregnancy. Increased sodium delivery to the distal nephron has been shown to be a determinant of aldosterone escape (Gonzalez-Compoy et al. 1989). Thus the large increase in GFR, and thus filtered sodium load, in pregnancy may also provide adequate distal sodium delivery to allow for the aldosterone escape phenomenon in spite of arterial underfilling. In other states of arterial undefilling, GFR is decreased (Schrier 1988).

Mild hyponatraemia and hypo-osmolality are characteristic of normal pregnancy (Davison et al. 1984). Thirst is also stimulated and vasopressin released at a lower plasma osmolality in pregnancy (Davison et al. 1984). Since vasopressin can be suppressed and stimulated at this lower plasma osmolality, the osmoreceptor for vasopressin may be reset at a lower level during pregnancy (Durr et al. 1981). Studies in rats suggest that the primary vasodilation and thus diminished vascular filling in pregnancy may be responsible for the release of vasopressin and the stimulation of thirst at a lower plasma osmolality than in the non-pregnant state (Durr et al. 1981). The stimulation of thirst appears to occur secondary to the nonosmotic stimulus of arterial underfilling in pregnancy. Sodium restriction has also been shown to lower plasma sodium concentration in the pregnant but not the non-pregnant rat (Barron 1987), another finding compatible with the theory of pregnancy as a state of arterial underfilling.

Thus there is substantial evidence that the primary circulatory change during pregnancy is peripheral arterial vasodilation with relative underfilling of the arterial circulation. This primary adaptation may then lead to a fall in BP, an increase in CO, stimulation of the renin-angiotensin-aldosterone system, nonosmotic stimulation of thirst and vasopressin release, and renal sodium and water retention with expansion of the ECF and plasma volume compartments. The results of the present study support this 'underfill' hypothesis.

10.6 Relationship of the Haemodynamic Changes to Other Hormonal and Bio-chemical Alterations during Pregnancy

The evidence in support of a primary arterial vasodilation hypothesis has been presented in the preceding discussion. This hypothesis would suggest that either a circulating or an autocrine vasodilator is the mediator of the early decrease in renal, pulmonary and systemic vascular resistances. The purpose of the following discussion is to review some of the hormonal and biochemical changes that may be responsible for the haemodynamic alterations during pregnancy.

Oestrogens; During pregnancy the concentrations of oestradiol and other oestrogens increase progressively from the luteal phase of the conceptual cycle through to term (Aspillaga et al. 1983). Administration of oestrogens to castrated ewes leads to an increase in CO, primarily due to an increase in HR, a decrease in BP, peripheral resistance and whole blood viscosity and an increase in blood volume (Ueland and Parer 1966, Ueda et al. 1986). Oestrogens have also been shown to increase myocardial contractility (Tanz 1963, Schaible et al. 1986). The haemodynamic effects of oestrogen in humans are similar except that the increase in CO is due to an increase in SV not HR and the effect on BP has been less consistent (Lehtovirta 1974, Walters and Lim 1969, Luotola et al. 1979, Slater et al. 1986). Sequential oestrogen-progestogen therapy in postmenopausal women has been shown to increase aortic VI by 25% (Pines et al. 1991). The renin-angiotensin-aldosterone system is also stimulated by oestrogens (Crane and Harris 1969). Thus oestrogens may be responsible for the changes in SV and blood volume that occur during pregnancy. Whether they are the primary vasodilating hormone of pregnancy remains uncertain.

Progesterone; Following an initial rapid rise in progesterone concentration during the luteal phase of the conceptual cycle, values plateau from weeks 4-8 and then increase progressively thereafter (Aspillaga et al.1983). Administration of progesterone in animals induced an increase in HR but no change in CO, BP, blood volume or myocardial contractility (Temma et al. 1983, Lumbers 1990). Limited human studies have confirmed these effects (Lehtovirta 1974, Gemelli et al. 1989). Thus while progesterone may be responsible for the early increase in HR there is no evidence to suggest that the hormone has vasodilatory or inotropic effects.

Prolactin, human chorionic gonadotrophin (HCG), **human placental lactogen** (HPL); All these hormones increase early during the first trimester of pregnancy (Aspillaga et al. 1983). Limited animal data has suggested that prolactin may decrease BP and increase blood volume (Bryant et al. 1973) however the haemodynamic effects of these hormones in humans have not been studied.

Catecholamines; When measured under carefully controlled basal conditions the concentrations of plasma adrenaline and noradrenaline do not appear to change during pregnancy although there does appear to be a blunted noradrenergic response to physiologic stimuli during late pregnancy (Barron et al. 1986).

Atrial natiuretic peptide (ANP); ANP is a peptide released from atrial myocytes in response to atrial distension which has natiuretic, diuretic and vasodilator properties. Longitudinal studies during pregnancy have suggested that concentrations of ANP and its prohormone rise during the second and third trimesters (Milsom et al. 1988, Merkouris et al. 1990) and increase further after delivery (Rutherford et al. 1987, Merkouris et al. 1990) presumably in response to changes in blood volume. While ANP is probably responsible for the postpartum diuresis it is unlikely that the hormone or the prohormone are responsible for the early vasodilation as neither are increased during the first trimester (Merkouris et al. 1990).

Prostaglandins; Both prostaglandin (PG) E_2 and prostacyclin (PGI_2) are potent vasodilators. Although PGE_2 is found in increased concentrations during pregnancy, its rapid inactivation by the pulmonary vasculature makes it an unlikely candidate as the primary vasodilator in pregnancy (Goodman et al. 1982). Prostacyclin is produced by endothelial cells and also by myometrium, decidua, chorion, amnion and trophoblast. Unlike PGE_2, PGI_2 escapes metabolism by the pulmonary vasculature (Ylikorkala and Makila 1985). Studies of the PGI_2 metabolite 6-oxo-$PG_{F1\alpha}$ have suggested that PGI_2 production is increased during pregnancy (Lewis et al. 1980, Bolton et al. 1981) and data from studies of urinary excretion of other PGI_2 metabolites support this (Goodman et al. 1982). However data from early pregnancy are very limited; Lewis et al. (1980) found no difference in 6-oxo-$PG_{F1\alpha}$ levels at less than 12 weeks gestation compared with non-pregnant controls and serial measurements by Bolton et al. (1981) suggested that elevated levels were limited to the second trimester of pregnancy. Further evidence against PGI_2 being the primary vasodilator of pregnancy comes from studies in which PGI_2 was infused into male volunteers (Gallery et al. 1985). Although this led to a significant fall in BP, no increase in renal plasma flow and GFR were found. Furthermore cyclooxygenase inhibitors have failed to normalize renal blood flow and GFR in conscious pregnant animals (Conrad and Colpoys 1986).

Calcitonin gene related peptide (CGRP); This circulating peptide is known to be a powerful dilator of pulmonary arteries and veins (McCormack et al. 1989). Stevenson et al. (1986) reported an increase in CGRP as early as weeks 10-12 of human pregnancy. The physiological role of this peptide in both pregnant and non-pregnant subjects remains to be determined.

Endothelium-derived relaxing factor (EDRF) and **endothelins**; Endothelium modulates vascular tone and reactivity by elaborating potent paracrine vasoconstrictor and dilator factors. EDRF acts as an endogenous vasodilator via release of nitric oxide and activation of vascular smooth muscle by cyclic guanosine monophospahate (cGMP) (Angus and Cocks 1989). Endothelin-1 (ET-1) is the most potent vasoconstrictor yet characterized and is likely to be the physiological antagonist of EDRF (Luscher et al. 1990). A number of workers have proposed that the vasodilation of pregnancy may be due to enhanced endothelium-dependent vascular relaxation (McLaughlin et al. 1989, Conrad and Vernier 1989). This may be due to increased EDRF mediated vasodilation and/or reduced ET-1 mediated vasoconstriction. Some in-vitro animal studies of acetylcholine-induced, EDRF mediated vascular relaxation have suggested enhanced endothelium-dependent relaxation in vessels from gravid compared with virgin animals (McLaughlin et al. 1989, Weiner et al. 1989). However Umans et al. (1990) failed to demonstrate a difference in basal EDRF release during pregnancy. Increases in vascular and whole animal cGMP, the second messenger mediating the effects of EDRF, have also been reported during pregnancy (Conrad and Vernier 1989, Whittemore and Conrad 1989). One cross-sectional study of ET-1 in pregnancy has reported reduced concentrations compared with non-pregnant women (Kamoi et al. 1990). It is interesting to note that oestrogen has recently been reported to increase the release of EDRF (Gisclard et al. 1988). While this work suggests that endothelial-derived factors may be involved in alterations in vascular tone during pregnancy, the relative importance and timing of these changes remains to be determined.

In summary, the exact hormonal events that mediate the haemodynamic changes during pregnancy are still undetermined. It seems likely that a vasodilator, perhaps with cGMP as its mediator, is present from very early in gestation. This may be EDRF, CGRP, one of the vasodilating prostaglandins or an as yet unidentified circulating or autocrine vasodilator. Whether oestrogen or one of the other placentally derived hormones, all of which increase very early during the first trimester, is the stimulus to the release of this vasodilator is unknown. However there is evidence that the early increase in HR may be mediated by progesterone while the later increases in SV and blood volume may be predominantly mediated by oestrogen.

10.7 Epilogue

Further progress in obstetrics must be founded on the understanding of the physiological changes that take place during the course of pregnancy. While virtually all organ systems undergo some degree of adaptation, the changes that occur within the cardiovascular system are undoubtedly some of earliest and most dramatic. Prior to starting this work many aspects of maternal cardiovascular adaptation were poorly understood. Much of the uncertainty stemmed from the lack of longitudinal data. The studies reported here have clarified some of these uncertainties and, as is the nature of research, they have also raised further questions.

We now need to know much more about the inter-relationships of the various vasoactive factors which may be responsible for the haemodynamic adjustments of pregnancy. From the clinical viewpoint, it is essential that we apply insights gained from physiological investigation to disease states. Limited haemodynamic studies in women with severe pre-eclampsia suggest that cardiovascular adaptations are in some way altered. Is this the primary abnormality or a secondary response ? Some patients with cardiac disease appear to be unable to adapt to the altered haemodynamic conditions of pregnancy. Can we use the information gained from physiological studies to predict such women ? Finally, and perhaps most important, a complete understanding of the pathophysiology of such conditions will allow a more rational basis for treatment.

Echocardiography has proved to be a valuable investigative tool. The accuracy, reproducibility and applicability of this non-invasive technique make it the ideal method for studying normal maternal (and fetal) cardiovascular changes. It is hoped that subsequent studies using these techniques will answer some of the remaining questions and thereby allow more appropriate management of women with preexisting and pregnancy-induced cardiovascular disease during pregnancy and delivery. This work is already in progress.

SUMMARY

Introduction

1. Previous studies had consistently shown that cardiac output increased during pregnancy although the pattern of change and the mechanisms underlying this increase remained unclear. Differing results probably reflected variations in investigative method and study design. There had not been a serial study of cardiac output during pregnancy, using a validated and reproducible non-invasive technique, in which subjects acted as their own pre-pregnant controls. Even less was known about the haemodynamic changes after delivery and during twin pregnancy.

2. Cardiac output can be measured by cross-sectional and Doppler echocardiography. Cardiac chamber size and ventricular function can be measured by M-mode echocardiography. Both techniques are non-invasive and have been validated against invasive methods.

Aims

1. To validate Doppler measurements of cardiac output against direct Fick measurements in non-pregnant subjects
2. To determine the reproducibility of cross-sectional, Doppler and M-mode echocardiographic measurements in pregnant and non-pregnant subjects.
3. To measure serially cardiac output (a) prior to and throughout singleton pregnancy (b) throughout the puerperium and (c) during twin pregnancy
4. To correlate the changes in cardiac output during pregnancy and the puerperium with M-mode echocardiographic measurements of cardiac chamber size and ventricular function.

Methods

1. All echocardiographic measurements were performed using a Hewlett-Packard 77020A system with the subjects in the left semi-lateral position. Cardiac output was measured at three intracardiac sites. Ascending aortic velocities were recorded using continuous wave Doppler and mitral and pulmonary velocities using pulsed Doppler. Aortic and pulmonary valve cross-sectional areas were calculated from the respective annular diameters measured by cross-sectional echocardiography. Mitral valve annular cross-sectional area was measured directly from cross-sectional echocardiographs. The systolic or diastolic velocity integral was determined by digitizing the respective velocity traces. Stroke volume was calculated as the product of velocity integral and cross-sectional area at each of the three valves. Cardiac output was calculated as the product of stroke volume and heart rate.
2. Left ventricular end-diastolic dimension, end-systolic dimension and total wall thickness were measured from standard left ventricular M-mode echocardiographs. End-diastolic left atrial dimension was measured from standard aortic/left atrial M-mode echocardiographs.

Several indices of left ventricular function (mean velocity of circumferential fibre shortening, fractional shortening, peak systolic and diastolic rates of change of dimension of the left ventricular cavity and posterior wall) were also determined from the left ventricular M-mode echocardiograph.

3. Validation of cardiac measurement by the Doppler method (Study 1); Simultaneous measurements of cardiac output by cross-sectional and Doppler echocardiography and the direct Fick method were performed in 15 non-pregnant subjects undergoing cardiac catheterization.

4. Reproducibility of cross-sectional, Doppler and M-mode echocardiographic measurements (Study 2); Echocardiographs were recorded from 14 non-pregnant women on two occasions 30-60 minutes apart. Recordings were repeated 1-3 months later. Ten of the subjects had further recordings 30-60 minutes apart at 16 weeks gestation. All recordings were numbered and analysed blindly.

5. Haemodynamic changes during singleton pregnancy (Study 3); Echocardiographic investigations were performed in 13 women on two occasions prior to conception and then as soon a possible after confirmation of pregnancy (mean gestation 5 weeks). Investigations were repeated at 8 weeks gestation and then monthly during pregnancy. All subjects were restudied 6 months after delivery.

6. Haemodynamic changes during the puerperium (Study 4); Echocardiographic investigations were performed in 15 women at 38 weeks gestation and then at 2,6, 12 and 24 weeks after delivery. Ten of the subjects who had a normal vaginal delivery were also studied 48 hours postpartum.

7. Haemodynamic changes during twin pregnancy (Study 5). Serial echocardiographic investigations were performed at monthly intervals in 10 women with twin pregnancy from 20 weeks gestation. Investigations were repeated 6 months after delivery.

Results

1. Study 1; Doppler flows correlated closely with direct Fick measurements (r = 0.87-0.93 SEE 0.40-0.55 l/min). The mean differences (± 2 SD) between the Fick and Doppler CO's were; -0.01 (±0.70) l/min for the aortic valve, -0.04 (± 0.86) l/min for the mitral valve and to -0.23 (± 0.80) for the pulmonary valve.

2. Study 2; For all echocardiographic measurements between subject variability was significantly greater than within subject variability and there was no significant difference between the variability of measurements performed 30-60 minutes and 1-3 months apart.

With the exception of peak rates of change of left ventricular dimensions, the mean percentage error for all other variables was less than 8%. Comparable results were obtained in pregnant subjects.

3. Study 3; Heart rate and cardiac output was increased by 5 weeks of pregnancy. Cardiac output continued to increase until 20 weeks gestation, due to an increase in stroke volume and a further increase in heart rate, reaching values 45% above those recorded prior to pregnancy. Thereafter there was no further change until delivery. Total systemic resistance fell during the first 20 weeks of pregnancy then increased slightly towards term. These changes were associated with an increase in left ventricular and left atrial end-diastolic dimension, evident by 12 weeks gestation, and an increase in all M-mode indices of left ventricular function, evident by 8 weeks gestation. Valve cross-sectional areas and left ventricular thickness increased progressively during pregnancy. All measurements has returned to pre-pregnancy values by 6 months after delivery

4. Study 4; Cardiac output remained elevated 48 hours after normal delivery. Between 48 hours and 2 weeks cardiac output fell substantially due to reductions in both heart rate and stroke volume. Thereafter there was a further fall in stroke volume such that by 6 months after delivery cardiac output was 32-34% below pregnancy values. Systemic resistance was increased by 2 weeks and there was a further slight increase at 24 weeks postnatally. Left ventricular and left atrial end-diastolic dimensions together with all indices of left ventricular function decreased during the first 6 postnatal weeks. Valve cross-sectional areas and left ventricular wall thickness were decreased by 12 weeks and there was a further reduction in wall thickness between 12 and 24 weeks.

5. Study 5; Cardiac output was increased by 20 weeks gestation, due to increases in both heart rate and stroke volume. Thereafter values remained essentially unchanged. Maximum values of cardiac output were 60% above those recorded after delivery and on average 15% higher than those recorded during singleton pregnancy, due primarily to a greater increase in heart rate. The increases in all other parameters were comparable to those seen during singleton pregnancy with the exception of left atrial dimension which increased more during twin pregnancy.

Discussion

1. During the first trimester there is a progressive increase in cardiac output. The changes in heart rate precede those in stroke volume. The increase in stroke volume is probably secondary to a fall in peripheral resistance (and therefore afterload) although myocardial contractility may also be augmented. Cardiac output continues to increase during the second trimester due to further elevations in heart rate and stroke volume. The changes in diastolic chamber size suggest that the increase in stroke volume during this period is related to

increased cardiac filling (preload). This is consistent with the reported changes in blood volume during pregnancy. Cardiac output remains unchanged during the third trimester while there is a further small increase in heart rate. There may be a slight reduction in stroke volume towards term possibly reflecting an increase in afterload and a reduction in contractility. During the first two weeks after delivery cardiac output falls due to a reduction in heart rate and stroke volume. The decline in stroke volume appears to reflect a reduction in preload and contractility, together with an increased afterload.

3. Pregnancy is also associated with increases in valve area and left ventricular wall thickness and mass. These structural changes develop later in pregnancy than do the functional changes and regress over a longer period after delivery. The changes in left ventricular dimensions are very similar to those seen in female athletes who engage in regular isotonic exercise.

4. The results of this work are consistent with the so-called underfill hypothesis of circulatory changes during pregnancy. According to this hypothesis peripheral arterial vasodilation is the primary circulatory change which leads to underfilling of the circulation. The consequences of this include decreased blood pressure, increased cardiac output secondary to afterload reduction, stimulation of the renin-angiotensin-aldosterone axis, nonosmotic stimulation of thirst and vasopressin release, and renal sodium and water retention with expansion of the extracellular fluid and plasma volume compartments. The factor or factors responsible for this vasodilation have yet to be clearly identified.

5. Echocardiography has proved to be a valuable investigative tool. The accuracy, reproducibility and applicability of this non-invasive technique make it an ideal method for studying maternal cardiovascular changes. Having determined the physiological changes that take place during normal pregnancy attention can now be focused on studying women with preexisting and pregnancy-induced cardiovascular disease.

REFERENCES

Adams JQ. Cardiovascular physiology in normal pregnancy: studies with the dye dilution technique. Am J Obstet Gynecol 1954; 67: 741-759.

Adams JQ, Alexander AM. Alterations in cardiovascular physiology during labour. Obstet Gynecol 1958; 12: 542-549.

Angelino PF, Siliquini PN, Actis-Dato A, Levi V, Revelli E. Nuovi concetti di emodinamica in gravidanza da indagini con cateterismo angiocardiaco. Minerva Ginecologica 1954; 15; 517-533.

Angus JA, Cocks TM. Endothelium-derived relaxing factor. Pharmacol Ther 1989; 41: 303-352.

Antani JA, Wayne HH, Kuzman WJ. Ejection phase indexes by invasive and noninvasive methods: An apexcardiographic, echocardiographic and ventriculographic correlative study. Am J Cardiol 1979; 43: 239-244.

Arima N. The echocardiographic observation of cardiac function in normal pregnancy and supine hypotensive syndrome. Igaku Kenkyu 1982; 52: 179-186.

Ascah KJ, Stewart WJ, Levine RA, Weyman AE. Doppler-echocardiographic assessment of cardiac output. Radiol Clin North Am 1985; 23: 659-670.

Ascah KJ, Stewart WJ, Gillam LD, Triulzi MO, Newell JB, Weyman AE. Calculation of transmitral flow by Doppler echocardiography: A comparison of methods in a canine model. Am Heart J 1989; 117: 402-411.

Aspillaga MO, Whittaker PG, Taylor A, Lind T. Some new aspects of the endocrinological response to pregnancy. Br J Obstet Gynaecol 1983; 90: 596-603.

Assali NS, Douglass RA, Baird WW, Nicholson DB, Suyemoto R. Measurement of uterine blood flow and uterine metabolism. IV. Results in normal pregnancy. Am J Obstet Gynecol 1953; 66: 248-253.

Assali NS, Rauramo L, Peltonen T. Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy. Am J Obstet Gynecol 1960; 79: 86-98.

Atkins AJF, Watt JM, Milan P, Davies P, Selwyn Crawford J. A longitudinal study of cardiovascular dynamic changes throughout pregnancy. Eur J Obstet Gynecol Reprod Biol 1981a; 12: 215-224.

Atkins AJF, Watt JM, Milan P, Davies P, Selwyn Crawford J. The influence of posture upon cardiovascular dynamics throughout pregnancy. Eur J Obstet Gynecol Reprod Biol 1981b; 12: 357-372.

Bader RA, Bader ME, Rose DJ, Braunwald E. Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization. J Clin Invest 1955; 34: 1524-1536.

Barratt-Boyes BG, Wood EH. Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an anlaysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. J Lab Clin Med 1958; 51: 72-90.

Barron JV, Sahn DJ, Valdez-Cruz LM, Lima CO, Goldberg SJ, Grenadier E, Allen HD. Clinical utility of two-dimensional Doppler echocardiographic techniques for estimating pulmonary to systemic blood flow ratios in children with left to right shunting atrial septal defect, ventricular septal defect or patent ductus arteriosus. J Am Coll Cardiol 1984; 3: 169-178.

Barron WM. Volume homeostasis during pregnancy in the rat. Am J Kidney Dis 1987; 9: 296-302.

Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine response to physiologic stimuli in normal human pregnancy. Am J Obstet Gynecol 1986; 154: 80-84.

Barwin BN, Roddie IC. Venous distensibility during pregnancy determined by graded venous congestion. Am J Obstet Gynecol 1976; 125: 921-923.

Bay WH, Ferris TF. Factors controlling plasma renin and aldosterone during pregnancy. Hypertension 1979; 1: 410-415.

Baylis C, Collins RC. Angiotensin II inhibition on blood pressure and renal hemodynamics in pregnant rats. Am J Physiol 1986; 250: F308-314.

Beard EF, Wood EH. Estimation of cardiac output by the dye dilution method with an ear oximeter. J Appl Physiol 1951; 4: 177-187.

Benedetti TJ, Cotton DB, Read JC, Miller FC. Hemodynamic observations in severe preeclampsia with a flow-directed pulmonary artery catheter. Am J Obstet Gynecol 1980; 136: 465-470.

Berkowitz RL, Berkowitz GS. Invasive studies during normal pregnancy. Obstet Gynecol 1990; 75: 1041-1042.

Bernstein DP. A new stroke volume equation for thoracic bioimpedance: theory and rationale. Crit Care Med 1986; 14: 904-909.

Bett JHN, Dryburgh LG. Beat-to-beat variation in echocardiographic measurements of left ventricular dimensions and function. J Clin Ultrasound 1981; 9: 119-125.

Bevan DR, Holdcroft A, Loh L, MacGregor WG, O'Sullivan JC, Sykes MK. Closing volume and pregnancy. Br Med J 1974; i: 13-15.

Bieniarz J, Crottogini JJ, Curuchet E, Romero-Salinas G, Yoshida T, Poseiro JJ, Caldeyro-Barcia R. Aortocaval compression by the uterus in late human pregnancy. II. An arterigraphic study. Am J Obstet GYnecol 1968; 100: 203-217.

Bilfinger TV, Lin CY, Anagnostropoulos CE. In vitro determination of accuracy of cardiac output measurement by thermal dilution. J Surg Res 1982; 33: 409-414.

Bishop VS, Peterson DF, Horwitz LD. Factors influencing cardiac performance. In; Cardiovascular Physiology II (Eds. Guyton AC, Cowley AW). University Park Press, Baltimore 1976; 239-273.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; I: 307-310.

Bogren H, Klipstein RH, Mohiaddin R, Underwood SR, Firmin DN, Rees RSO, Longmore DB. Pulmonary artery blood flow patterns studied by magnetic resonance. Br

Heart J 1988; 59: 141-142.

Bolton PJ, Jogee M, Myatt L, Elder MG. Maternal plasma 6-oxo-prostaglandin F1α levels throughout pregnancy: a longitudinal study. Br J Obstet Gynecol 1981; 81: 1101-1103.

Bom N, Lancee CT, Honkoop J, Hugenholtz PC. Ultrasonic viewer for cross-sectional analyses of moving cardiac structures. Biomed Eng 1971; 6: 500-503.

Bornstein A. Eine Methode zur vergleichenden Messung des Herzschlagvolumens beim Menschen. Pflug Arch ges Physiol 1910; 132: 307-318.

Bouchard A, Blumlein S, Schiller NB, Schlitt S, Byrd BF, Ports T, Chatterjee K. Measurement of left ventricular stroke volume using continuous wave Doppler echocardiography of the ascending aorta and M-mode echocardiography of the aortic valve. J Am Coll Cardiol 1987; 9: 75-83.

Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. Circulation 1955; 12: 557-566.

Braunwald E. Mechanisms of cardiac contraction and relaxation. In: Heart Disease 3rd Edition. Saunders, Philadelphia 1988;401-425.

Brehm H. Die korrelation zwischen blutkreislauf und mensuellem cyclus. Archiv fur Gynakologie 1953; 184; 103-108.

Brehm H, Kindling E. Der Kreislauf wahrend Schwangerschaft und Wochenbett. Archiv fur Gynakologie 1955; 185: 696-712.

Brown OR, Harrison DC, Popp RL. An improved method for echocardiographic detection of left atrial enlargement. Circulation 1974; 50: 58-64.

Bryant EE, Douglas BH, Ashburn AD. Circulatory changes following prolactin administration. Am J Obstet Gynecol 1973; 115: 53-57.

Buchan PC. Maternal and fetal blood viscosity throughout normal pregnancy. J Obstet Gynaecol 1984; 4: 143-150.

Bullock RE, Appleton D, Griffiths C, Albers CJ, Amer H, Hall RJC. Precision of digitized M-mode echocardiograms for clinical practice. Eur Heart J 1984; 5: 941-947.

Burg JR, Dodek A, Kloster FE, Metcalfe J. Alterations of systolic time intervals during pregnancy. Circulation 1974; 49: 560-564.

Burwell CS, Straythorn WD, Flickinger D, Corlette MB, Bowerman EP, Kennedy JA. Circulation during pregnancy. Arch Intern Med 1938; 62: 979-1003.

Burwell CS. The placenta as a modified arteriovenous fistula considered in relation to the circulatory adjustments to pregnancy. Am J Med Sci 1938; 195: 1-7.

Buttrick PM, Schaible TF, Malhotra A, Mattioli S, Scheuer J. Effects of pregnancy on cardiac function and myosin enzymology in the rat. Am J Physiol 1987; 252: H846-H850.

Campbell DM, Campbell AJ. Arterial blood pressure - the pattern of change in twin pregnancies. Acta Genet Med Gemellol 1985; 34: 217-223.

Campbell DM, Haites N, MacLennan F, Rawles J. Cardiac output in twin pregnancy. Acta Genet Med Gemellol 1985; 34: 225-228.

Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. Am J Obstet Gynecol 1989; 161: 1449-1453.

Capeless EL, Clapp JF. When do cardiovascular parameters return to preconception values ? Am J Obstet Gynecol 1991; 165: 883-886.

Carabello BA, Spann JF. The uses and limitations of end-systolic indexes of left ventricular function. Circulation 1984; 69: 1058-1064.

Carruth JE, Mirvis SB, Brogan DR, Wenger NK. The electrocardiogram in normal pregnancy. Am Heart J 1981; 102: 1075-1078.

Castillon G, Weissenburger J, Rouffet M, Castillon V, Barrat J. Etude échocardiographique des modifications hémodynamiques de la grossesse. J Gynecol Obstet Biol Reprod 1984; 13: 499-505.

Caton D, Banner TE. Doppler estimates of cardiac output during pregnancy. Bull N Y Acad Med 1987; 63: 727-731.

Cellina G, Binaghi P, Limonta A, Locicero G, Montanari C, Brina A. Modificazione dei tempi sistolica durante la gravidanza e il puerperio. G Ital Cardiol 1981; 11: 63-67.

Chandraratna PA, Nanna M, McKay C, Nimalasuriya A, Swinney R, Elkayam U, Rahimtoola SH. Determination of cardiac output by transcutaneous continuous-wave ultrasonic Doppler computer. Am J Cardiol 1984; 53: 234-237.

Chapman CB, Taylor HL, Borden C, Ebert RV, Keys A, Carlson WS. Simultaneous determination of the resting arteriovenous difference by the acetylene and direct Fick methods. J Clin Invest 1950; 29: 651-659.

Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S. Determination of stroke volume and cardiac output during exercise: comparison of two-dimensional and Doppler echocardiography, Fick oximetry, and thermodilution. Circulation 1987; 76: 539-547.

Claflin KS, Alverson DC, Pathak D, Angelus P, Backstrom C, Werner S. Cardiac output determinations in the newborn. Reproducibility of the pulsed Doppler velocity measurement. J Ultrasound Med 1988; 7: 311-315.

Clapp JF. Maternal heart rate in pregnancy. Am J Obstet Gynecol 1985; 152: 859-860.

Clapp JF, Seaward BL, Sleamaker RH, Hiser J. Maternal physiological adaptations to early pregnancy. Am J Obstet Gynecol 1988; 159: 1456-1460.

Clark C, Schultz DL. Velocity distribution in aortic flow. Cardiovasc Res 1973; 7: 601-613.

Clark RD, Korcuska K, Cohn K. Serial echocardiographic evaluation of left ventricular function in valvular disease, including reproducibility guidelines for serial studies. Circulation 1980; 62: 564-575.

Clark SL, Cotton DB, Lee WL, Bishop C, Hill T, Southwick J, Pivarnik J, Spillman T, De Vore GR, Phelan J, Hankins GDV, Benedetti TJ, Tolley D. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989; 161: 1439-1442.

Clarke PR, Hill CR. Physical and chemical aspects of ultrasonic disruption of cells. J Acoust Soc Med 1970; 47: 649-658.

Clarke-Pearson DL, Jelovsek FR. Alterations of occlusive cuff impedance plethysmography results in the obstetric patient. Surgery 1981; 89: 594-598.
Colditz RB, Josey WE. Central venous pressure in the supine position during normal pregnancy. Obstet Gynecol 1970; 36: 759-772.
Collier CR. Determination of mixed venous CO_2 tensions by rebreathing. J Appl Physiol 1956; 9: 25-29.
Collins HW, Kronenberg MW, Byrd BF. Reproducibility of left ventricular mass measurements by two-dimensional and M-mode echocardiography. J Am Coll Cardiol 1989; 14: 672-676.
Conrad KP, Vernier KA. Plasma level, urine excretion, and metabolic production of cGMP during gestation in cats. Am J Physiol 1989; 257: R847-853.
Conway J, Lund-Johansen P. Thermodilution method for measuring cardiac output. Eur Heart J 1990; 11 (Suppl 1): 17-20.
Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR. Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. Circulation 1972; 46: 914-923.
Cournand A, Ranges HA. Catheterization of the right auricle in man. Proc Soc Exper Biol N Y 1941; 46: 462-466.
Crane MG, Harris JJ. Plasma renin activity and aldosterone excretion rate in normal subjects. I. Effect of ethinyl estradiol and medroxyprogesterone acetate. J Clin Endocr 1969; 29: 550-557.
Daily E, Shroeder J. In; Techniques in Bedside Hemo-dynamic Monitoring. Mosby, St Louis 1981; 110-131.
Damen J, Bolton D. A prospective analysis of 1400 pulmonary artery catheterizations in patients undergoing cardiac surgery. Acta Anaesthesiol Scand 1986; 30: 386-392.
Dancy M. Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis. Br Heart J 1986; 55: 155-161.
Daniel MK, Bennett B, Dawson AA, Rawles JM. Haemoglobin concentration and linear cardiac output, peripheral resistance, and oxygen transport. Br Med J 1986; 292: 923-926.
Darsee JR, Walter P, Nutter DO, Clapham DE. Transcutaneous Doppler method of measuring cardiac output. II. Non-invasive measurement by transcutaneous Doppler aortic blood velocity integration and M mode echocardiography. Am J Cardiol 1980; 46: 613-618.
Davidson DM, Covell JW, Malloch CI, Ross J. Factors influencing indices of left ventricle contractility in the conscious dog and in man. Cardiovasc Res 1974; 8: 299-307.
Davies P, Francis RI, Docker MF, Watt JM, Selwyn Crawford J. Analysis of impedance cardiography longitudinally applied in pregnancy. Br J Obstet Gyaecol 1986; 93: 717-720.
Davison JM, Dunlop W. Renal hemodynamics and tubular function in normal human pregnancy. Kidney Int 1980; 18: 152-161.
Davison JM, Noble MCB. Serial changes in 24-hour creatinine clearance during normal

menstrual cycles and the first trimester of pregnancy. Br J Obstet Gynaecol 1981; 88: 10-17.

Davison JM, Gilmore EA, Durr J, Robertson GL, Lindheimer MD. Altered osmotic thresholds for vasopressin and thirst in human pregnancy. Am J Physiol 1984; 246: F105-109.

de Leeuw PW, Birkenhager WH. Some comments on the usefulness of measuring cardiac output by dye dilution. Eur Heart J 1990; 11 (Suppl 1): 13-16.

de Schwarcz SB, Aramendia P, Taquini AC. Variaciones hemodinamicas en el embarazo normal. Medicina B Aires 1964; 24: 113-118.

de Swiet M, Talbert DG. The measurement of cardiac output by electrical impedance plethysmography. Are the assumptions valid? Br J Obstet Gynaecol 1986; 93: 721-726.

de Leonardis V, Cinelli P. Evidence of no interobserver variability in M-mode echocardiography. Clin Cardiol 1986; 9: 324-326.

de Zuttere D, Touche T, Saumon G, Nitenberg A, Prasquier R. Doppler echocardiographic measurement of mitral flow volume: validation of a new method in adult patients. J Am Coll Cardiol 1988; 11: 343-350.

Debestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, Henry WL. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. Am J Cardiol 1987; 59: 662-668.

DeFares JG. Determination of $PvCO_2$ from the exponential CO_2 rise during rebreathing. J Appl Physiol 1958; 13: 159-164.

Delemarre BJ, Bot H, Pearlman AS, Visser CA, Dunning AJ. Diastolic flow characteristics of severly impaired left ventricles: a pulsed Doppler ultrasound study. J Clin Ultrasound 1987; 15: 115-119.

DeMaria A, Neumann A, Lee G, Fowler W, Mason DT. Alterations in ventricular mass and performance induced by exercise training in man evaluated by echocardiography. Circulation 1978; 57: 237-244.

DeMaria A, Neumann A, Schubart PJ, Lee G, Mason DT. Systemic correlation of cardiac chamber size and ventricular performance determined with echocardiography and alterations in heart rate in normal persons. Am J Cardiol 1979; 43: 1-10.

Dericbourg C, Tribouilloy C, Kugener H, Avinee P, Rey JL, Lesbre JP. Mesure non invasive du débit cardiaque par échocardiographie doppler pulsé. Arch Mal Coeur 1990; 83: 237-244.

Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977; 55: 613-618.

Distante A, Moscarelli E, Rovali D, L'Abbate A. Monitoring of changes in cardiac output by transcutaneous aortovelography, a non-invasive Doppler technique: comparison with thermodilution. J Nucl Med All Sci 1980; 24: 171-175.

Dittman H, Voelker W, Karsch K-R, Seipel L. Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography. J Am Coll Cardiol 1987; 10: 818-823.

Dodge HT, Baxley WA. Left ventricular volume and mass and their significance in heart disease. Am J Cardiol 1969; 23: 528-537.

Donovan KD, Dobb GJ, Woods WPW, Hockings BE. Comparison of transthoracic electrical impedance and thermodilution for measuring cardiac output. Crit Care Med 1986; 14: 1038-1044.

Doppler CJ. Uber das farbige Licht der Doppelsterne und eineger anderer Gestirne des Himmels. Abhandlungen der Koniglishen Bohmischen Gesellschaft der Wissenchaften 1842; 11: 465-482.

Du Bois D, Du Bois E. A formula to estimate the approximate surface area if height and weight be known. Arch Int Med 1916; 17: 863-871.

Dubin J, Wallerton DC, Cody RJ, Devereux RB. Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determinations. Am Heart J 1990; 120: 116-123.

Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynecol 1981; 88: 1-9.

Durr JA, Stamoutsos B, Lindheimer MD. Osmoregulation during pregnancy in the rat. Evidence for resetting of the threshold for vasopressin secretion during gestation. J Clin Invest 1981; 68: 337-346.

Easterling TR, Watts DH, Schmucker BC, Benedetti TJ. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observations in pre-eclampsia. Obstet Gynecol 1987; 69: 845-850.

Easterling TR, Schmucker BC, Benedetti TJ. The hemodynamic effects of orthostatic stress during pregnancy. Obstet Gynecol 1988; 72: 550-552.

Easterling TR, Benedetti TJ, Carlson KL, Watts DH. Measurement of cardiac output in pregnancy by thermodilution and impedance techniques. Br J Obstet Gynaecol 1989a; 96: 67-69.

Easterling TR, Benedetti TJ. Techniques differ in use of Doppler ultrasonography. Am J Obstet Gynecol 1989b; 161: 1748-1749.

Easterling TR, Benedetti TJ. Measurement of cardiac output by impedance cardiography. Am J Obstet Gynecol 1990a; 163: 1104-1106.

Easterling TR, Carlson KL, Schmucker BC, Brateng DA, Benedetti TJ. Measurement of cardiac output in pregnancy by Doppler technique. Am J Perinatol 1990b; 3: 220-222.

Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstet Gynecol 1990c; 76: 1061-1069.

Eastham RD. Plasma viscosity estimation in the improved haematological screening of antenatal patients. J Obstet Gynaecol Brit Commonw 1965;72: 763-764.

Edler I, Hertz CH. Use of ultrasonic reflectoscope for continuous recording of movements of heart walls. Kung Fysiograf Sallsk Lund Fordhandl 1954; 24: 40.

Edler I, Gustofson A, Karlefors T, Christenson B. Ultrasound cardiography. Acta Med

Scand 1961; 370 (Suppl) 68-170.
Edler I, Lindstrom K. Ultrasonic Doppler technique used in heart disease. I. An experimental study. Ultrasono Graphia Medica Separatum. 1st World Congress on Ultrasonic Diagnosis in Medicine and SIDUO III. (Ed, Bock J, Ossoing K). Verlag der Wiener Medizinischen Akademia 1969; 455-476.
Eldridge MW, Alverson DC, Howard EA, Berman W. In; Pulsed Doppler ultrasound: Principles and Instrumentation. (Ed, Berman W). Futura, New York 1983; 5-40.
Eliasch H, Lagerlof H, Bucht H, Ek J, Eriksson K, Bergstrom J, Werko L. Comparison of the dye dilution and the direct Fick methods for the measurement of cardiac output in man. Scand J Clin Lab Invest 1954; 7 (Suppl 20): 73-78.
Enein M, Zina AAA, Kassem M, El-Tabbakh G. Echocardiography of the pericardium in pregnancy. Obstet Gynecol 1987; 69: 851-853.
Ernst C, Weiss R. Ueber das zirkulatonsche Minutenvolumen bei Kreislaufdecompensierten. Klin Wschr 1930; 9: 2393-2395.

Fagard R, Van den Broeke C, Vanhees L, Staessen J, Amery A. Noninvasive assessment of systolic and diastolic left ventricular function in female runners. Eur Heart J 1987; 8: 1305-1311.
Fagard R, Conway J. Measurement of cardiac output: Fick principle using catheterization. Eur Heart J 1990; 11 (Suppl 1): 1-5.
Fegler G. Measurement of cardiac output in anaesthetized animals by the thermodilution method. Quart J Exptl Physiol 1954; 39: 153-164.
Feigenbaum H, Wolfe SB, Popp RL, Haine CL, Dodge HT. Correlation of ultrasound with angiocardiography in measuring left ventricular diastolic volume. Am J Cardiol 1969; 23: 111 (Abstract).
Feigenbaum H. In; Echocardiography. Lea and Fabiger, Philadelphia 1986; 1-126.
Felner JM, Blumenstein BA, Schlant RC, Carter AD, Alimurung BN, Johnson MJ, Sherman SW, Klicpera MW, Kutner MH, Drucker LW. Sources of variability in echocardiographic measurements. Am J Cardiol 1980; 45: 995-1004.
Ferguson RJ, Faulkner JA, Julius S, Conway J. Comparison of cardiac output determined by CO_2 rebreathing and dye dilution methods. J Appl Physiol 1968; 25: 450-454.
Ferrazza A, Marino B, Giusti V, Affinito V, Ragonese P. Usefulness of left and right oblique subcostal view in the echo-Doppler investigation of pulmonary arterial blood flow in patients with chronic obstructive pulmonary disease. Chest 1990; 98: 286-289.
Fick A. Ueber die Messung des Blutquantums in der Herzventrikeln. SB phys-med Ges Wurzburg 1870; 16.
Fifer MA, Braunwald E. End-systolic pressure-volume and stress-length relations in the assessment of ventricular function in man. In; Advances in Cardiology Vol 32 (Ed, Spodick DH); Karger, Basel 1985; 36-55.
Fisher DC, Sahn DJ, Friedman MJ, Larson D, Valdes-Cruz LM, Horowitz S, Goldberg

SJ, Allen HD. The mitral valve orifice method for noninvasive two-dimensional echo Doppler determinations of cardiac output. Circulation 1983; 67: 872-877.
Forssmann W. Die Sondierung des rechten Herzens. Klin Wschr 1929; 8: 2085-2087.
Fox IJ, Brooker LGS, Heseltine DW, Essex HE, Wood EH. A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. Proc Staff Meet Mayo Clin 1957; 32: 478-486.
Fortuin NJ, Wood WP, Sherman ME, Craige E. Determination of left ventricular volume by ultrasound. Circulation 1971; 44: 575-584.
Fortuin NJ, Hood WP, Craige E. Evaluation of left ventricular function by echocardiography. Circulation 1972; 46: 26-35.
Francis GS, Hagan AD, Oury J, O'Rourke RA. Accuracy of echocardiography for assessing aortic root diameter. Br Heart J 1975; 37: 376-378.
Frank O. Zur dynamik des herzmuskels. Zeitschrift Fur Biologie 1895; 32: 370.
Frank O. Die Grundform des arteriellen Pulses. Erste Abhandlung. Mathematische Analyse. Zeitschrift Fur Biologie 1899; 37: 483.
Fraser CB, Light LH, Shinebourne EA, Buchtal A, Healy MJR, Beardshaw JA. Transcutaneous aortovelography in adults and children. Eur J Cardiol 1976; 4: 181-189.

Gallery EDM, Ross M, Grigg R, Bean C. Are the renal functional changes of human pregnancy caused by prostacyclin. Prostaglandins 1985; 30: 1019-1029.
Gammeltoft SA. Recherches sur le débit cardiaque par minute pendant la grossesse. Compt rend Soc de Biol 1926; 94: 1099-1101.
Ganong WF. Cardiovascular regulatory mechanisms. In; Review of Medical Physiology 8th Edition. Lange, Los Altos 1977; 443-452.
Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJC. A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 1971; 27: 392-396.
Gardin JM, Dabestani A, Matin K, Allfie A, Russell D, Henry WL. Reproducibility of Doppler aortic blood flow measurements: studies on intraobserver, interobserver and day-to-day variability in normal subjects. Am J Cardiol 1984; 54: 1092-1098.
Gardin JM, Tobis JM, Dabestani A, Smith C, Elkayam U, Castleman E, White D, Allfie A, Henry WL. Superiority of two-dimensional measurement of aortic vessel diameter in Doppler echocardiographic estimates of left ventricular stroke volume. J Am Coll Cardiol 1985; 6: 66-74.
Gauer OH, Henry JP. Neurohormonal control of plasma volume. In; Cardiovascular Physiology II.(Eds. Guyton AC, Cowley AW). University Park Press, Baltimore 1976; 145-190.
Geddes LE, Baker LE. Thoracic impedance changes following saline injection into right and left ventricles. J Appl Physiol 1972; 33: 278-285.
Gemelli M R, Falcone M, Leone G, Pacelli M, Galeotta G, Clemenzia G. Cardiovascular effects induced by progesterone administration. Panminerva Medica 1989; 31: 28-29.
Gibson DG. Estimation of left ventricular size by echocardiography. Br Heart J 1973; 35:

128-134.
Gibson DG, Brown DJ. Measurement of peak rates of left ventricular wall movement in man. Comparison of echocardiography with angiocardiography. Br Heart J 1975; 37: 677-683.
Gillam LD, Kritzer GL, Ascah KJ, Wilkins GT, Marshall JE. Which cardiac valve provides the best estimates of cardiac output in humans. Circulation 1985; 72: III-99 (Abstract 393).
GinsburgJ, Duncan SLB. Peripheral blood flow in normal pregnancy. Cardiovasc Res 1967; 1: 132-137.
Gisclard V, Miller VM, Vanhoutte PM. Effect of 17β-estradiol on endothelium-dependent responses in the rabbit. J Pharmacol Exp Ther 1988; 244: 19-22.
Gisvold SE, Brubakk AO. Measurement of instantaneous blood-flow velocity in the human aorta using pulsed Doppler ultrasound. Cardiovasc Res 1982; 16: 26-33.
Goldberg SJ, Areias J, Spitaels SEC, de Villeneuve VH. Use of time interval histographic output from echo Doppler to detect left-to-right atrial shunts. Circulation 1978; 58: 147-154.
Goldberg SJ, Sahn DJ, Allen HD, Valdes-Cruz LM, Hoenecke H, Carnahan Y. Evaluation of pulmonary and systemic blood flow by 2-dimensional Doppler echocardiography using fast Fourier transform spectral analysis. Am J Cardiol 1982; 50: 1394-1400.
Goldberg SJ, Dickinson DF, Wilson N. Evaluation of an elliptical area technique for calculating mitral blood flow by Doppler echocardiography. Br Heart J 1985; 54: 68-75.
Goldberg SJ, Allen HD, Marx GR, Donnerstein RL. In: Doppler Echocardiography. Philadelphia: Lea & Fabiger, 1988: 1-186.
Gonzalez-Compoy JM, Romero JC, Knox FC. Escape from the sodium-retaining effects of mineralocorticoids: Role of atrial natiuretic factor and intrarenal hormone systems. Kidney Int 1989; 35: 767-777.
Goodman RP, Killam AP, Brash AR, Branch RA. Prostacyclin production during pregnancy: comparison of production during normal pregnancy and pregnancy complicated by hypertension. Am J Obstet Gynecol 1982; 142: 817-821.
Goodrich SM, Wood JE. Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy. Am J Obstet Gynecol 1964; 90: 740-744.
Gotshall RW, Wood VC, Miles DS. Comparison of two impedance cardiographic techniques for measuring cardiac output in critically ill patients. Crit Care Med 1989; 17: 806-811.
Granerus G, Elg R. Stroke volume measurement by impedance cardiography using a formula based on the Δz waveform. Clin Phys Physiol Meas 1982; 3: 131-139.
Greenfield JC, Patel DJ. Relation between pressure and diameter in the ascending aorta of man. Circ Res 1962; 10: 778-781.
Greenfield JC, Griggs DM. Relation between pressure and diameter in main pulmonary

artery of man. J Appl Physiol 1963; 18: 557-559.
Gréhant N, Quinquaud CE. Recherche experimentales sur la mesure du volume de sang qui traverse les poumons en un temps donne. C R Soc Biol Paris 1886; 30: 159.
Griffiths CJ, Murray A, Hunter S. Computer assisted M-mode echocardiogram analysis. Clin Phys Physiol Meas 1982; 3: 103-114.
Grollman A. Physiological variations of the cardiac output of man. The constancy of the cardiac output from day to day throughout the year. Am J Physiol 1930; 93: 536-543.
Gross DR, Miller DL, Williams AR. A search for ultrasonic cavitation within the canine cardiovascular system. Ultrasound Med Biol 1985; 11: 85-97.
Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975; 56: 56-64.
Guyton AC. Circulatory physiology: cardiac output and its regulation. WB Saunders, Philadelphia 1963; 39.

Haendchen RV, Povzhitkov M, Meerbaum S, Maruer G, Corday E. Evaluation of changes in left ventricular end-diastolic pressure by left atrial two-dimensional echocardiography. Am Heart J 1982; 104: 740-744.
Haites NE, McLennan F, Mowat DHR, Rawles JM. Assessment of cardiac output by the Doppler ultrasound technique alone. Br Heart J 1985; 53: 123-129.
Hamilton WF. Notes on the development of the physiology of cardiac output. Fed Proc 1945; 4: 183-195.
Hamilton WF, Riley RL, Attyah AM, Cournand A, Fowell DM, Himmelstein A, Noble RP, Remington JW, Richards DW, Wheeler NC, Witham AC. Comparison of the Fick and dye injection methods of measuring the cardiac output in man. Am J Physiol 1948; 153: 309-321.
Hamilton HFH. The cardiac output in normal pregnancy. J Obstet Gynaecol Brit Emp 1949; 56: 548-552.
Hamilton HFH. Blood viscosity in pregnancy. J Obstet Gynaecol Brit Commonw 1950; 57: 530-538.
Hanrath P, Schluter M, Kremer P, Thier W, Meenen S, Weiter R. Assessment of left ventricular function in hypertrophic cardiomyopathy by echocardiography. Eur Heart J 1983; 4 (Suppl F): 39-46.
Hart MV, Mortom MJ, Hosenpud JD, Metcalfe J. Aortic function during normal human pregnancy. Am J Obstet Gynecol 1986; 154: 887-891.
Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J 1978; 40: 131-140.
Hatle L, Angelsen B. Blood velocity measurements using the Doppler effect of backscattered ultrasound. In; Doppler Ultrasound in Cardiology. Lea and Fabiger, Philadelphia 1985; 32-73.
Hausdorf G, Gluth J, Nienaber CA. Non-invasive assessment of end-systolic pressure-length and stress-shortening relationships in normal individuals: significance of different

loading conditions induced by methoxamine and angiotensin II. Eur Heart J 1987; 8: 1099-1108.

Hendricks CH, Quilligan EJ. Cardiac output in pregnancy. Correlation between Evans blue dye and blood pressure methods. Circ Res 1955; 3: 506-509.

Hendricks CH, Quilligan EJ. Cardiac output during labor. Am J Obstet Gynecol 1956; 71:953-972.

Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation 1980; 62: 1054-1061.

Hillis LD, Firth BG, Winniford MD. Analysis of factors affecting the variability of Fick versus indicator dilution measurements of cardiac output. Am J Cardiol 1985; 56: 764-768.

Hinderliter AL, Fitzpatrick A, Schork N, Julius S. Research utility of noninvasive methods of measurement of cardiac output. Clin Pharmacol Ther 1987; 41: 419-425.

Hirata T, Wolfe SB, Popp RL, Helmen CH, Feigenbaum H. Estimation of left atrial size using ultrasound. Am Heart J 1969; 78: 43-52.

Hirata F, Nishida N, Kanamura S, Tsuya T, Hirata S, Ishikawa M, Kanemitsu H, Ishikawa K, Inagaki T. Non-invasive estimates of hemodynamics in normal pregnancy. J Cardiogr 1984; 14: 775-784.

Hodges M, Downs JB, Mitchell LA. Thermodilution and Fick cardiac index determinations following cardiac surgery. Crit Care Med 1975; 3: 182-184.

Hoit BD, Rashwan M, Watt C, Sahn DJ, Bhargava V. Calculating cardiac output from transmitral volume flow using Doppler and M-mode echocardiography. Am J Cardiol 1988; 62: 131-135.

Holen J, Aaslid R, Landmark K, Simonsen S. Determination of pressure gradient in mitral stenosis with a non-invasive ultrasound Doppler technique. Acta Med Scand 1978; 199: 455-460.

Hudson I, Houston A, Aitchison T, Holland B, Turner T. Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound. Arch Dis Child 1990; 65: 15-19.

Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man. Circulation 1983; 67: 593-602.

Hutchins GM, Bulkley BH, Moore GW, Piasio MA, Lohr FT. Shape of human cardiac ventricles. Am J Cardiol 1978; 41: 646-654.

Hytten FE, Leitch I. Cardiovascular dynamics. In: The Physiology of Human Prgnancy. Blackwell, Oxford 1971: 69-110.

Hytten FE, Lind T. Diagnostic Indices in Pregnancy. Ciba-Geigy, Basle; 37.

Hytten FE.Blood volume changes in normal pregnancy. In: Clinics in Haematology. Vol 14 (Ed. Letsky EA).WB Saunders, London 1985: 601-612.

Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Hauge S, Otterstad JE, Simonsen S, Myhre E. Determination of cardiac output by Doppler echocardiography. Br Heart J 1984; 51: 54-

60.
Ihlen H, Endresen K, Myreng Y, Myhre E. Reproducibilty of cardiac stroke volume estimated by Doppler echocardiography. Am J Cardiol 1987a; 59: 975-978.
Ihlen H, Endresen K, Golf S, Nitter-Hauge S. Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermodilution technique and evaluation of reproducibility. Br Heart J 1987b; 58: 455-459.
Ihrman I. A clinical and physiological study of pregnancy in a material from Northern Sweden. VI. The arterial blood pressure at rest and in orthostatic test during and after pregnancy. Acta Soc Med Upsalien 1960a; 65: 315-325.
Ihrman K. A clinical and physiological study of pregnancy in a material from Northern Sweden. VII. The heart volume during and after pregnancy. Acta Soc Med Upsalien 1960b; 65: 326-334.
Innes JA, Mills CJ, Noble MIM, Murphy K, Pugh S, Shore AC, Guz A. Validation of beat by beat pulsed Doppler measurements of ascending aortic blood velocity in man. Cardiovasc Res 1987; 21: 72-80.

James CF, Banner T, Levelle P, Caton D. Noninvasive determination of cardiac output throughout pregnancy. Anesthesiology 1985; 63: A434 (Abstract).
Jansen JRC, Wesseling KH, Settels JJ, Schreuder JJ. Continuous cardiac output monitoring by pulse contour during cardiac surgery. Eur Heart J 1990; 11 (Suppl 1); 26-32.
Johnson RL, Gilbert M, Meschia G, Battaglia FC. Cardiac output distribution and uteroplacental blood flow in the pregnant rabbit: a comparative study. Am J Obstet Gynecol 1985; 151: 682-686.

Kagiya A, Shiratori H, Shinagawa S, Seki K. Systolic time intervals and impedance cardiogram in pregnant and toxemic women. Nippon Sanka Fujinka Gakkai Zasshi 1984; 36: 1087-1094.
Kallay MC, Hyde RW, Smith RJ, Rothbard RL, Schreiner BF. Cardiac output by rebreathing in patients with cardiopulmonary diseases. J Appl Physiol 1987; 63: 201-210.
Kalmanson D, Veyrat C, Chiche P. Atrial versus ventricular contribution in determining systolic venous return. Cardiovasc Res 1971; 5: 293-302.
Kamoi K, Sudo N, Ishibashi M, Yamaji T. Plasma endothelin-1 levels in patients with pregnancy-induced hypertension. N Eng J Med 1990; 323: 1486-1487.
Karliner JS, Gault JH, Eckberg D, Mullins CB, Ross J. Mean velocity of fiber shortening. A simplified measure of left ventricular myocardial contractility. Circulation 1971; 44: 323-333.
Kass DL, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. Circulation 1987; 76: 1422-1436.

Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. Circulation 1978; 58: 434-441.
Kelleher C, Joyce C, Kelly G, Ferriss JB, Blood pressure alters during the normal menstrual cycle. Br J Obstet Gynaecol 1986; 93: 523-526.
Kennedy JW, Baxley WA, Figley MM, Dodge HT, Blackmon JR. Quantitative angiocardiography. I. The normal left ventricle in man. Circulation 1966; 34: 272-278.
Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. Br Med J 1964; I: 532-533.
Kinney EL, Cortada X, Ventura R. Cardiac size and motion during water immersion: Implications for volume homeostasis. Am Heart J 1987; 113: 345-349.
Kinsman JM, Moore JW, Hamilton WF. Studies on the circulation. Injection method; physical and mathematical considerations. Am J Physiol 1929; 89: 322-330.
Kiowski W, Randall OS, Steffens TG, Julius S. Reliability of echocardiography in assessing cardiac output. A comparative study with a dye dilution technique. Klin Wochenschr 1981; 59: 1115-1120.
Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H. Noninvasive evaluation of pulmonary hypertension by pulsed Doppler technique. Circulation 1983; 68: 302-309.
Kjeldesn J. Haemodynamic investigations during labour and delivery. Acta Obstet Gynecol Scand 1979; 89 (Suppl): 77-195.
Klipstein RH, Firmin DN, Underwood SR, Rees RSO, Longmore DB. Blood flow patterns in the human aorta studied by magnetic resonance. Br Heart J 1987; 58: 316-323.
Kolev N, Lazarova M, Lengyel M. Doppler two-dimensional echocardiographic determinations of right ventricular output and diastolic filling. J Cardiogr 1986; 16: 659-667.
Korner PI, Shillingford JP. The quantitative estimation of valvular incompetence by dye dilution curves. Clin Sci 1955; 14: 553-573.
Kristensen BO, Goldberg SJ. Number of cardiac cycles required to accurately determine mean velocity of blood flow in the ascending aorta and pulmonary trunk. Am J Cardiol 1987; 60: 746-747.
Kristensen BO. Assessment of left ventricular hypertrophy by electrocardiography, chest roentgenography and echocardiography, a review. Scand J Clin Lab Invest 1989; 196: 42-47.
Krogh A, Lindhard J. Measurements of the blood flow through the lungs of man. Skand Arch Physiol 1912; 27: 100-125.
Kronik G, Slany J, Mosslacher H. Comparative value of eight M-mode echocardiographic formulas for determining left ventricular stroke volume. Circulation 1979; 60: 1308-1316.
Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerospace Med 1966; 37: 1208-1212.
Kugler JD, Gutgesell HP, Nihill MR. Instantaneous rates left ventricular wall motion in

infants and children. Ped Cardiol 1980; 1: 16-21.
Kupari M. Reproducibility of M-mode echocardiographic assessment of left ventricular function. Significance of temporal range of measurements. Eur Heart J 1984; 5: 412-418.
Kurokawa S, Takahashi M, Katoh Y, Muramatsu J, Kikawada R. Noninvasive evaluation of the ratio of pulmonary to systemic flow in ventricular septal defect by means of Doppler two-dimensional echocardiography. Am Heart J 1988; 116: 1033-1044.

Labovitz AJ, Buckingham TA, Habermehl K, Nelson J, Kennedy HL, Williams GA. The effects of sampling site on the two-dimensional echo-Doppler determination of cardiac output. Am Heart J 1985; 109: 327-332.
Ladipo GOA, Dunn FG, Pringle TH, Bastian B, Lawrie TDV. Serial measurements of left ventricular dimensions by echocardiography. Assessment of week-to-week, inter- and intraobserver variability in normal subjects and patients with valvular heart disease. Br Heart J 1980; 44: 284-289.
Laird WP, Fixler DE. Echocardiographic estimation of pulmonary, systemic flow in children with patent ductus arteriosus. Circulation 1974; 50 (Suppl IV): 184 (Abstract).
Laird-Meeter K, Van De Ley G, Bom TH, Wladimiroff JW. Cardiocirculatory adjustments during pregnancy - An echocardiographic study. Clin Cardiol 1979; 2: 328-332.
Lee W, Rokey R, Cotton DB. Noninvasive maternal stroke volume and cardiac output determinations by pulsed Doppler echocardiography. Am J Obstet Gynecol 1988; 158: 505-510.
Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. Clin Sci 1967a; 32: 453-465.
Lees MM, Taylor SH, Scott DB, Kerr MG. A study of cardiac output at rest throughout pregnancy. J Obstet Gynaecol Br Commonw 1967b; 74: 319-328.
Lehtovirta P. Haemodynamic effects of combined oestrogen / progestogen oral contraceptives. J Obstet Gynaecol Br Commonw 1974; 81: 517-525.
Levett JM, Replogle RL. Thermodilution cardiac output: A critical analysis and review of the literature. J Surg Res 1979; 27: 392-404.
Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425-431.
Lewis PJ, Prostacyclin in pregnancy. Br Med J 1980; II: 1581-1582.
Lewis RP, Rittgers SE, Forester WF, Boudoulas H. A critical review of the systolic time intervals. Circulation 1977; 56: 146-158.
Light LH. Transcutaneous observation of blood velocity in the ascending aorta. J Physiol 1969; 204: 1P-2P (Abstract).
Liljestrand G, Stenstrom N. Clinical studies on the work of the heart during rest. III. Blood flow in cases of increased arterial blood pressure with observations on the influence of pregnancy on the blood flow. Acta Med Scand 1926; 63: 142-152.

Lim YL, Walters WAW. Systolic time intervals in normotensive and hypertensive human pregnancy. Am J Obstet Gynecol 1976; 126: 26-32.

Limacher MC, Ware A, O'Meara ME, Fernandez GC, Young JB. Tricuspid regurgitation during pregnancy: Two-dimensional and pulsed Doppler echocardiographic observations. Am J Cardiol 1985; 55: 1059-1062.

Lindhard J. Uber das Minutenvolum des Herzens bei Ruhe und bei Muskelarbeit. Pflugers Arch ges Physiol 1915; 161: 233-253.

Loeber CP, Goldberg SJ, Allen HD. Doppler echocardiographic comparison of flows distal to the four cardiac valves. J Am Coll Cardiol 1984; 4: 268-272.

Loeber CP, Goldberg SJ, Donnerstein RL, Butler MA. Time variability of cardiac output and stroke volume in persons without cardiac disease. Am J Cardiol 1987a; 59: 714-716.

Loeber CP, Goldberg SJ, Marx GR, Carrier M, Emery RW. How much does aortic and pulmonary artery area vary during the cardiac cycle. Am Heart J 1987b; 119: 95-100.

Looyenga DS, Liebson PR, Bone RC, Balk RA, Messer JV. Determination of cardiac output in critically ill patients by dual beam Doppler echocardiography. J Am Coll Cardiol 1989; 13: 340-347.

Lucas CL, Keagy BA, Hsiao HS, Johnson TA, Henry GW, Wilcox BR. The velocity profile in the canine ascending aorta and its effects on the accuracy of pulsed Doppler determinations of mean blood velocity. Cardiovasc Res 1984; 18: 282-293.

Lumbers ER. Effects on sheep blood pressure of treatment with angiotensin, steroids and salt. Clin Exp Pharm Physiol 1990; 17: 315-319.

Lund CJ. Studies on the iron-deficiency anaemia of pregnancy, including plasma volume, total hemoglobin, erythrocyte protoporphyrin in treated and untreated normal and anaemic patients. Am J Obstet Gynecol 1951; 62: 947-961.

Lund-Johansen P. The dye dilution method for measurement of cardiac output. Eur Heart J 1990; 11 (Suppl 1): 6-12.

Lundstrom NR, Mortensson W. Clinical application of echocardiography in infants and children. II. Estimation of aortic root diameter and left atrial size. A comparison between echocardiography and angiocardiography. Acta Paediatr Scand 1974; 63: 33-41.

Luotola H, Pyorala T, Lahteenmaki P, Toivanen J. Haemodynamic and hormonal effects of short-term oestradiol treatment in postmenopausal women. Maturitas 1979; 1: 287-294.

Luscher TF, Yang Z, Tschudi M, von Segesser L, Stulz P, Boulanger C, Siebenmann R, Turina M, Buhler FR. Interaction between endothelin-1 and endothelium-derived relaxing factor in human arteries and veins. Circ Res 1990; 66: 1088-1094.

Lusiani L, Ronsisvalle G, Bonanome A, Visona A, Castellani V, Macchia C, Pagnan A. Echocardiographic evaluation of the dimensions and systolic properties of the left ventricle in freshman athletes during physical training. Eur Heart J 1986; 7: 196-203.

Lynch PR, Bove AA. Patterns of blood flow through the intact heart and its valves. In; Prosthetic Heart Valves. (Ed. Brewer LA). CC Thomas, Illinois 1969;24-33.

MacGillivray I, Campbell D, Duffus GM. Maternal metabolic response to twin

pregnancy in primigravidae. J Obstet Gynaecol Brit Commonw 1971; 78: 530-534.

MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. Clin Sci 1969; 37: 395-407.

MacLennan BA, Maguire C, Campbell NPS. Doppler echocardiographic determination of flow from five cardiac locations: a comparison with thermodilution. Br Heart J 1986; 55: 517 (Abstract).

McCall ML. Cerebral blood flow and metabolism in toxemias of pregnancy. Surg Gynec Obstet 1949; 89:715-721.

McCormack DG, Mak JCW, Coupe MO, Barnes PJ. Calcitonin gene-related peptide vasodilation of human pulmonary vessels. J Appl Physiol 1989; 67: 1265-1270.

McDonald KM, Taher MS, Schrier RW. Effect of competitive inhibitor of angiotensin on renin release and arterial pressure. In; Recent Advances in Hypertension Vol 1. (Eds; Milliez P, Safar M). Boehringer Ingelheim, Monte Carlo 1975; 231-245.

McLaughlin MK, Griggs K, Crandall ME. Pregnancy enhances endothelium-dependent relaxation. Proc Ann Meet Soc Gynecol Invest 1989; 171 (Abstract).

McLennan CE. Antecubital and femoral venous pressure in normal and toxemic pregnancy. Am J Obstet Gynecol 1945; 43: 568-572.

McLennan FM, Haites NE, Mackenzie JD, Daniel MK, Rawles JM. Reproducibility of linear cardiac output measurement by Doppler ultrasound alone. Br Heart J 1986; 55: 25-31.

McLennan FM, Haites NE, Rawles JM. Stroke and minute distance in pregnancy: a longitudinal study using Doppler ultrasound. Br J Obstet Gynaecol 1987; 94: 499-506.

Mackenzie JD, Haites NE, Rawles JM. Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers. Br Heart J 1986; 55: 14-24.

Maeda M, Yokota M, Iwase M, Miyahara T, Hayashi H, Sotobata I. Accuracy of cardiac output measured by continuous wave Doppler echocardiography during dynamic exercise testing in the supine position in patients with coronary artery disease. J Am Coll Cardiol 1989; 13: 76-83.

Magnin PA, Stewart JA, Myers S, Von Ramm O, Kisslo JA. Combined Doppler and phased-array echocardiographic estimation of cardiac output. Circulation 1981; 63: 388-392.

Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. Arch Path 1967; 83: 336-341.

Mangiarotti R, Martinotti R, Monzani V, Sardella F, Pierini A, Pastori M, Randazzo A. Influence of the heart rate on mean circumferential shortening velocity: Echocardiographic study of 183 normal subjects. Cardiology 1986; 73: 347-353.

Marino P, Zanolla L, Nidasio GP, Nicolosi GL, Fabbri A. Interpretative reproducibility of two-dimensional echocardiographic images. Analysis of intraobserver, interobserver and beat to beat reproducibility of the mitral valve orifice. Eur Heart J 1983; 4: 733-737.

Marshall EK, Grollman A. A method for the determination of the circulation minute

Marshall EK, Grollman A. A method for the determination of the circulation minute volume in man. Am J Physiol 1928; 86: 117-137.
Martin MA. Assessment of correction formula for echocardiographic estimations of left ventricular volumes. Br Heart J 1978; 40: 294-296.
Maruta S. The observation of the maternal hemodynamics during labor and cesarean section. Nippon Sanka Fujinka Gakkai Zasshi 1982; 34: 776-784.
Masaki DI, Greenspoon JS, Ouzounian JG. Measurement of cardiac output in pregnancy by thoracic electrical bioimpedance and thermodilution. Am J Obstet Gynecol 1989; 161: 680-684.
Mashini IS, Albazzaz SJ, Fadel HE, Abdulla AM, Hadi HA, Harp R, Devoe LD. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. Am J Obstet Gynecol 1987; 156: 1208-1213.
Matsunaga T. Studies on maternal hemodynamics during normal pregnancy: Correlation between maternal hemodynamics and fetal growth. Nippon Sanka Fujinka Gakkai Zasshi 1984; 36: 795-804.
Mehta N, Iyawe VI, Cummin RC, Bayley S, Saunders KB, Bennett ED. Validation of a Doppler technique for beat-to-beat measurement of cardiac output. Clin Sci 1985; 69: 377-382.
Meijboom EJ, Horowitz S, Valdes-Cruz LM, Sahn DJ, Larson DF, Lima CO. A Doppler echocardiographic method for calculating volume flow across the tricuspid valve: correlative laboratory and clinical studies. Circulation 1985; 71: 551-556.
Meijboom EJ, Horowitz S, Valdes-Cruz LM, Larson DF, Bom N, Rijsterborgh H, Lima CO, Sahn DJ. A simplified mitral valve method for two-dimensional echo Doppler blood flow calculation: Validation in an open-chest canine model and initial clinical studies. Am Heart J 1987a; 113: 335-340.
Meijboom EJ, Rijsterborgh H, Bot H, de Boo JAJ, Roelandt JRTC, Bom N. Limits of reproducibility of blood flow measurements by Doppler echocardiography. Am J Cardiol 1987b; 59: 133-137.
Merkouris RW, Miller FC, Catanzarite V, Rigg LA, Quirk G, Vesley DL. Increase in the plasma levels of the N-terminal and C-terminal portions of the prohormone of atrial natiuretic factor during normal pregnancy. Am J Obstet Gynecol 1990;162: 859-864.
Miller DE, Gleason WL, McIntosh HD. A comparison of the cardiac output determination by the direct Fick method and the dye-dilution method using indocyanine green dye and a cuvette densitometer. J Lab Clin Med 1962; 59: 345-350.
Miller MW, Church CC, Barnett SB. Bioeffects of Doppler ultrasound. In; Doppler ultrasound measurement of maternal-fetal hemodynamics (Eds, Maulik D, McNellis D). Perinatology Press, New York 1987; 105-114.
Miller WE, Richards KL, Crawford MH. Accuracy of mitral Doppler echocardiographic cardiac output determinations in adults. Am Heart J 1990; 119: 905-910.
Milsom I, Forssman L, Sivertsson R, Dottori O. Measurement of cardiac stroke volume by impedance cardiography in the last trimester of pregnancy. Acta Obstet Gynecol Scand

Milsom I, Forssman L, Biber B, Dottori O, Sivertsson R. Measurement of cardiac stroke volume during cesarean section: a comparison between impedance cardiography and the dye dilution technique. Acta Anaesthesiol Scand 1983b; 27: 421-426.

Milsom I, Hedner J, Hedner T. Plasma atrial natiuretic peptide (ANP) and maternal hemodynamic changes during normal pregnancy. Acta Obstet Gynecol Scand 1988; 67: 717-722.

Mitchell AM, Cournand A. Fate of circulating lactic acid in human lung. J Clin Invest 1955; 34: 471-476.

Monoson PA, O'Rourke RA, Crawford MH, White DH. Measurements of left ventricular wall thickness and systolic thickening by M mode echocardiography: interobserver and intrapatient variability. J Clin Ultrasound 1978; 6 : 252-258.

Mooney P, Dalton KJ, Swindells HE, Rushant S, Cartwright W, Juett D. Blood pressure measured telemetrically from home throughout pregnancy. Am J Obstet Gynecol 1990; 163: 30-36.

Moutquin JM, Rainville C, Giroux L, Raynauld P, Amyot G, Bilodeau R, Pelland N. A prospective study of blood pressure in pregnancy: prediction of preeclampsia. Am J Obstet Gynecol 1985; 151: 191-196.

Mulholland HC, Boyle D McC. The effect of posture on the cardiac output during the last six weeks of pregnancy. Am Heart J 1968; 76: 291-293.

Murray JA, Johnston J, Reid JM. Echocardiographic determination of left ventricular dimensions, volumes and performance. Am J Cardiol 1972; 30: 252-257.

Myhrman P, Granerus G, Karlsson K, Lundgren Y. Cardiac output in normal pregnancy measured by impedance cardiography. Scand J Clin Lab Invest 1982; 42: 513-520.

Nadeau S, Noble WH. Limitations of cardiac output measurements by thermodilution. Can Anaesth Soc J 1986; 33: 780-784.

Nagger CZ, Dobnik DB, Flessas AP, Kripke BJ, Ryan TJ. Accuracy of the stroke index as determined by the transthoracic electrical impedance method. Anesthesiology 1975; 42: 201-205.

Newman B. Cardiac output changes during Caesarean section. Anaesthesia 1982; 37: 270-273.

Nicolosi GL, Pungercic E, Cervesato E, Moden L, Zanuttini D. Analysis of interobserver and intraobserver variation of interpretation of the echocardiographic and Doppler flow determination of cardiac output by the mitral orifice method. Br Heart J 1986; 55: 446-448.

Nicolosi GL, Pungercic E, Cervesato E, Pavan D, Modena L, Moro E, Dall'Aglio V, Zanuttini D. Feasibility and variability of six methods for the echocardiographic and Doppler determination of cardiac output. Br Heart J 1988; 59: 299-303.

Niederle P, Stárek A, Jerek V, Jezkova J, Hes I, Michaljanic A. Assessment of stroke volume and cardiac output by Doppler echocardiography. Cor Vasa 1988; 30: 338-344.

Nielsen OW, Hansen S, Christensen P, Gronlund J. Repeatability of the acetylene

rebreathing method in measuring cardiac output: influence of acetylene concentration. Acta Anaesthesiol Scand 1990; 34: 354-357.

Nishimura RA, Callahan MJ, Schaff HV, Ilstrup DM, Miller FA, Tajik AJ, Noninvasive measurement of cardiac output by continuous-wave Doppler echocardiography: initial experience and review of the literature. Mayo Clin Proc 1984; 59: 484-489.

Nolton WE, Ehrlich EN. Sodium and mineralocorticoids in normal pregnancy. Kidney Int 1980; 18: 162-172.

Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. Br Heart J 1990; 63: 93-97.

O'Connell JB, Costanzo-Nordin MR, Subramanian R, Robinson JA, Wallis DE, Scanlon PJ, Gunnar RM. Peripartum cardiomyopathy: clinical, hemodynamic, histologic and prognostic characteristics. J Am Coll Cardiol 1986; 8: 52-56.

O'Rourke RA, Hanrath P, Henry WH, Hugenholz PG, Pisa Z, Roelandt J, Tanaka M. Report of the Joint International Society and Federation of Cardiology / World Health Organization Task Force on recommendations for standardization of measurements from M-mode echocardiograms. Circulation 1985; 69: 854A-857A.

Okamoto M, Tsubokurs T, Morishita K, Nakagawa H, Yamagata T, Kawagoe T, Hondo T, Tsuchioka Y, Matsuura H, Kagiyama G. Effects of volume loading on left atrial systolic time intervals. J Clin Ultrasound 1991; 19: 405-4111.

Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. I. A two-dimensional echocardiographic method and findings in normal subjects. Circulation 1981; 64: 113-120.

Palmer AJ, Walker AHC. The maternal circulation in normal pregnancy. J Obstet Gynaecol Brit Emp 1949; 56: 537-547.

Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. J Physiol 1914; 48: 357-374.

Pearson ES, Hartley HO. Biometrika Tables for Statisticians. Volume I. Cambridge University Press, London 1966; 52-55.

Peeters LLH, Grutters G, Martin CB. Distribution of cardiac output in the unstressed pregnant guinea pig. Am J Obstet Gynecol 1980; 138: 1177-1184.

Petrie JC, O'Brien ET, Littler WA, de Swiet M. Recommendations on blood pressure measurement. British Hypertension Society. Br Med J 1986; 293: 611-615.

Phippard AF, Horvath JS, Glynn EM, Garner MG, Fletcher PJ, Duggin GG, Tiller DJ. Circulatory adaptation to pregnancy - serial studies of haemodynamics, blood volume, renin and aldosterone in the baboon (Papio hamadryas). J Hypertens 1986; 4: 773-779.

Pickles VR. Blood-flow estimations as indices of mammary activity. J Obstet Gynaecol Brit Emp 1953; 60: 301-311.

Pines A, Fisman EZ, Levo Y, Averbuch M, Lidor A, Drory Y, Finkelstein A, Hetman-

Peri M, Moshkowitz M, Ben-Ari E, Ayalon D. The effects of hormone replacement therapy on normal postmenopausal women: measurements of Doppler-derived parameters of aortic flow. Am J Obstet Gynecol 1991; 164: 806-812.

Pirani BBK, Campbell DM, MacGillivray I. Plasma volume in normal first pregnancy. J Obstet Gynaecol Brit Commonw 1973; 80: 884-887.

Pivarnik JM, Lee W, Clark SL, Cotton DB, Spillman HT, Miller JF. Cardiac output responses of primigravid women during exercise determined by the direct Fick technique. Obstet Gynecol 1990; 75: 954-959.

Plesch J. Hamodynamische studien. Z exp Path Therap 1909; 6: 380-618.

Poiseuille JLM. Recherches expérimentales sur le mouvement des liquides dans les tubes de trés-petites diamétres. Mémoires présentes par divers savanta a l'Acad Sci de l'Institut de France 1846; 9: 433.

Pombo JF, Troy BL, Russell RO. Left ventricular volumes and ejection fraction by echocardiography. Circulation 1971a; 43: 480-490.

Pombo JF, Russell RO, Rackley CE, Foster GL. Comparison of stroke volume and cardiac output determination by ultrasound and dye dilution in acute myocardial infarction. Am J Cardiol 1971b; 27: 630-635.

Popp RL, Harrison DC. Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. Circulation 1970; 41: 493-502.

Powner DJ, Dahl D, Shucker L. Ear densitometer cardiac outputs versus thermodilution outputs. Crit Care Med 1984; 12: 148-149.

Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM, Reed GP, Bruce DM. Blood volume changes in pregnancy. II. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, cesarean section, cesarean section plus total hysterectomy. Am J Obstet Gynecol 1962; 84: 1271-1278.

Pridjian G, Lang R, Feldman T, Borow K, Lindheimer. M. Cardiac output and load independent left ventricular contractility in preeclampsia assessed noninvasively. 6th International Congress of the International Society for the Study of Hypertension in Pregnancy, Montreal 1988; Abstract 253.

Pyorala T. Cardiovascular response to the upright position during pregnancy. Acta Obstet Gynecol Scand 1966; 45 (Suppl 5): 44-74.

Quilligan EJ, Tyler C. Postural effects on the cardiovascular status in pregnancy: a comparison of the lateral and supine positions. Am J Obstet Gynecol 1959; 78: 465-471.

Quinones MA, Gaasch WH, Alexander JK. Echocardiographic assessment of left ventricular function. Circulation 1974; 50: 42-51.

Quinones MA, Gaasch W, Alexander JK. Influence of acute changes in preload, afterload, contractile state, and heart rate on ejection and isovolumic indices of myocardial contractility in man. Circulation 1976; 53: 293-302.

Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Chest 1978; 74: 59-65.

Reckelhoff JF, Samsell L, Baylis C. Failure of an acute 10-15% plasma volume expansion in the virgin female rat to mimic the increased glomerular filtration rate and altered glomerular hemodynamics seen at midterm pregnancy. Clin Exp Hypertens Pregnancy 1989; B8: 533-549.

Reddy PS, Curtiss EI, Bell B, O'Toole JD, Salerni R, Leon DF, Shaver JA. Determinants of variation between Fick and indicator dilution estimates of cardiac output during diagnostic catheterization. Fick vs. dye cardiac outputs. J Lab Clin Med 1976; 87: 568-576.

Reed JH, Wood EH. Use of dichromatic earpiece densitometry for determination of cardiac output. J Appl Physiol 1967; 23: 373-380.

Rees GB, Stainer K, Broughton Pipkin F, Symonds EM. The carbon dioxide rebreathing technique to measure cardiac output in pregnancy and pre-eclampsia. 6th International Congress, International Society for the Study of Hypertension in Pregnancy. Abstract 254.

Reichek N, Helak J, Plappert T, St John Sutton M, Weber K. Anatomic validation of left ventricular mass estimates from clinical two-dimensional echocardiography: initial results. Circulation 1983; 67: 348-352.

Remington JW, Noback CR, Hamilton WF, Gold JJ. Volume elasticity characteristics of the human aorta and prediction of the stroke volume from the pressure pulse. Am J Physiol 1948; 298: 298-308.

Reybrouck T, Fagard R. Assessment of cardiac output at rest and during exercise by a carbon dioxide rebreathing method. Eur Heart J 1990; 11 (Suppl 1): 21-25.

Rijsterborgh H, Mayala A, Forster T, Vletter W, Van der Borden B, Sutherland GR, Roelandt J. The reproducibility of continuous wave Doppler measurements in the assessment of mitral stenosis or mitral prosthetic function: the relative contributions of heart rate, respiration, observer variability and their clinical relevance. Eur Heart J 1990; 11: 592-600.

Robinson PS, Crowther A, Jenkins BS, Webb-Pebloe MM, Coltart DJ. A computerized dichromatic earpiece densitometer for the measurement of cardiac output. Cardiovasc Res 1979; 13: 420-426.

Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. Br Med J 1987; 295: 1169-1172.

Robson SC, Murray A, Peart I, Heads A, Hunter S. Reproducibility of cardiac output measurement by cross sectional and Doppler echocardiography. Br Heart J 1988; 59: 680-684.

Robson SC, Boys RJ, Hunter S, Dunlop W. Maternal hemodynamics after normal delivery and delivery complicated by postpartum hemorrhage. Obstet Gynecol 1989a; 74: 234-239.

Robson SC, Dunlop W, Hunter S, Boys R, Bryson M. Haemodynamic changes associated with caesarean section under epidural anaesthesia. Br J Obstet Gynaecol 1989b; 96: 642-647.

Robson SC, Dunlop W, Boys RJ, Hunter S. Haemodynamic effects of breast feeding.

Br J Obstet Gynaecol 1989c; 96: 1106-1108.

Robson SC, Mutch E, Boys RJ, Woodhouse KW. Apparent liver blood flow during pregnancy: a serial study using indocyanine green clearance. Br J Obstet Gynaecol 1990; 97: 720-724.

Robson SC, Hunter S, Boys RJ, Dunlop W. Serial changes in pulmonary haemodynamics during human pregnancy: a non-invasive study using Doppler echocardiography. Clin Sci 1991; 80: 113-117.

Robson SC, Richley D, Boys RJ, Hunter S. Incidence of Doppler regurgitant flow velocities during normal pregnancy. Eur Heart J 1992; 13: 84-87.

Roelandt J. Comprehensive M-mode and two-dimensional echocardiographic examination: Anatomy, technique, image orientation and specific clinical applications. In; The practice of M-mode and two-dimensional echocardiography. Martinus Nijhoff, The Hague 1983; 17-50.

Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. Circulation 1985; 71: 543-550.

Romney SL, Reid DE, Metcalfe J, Burwell CS. Oxygen utilization by the human fetus in utero. Am J Obstet Gynecol 1955; 70: 791-797.

Rose JS, Nanna M, Rahimtoola SH, Elkayam U, McKay C, Chandraratna PAN. Accuracy of determination of changes in cardiac output by transcutaneous continuous-wave Doppler computer. Am J Cardiol 1984; 54: 1099-1101.

Rosenfeld CR. Distribution of cardiac output in ovine pregnancy. Am J Physiol 1977; 232: H231-H235.

Roy SB, Malkani PK, Virik R, Bhatia ML. Circulatory effects of pregnancy. Am J Obstet Gynecol 1966; 96: 221-225.

Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy. II. Cardiac output and left ventricular work in multiple pregnancy. Am J Obstet Gynecol 1966a; 95:781-786.

Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy. III. Cardiac rate, stroke volume, total peripheral resistance, and central blood volume in multiple pregnancy. Synthesis of results. Am J Obstet Gynecol 1966b; 95: 787-794.

Rubler S, Schneebaum R, Hammer N. Systolic time intervals in pregnancy and the postpartum period. Am Heart J 1973; 86: 182-188.

Rubler S, Damani PM, Pinto ER. Cardiac size and performance during pregnancy estimated with echocardiography. Am J Cardiol 1977; 40: 534-540.

Runciman WB, Ilsley AH, Roberts JG. Thermodilution cardiac output - a systematic error. Anaesth Intensive Care 1981; 9: 135-139.

Rushmer RF. The cardiac output. In; Cardiovascular Dynamics. WB Saunders, Philadelphia 1961; 53-84.

Russell AE, Smith SA, West MJ, Aylward PE, McRitchie RJ, Hassam RM, Minson RB, Wing LMH, Chalmers JP. Automated non-invasive measurement of cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution and thermodilution. Br

Heart J 1990; 63: 195-199.

Rutherford AJ, Anderson JV, Elder MG, Bloom SR. Release of atrial natiuretic peptide during pregnancy and immediate puerperium. Lancet 1987; I: 928-929.

Sady SP, Carpenter MW, Thompson PD, Sady MA, Haydon B, Coustan DR. Cardiovascular response to cycle exercise during and after pregnancy. J Appl Physiol 1989; 66: 336-341.

Sady MA, Haydon BB, Sady SP, Carpenter MW, Thompson PD, Coustan DR. Cardiovascular response to maximal cycle exercise during pregnancy and at two and seven months post partum. Am J Obstet Gynecol 1990; 162: 1181-1185.

Sahn DJ, Valdes-Cruz LM. New advances in two-dimensional Doppler echocardiography. Progr Cardiovasc Dis 1986; 28: 367-382.

Saito Y, Goto T, Terasaki H, Hayashida Y, Morioka T. The effects of pulmonary circulation pulsatility on the impedance cardiogram.Arch Int Physiol Bioch 1983; 91: 339-344.

Salmasi AM, Salmasi SN, Doré C, Nicolaides AN. Non-invasive assessment of changes in aortic blood velocity and its derivatives with exercise in normal subjects by Doppler ultrasound. J Cardiovasc Surg 1987; 28: 321-327.

Sanders SP, Yaeger S, Williams RG. Measurment of systemic and pulmonary blood flow and QP/QS ratio using Doppler and two-dimensional echocardiography. Am J Cardiol 1983; 51: 952-956.

Sanderson JE, Trail TA, St John Sutton MG, Brown DJ, Gibson DG, Goodwin JF. Left ventricular relaxation and filling in hypertrophic cardiomyopathy. AN echocardiographic study. Br Heart J 1978; 40: 596-601.

Satomura S. A study on examining the heart with ultrasonics. I. Principles; II. Instrument. Jpn Circ J 1956; 20: 227-240.

Schaible TF, Murphy A, Ciambrone G, Scheuer J. Effects of sex hormones on cardiac function in female rats. J Am Coll Cardiol 1986; 7: 122A (Abstract).

Schlant RC, Sonnenblick EH. Normal physiology of the cardiovascular system. In: The Heart Arteries and Veins 7th Edition (Ed. Hurst JW). McGraw-Hill, New York 1990; 35-71.

Schmidt RH. Uber die Herzarbeit in der Fruhschwangerschaft in der Ruhe und nach Arbeitsversuchen. Monatschr f Geburtsh u Gynak 1932; 90: 83-99.

Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. N Eng J Med 1988; 319: 1127-1134.

Schrier RW, Briner VA. Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: implications for pathogenesis of preeclampsia-eclampsia. Obstet Gynecol 1991;77: 632-639.

Schultz DL, Tunstall-Pedoe DS, Lee G de J, Gunning AJ, Bellhouse BJ. Velocity distribution and transition in the arterial system. In; Circulatory and Respiratory Mass

Transport. (Eds, Wolstenholme GEW, Knight J). J & A Churchill, London; 172-199.
Schwarz R. Das Verhalten des Kreislaufs in der normalen Schwangerschaft. Archiv fur Gynakologie 1964; 199: 549-570.
Secher NJ, Arnsbo P, Heslet Anderson L, Thompson A. Measurement of cardiac stroke volumes in various body positions in pregnancy and during caesarean section: a comparison between thermodilution and impedance cardiography. Scand J Lab Invest 1979; 39: 569-576.
Seed WA, Wood NB. Velocity patterns in the aorta. Cardiovasc Res 1971; 5: 319-330.
Seely RD, Nerlich WE, Gregg DE. A comparison of cardiac output determination by the Fick procedure and a direct method using a rotameter. Circulation 1950; 1: 1261-1266.
Selzer A, Sudrann RB. Reliability of the determination of cardiac output in man by means of the Fick principle. Circ Res 1958; 6: 485-490.
Sequeira RF, Light LH, Cross G, Raftery EB. Transcutaneous aortovelography. A quantitative evaluation. Br Heart J 1976; 38: 443-450.
Siegert R, Hanrath P, Bleifeld W, Kupper W, Mathey D. Abnormal relaxation and diastolic filling pattern in different forms of LV hypertrophy. Circulation 1978; 58 (Suppl II): 52 (Abstract).
Skaerpe T, Hegrenes L, Ihlen H. Cardiac output. In; Doppler Ultrasound in Cardiology. (Eds. Hatle L, Angelsen B). Lea and Fabiger, Philadelphia 1985; 306-317.
Slater AJ, Gude N, Clarke IJ, Walters WAW. Haemodynamic changes and left ventricular performance during high-dose oestrogen administration to male transsexuals. Br J Obstet Gynaecol 1986; 93: 532-538.
Slemons JM, Goldsborough FC. The obstetrical significance of the blood pressures and their relation to the work of the heart. John Hopkins Hosp Bull 1908; 19: 194-196.
Spiller P, Webb-Peploe MM. Blood flow. Eur Heart J 1985; 6 (Supplement C): 11-18.
Smith SA, Russell AE, West MJ, Chalmers J. Automated non-invasive measurement of cardiac output: comparison of electrical bioimpedance and carbon dioxide rebreathing techniques. Br Heart J 1988; 59: 292-298.
Spinelli JC, Valentinuzzi ME. Stroke volume in the dog: measurements by the impedance technique and thermodilution. Medical Progress through Technology 1983; 10: 45-53.
Sramek BB, Rose DM, Miyamoto A. Stroke volume equation with a linear base impedance model and its accuracy as compared to thermodilution and magnetic flowmeter techniques in humans and animals. In; Proceedings of the Sixth International Conference on Electrical Bioimpedance. Zadar, Yugoslavia 1983; 38.
Stander HJ, Cadden JF. The cardiac output in pregnant women. Am J Obstet Gynecol 1932; 24: 13-19.
Stead EA, Warren JV, Merrill AJ, Brannon ES. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations of the effects of anxiety and tilt. J Clin Invest 1945; 24: 326-331.
Steegers EAP, van Lakwijk HPJM, Benaad Thj, Tan ACITL, Fast JH, Jongsma HW, de Boo T, Hein PR. Atrial natiuretic peptide (ANP) in normal pregnancy; a longitudinal

study. Clin Exper Hyper Preg 1990; B9: 273-292.
Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis 1982; 126: 1001-1004.
Stevenson JC, MacDonald DWR, Warren RC, Booker MW, Whitehead MI. Increased concentration of circulating calcitonin gene related peptide during normal human pregnancy. Br Med J 1986; 293: 1329-1330.
Stewart GN. The pulmonary circulation time, the quantity of blood in the lungs and the output of the heart. Am J Physiol 1921; 58: 20-44.
Stewart WJ, Jiang L, Mich R, Pandian N, Guerrero JL, Weyman AE. Variable effects of changes in flow rate through the aortic, pulmonary and mitral valves on valve area and flow velocity: impact on quantitative Doppler flow calculations. J Am Coll Cardiol 1985; 6: 653-662.
Symonds EM. Renin-angiotensin system in normal and hypertensive pregnancy. In; Prostacyclin in pregnancy (Eds; Lewis PJ, Moncada S, O'Grady J). Raven Press, New York 1983: 91-98.
Szlachcic J, Massie BM, Greenberg B, Thomas D, Cheitlin M, Bristow JD, Anderson C, Solin R, McDonald R, Smienczuk D. Intertest variability of echocardiographic and chest X-ray measurements: implications for decision making in patients with aortic regurgitation. J Am Coll Cardiol 1986; 7: 1310-1317.

Tanz RD. Inotropic effects of certain steroids upon heart muscle. Rev Can Biol 1963; 22: 147-163.
Taylor SH, Shillingford JP. Clinical applications of Coomassie Blue. Br Heart J 1959; 21: 497-504.
Taylor DEM, Whammond JS. Velocity profile and impedance of the healthy mitral valve. In; The Mitral Valve. A Pluridisciplinary Approach (Ed. Kalmanson D). Edward Arnold, London; 127-136.
Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976; 37: 7-11.
Temma K, Ng Y-C, Brody TM, Akera T. Effects of progesterone derivatives on sodium pump activity and force of myocardial contraction in isolated guinea pig heart. Res Comm Chem Path Pharm 1983; 41: 51-63.
Ter Haar GR, Williams AR. Biophysical and physiological consequences of ultrasonic irradiation of tissue. In; Recent Advances in Ultrasonic Diagnosis. (Eds. Kurjak A, Kratochwil A). Excerpta Medica, Amsterdam 1981; 33-36.
Ter Haar G, Daniels S, Estaugh KC, Hill CR. Ultrasonically induced cavitation in vivo. Br J Cancer; 1982 (Suppl V): 151-160.
Thaler I, Manor D, Itskovitz J, Rottem S, Levit N, Timor-Tritsch I, Brandes JM. Changes in uterine blood flow during human pregnancy. Am J Obstet Gynecol 1990; 162:

121-125.

Thomasson B. Cardiac output in normal subjects under standard basal conditions. The repeatability of measurements by the Fick method. Scand J Clin Lab Invest 1957; 9: 365-376.

Thompson JA, Hays PM, Sagar KB, Cruikshank DP. Echocardiographic left ventricular mass to differentiate chronic hypertension from preeclampsia during pregnancy. Am J Obstet Gynecol 1986; 155: 994-999.

Thomson KJ, Hirsheimer A, Gibson JG, Evans WA. Studies on the circulation in pregnancy. III. Blood volume changes in normal women. Am J Obstet Gynecol 1938; 36: 48-55.

Thoresen M, Wesche J. Doppler measurements of changes in human mammary and uterine blood flow during pregnancy and lactation. Acta Obstet Gynecol Scand 1988; 67: 741-745.

Touche T, de Zuttere D, Nitenberg A, Prasquier R, Gourgon R. Echo-Doppler quantitation of transmitral flow: a new method tested in adult subjects. J Am Coll Cardiol 1985; 5: 425 (Abstract).

Traill TA, Gibson DG, Brown DJ. Study of left ventricular wall thickness and dimension changes using echocardiography. Br Heart J 1978; 40: 162-169.

Triebwasser JH, Johnson RL, Burpo RP, Campbell JC, Reardon WC, Blomqvist CG. Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. Aviat Space Environ Med 1977; 48: 203-209.

Troy BL, Pombo J, Rackley CE. Measurement of left ventricular wall thickness and mass by echocardiography. Circulation 1972; 30: 602-611.

Ueda S, Fortune V, Bull BS, Valenzuela GJ, Longo LD. Estrogen effects on plasma volume, arterial blood pressure, interstitial space, plasma proteins, and blood viscosity in sheep. Am J Obstet Gynecol 1986; 155: 195-201.

Ueland K, Parer JT. Effects of estrogens on the cardiovascular system of the ewe. Am J Obstet Gynecol 1966; 96: 400-404.

Ueland K, Novy MJ, Peterson EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise 1969; 104: 856-864.

Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. Am J Obstet Gynecol 1976; 126: 671-677.

Umans JG, Lindheimer MD, Barron WM. Pressor effect of endothelium-derived relaxing factor inhibition in conscious virgin and gravid rats. Am J Physiol 1990; 259: F293-F296.

Valdes-Cruz LM, Horowitz S, Sahn DJ, Mesel E, Fisher DC, Larson D, Scagnelli S. A simplified mitral valve method for 2D echo Doppler cardiac output. Circulation 1983; 68 (Suppl III); 230 (Abstract).

Van Slyke DD, Neill JM. The determination of gases in blood and other solutions by

vacuum extraction and manometric measurement. J Biol Chem 1924; 61: 523-573.
Vandenbogaerde JF, Scheldewaert RG, Rijckaert DL, Clement DL, Colardyn FA. Comparison between ultrasonic and thermodilution cardiac output measurements in intensive care patients. Crit Care Med 1986; 14: 294-297.
Veille JC, Morton MJ, Burry KJ. Maternal cardiovascular adaptations to twin pregnancy. Am J Obstet Gynecol 1985;153: 261-263.
Vignola PA, Bloch A, Kaplan AD, Walker HJ, Chiotellis PN, Myers GS. Interobserver variability in echocardiography. J Clin Ultrasound 1977; 5: 238-242.
Visscher MB, Johnson JA. The Fick principle. Analysis of potential errors in its conventional application. J Appl Physiol 1953; 5: 635-638.
Vliers ACAP, Visser KR, Zulstra WG. Analysis of indicator distribution in the determination of cardiac output by thermal dilution. Cardiovasc Res 1973; 7: 125-132.
Voogd PJ, Rijsterborgh H, Lubsen J, Arntzenius AC, Monsjou LK, Godijn EH. Reference ranges of echocardiographic measurements in the Dutch population. Eur Heart J 1984; 5: 762-770.
Vorys N, Ullery JC, Hanusek GE. The cardiac output changes in various positions in pregnancy. Am J Obstet Gynecol 1961; 82: 1312-1321.

Wade OL, Bishop JM. Cardiac Output and Regional Blood Flow. Blackwell, Oxford: 1962.
Wade MR, Chandraratna PAN, Reid CL, Lin S, Rahimtoola SH. Accuracy of nondirected and directed M-mode echocardiography as an estimate of left atrial size. Am J Cardiol 1987; 60: 1208-1211.
Wallenburg HCS. Hemodynamics in hypertensive pregnancy. In; Hypertension in Pregnancy. (Ed, Rubin PC). Elsevier, Amsterdam 1988: 66-101.
Wallerson DC, Ganau A, Roman MJ, Devereux RB. Measurement of cardiac output by M-mode and two-dimensional echocardiography: application to patients with hypertension. Eur Heart J 1990; 11 (Suppl 1): 67-78.
Walters BNJ, Thompson ME, Lee A, de Swiet M. Blood pressure in the puerperium. Clin Sci 1986; 71: 589-594.
Walters WAW, MacGregor WG, Hills M. Cardiac output at rest during pregnancy and the puerperium. Clin Sci 1966; 30: 1-11.
Walters WAW, Lim YL. Cardiovascular dynamics in women receiving oral contraceptive therapy. Lancet 1969; II: 879-881.
Warner HR, Swan JC, Conolly D, Tompkins RG, Wood EH. Quantitation of beat-to-beat changes in stroke volume from the aortic pulse contour in man, J Appl Physiol 1953; 5: 495-507.
Warren JV, Stead EA, Brannon ES. The cardiac output in man: a study of some of the errors in the method of right heart catheterization. Am J Physiol 1946; 145: 458-464.
Waters J, Kwan OL, Kerns G, Takeda P, Low R, Booth D, DeMaria A. Limitations of Doppler echocardiography in the calculation of cardiac output. Circulation 1982; 66 (Suppl

II): 122 (Abstract).
Weiner C, Martinez E, Zhu LK, Ghodsi A, Chestnut D. In vitro release of endothelium-derived relaxing factor by acetylcholine is increased during guinea pig pregnancy. Am J Obstet Gynecol 1989; 161: 1599-1605.
Weinstein L, Janjan N, Droegemueller W, Katz MA. Forearm plethysmography in normotensive and hypertensive pregnant women. South Med J 1981; 74: 1230-1232.
Weisel RD, Berger RL, Hechtman HB. Measurement of cardiac output by thermodilution. N Engl J Med 1975; 292: 682-684.
Weiss S. Ueber die Mehrleistung der Herzens wahrend der Schwangerschaft. Klin Wschr 1924; 3: 106-108.
Werko L, Bucht H, Lagerlof H, Holmgren A. Cirkulationen vid graviditet. Nord Med 1948; 40: 1868-1869.
Werko L, Berseus S, Lagerlof H. A comparison of the direct Fick method and Grollman method for determination of the cardiac output of man. J Clin Invest 1949a; 28: 516-520.
Werko L, Langerlof H, Bucht H, Wehle B, Holmgren A. A comparison of the Fick and Hamilton methods for the determination of cardiac output in man. Scand J Clin Lab Invest 1949b; 1: 109-113.
Werko L, Lagerlof H, Bucht H, Holmgren A. Circulatory changes in pregnancy. Acta Med Scand 1950; Suppl 239: 263.
Werko L. Pregnancy and heart disease. Acta Obstet Gynecol Scand 1954; 33: 162-210.
Wesseling KH, de Wit B, Weber JAP, Smith NT. A simple device for the continuous measurement of cardiac output. Its model basis and experimental verification. Adv Cardiovasc Phys 1983; 5 (Suppl II): 16-52.
White SW, Quail AW, de Leeuw PW, Traugott FM, Brown WJ, Porges WL, Cottee DB. Impedance cardiography for cardiac output measurement: An evaluation of accuracy and limitations. Eur Heart J 1990; 11 (Suppl 1): 79-92.
Whittmore SL, Conrad KP. Stimulation of cyclic guanosine-3'5'-monophosphate (cGMP) production by methylcholine differs in aortae from pregnant and virgin rats. Physiologist 1989; 32: 186 (Abstract).
Wilmore JH, Farrell PA, Norton AC, Cote RW, Coyle EF, Ewy GA, Temkin LP, Billing JE. An automated, indirect assessment of cardiac output during rest and exercise. J Appl Physiol 1982; 52: 1493-1497.
Willis DC, Caton D, Levelle JP, Banner T. Cardiac output response to prostaglandin E2-induced abortion in the second trimester. Am J Obstet Gynecol 1987; 156: 170-173.
Wilson N, Goldberg SJ, Allen HD, Marx GR, Loeber CP. Does transducer selection affect aortic arch velocities. Am Heart J 1987; 113: 878-885.
Wong DH, Onishi R, Tremper KK, Reeves C, Zaccari J, Wong AB, Miller JB, Cordero V, Davidson J. Thoracic bioimpedance and Doppler cardiac output measurement: learning curve and interobserver reproducibility. Crit Care Med 1989; 17: 1194-1198.
Woythaler JN, Singer SL, Kwan OL, Meltzer RS, Reubner B, Bommer W, DeMaria A. Accuracy of echocardiography versus electrocardiography in detecting left ventricular

hypertrophy: comparison with postmortem mass measurements. J Am Coll Cardiol 1983; 2: 305-311.

Wyse SD, Pfitzner J, Rees A, Lincoln JCR, Branthwaite MA. Measurement of cardiac output by thermal dilution in infants and children. Thorax 1975; 30: 262-265.

Yang SS, Bentivoglio LG, Maranahao V, Goldberg H. Flow resistance. In; From Cardiac Catheterization Data to Hemodynamic Parameters. FA Davis, Philadelphia 1978; 89-91.

Ylikorkala O, Makila U-M. Prostacyclin and thromboxane in gynaecology and obstetrics. Am J Obstet Gynecol 1985; 152: 318-329.

Zemel MB, Zemel PC, Berry S, Norman G, Kowalczyk C, Sokol RJ, Standley PR, Walsh MF, Sowers JR. Altered platelet calcium metabolism as an early predictor of increased vascular resistance and preeclampsia in urban black women. N Engl J Med 1990; 323: 434-438.

Zhang Y, Nitter-Hauge S, Ihlen H, Myhre E. Doppler echocardiographic measurement of cardiac output using the mitral orifice method. Br Heart J 1985; 53: 130-136.

Zierler KL. Theoretical basis of indicator-dilution methods for measuring flow and volume. Circ Res 1962; 10: 393-407.

Zimmerman HA. A preliminary report on intracardiac catheterization studies during pregnancy. J Lab Clin Med 1950; 36: 1007-1008 (Abstract).

Zoghbi WA, Quinones MA. Determination of cardiac output by Doppler echocardiography: A critical appraisal. Herz 1986; 11: 258-268.