THE USE OF PULSED DOPPLER ULTRASOUND IN THE EVALUATION OF LEFT VENTRICULAR DIASTOLIC BEHAVIOUR

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Formal Declaration

I declare that I have written this dissertation presented to the University of Edinburgh for the Degree of Doctor of Medicine, that it is based upon my own observations and that, except where indicated, the data were collected and analysed by me.

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ABSTRACT OF THESIS

Pulsed Doppler ultrasound is a noninvasive technique which can be used to record the instantaneous velocity of blood flow from specified regions of the heart and great vessels. The flow pattern of blood entering the left ventricle through the mitral valve during left ventricular diastole can be recorded using this technique. Transmitral diastolic blood flow velocities were recorded in 54 healthy volunteers. The effect of respiration and physiological variables on measurements derived from these transmitral recordings were assessed. The effects of respiration on transmitral flow were found to be highly significant. The inherent variability of transmitral flow velocity spectra over time was investigated in 50 unselected patients and the effects of operator and interpretative variation in the recording and analysis of transmitral spectra investigated. Clinically acceptable observer variability for recording and measurement of transmitral flow was observed. Small inherent variation of certain pulsed Doppler parameters was established. The relationship between left ventricular relaxation measured by M-mode echocardiography and pulsed Doppler transmitral flow parameters was examined in 35 healthy subjects. Close correlation was found to exist between early diastolic events measured by the Doppler technique and rate of diastolic ventricular expansion. Simultaneous recordings of left ventricular diastolic pressure and transmitral

diastolic flow were performed in 50 patients undergoing clinical assessment of ischaemic heart disease. While significant correlation was observed between direct pressure measurements and several pulsed Doppler parameters of diastolic flow, reliable clinical prediction of diastolic ventricular pressure using pulsed Doppler velocimetry was not found to be possible.

An original microcomputer based system for the analysis of transmitral blood flow velocity spectra was designed and computer programmes for use with this system were developed.

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The purpose of this thesis

In the patient with heart disease of any aetiology, the nature and extent of impairment of left ventricular myocardial function acts as a major determinant of morbidity and mortality. The presence of left ventricular dysfunction influences the effectiveness of pharmacological intervention and the success of surgical treatment.

The clinical expression "ventricular function" is conveniently used to convey the status of global left ventricular myocardial performance in terms of the ability of the left ventricle to eject blood. This simple expression of pump efficiency is therefore of considerable diagnostic and prognostic value. In the diagnostic context, recognition of abnormal ventricular function may be the first sign of underlying cardiac disease while prognostically, it relates both to the nature and severity of symptoms and to life expectancy. The study of ventricular function at rest and on exercise may also be used to gauge the functional reserve of the left ventricle and its response to therapy. An important drawback of this terminology is that it fails to convey any measure of the contribution of the left ventricular filling or "pump priming" phase of the cardiac ejection cycle during ventricular diastole in relation to ventricular function as a whole. The distinction and evaluation of the separate systolic and diastolic components of left ventricular performance is of practical as well as theoretical importance in the assessment of cardiac disease. In the genesis of chronic left ventricular disease, detectable abnormalities of diastolic filling commonly precede systolic dysfunction and may thus be the first and only indicator of an underlying cardiac disorder. Significant left ventricular diastolic dysfunction may exist in the absence of systolic dysfunction and may go undetected unless a specific search is made for it. In the treatment of ventricular disease the presence of diastolic dysfunction may assume particular importance, as some forms of treatment aimed at improving ventricular systolic function may be of no benefit or even be detrimental to diastolic performance.

Increased clinical awareness of the importance of ventricular diastolic dysfunction in the manifestation of cardiac signs and symptoms has in turn prompted the search for accurate and reliable techniques for the recognition and quantification of abnormal ventricular diastolic function. Ideally such a technique should be accurate and non-hazardous, with a high degree of patient acceptability and be readily repeatable to allow serial studies of the natural history of ventricular dysfunction and its response to therapy. Such a technique should also be applicable in a wide variety of clinical settings and be suitable for appropriate population screening.

The determinants of left ventricular diastolic function are diverse and their relationship complex . It may be, therefore, that no single method of assessing left ventricular diastolic function is adequate to express the interactions of these variables when diastolic function is abnormal. However, the importance of ventricular diastolic dysfunction as an early manifestation of cardiac disease and its role in producing cardiac symptoms when systolic function is normal, or near normal, has prompted numerous investigators to attempt to develop clinically valid measurements of diastolic function which will allow the recognition and serial evaluation of disordered diastolic function, the effect of disease progression and response to therapy.

Established methods for the clinical assessment of left ventricular diastolic function include cardiac catheterisation and angiocardiography, radionuclide angiography, M-mode echocardiography and cross-sectional echocardiography. While all of these invasive and non-invasive techniques for assessing left ventricular diastolic function have been clinically validated, each has certain advantages and is subject to certain limitations.

Cardiac catheterisation provides accurate haemodynamic and angiographic measurements of diastolic ventricular events. The technique requires a high degree of operator skill, is expensive both in terms of personnel and equipment and carries a small but significant morbidity and mortality even in experienced hands. Invasive haemodynamic measurements are unsuitable for frequent serial assessment of left ventricular function and cannot be used as a screening technique for the detection of diastolic dysfunction in large populations. While accurate data regarding ventricular pressure and the course of ventricular relaxation can be obtained, derived expressions of diastolic function such as the modulus of chamber stiffness or time constant of relaxation do not translate well into clinical practice, especially for the general physician who may undertake the care of patients with both acute and chronic left ventricular disease. Measurement of left ventricular end-diastolic pressure is commonly undertaken at left heart catheterisation, despite the difficulties inherent in interpretation of the pressure-volume relationship and has remained a clinically useful yardstick of diastolic ventricular function.

Radionuclide angiography, like left heart catheterisation involves the use of relatively high doses of ionising radiation which limits its applicability for serial estimates of diastolic function, especially in the paediatric population. Because the radiopharmaceutical must be prepared from a generator, the timing of studies must be relatively fixed making emergency studies more difficult. The equipment is costly and in most cases static and time-consuming off-line analysis of data is required. There

is a slow acquisition rate using electrocardiographic gating to summate the activity from several cardiac cycles. This poses difficulties for data acquisition in patients where the heart rate varies significantly during the study. Because the summated image for diastolic events is usually divided into 32 frames, the temporal resolution of radionuclide angiography is restricted. Comparison of beat to beat variation in diastolic events is not possible using this technique.
M-mode and cross-sectional echocardiography, like cardiac catheterisation, require a high degree of operator skill. The high temporal resolution of M-mode echocardiography provides a significant advantage in the examination and timing of diastolic ventricular events and the plots of minor axis dimension against time are well suited for serial analysis. The major difficulties encountered in applying M-mode echocardiography to the assessment of ventricular diastolic function relate to the relatively high incidence of technically inadequate examinations and to interobserver variability due mainly to differences in transducer alignment for making measurements of left ventricular dimensions.

Pulsed Doppler transmitral blood flow velocimetry provides a further method for the study of events during left ventricular diastole. An ultrasound beam is used to determine the instantaneous velocity of blood flow within a small region close to the mitral valve. Information regarding absolute and relative flow velocities in early and late diastole can be obtained and within certain limitations, estimates of volumetric flow into the left ventricle are possible. The temporal resolution of pulsed Doppler velocimetry is good and allows analysis of the timing of the components of ventricular diastole. Application of an equation known as the modified Bernoulli equation to the velocity data makes it possible to calculate instantaneous pressure differences between the left ventricle and atrium.

While numerous reports suggest that pulsed Doppler velocimetry of transmitral blood flow velocity offers a sensitive technique for the detection and assessment of diastolic ventricular function, only limited data is available regarding the inherent variability of the transmitral flow pattern and its stability over time. For serial studies of disease progression or therapeutic intervention, these must be established. Until the advent of pulsed Doppler echocardiography, M-mode echocardiography arguably offered the best noninvasive means of evaluation of left ventricular diastolic function at the bedside. A small number of published reports suggest however that while the pulsed Doppler technique may be technically easier and with less observer variability, the relationship between parameters of left ventricular diastolic behaviour determined by both techniques is poor. Therefore pulsed Doppler may be complementary rather than an alternative to M-mode echocardiography. The unique ability of pulsed Doppler transmitral blood flow velocity spectra to yield instantaneous atrio-ventricular pressure gradients has prompted considerable interest in the possibility of indirect measurement of left ventricular diastolic pressures. Diverse methodology, differing study populations and the possible effects of concomitant therapy may be responsible for the apparently contradictory results from various authors who have examined this relationship.

This thesis addresses the application of pulsed Doppler ultrasound to the study of normal and disordered ventricular diastolic function. While numerous reports of the application of the pulsed Doppler technique to the study of diastolic ventricular function already exist, relatively little is known about the reliability and reproducibility of the technique. Normal Doppler characteristics of ventricular diastolic filling are poorly understood and only a few correlative studies have been undertaken in an attempt to relate Doppler parameters of diastolic function to more established methods of assessing ventricular diastolic function. This dissertation attempts to examine some aspects the clinical value of pulsed Doppler ultrasound in the study of ventricular diastolic function. The reproducibility of derived Doppler measurements and the effect of interobserver variation has been assessed, as this is clearly of fundamental importance before any technique is applied in clinical practice. The characteristics of normal and abnormal diastolic function have been observed and correlative studies have then been undertaken to investigate the relationships between pulsed Doppler transmitral blood flow velocimetry, M-Mode echocardiography and direct haemodynamic measurements in the evaluation of left ventricular diastolic behaviour.

Chapter 1

Left ventricular diastolic function

Omnis de scrutio de pereculosa est - Erasmus

Introduction

The term diastole is derived from the greek meaning "a drawing asunder, expansion". In medical terms it has come to be defined as "the relaxation of a hollow organ, which when applied to the heart refers to the resting period between successive beats." (Black's Medical Dictionary)

In 1628 , in his treatise "De motu cordis", William Harvey advanced the concept of alternate contraction and relaxation of a muscular pump to explain the pulsatile nature of cardiac function and blood flow (Harvey 1628). The constellation of symptoms and physical signs which result from disordered cardiac function to produce congestive heart failure or "dropsy" was recognised by 18th century physicians and when William Withering successfully treated several patients with congestive heart failure using a preparation of digitalis purpura, he introduced a potent inotrope whose effects on ventricular systolic function remain of importance in modern cardiological practice (Withering 1785). It is axiomatic that in order to maintain cardiac output the left ventricle must be able to both to eject in systole and to fill with a given amount of blood during diastole. Filling of the left ventricle during diastole has been shown to involve complex interactions between passive and active properties of the left ventricle and atrium (Carroll 1983a). The stiffness of the left ventricle (Yellin 1980), atrio-ventricular pressure gradient and atrial contraction (Noble 1969, Williams 1965) are each important determinants of left ventricular filling and their interaction may be derranged in the presence of myocardial disease (Carroll 1983b, Mann 1977). Diastolic relaxation of the left ventricle is an active, rather than passive, process which requires energy to redistribute calcium ions which have become bound to the myofibrils during systole (Grossman 1976, Langer 1974). It has been estimated that up to 15% of the energy requirements of the heart are taken up by myocardial relaxation (Langer 1974).

Diastolic ventricular function as a clinical concept

The concept and clinical significance of abnormal left ventricular systolic or contractile function on the genesis of symptoms and signs of heart failure has long been recognised (Weber 1979). It was, however, as recently as 1972 that Dodek et al first reported their findings in a series of patients presenting with recurrent pulmonary oedema in whom cardiac size and ventricular systolic function were apparently within normal limits. These authors first introduced the term "stiff heart" to emphasise the relationship of these clinical features to a primary abnormality of diastolic ventricular filling rather than contraction as the cause for their patients' clinical presentation (Dodek 1972). The presence of left ventricular diastolic dysfunction has since been reported in the presence of a variety of disease states including coronary artery disease, left ventricular hypertrophy, cardiomyopathy and hypertension (Carroll 1983, Mann 1977, Sasayama 1985, Mann 1979, Barry 1974, Smith 1985, Hanrath 1980, Spirito 1985, Inouye 1984). Abnormal left ventricular relaxation has been shown to develop before detectable systolic dysfunction (Brutsaert 1980) and detection of such abnormalities may therefore provide early indication of underlying myocardial disease. The clinical importance of recognition of abnormal left ventricular diastolic function in patients with congestive cardiac failure is stressed in two more recent studies by Dougherty (1984) and Soufer (1985). Both authors found a high incidence of left ventricular diastolic dysfunction in patients with signs and symptoms of congestive failure who were shown to have normal or virtually normal left ventricular systolic function. In addition, abnormal diastolic function was commonly observed when systolic dysfunction was present. Quantitation of the extent to which left ventricular diastolic dysfunction contributes to symptoms, signs and prognosis in disease affecting the left ventricle is largely unresolved. In the clinical setting, it has been possible to evaluate left ventricular systolic function using the relatively simple index of left ventricular ejection fraction measured by angiocardiography (Greene 1967, Sandler 1968, Kennedy 1970, Tobis 1983), echocardiography (Gutgessell 1977, Quinones 1978) or radionuclide angiography (Marshall 1977, Schelbert 1975, Jengo 1978) and to relate this to cardiac symptoms, functional cassification and prognosis. No such single simple index of left ventricular diastolic function has yet gained wide clinical acceptance.

Early Research into the Diastolic Function of the Left Ventricle

The events ocurring during left ventricular diastole were first described in 1906 by Henderson and colleagues who employed a simple mechanical device to measure the volume of the ventricles of anaesthetised open-chest dogs during the cardiac cycle (Henderson 1906). These early results showed that rapid ventricular filling occurred at the onset of diastole followed by a period of diastasis where little or no further filling was apparent. Further work by Straub in 1910 using similar apparatus divided the phases of left ventricular diastolic filling into those of rapid early filling, left ventricular diastasis and late filling due to atrial contraction which had not been reported by Henderson et al (Straub 1910). Wiggers and Katz detailed the effects of venous return, arterial pressure and cycle length on systolic and diastolic events using heart lung preparations (Wiggers and Katz 1921 a,b). Several decades later, further publications by Bloom (1956), Brecher (1956, 1958) and Tyberg (1970) argued the possible contribution of a mechanism of left ventricular diastolic suction as a primary physiological mechanism of cardiac filling. This latter postulate remained the subject of much controversy between the authors and was re-investigated by Sabbah who concluded that while in abnormal situations, such as the presence of mitral valve disease, negative ventricular pressure could be demonstrated, diastolic suction was unlikely to contribute to ventricular diastolic filling in the normal heart (Sabbah 1980).

Assessment of Left Ventricular Diastolic Function in Man

Methods of clinical measurement of events in the human heart during left ventricular diastole can be divided into two broad categories of invasive and non-invasive techniques. The invasive techniques are those of cardiac catheterisation, where pressure measurements are made from polyethylene catheters introduced into the cardiac chambers via the great vessels, and angiocardiography, where the mechanical activity of the heart is recorded on cine film after a bolus injection of contrast into the left ventricle. Established non-invasive techniques are those of apex and phonocardiography, echocardiography and radionuclide angiography.

Invasive Assessment of Left Ventricular Diastolic Function

In the late 1960's and early 1970's attention was focused on the investigation of diastolic ventricular function using invasive catheter measurements to determine the relationship between left ventricular pressure and volume. This work had initially been undertaken using animal preparations (Noble 1969, Diamond 1971, Hood 1970). Invasive catheter studies of left ventricular compliance by Bristow et al (1970) showed the presence of abnormal left ventricular compliance in the presence of coronary artery disease in man. Diamond and colleagues went on to relate the abnormalities of diastolic function observed to immediate prognosis following acute myocardial infarction (Diamond 1972).

Left ventricular diastolic function measured by invasive catheter studies has allowed the delineation of three major components of diastolic function which are denoted as chamber stiffness, myocardial stiffness and ventricular relaxation (Gaasch 1972, Gaasch 1976, Mirsky 1984). In addition to these three variables, measurement of the instantaneous rate of left ventricular filling can be obtained from analysis of left ventricular cineangiograms obtained during contrast angiocardiography (Hammermeister and Warbasse 1974b). Each of these characteristics will be considered in greater detail below.

1) <u>Left Ventricular Chamber stiffness</u>

The chamber stiffness of the left ventricle is defined by the relationship between ventricular volume and pressure (dP/dV) and is a measure of the ability of the chamber to distend under pressure. The reciprocal of chamber stiffness (dV/dP) is known as the operative volume distensibility or compliance of the left ventricle (Gaasch 1976). The relationship between pressure and volume in the left ventricle is curvilinear and Gaasch has determined that changes of compliance may be reflected both by change of the pressure-volume curve and displacement of that curve. The factors which produce these effects include ventricular scarring, hypertrophy and volume overload. Changes of the operating level of left ventricular diastolic pressure can therefore alter the compliance of the ventricle without changing the overall pressure-volume curve. Mirsky argues therefore that this measure of left ventricular compliance is unsuitable for inter-subject comparisons and has proposed a method of comparing volume-pressure relationships at common pressure levels (Mirsky 1984). Because the left ventricular diastolic pressure-volume curve can be fitted by an exponential equation, a modulus or index of chamber stiffness (Kp) can be derived from it using the formula dP/dV = Kp + B, where p equals left ventricular pressure, B is a data constant and Kp is the modulus of chamber stiffness (Gaasch 1972).

2) Left Ventricular Muscle stiffness

Muscle stiffness refers to the intrinsic property of the left ventricular myocardium to resist stretching when a stress is applied to it. The modulus of muscle stiffness or Ks is the slope of the relationship between left ventricular diastolic wall stress and the elastic stiffness of the ventricular muscle (Gaasch 1976). The left ventricular pressure-volume curve is influenced by a large number of variables which have been summarised by Glantz and Parmley (1978). Factors which affect the pressure-volume relationship may be acute or chronic and include ischaemia (Bristow 1970, McLaurin 1973, McCans 1973, Barry 1974), drugs (Coltart 1975, Brodie 1977, Alderman 1976), hypertrophy (Gaasch 1975, Grossman 1974a,b), pressure and volume overloading (Gaasch 1972, Grossman 1974). Glantz has proposed five potential mechanisms by which the altered left ventricular pressure-volume relationship may be affected (Glantz 1978). These are changes in cardiac geometry, interaction between the right and left ventricles, changes in the passive mechanical properties of the myocardium, incomplete relaxation from preceding systole and engorgement of the coronary circulation.

3) Left Ventricular Relaxation

Mechanical relaxation of the heart is the process by which the heart returns to its precontractile configuration (Brutsaert 1980, Brutsaert 1978). Grossman and Langer have elucidated the processes which occur in the ventricular myocardium during relaxation (Grossman 1976, Langer 1974). Calcium ions are actively transported to the sarcoplasmic reticulum from troponin myofibrils by a calcium sequestering system causing reorganisation of the actin-myosin bridges which are formed during ventricular activation, a process which is energy dependent (Langer 1974). The factors which interact to control ventricular relaxation include loading, inactivation, non-uniformity of distribution of load and inactivation in space and time (Brutsaert 1984). Relaxation of the left ventricle was investigated in animal experiments using measurement of the peak rate of change in intraventricular pressure (peak negative dP/dt) as an index of relaxation (Weiss 1976, Cohn 1972). Weisfeldt (1974) introduced a further concept based on the curve of ventricular dP/dt from which a time constant of relaxation tau was derived. Tau is defined as the time required for the cavity pressure at -(dP/dt)min to be reduced by one half. Tau has been shown to be independent of preload (Gaasch 1986) but shortened by increase in ventricular afterload (Karliner 1977).

4) Measurement of the Rate of Left Ventricular Diastolic Filling

The rate of filling of the left ventricle is dependent upon the interaction between the left atrium and ventricle, atrio-ventricular pressure gradient (Yellin

1980) the operative stiffness or compliance of the ventricle (Gaasch 1976) and the force and duration of atrial systole (Noble 1969). In 1974 Hammermeister and Warbasse reported a clinical angiographic technique for the quantification of rate of left ventricular filling which used a technique of frame by frame analysis of single plane left ventricular angiograms to calculate instantaneous change of volume over time (dV/dt), contribution to ventricular filling by atrial systole and end-diastolic left ventricular volume (Hammermeister and Warbasse 1974 a) and b). Using this method they were able to demonstrate abnormal early diastolic filling and an increased contribution by atrial systole to filling which they related to abnormal ventricular compliance in patients with ischaemic heart disease. Contradictory results were reported by Carroll and colleagues who found that early diastolic filling was not impaired in patients with ischaemic heart disease, although tau was significantly prolonged. They argued that normal passive diastolic filling was preserved at the expense of elevated atrial pressures in early diastole and found that in the presence of ischaemia, late diastolic filling was restricted (Carroll 1983 b).

<u>Invasive assessment of left ventricular diastolic function in the clinical setting</u>

Although considerable depth of insight into left ventricular diastolic function has been gained through detailed invasive studies, such as those of Gaasch, Brutsaert and Grossman, invasive clinical assessment of diastolic function has tended to rely on more simple, and less time consuming measurements. Direct measurement of left ventricular end-diastolic pressure is routinely undertaken during diagnostic cardiac catheterisation as part of the overall assessment of left ventricular function (Grossman 1986). Since the introduction of flow directed balloon tipped pressure monitoring catheters by Swan and Ganz, indirect measurement of left ventricular diastolic pressure by means of pulmonary artery wedge pressure has been possible both for diagnostic purposes and in clinical monitoring of critically ill and postoperative patients (Swan 1970). This latter technique can be carried out at the bedside in the intensive or coronary care unit and provides precise haemodynamic data regarding the effects of drug therapy and fluid replacement on left ventricular loading. Left ventricular end-diastolic pressure is an expression of the ventricular pressure-volume relationship and reflects the left ventricular wall stress at the end of diastolic filling (Gaasch 1972). With increasing chamber stiffness (decreased compliance), increasing ventricular wall stress is required for a given volume of blood to enter the left ventricle during diastole. This increases ventricular end-diastolic pressure. Pathological states such as ischaemic heart disease, which lead to myocardial fibrosis and decreased chamber compliance may therefore be accompanied by an elevation of the end-diastolic pressure within the left ventricle. Raised values of left ventricular end-diastolic pressure may serve to alert the clinician to the presence of myocardial disease and are used clinically as an index of abnormal left ventricular function or abnormal left ventricular loading. When measurements are taken directly from the left ventricular cavity, the end-diastolic pressure is measured from the ventricular pressure trace either before or immediately after the atrial systolic pressure wave. When the atrial wave is indistinct or absent, end-diastolic pressure is measured at the onset of the ventricular depolarisation complex of the electrocardiogram. If measurements of left ventricular pressure are being made indirectly from the pulmonary artery wedge position then it is usual to use the mean of the recorded waveform to indicate left ventricular diastolic pressure. Gaasch and others have delineated the complexities of the left ventricular pressure volume relationship (Bristow 1970, McLaurin 1973, McCans 1973, Barry 1974, Coltart 1975, Brodie 1977, Alderman 1976, Gaasch 1972 1975, Grossman 1974). End-diastolic pressure is influenced by several interacting variables including ventricular wall stiffness, intrathoracic tension and intravascular volume (Grossman 1974 a,b 1976). For this reason elevated end-diastolic pressure need not always accompany the presence of even advanced ventricular disease. For instance, it may be possible to record normal left ventricular end-diastolic pressure in the presence of abnormal left ventricular chamber compliance if the circulating volume has been significantly reduced by prior diuretic therapy. Conversely, elevated end-diastolic pressure may result from too rapid postoperative replacement of intravascular volume in individuals with normal cardiac function. Nevertheless, the finding of a raised value of end-diastolic pressure remains clinically useful as an indicator of the presence of acute or chronic left ventricular disease. Furthermore, changes in the recorded level of end-diastolic pressure may provide valuable information about disease progression or the effects of medical or surgical treatment on cardiac performance. Despite its obvious limitations, end-diastolic pressure remains a useful index of left ventricular diastolic function.

Noninvasive Assessment of left Ventricular Diastolic Function

Apexcardiography

As early as 1861, Chaveau had investigated the relationship between praecordial impulses and changes in intracardiac pressure (Chaveau 1861). The modern technique of apexcardiography uses a small transducer applied at or near the cardiac apex beat of a patient in the left lateral decubitus position to record the mechanical impulses produced by the events of the cardiac cycle (Craige 1974). The usual configuration of the apexcardiogram trace in diastole is that of a rapid filling wave that begins from a "0" point which corresponds to maximum negative intraventricular pressure followed by a slow filling wave and late diastolic "a" wave due to atrial systole (Willems 1971, Manolas 1975). Abnormalities of the rapid filling wave and prominence of the late "a" wave have been demonstrated in abnormal compliance states of the left ventricle. (Gibson 1974, Voigt 1970). The wide range of normal values within the healthy population limits the clinical applicability of apexcardiography in the investigation of diastolic dysfunction and does not allow accurate estimation of left ventricular end-diastolic pressure (Craige 1974). Venco et al have demonstrated the value of combined apexcardiography with M-mode echocardiography in the detection of incoordinate wall motion in the presence of ischaemic heart disease and Kolev showed the usefulness of the first derivative of the apex cardiogram trace in the evaluation of cardiomyopathy (Venco 1977, Kolev 1981). Apexcardiography is now less frequently used in the investigation of left ventricular diastolic dysfunction.

M-mode Echocardiography

M-mode echocardiography is a well established technique for the study of diastolic function of the left ventricle (Gibson 1975, Chen 1979, Gibson 1979, Hanrath 1980, Sanderson 1977). The reflected echoes from a narrow beam of ultrasound generated from a single crystal transducer directed at the heart are used to build up a cathode ray image of the relative motion of cardiac structures on a moving timebase (Feigenbaum 1986). The image can be stored on magnetic tape or more usually recorded onto dry silver paper to produce a hard copy trace. The very rapid pulse repetition frequency of dedicated M-mode echocardiographic equipment (approximately 1000/sec) gives excellent temporal resolution of the diastolic events of the cardiac cycle (Popp 1969, Gibson 1973). One of the earliest reported uses of M-mode echocardiography in the assessment of diastolic events was for recognition of abnormal rates of diastolic closure of the mitral valve in patients with mitral stenosis (Edler 1956). Subsequent investigation revealed that abnormalities of this mitral closure slope were frequently present in the presence of disordered left ventricular diastolic function and elevated left ventricular end-diastolic pressures, although this latter finding was shown to be relatively insensitive and non-specific (De Maria 1976, Quinones 1974, Konecke 1973). Other changes in the pattern of mitral valve motion in diastole such as the presence of abnormal bumps or notches may be present on the M-mode recording in abnormal ventricular compliance states (Konecke 1973, Lewis 1978). By relating the movement of the anterior mitral valve leaflet to the motion of the posterior left ventricular wall, Upton et al were able to demonstrate abnormal outward wall motion in patients with ischaemic heart disease (Upton 1976 a,b). Further information regarding the diastolic behaviour of the left ventricle during the isovolumic relaxation period can be obtained by combining such echocardiographic measurements with phonocardiography (Chen 1979, Doran 1978). Using appropriate transducer alignment, a plot of the left ventricular minor dimension against time can be obtained. Computer assisted analysis of this plot allows the instantaneous rate of change of left ventricular diastolic dimension and its relationship to time can be derived (Gibson 1973). This technique of digitised M-mode echocardiography has been applied widely to the study of diastolic ventricular function (Sanderson 1978, St John Sutton 1978, Gibson 1975, Gibson 1979, Hanrath 1980, Lawson 1986). The transducer is directed from a left parasternal position so that an image of the left ventricular septum and posterior left ventricular free wall is obtained just distal to the level of the tips of the mitral valve leaflets. Correct orientation of the ultrasound beam is essential if accurate recordings are to be obtained. Simultaneous recording of a phonocardiogram of the heart may be superimposed on the trace of the left ventricle for the timing of diastolic events (Chen 1979). Computer assisted analysis of such recordings, as described by Gibson, allows a number of derived measurements to be obtained from the M-mode trace (Gibson 1973). These include the left ventricular isovolumic period, which is the interval between the deflection on the phonocardiographic trace caused by closure of the aortic valve and the opening of the mitral valve, the instantaneous rate of change of left ventricular minor axis dimension and the peak rate of increase of left ventricular dimension. Using these M-mode measurements, abnormalities of isovolumic relaxation can be reliably detected and abnormal rates of left ventricular diastolic relaxation have been described in association with left ventricular hypertrophy, valvular heart disease, cardiomyopathy and ischaemic heart disease (Gibson 1973, Gibson 1975, Upton 1976 a,b St John Sutton 1978, Sanderson 1978, Chen 1979, Gibson 1979, Hanrath 1980, Lawson 1986). As well as these more complex derived parameters, M-mode echocardiography may also be used in the measurement of left ventricular end-diastolic dimensions (Feigenbaum 1972, Gibson 1973) and wall thickness which are frequently abnormal in conditions causing diastolic ventricular dysfunction (Devereux 1977 Bennett 1974, Traill 1978). While having the advantages of being noninvasive and free from ionising radiation, M-mode echocardiography is subject to certain limitations. These relate to a relatively high incidence of technically inadequate studies and the potential influence of operator and interpretative variability (Sahn 1978, Pollick 1983, Bullock 1984). Like all echocardiographic methods, difficulties in obtaining recordings of suitable quality for quantitative analysis may be encountered and these are largely dependent upon patient characteristics such as the shape of the chest wall and the presence of concomitant respiratory disease (Feigenbaum 1986). Technically inadequate echocardiographic recordings have been reported in up 20% of patients attending for examination (Bansal 1980). Where quantitative aspects of left ventricular function are under consideration, the need for technically adequate, high quality recordings of left ventricular septal and free wall echoes has been stressed (Sahn 1978). An important potential source of error in M-mode echocardiographic estimation of left ventricular relaxation and dimensions is transducer position due to the variable relationship between the position of the heart and the rib interspaces (Chang 1975, Popp 1975, Pollick 1983). Inherent or biological variability in left ventricular M-mode measurements has also been shown to be large and Pollick has suggested that serial measurements over more than one day may be required for adequate investigation of left ventricular dimensions by M-mode echocardiography (Pollick 1983). These factors combine to make the dedicated M-mode echocardiographic examination an often difficult and demanding part of a cardiac ultrasound examination. It is now more usual for M-mode recordings to be made from an M-mode trace derived from the real time two dimensional scan. The pulse repetition frequency in these circumstances is usually between 30 and 60 cycles per second making it more difficult to appreciate subtle abnormalities of wall motion abnormality (Feigenbaum 1986).

Two-dimensional Echocardiography

While M-mode echocardiography provides a single so-called "ice-pick" view through the left ventricular cavity, from a parasternal position, two-dimensional echocardiography visualises almost the entire ventricle in a single plane. Although the slower sampling rate of two-dimensional scanning is less well suited to the evaluation of rapidly occurring diastolic events, off-line frame by frame analysis of left ventricular two-dimensional echocardiograms in one or more planes by computer assisted tracing of the ventricular endocardial echoes has been used for calculation of the instantaneous ventricular volume and rate of filling (Fukaya 1978, Schiller 1979). The problems of lateral resolution and echo dropout (Geiser 1982) can make accurate identification of the ventricular endocardium difficult and introduce error into the calculation of ventricular volume and filling rate and volumes obtained are usually less than those calculated from contrast angiography (Erbel 1983, Hahn 1982). Two-dimensional echocardiography has attained a relatively minor role in the clinical assessment of left ventricular diastolic performance.

Radionuclide Angiography

The technique of radionuclide angiography uses a scintillation detector placed close to the chest wall to detect radioactivity within the cardiac chambers from an intravenously administered radiopharmaceutical (Berger 1979). Diastolic time-activity curves may be generated either from a bolus of radio-isotope as it passes through the ventricle (first pass technique) or from serial acquisition of activity over several cardiac cycles (gated blood pool imaging). Both first pass and gated blood pool techniques have been used in the clinical evaluation of left diastolic ventricular filling (Bonow 1981 a,b Reduto 1981, Snider 1985). Despite the theoretical limitations imposed by a slow sampling rate, usually 32 per diastolic cycle, radionuclide angiography has compared favourably with cineangiography for measurement of peak left ventricular filling rate and shows close correlation with peak negative rate of change of left ventricular diastolic pressure (Seals 1986, Magorien 1984). The clinical applications of radionuclide angiography include assessment of ventricular diastolic function in coronary artery disease (Miller 1983, Yamagashi 1984, Mancini 1983) and cardiomyopathy (Sugrue 1986, Betocchi 1986, Bonow 1983). The most important practical limitation in the application of radionuclide angiography to assessing left ventricular filling is the large whole body dose equivalent of radiation (approximately 6 mSv) due to the administered isotope. This is especially important where repeat examinations are required. Timing of studies is limited because of the need for specially prepared radiopharmaceuticals and the problem of radioactive decay. Because the equipment is usually static, it cannot be used in the ward or intensive care unit.

Chapter 2

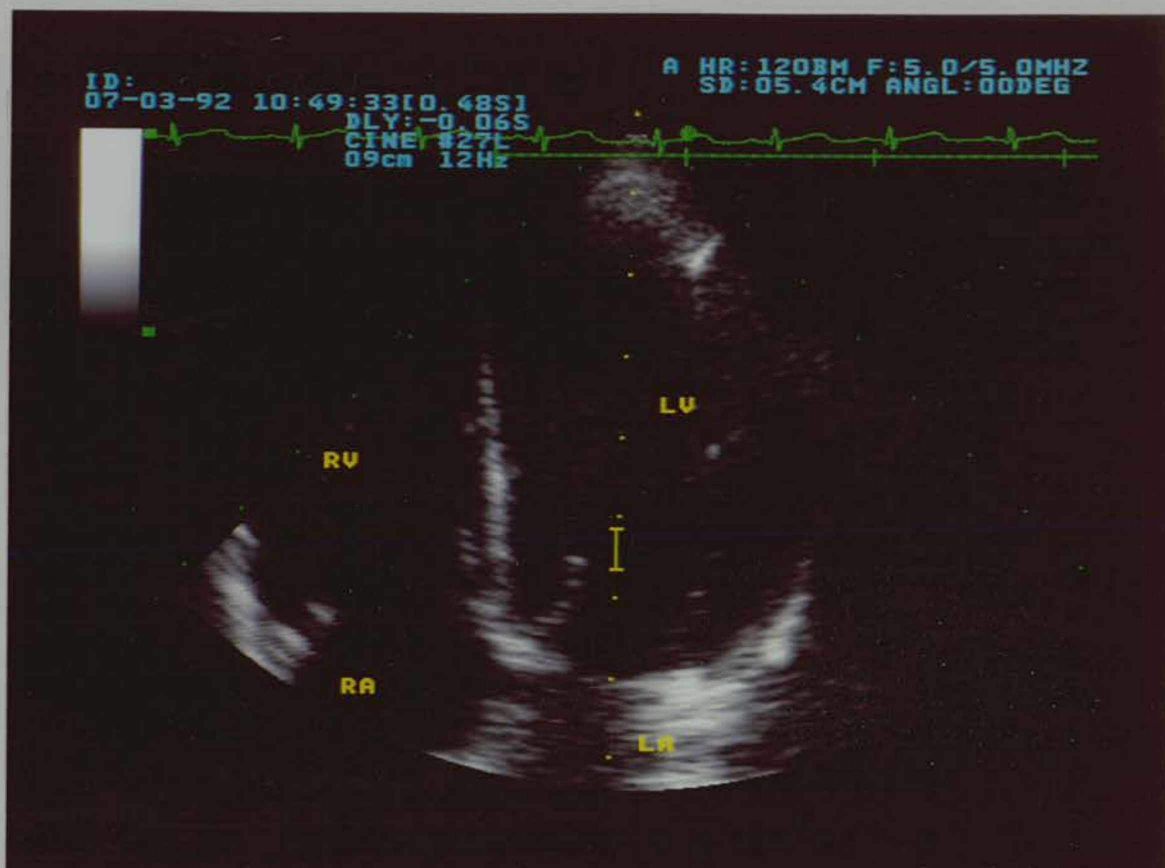
Pulsed Doppler Velocimetry in the assessment of left ventricular diastolic function.

Using a suitable frequency of transmitted ultrasound and with the pulsed Doppler beam adjusted to record events at or near the mitral valve annulus, the frequency shifts caused by red blood cells entering the left ventricle during diastole may be detected and from this frequency data, the instantaneous velocity of flow may then be derived (Kitabatake 1982, Hatle 1985). This is demonstrated in Figure 2.1. Analysis of the peak flow velocities and change of instantaneous transmitral blood flow velocity over time forms the basis of pulsed Doppler evaluation of left ventricular diastolic function. The ability of this technique to provide easily quantifiable data relating to dynamic left ventricular diastolic events without the use of ionising radiation or the need for invasive studies has prompted numerous investigators to apply it to a wide spectrum of cardiac disease (Danford 1986).

Transmitral blood flow velocities in normal subjects

In normal subjects in sinus rhythm, the pattern of diastolic filling recorded by pulsed Doppler at the mitral valve has been shown to be biphasic, with an early diastolic filling wave (E) during the passive phase of ventricular filling and a second or late filling

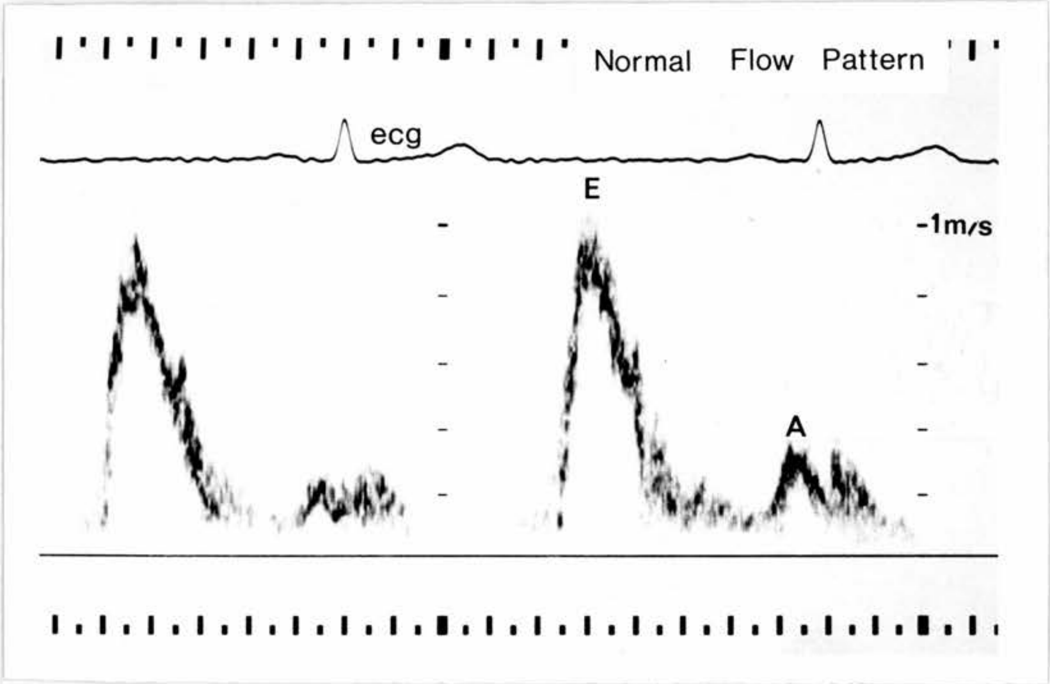
Figure 2.1



<u>Pulsed Doppler recording of transmitral blood flow.</u>

The direction of the pulsed ultrasound beam is displayed by a radial cursor superimposed on the cross sectional image. The sample volume position is marked on screen by two smaller parallel lines. Normal biphasic transmitral diastolic flow is shown in Figure 2.2.
(LA - left atrium, LV - left ventricle, RA - right atrium, RV - right ventricle)

Figure 2.2



<u>Normal transmitral flow velocity pattern.</u>

Recording of instantaneous transmitral blood flow velocities yields a biphasic waveform with peak early and atrial flow velocity peaks. In young adults, peak E velocity is greater than peak A velocity.

(E - peak early flow velocity, A - peak atrial flow velocity, ecg - electrocardiogram) wave (A) which occurs with atrial contraction. These two phases are separated by a period of variable duration during which the velocity trace falls towards or may reach zero (Hatle 1985, Kitabatake 1982). Both the position of the pulsed Doppler sample volume and the precise imaging view chosen to obtain transducer alignment have been found to affect the recorded transmitral velocity waveform (Hatle 1985, Gardin 1986, Van Dam 1988). Assuming correct orientation of the ultrasound beam to the direction of blood flow, the depth at which the sample volume is set has a small but significant effect on peak early velocity which increases as the sample volume moves from the atrial side of the mitral annulus into the left ventricular cavity (Hatle 1985, Van Dam 1988). When an apical four chamber view is used to guide transducer alignment to transmitral blood flow, the values obtained for peak early and late flow velocities are slightly higher than when an apical two-chamber view is selected (Gardin 1986). These basic but important findings underscore the importance of carefully standardised technique for transducer placement and sample volume position when serial or intersubject comparisons of diastolic function using pulsed Doppler are to be undertaken or when different groups of investigators wish to compare data. By convention the early passive and late atrial components of the transmitral blood flow velocity waveform are displayed as positive deflections from the zero baseline. An example recording of normal transmitral diastolic blood flow is shown in Figure 2.2. The pulsed Doppler waveforms may be recorded onto videotape or more usually a strip-chart recorder for subsequent analysis. Normal values for the peak early and late filling velocities have been established (Wilson 1985, Van Dam 1988) and changes in the expected normal values with advancing age have been described (Van Dam 1988, Miyatake 1984, Spirito 1988a, Miller 1986, Kuo 1987). These latter authors have all found that with increasing age, the peak early filling velocity decreases while the peak atrial velocity shows compensatory increase. In addition, the ratio of early (E) to late (A) velocities (E/A ratio) shows a progressive decrease with age (Spirito 1988a, Kuo 1987). However, while trends for each of the peak velocities and their ratios have been established, the range of normality is large in each case.

Effects of physiological variables on transmitral flow velocities

The effect of physiological variables on the transmitral waveform has been investigated by several groups (Gardin 1987, Van Dam 1988, Graettinger 1987, Uiterwaal 1989, Dabestani 1988). Gardin and colleagues analysed the relationship between transmitral blood flow velocity spectra and gender, body surface area and blood pressure. They reported significant positive correlation between the ratio of A and E velocities and late diastolic time velocity integral with systolic blood pressure while all other variables studied were found to be unrelated to the transmitral flow pattern (Gardin 1987). Van Dam et al found no significant relationship between any derived Doppler parameter and gender, body surface area, age or blood pressure (Van Dam 1988). In a study of normotensive young adults, Graettinger showed significant correlation between diastolic blood pressure and the A/E ratio in normal subjects and patients with subtle electrocardiographic abnormalities (Graettinger 1987). In a further study of diastolic filling in male subjects with a family history of hypertension, Graettinger observed that early shift towards the pattern of ventricular filling seen in hypertensive patients was detectable (Graettinger 1991). Voutilainen et al showed that increasing diastolic blood pressure appeared to correlate with a fall in indices of early diastolic filling (Voutilainen 1991). The precise relationship, if any, between transmitral flow and blood pressure remains uncertain and may be further complicated by the effects of other influences including age, heart rate and consitutional factors. Sudden changes in blood pressure in healthy individuals do not appear to influence transmitral diastolic blood flow in a predictable manner (Smith 1989). Analysis of the effect of respiration on the transmitral flow velocity waveform has shown that peak early velocity falls significantly on inspiration as does the early time-velocity integral (Dabestani 1988, Uiterwaal 1989). No such significant change in the peak atrial velocity has been shown except when it is measured on the atrial side of the mitral valve (Uiterwaal 1989). The mean mitral diastolic flow velocity was shown to fall significantly during inspiration in a small study of four patients by Meijboom (1987). These findings have relevance to the off-line measurement of pulsed Doppler parameters of diastolic ventricular function. Measurements must be made either from a specified phase of respiration or the arithmetic average of serial measurements from consecutive flow complexes during the same respiratory cycle must be taken (Uiterwaal 1989). The method of averaging has been used in the vast majority of pulsed Doppler studies of ventricular diastolic function although the chosen number of complexes for analysis and averaging has varied quite widely between authors. Dabestani has advocated that all measurements be taken at end-expiration in an attempt to standardise results but this methodology has not gained widespread acceptance (Dabestani 1988). The effect of respiration has been claimed to have no significant effect upon the ratio of peak early and late velocities in adults and it has therefore been proposed that this simple derived measurement may be made from transmitral blood flow velocity patterns without reference to phase of respiration (Uiterwaal 1989). However, Riggs and Snider have shown that both peak E velocity and the ratio of early and late flow velocities vary significantly in children during respiration (Riggs 1989). The effect of respiration on other variables such as rate of acceleration to peak early velocity and rate of deceleration from peak early velocity are not reported. Smith et al found that even small changes in heart rate could significantly alter the ratio of early and late filling velocities and advise caution in the interpretation of transmitral filling data where heart rate is not controlled (Smith 1989).

Reproducibility of transmitral flow velocity recordings

Relatively little published data exists regarding the limits of reproducibility and variability of pulsed Doppler transmitral blood flow velocity recordings. The inherent stability and variability of transmitral flow velocity patterns and the factors which may influence them over time are poorly understood. Both Fast et al and Spirito have reported clinically acceptable reproducibilty for the recording and analysis of some parameters derived from transmitral Doppler flow velocity spectra (Fast 1988, Spirito 1988b). Both of these investigators chose small groups of healthy volunteers to evaluate reproducibility. In a study of 12 normal adults, Spirito found that while Doppler indices of isovolumic relaxation and early diastolic filling showed little variability, the maximum atrial flow velocity and ratio of early and late velocities showed statistically significant variability which would limit the use of these latter measurements in the clinical setting (Spirito 1988b). He suggests therefore that simple measurements such as the E/A ratio which may appear to be useful in the detection of ventricular diastolic dysfunction, may be inadequate for serial studies of left ventricular diastolic performance. Fast et al concluded that the best reproducibility was for measurements of peak early and late flow velocity while measurments of acceleration and deceleration to peak velocity showed significant variations of up to 25% (Fast 1988). These latter results would impose serious restrictions on the use of transmitral velocimetry in comparative or serial studies of diastolic ventricular function where measurements other than those of peak velocity were required. In the study by Spirito, all recordings were made over a period of one to two days and the possible effects of longer time intervals between Doppler examinations on the reproducibility of transmitral spectra were not considered. The work by Fast (1988) considered three different aspects of reproducibility in the recording and analysis of transmitral blood flow velocity measurements. Firstly, they compared pulsed Doppler spectra recorded at different sites in relation to the mitral annulus. Measurements of transmitral blood velocities were made in all subjects at 1cm proximal and 1cm distal to the mitral annulus. They concluded that better reproducibility was obtained if pulsed Doppler sampling was from within the left atrial cavity. This site for placement of the sample volume had not previously been advocated in studies of left ventricular diastolic function using pulsed Doppler ultrasound. The authors unfortunately did not specify whether maximal velocity of atrial or passive phase of filling was used to define the optimal signal for analysis. Hatle draws attention to the variation in the relative peak velocity of these two phases as the sample volume is withdrawn from left atrium to left ventricular inflow (Hatle 1985). Although a sampling point 1 cm proximal to the annulus is specified in the study by Fast, the possible influence of further angulation and steering of the beam is not discussed. Secondly, Fast and colleagues analysed repeat transmitral flow recordings taken at an interval of three months and found no significant variation in the paired measurements of several transmitral flow velocity parameters. Thirdly, they investigated automated processing of "raw" Doppler data to avoid observer bias. While peak velocity measurements showed the smallest variation, peak acceleration showed greater variability due to spectral dispersion. For the study of serial changes in left ventricular diastolic function by any method, the effect of age itself on diastolic events must be taken into account. From the work of Gardin (1987), Miyatake (1984) and Kuo et al (1984) it is clear that with advancing age, changes in the absolute and relative values for the maximal early and late filling velocity peaks occur. These observed changes may reflect the augmentation of left ventricular filling due to atrial systole which is believed to occur with age (Bryg 1987). Therefore recordings taken after long intervals even in apparently healthy subjects might be expected to demonstrate significant changes in the relative sizes of early and late filling waves. Whether it might be possible to account for this physiological effect by the use of an appropriate age correction factor is not known. Because the Doppler technique allows rapid, non-invasive and readily repeatable analysis of ventricular filling dynamics, it is also potentially very well suited to longitudinal studies of left ventricular diastolic behaviour. The possibility of assessing effects of therapeutic and other interventions in a variety of clinical situations exists. Before widespread clinical application of such methodology to the assessment of left ventricular diastolic function in patients with cardiac disease, it is essential that the extent of variability inherent in the recording and interpretation of diastolic flow velocity spectra is established. If longitudinal studies of diastolic ventricular behaviour are to be undertaken, then the temporal stability of the parameters of diastolic function derived from these recordings must also be known. While the data obtained from the work of Fast and Spirito yield important insights into the validity of pulsed Doppler velocimetry for cross-sectional and longitudinal studies of diastolic ventricular function in normal individuals, it is as yet unjustified to assume that these findings can be extrapolated to include patients with ventricular disease of diverse aetiologies (Fast 1988, Spirito 1988b). Furthermore, the individuals chosen by these investigators represent a carefully selected group chosen principally because of their suitability for pulsed Doppler and echocardiographic examinations. With regard to the effect of operator error on the transmitral flow recording, Spirito (1988b) found this to be smaller than inherent variability in the transmitral complex. In this same study, variability due to reader in measuring the transmitral flow complexes was shown to be only a small component of variability. When combining two-dimensional echocardiography with transmitral blood flow velocity measurements for the calculation of cardiac output, Nicolosi and collegues found a similarly small effect of interpretative error (Nicolosi 1986). Measurements of peak flow velocities can be made directly from hard copy while more detailed analysis is usually undertaken by means of a digitising pad interfaced with a microcomputer (Kitabatake 1982, Fujii 1985). In a novel approach to the analysis of transmitral flow velocity spectra, direct measurements have been made from the digital output of the pulsed Doppler velocimeter by computer processing of raw data in such a way as to avoid the influence of observer variability when digitising transmitral flow complexes (Fast 1988). This technique has not been reported by other observers and does not seem suitable for routine clinical use. The possible quantitative effects of differing analysis systems upon derived measurements of diastolic behaviour from transmitral complexes has not been addressed.

Derived measurements from pulsed Doppler transmitral flow velocity patterns.

The ease with which transmitral flow velocity complexes can be recorded (Kitabatake 1982) and the suitability of the time-velocity plot for computer assisted planimetry has resulted in the introduction of a large variety of measurements derived from transmitral flow spectra in the investigation of left ventricular diastolic function by pulsed Doppler velocimetry and in correlative studies between pulsed Doppler and other modalities.(Rokey 1985, Fujii 1985, Snider 1985, Channer 1986). These variously proposed pulsed Doppler parameters of diastolic function can be broadly divided into direct velocity measurements and derivatives of the instantaneous flow velocity waveform and measurements of volumetric filling rates.

Figure 2.3 summarises these various parameters diagrammatically.

Peak E and peak A velocity represent the peak instantaneous flow velocities in early and late diastole respectively (Kitabatake 1982). Use of the modal velocity, which is represented by the darkest portion of the curve, has been recommended for the measurement of peak velocities (Wilson 1985). Acceleration half time from baseline to peak E velocity and deceleration half time from peak E to baseline have been used as indices of early diastolic filling rates in coronary artery disease (Fujii 1985). These measurements are an expression of

Figure 2.3

Parameters derived by analysis of the pulsed Doppler transmitral waveform

E - peak early flow velocity

A - atrial peak flow velocity

Acc - slope of acceleration to peak E velocity

Dec - slope of deceleration from peak E velocity

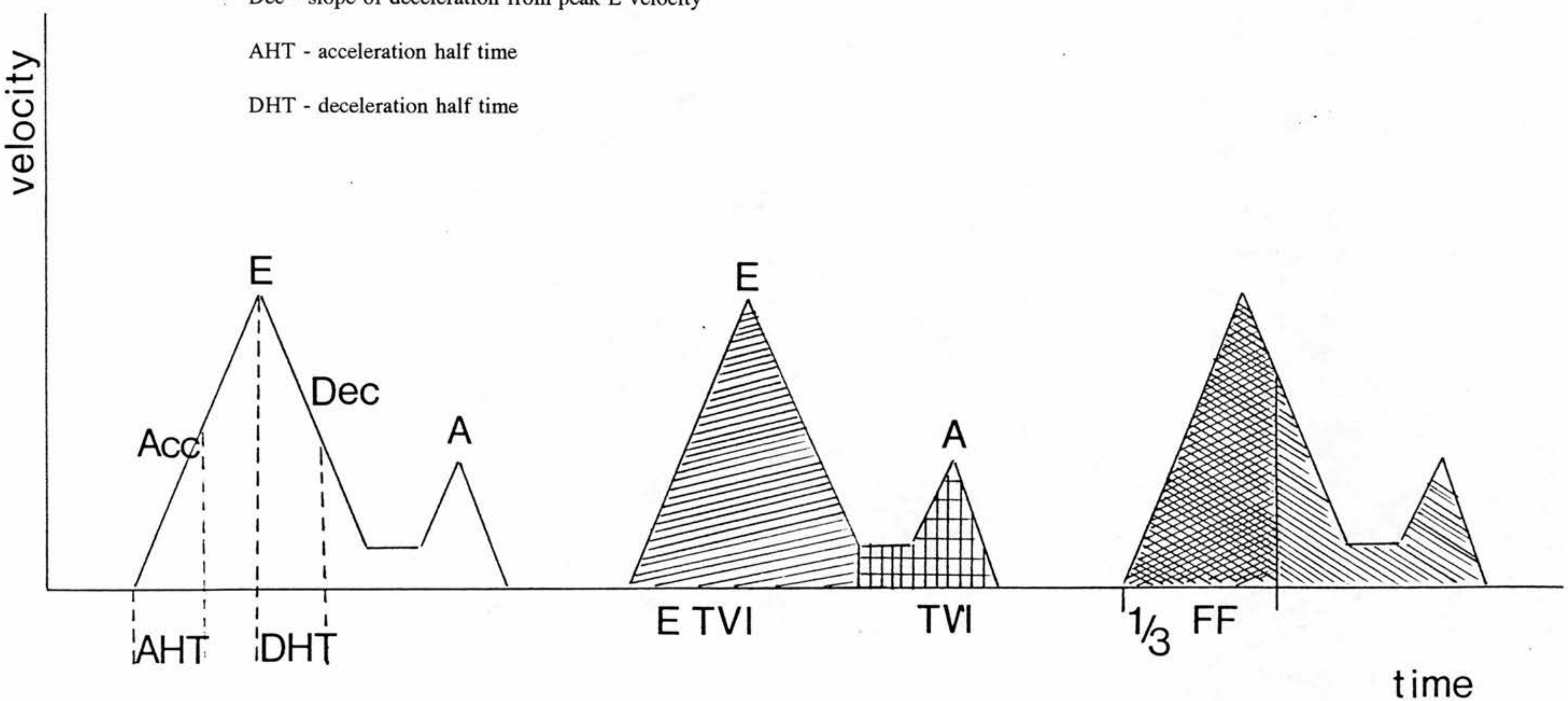
AHT - acceleration half time

DHT - deceleration half time

E TVI - early time velocity integral

A TVI - atrial time velocity integral

1/3 FF - one third filling fraction



the slope of the curve to and from the peak early velocity and other investigators have preferred to make direct measurements of the slope of acceleration and deceleration to and from peak E velocity. Measurement of the slope of deceleration from peak E has been shown to correlate closely with radionuclide assessment of diastolic ventricular filling (Spirito 1986a). The ratio of the peak early and late velocities (E/A ratio) has become a commonly cited index of left ventricular diastolic function that may provide both quantitative and qualitative information regarding the relative contributions of the passive and active phases of ventricular diastolic filling (Kitabatake 1982, Fujii 1985, Snider 1985, Takenaka 1986 a b, Channer 1986, Appleton 1988a). However, Miyatake (1984), Kuo (1987) and Spirito (1988a) have stressed the importance of age related changes in the relationship between early and late ventricular diastolic filling which must be taken into account in the interpretation of diastolic flow patterns. Furthermore, Appleton and colleagues have suggested that disease progression can alter the E/A ratio in a sometimes unpredictable fashion so that the presence of underlying abnormalities of diastolic function may be masked (Appleton 1988a). The time velocity integral is the area beneath the transmitral velocity curve. It can be divided into early, late and total time velocity integrals. The use of the time velocity integral as a linear measure of flow or "stroke distance" has been successfully used to calculate cardiac output (Lewis 1984). The one third filling fraction, obtained from planimetry of the early filling wave has also been shown to be of potential value as a measure of early diastolic filling (Pearson 1986a). By combining direct measurement of the mitral valve cross-sectional area with measurement of instantaneous flow velocity rate, it is possible to calculate instantaneous left ventricular filling rate (Rokey 1985). While certain assumptions are required with regard to the calculation of the mitral valve orifice, Rokey et al found close correlation between Doppler and angiographic measurements of peak ventricular filling rates using this method (Rokey 1985). As well as the use of the transmitral waveform velocities to derive dynamic parameters of left ventricular filling, the plot of instantaneous transmitral flow velocity over time can be directly related to the instantaneous atrioventricular pressure difference. This is accomplished using the modified Bernoulli equation which is a clinically simplified and validated expression of the mathematical relationship between pressure drop and flow velocity across an orifice or obstruction (Hatle 1978 1979, Requarth 1984, Vasko 1984). The modified Bernoulli equation is expressed as:

$$P1 - P2 \text{ (mm Hg)} = 4(V2 - V1)^2$$

where P1 - P2 = pressure gradient

V1 = flow velocity (m/sec) proximal to the orifice or obstruction

V2 = flow velocity (m/sec) distal to the orifice or obstruction

Thus the transmitral flow velocity pattern reflects the diastolic events in the left ventricle both in terms of instantaneous flow velocity and atrioventricular pressure difference over time. While the measurement of flow velocity provides an absolute value, the calculation of atrioventricular pressure difference allows measurement of the relative pressure difference between the two left heart chambers. The possibility of using this measurement of relative pressure difference for non-invasive estimation of left ventricular diastolic pressures has been the subject of several correlative studies (Drinkovic 1986, Channer 1986, Kuecherer 1988a, Lin 1988, Appleton 1988a, Choong 1987 a b, Stork 1989). The atrioventricular pressure half-time is defined as the time taken for the initial atrioventricular pressure difference to halve (Hatle 1979). This parameter can be easily measured from the transmitral flow velocity waveform and has been widely accepted as a clinically useful index of the severity of mitral valve stenosis (Hatle 1978). In the absence of mitral valve stenosis, it provides a measure of the rate of atrioventricular pressure gradient decay.

Correlative studies of pulsed Doppler transmitral velocimetry and other modalities in the assessment of left ventricular diastolic function

Cineangiography and pulsed Doppler velocimetry

Validation of the calculation of peak rate of left ventricular diastolic filling against cineangiography was undertaken in hypertensive children by Rokey (1985). Frame by frame analysis of the left ventricular cineangiogram was used to calculate the peak ventricular filling rate, normalised peak filling rate and first half filling fraction. While peak early diastolic flow velocity showed a reasonably significant correlation with peak angiographic filling rate, more impressive correlation was demonstrated between pulsed Doppler echocardiographic filling rate and angiographic filling rate, despite the limitations and assumptions encountered in determining the cross-sectional mitral valve area during diastole (Rokey 1985, Ormiston 1981, Lewis 1984). Significant correlation between pulsed Doppler velocimetric and angiographic peak left ventricular filling rates have also been shown in adults with aortic stenosis (Sheikh 1989).

Radionuclide angiography and pulsed Doppler velocimetry

Investigation of the relationship between pulsed Doppler transmitral flow velocities and radionuclide measurements of left ventricular filling has been undertaken by

Spirito (1986a), Friedman (1986), Pearson (1986a) and Bowman (1988a). Spirito and colleagues found that pulsed Doppler measurement of peak early flow velocity compared favourably with radionuclide determination of volumetric filling rate in distinguishing normal from abnormal diastolic ventricular function (Spirito 1986a). Furthermore they showed good correlation between the Doppler E/A ratio and the ratio of ventricular and atrial filling measured by scintigraphy and the slope of descent from peak E velocity correlated closely with peak radionuclide angiographic filling rate. Friedman et al (1986), demonstrated similarly impressive correlations between pulsed Doppler and scintigraphic measurements of fractional filling in early and late diastole and between the timing of events measured by both techniques although comparison of peak filling rates showed no significant correlation. Pearson compared the one third filling and percent atrial filling fractions from pulsed Doppler and radionuclide angiography and found a close relationship between results but like Friedman was unable to find a significant correlation for normalised peak filling rates (Pearson 1986a, Friedman 1986). In a later study by Bowman and colleagues, some of the technical difficulties of normalisation of peak Doppler filling rate were overcome by the introduction of a normalisation to mitral stroke volume as opposed to end-diastolic volume. It was argued that this would reduce error in the measurement of Doppler echocardiographic peak filling rate (Bowman 1988a). Further verification of this methodology is not yet available. The advantages of pulsed Doppler transmitral velocimetry over radionuclide angiography include the avoidance of ionising radiation, which in the case of radionuclide angiography gives a body dose equivalent of approximately 6m Sv per study. Where serial studies are required this is a major consideration. The sampling rate of pulsed Doppler spectral analysis at 200 per second is superior to the temporal resolution of gated radionuclide studies which divide the diastolic portion of the cycle into between 16 and 32 segments (Freidman 1986).

M-mode echocardiography and pulsed Doppler velocimetry

Attempts have been made to delineate the relationship between pulsed Doppler and M-mode echocardiography in normal and diseased left ventricles (Spirito 1986a, Pearson 1987, Shapiro 1988, Ng 1989, Ng 1990, Lee 1991). With the exception of measurement of the duration of the isovolumic relaxation period measured by both techniques (Spirito 1986), only weak correlations have been found between pulsed Doppler and M-mode echocardiographic parameters of left ventricular diastolic function. Pearson reported a significant correlation between the normalised rate of left ventricular chamber enlargement and Doppler-derived peak ventricular filling rate (Pearson 1987). Spirito was unable to demonstrate any such association although a weak relationship between the slope of descent from peak early filling velocity and rate of left ventricular chamber enlargement was found (Spirito 1986b). In a study of 50 patients with left ventricular hypertrophy, Shapiro showed that both the ratio of early and late velocity peaks and the velocity half time, an expression of the slope of deceleration, correlated with peak rate of left ventricular dimension increase (Shapiro 1988). While no clear relationship has been demonstrated between the pulsed Doppler echocardiographic and M-mode techniques in assessing diastolic events, both techniques were shown to be in close agreement in distinguishing normal from abnormal diastolic ventricular function and pulsed Doppler may be more sensitive in the detection of early or subtle abnormalities of function when M-mode parameters are still within the normal range (Spirito 1986b, Pearson 1987). However, the findings of Lee et al are contradictory and show that M-mode indices of diastolic dysfunction are more consistently abnormal in the assessment of rapid ventricular filling (Lee 1991). Shapiro used a combination of apexcardiography, M-mode echocardiography and pulsed Doppler echocardiography to delineate the possible relationships between clinically established parameters of diastolic function in the presence of left ventricular hypertrophy and concluded that the lack of clear correlations between different methods was likely to reflect the differing physiological basis on which the measurements were based (Shapiro 1988). Ng et al have also stressed the complex disturbances of left ventricular filling within apparently homogeneous patient groups and advocate a combined noninvasive approach to the assessment of diastolic function (Ng 1989,1990). While both Spirito and Pearson included small control groups of healthy volunteers in their studies, in each case the age range of the normal controls was large. Therefore, the effects of age on the relationship between transmitral spectra and the digitised M-mode trace may have influenced their results. A further consideration which may explain the lack of clear correlations in this previous work is the heterogeneous makeup of their study populations. In particular, it is not clear whether patients with coronary artery disease were included within the study. Coronary artery disease is known to cause regional wall motion abnormalities on M-mode echocardiography (Gibson 1977) and changes in the transmitral waveform (Kitabatake 1982, Fujii 1985) which might affect their relationship in an unpredictable manner. Whether concomitant drug therapy could further complicate the comparative assessment of diastolic function by pulsed Doppler and M-mode in not clear. A large proportion of subjects studied by Pearson were taking vasoactive medication while these details are not discussed by Spirito or Shapiro (Pearson 1987, Spirito 1986b, Shapiro 1988). In view of these considerations, while no clear relationship between pulsed Doppler transmitral flow velocities and M-mode measurement of left ventricular relaxation has emerged, further examination of this area is therefore justified.

Intracavitary pressure measurements and pulsed Doppler velocimetry

In the absence of mitral valve obstruction, the Doppler frequency shift recorded at the level of the mitral valve is directly related to the instantaneous pressure difference between the left atrium and ventricle during left ventricular filling. The modified Bernoulli equation can be used to calculate the atrioventricular pressure from the instantaneous peak flow velocity (Hatle 1978). The knowledge that derived measurements from pulsed Doppler velocimetry yield impressive correlations with invasive measurements at other sites within the heart and great vessels (Hatle 1985, Goldberg 1982) presented the exciting prospect of a means of end-diastolic pressure measurement based on Doppler determined left ventricular filling dynamics. Clinically reliable detection of abnormal left ventricular end-diastolic pressure was found to be possible by Channer et al who related the ratio of the early and late filling velocities to end-diastolic pressure in patients with ischaemic heart disease. It was reported that the finding of a ratio of greater than 2 between the E and A velocities was always associated with an end-diastolic pressure of greater than 20 mm Hg (Channer 1986). A non-simultaneous study of Doppler and diastolic pressure measurement by Kuecherer found further evidence to relate abnormal filling dynamics assessed by pulsed Doppler to high levels of diastolic intraventricular pressure. Again, high levels of left ventricular end-diastolic pressure (LVEDP) were related to an increase in the early to late filling velocity ratio as measured by Doppler (Kuecherer 1988a). Acceptable predictive accuracy in detecting patients with markedly abnormal LVEDP using transmitral blood flow velocity measurements was demonstrated. While both of these authors demonstrate a statistical relationship between end-diastolic pressure and the ratio of time-velocity integrals, analysis of their own data plots confirms that prediction of end-diastolic pressure in individual cases is impossible. In Channner's study, a ratio for the time-velocity integrals of 2:1 was associated with end-diastolic pressure ranging between 8 and 35mm Hg and in Kuecherer's report a ratio between the early and late time-velocity waves of 2 was associated with end-diastolic pressures ranging from 10 to 35mm Hg. Both groups found that a ratio of greater than 2 between the early and late filling waves was always associated with end-diastolic pressure of 20mm Hg or greater. Kuecherer's results show that an end-diastolic pressure of 20mm Hg can be associated with a time-velocity integral ratio varying between 0.5 and 4.5 and demonstrate that the majority of patients with end-diastolic pressure of greater than 20mm Hg have ratios of less than 2. Both in this and Channer's study, the scatter of results suggests that simple regression analysis may be unjustified and that the patients with markedly elevated pressure values may belong to a different subset of patients. The assumption made by these authors that early to late time-velocity ratio increases with increasing diastolic pressure is partly based upon previous work by Greenberg et al who demonstrated that with increasing ventricular diastolic pressure, atrial augmentation becomes less effective (Greenberg 1979). However there is conflicting data to this point by Rahimtoola et al who demonstrated an increase in atrial augmentation in the presence of ischaemic heart disease (Rahimtoola 1975). A further correlative study between pulsed Doppler velocimetry and pressure data was undertaken by Lin and colleagues. They performed simultaneous pulsed Doppler velocimetric and high fidelity pressure recordings in patients with a variety of cardiac diseases and were unable to confirm the results of Channer and Kuecherer. However, they found that the A/E ratio, deceleration half-time and acceleration half-time from peak early flow velocity had up to 100% predictive value in detecting abnormal values of maximum -dp/dt and time constant of relaxation (Lin 1988). In subjects with aortic stenosis, weak correlation between left ventricular end-diastolic pressure and atrial filling velocity (A) was found by Sheikh and colleagues (Sheikh 1989). In contradistinction to the results of Lin, these latter authors were unable to find any correlation between pulsed Doppler measurements and -dp/dt, Tau or Kp. In further data reported by Stork et al, highly significant correlation between left ventricular end-diastolic pressure and the ratio of atrial and early flow velocity peaks was found to exist

(Stork 1989). Stork found that as end-diastolic pressure increased, the contribution of ventricular filling due to atrial systole increased. These results are in direct contradiction of those of Channer and Kuecherer (Channer 1986, Kuecherer 1988a). Choong has evaluated the effect of ventricular preload on the pulsed Doppler diastolic waveform and showed that changes caused by the administration of small doses of nitroglycerin could mimic the effects previously ascribed to abnormalities of diastolic relaxation (Choong 1987a). In the data reported by Channer, Kuecherer, Lin and Stork, study patients were continued on their usual cardioactive medications prior to combined Doppler and pressure measurements (Channer 1986, Kuecherer 1988a, Lin 1988, Stork 1989). The possible effects of vasoactive therapy, given alone or in combination, on the transmitral flow pattern are poorly understood. Whether differing combinations of drugs could influence transmitral waveforms independent of diastolic pressure is unknown. Heterogeneity of study populations and the effects of drug therapy might account for some of the apparent discrepancies between the results published by these different authors. In the case of Kuecherer's data, the effect of drug therapy may be especially important as pulsed Doppler velocimetric and pressure measurements were made non-simultaneously (Kuecherer 1988a). Although Appleton's work also yielded weak correlations between diastolic pressure and pulsed Doppler measurements, he stresses the potential complexity of direct comparison between pulsed Doppler and haemodynamic variables because of the interplay of the effects of atrial pressure, cardiac output, therapy and disease progression on the transmitral waveform (Appleton 1988a). Despite the claims by Stork et al, considerable controversy remains regarding the possibility of simple bedside estimation of left ventricular end-diastolic pressure using transmitral pulsed Doppler velocimetry.

The application of transmitral pulsed Doppler velocimetry to the study of left ventricular disease.

Pulsed Doppler evaluation of left ventricular diastolic filling in ischaemic heart disease

Initial reports of left ventricular filling dynamics using pulsed Doppler in the presence of coronary artery disease focused on the findings in chronic ischaemia (Kitabatake 1982, Fujii 1985). In the first study of left ventricular diastolic filling after myocardial infarction, Kitabatake found, in common with hypertension and hypertrophic cardiomyopathy, that the peak early filling velocity (E) was significantly decreased compared to age matched controls. The late filling velocity A was found to be increased suggesting that the observed impairment of early diastolic filling was compensated by increased atrial contraction after myocardial infarction. While the pulsed Doppler flowmeter used in this early work was relatively unsophisticated and the spectral display of poor quality, these observations were subsequently verified by the data of Fujii (1985). In this study of diastolic filling in coronary artery disease, patients were divided into subgroups on the basis of the arteries involved and presumed territory of infarction. Although the methodology differed from that of Kitabatake (1982) with regard to sample volume placement, the finding of impaired early peak ventricular filling velocity with compensatory increase in atrial transport velocity was demonstrated in all subgroups. In addition, the early filling wave showed prolonged acceleration and deceleration half-times in most of the subgroups of myocardial infarction. From this, the conclusion was drawn that while peak early filling velocity was decreased, the duration of early filling was prolonged. It did not prove possible to differentiate the coronary arterial territory involved simply by pulsed Doppler characteristics (Fujii 1985). The presence of an abnormal E/A ratio in the presence of ischaemic heart disease was explored further by Visser (1986) who tried to use the E/A ratio as a prognostic index in the recovery phase of myocardial infarction. Profound changes of the ratio of early and late filling velocities were demonstrated to be a reliable indicator of poor prognostic outcome. Evaluation of left ventricular filling during exercise in coronary artery disease was reported by Kuecherer in a small study comparing normal subjects and patients with IHD and normal left ventricular systolic function at rest and during exercise (Kuecherer 1988b). Surprisingly, no technical limitation due to the effects of deepened respiration or patient movement on the quality of pulsed Doppler recordings was reported. The early diastolic filling velocity was found to decrease during bicycle exercise in patients with coronary artery disease and the ratio of the early and late diastolic filling times was similarly reduced during exercise. These changes did not occur in control subjects. While this methodology does not allow simple conclusions to be drawn regarding the haemodynamic significance of coronary artery disease, early detection of coronary artery disease appears possible with a high degree of sensitivity. Using treadmill exercise testing combined with pulsed Doppler and thallium redistribution studies, Mitchell and colleagues showed that an increase in mean transmitral velocity of less than 50% had a high predictive value for the presence of stress induced ischaemia (Mitchell 1988). Unlike Kuecherer, Mitchell found that percentage changes in E/A ratio did not differ significantly between controls and patients during exercise. Whether or not this pattern of exercise induced change in the E/A ratio is specific for coronary artery disease requires further clarification. In the first few days following myocardial infarction, it has been shown that early diastolic filling is acutely impaired. This myocardial "stunning" shows subsequent improvement over the first week following infarction (Williamson 1990). The ease with which serial recordings of left ventricular filling can be made using pulsed Doppler has led to its application to the study of diastolic events occurring during and after percutaneous transluminal coronary angioplasty (PTCA). Acute reversible changes in left ventricular diastolic filling velocities are caused by transient coronary artery occlusion due to PTCA balloon inflation (Labovitz 1987, de Bruyne 1989) and have been shown to precede other indices of myocardial ischaemia such as the electrocardiogram and systolic wall motion abnormalities (Labovitz 1987). These findings add further weight to the importance of diastolic ventricular dysfunction in the manifestation of coronary artery disease and confirm the sensitivity of pulsed Doppler transmitral blood flow velocimetry in detecting diastolic function abnormalities. In similar patients, Bowman et al (1988b) found that both peak early and late velocities decreased significantly during the acute ischaemia caused by angioplasty. Therefore, the compensatory rise in left atrial filling velocity documented in chronic ischaemia (Kitabatake 1982, Fujii 1985, Kuecherer 1988b, Mitchell 1988) must occur during an intermediate phase after ischaemia. The acute changes due to transient coronary artery occlusion in transmitral flow, resolve soon after balloon deflation (Labovitz 1987, Bowman 1988b). While Wind et al (1987) failed to show any improvement in diastolic filling abnormalities 24 hours after angioplasty, Masuyama and colleagues were able to document significant improvement in peak early diastolic filling by pulsed Doppler in the week following coronary angioplasty (Masuyama 1988). The improvement in early diastolic filling was seen to be greatest in those with severe coronary lesions prior to angioplasty. Revascularisation by coronary artery surgery has been reported to dramatically improve early diastolic filling as early as one week after bypass (Lawson 1988). Increase in early diastolic flow velocity has been found within the first 24 hours following angioplasty and does not appear to be significantly influenced by the success of revascularisation (Castello 1990). Where dilatation of a non-infarct related vessel is performed, the increase in peak early filling velocity and ratio early to late filling velocities appears to be greater than if an infarct related vessel is dilated and this may relate to the amount of viable myocardium reperfused in each case (Masuyama 1991).

Pulsed Doppler assessment of left ventricular diastolic filling in left ventricular hypertrophy

a) Hypertophic Cardiomyopathy

Abnormal left ventricular diastolic filling patterns have been demonstrated in both adults and children with hypertrophic cardiomyopathy (Kitabatake 1982, Oki 1983, Takenaka 1986a, Gidding 1986). In his study of patients with hypertrophic cardiomyopathy, coronary disease and hypertension, Kitabatake found that, as in the other two groups, early diastolic peak flow velocity was decreased in hypertrophic cardiomyopathy with compensatory increase in atrial filling velocity. A striking decrease in the rate of deceleration of the slope from peak E was found in the presence of hypertrophic cardiomyopathy and to a lesser extent in coronary disease and hypertension. These findings suggest that early passive diastolic filling is prolonged in hypertrophic cardiomyopathy with reduced peak filling rate. This is in contradiction to previously reported angiographic data which showed near normal peak filling rate in hypertrophic cardiomyopathy (Sanderson 1977). Whereas Rokey et al showed a clear correlation between angiographic and pulsed Doppler measurement of peak filling rate, this apparent discrepancy between the findings of Kitabatake (1982) and Sanderson (1977) suggests therefore that comparison of peak angiographic and Doppler measurements may not be universally applicable (Rokey 1985). On the other hand, the methodology of both Kitabatake and Sanderson showed early diastolic filling to be prolonged in hypertrophic cardiomyopathy. The findings of Kitabatake et al were confirmed by Oki (1983) and Maron (1987) in a study of over 100 patients with hypertrophic cardiomyopathy. The latter author showed a high incidence of diastolic filling abnormalities in the presence of hypertrophic cardiomyopathy over the whole spectrum of the disease, irrespective of the presence or absence of left ventricular outflow obstruction. Gidding found that in children, reduction of peak early filling velocity and reduction in the area beneath the E wave were present in hypertrophic cardiomyopathy while no change in the peak A velocity was recorded (Gidding 1986). The authors stressed that pulsed Doppler measurements had been made with patients taking calcium antagonist medication which may have affected the results obtained. In addition all patients with hypertrophic cardiomyopathy were found to have co-existing mitral regurgitation. Takenaka drew attention to the possible effects of concurrent mitral regurgitation in the presence of hypertrophic cardiomyopathy in altering or "masking" the expected abnormalities of diastolic function (Takenaka 1986a). Subgroup analysis of the patients within this study showed that significant abnormalities of diastolic transmitral blood flow velocity patterns were seen in those patients without systolic anterior motion of the mitral valve. Two thirds of the patients with systolic anterior motion of the mitral valve were found to have mitral regurgitation. It was argued that the increase in left atrial pressure and volume loading resulting from mitral regurgitation would lead to a higher early diastolic peak flow velocity because of the resulting increase in atrioventricular pressure gradient and so mask the effects of hypertrophic cardiomyopathy (Takenaka 1986a). Further weight is added to this argument by a later study of secondary left ventricular hypertrophy which confirmed the tendency of mitral regurgitation to normalise left ventricular filling patterns in the presence of ventricular hypertrophy (Shaikh 1988). According to Spirito, the transmitral flow abnormalities detected in hypertrophic cardiomyopathy are largely independent of the degree of left ventricular hypertrophy (Spirito 1990).

b) <u>Secondary left ventricular hypertrophy</u>

Correlating pulsed Doppler echocardiographic findings with clinical, electrocardiographic and M-mode findings in children with systemic hypertension, Snider found that transmitral blood flow velocity patterns were frequently abnormal when all other parameters were normal. It was concluded that pulsed Doppler transmitral flow velocimetry might therefore be superior to other techniques for the early detection of diastolic filling abnormalities (Snider 1985). Changes in the fractional filling in early and late diastole due to systemic hypertension have also been demonstrated in adults (Gardin 1986, Pearson 1988b, Shapiro 1988), with marked reduction in peak early velocity and compensatory increase in peak atrial velocity. Almost identical changes in left ventricular filling patterns occur in left ventricular hypertrophy due to aortic valve disease (Pearson 1987, Shapiro 1988). However, no demonstrable correlation between severity of aortic stenosis and disturbance of transmitral flow pattern has been found. Otto found that the diastolic filling velocity is increased in the presence of left ventricular hypertrophy in aortic stenosis, but that "normalisation" of transmitral flow occurred when end-diastolic pressure was significantly elevated (Otto 1989). In hypertensive patients, Bonaduce et al showed a strong inverse correlation between left ventricular diastolic filling rate derived by pulsed Doppler and left ventricular muscle mass (Bonaduce 1989).

c) Left-ventricular hypertrophy in athletes

Cardiac muscle hypertrophy is a consequence of athletic training (Morganroth 1975, Gilbert 1977) and pulsed Doppler has been used to investigate the consequences for left ventricular diastolic function in athletes undertaking various forms of activity (Finklehor 1986, Pearson 1986b, Douglas 1986, Fagard 1987 a,b). In a study of 15 endurance athletes, Finklehor found that early diastolic filling of the left ventricle was not significantly different from the control group while atrial filling was reduced (Finklehor 1986). The results of Douglas (1986) similarly showed elevation of the peak E to peak A ratio in endurance athletes. In contradiction to the work of Finklehor and Douglas, two studies of endurance athletes by Fagard and colleagues, failed to reveal any significant differences between pulsed Doppler parameters of diastolic function between athletes and normal controls. The reasons for these discrepancies is not clear as patient selection, technique and interpretation of pulsed Doppler measurements was very similar in all cases. However, all studies were in agreement that early diastolic function is unaltered in athletes with left ventricular hypertrophy. Pearson has also documented the absence of diastolic filling abnormalities in weight lifters with cardiac hypertrophy (Pearson 1986b). More recent data in athletes at rest and during exercise concluded that while transmitral parameters are not significantly different at rest, significant enhancement of early diastolic filling occurs during exercise (Nixon 1991).

Pulsed Doppler assessment of left ventricular constriction and restriction

Louie et al used pulsed Doppler transmitral velocimetry to investigate the possible effect of right ventricular pressure overload on left ventricular diastolic filling and observed that a significant reduction in the early diastolic time velocity integral occurred (Louie 1986). The major implication from this study is that the configuration of the interventricular septum has a significant detrimental effect on early diastolic ventricular filling. Lavine showed that reduction of early diastolic filling with compensatory atrial activity resulted only in the presence of right ventricular enlargement associated with right ventricular systolic pressures in excess of 40mm Hg (Lavine 1988). While the authors present cogent arguments that interventricular septal geometry accounts for the reported findings, the results of Fujii show that similarly abnormal patterns of diastolic filling may occur in ischaemic heart disease independently of the site of distribution of lesions (Fujii 1985). While providing an important insight into the influence of mechanical factors on left ventricular diastolic filling, the results of Louie and Lavine are unlikely to be specific to a single disease entity (Louie 1986, Lavine 1988).An early report of the use of pulsed Doppler in 4 patients with constrictive pericarditis by Agatston (1984) found early filling velocities to be increased but early diastolic filling to be abbreviated. Appleton examined the effect of pericardial tamponade on ventricular filling patterns and found that acute constriction led to increased respiratory variation in the transmitral flow velocities (Appleton 1988b). The clinical implication from this work is that pulsed Doppler might help to differentiate those subjects where pericardial effusion had produced haemodynamic compromise, although its contribution in clinical practice might be expected to be limited. Appleton, Hatle et al have also addressed the pulsed Doppler characteristics caused by restrictive left ventricular disease and found that while early velocities were similar to controls, peak atrial velocities were reduced (Appleton 1988c). In addition, early diastolic filling was found to be significantly shortened in restrictive disease states suggesting rapid equalisation between atrial and ventricular pressures in early diastole. Whether this is due to atrial or ventricular factors or a combination of both cannot be ascertained from this data.

Pulsed Doppler in dilated cardiomyopathy

In the presence of dilated cardiomyopathy, reduction of peak early velocity and the ratio of early and late filling velocities was demonstrated by Takenaka (1986b). The presence of mitral regurgitation was found to hide these abnormalities in a way analogous to that shown in hypertrophic cardiomyopathy and secondary left ventricular hypertrophy (Takenaka 1986a, Shaikh 1988). Other preliminary reports from Simons and Aguirre have shown the importance of identifying diastolic filling abnormalities in patients presenting with congestive heart failure when systolic function may still be normal (Simons 1986, Aguirre 1987). The importance of cardiomyopathy in the prognosis in diabetes mellitus (Kannel 1974, Regan 1983) has prompted two studies of evaluation of left ventricular diastolic function in diabetics (Zarich 1988, Takenaka 1988). Even in asymptomatic diabetics, left ventricular transmitral blood flow velocity inflow patterns reflect subclinical diastolic dysfunction and have been proposed as a means for serial evaluation of cardiac function. Impaired diastolic filling with reduction in peak early flow velocity and early to atrial flow velocity ratio is also known to occur in asymptomatic chronic alcoholics (Kupari 1990).

Other applications of pulsed Doppler in left ventricular diastolic function

Valantine (1987) and Desruennes (1988), have studied the diastolic function of the transplanted heart using pulsed Doppler. Valantine examined the effects of timing of the recipient atrial contraction on the diastolic events in the donor ventricle and atrium and stressed that if pulsed Doppler is to be used in the detection of allograft rejection then careful analysis of timing of recipient and donor hearts is required. In a clinical study of patients with and without other evidence of rejection, the transmitral pressure half-time was found to be a useful non-invasive indicator of graft rejection (Desruennes 1988). In this later study, the potential effects of timing of diastolic events according to Valantine were recognised (Valantine 1987).

Appleton (1987) and Johnson (1988) have shown that using pulsed Doppler velocimetry, abnormalities of left ventricular diastolic function can be detected and serially monitored in premature infants. The clinical application of this data has yet to be established. The study of transmitral flow has even been undertaken in the unborn child. In a large cohort of Doppler studies of the human foetus, Reed et al (1986) documented serial changes in the contribution of late and early diastolic filling as pregnancy progressed.

Pulsed Doppler evaluation of therapeutic intervention on ventricular diastolic function

Monitoring early and late diastolic filling velocities during manipulation of the mode of atrial and ventricular pacing has been used to study the effects of varying atrioventricular delay and to optimise sequential cardiac pacemaker function (Pearson 1988a, Rokey 1988, Iwase 1986, Stewart 1984). The effects of percutaneous coronary angioplasty on diastolic transmitral flow are discussed above. A small number of reports are also available concerning the effects of therapeutic intervention on diastolic filling patterns. Vandenberg (1988a) in a study of normal subjects observed that, after the administration of sublingual nitrates, both the peak E velocity and E/A ratio decreased and early diastolic filling was prolonged. At the same time the early time velocity integral did not show a significant change. The effect of preload reduction on diastolic filling waveforms after nitrates was also investigated by Choong (1987a,b) and Leeman (1986) who used upright tilting to decrease atrial preload. Preload reduction by limb cuff inflation was also shown to decrease peak early filling velocity in normal subjects while atrial peak flow velocity did not significantly alter (Triulzi 1990). The effect of preload reduction on the diastolic transmitral blood flow velocity waveform has important implications where serial studies of left ventricular function and cross-sectional studies are undertaken because it introduces an important variable which must be accounted for before meaningful comparisons of data can be made. Vandenburg has suggested that the early time velocity integral might be more suitable for serial measurements as he found it to be relatively unaffected by changes in preload. In the analysis of diastolic filling patterns during nitrate infusion, Choong et al (1987b) showed like

Vandenburg that peak E velocity, the rate of deceleration from early peak velocity and E to A ratio were signficantly altered by changes in preload. He concluded, like Triulzi, that reduction in preload could therefore mimic the changes reported in the presence of abnormal left ventricular diastolic function (Kitabatake 1982, Fujii 1985, Takenaka 1986 a b, Gidding 1986, Choong 1987b, Triulzi 1990). Significant effects on abnormal left ventricular diastolic filling, with a shift towards increased early diastolic filling were demonstrated in patients with coronary artery disease after beta-blockade by Myreng et al (Myreng 1988). Whether the observed improvements were related to reduction in myocardial ischaemia or due to direct effects on the myocardium was not established and other possible mechanisms such as the effect on heart rate and atrial pressure may have contributed to the changes documented. Caution is therefore required in equating the effects of beta-blockers to an improvement in diastolic ventricular function and it is possible that these effects merely mask abnormalities of diastolic function without producing a favourable clinical benefit. The benefits of calcium antagonist therapy in patients with hypertrophic cardiomyopathy have been reported by Iwase (1987). Iwase and colleagues compared transmitral blood flow velocity patterns in normal subjects to patients with hypertrophic cardiomyopathy before and after exercise. Administration of diltiazem, a calcium antagonist, was found to normalise the ventricular filling velocities, causing a significant increase in peak E in those patients with hypertrophic cardiomyopathy and allowed a normal response to exercise. These results appear to reflect previously reported haemodynamic data relating to the beneficial effects of verapamil, another calcium antagonist, in hypertrophic cardiomyopathy (Hanrath 1983) and the effects of verapamil on hypertrophic cardiomyopathy in children assessed using radionuclide angiography (Shaffer 1988). Peak early filling velocity (E) may be influenced by the administration of inotropic agents such as dobutamine which causes a rise in peak E velocity (Vandenburg 1988), although whether this is an effect related to increased volume flow or to changes in ventricular dynamics was not assessed.

Chapter 3

Pulsed Doppler Blood Flow Velocimetry

The history and development of pulsed Doppler blood flow velocity measurement

The Doppler effect

The fundamental principle on which the study of blood flow velocity by pulsed wave ultrasound is based was first proposed by the Austrian physicist Johan Christian Doppler in 1842. In his paper entitled "Ueber das farbige licht der Doppelsterne und einigerandere gestirne des Himmels" , Doppler described the apparent shift towards lower frequencies, the "red end" of the visible spectrum, in light travelling from distant stars (Doppler 1842). He postulated that this effect occurred because these stars were moving away from the Earth at high speed and concluded that the observed change in the colour of light coming from these stars depended upon the relative motion between the observer and star. This phenomenon, now commonly referred to as the Doppler Shift, can also be observed in relation to energy of different wavelengths including sound. The Doppler effect applied to sound was subsequently demonstrated in 1845 by a Dutch scientist Bays Ballot. Two musicians with perfect pitch were asked to play the same note. One stood on a moving railway carriage while the other stood at the side of the railway track. As the locomotive approached and passed the stationary player, it was recorded by the observers that the note from the moving musician's horn was in comparison first higher and then slightly lower as the train moved away (Ballot 1845). Perhaps the best known everyday example of this phenomenon is the change in pitch of a car horn or engine as it approaches and then passes a stationary observer. Compression of the sound wave front as the vehicle approaches the observer leads to a rise in the audible pitch from the horn and this is followed by lowering of the pitch due to rarefaction of the wave front as the car moves away.

Principles of Ultrasound

Ultrasound is the name given to soundwaves that have frequencies above the normal range of human hearing or greater than 20,000 cycles per second. It is generated by the application of a high voltage field to a single or array of piezo-electric ("pressure-electric") crystals and the frequencies of ultrasound used clinically for diagnosis are in the range of 1 to 7 MHz. (1 MHz = 1 million cycles per second) Ultrasound can be generated as a continuous beam or as a pulsed beam depending on how the applied electric field is generated. By varying the physical characteristics of the transducer and controlling the sequence of activation of individual transducer elements, the beam size, focusing and resolution of the system can be altered (Morgan 1978).

The behaviour of a beam of ultrasound of specific frequency in a given medium depends on the acoustic impedance of that medium and may be expressed by the equation :

$$Z = pv$$

where Z is the acoustic impedance of the medium in Rayls

p is the density of the medium in gcm

v is the velocity of sound in cms^{-1}

Fortunately, for human soft tissues, acoustic impedance varies by only very small amounts and the velocity of the ultrasound beam is therefore virtually constant at 1540 metres per second (Goldman 1956, Kossoff 1973). As ultrasound passes through biological tissues it undergoes a combination of absorption, refraction and reflection. In pulsed Doppler velocimetry, it is the reflected ultrasound that it used to determine the velocity of flow of blood (Satumora 1956, Franklin 1961). Reflection of ultrasound occurs at the interface between tissues of differing acoustic impedance. The amount of reflected ultrasound can be expressed by the equation :

$$R = \frac{(Z2 - Z1)}{(Z2 + Z1)}$$

where Z2 is the acoustic impedence of medium 2

Z1 is the acoustic impedence of medium 1

Kato and Reid have shown that red blood corpuscles act as the primary source of backscattered ultrasound from a moving column of blood (Kato 1962, Reid 1969).

Continuous wave ultrasound blood flow velocimetry

Continuous wave Doppler flow velocimetry is performed using two transducer elements mounted within the same casing and connected to ultrasound generator and receiver circuitry. One transducer element continuously transmits ultrasound while the other acts as a receiver. Analysis of the change in frequency of the reflected ultrasound beam compared to the transmitted frequency is used to calculate blood flow velocity (Franklin 1961). The first reported application of the Doppler principle to the study of blood flow within the heart was by Satumora (Satumora 1956). Using an ultrasound transmitter and receiver applied to the skin, it was possible to record the shift in frequency of a continuous beam of transmitted ultrasound caused by movements of the cardiac chambers and the blood within them. The work of Kato confirmed that the signals obtained from a moving column of blood were indeed caused by scattering of ultrasound from groups of moving red blood cells (Kato 1962). Franklin produced a similar device which used continuous wave ultrasound to generate a signal which when coupled to a frequency meter gave accurate measurements of blood flow velocity up to 100 cms^{-1} in animals (Franklin 1961). This was used to record blood flow velocity patterns directly from the aorta of anaesthetised dogs. Further studies by Edler (1969), Kalmanson (1969,1972,1975) and Benchimol (1973) described the use of implanted and catheter mounted ultrasound transducers to measure the flow velocity of blood in the cardiac chambers and diastolic blood flow across the mitral valve. In 1964, Baker introduced a device intended for transcutaneous measurement of blood flow velocity in Man and from this prototype, the first commercial continuous wave Doppler velocimeter was developed. This device allowed the measurement of blood flow velocity but did not allow discrimination of the direction of flow (Baker 1964). A very important further advance came, therefore, with the introduction of electronic circuitry that allowed the direction of blood flow to be determined in relation to the ultrasound transmitter by McLeod (McLeod 1967). In continuous wave Doppler velocimetry, the reflected signal comprises backscattered ultrasound from a number of tissues and structures various depths from the ultrasound transducer. In the heart this may include valvular structures, myocardial tissue and blood moving in more than one chamber simultaneously. Frequency shifts caused by reflection of the ultrasound beam from all of these structures are recorded by the receiving transducer. Therefore, the major limitation of continuous wave Doppler velocimetry in the study of intracardiac blood flow velocity patterns is that it does not allow accurate determination of the site from which any given reflected signal has been received (Baker 1970). This problem of distance resolution is referred to as the range ambiguity of continuous wave ultrasound.

Pulsed wave Doppler blood flow velocimetry

The problem of range ambiguity in continuous wave blood flow velocity measurement was overcome independently and almost simultaneously by three groups of investigators led by Baker (1970) , Peronneau (1969) and Wells (1969) who developed very similar Doppler instruments. They each described a technique where the ultrasonic beam was alternately transmitted and received in discrete pulses or packets of ultrasound energy using the same piezo-electric transducer crystal. By means of electronic timing the reflected ultrasound from a specified distance from the transducer crystal could be recorded. This is the process of electronic gating and is described in more detail below. Thus the limitation of range determination of backscattered ultrasound was largely overcome allowing blood flow velocities at specified sites within the cardiac chambers and great vessels to be studied. Initially, transcutaneous Doppler ultrasound examinations were performed without first imaging the structure under investigation (Baker 1970). In 1973, Johnson described the use of M-Mode echocardiography to assist in determining the electronically gated depth from which backscattered signals were recorded (Johnson 1973). The following year, Barber and colleagues introduced an echocardiographic system that combined the facility for pulsed Doppler recording of intracardiac flow velocities with simultaneous cross-sectional echocardiographic imaging (Barber 1974). The imaging and pulsed Doppler units shared a common tranducer which could be switched between Doppler and imaging modes. This important innovation allowed more rapid identification of the region of interest and gave the operator guidance in achieving optimum transducer alignment to blood flow. Determination of the site from which reflected ultrasound was received (range gating) was made easier by the superimposition of an electronic cursor which marked the sampling position on the real time cross-sectional image.

Spectral Analysis of Backscattered Ultrasound

The backscattered ultrasound which reaches the ultrasound transducer whilst it is in receiving mode comprises multiple signals of varying frequencies and amplitude (Peronneau 1969, Baker 1970). Of central importance in quantitative analysis of these signals is some form of further processing of these complex signals. It is very fortunate that the Doppler frequency shifts produced by blood moving within the heart and great vessels lie within range audible to the human ear. Thus a simple audio output from the Doppler velocimeter can provide important clues about the velocity and type of blood flow encountered and may be used to direct the Doppler beam and placement of the Doppler sample volume (Johnson 1973). However, for quantitative evaluation of these signals some form of electronic processing is required. A number of different methods have been applied to the analysis of backscattered ultrasound in pulsed Doppler velocimetry. The first was described by Larch et al who used an instrument known as the zero-crossing counter (Larch 1977). The zero-crossing meter comprises a frequency meter which produces an output voltage that is directly proportional to the number of times that a given input voltage crosses the zero line per unit of time. The zero-crossing voltage occurs when the Doppler frequency shift passes through the zero-point of its sine wave and so higher input frequencies generate a larger output voltage. This type of device was employed in Doppler instruments used by Baker (1964) and Franklin (1961), but did not allow analysis of the components of the summated frequency shift detected by the transducer. Ward (1976), Diagle (1977) and Larch (1977) went on to describe and evaluate a second method of signal processing known as the time interval histogram method of spectral analysis which proved to be of limited value and did not find wide clinical application. Electronic filtering of reflected Doppler signals using "band pass" filters was first proposed by Kanekos (Kanekos 1968). The technique involved taking a pre-recorded portion of the received signal and playing it back through an electronic filter set at the frequency of interest. The amplitude of this frequency over time could then be plotted. By repeating this process with the band pass filter set at different levels, a graphical representation of the amplitude of the component frequencies over time could be produced. Initially, this analysis was undertaken off-line after the clinical examination and was time-consuming. The ability to process such signals on-line was made possible using equipment developed by Light (Light 1970). This method used a number of band pass filters set at predetermined levels which simultaneously produced parallel plots of amplitude against time. The evolution of digital processing of electronic signals in the late 1970's led to the now widely used method of Fast Fourier Transform for spectral analysis of pulsed Doppler signals. In 1807 the french mathematician Fourier proposed the concept that any complex signal could be described in terms of a number a key frequencies and their harmonics provided that the signal could be adequately described mathematically as a function of time. Thus the spectral distribution of backscattered ultrasound can be calculated mathematically without the need for electronic filtering. The great speed of computer based processing allows this analysis to be achieved almost instantaneously. Bomner (1978) Cannon (1982) and Wille (1977) were among the first investigators to apply this digital processing technique clinically to the study of abnormal blood flow in valvular heart disease. Digital Fast Fourier Transform spectral analysis is currently used in all commercially available Doppler echocardiographic equipment.

Doppler Theory

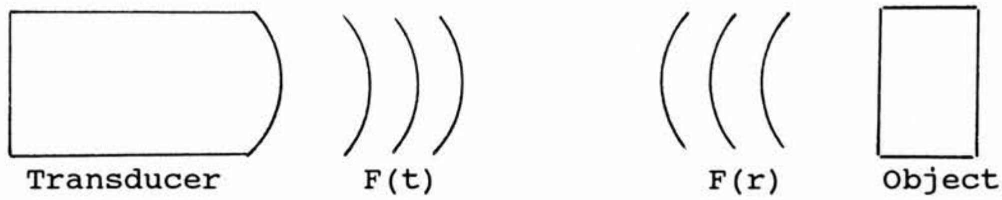
If a beam of an ultrasound of constant frequency is directed towards a stationary ultrasound reflector, then the frequency and wavelength of any reflected ultrasound remains unchanged from that of the source [Fig 3.1a]. If the reflector is moving towards the ultrasonic source then the reflected ultrasound will be increased in frequency and decreased in wavelength relative to the transmitted frequency [Fig 3.1b]. Conversely, if the reflector is moving away from the ultrasound source, then the reflected ultrasound will show a relative decrease in frequency and increase in wavelength [Fig 3.1c] to the transmitted source. The observed difference between the frequency of the transmitted and received ultrasound signals is called the frequency shift or Doppler shift. The frequency shift may either be positive or negative and varies in proportion to the velocity of a given target relative to the ultrasound source. It is from this measurement of frequency shift that ultrasonic measurement of blood flow velocity within the heart and great vessels is derived.

Ultrasonic Blood Flow Velocity Measurement

When ultrasound is used to determine the velocity of a moving column of blood it is the red blood cells themselves which act as the main reflector of soundwaves (Kato 1962, Reid 1969, Shung 1976). If the ultrasound source remains stationary and both the frequency of transmitted ultrasound and the speed of travel of the ultrasound wavefront known, then the frequency shift between the transmitted and received ultrasound signals due to the motion of the red cells can be determined. The

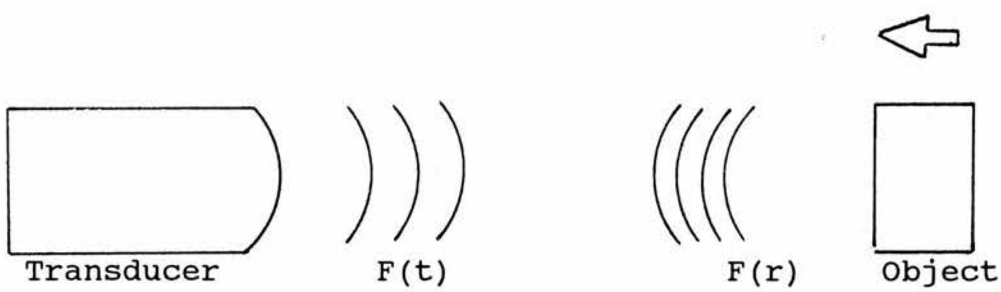
Figure 3.1

a)



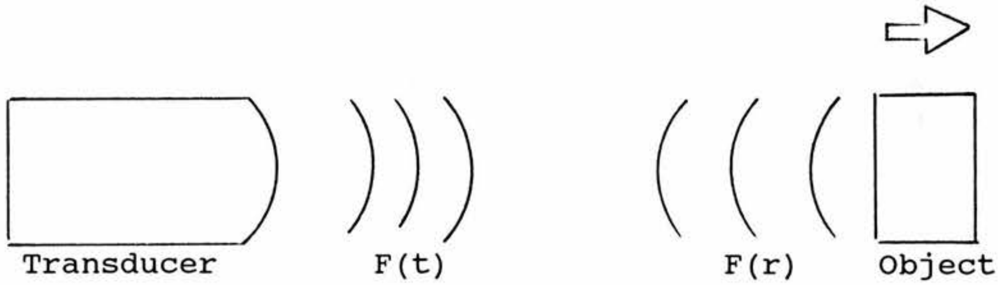
For stationary object F(t) equals F(r)

b)



For object moving towards transducer F(t) is less than F(r)

c)



For object moving away from transducer F(t) is greater than F(r)

F (t) = transmitted frequency
F (r) = received frequency

frequency shift can in turn be used to calculate the velocity with which the column of red blood cells is moving relative to the ultrasound source. The velocity of ultrasound travelling through human tissues is known (Goldman 1956) and the frequency of the transmitted ultrasound can be controlled. Using the following equation whose derivation is described by Atkinson and Woodcock (1982) it is therefore possible to calculate the velocity of a column of red blood cells.

$$\text{Frequency Shift} = \frac{2.f.v.\cos\theta}{c} \qquad \text{[Equation 1]}$$

$$\text{from which } v = \frac{\text{Frequency shift}.c}{2.f.\cos\theta}$$

where f = frequency of transmitted ultrasound

v = velocity of red blood cells

c = velocity of ultrasound in human tissues (propagation velocity)

θ = incident angle between the ultrasound beam and direction of blood flow.

It can be seen that frequency shift is directly proportional to the velocity of blood flow. For clinical discussion in cardiac pulsed Doppler velocimetry it has become usual to refer to the derived velocity of flow rather than frequency shift.

Effect of incident angle on flow velocity measurement

Blood flow is vectorial, having both directional and velocity components. With reference to Equation 1 it can be seen that the frequency shift of reflected ultrasound from moving red blood cells is dependent both upon the velocity of flow and the cosine of the angle between the transmitted ultrasound beam and direction of flow (θ). To accurately calculate blood flow velocity, the angle θ must therefore be known. Unfortunately, in the clinical setting, it is not possible to directly measure the angle between the ultrasound beam and direction of flow and this can only be assumed or indirectly estimated. In these circumstances calculation of flow velocity must be made assuming that angle to flow is zero. The practical technique involved in achieving the best alignment to flow is discussed in chapter 4. The cosine of θ varies by only a small amount within $\pm$ 20 degrees (cos 20 = 0.94) and so within these limits small errors in alignment to blood flow would be expected to produce a maximum error of $\pm$6% in calculated blood flow velocity.

Pulsed Doppler Electronic Range Gating

The propagation velocity of ultrasound in biological tissues is virtually constant (Goldman 1956) and therefore the time taken for a given pulse of transmitted ultrasound to return from a reflector at a known distance from the transducer can be calculated. This is the principle of range gating of pulsed wave Doppler velocimetry. The ultrasound beam is emitted as a series of discrete bursts or pulses the timing of which is under electronic control. Between each pulse, the ultrasonic transducer acts as a receiver of reflected ultrasound. By sampling the returning signals at preselected intervals, the transducer can act as a receiver when backscattered signals from a given distance or depth from the transducer are expected to return to the transducer crystal. In terms of blood flow velocity measurement, the signals received when this electronic "gate" is open will be the a summation of the frequency shifts produced by the movement of groups of red blood cells within a specified region which is termed the Doppler sample volume. Increasing the time interval between successive openings of the gate will increase the depth from which signals are received. Increasing the duration for which the time gate is open will allow reflected ultrasound from a larger sample volume to be received.

Pulsed Doppler Sample Volume

The depth from which reflected ultrasound is collected at the transducer crystal is determined by the timing and duration of electronic gating. The region from which these signals arise is referred to as the sample volume, the characteristics of which were described by Jorgensen and Baker (Jorgensen 1973). It is shaped like a teardrop whose length is proportional to the duration of the receiving interval and whose width is a function of the transducer radius, far field divergence of the ultrasound beam and the wavelength of the transmitted ultrasound beam. In combined cross-sectional imaging and Doppler echocardiographic instruments, the sample volume is marked on the cathode ray screen by an electronic cursor which shows both the position of the sample volume in relation to the surrounding structures and its length. While the length of the sample volume can be adjusted, the width of the sample volume cannot be altered by the operator.

<u>Pulse Repetition Frequency and Aliasing</u>

After an ultrasound pulse train has been emitted, reflected ultrasound from a specified depth must be received at the transducer before the next pulse is transmitted if ambiguity about the origin of backscattered signals is to be avoided. The limitation imposed by depth on pulse repetition frequency (PRF) is given by the formula: $PRF = 0.5 \frac{c}{D}$

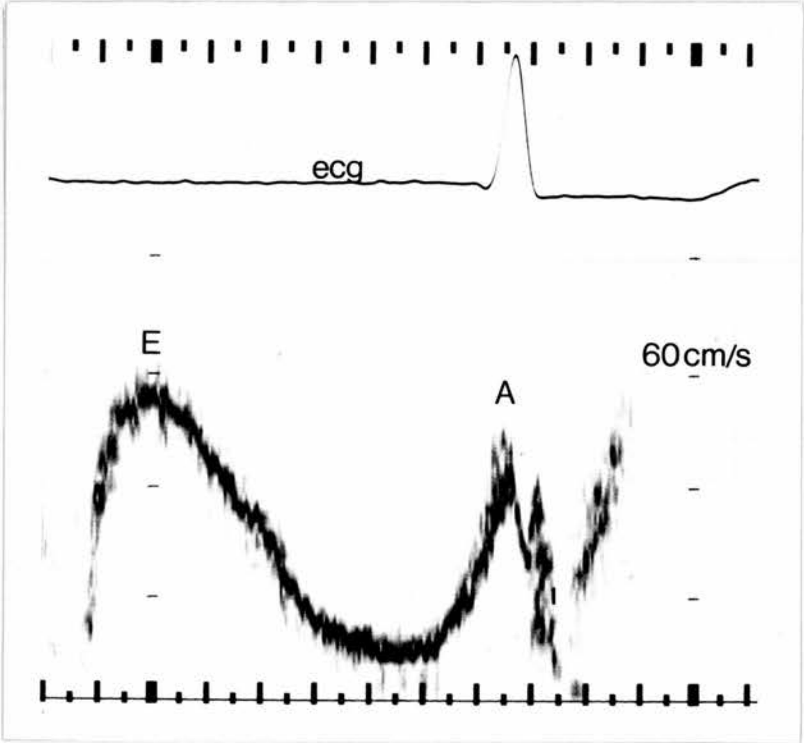
where c is the speed of ultrasound in tissues and D the distance between the transducer surface and target. Pulse repetition frequency in turn imposes an important limitation on the maximum frequency shift that can be measured using pulsed Doppler. For accurate interpretation of a given frequency, sampling of that frequency must occur at least twice during the period of one complete cycle of that frequency (Nyquist 1928, Shannon 1948). As the rate of pulsed Doppler sampling is determined by the pulse repetition frequency, this means that the highest frequency shift which can be decoded will be one half of the pulse repetition frequency (PRF) of the Doppler instrument. Higher frequency shifts can be recorded using lower frequency transducers. In practical terms, using a 2.25 MHz transducer, this allows measurement of flow velocity up to 170 cms^{-1}. If the highest frequency component of the received signal is greater than twice the PRF, then the "Nyquist limit" is said to have been exceeded. When this occurs, accurate signal analysis is not possible because of uncertainty about the points on the frequency sample which have been sampled. A spectral display which appears to wrap around itself is produced, a phenomenon referred to as pulsed Doppler aliasing (Hatle 1985). After the Nyquist limit has been exceeded, flow velocity measurement is not possible although the presence of aliasing may alert the operator to the presence of high velocity and often pathological flow. Because continuous wave Doppler instruments continuously sample the backscattered ultrasound beam, for practical purposes the Nyquist limit is never exceeded. The ability of continuous wave Doppler to quantify high flow velocities is one of its chief applications (Hatle 1985). Because of the limitation of range ambiguity in continuous wave Doppler a combination of both pulsed and continuous wave Doppler is neccessary in many clinical situations. Another method of overcoming the limitation of PRF in pulsed Doppler examinations is by the use of a high pulse repetition frequency technique. If the PRF is increased above the limits set by the equation : $PRF = 0.5 \frac{c}{D}$

then reflected ultrasound will be received from a number of sites simultaneously when the transducer is in receiving mode. If the PRF is exactly doubled, two sample volumes with a fixed distance between them are produced. When the electronic receiving gate is open, reflected ultrasound from both sample volumes will be received. Because of the higher PRF, higher velocities can be measured. Range ambiguity has however been introduced because the site from which the signal emanates is not accurately known. (Kent 1983, Pearlman 1983).

Modal Velocity

Figure 3.2 shows an example of pulsed Doppler spectral flow velocity analysis from the left ventricular inflow. While overall spectral dispersion is small, a prominent dark band may be traced through the central portion of the curve. This band indicates the component frequency shift of highest intensity in the received signal plotted against time. As the intensity of each frequency component relates in turn to the number of red blood cells producing this frequency shift, the dark band represents the median velocity of red cells within the sample volume specified. It is referred to as the modal velocity of blood flow. Recognition of the modal velocity is of practical importance in analysis of pulsed Doppler spectra and is discussed later.

Figure 3.2



<u>Pulsed Doppler transmitral flow velocity recording in a patient with hypertrophic cardiomyopathy.</u>

The modal velocity is denoted by the darkest part of the spectral plot and represents the instantaneous flow velocity of the majority of red blood cells within the sample volume.

(E - peak early velocity, A - peak atrial velocity
ecg - electrocardiogram)

The Pulsed Doppler Velocimeter

A diagrammatic outline of a pulsed Doppler velocimeter is shown in Fig 3.3. A brief description of each of the component parts and its function follows.

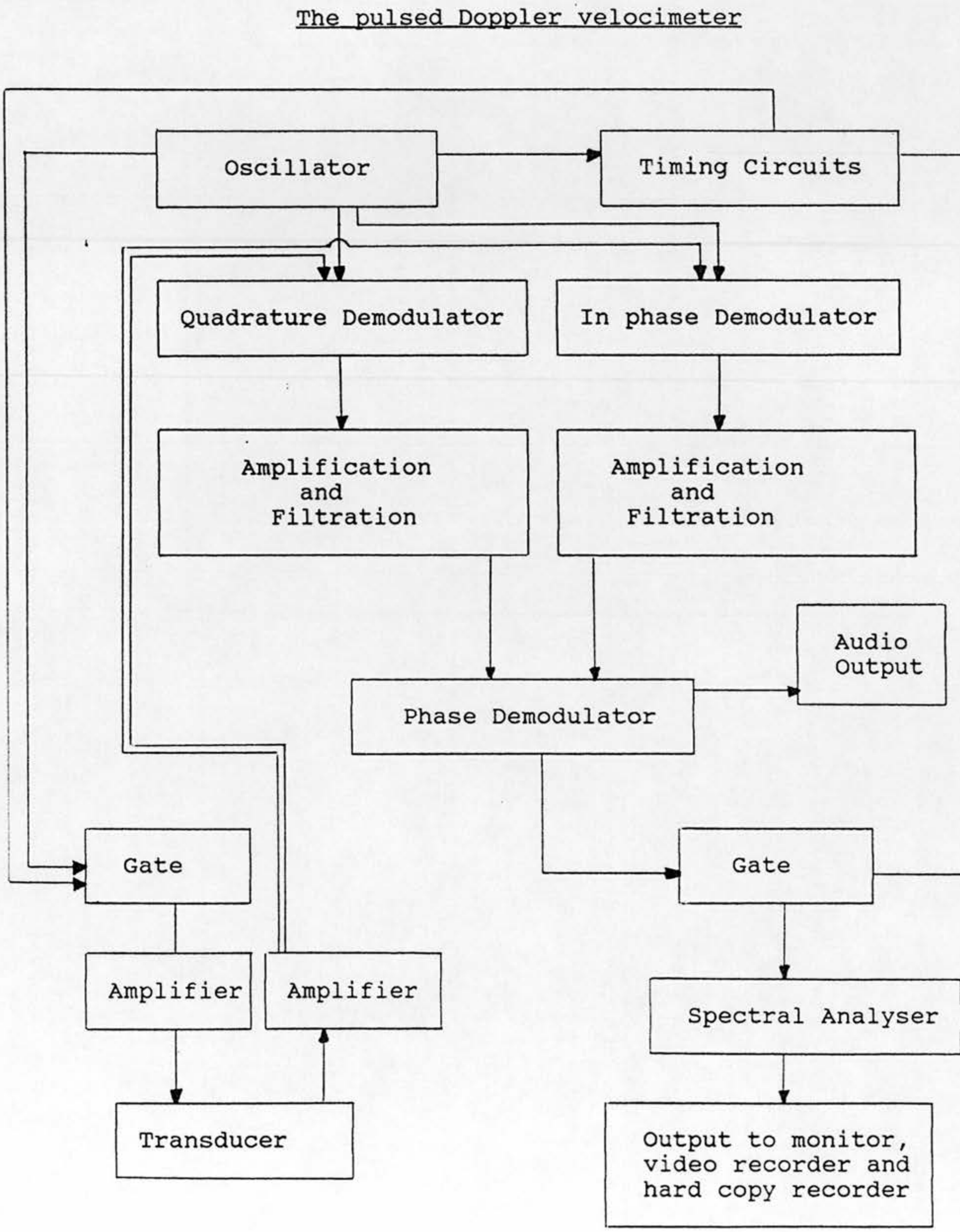
Oscillator and Timing Circuits

The primary oscillator provides a suitable frequency for transmission. This is usually of the range of 2.25 to 5 MHz. The oscillator signal is used to calculate the Doppler shift and in addition it provides a phase reference signal for subsequent demodulation of the backscattered signals. The output from the oscillator is coupled to a power amplifier for exciting the transmitting transducer. The pulse repetition frequency of the transmitted beam is determined by timing circuits which also control the periodicity of sampling of the demodulated signal for spectral analysis.

Ultrasonic Transducer

The ultrasound transducer acts both as a transmitter and receiver of ultrasound. Ultrasonic transducers are constructed from a thin piece of piezo-electric crystal which is sandwiched between two foil electrodes. A number of crystals may be incorporated within an electronically controlled array or a large single crystal transducer element may be used in a mechanical sector scanning transducer. The latter type of transducer was used in

Figure 3.3


The pulsed Doppler velocimeter
Oscillator
Timing Circuits
Quadrature Demodulator
In phase Demodulator
Amplification
and
Filtration
Amplification
and
Filtration
Audio
Output
Phase Demodulator
Gate
Gate
Amplifier
Amplifier
Spectral Analyser
Transducer
Output to monitor,
video recorder and
hard copy recorder

the experimental part of this dissertation. The crystal is mounted at one end of the plastic transducer casing within an oil based sound coupling medium. A slightly convex plastic lens mounted in front of the crystal is used to partially focus the ultrasound beam. For cross-sectional imaging the crystal is rocked back and forth on a motorised cradle. When the transducer is switched for pulsed Doppler velocimetry, the crystal is in a fixed forward facing position. When an electrical field is applied across the transducer electrodes the crystal distorts because of its piezo-electric characteristics and when the field is removed the crystal resumes its shape. If a sine or sawtooth wave is applied across the electrodes alternate expansion and contraction of the crystal is produced, resulting in alternate wave fronts of compression and rarefaction. Propagation of these wave fronts through adjacent media produces a beam of ultrasound waves. The wavelength and frequency of sound energy emitted is dependent upon the physical characteristics of the transducer crystal. For transducers of 3.5 and 2.25 MHz the approximate distance between successive sound waves is 0.44 and 0.69mm respectively. Amplitude of soundwave emission is controlled by varying the voltage applied across the transducer electrodes which in turn affects the amount of distortion of the piezo-electric crystal. The voltages used are typically between 50 and 300 volts. The maximum power output of commercially available ultrasound transducers is 40 to 50 milliwatts. The piezo-electric characteristics of the transducer crystal act in reverse to receive ultrasound. When soundwaves strike the transducer crystal it is distorted between the foil electrodes and this generates a weak electrical signal of the order of a few microvolts. Electronic filtration, amplification and further processing of the received signal allows it to be recorded or displayed on a cathode ray tube.

Doppler Demodulator

The Doppler demodulator comprises electronic circuitry for the analysis of the received ultrasound signals. There are inputs from the primary oscillator and receiver. A technique of electronic summation of the transmitted and received frequencies is used to determine the frequency shift. Because these frequencies are different, they are out of phase and summation produces a "beat" frequency equal to the difference between the two. The beat signal is demodulated by rectification and is then filtered. The resulting signal is the Doppler frequency shift.

Directional Flow Detection

In order to determine the direction of movement producing a given frequency shift within the sample volume, two Doppler demodulators are used. Both receive a reference signal from the Doppler oscillator. One signal is called the in-phase reference signal while that to the second demodulator is phase shifted by 90 degrees and is known as the quadrature reference. The received signal undergoes simultaneous demodulation through both channels and after amplification, both outputs are fed to a phase detector which is adjusted to identify signals produced by flow towards or away from the transducer. The electronic circuits are calibrated so that backscattered ultrasound from blood cells moving towards the ultrasound beam produce a positive frequency shift. By convention this is displayed as an upward deflection from the baseline on the cathode ray screen. Red cells moving away from the advancing ultrasound waves produce a negative frequency shift that results in a downward deflection of the frequency-time curve.

Thump and low-pass filters

As well as backscattered signals caused by the movement of blood within the cardiac chambers or blood vessels, low frequency but high amplitude signals are received from body wall structures or moving cardiac valves. Because of their amplitude, there is a risk of overloading the amplifiers used to boost the demodulated signals and for this reason the demodulated signal is passed through a "thump" filter to remove low frequency signals. A low-pass filter is used to remove frequencies above the expected Doppler frequencies to improve the signal to noise ratio of the display.

Spectral Analyser

The pattern of blood flow within the heart and great vessels is complex. While the central portion of a moving stream of blood may be laminar, with most red cells moving at the same direction and speed, turbulence and eddy currents may be encountered towards the edges of the column of flow (Hatle 1985). Reflected ultrasound from a moving column of blood is therefore likely to comprise many signals with differing intensities, directions and frequencies. Intensity varies with the density or number of red blood cells and frequency varies with velocity of the red cells. The composition of the received signal has been likened to the ultrasonic equivalent of an orchestra tuning where many different instruments are being played at different pitches and intensities all at once. Some qualitative information about the nature of blood flow can be gained from the audio signal alone but for quantitative analysis of this data further processing is required. The spectral analyser achieves this by repeated sampling of the complex reflected signals and analysing each of these samples to determine its composition in terms of the component frequencies of the signal and their relative intensities. This is microprocessor controlled and employs the Fast Fourier Transform method of analysis described above.

The spectral analyser operates in the following manner:

1) The demodulated pulsed Doppler signal is amplified filtered and sampled at intervals of 5 milliseconds.

2) Digital electronic analysis divides the sampled signal into as many as 128 discrete frequency bands or frequency "bins".

3) The intensity or amplitude of energy passing through each of these frequency bins is recorded in temporary memory every 5 milliseconds.

4) The recorded information for the 5 millisecond sample analysed is displayed on a cathode ray screen. The information is displayed in the form of a vertical band of pixels. The intensity of each pixel is determined by the recorded amplitude of the given frequency corresponding to it.

5) Steps 1) to 4) are repeated at 5 millisecond intervals so that a curve is generated on the cathode ray screen representing the change in the component frequencies of the received signal over time. A representative plot recorded on dry silver paper is shown in Fig 3.2.

In clinical practice, most commercially available cardiac pulsed Doppler echocardiographs convert the plot of frequency shift against time to one of velocity against time.

<u>Output Devices</u>

Because the Doppler shifts produced by the movement of blood in the heart and great vessels lie within the audible range, a loudspeaker or headphones provides a direct audio output during the pulsed Doppler echocardiographic examination. Sometimes, one audio channel is used for signals resulting from blood moving towards the transducer while the other channel is used for signals caused by blood moving away to produce a useful stereophonic effect. Where the flow of blood within the sample volume is uniform, a relatively pure tone audio signal results while in the presence of turbulent flow, the mixture of frequency shifts causes a harsh signal. The output from the spectral analyser may be displayed on a cathode ray oscilloscope and then recorded onto a hard copy medium such as dry silver paper. Alternatively, the signals may be recorded using electromagnetic videotape for later retrieval.

Chapter 4

Study Design, Equipment and Methodology

All pulsed Doppler echocardiographic examinations, associated M-mode echocardiographic examinations and cardiac catheterisations were performed between December 1987 and February 1989 in the Noninvasive Heart Unit and Department of Cardiology at Killingbeck Hospital Leeds. A three month period prior to the commencement of the clinical studies was devoted to the development of an original video-based system for computer assisted analysis of pulsed Doppler flow velocity spectra.

Study Design

The experimental work of this thesis was divided into four sections each of which was designed to examine specific aspects of the application of pulsed Doppler echocardiography to the study of left ventricular diastolic function. Firstly, a study of the transmitral flow velocity patterns in healthy adult volunteers was undertaken. By undertaking this study it was intended to gain familiarity with the Doppler echocardiographic equipment and to establish normal values derived from the analysis of transmitral flow patterns. In addition, the relationship between transmitral flow velocity waveforms, body surface area, blood pressure and respiration was examined. The second experimental study was designed to investigate the variability of transmitral flow velocities over time in an unselected population of patients attending for routine ultrasound examination and the suitability of the technique for serial study of left ventricular diastolic function. By establishing the expected range of inherent variability of transmitral parameters due to the summated effects of interobserver error and biological variability it was hoped to determine the accuracy and reliability of transmitral flow velocity measurements for any subsequent investigation of the effects of disease progression and therapeutic intervention on left ventricular diastolic function using pulsed Doppler velocimetry. The suitability of the pulsed Doppler technique both in terms of technical quality and patient acceptability was also assessed as this is of fundamental importance with regard to serial study of ventricular function. The third section of the experimental work was undertaken to examine the relationship between the rate of left ventricular diastolic relaxation and transmitral flow velocities in normal subjects. The reported ease with which transmitral flow velocimetry can be performed and the widely reported comparative difficulties encountered in M-mode evaluation of diastolic filling justifies the search for a definable relationship between the two techniques which might allow the substitution of the apparently simpler and more reliable pulsed Doppler echocardiographic evaluation of diastolic ventricular function. In order to diminish the effects of occult or subclinical ventricular disease, especially on the M-mode measurements, this study was undertaken in healthy adults who were further screened with regard to their suitability for high quality M-mode examinations. In the final experimental section, investigation of the possible relationship between direct measurement of intracavitary ventricular diastolic pressure and transmitral flow patterns was considered. Clearly, there would be a large number of possible clinical applications for pulsed Doppler transmitral flow velocimetry if some constant and definable relationship could be established between end-diastolic left ventricular pressure and transmitral flow patterns.

Study Populations

For the studies of normal transmitral flow velocity patterns, physiological variation in the transmitral flow velocity pattern and the correlative study between pulsed Doppler and M-mode echocardiography, healthy volunteers were recruited from within the staff of Killingbeck Hospital and from a fitness club based at a local swimming pool. All volunteers were symptom free with no significant past medical history and taking no medication. The ages of these volunteers ranged from 18 to 32 years. In each case, cardiovascular examination including blood pressure measurement revealed no abnormality. No volunteer was included in more than one clinical study. 50 patient volunteers were recruited from within the patients attending the Noninvasive Heart Unit at Killingbeck Hospital to take part in the study of variability and reproducibility of transmitral flow velocity spectra in haemodynamically stable subjects. The majority of these patients suffered from chronic ischaemic heart disease while the remainder included patients with valvular heart disease, cardiomyopathy and hypertension. 64 patients undergoing investigation for suspected ischaemic heart disease underwent simultaneous measurement of intraventricular pressure and transmitral blood flow velocity recordings. From this group, 50 suitable patients were found in whom technicaly adequate paired recordings were compared. Further details of each subgroup are given in the individual study protocols at the beginning of the chapters dealing with the experimental work.

Doppler Echocardiographic Equipment

All of the combined pulsed Doppler and cross-sectional echocardiographic examinations were performed using either the Honeywell Ultra Imager or Biosound ND-256 ultrasonographs. The latter machine is the second "generation" of the Ultra Imager and while the external casing and electronic controls differ between the two machines, both incorporate the same pulsed Doppler generator, spectral analyser and display. In both machines, the transducers are of the mechanical sector scanning type and are shared between the pulsed Doppler module and cross-sectional imaging circuitry. The transducers were either 3.5 or 2.25 MHz frequencies and a 30, 40 or 60 degree sector can be selected for imaging purposes. When used in the combined pulsed Doppler and cross-sectional imaging mode, the image of the part under examination is displayed as an inverted triangle with structures closest to the surface displayed at the top of a monitor screen. A radial line cursor is superimposed on the cross-sectional image and its position on the image is controlled by a joystick mechanism on the control panel of the ultrasonograph. An electronic sample volume cursor is displayed on the radial line and shows both the depth and size of the pulsed Doppler sample volume and displays the angle of incidence between the central part of the ultrasound beam and the region under investigation. Once the sample volume has been correctly positioned, depression of a switch on the ultrasound machine freezes the real-time image and changes the function of the transducer to pulsed Doppler mode only. To visually re-check the sample volume position it is possible either to switch back to combined Doppler-imaging for a few seconds or to obtain a periodic image update which is under control of the machine. Once in Doppler mode, the operator is provided with an audio signal of the frequency shifts from the region of the sample volume, and a spectral display of those frequency shifts on the monitor. The electronic display plots velocity on the y-axis against time on the x-axis. The speed of the sweep of the x-axis can be varied to simulate a moving paper speed of 25, 50 and 100 mm per second. The instantaneous blood flow velocity is displayed with reference to a zero baseline the position of which can be varied on the display monitor screen. This baseline was set so that it appeared at or close to the bottom of the display monitor screen. Because of the range of flow velocities at the mitral valve and the depth of sampling, aliasing of the reflected ultrasound signal was not encountered.

The maximum velocities that can be recorded using this equipment before aliasing occurs are given below:

Transducer frequency	Sample Volume Depth		
	0-6 cm	6-10 cm	10-16 cm
2.25 MHz	$\pm 225 cms^{-1}$	$\pm 135 cms^{-1}$	$\pm 85 cms^{-1}$
3.5 MHz	$\pm 145\ cms^{-1}$	$\pm 87 cms^{-1}$	$\pm 54 cms^{-1}$

The Doppler transceiver operates by emitting an excitation pulse of 4 cycles of the nominal frequency of the transducer. The receiver gain for range gated echoes may be varied over 60 decibels (dB). Three transmit repetition rates are provided by the system to allow a greater velocity range without aliasing as the sample volume depth is varied. The pulse repetition frequency (PRF) is changed automatically at depths of 6 and 10 cm from the transducer and the actual values are summarised below:

Depth	PRF	FFT sample rate
6 cm	13 KHz	16.667 KHz
10cm	7.8 KHz	10 KHz
16cm	4.875 KHz	6.25 KHz

In both machines spectral analysis is achieved by means of Fast Fourier Transform (FFT). The Honeywell and Biosound spectral analysers are based on equipment initially developed by the United States military. Full details of the exact circuitry and function of the spectral analyser have not been released by the ultrasound company. The quadrature and analogue data received is sampled at a rate of approximately 1.28 times the PRF and stored in a 1024 by 12 bit frame memory. A frame, consisting of 128 complex samples is processed every 5 msec. During FFT processing, a frame undergoes analysis into 128 frequency bins. Amplitude analysis of each bin provides a relative brightness for subsequent display on the monitor. The display grey scale is normalised to the maximum amplitude detected. The number of calculated FFT bins that can be displayed may be varied between 20 and 99 by changing the Doppler zero position and Doppler range on the main console. Electronic interpolation occurs in the graphic display to give a display of 284 to 396 pixels.

After any neccessary adjustments in transducer position, sample volume position and transducer angulation have been made to obtain the best possible pulsed Doppler signal, depression of a footswitch allows the Doppler signal to be recorded on dry silver recording paper. Both machines use a Honeywell LS-8 hard copy recorder which allows recording speeds of 25, 50, 75 and 100 mms^{-1} Instantaneous switching between speeds is possible by a switch on the main control console. All recordings were made at a paper speed of 100 mms^{-1}. Further depression of the footswitch ceases the paper motion. An alternative method of recording the pulsed Doppler complexes is onto an electromagnetic video tape. The tape records at a fixed speed but the sweep speed of the monitor display can be varied as described above. Off-line computer analysis of the recorded pulsed Doppler signals is then possible by transferring the videotape to a video-recorder connected to the digitising computer described in the following section.

Physiological Inputs

Both of the combined cross-sectional and pulsed Doppler echocardiographs are modified to include additional input channels. Three separate sockets on the side of the ultrasonograph are connected to individual amplification circuits which are then relayed to the monitor screen. The incoming signals undergo analogue to digital conversion at a sampling rate of 4 KHz. The output signals from these channels are displayed on the monitor screen at maximum brightness and sweep from right to left. Separate controls allow calibration and positioning of the baseline for each channel display screen. This arrangement allows simultaneous display of the patient's electrocardiogram, phonocardiogram and up to two amplified pressure traces from intravascular or intracardiac pressure monitoring catheters. The pulsed wave Doppler ultrasound signal can then be recorded either on dry silver paper or videotape with these additional signals overlaid on the Doppler signal trace allowing simultaneously occurring physiological events to be recorded on a beat to beat basis. This facility was used during the simultaneous recording of transmitral blood flow velocities and intracardiac pressure.

Clinical technique for recording of transmitral blood flow velocity spectra using pulsed Doppler velocimetry

General

Cardiac ultrasound techniques are operator dependent (Feigenbaum 1986) and so the need for standardisation both within and between observers is of paramount importance if reliable results are to be obtained or comparative clinical studies are to be undertaken (Sahn 1978). Therefore, careful patient preparation and meticulous examination technique were deemed essential in all of the experimental work undertaken. As well as the need to acquire technically adequate recordings for later analysis, strict rejection criteria for unsuitable recordings were imposed. In undertaking pulsed Doppler velocimetry, the operator requires a good working knowledge of surface and cardiac anatomy, normal and anomalous patterns of blood flow and a clear understanding of Doppler principles. The importance of close alignment of the ultrasound beam to direction of flow in order to obtain adequate quantitative information was discussed in chapter 3. This alignment is an important difference between Doppler velocimetry and other forms of cardiac ultrasound where the best signals are obtained with the ultrasound beam at right angles to the structures of interest.

Patient Preparation

A relaxed and informed patient is better able to co-operate with cardiac ultrasound examinations. The purpose and nature of the examination was firstly explained to each patient and any anxieties allayed. The examinations were performed in a warm room to help relaxation. The patient was then positioned in a left lateral decubitus position with the left arm flexed and behind the head. This position allows the cardiac apex to move towards the left chest wall reducing the amount of interposed tissue. Because of the variability in chest wall shape further small changes in the patient's position such as slight further rotation to the left or raising the torso slightly were often required to obtain the best acoustic window for the examination. The patients were asked to breathe normally during the examination. Prior to all examinations, the patient was allowed to rest quietly for about 5 minutes to allow pulse and respiratory rates to return to their resting levels. In anxious patients a longer interval was sometimes required before proceeding to the pulsed Doppler examination. While a number of patients expressed some initial anxiety on hearing the amplified Doppler signals this was never enough to interfere with the examination. When pulsed Doppler recordings of transmitral blood flow velocity were made in the cardiac catheterisation laboratory, the patients were supported by a foam wedge or pillows to bring them into a left lateral decubitus position.

Transducer Position

Optimum Doppler signals are obtained when the ultrasound beam is aligned as closely as possible to the direction of blood flow (Baker 1970). For recording transmitral diastolic flow velocity spectra the most commonly reported method of achieving this alignment is by positioning the transducer over or just internal to the cardiac apex which usually lies internal to the left nipple in the fifth intercostal space anteriorly (Kitabatake 1982, Gardin 1987). This method of transducer placement was chosen and from this starting position, using cross-sectional imaging, small changes in transducer position were made until an apical four chambered view was obtained. Using the image to guide alignment of the ultrasound beam to blood flow, the image was then adjusted until the Doppler line cursor was positioned as close to an angle of 90 degrees to the mitral valve annulus as possible. This is shown in figure 2.1. The sample volume was then placed in the region of the mitral valve at the point of maximum diastolic separation of the mitral valve leaflet tips. Rarely, because of chest shape or heart position other transducer positions were found to be better to achieve alignment to flow such as the apical two chambered view described by Gardin (Gardin 1987). While the cross-sectional image was used to guide transducer positioning, the Doppler audio and spectral signals were used to achieve optimum alignment to flow before transmitral blood flow velocity recordings were made.

Alignment of ultrasound beam with transmitral blood flow

While it is feasible to obtain accurate alignment between the ultrasound beam and transmitral blood flow without first imaging the left ventricle and mitral valve, the speed of the examination is shortened by using the combined imaging and Doppler technique. However, after approximate transducer position and sample volume depth had been selected, the imaging mode was then switched off. The spectral characteristics, peak flow velocity and audio characteristics of the Doppler signal were then used to achieve optimum alignment to flow. Despite the apparent alignment with transmitral diastolic flow achieved by using the combined imaging and Doppler method, the angle to flow remains unknown and must be deduced from a number of other considerations:

1) Maximum velocity shift - the instantaneous Doppler spectral display provides beat to beat representation of the flow velocity under examination. The maximum flow velocity that can be obtained by changing transducer angulation represents the maximum Doppler shift. This occurs, by definition, when the best possible alignment to flow is achieved.

2) Audio signal - both the intensity and quality of the Doppler audio signal provide important information to guide the operator. In the absence of mitral valve obstruction, transmitral flow is laminar with the great majority of red blood cells moving at the same velocity and in the same direction at a given instant. The corresponding audio signal is therefore of a "pure-tone" and is typically whistling in character. Failure to align correctly with flow results in loss of this pure tone signal and may introduce other, usually lower, frequencies from surrounding valve and chamber wall structures.

3) Spectral display - for the same reasons that lead to a pure audio signal with correct alignment to laminar flow, spectral analysis produces a well-defined modal velocity band with very little spectral dispersion.

4) Signal to noise ratio - accurate alignment to flow results in a diminution of interference in the received signal giving a high signal to noise ratio.

Therefore the characteristics of the Doppler audio signal and spectral display provide confirmation of optimal alignment to flow. Failure to obtain a pure tone audio signal and the appearance of wide spectral dispersion with low signal to noise ratio implies that alignment is poor.

Computer Assisted Analysis of Transmitral Pulsed Doppler Flow Velocity Spectra

Suitable equipment for the detailed analysis of transmitral blood flow velocity patterns was not available at the time of commencing data collection for this thesis. Therefore, before undertaking any clinical studies, an initial three month period was devoted to the design and construction of an original microcomputer based system for analysis of the transmitral blood flow velocity spectra subsequently recorded. The original computer programmes were designed so that further routines could be added as experience with the system was obtained and the final dedicated computer programmes were developed through a series of prototype versions. Experience in writing the pulsed Doppler analysis programmes was then applied to the construction of a programme for the analysis of M-mode traces used in Chapter 7. The whole analysis system was later further developed to provide an integrated echocardiographic analysis and reporting system for clinical use in the Noninvasive Unit at Killingbeck Hospital.

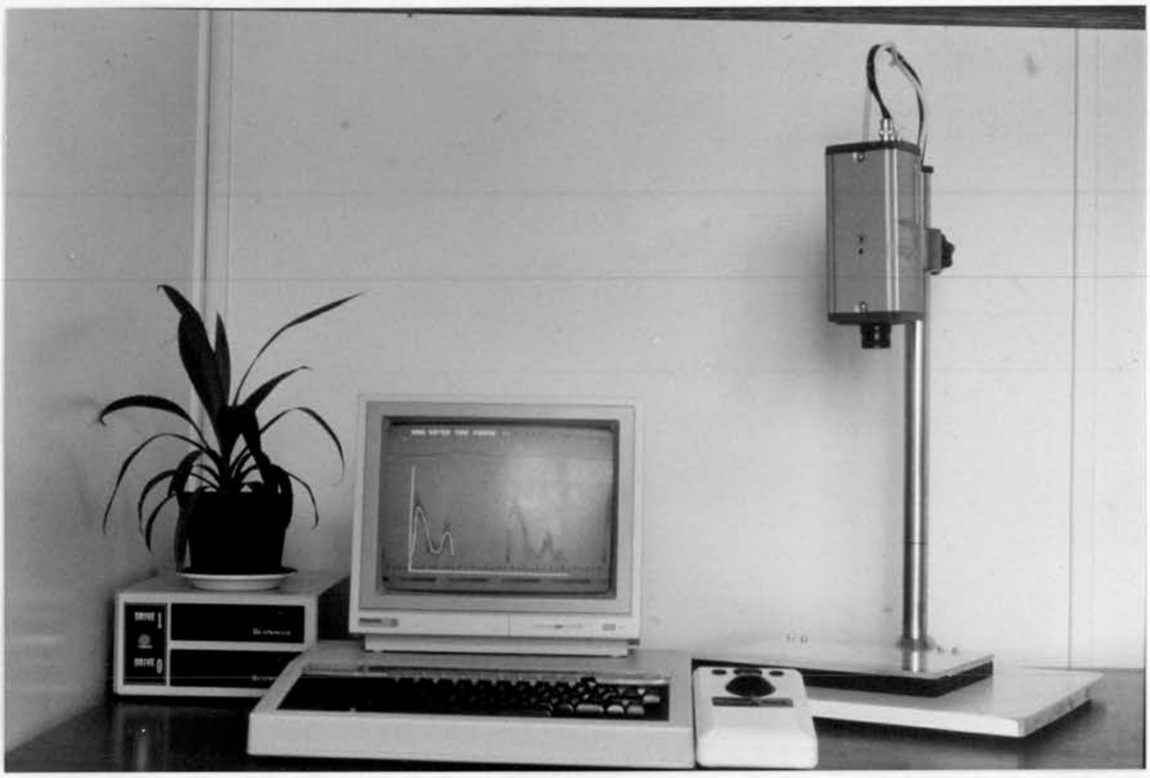
Video Camera based Doppler Analysis System

The microcomputer based digitising system is shown in Figure 4.1 Like all computer based systems its components can be divided into computer hardware and software. These are now described in more detail.

Computer Hardware

The analysis system is based around a commercially available BBC model B microcomputer. The microcomputer consists of a keyboard and has input ports from the floppy disc drives, trackerball attachment and videocamera. Output from the computer goes to a monitor screen and to a dot matrix printer. The microprocessor is controlled using programmes written in a programming language known as BBC Basic. The video camera is a Vidicon type (Panasonic VV-1500/B) and is mounted on a stand to allow easy adjustment of height for magnification. The video camera holder also has a plinth on which the trace for analysis is placed after being clamped within the perspex holder. Focus and brightness are controlled by moveable rings around the lens mount. Parallel connections are made between the camera and both monitor and microcomputer so that the video camera image is simultaneously fed to the monitor screen and computer input port. The computer programme generates an electronic cursor which can be used to define points and draw lines which are superimposed on the monitor screen image. The electronic cursor is steered by means of a

Figure 4.1



The computer system developed for analysis of transmitral pulsed Doppler recordings. The electronic cursor is moved using the trackerball attachment seen to the right of the keyboard. Movement of the video camera on its gantry allows optimal magnification of the waveform being measured.

trackerball attachment. The trackerball is a small desktop unit with a ball mounted in a plastic cage. The ball is moved by fingertip control and the mechanism within the trackerball unit generates a small current which is used to cause movement of the electronic cursor on the monitor screen that is proportional to the movement of the trackerball both in direction, speed and distance. By means of two switches on the trackerball, certain points may be specified on the monitor screen image which are then stored in the temporary memory of the computer. This facility is used to define the beginning and end points of an area of interest and to enter the calibration data. If a waveform is judged to have been incorrectly or inaccurately traced, then depression of another switch on the trackerball cancels the information held in the computer memory and resets the computer for further measurements.

As well as video camera images of hard copy recordings the playback output from a VHS videorecorder can be fed directly to the microcomputer and monitor screen. By pausing the images during playback, a frozen image of a single or group of transmitral flow velocity waveforms can be selected for analysis. Therefore Doppler signals may be analysed without prior recording onto hard copy, although in these circumstances no magnification of the image is then possible. The data generated after analysis of a particular waveform or region of interest, can be fed directly to the dot matrix printer or alternatively can be stored onto floppy disc for later retrieval.

Computer Software

The computer programme developed for the analysis of transmitral pulsed Doppler flow velocity waveforms was tailored for use with the computer hardware described above. The analysis programme allows measurement and calculation of a given curve or area in relation to pre-calibrated X and Y axes. For the analysis of transmitral blood flow velocity waveforms, the Y axis is calibrated in cms^{-1} while the X axis is calibrated in milliseconds. The numerical parameters to be derived from the transmitral blood flow velocity patterns were modified during development of the digitising system and because of the flexible nature of such a programme, different versions were developed with varying degrees of complexity. A routine clinical Doppler analysis programme and a separate research orientated analysis programme were eventually produced. They differ in the number of measurements made from each Doppler trace and the clinical analysis programme is incorporated with a package for analysis of aortic flow patterns, M-mode traces and cross-sectional echocardiography.

The research computer programme allows the measurement of peak velocities, mean and instantaneous acceleration and deceleration and planimetry of areas beneath a specified curve or part of a curve. In order that the computer recognises the constituent parts of the transmitral blood flow velocity curve certain definitions were incorporated into the programme routines. Each of these definitions was entered into the programme as a series of expressions combining to produce a flow chart or algorithm through which the programme must then operate. The programme is built up as a series of line statements which number several hundreds. The listings of these commands are not included in the thesis but a summary of the mode of operation follows.

The peak early velocity is defined as the highest measured velocity from the baseline after a point marking the beginning of the curve under analysis but before a second upward slope in the curve. This means that the computer cannot mistake the early (E) and late (A) velocity peaks. The mean acceleration to E is measured from the average slope of the curve between the starting point and the peak early velocity. Mean deceleration from E is defined as the average slope from the peak early velocity to the baseline or until a second upward slope in the waveform is detected. Peak A velocity is defined as the highest measured velocity after the point where the first upward deflection of the curve begins following the peak E velocity.

The digitising programme is interactive, so that at each stage of the data input, the operator is asked to define points or enter numerical information through a series of prompt messages on the monitor screen. The computer can also inform the operator if errors have occurred. For instance, if the two points used for Y axis calibration do not lie on the same vertical line, then the computer will not accept these values for calibration.

Operation of the Digitising System

A number of stages are followed in the analysis of each pulsed Doppler trace:

1) The hard copy trace to be analysed is placed within a holder comprising a baseplate with a thin hinged perspex sheet to ensure that it is completely flat. The holder is then mounted on the plinth below the video camera and fixed in position.

2) The video camera is adjusted so that the trace to be analysed lies within a reference area on the monitor screen that is outlined by a box. The waveform under analysis is magnified as much as possible by altering the height of the video camera lens so that it appears as large as possible while still within the reference area seen on the monitor screen. This maneouvre serves to reduce error of planimetry to the minimum.

3) The trackerball is used to calibrate the reference area. The cursor is steered firstly to the zero velocity baseline and a point marked by depressing the trackerball switch. A second point on the velocity scale is then chosen, for instance 100 cms^{-1}, and entered by depressing the switch on the trackerball. The computer then provides an onscreen prompt "What is this velocity in cms^{-1}" and the operator enters the appropriate number from the computer keyboard. The computer memory then uses this information to calibrate the vertical height of

the reference area. Time in milliseconds is then defined on the X-axis in the same way. Two points separated by a known interval in msec are entered into the computer memory and again after the prompt "What is this interval in msec " the operator enters the appropriate value to allow calibration of the time axis of the monitor screen.

4) The trackerball is then used to define the beginning and end-points of the velocity waveform being analysed by placing the cross-hair cursor at these points and depressing the trackerball switch to enter these co-ordinates on the temporary computer memory. To avoid error caused by not properly orientating the hard copy trace, the computer will produce an error message if the Y co-ordinates of the beginning and end-points of the trace are not the same. The beginning and end of the area of "interest" has now been entered in computer memory.

5) The trackerball is used to draw around the velocity waveform between the defined beginning and end-points.

6) The curve traced out and the area beneath the computer generated curve is then analysed by the computer with comparison to the previously defined velocity and time scales. This numeric information is then stored in temporary memory before further calculation of the derived parameters specified.

7) In addition the operator may define up to four additional slopes of the spectral waveform for further

analysis. This is achieved using a computer generated cursor transected by a line. The slope of the line can be altered using the trackerball and can be placed anywhere along the curve to measure the rate of change of velocity of a given slope.

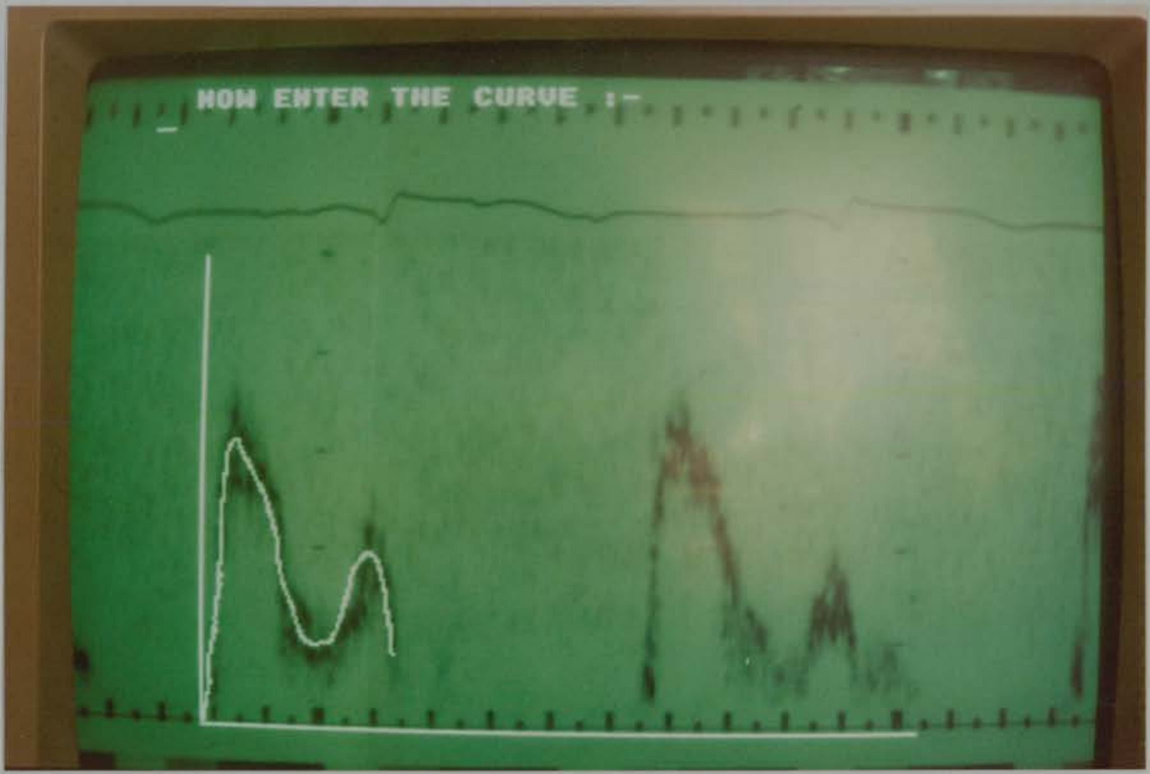
Figure 4.2 shows the monitor display during operation of the digitising computer.

The function of this digitising system is very similar in concept and operation of digitising systems which use a digitising tablet and pen interfaced to a microcomputer. The video camera capture method was however chosen in preference to this for a number of reasons.

1) The height of the camera can be adjusted to allow the waveform under consideration to fill the greatest portion of the screen possible. This means that the inherent error in planimetry of a curve can be minimised. This cannot be achieved using pen and tablet systems where even minor errors in planimetry may result in large errors in derived values from a waveform only a few centimetres in height.

2) Because the observer does not touch the trace after it has been positioned beneath the video camera, inadvertent movement of the trace is not possible. This can be a problem using digitising tablets where the trace cannot be securely fixed before planimetry.

Figure 4.2



After calibration for velocity and time, the waveform under analysis is traced using the electronic cursor. In all cases modal velocity was chosen for planimetry.

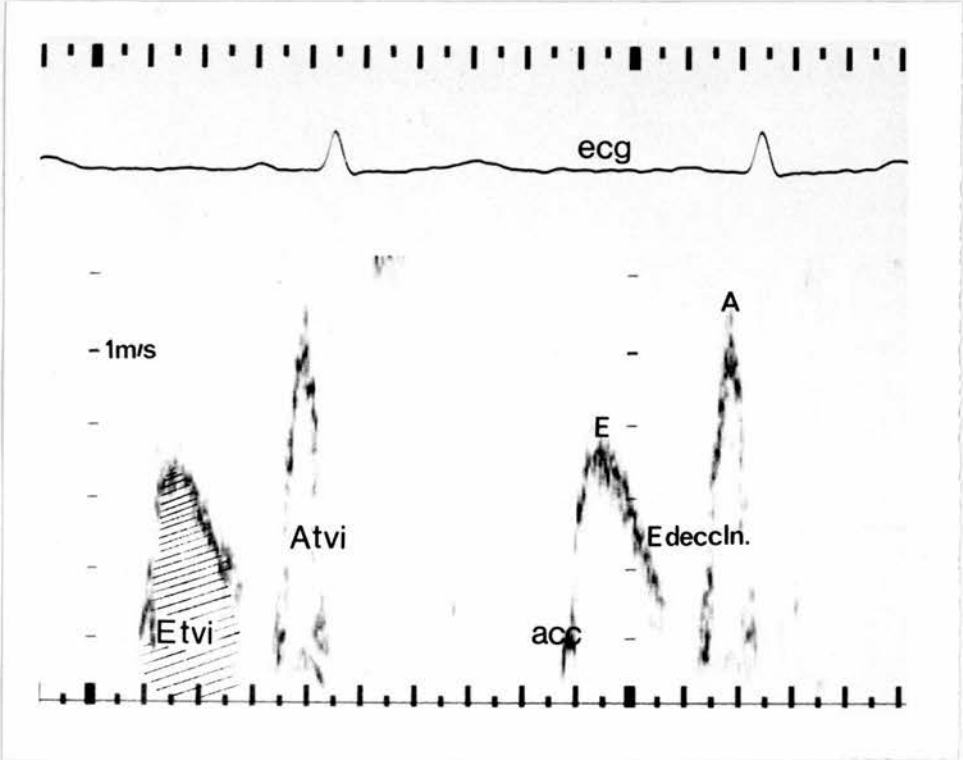
3) The video based digitising programme superimposes a computer generated curve around the waveform being analysed. This allows the observer to confirm that accurate planimetry has been performed before any derived measurements are made. If planimetry appears inadequate, then the waveform can be retraced. Using pen and tablet systems, no such confirmation of accuracy of planimetry is possible.

The final version of the digitising programme used for the clinical studies undertaken in this thesis allows the following measurements to be made from each transmitral flow velocity waveform:

Peak early flow velocity (E)
Peak atrial flow velocity (A).
Time velocity integral beneath early filling wave
Time velocity integral beneath atrial filling wave
Mean rate of acceleration to peak E velocity
Initial rate of deceleration from peak early velocity
Mean rate of deceleration from peak early velocity

These are shown in Figure 4.3.

Figure 4.3



<u>Derived measurements from pulsed Doppler transmitral flow velocity spectra</u>

The digitising system allows measurement of velocity peaks, slopes of specified portions of the velocity trace and areas beneath the filling waves.

(E - peak early flow velocity, A - peak atrial flow velocity, E tvi and A tvi - time velocity integrals beneath early and late filling waves respectively, acc - mean rate of acceleration from baseline to peak E, E decln - rate of deceleration from peak E to baseline. The slope from the first half of deceleration and the mean slope are measured)

Chapter 5

Pulsed Doppler transmitral blood flow velocity patterns in healthy adults.

Introduction

Before proceeding to correlative studies of pulsed Doppler velocimetry in determining diastolic behaviour of the left ventricle, a preliminary investigation of transmitral blood flow velocity characteristics in normal volunteers was undertaken. The objectives of this initial study were:

1) To gain familiarity with the pulsed Doppler echocardiographic equipment and its operation.

2) To develop competence in the clinical technique of pulsed Doppler examination of transmitral blood flow velocities.

3) To determine the feasibility of obtaining technically adequate pulsed Doppler recordings of transmitral flow in healthy volunteers.

4) To define the characteristics of the transmitral waveform in health and to document the expected normal values for parameters of left ventricular diastolic events measured by pulsed Doppler in a population of healthy adults.

5) To determine the variation in transmitral flow velocity characteristics during the respiratory cycle.

6) To examine the characteristics of the slope of deceleration from the peak early flow velocity to the baseline. This was undertaken to determine whether measurement of the first half of the slope could be reliably extrapolated to the whole slope in circumstances where this could not be directly measured.

7) To examine the relationship between derived parameters of transmitral flow, body surface area, and blood pressure.

8) To examine the influence of gender on the transmitral blood flow velocity waveform.

Methodology

Study Population

The population studied comprised 54 healthy volunteers recruited from within the staff and friends of Killingbeck Hospital Leeds. There were 29 female subjects and 26 male subjects with a mean age of 25 years (range 21 to 30 years). No volunteer had any history of cardiovascular or respiratory disease. All were free from cardiorespiratory symptoms , normotensive and taking no regular medication. All volunteers were in sinus rhythm with heart rates between 49 and 82 beats per minute. In each case preliminary clinical examination was performed to exclude the presence of cardiac murmurs. The height and weight of each subject was recorded and the body surface area calculated using nomograms based on the formula of Dubois and Dubois. (Dubois 1916). The resting blood pressure was recorded immediately prior to the pulsed Doppler echocardiographic examination, diastolic pressure being determined using the fifth phase muffling of the conducted sounds. The mean systolic pressure was 122 ± 16 mm Hg and mean diastolic pressure was 68 ± 10 mm Hg. The mean body surface area was 1.92 square metres (range 1.38 to 2.1).

Clinical Pulsed Doppler Examinations of Transmitral Blood Flow Velocities

All subjects attended for examination in late afternoon. A clinical history was taken and cardiorespiratory examination was performed in each case. After the subject had rested in a left lateral decubitus position for at least 5 minutes, pulsed Doppler spectral recordings of transmitral blood flow velocity were made with the subject in quiet respiration using the methodology described in chapter 4. The transmitral flow velocity spectra were recorded over 5 to 10 consecutive respiratory cycles onto dry silver paper using a paper speed of 100 mms^{-1}. Simultaneous recording of chest wall excursion was made using a strain gauge which was coupled to a Smith Kline Echocardiograph. The recording was made at 100 mms^{-1} and synchronised with the pulsed Doppler recording by means of an electronic calibration pulse at the beginning of each recording.

Analysis of Pulsed Doppler Flow Velocity Spectra

All hard copy traces were measured using the microcomputer based digitising system already described. Study of the slope of deceleration from the peak early filling velocity to the baseline allowed minor changes in the computer software to be made and this point is discussed later. The mean values obtained by planimetry of the consecutive transmitral blood flow velocity waveforms in a single respiratory cycle were used to obtain mean values for the following transmitral flow velocity parameters:

Peak E velocity
Peak A velocity
Acceleration to peak E
Deceleration from peak E
Early and late flow velocity integrals
Ratio of peak E and A velocities

Deceleration from the peak E velocity was measured both from the first half of the slope (initial deceleration) and from the whole slope (mean deceleration). Both values were measured to establish whether they differed significantly. There were two reasons why this was undertaken. Firstly, because of the increased spectral dispersion which may be observed during the latter part of the deceleration phase of the early filling wave, it was hoped to establish whether measurement of modal velocity in the first half of the deceleration slope alone might avoid the difficulties encountered in trying to determine modal velocity where spectral dispersion was too wide for optimal digitisation. This might in turn help to reduce observer bias when digitising complexes to obtain both the rate of deceleration from peak early velocity and the early time velocity integral. Secondly, in those circumstances where there is fusion of the E and A waves due to rapid heart rate, it is not possible to trace the deceleration slope to the baseline. If the mean slope of deceleration could be derived from the initial slope, then extrapolation of the curve for time-velocity integral calculation would be possible.

To analyse the changes in the transmitral flow velocity waveform during the respiratory cycle, the maximum and minimum values of each of the above parameters was measured from a chosen respiratory cycle in each volunteer. The same respiratory cycle was also used for calculation of the mean values. The minimum value for each parameter was subtracted from the maximum and the difference used in subsequent calculations.

Statistical Methods

For the population studied the mean and standard deviation for each of the parameters of transmitral blood flow was calculated. The absolute mean and standard deviation for variation in each of the derived parameters during the respiratory cycle was calculated. The variation in each parameter with respiration was also calculated as a percentage change between maximum and minimum values over the respiratory cycle. All derived parameters showed a normal distribution. Comparison of the maximum and minimum values obtained for each parameter during respiration was made using Students paired T-test. The level of statistical probability was taken to be $p < 0.05$. The values obtained for the mean slope of descent from peak E to the baseline were compared to the slope obtained in the first half of the deceleration curve using Students paired t-test. Linear regression analysis was undertaken to derive correlation coefficients between each pulsed Doppler parameter and body surface area, systolic and diastolic blood pressure. $p < 0.05$ was chosen as the level of statistical significance. The influence of gender on each of the pulsed Doppler parameters was tested using Students unpaired t-test.

Results

Feasibility of transmitral blood flow velocity recordings using pulsed Doppler in normal subjects

Using an apical four chamber view as a starting point to obtain alignment between the ultrasound beam and blood flow, technically adequate recordings of transmitral blood flow velocity were possible in all cases. While initially, it was necessary to frequently refer to the cross-sectional image to guide transducer alignment, it was found that with increasing experience, the image was of most value in initially determining sample volume placement, while the intensity and quality of the audio signal was more valuable in the fine adjustment of transducer alignment. Increasing familiarity with the pulsed Doppler equipment allowed the examinations to be performed with a mean duration of less than 5 minutes. There was a high degree of patient acceptability, the only occasional complaint being of mild anxiety due to the audio signal of the Doppler equipment.

<u>The transmitral blood flow velocity waveform in health</u>

In all subjects the transmitral flow velocity waveform was found to have a biphasic appearance with an initial early filling wave (E) whose initial upstroke began after the ventricular depolarisation complex of the simultaneously recorded electrocardiogram. A second and much smaller filling wave (A) was coincident with atrial systole. An example recording from one volunteer is shown in figure 2.2. In all cases , the E wave was of greater magnitude than the A wave and therefore the E/A ratio was always greater than unity. At the beginning of the E wave, there is a brisk upstroke from the reference baseline of zero velocity which continues to the peak E velocity. The slope of this line is used to calculate the rate of acceleration to peak E velocity by relating slope to the timebase of the recording. In the great majority of subjects, this initial upstroke showed only minimal spectral dispersion. In 11 subjects, small deviations from the baseline were observed before the rapid upstroke to peak E, the origin of which were not determined by this study. However, these spectral signals usually corresponded to low amplitude, low frequency audio signals which were presumed to be due to inadvertant insonation of chamber wall movement or valvular structures. Recognition of this artefact was found to be of practical importance when digitising the transmitral velocity signal in order to avoid possible ambiguity as to the starting point of the transmitral blood flow velocity waveform. In all subsequent experimental sections, the beginning of the transmitral waveform was defined as that initial positive deflection from the baseline which was in direct continuity with upstroke to peak E velocity. The slope of acceleration to E was only rarely a straight line and in a small number of subjects showed significant variation in its course. Following the peak early velocity, the waveform slopes downwards to the baseline. Relating the slope of this curve to the timebase provides a measure of the rate of deceleration of the flow of blood entering the left ventricle in the region of the sample volume after the early maximal flow velocity peak. As was found in the case of the slope of acceleration, the deceleration slope may show a variety of configurations and was rarely a straight line. An important additional aspect of the slope of deceleration from peak E is that it consistently showed greater spectral widening or dispersion as the curve tended towards the zero baseline. The presence of this spectral dispersion was found in some instances to introduce appreciable difficulty into the planimetry of the deceleration slope because of the loss of the modal velocity band. The slope of deceleration from peak E was found to reach or come very close to the baseline in all subjects. The A peak velocity was coincident with atrial systole denoted by the P wave of the electrocardiogram. Following the peak A velocity, the slope of the transmitral waveform reached the zero baseline before the next ventricular systole.

<u>Derived values from transmitral flow velocity waveforms in healthy adults</u>

The mean values and standard deviations of each of the derived parameters measured from transmitral blood flow velocity spectra are summarised in table 5.1.

<u>Effect of respiration on transmitral flow velocity waveforms</u>

During inspiration, the peak early and late filling velocities fell and were observed to increase during expiration (Figure 5.1). The mean absolute difference for peak E velocity was 9 ± 3 cms^{-1}, for slope of acceleration to peak E was 2.34 ± 0.95 ms^{-1}, for initial slope of deceleration from peak E was 3.1 ± 1.44 ms^{-1} and for mean slope of deceleration from peak E was 1.0 ± 0.57 ms^{-1}. The mean absolute difference over the respiratory cycle for the early time velocity integral was 174$\pm$85 cmmsec, for the peak A velocity 10$\pm$5 cms^{-1}, for the atrial time velocity integral 85$\pm$52 cmmsec and for the E/A ratio was 0.73$\pm$0.38. Table 5.2 summarises the mean absolute differences obtained from the maximum and minimum values recorded for each of the measured parameters during the respiratory cycle. These differences represent a mean percentage variation of 11.5% for peak E velocity, 24.8% for slope of acceleration to peak E, 40% for the initial slope of deceleration from peak E, 24.5% for the mean slope of deceleration from E, 16% for the early time velocity integral, 26% for the peak atrial flow velocity, 28.7% for the atrial time-velocity integral and 23% for the E/A ratio. Table 5.3 summarises mean percentage variation of each of the recorded parameters with respiration.

In the case of each of the pulsed Doppler parameters measured, the difference between maximum and minimum values during respiration was found to be significant with $p < 0.001$ for all parameters. These results are summarised in table 5.4.

<u>Slope of deceleration from peak E to baseline</u>

Comparison of the values obtained for the slope of descent from peak E in its first and second halves using Students paired t-test showed a highly significant difference between the two sets of values with a value for p of less than 0.001.

Correlation between pulsed Doppler measurements, body surface area and blood pressure.

No statistically significant correlation was found between any of the measured pulsed Doppler parameters of transmitral flow and body surface area or systolic blood pressure. A weak negative correlation was found between the ratio of the early and late velocity peaks and diastolic blood pressure ($r -0.39$ $p < 0.05$). These results are summarised in tables 5.5, 5.6 and 5.7.

Influence of gender on transmitral velocity waveform

No statistically significant difference was found between the male and female volunteers for any of the measured pulsed Doppler parameters. These results are summarised in table 5.8.

Table 5.1

<u>Derived values from transmitral waveforms in healthy adults</u>

Pulsed Doppler parameter	Mean$\pm$SD
Peak early velocity (E)	69.2$\pm$14.6 cms^{-1}
Acceleration to peak E velocity	11.1$\pm$3.5 ms^{-1}
E time-velocity integral	1013$\pm$285 cmmsec
Initial deceleration from E	7.9$\pm$9.1 ms^{-1}
Mean deceleration from E	3.4$\pm$1.0 ms^{-1}
Peak atrial velocity (A)	35.1$\pm$12.2 cms^{-1}
A time-velocity integral	303$\pm$117 cmmsec
E/A ratio	2.3$\pm$0.78

n = 54

Table 5.2

<u>Absolute differences recorded in transmitral flow velocity parameters with respiration</u>

Pulsed Doppler parameter	Absolute difference Mean$\pm$SD	Range
Peak E velocity	9 ± 3 cms^{-1}	4 to 14
Acceleration to peak E	2.34 ± 0.95 ms^{-1}	0.71 to 3.72
Initial deceleration from E	3.1 ± 1.44 ms^{-1}	1.1 to 5.96
Mean deceleration from E	1.0 ± 0.57 ms^{-1}	0.13 to 2.1
E time-velocity integral	174 ± 85 cmmsec	82 to 374
Peak A velocity	10 ± 5 cms^{-1}	3 to 18
A time-velocity integral	85 ± 52 cmmsec	13 to 192
E/A ratio	0.73 ± 0.38	0.32 to 1.52

n = 54

Table 5.3

Mean percentage variation in transmitral flow velocity parameters with respiration

Pulsed Doppler parameter	Mean respiratory variation (%age)
Peak E velocity	11.5 %
Acceleration to peak E	24.8 %
Initial deceleration from E	40 %
Mean deceleration from E	24.5 %
E time-velocity integral	16 %
Peak A velocity	26 %
A time-velocity integral	28.7 %
E/A ratio	23 %

n = 54

Table 5.4

<u>Comparison of maximum and minimum values obtained from transmitral waveform by paired t-test</u>

Pulsed Doppler parameter	P Value
Peak E velocity	$p < 0.001$
Acceleration to peak E	$p < 0.001$
Initial deceleration from E	$p < 0.001$
Mean deceleration from E	$p < 0.001$
E time-velocity integral	$p < 0.001$
Peak A velocity	$p < 0.001$
A time-velocity integral	$p < 0.001$
E/A ratio	$p < 0.001$

$n = 54$

Table 5.5

Correlation between pulsed Doppler parameters and body surface area

Pulsed Doppler parameter	Correlation coefficient (r)	Probability
Peak E velocity	0.21	NS
Acceleration to peak E	0.10	NS
Initial deceleration from E	-0.11	NS
Mean deceleration from E	0.001	NS
E time-velocity integral	0.28	NS
Peak A velocity	0.05	NS
A time-velocity integral	0.24	NS
E/A ratio	0.16	NS

n = 54

Table 5.6

Correlation between pulsed Doppler parameters and systolic blood pressure

Pulsed Doppler parameter	Correlation coefficient (r)	Probability
Peak E velocity	0.16	NS
Acceleration to peak E	-0.23	NS
Initial deceleration from E	0.12	NS
Mean deceleration from E	0.06	NS
E time-velocity integral	0.02	NS
Peak A velocity	0.27	NS
A time-velocity integral	0.13	NS
E/A ratio	0.29	NS

n = 54

Table 5.7

<u>Correlation between pulsed Doppler parameters and diastolic blood pressure</u>

Pulsed Doppler parameter	Correlation coefficient (r)	Probability
Peak E velocity	0.20	NS
Acceleration to peak E	0.13	NS
Initial deceleration from E	0.25	NS
Mean deceleration from E	-0.14	NS
E time-velocity integral	-0.17	NS
Peak A velocity	0.09	NS
A time-velocity integral	0.13	NS
E/A ratio	-0.39	$p < 0.05$

n = 54

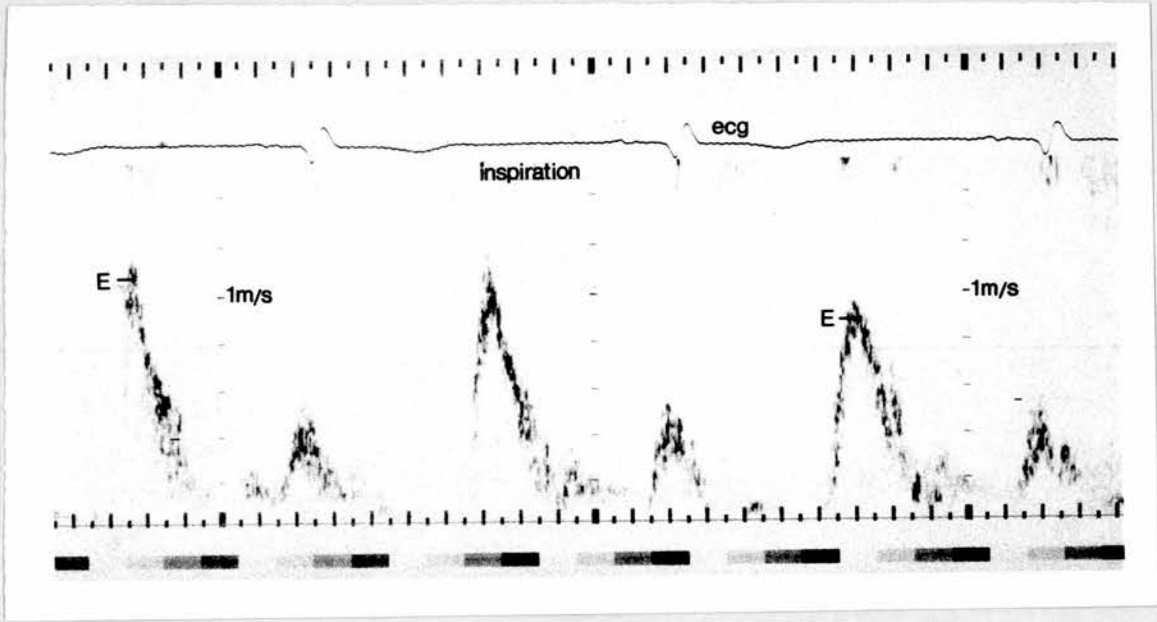
Table 5.8

Comparison between transmitral waveforms in male and female subjects

Pulsed Doppler parameter	Probability
Peak E velocity	NS
Acceleration to peak E	NS
Initial deceleration from E	NS
Mean deceleration from E	NS
E time-velocity integral	NS
Peak A velocity	NS
A time-velocity integral	NS
E/A ratio	NS

n = 54

Figure 5.1



<u>Respiratory variation in peak transmitral velocities</u>

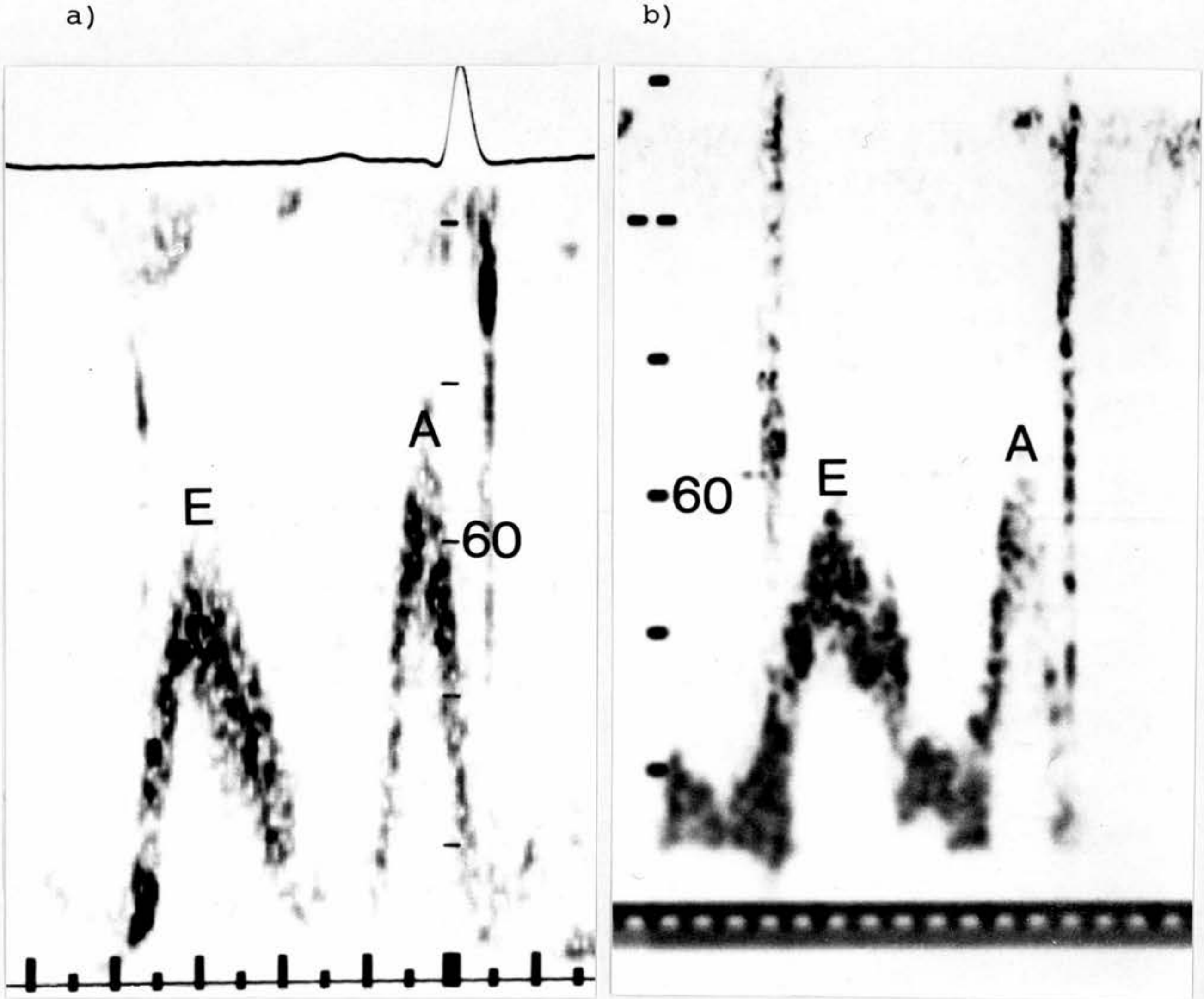
During inspiration the peak early (E) and atrial (A) filling velocities were found to decrease.
(ecg - electrocardiogram)

Discussion

In this group of healthy volunteers it was feasible to obtain technically satisfactory transmitral blood flow velocity recordings in all cases. Satisfactory recordings were judged to be those where there was a clearly defined spectral trace with low spectral dispersion, high signal to noise ratio and clearly defined beginning and end-points. The ease with which pulsed Doppler recordings of transmitral blood flow can be obtained has been previously reported (Kitabatake 1982) although the exact incidence of technically inadequate or failed pulsed Doppler examinations has not been documented. Technical adequacy of other echocardiographic recordings is dependent on several factors including the shape and thickness of the chest wall, the operator and the equipment used (Feigenbaum 1986). The effect of operator variability has been investigated by Spirito and Meijboom and appears to be small, at least in carefully selected healthy subjects (Meijboom 1987, Spirito 1988b). This preliminary study did not address the issue of operator variability. The quantitative effects of chest wall shape and thickness and type of pulsed Doppler equipment used in making pulsed Doppler recordings of transmitral blood flow is unknown. The quality of spectral display available differs appreciably between different commercially produced pulsed Doppler equipment. The possible resultant quantitative differences in pulsed Doppler spectra recorded using different machines has not been determined. Examples of two hard copy traces produced by commercially available machines in the same individual are shown in Fig 5.2 a) and b). The apparent differences in spectral display could considerably influence planimetry. Comparison of the relative difficulties encountered in analysing traces produced by different equipment and the possible quantitative effects on derived parameters of transmitral blood flow is an area where further clarification is needed especially if different groups of investigators are to undertake cooperative or comparative studies. Pulsed Doppler recording of transmitral blood flow velocity can be performed quickly and has high patient acceptability. A sensation of anxiety was reported by three volunteers during pulsed Doppler velocimetric recordings. Smith has reported the effects of changes in heart rate on the transmitral flow pattern (Smith 1989) and it is therefore advisable to ensure that the patient is relaxed and in a resting state before the recordings are made to exclude, as far as possible, the effects of tachycardia and tachypnoea on the recordings.

The normal ranges of values obtained from analysis of the transmitral waveforms in this study population are in keeping with those reported by other investigators (Gardin 1987, Wilson 1985, Spirito 1988b) for young healthy adults. The effect of age in altering the transmitral blood flow velocity waveform has been stressed by Kuo, Miller, Miyatake and others, but was not addressed in this present study because of the small age

Figure 5.2



Recordings of transmitral flow velocity spectra made in the same subject using different pulsed Doppler equipment is shown. The degree of spectral dispersion is greater in the recording shown in figure 5.2 b), especially for the slope of deceleration from E.
(E - peak early flow velocity, A - peak atrial flow velocity, 60 cms^{-1} shown on velocity scales)

range within the population of volunteers (Kuo 1987, Miyatake 1984, Miller 1986, Gardin 1987). Therefore while these normal values may serve as a reference for transmitral flow characteristics in young adults, it would not be justified to apply them in older patients.

Variation of the transmitral waveform with respiration

Statistically significant differences were found to occur during normal respiration for each of the chosen transmitral flow velocity parameters ($p < 0.001$), with a mean percentage variation of 24 % comparing the maximum and minimum values obtained for each parameter. The smallest variation (11.5%) was found for the peak E velocity. While the absolute difference in peak A velocity over the respiratory cycle was of a similar value (10 ± 5 cms^{-1}), expressed as a percentage change, peak A velocity varied by a mean of 26%. This latter finding contradicts previously reported data regarding the effect of respiration on peak atrial flow velocity (Uiterwaal 1989, Dabestani 1988). In their study of pulsed Doppler transmitral blood flow velocity spectra, Uiterwaal and colleagues found no significant effect on the ratio of early and late flow velocities with respiration. Similarly, Dabestani reported that the ratio of peak flow velocities was not appreciably affected by respiration. In contradiction to the results of these authors, the results obtained in this study population of healthy adults showed significant variation in the E/A ratio over the respiratory cycle. (Dabestani 1988). This discrepancy can be accounted for in part by the variation in peak atrial flow velocity with respiration in this group of healthy volunteers. Neither Dabestani nor Uiterwaal were able to show a statistically significant change in this parameter with respiration. Whether methodological differences can account for this observation is not clear. In the study by Dabestani, the sample volume was placed at the level of the mitral valve orifice while Uiterwaal used a point 1 cm distal to the mitral annulus. By using the point of maximum separation of the mitral leaflets and then adjusting the sample volume and transducer angulation to obtain the highest velocity shift, the transmitral velocities in this study may have been recorded further on the ventricular side of the mitral valve. Neither Gardin nor Fast found sample volume placement to affect the E/A ratio, but the possible effect of sample volume placement on respiratory variation was not mentioned by these authors (Fast 1988, Gardin 1986). While the mean values reported by Dabestani and Uiterwaal for peak atrial velocities are very close to those found in this group of volunteers, the values obtained for peak early velocity are slightly lower than in this group. This may reflect differences due to sampling position or inherent differences in populations (Dabestani 1988, Uiterwaal 1989).

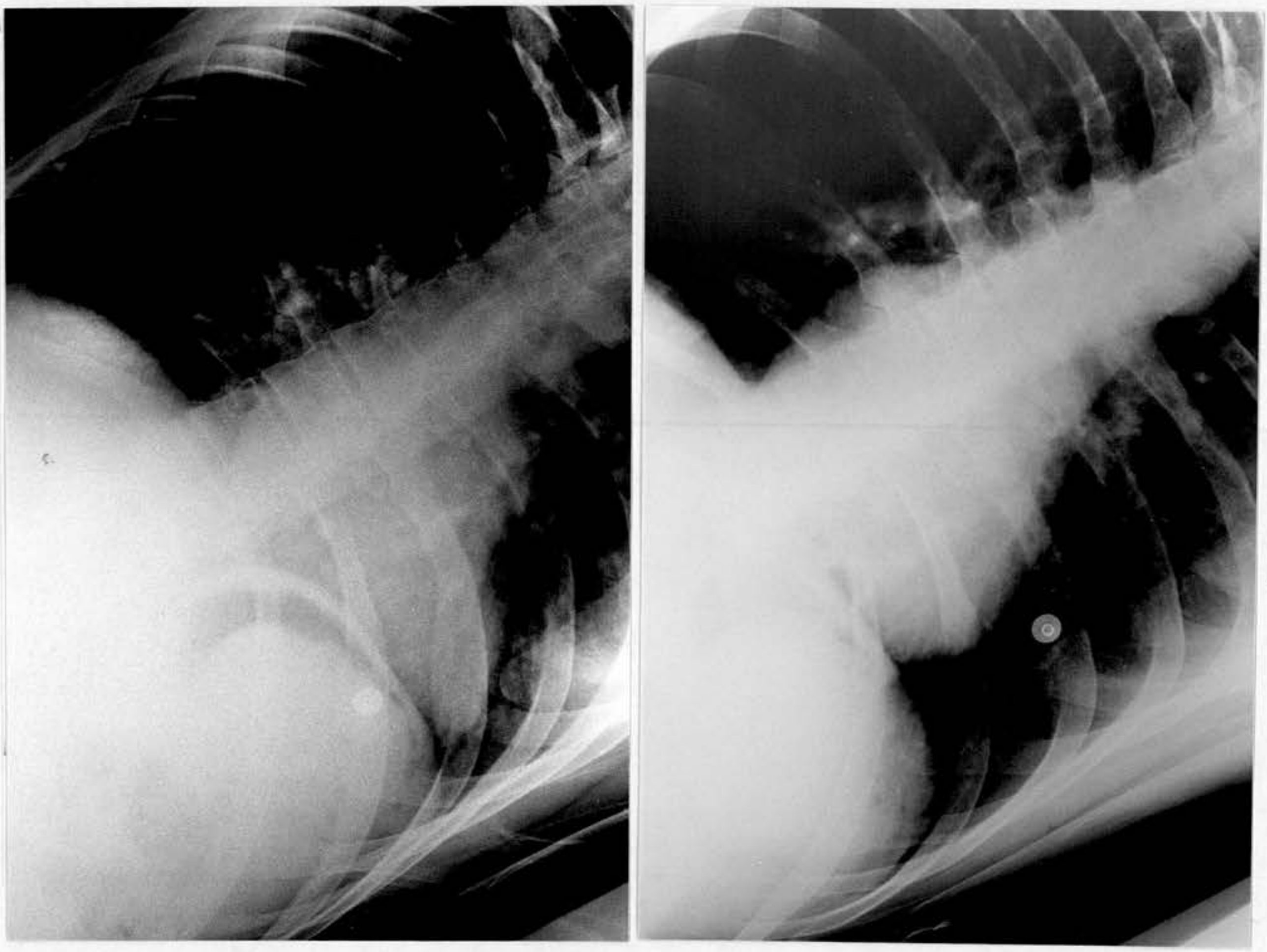
The early time velocity integral showed a relatively small respiratory variation of 16% in keeping with peak E velocity but this was statistically significant. A larger variation in the atrial time velocity integral was found in keeping with the observed variation in peak atrial velocity. The mean rate of acceleration to peak E and deceleration from peak E showed similar respiratory variation while a much greater variation in the slope of the first half of the early deceleration was observed. In all cases these variations were significant at the $p < 0.001$ level.

Variation in transmitral flow velocity waveforms during the respiratory cycle has been linked to the effects of changing intrapleural pressure on the flow of blood into the right heart, the distensibility of the pulmonary vascular bed and the restriction of left ventricular ejection (Dabestani 1988, Uiterwaal 1989). A further important consideration is the movement of the heart itself during the cardiac and respiratory cycle. As the left ventricle contracts it moves towards its own apex producing the characteristic apex beat used clinically to locate the left ventricle and detect left ventricular enlargement. During diastole the left ventricle moves away from the chest wall. Craniocaudal movement of the heart within the thorax due to diaphragmatic movement occurs with respiration. The ultrasound transducer remains in a fixed position on the chest wall, usually located in the fourth or fifth rib interspace. While limiting the respiratory movement of the heart by asking the subject to breathe quietly is possible, the position of the pulsed Doppler sample volume in relation to the left ventricular inflow is therefore constantly changing during the cardiorespiratory cycle. This point is illustrated by the two chest radiographs in Fig 5.3 taken of a subject in the left lateral decubitus position. The position of the apex beat was marked by a metal marker and its change in position relative to the cardiac silhouette after moderate inspiration is shown. The observed changes in transmitral diastolic velocities with respiration led Dabestani et al to propose that all recordings of transmitral flow be made at end-expiration in an attempt to standardise results (Dabestani 1988). Riggs has also stressed the need for standardisation of phase of respiration during assessment of diastolic filling in children (Riggs 1989). This standardisation could be achieved either by the use of superimposed strain gauge respiratory traces or by asking the patient to breathe out fully before the pulsed Doppler recordings were made. There are no reports to indicate that this technique has been widely accepted or applied clinically, while most investigators have preferred to use the mean values of derived measurements obtained from consecutive transmitral complexes for quantitative studies of left ventricular diastolic filling. There has been no standardisation of the number of consecutive complexes that should be analysed in order to arrive at these mean values. The significant differences which are recorded in the transmitral flow velocity waveform during respiration make the averaging of consecutive complexes mandatory. In this group of healthy volunteers, this was most commonly the mean of four five or six consecutive

Figure 5.3

a) Chest radiograph taken at end of expiration

b) Chest radiograph after moderate inspiration



These two chest radiographs were taken with a horizontal beam and the subject lying in the left lateral decubitus position. A metallic marker was placed on the chest wall over the apex beat. After moderate inspiration the relative positions of the metal marker and cardiac silhouette are considerably altered. Movement between transducer and cardiac structures may contribute to the observed changes in transmitral flow velocities during respiration.

transmitral flow complexes. Where clinical cross-sectional or longitudinal studies of left ventricular diastolic filling using pulsed Doppler velocimetry are to be undertaken, averaging of consecutive values will be neccessary to minimise error due to respiration.

The highly significant difference between the slopes measured in the first half of deceleration from the peak E velocity and the mean deceleration slope confirms that the initial slope cannot be extrapolated to the baseline either when spectral dispersion is increased or when there is fusion of the E and A waves. There are two main implications from this finding. Firstly, when wide spectral dispersion occurs in the deceleration slope from peak E, it may be impossible to identify modal velocity, making such traces inadequate for quantitative analysis. Secondly, calculation of the time velocity integral under the early filling wave cannot use a technique of extrapolation of the curve, as this remains unknown. This observation led to a modification of the computer programme for the digitising computer described in chapter 4. Where the computer "recognised" the beginning of the A wave in cases of fused E and A waves, the software was programmed to drop a perpendicular to the baseline to define the end of the E wave for the purpose of calculating the early time velocity integral.

The absence of any statistically significant correlation between the chosen transmitral flow velocity parameters and body surface area is in agreement with the reported results of Van Dam and Gardin et al (Van Dam 1988, Gardin

1987). No correlation was found between systolic blood pressure and any of the chosen pulsed Doppler parameters. In his study of normotensive teenagers, Graettinger similarly failed to demonstrate a correlation between pulsed Doppler parameters and systolic pressure. Gardin et al, however, found strong correlations between systolic blood pressure and both the ratio of the peak flow velocities and the atrial time velocity integral (Graettinger 1987, Gardin 1987). A weak negative correlation was found between diastolic blood pressure and the ratio of the early and late velocity peaks. This finding is in agreement with the data of Graettinger who demonstrated correlation between the ratio of peak velocities and diastolic blood pressure. No such relationship was found by Gardin who instead found correlation between the ratio of peak velocities and systolic blood pressure. The explanation for this discrepancy may relate to the age differences between the populations studied. While all of the subjects in Graettingers study were within a small age range, those of Gardins study population ranged between 21 and 78 years (Graettinger 1987, Gardin 1987). Therefore, the effects of age itself on the transmitral waveform may have introduced a further variable into the relationship between transmitral flow parameters and blood pressure.

Summary

Transmitral flow velocity spectra were successfully recorded in a group of healthy volunteers using the methodology set out in chapter 4. Using the flow velocity spectra obtained, normal values of derived parameters were obtained. The values obtained in this group of volunteers for peak early and atrial flow velocity showed close agreement with those published elsewhere. Significant respiratory variation was observed in all of the derived measurements made from the transmitral waveform. This confirms the need either for averaging of consecutive values obtained during the respiratory cycle or standardisation of recordings at a fixed point in respiration. No correlation was found to exist between systolic blood pressure, body surface area or gender and the derived Doppler parameters described above. A weak negative corelation was found between diastolic blood pressure and the ratio of the early and late peak flow velocities. Modification of the analysis programme to calculate the slope of deceleration from the first part of the curve was found to be unjustified.

Chapter 6

Reproducibility and variability of transmitral flow velocity spectra

Introduction

Before pulsed Doppler transmitral flow velocimetry can be applied clinicaly to the assessment of left ventricular diastolic function in patients with cardiac disease, it is essential that the extent of variability inherent in the recording and interpretation of diastolic flow velocity spectra are established. If longitudinal studies of diastolic ventricular behaviour are to be undertaken, then the temporal stability of the parameters of diastolic function derived from these recordings must also be known. While the data obtained from the work of Fast and Spirito yield important insights into the validity of pulsed Doppler velocimetry for cross-sectional and longitudinal studies of diastolic ventricular function in normal individuals, it is not neccessarily justified to assume that these findings can be extrapolated to include patients with ventricular disease of diverse aetiologies and of different suitability for pulsed Doppler echocardiographic examinations (Fast 1988, Spirito 1988b).

The aims of this study were:

1) To document the frequency with which technically

adequate paired recordings of transmitral blood flow velocity could be obtained in unselected patients and to determine those factors which might exclude patients from serial studies of left ventricular diastolic filling using transmitral blood flow velocity spectra.

2) To determine the limits of variability of measurements derived from transmitral blood flow velocity spectra measured on separate occasions in haemodynamically stable patients.

3) To examine the effect of operator variability in recording transmitral blood flow velocities in unselected patients.

4) To analyse the limits of intra and interobserver variation in computer assisted analysis of pulsed Doppler transmitral flow velocity spectra.

Methods

Study Population

The variability of transmitral flow velocity patterns recorded by pulsed Doppler velocimetry was prospectively studied in 50 patients recruited after referral for routine diagnostic ultrasound examinations. This study group was obtained after initial screening of 162 patients. The remaining 42 outpatients and 8 inpatients were asked to return for follow-up pulsed Doppler examinations at intervals varying between 2 days and 4 weeks between initial and follow-up studies was 21 days. In 28 patients the ratio of the early and late flow velocity peaks was greater than unity at the time of first attendance while in the remaining 22 reversal of the early to late flow velocity ratio was present. The study group comprised 32 male and 18 female patients with a median age of 64.5 years (range 1 to 82 years). Twenty five patients had clinical or electrocardiographic evidence of ischaemic heart disease, 15 had left ventricular hypertrophy in association with aortic valve stenosis and 6 had hypertension related left ventricular hypertrophy. Of the remainder, two patients had dilated cardiomyopathy and two were apparently normal, having been referred for the echocardiographic exclusion of valvular disease. In 17 patients some degree of mitral regurgitation was detected using either pulsed wave or combined pulsed and continuous wave Doppler ultrasound. 42 patients were taking one or more cardioactive drugs on a regular basis. No patient's medical therapy was altered between initial and follow-up attendances and as far as possible the time of day at which the Doppler studies was performed was kept the same. All patients were in sinus rhythm at both attendances. The mean heart rate at the time of pulsed Doppler recordings was 78 beats per minute (range 52 to 98) at first attendance and 82 beats per minute (range 50 to 96) at follow-up.

<u>Pulsed Doppler Recordings</u>

All Doppler recordings were conducted according to the criteria set out in Chapter 4. 2.25 or 3.5 MHz transducers were selected according to the imaging requirements of the diagnostic study with transmitral flow velocity recordings being made after cross-sectional imaging and other Doppler recordings were completed. Patients were examined at rest in quiet respiration in the left lateral decubitus position. The transmitral flow velocities were recorded onto a strip chart recorder with a paper speed of 100 mms^{-1} for later computer assisted analysis.

Analysis of pulsed Doppler traces

All hard copy traces were analysed using the previously described microcomputer based digitising system. The readers of hard copy traces were masked both to the identity of the patients and date of attendance. Peak modal velocity was chosen for digitisation.

Design of Study

1) Suitability of patients for paired transmitral blood flow velocity recordings

To establish the feasibility with which patients could be recruited for serial studies of left ventricular filling measured by pulsed Doppler, 50 patients between the ages of 1 and 82 years were recruited from patients routinely attending the cardiac ultrasound department over a period of six weeks. The reasons for exclusion from the study were recorded. The exclusion criteria used are given below:

Significant mitral valve disease
Prosthetic mitral valves
Atrial fibrillation or other arrhythmias
Heart rate above 100 beats per minute.
Technically inadequate transmitral pulsed Doppler flow velocity spectra
Unwillingness or inability to return for follow-up examination
Recent change in symptoms or medication

An explanation of the nature and purpose of the examination was given to each patient considered suitable for repeat study at the initial attendance.

<u>2) Variability of measurements made from pulsed Doppler of transmitral blood flow velocity spectra recorded on separate occasions.</u>

The pulsed Doppler examinations were performed by myself and any one of five other technical or medical staff working within the cardiac ultrasound department who had agreed to participate in the study. At the time of follow-up examinations, the operator was unaware of the flow velocity results from the previous attendance. Eight patients were studied by the same operator at both attendances while the remainder were studied by different operators at each attendance. The hard copy traces were coded and saved for later analysis.

3) Operator variability in transmitral flow velocity recording.

To investigate the influence of operator bias in recording transmitral blood flow velocity, recordings of transmitral flow velocities were undertaken by two operators independently at either the first or second attendance in 25 subjects. In each case, the patient was asked to remain resting on the examination couch between the two recordings which were made within 5 minutes of each other. The second operator was unaware of the results of the preceding examination. The peak modal early and late filling velocities were measured for each of six consecutive transmitral blood flow velocity spectra and the arithmetic mean of these values was used in subsequent analysis.

4) Observer variability in computer assisted analysis of pulsed Doppler transmitral flow velocity spectra

For each attendance, the following measurements were made from each of five consecutive transmitral flow velocity complexes:

1) Peak E velocity
2) Mean rate of acceleration to peak E velocity
3) Initial rate of deceleration from peak E velocity
4) Mean rate of deceleration from peak E
5) Early diastolic time velocity integral
6) Peak A velocity

7) Atrial systolic time velocity integral

8) E to A ratio

a) <u>Interobserver variability</u>

To test the inter-observer variation for computer assisted analysis of hard copy transmitral flow velocity recordings, 20 hard-copy flow velocity recordings selected from the study group were presented to two independent observers for planimetry.

b) <u>Intraobserver variability</u>

To test intraobserver variation for computer assisted analysis of hard copy traces of transmitral flow velocities, 10 hard copy traces were planimetered on two separate occasions one week apart by the same observers. The traces were presented in random order.

<u>Statistical Methods</u>

1) <u>Variability of transmitral blood flow velocity spectra measured on separate occasions.</u>

The mean values obtained at each attendance from the averages of five consecutive flow velocity complexes for each of the chosen derived parameters were compared using Students paired T-test. The level of statistical significance was taken to be p less than 0.05. In addition, the unsigned differences between the averaged values of the derived parameters from each attendance were calculated for each of eight parameters chosen. The absolute difference was calculated so that the possibility of cancellation by opposing signs was avoided. The percentage difference in the eight derived parameters was calculated with respect to the value obtained at the initial attendance.

2) <u>Operator variability in recording transmitral blood flow velocity spectra.</u>

The absolute unsigned differences between the values for peak E and peak A velocity were calculated from the means of five consecutive complexes recorded by different operators in 25 subjects.

3) <u>Intra-observer variability in computer assisted analysis of transmitral blood flow velocity spectra.</u>

The mean coefficient of variation was calculated from the paired values of each of the chosen parameters obtained by repeated planimetry of 10 transmitral flow velocity complexes on two separate occasions.

4) <u>Inter-observer variability in computer assisted analysis of transmitral blood flow velocity spectra</u>

The mean coefficient of variation was calculated from the paired values of the chosen pulsed Doppler measurements made from 20 transmitral flow velocity recordings by two independent observers.

Results

Suitability of patients attending ultrasound department for serial studies of transmitral blood flow velocities

The 50 patients included in the follow-up study were recruited from 162 patients attending for routine cardiac ultrasound examination. The reasons for exclusion from the study of paired pulsed Doppler recordings are given below.

Reason for exclusion	Number
Recent change in symptoms or treatment	21
Mitral stenosis	25
Prosthetic mitral valve	15
Arrhythmia/Tachycardia	13
Technically inadequate Doppler study	19
Refusal of second examination	2
Inability to return for follow-up	17
	112

Variability of transmitral blood flow velocity spectra measured on separate occasions.

The mean values obtained for each of the eight measurements made from the transmitral flow velocity complexes on two occasions are summarised in table 6.1. The absolute differences obtained for each of the chosen parameters on two separate attendances were 8 ± 5 cms^{-1}

for peak E velocity (14.2%), 2.9±2.2 ms^{-1} for acceleration to peak E (33.4%), 1.2±0.9 ms^{-1} for initial rate of deceleration from peak E (28%), 0.5±0.4 ms^{-1} for mean rate of deceleration from peak E (22%), 100±78 cmmsec for early time velocity integral (12.7%), 72±54 cmmsec for atrial time velocity integral (13.5%) and 0.15±0.2 for the E/A ratio (13.5%). These absolute differences and differences expressed as a percentage change are summarised in tables 6.2 and 6.3 respectively. No statistically significant change was observed for the values of peak E velocity, mean deceleration from peak E, early and atrial time velocity integrals and the E/A ratio recorded on two separate occasions. Statistically significant differences were, however, observed between the values of peak A velocity, acceleration to peak E velocity and initial deceleration from peak E velocity measured on separate occasions. These results are summarised in table 6.4.

Operator variability in recording transmitral blood flow velocity spectra.

The mean absolute difference obtained for peak E velocity recorded by two independent operators in 25 patients was 3.8±2.3 cms^{-1} (5±4%). The mean absolute difference for peak A velocity recorded by two independent operators was 3.2±2.2 cms^{-1} (7±5%). These results are shown in 6.5a and 6.5b.

Observer variability in computer assisted analysis of transmitral blood flow velocity spectra.

The coefficients of variation for inter and intraobserver variation in computer assisted planimetry of transmitral flow velocity spectra are shown in table 6.6.

Table 6.1

<u>Derived measurements made from transmitral flow velocity recordings at two attendances</u>

Parameter	1st attendance	2nd attendance
Peak E velocity	57 ± 17.5 cms^{-1}	58.7 ± 17.7 cms^{-1}
Peak A velocity	63.5 ± 23.5 cms^{-1}	66.3 ± 24.3 cms^{-1}
E/A ratio	1.0 ± 0.46	1.0 ± 0.54
Mean acceleration to peak E	9.6 ± 4.2 ms^{-1}	10.9 ± 4 ms^{-1}
Initial deceleration from E	4.5 ± 2 ms^{-1}	4.7 ± 2.4 ms^{-1}
Mean deceleration from E	2.6 ± 1.1 ms^{-1}	2.8 ± 1.3 ms^{-1}
E time-velocity integral	802 ± 192 cmmsec	738 ± 224 cmmsec
A time-velocity integral	523 ± 170 cmmsec	514 ± 207 cmmsec

n = 50

Table 6.2

<u>Absolute differences for paired measurements made from transmitral flow spectra at first and second attendances</u>

Measured parameter	Mean difference between 1st and 2nd attendance	Range
Peak E velocity	8$\pm$5 cms^{-1}	1 to 20
Peak A velocity	7.7$\pm$2.2 cms^{-1}	0 to 21
Acceleration to peak E	2.9$\pm$2.2 ms^{-1}	0.02 to 8.7
Initial deceleration from E	1.2$\pm$0.9 ms^{-1}	0 to 3.3
Mean deceleration from E	0.5$\pm$0.4 ms^{-1}	0 to 1.4
E time-velocity integral	100$\pm$78 cmmsec	2 to 320
A time-velocity integral	72$\pm$54 cmmsec	2 to 202
E/A ratio	0.15$\pm$0.2	0 to 0.9

n = 50

Table 6.3

Percentage differences for paired measurements made at first and second attendances

Parameter	Mean percentage change
Peak E velocity	16±13%
Peak A velocity	14.2±12%
Acceleration to peak E	33.4±33%
Initial deceleration from E	28±23%
Mean deceleration from E	22±20%
E time-velocity integral	12.7±9%
A time-velocity integral	13.5±9%
E/A ratio	13.5±14%

n = 50

Table 6.4

<u>Mean values for each parameter measured on separate occasions compared by Students paired t-test</u>

Parameter	Probability
Peak E velocity	NS
Peak A velocity	0.03
Acceleration to peak E	< 0.001
Initial deceleration from E	0.03
Mean deceleration from E	NS
E time-velocity integral	NS
A time-velocity integral	NS
E/A ratio	NS

n = 50

Table 6.5

Operator variability in recording transmitral blood flow velocity spectra.

a) Absolute differences in peak E and A velocities recorded by independent operators

Measurement	Absolute difference $\pm$SD	Range
Peak E velocity	3.8 ± 2.3 cms^{-1}	0 - 8
Peak A velocity	3.2 ± 2.2 cms^{-1}	0 - 7

b) Difference in peak E and A velocities expressed as percentages

Measurement	Percentage difference. Mean$\pm$SD
Peak E velocity	5 ± 4%
Peak A velocity	7 ± 5%

Table 6.6

<u>Coefficients of variation for observer variability in computer assisted analysis of transmitral blood flow velocity spectra.</u>

Pulsed Doppler parameter	Intraobserver		Interobserver
	Observer 1	Observer 2	
Peak E velocity	2.5 %	3.1 %	4%
Acceleration to peak E	5.4 %	5.6 %	6.2%
Initial deceleration from E	7.2 %	8.2%	8.4 %
Mean deceleration from E	6.2 %	7.1 %	7.4 %
E time-velocity integral	2.2 %	2.8 %	3.1 %
Peak A velocity	2.4 %	2.5 %	3.2 %
A time-velocity integral	3.5 %	4 %	4.3 %

n = 50

Discussion

Feasibility of obtaining paired recordings of transmitral blood flow velocity spectra from an unselected population.

In order to recruit a study group of 50 patients for paired recordings of transmitral blood flow velocity spectra, an initial population of 162 patients was screened. Of the 112 patients excluded this was because of technically inadequate pulsed Doppler recordings at first attendance in 19 patients or 12% of the population screened. The criteria used to exclude these patients on the basis of pulsed Doppler recordings were :

1) Lack of clear definition of beginning or end-points of flow velocity curve.
2) Unacceptable signal to noise ratio with ill-defined or intermittently broken flow velocity curve
3) Wide spectral dispersion with poorly defined modal velocity.
4) Failure to record five or more consecutive transmitral flow velocity complexes

In the 19 patients excluded from further study by these criteria, failure to obtain adequate Doppler information was associated in 11 cases with technically inadequate cross-sectional imaging and non-diagnostic examinations. This implies that the major limitation in recording transmitral flow relates to patient characteristics. The effects of obesity, chronic lung disease and chest wall shape are well known to influence the success of cardiac ultrasound examinations (Bansal 1980, Feigenbaum 1986). In the remaining eight patients adequate Doppler information was not obtained despite acceptable cross-sectional imaging and adequate alignment to direction of transmitral blood flow, the reasons for which are unclear. Of the 162 patients screened, 93 were excluded from further study because of other factors such as the presence of mitral stenosis, recent change in symptomatology and cardiac arrhythmias. The frequency with which patients are excluded is a function of the nature of pathology within the referral group to a particular ultrasound department and to a large extent will be influenced by the particular interests and work in and around that institution. Killingbeck Hospital, where these patients were recruited, is a regional cardiothoracic surgical unit with a large attendance by patients either awaiting or having follow-up for coronary bypass or heart valve surgery. Because of referral patterns from local general practitioners, many patients attending for ultrasound examinations will have experienced a recent change in symptoms or will have started new drug therapy. In the setting of a district general hospital, the spectrum of cardiac disease might differ considerably and affect the frequency with which patients would be suitable for follow-up examinations of transmitral blood flow velocity recordings.

In the 50 patients subsequently returning for follow-up, technically adequate paired recordings were obtained in all cases. This finding suggests that serial pulsed

Doppler recordings of acceptably high quality can be obtained in any patient if initial assessment according to strict criteria, confirms their suitability for pulsed Doppler velocimetry of transmitral blood flow. However, in almost 12% of unselected patients it may be impossible to obtain adequate pulsed Doppler flow velocity spectra to allow comparative studies to be undertaken. This represents a significant limitation to the clinical applicability of the technique for serial study of left ventricular diastolic filling.
Using a combined pulsed and continuous wave technique it was possible to detect minor degrees of mitral valve regurgitation in a significant proportion of patients. In the group of patients studied, 34% were found to have detectable mitral regurgitation which was judged to be clinically mild or insignificant. If even minor degrees of mitral valve regurgitation were also used as an exclusion criterion, this would further significantly limit the number of patients suitable for paired recordings of transmitral blood flow velocity spectra. Takenaka (1986a) and Shaikh (1988) have discussed the possible effects of mitral regurgitation in masking abnormal transmitral flow and the possibility of subtle changes due to varying degrees of mitral regurgitation. While the pulsed Doppler examination was found to have a high degree of patient acceptability, a small number of patients were unwilling to return for further examination and so could not be included in follow-up.

Variability of measurements made from pulsed Doppler recordings of transmitral blood flow velocity spectra recorded on separate occasions

The results obtained from comparison of the derived parameters of transmitral blood flow velocity spectra obtained on separate occasions after a mean interval of 21 days are summarised in table 6.2. For measurements of peak early and late flow velocities, a mean variation of 15% was found by comparing the second to the first set of recorded values. No statistically significant change in peak early flow velocity was found between the two sets of values (p NS), while variation in peak atrial velocity was statistically significant (p 0.03). However, the ratio of early and late flow velocities did not differ significantly between attendances. The early time-velocity integral did not alter significantly between attendances and there was no significant change in the slope of deceleration from peak E velocity. These results suggest that in haemodynamically stable inividuals, pulsed Doppler parameters of the early phase of diastolic filling show small variation. Therefore, the use of these parameters for longitudinal studies of disease progression or therapy may be justified. In the clinical context, however, mean variation of approximately 15% can be expected for any of these parameters in haemodynamically stable subjects and the effect of therapy or disease progression would have to be appreciably greater to achieve statistical significance.

Spirito also found that measurements of the early phase of the transmitral blood flow velocity waveform showed little variability when measured on separate occasions (Spirito 1988b). In contradiction to the results of this present study, Spirito et al found that the ratio of peak early and late flow velocities showed significant variation with time. In their study of normal volunteers, Fast et al found the best reproducibility for measurements of peak early and late filling velocities over time. In keeping with the results of this study, Fast reported much greater variation in the slope of acceleration at the onset of the early filling wave (Fast 1988).

Operator variability in recording transmitral blood flow velocity spectra.

The values recorded by independent operators in 25 patients showed very small absolute differences, small percentage variability and did not reach statistical significance. While only the peak flow velocities were considered, the close agreement between operators confirms that satisfactory alignment between the ultrasound beam and flow must have been achieved. Very similar absolute differences for measurement of peak early low velocity were reported by Spirito (1988b). All five operators involved in making the pulsed Doppler recordings of the patients who progressed to the second part of the study used the same recording technique. However, the effect of significant unrecognised operator error cannot be overlooked when considering the variability of transmitral blood flow velocity spectra over time. As not all measurements in this study were duplicated, the precise effect of operator variability remains unknown.

Observer variability in computer assisted analysis of transmitral blood flow velocity spectra.

The small coefficients of variation found for inter and intra-observer variation in measurement of peak flow velocities and time-velocity integrals confirm that the video based computer assisted planimetry system developed is suitable for clinical assessment of these variables. Greater variability was found for measurement of the slopes of acceleration and deceleration to peak early velocity. It is likely that this finding relates to the difficulties encountered in determining the modal velocity where greater spectral dispersion occurs. Therefore, errors in determining the modal slope during planimetry are likely to have contributed significantly to the greater longitudinal variability found for measurements of acceleration to E and initial deceleration from E. In measurement of the slope of acceleration, recognition of the beginning of the upward slope can be difficult because of low frequency signals superimposed at the base of the trace, but where only high quality traces are accepted, this effect can be minimised.

Qualitative aspects of the transmitral flow velocity profile

Sudden changes in the E/A ratio, such as reversal of the usual pattern of a larger early and smaller late filling wave, have been used as a marker of significant alteration of left ventricular diastolic function (Visser 1986, Mitchell 1988). Changes that occur with age in both absolute values of peak E and A velocities and their ratio have been documented (Miyatake 1984, Miller 1986, Kuo 1987) and it has been shown that with advancing age, the peak E velocity tends to decrease while peak A velocity shows a compensatory increase. The E to A ratio decreases progressively with age. Of the 50 patients examined, 3 who had an E/A ratio of greater than one at initial attendance were found to have a reversed E/A ratio at follow-up. One patient with an initially reversed E/A ratio was found to have a ratio in excess of one at follow-up examination. This finding suggests that in a given individual, the ratio of early and late flow velocity peaks is unlikely to show any qualitative change over this relatively small time interval. While such a division of patients into groups having E/A ratios of greater or less than one is simplistic, the recognition of sudden changes in the ratio of early and late velocities might alert the clinician to otherwise unsuspected changes in ventricular diastolic performance and prompt more detailed analysis of the transmitral flow velocity pattern. Furthermore, the small variability between the two sets of values for E/A ratio confirms that dramatic changes in the ratio are unlikely to be a result of technical factors alone.

Other possible sources of variability of transmitral flow velocity spectra over time

While in all cases, the patients' symptoms were unchanged over the interval between pulsed Doppler examinations, the possibility of silent progression of disease and its effect on transmitral flow cannot be excluded. While therapy was unchanged in all cases, possible variations in peak activity of cardioactive drugs due to timing of ingestion and absorption of medication could have influenced the transmitral waveform. Nitrates, beta-blockers and calcium antagonists have all been demonstrated to alter the transmitral blood flow velocity pattern and almost all patients studied were taking one or more of these on a regular basis (Choong 1987a, Myreng 1988, Iwase 1987). The patient's state of hydration cannot be measured directly. Choong (1987) showed that changes in preload altered the peak filling velocities and varying preload due to the altered hydration resulting from diuretic ingestion might significantly affect the diastolic filling pattern. No clear relationship between heart rate and transmitral blood flow velocity pattern has been established. Although the mean difference in heart rate at the time of initial and follow-up examinations was small, no correction was made for heart rate in the analysis of pulsed Doppler spectra.

Summary

Where initial screening identifies a patient suitable for follow-up pulsed Doppler recording of left ventricular filling, satisfactory repeat examinations can be obtained in all cases.

No statistically significant variation was found between repeated measurements of peak early flow velocity, early time-velocity integral, mean rate of deceleration from E and the E/A ratio in haemodynamically stable patients over a mean interval of 21 days. For measurements of acceleration to peak early velocity and atrial flow velocity, statistically significant changes are observed over a mean interval of 21 days.

The effect of operator variability for the recording of peak E and A velocity is small. This confirms that by the use of a carefully standardised technique, adequate alignment to direction of blood flow can be achieved.

The effect of observer variability in computer assisted analysis of transmitral blood flow velocity spectra was found to be small for measurements of peak velocity and time velocity integrals but larger for measurements of acceleration and deceleration slopes.

Chapter 7

The relationship between M-mode and pulsed Doppler echocardiographic indices of left ventricular diastolic function

Aim of this Study

The aim of this study was to investigate whether a definable relationship existed between the timing and rate of left ventricular relaxation measured using M-mode echocardiography and derived measurements from the transmitral blood flow velocity spectra recorded using pulsed Doppler velocimetry in healthy subjects.

Study Population

The study group comprised 35 healthy volunteers recruited from within the staff of Killingbeck Hospital Leeds, friends and relatives of hospital patients and attenders at a local fitness centre. None of the subjects selected had been involved in the earlier study of normal transmitral flow velocity characteristics. A larger number of subjects were initially screened for this study. It was found that while in almost all of the volunteers screened it was possible to obtain satisfactory pulsed Doppler recordings of transmitral blood flow, in a substantial proportion of cases the quality of M-mode traces was deemed to be inadequate for the purpose of the study. The mean age of these volunteers was 27 years with a range between 18 and 32 years. All subjects were asymptomatic and taking no medication at the time of the combined pulsed Doppler and M-mode recordings. All subjects were normotensive and in sinus rhythm. In all cases, prior to simultaneous pulsed Doppler and M-mode recordings, a preliminary combined imaging and Doppler echocardiographic examination was undertaken to exclude the presence of myocardial or valvular disease.

M-mode Recordings

The M-mode recordings were made with subjects in a lateral decubitus position having rested for at least five minutes. All M-mode recordings were made using a Smith-Kline echocardiograph. This is a dedicated M-mode machine which uses a small 2.25 MHz single crystal trasducer to produce an "ice-pick" or single line view of the left ventricular chamber by building up an image from reflected echoes coming from the left ventricular septum and posterior free wall. The beam was directed from a left parasternal position towards the mitral valve leaflets, the correct position for recording being determined by aligning the beam just distal to the level of the tips of the mitral valve leafets and perpendicular to the posterior ventricular wall (Sahn 1978). By displaying the reflected echoes on the y-axis of the oscilloscope display and having a moving timebase on the x-axis, the movement of the structures under investigation is displayed as a function of time. Hard copy M-mode recordings were made at a paper speed of 100 mms^{-1} for later analysis on dry silver paper. Recordings were made over several consecutive respiratory cycles. The M-mode echocardiograph has physiological input channels for electrocardiogram and phonocardiogram which were simultaneously recorded with the M-mode traces. An example recording is shown in Figure 7.1.

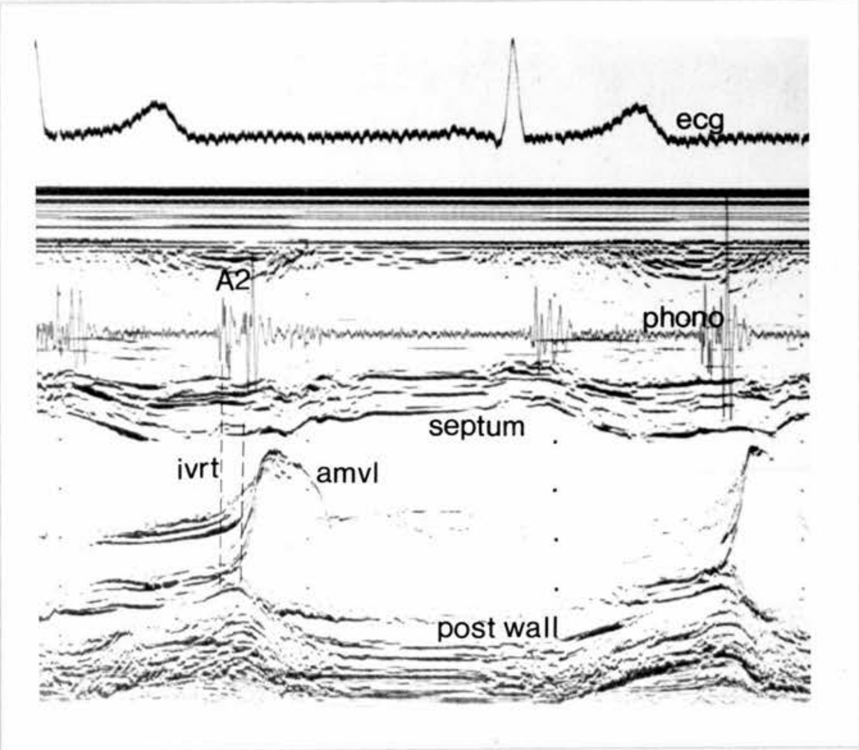
Pulsed Doppler recordings

Pulsed Doppler recordings of transmitral blood flow were made immediately after the M-mode recordings. In all cases the Honeywell Ultra Imager was used allowing the superimposition of electrocardiogram and phonocardiogram on the pulsed Doppler signal. The methodology described in Chapter 4 was used. The position of the subject was not changed between recordings. Transmitral blood flow velocity spectra were recorded for several consecutive respiratory cycles onto dry silver paper at a speed of 100 mms^{-1}. An example recording is shown in Figure 7.2.

Phonocardiographic recordings

All phonocardiographic recordings were made using suction transducers sited in a left parasternal position to obtain a clear impulse due to aortic valve closure. The Honeywell Ultra Imager uses digital processing for amplification and filtration of the phonocardiographic signal while the Echoline M-mode machine employs analogue signal processing.

Figure 7.1

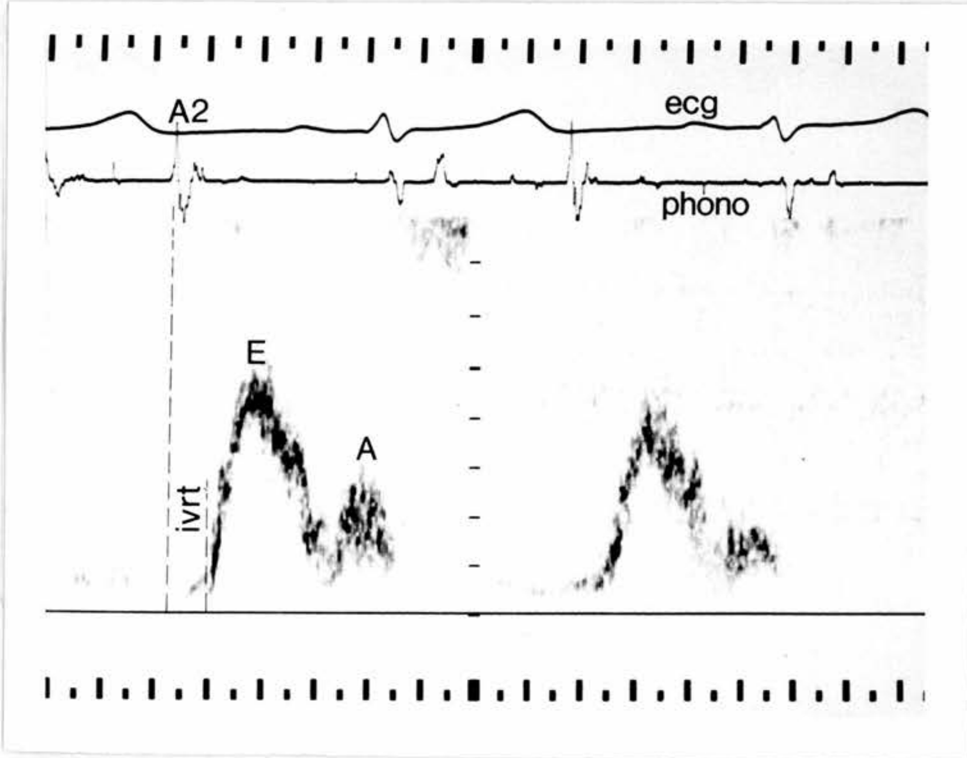


Combined M-mode and phonocardiographic recording

Changes in dimension of minor axis left ventricular dimension were measured by planimetry of the septal and posterior wall echoes. Simultaneous phonocardiographic recording was used to measure left ventricular isovolumic relaxation time.

(ivrt - isovolumic relaxation time, amvl - anterior mitral valve leaflet, phono - phonocardiogram, ecg - electrocardiogram, A2 - deflection caused by aortic valve closure)

Figure 7.2



Combined pulsed Doppler and phonocardiographic recording

As well as measurements made directly from the transmitral waveform, simultaneous phonocardiographic recording allowed measurement of the interval between aortic valve closure and the beginning of transmitral flow.

(ivrt - isovolumic relaxation time, E - peak early flow velocity, A - peak atrial flow velocity, A2 - deflection due to aortic valve closure, phono - phonocardiogram, ecg - electrocardiogram)

Analysis of Hard Copy Traces

Matching of R-R intervals

In each subject the hard copy traces recorded over several respiratory cycles were compared and using the electrocardiogram trace, an M-mode and a pulsed Doppler complex with exactly equal R-R interval were identified for later analysis. By running both hard copy recorders simultaneously before each subject was studied, identical paper speed was confirmed by means of an electronic calibration pulse fed simultaneously into one of the physiological input channels of each machine.

Analysis of Pulsed Doppler Recordings

All pulsed Doppler traces were digitised using the previously described microcomputer based digitising system. Each of the transmitral flow velocity waveforms selected was digitised six times and the average of these values was used for subsequent statistical analysis. The measurements made from the pulsed Doppler transmitral spectra obtained were:

1) Interval between the phonocardiographic deflection caused by aortic closure (A2) and the onset of transmitral flow.
2) Peak flow velocity in early diastole
3) Early diastolic time velocity integral
4) Mean slope of deceleration from peak E.
5) Ratio of peak E to peak A velocity.

Analysis of M-mode Recordings

Analysis of M-mode hard copy recordings of left ventricular diastolic relaxation was undertaken using measurement software developed specially for use with the microcomputer based digitising system employed for analysis of pulsed Doppler echocardiographic traces. A suitable computer programme was developed from the same programme framework which had been previously written. As with Doppler analysis, the stand mounted video camera was used to provide an onscreen image for subsequent computer assisted planimetry. The operation of the M-mode digitising programme follows similar principles to the pulsed Doppler analysis programme. Its operation is now described.

The hard copy trace under analysis is placed within a perspex holder and positioned beneath the video camera. The height of the video camera is adjusted on its gantry to allow the M-mode complex to occupy the greatest portion of the screen possible. Calibration of the screen is then made for distance on the y-axis and time on the x-axis using centimetre and second markers provided on the hard copy trace. The computer screen then prompts the operator to trace the ventricular free wall and septum in turn within a predefined area of interest using the electronic cursor. The predefined area of interest began at the point of aortic valve closure and ended at the onset of ventricular depolarisation on the electrocardiogram. From the trace obtained the computer software then plots the actual dimension as a function of time and its first derivative, the rate of change of dimension, against time. An electronic cursor can then be placed at any point along these curves to obtain a numerical value for both actual dimension and rate of change of dimension. The rate of change of dimension "normalised" to the end diastolic dimension of the left ventricle is also calculated for any point specified by the electronic cursor.

The following measurements were made from the selected cardiac cycle from each subject's M-mode trace:

1) Interval between aortic valve closure (A2) and the point of separation of the mitral valve leaflets.

2) Maximum rate of change of left ventricular minor dimension during diastole [dD/dt].

3) Maximum rate of change of left ventricular minor axis normalised to left ventricular end-diastolic dimension [dD/dt/D].

Observer Variability in digitisation of hard copy traces

Intraobserver variability for digitisation of M-mode traces was tested by the same observer (DE) digitising 10 M-mode complexes on four separate occasions. The traces were presented in random order without knowledge of the subjects identity. The 10 sets of values obtained for peak dD/dt and normalised dD/dt were used for calculation of coefficients of variation.

Intraobserver variability for digitisation of pulsed Doppler flow velocity spectra was tested by digitising selected transmitral waveforms from the same 10 subjects on four separate occasions. The traces were presented in random order without knowledge of the subject's identity. The 10 sets of values obtained for peak E velocity, E time velocity integral, slope of deceleration from peak E, the ratio of E to A and the ratio of the early and late time velocity integrals were used for calculation of the coefficients of variation.

Statistical Methods

The mean values of six measurements of each pulsed Doppler and M-mode variable were used for subsequent statistical analysis. The relationship between pulsed Doppler parameters and digitised M-mode measurements were compared using linear regression analysis. The level of statistical significance was chosen as $p < 0.05$. Intraobserver variability for digitisation of hard copy M-mode tracings was expressed using the means of the coefficients of variation for each of the measurements described. The coefficient of variation is defined as the ratio of the standard deviation and the mean of four successive measurements expressed as a percentage.

Results

The values obtained for Doppler indices and M-mode measurements from matched RR intervals in 35 subjects are summarised in Table 7.1 and 7.2 respectively.

Relationship between pulsed Doppler and M-mode indices of left ventricular diastolic function

Close correlation was found between measurements of isovolumic relaxation period using M-mode echocardiography and the interval between aortic valve closure and the onset of transmitral flow determined using pulsed Doppler velocimetry.(r 0.69 $p < 0.001$). There was significant correlation between the peak rate of change of dimension of the left ventricle (dD/dt) and the early time velocity integral (r 0.37 p 0.03). This data is plotted in figure 7.3. No statistically significant correlation was shown between peak dD/dt and any of the other pulsed Doppler variables measured. Positive correlation was found between the normalised peak rate of change of left ventricular dimension and peak early flow velocity (r 0.47 p 0.005). A plot of this data is shown in figure 7.4. No correlation was found between normalised peak dD/dt and any of the other pulsed Doppler parameters. These results are summarised in Table 7.3 and 7.4.

Table 7.1

Pulsed Doppler transmitral flow velocity measurements from matched R-R intervals

Pulsed Doppler parameter	Mean$\pm$SD
Peak E velocity	76$\pm$28 cms^{-1}
E time-velocity integral	1009$\pm$540 cmmsec
Mean deceleration from E	3.3$\pm$2 ms^{-1}
E/A ratio	2.4$\pm$1.6
E TVI/ A TVI ratio	3.7$\pm$2.4
Isovolumic relaxation time	64$\pm$20 msecs

n = 35

Table 7.2

M-mode measurements made from matched R-R intervals

M-mode parameter	Mean$\pm$SD
Peak dD/dt	15.9$\pm$3.8 cms^{-1}
Normalised dD/dt	2.5$\pm$2
Isovolumic relaxation time	65$\pm$22 msecs

n = 35

Table 7.3

<u>Correlation between pulsed Doppler parameters and peak rate of change of left ventricular dimension for matched RR intervals</u>

Pulsed Doppler parameter	Correlation coefficient (r)	Probability
Peak E velocity	0.29	NS
E time-velocity integral	0.37	0.03
Mean deceleration from E	- 0.08	NS
E/A ratio	0.22	NS
E TVI/ A TVI ratio	0.28	NS

n = 35

Table 7.4

Correlation between pulsed Doppler parameters and normalised peak rate of change of left ventricular dimension for matched RR intervals

Pulsed Doppler parameter	Correlation coefficient (r)	Probability
Peak E velocity	0.47	0.005
E time-velocity integral	0.26	NS
Mean deceleration from E	0.02	NS
E/A ratio	0.18	NS
E TVI/ A TVI ratio	0.08	NS

n = 35

Figure 7.3

Plot of early time-velocity integral against peak dD/dt

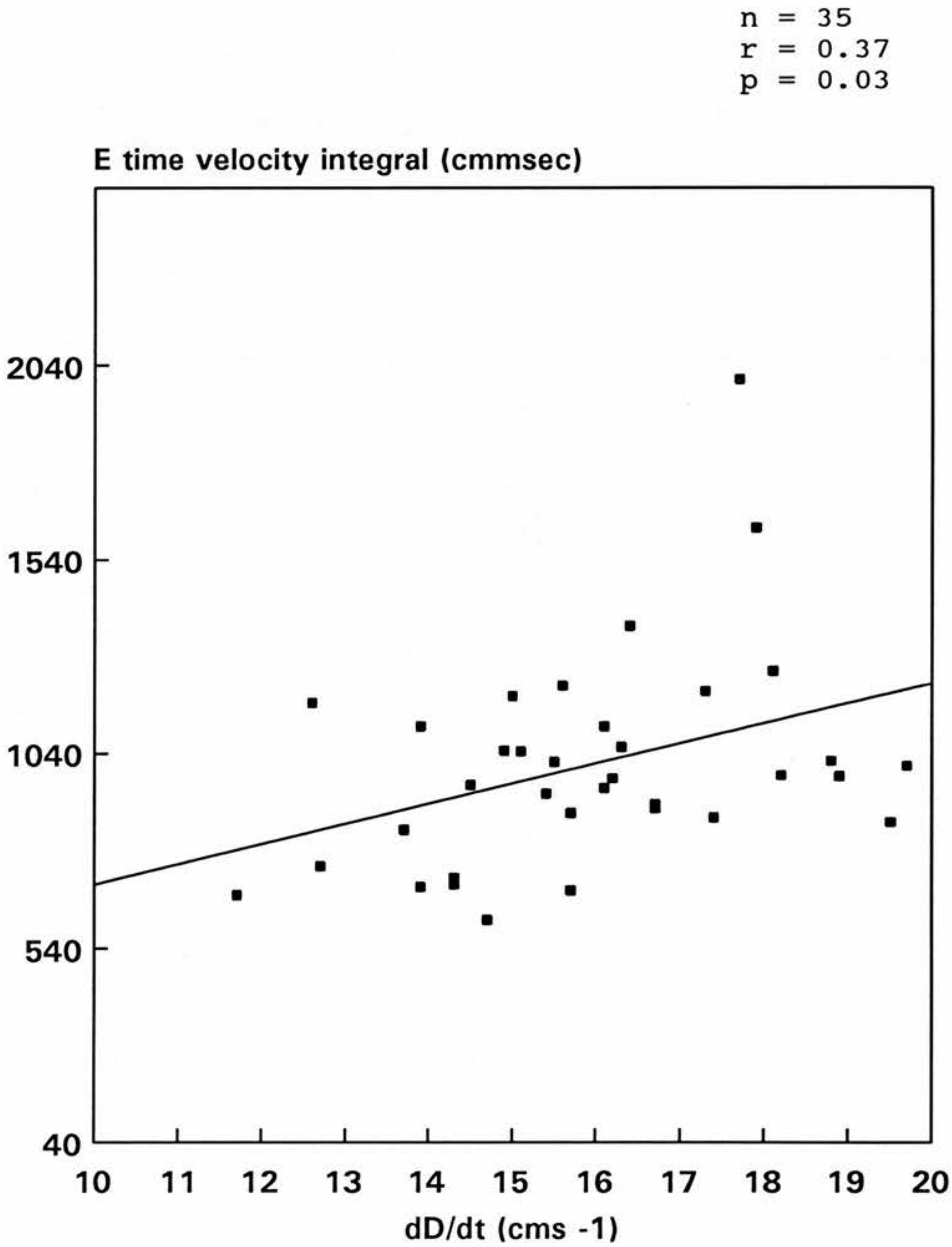
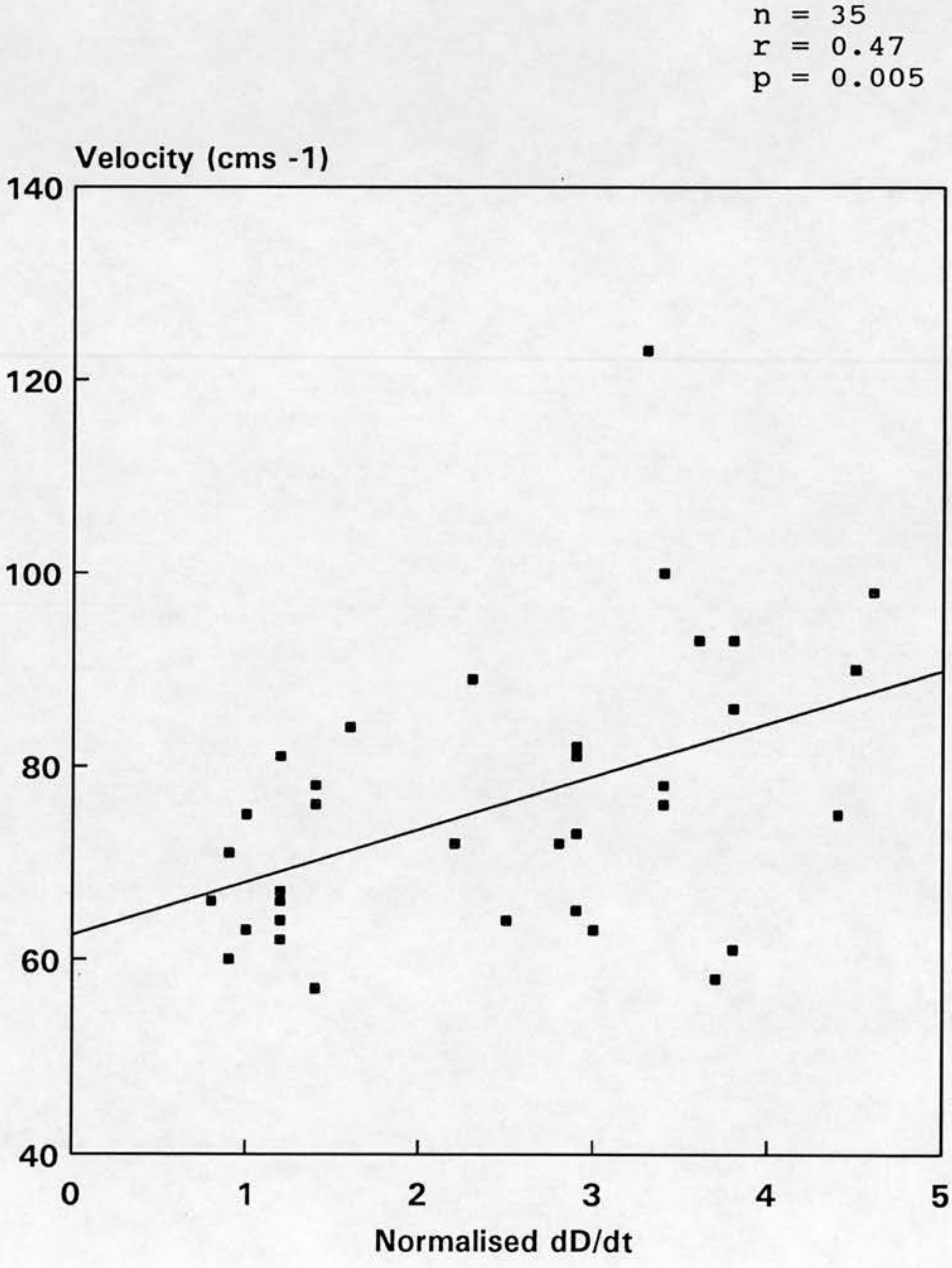


Figure 7.4

Plot of peak E velocity against normalised dD/dt



Observer Variability

1) Intraobserver variability in measurement of left ventricular isovolumic relaxation

The mean coefficient of variation for repeated measurements of left ventricular isovolumic relaxation period from M-mode tracings in 10 patients was 6.4% and for isovolumic relaxation period measured from pulsed Doppler waveforms was slightly greater at 7.5%.

2) Intraobserver variability in measurement of peak rate of left ventricular chamber enlargement

The mean coefficient of variation for repeated measurements of peak rate of increase of left ventricular dimension was 9.2% and for normalised peak rate of increase of left ventricular dimension was 10.4%.

3) Intraobserver variability in measurement of pulsed Doppler transmitral flow velocity spectra

The mean coefficients of variation for repeated measurements of selected pulsed Doppler indices were 3.5% for peak E velocity, 3.3% for the early diastolic time velocity integral, 7.5% for the mean slope of deceleration from peak E, 8.5% for the ratio of E/A and 5.4% for the ratio of the early and late time velocity integrals.

Discussion

This investigation was confined to a comparison of pulsed Doppler and M-mode echocardiographic indices of left ventricular diastolic events in healthy, active individuals who were judged to be ideal echocardiographic subjects. By excluding older individuals it was hoped to exclude the influences of occult coronary artery disease or other subclinical myocardial disease on the mechanism of left ventricular relaxation and filling. By accepting only those individuals in whom M-mode echocardiograms of high quality could be obtained, it was hoped that the influence of technical factors on the recorded waveforms could be minimised. Despite the suitability of all subjects for both pulsed Doppler and M-mode echocardiographic studies of left ventricular diastolic function, it was found that the effect of normal respiration on the M-mode traces often allowed only two or three diastolic intervals to be recorded before the signals became suboptimal and clear septal and free wall echoes were lost. The effect of respiration on transmitral flow velocity spectra rarely caused this technical difficulty. It was for this reason that matching of single cardiac cycle lengths was chosen for comparison of pulsed Doppler and M-mode measurements. Otherwise, averages of different numbers of cardiac cycles would have been necessary for each of the recording modalities.

Comparison of the measurement of the left ventricular isovolumic relaxation period yielded close correlation between the values obtained from M-mode and pulsed Doppler traces (r 0.69 $p < 0.001$). While measurement of the isovolumic relaxation period is not truly a Doppler derived parameter, this correlation suggests that simultaneous recording of pulsed Doppler transmitral spectra with a phonocardiographic trace superimposed is a clinically acceptable alternative to combined M-mode and phonocardiography. Furthermore, it confirms that transmitral flow measured using pulsed Doppler velocimetry begins at or close to the instant of separation of the mitral leaflets as recorded using M-mode echocardiography. The close agreement between measurement of isovolumic relaxation using these two techniques was first reported by Spirito (1986b). With some exceptions, most commercially available combined imaging and Doppler echocardiographic equipment does not provide a facility for phonocardiography. Therefore, the possibility for routine measurement of isovolumic relaxation from pulsed Doppler transmitral flow spectra does not exist using such equipment. Comparison of M-mode measurements of rate of change of left ventricular minor axis dimension with Doppler derived parameters failed to yield statistically significant correlation with only two exceptions. A statistically significant positive correlation was found between peak rate of increase of left ventricular dimension and the time velocity integral beneath the early filling wave E (r 0.37 $p = 0.03$). The time velocity integral is a measure of the proportion of blood entering the left ventricle during early diastole (Snider 1985, Rokey 1985). The use of the early diastolic time velocity integral has been described for calculation of peak left ventricular filling rate and cardiac output (Hoit 1988), although its exact relationship to volumetric flow is not established due to the non-linear relationship between mitral valve area and flow volume (Fisher 1983, Stewart 1985). In this study, volumetric filling rates were not calculated and the time velocity integral was regarded as a linear measure of flow analagous to aortic stroke distance (Haites 1985). It appears therefore that the rate of increase of left ventricular minor axis dimension and this linear measure of early diastolic flow may be similar expressions of the efficiency of early diastolic filling of the left ventricle. However, no significant correlation was found between the ratio of early and late time velocity integrals and peak rate of change of left ventricular dimension. Thus, the relative contribution of atrial contraction to left ventricular filling does not appear to relate in a predictable manner to the preceding passive phase of chamber filling. This latter finding is in agreement with Pearson and Spirito who found no correlation between peak rate of left ventricular chamber enlargement and the ratio of time velocity integrals (Pearson 1987, Spirito 1986b). Shapiro, on the other hand, was able to demonstrate a significant correlation between peak rate of left ventricular dimension increase and the ratio of late and early flow velocities (Shapiro

1988). In my study, a statistically significant relationship was found to exist between peak early filling velocity and the peak rate of change of left ventricular minor axis dimension normalised to end-diastolic dimension (r 0.47 p 0.005). Pearson (1987) reported close correlation between normalised rate of chamber enlargement and peak early filling rate, which is the product of the peak E velocity and mitral annulus cross-sectional area. It is not clear why the normalised rate of change of dimension should show close correlation with peak early filling velocity while this was not the case for peak rate of dimension increase not normalised in this way. No correction of the pulsed Doppler parameters was attempted. The association between peak early filling velocity and normalised rate of chamber enlargement again suggests that both reflect the rate of passive ventricular filling in early diastole.

Unlike the studies by Pearson (1987) Spirito (1986b) and Shapiro (1988), this investigation was confined to observations in normal subjects within a small age range who were ideal echocardiographic subjects. These other studies have focused largely on the differences in left ventricular diastolic behaviour in normal and hypertrophied ventricles. Spirito et al found that both pulsed Doppler and M-mode were in agreement in distinguishing normal from abnormal left ventricular diastolic function while the study by Pearson found pulsed Doppler superior for the detection of diastolic filling abnormalities (Spirito 1986b, Pearson 1987).

However, with the exception of measurement of isovolumic relaxation, neither of these reports was able to find a clinically useful pulsed Doppler variable which might be practically employed in place of M-mode echocardiographic measurements of left ventricular diastolic behaviour. Therefore while pulsed Doppler is claimed to be more sensitive than M-mode echocardiography for the detection of diastolic dysfunction (Snider 1985, Pearson 1987), meaningful quantification of the observed patterns of filling is not yet possible. More recently, Lee has shown that M-mode echocardiography was more consistent for the detection of abnormalities of rapid left ventricular filling in the presence of left ventricular hypertrophy and suggests that these are complementary rather than interchangeable techniques for assessing diastolic events (Lee 1991). There are several possible reasons why pulsed Doppler velocimetry and M-mode echocardiographic asessment may fail to show closer correlation. As Shapiro points out, the different techniques may not reflect the same underlying physiological processes, even in apparently healthy subjects (Shapiro 1988). Measurement of the diastolic left ventricular minor axis dimension, while a sensitive marker of abnormal left ventricular relaxation (Gibson 1979, Hanrath 1980), may not reflect the behaviour in terms of global filling (Gibson 1975). Pulsed Doppler transmitral velocimetry measures the instantaneous changes in blood flow velocity at the mitral valve that relate to global events within the left ventricle during diastole. The pattern of transmitral flow is subject to the interplay of variables including left atrial preload (Choong 1987a), and abnormalities of left ventricular myocardium (Snider 1985, Kitabatake 1982, Fujii 1985) whose combined effects on the transmitral waveform are incompletely understood. While related by the same process, the rate of increase of left ventricular dimension and the transmitral waveform may not be expressions of the same governing influences.

Technical limitations

Technical factors which may have influenced the observed relationship between M-mode and pulsed Doppler measurements of left ventricular diastolic function include variability in M-mode and pulsed Doppler recording technique and intra-observer variability in computer assisted analysis of both transmitral flow velocity spectra and M-mode recordings. Variability of repeated measurement from the M-mode recordings was consistently higher than for the chosen Doppler parameters. The problem of variability in measurement of peak rate of left ventricular enlargement is widely reported (Bullock 1984, Pollick 1983, Sahn 1978) and it has been recommended that repeated digitisation be undertaken at least four times for estimation of peak rate of left ventricular enlargement from M-mode recordings. In a comparative study of pulsed Doppler and M-mode in hypertensive children, Snider found larger variability in digitised measurements of M-mode recordings compared to pulsed Doppler recordings although to a lesser degree than in this study (Snider 1985). Because of the difficulties encountered in obtaining more than a few consecutive M-mode complexes due to the effects of respiration, matching of cardiac cycle length was used to select the complexes for analysis. However, examination of the RR' intervals immediately preceding the chosen complexes in both hard copy recordings often revealed small differences. The posible effect of these variations in preceding cycle length on the relationship between pulsed Doppler and M-mode parameters is unknown. Despite this, it seemed unjustified to average the values from different numbers of consecutive cycles in the same patients for comparison.

Summary

Comparison of the isovolumic relaxation period measured using M-mode echocardiography and the interval between aortic closure and onset of mitral flow detected by pulsed Doppler ultrasound showed close agreement. Thus measurement of the isovolumic relaxation period is possible using simultaneous pulsed Doppler echocardiographic and phonocardiographic recordings. Significant correlation was found between the time velocity integral beneath the early transmitral filling wave and the peak rate of increase of left ventricular minor axis dimension. Significant correlation was also found between peak early diastolic flow velocity and the normalised rate of increase of left ventricular minor axis dimension. No correlation was found between any of the other derived pulsed Doppler and M-mode measurements.

Chapter 8

The relationship between transmitral blood flow velocity spectra and left ventricular end-diastolic pressure.

Introduction

Aims and Objectives of Study

Previously reported data has suggested that pulsed Doppler velocimetry may offer a reliable means for the calculation of left ventricular end-diastolic pressure (Channer 1986, Kuecherer 1988a, Stork 1989). However, no clinically valid application for pulsed Doppler velocimetry in end-diastolic pressure measurement emerged from the work of Channer (1986) and Kuecherer (1988a). The data from Stork et al appears to allow accurate prediction of end-diastolic pressure using transmitral flow patterns but directly contradicts the relationship between diastolic pressures and transmitral spectra found in these previous studies (Stork 1989). Further results have emerged to suggest that accurate end-diastolic pressure estimation is not possible using pulsed Doppler velocimetry (Lin 1988, Appleton 1988a). This part of the experimental work was therefore undertaken to re-examine and attempt to define the relationship between pulsed Doppler transmitral flow velocity spectra and left ventricular end-diastolic pressure. In particular it was hoped to establish whether pulsed Doppler transmitral flow velocimetry offered a simple bedside technique for the accurate estimation of end-diastolic pressure that might be suitable for general and intensive care applications.

Methodology

Study Patients

64 patients undergoing elective cardiac catheterisation and coronary angiography for diagnosis and assessment of suspected ischaemic heart disease were included in the initial study group. Technically adequate pulsed Doppler recordings of transmitral flow velocity could not be satisfactorily obtained in 8 cases and a further 6 patients were excluded because of the presence of significant mitral regurgitation detected by contrast angiography. The remaining 50 patients comprised the study population. There were 35 male and 15 female patients with a mean age of 63 years (range 38 to 72). All patients were in sinus rhythm and the mean heart rate at the time of simultaneous Doppler and pressure recordings was 75 $\pm$12 beats per minute and mean intra-arterial pressure 145/85. Mitral valve disease was excluded by cross-sectional echocardiography and pulsed Doppler prior to cardiac catheterisation and the absence of mitral regurgitation was confirmed by left ventricular angiography prior to making the pressure and Doppler measurements. With the exception of beta-blockers, vasoactive medication was discontinued, where possible, four hours prior to cardiac catheterisation. 22 patients

were taking beta-blockers at the time of the combined recordings and 7 of these patients had also received calcium antagonists or nitrates within the four hours preceding catheterisation.

Pressure Recording protocol

Left ventricular diastolic pressure was recorded using a 125 centimetre fluid filled French gauge 8 pigtail type catheter (Cordis). The catheter was connected to a manifold mounted Gould P-50 micromanometer with mid-chest used as the zero point. The micromanometer was connected to a Siemens amplification module for pressure signal amplification and the output signal from this module fed to the pressure channel input of the Honeywell Ultra-Imager. The frequency response of the transducer system is flat to 18 Hz with less than 10% deviation to 25 Hz. After the completion of selective coronary angiography and left ventricular angiography, the patient was allowed to rest for 5 minutes before combined pressure and Doppler recordings were undertaken. This was to ensure that the patient was haemodynamically stable, comfortable and free from any adverse effects due to contrast ventriculography.

Pulsed Doppler Velocimetry

The patient was placed in the left lateral decubitus position on the catheter table and supported if neccessary by means of a shaped wedge. Recordings were made in quiet respiration using the methodology described in chapter four. The position of the ventriculography catheter was adjusted if neccessary prior to pulsed Doppler recording if it was seen on cross-sectional imaging to lie across the orifice of the mitral valve in such a manner as to cause acoustic interference. Figures 8.1a and 8.1b show combined pressure and pulsed Doppler recordings in progress following left ventricular angiography.

Hard copy recordings

Combined recordings of pressure, electrocardiogram and phonocardiogram were made with pressure and Doppler on dry silver paper for subsequent analysis. A paper recording speed of 100mms^{-1} was used.
An example recording is shown in Figure 8.1c.

Analysis of Doppler flow velocity spectra

All hard copy recordings were analysed using the previously described digitising sytem. The following measurements were made for each of the five consecutive waveforms:

1) Peak early velocity (E)
2) Peak atrial filling velcity (A)
2) Time-velocity integrals beneath E and A filling waves
3) Mean rate of acceleration to peak E velocity
4) Initial slope of deceleration from early peak velocity.

Figure 8.1a

Combined recording of left ventricular pressure and transmitral blood flow velocity in progress

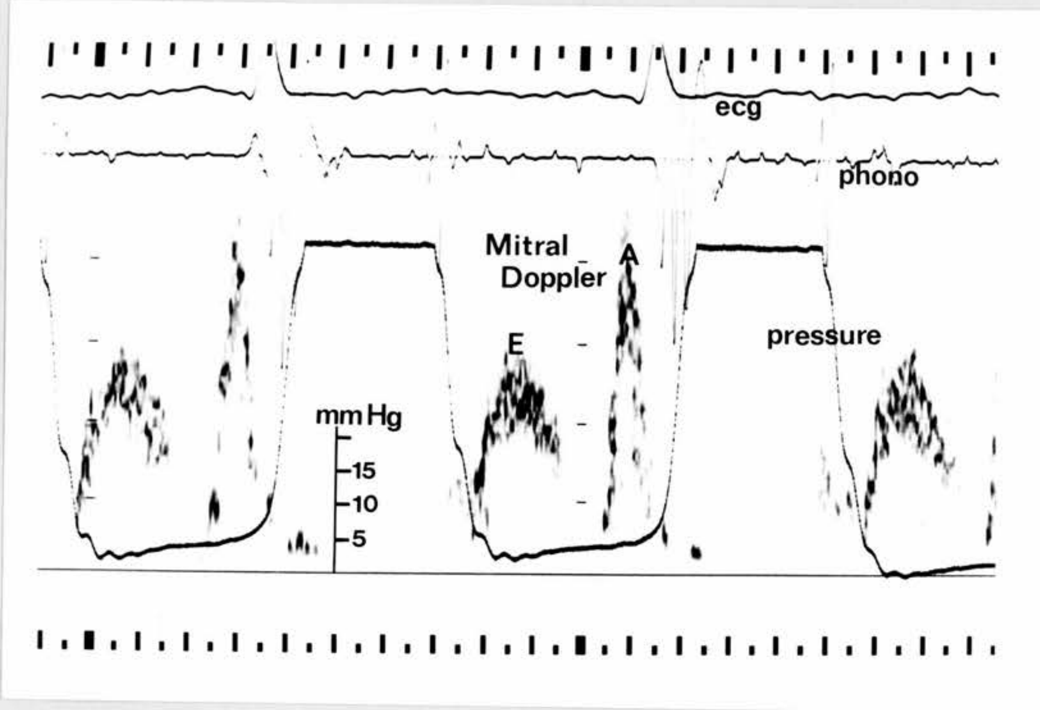
Following contrast ventriculography the patient was placed in a left lateral decubitus position prior to the combined pressure and pulsed Doppler recordings.

Figure 8.1 b

Combined recording of left ventricular pressure and transmitral blood flow velocity in progress

After optimal alignment with transmitral diastolic flow was obtained, combined pulsed Doppler and pressure recordings were made on to dry silver paper with a recording speed of 100 mms^{-1}.

Figure 8.1c



Simultaneous transmitral pulsed Doppler and intracavitary left ventricular pressure recording

Recordings were made with the patient in quiet respiration. The same five consecutive cycles were used for pressure and pulsed Doppler measurements.

(E - peak early flow velocity, A - peak atrial flow velocity, press - left ventricular pressure in mmHg, ecg - electrocardiogram, phono - phonocardiogram)

5) Mean rate of deceleration from peak early velocity to baseline.
6) Transmitral pressure half time.
7) Ratio of early to late flow velocity peaks
8) Ratio of early and late time-velocity integrals.

The arithmetic mean obtained from the analysis of five consecutive waveforms for each of these parameters was used for subsequent statistical analysis.

Analysis of end-diastolic pressure measurements

Left ventricular end-diastolic pressure was measured for the same five consecutive cardiac cycles from which the pulsed Doppler measurements were made. The intraventricular pressure was measured both immediately before atrial systole and at the onset of the electrocardiographic QRS complex. The mean of each of these sets of values was used for statistical analysis.

Statistical methods

Linear regression analysis was performed to obtain correlation coefficients between each of the selected pulsed Doppler parameters and left ventricular end-diastolic pressure measured pre and post atrial contraction. The level of statistical significance chosen was $p < 0.05$. To examine whether the pulsed Doppler transmitral flow velocity spectra from individuals with end-diastolic pressures greater than 20mm Hg differed significantly from the remainder of the study population, unpaired t-testing was applied to each of the measured parameters to test the null hypothesis that the population means were equal. The level of statistical significance chosen was $p < 0.05$.

Results

Coronary Angiographic Findings

9 (18%) patients had angiographically normal coronary arteries. 17 (34%) patients had single vessel disease affecting the left anterior descending territory in 13 cases and the right coronary artery in a 4 cases. 11 (22%) patients had three vessel disease and the remaining 13 patients (26%) had significant lesions affecting two vessels.

End-diastolic pressure measurement

The median left ventricular end-diastolic pressure (EDP) measured before atrial systole was 11mm Hg (range 4 to 24) and post atrial contraction was 16mm Hg (range 4 to 32). Further analysis of pressure recordings according to coronary angiographic findings showed that while those patients with coronary artery disease tended to have higher values of both pre and post 'a' end-diastolic pressure measurements, this was not statistically significant. These results are summarised in table 8.1.

Table 8.1

End-diastolic pressure measurements grouped according to pattern of vessels involved

Vessel diseased	Pre-a EDP (mm Hg)	Post-a EDP (mm Hg)
None (n=9)	10.3±3	14.7±3
RCA only (n=4)	13.2±5	17.2±7
LAD only (n=13)	11.5±5	15.8±6.8
LAD and Cx (n=8)	9.7±3.5	15±3.5
LAD and RCA (n=4)	9.8±3	15.8±6
3 vessel (n=11)	10.8±4	16.4±5.5

n = 50

Correlation between pulsed Doppler transmitral flow spectra and end-diastolic pressure measurements

These results are summarised in tables 8.2 and 8.3. Plots of the statistically significant correlations are shown in figures 8.2 to 8.8.

Peak early flow velocity

A positive correlation of 0.39 (p 0.005) was found between peak E velocity and end-diastolic pressure measured before atrial systole and correlation of 0.41 (p

0.003) for end-diastolic pressure measured after atrial systole. Plots of this data are shown in figures 8.2 and 8.3.

Peak atrial flow velocity

There was no significant correlation between peak atrial flow velocity and end-diastolic pressure measured either before or after atrial systole.

Ratio of early to late flow velocities

There was no significant correlation between the ratio of early and late flow velocity peaks and end-diastolic pressure measured before or after atrial systole.

Ratio of early and late flow velocity integrals

There was no correlation between the ratio of the early and late time-velocity integrals and end-diastolic pressure before or after atrial systole.

Rate of acceleration to peak early velocity

No correlation was found to exist between the mean rate of acceleration to the early flow velocity peak and end-diastolic pressure.

Rate of deceleration from peak early flow velocity

A positive correlation coefficient of 0.42 (p 0.002) was found between the slope of initial rate of deceleration from peak E velocity and pre 'a' end-diastolic pressure and there was a correlation of 0.47 ($p < 0.001$) between the initial rate of deceleration and the post 'a' end-diastolic pressure. Correlation coefficients of 0.4 (p 0.003) and 0.5 ($p < 0.001$) were found between the mean rate of deceleration from E peak and the pre and post 'a' values of end-diastolic pressure respectively. This data is shown in figures 8.4 to 8.7.

Pressure half time

There was a weak negative correlation between pressure half time and pre 'a' end-diastolic pressure (r -0.24, p 0.1). A negative correlation of -0.4 was found between pressure half time and end-diastolic pressure following atrial systole (p -0.004). This data is plotted in figure 8.8.

Pulsed Doppler transmitral flow velocity patterns in patients with elevated end-diastolic pressure.

Statistically significant differences were found to exist between patients with post 'a' end-diastolic pressures of 20mm Hg or more and the remainder of the population for the following parameters derived from the pulsed Doppler flow velocity spectra:

1) Initial rate of deceleration from peak E velocity.
2) Mean rate of deceleration from peak E velocity
3) Early time-velocity integral
3) Ratio of E wave and A wave time-velocity integrals.

These findings are summarised in table 8.4.

Table 8.2

Correlation between pulsed Doppler parameters and end-diastolic pressure measured before atrial systole

Doppler parameter	Correlation	P value
Peak E velocity	0.39	0.005
Acceleration to E	- 0.007	NS
Initial deceleration	0.42	0.002
Mean deceleration	0.41	0.003
E time-velocity integral (E TVI)	0.22	NS
Peak A velocity	- 0.01	NS
A time-velocity integral (A TVI)	- 0.08	NS
E/A ratio	0.25	NS
E TVI /A TVI ratio	0.17	NS
Pressure half time	- 0.24	NS

n = 50

Table 8.3

Correlation between pulsed Doppler parameters and end-diastolic pressure measured after atrial systole

Doppler parameter	Correlation	P value
Peak E velocity	0.41	0.003
Acceleration to E	0.08	NS
Initial deceleration	0.47	< 0.001
Mean deceleration	0.50	< 0.001
E time-velocity integral (E TVI)	0.14	NS
Peak A velocity	0.04	NS
A time-velocity integral (A TVI)	- 0.05	NS
E/A ratio	0.21	NS
E TVI /A TVI ratio	0.07	NS
Pressure half time	- 0.4	0.004

n = 50

Table 8.4

Comparison of pulsed Doppler parameters according to post 'a' end-diastolic pressure measurements

Doppler parameter	EDP < 20 mmHg (n=41)	EDP > 20 mmHg (n=9)	Probability
Peak E velocity (cms^{-1})	58.6±16.5	69.3±15	NS
Acceleration to E (ms^{-1})	9.1±4.9	8.7±3.9	NS
Initial deceleration (ms^{-1}	4.3±1.9	5.4±2.6	$0.05<p<0.1$
Mean deceleration (ms^{-1})	2.9±1.2	3.9±2.3	< 0.01
E TVI (cmmsec)	781±251	844±144	$0.05<p< 0.1$
Peak A velocity (cms^{-1})	52.9±14	51±10.8	NS
A TVI (cmmsec)	493±159	438±109	NS
E/A ratio	1.2±0.5	1.4±0.3	$0.05<p<0.1$
E TVI/A TVI ratio	1.8±0.9	2.0±0.3	< 0.01
Pressure half time	53±12	51±9	NS

n = 50

E TVI - early diastolic time velocity integral

A TVI - atrial time velocity integral

Figure 8.2

<u>Plot of peak early flow velocity against pre 'a' end-diastolic pressure</u>

n = 50
r = 0.39
p = 0.005

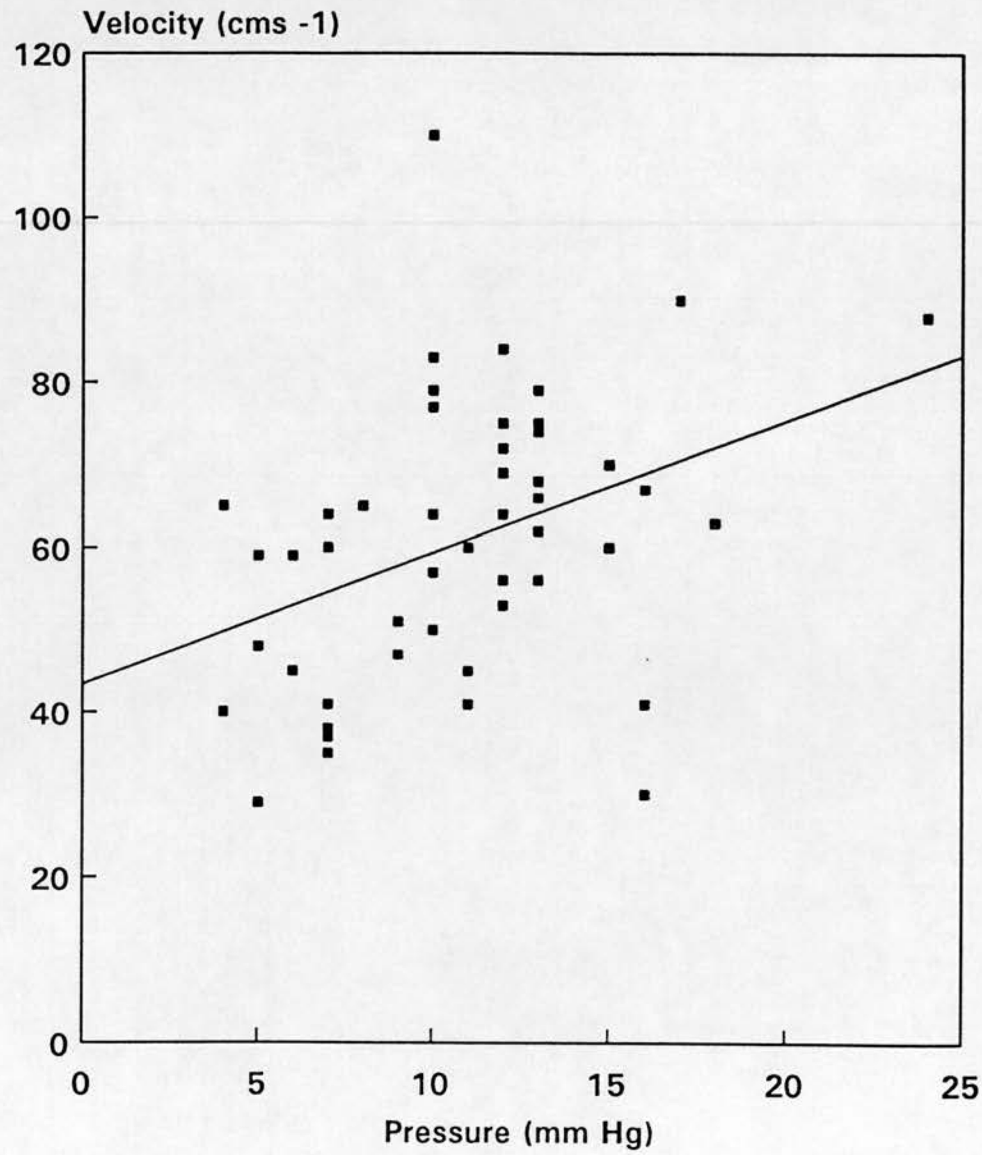


Figure 8.3

<u>Plot of peak early flow velocity against post 'a' end-diastolic pressure</u>

n = 50
r = 0.41
p = 0.003

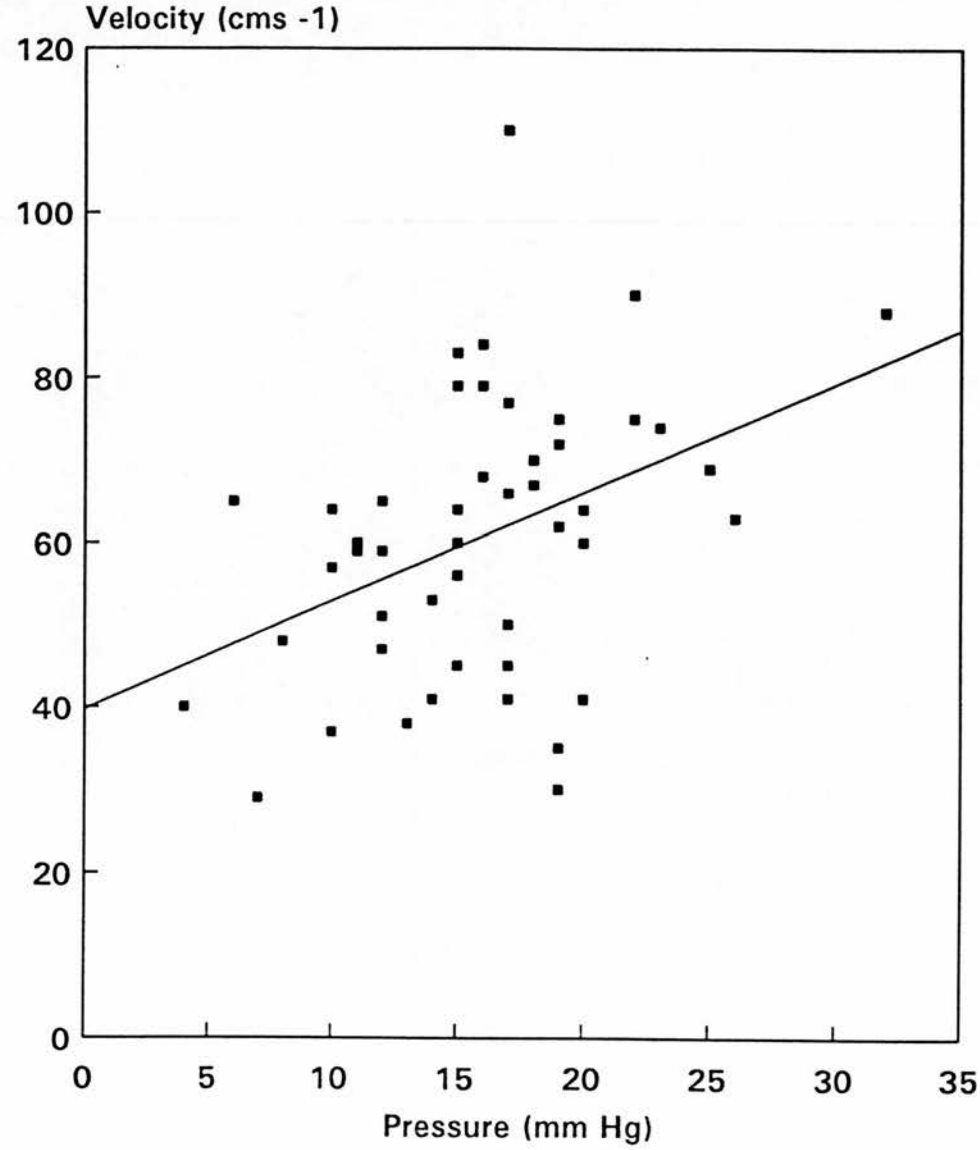


Figure 8.4

Plot of slope of initial deceleration from peak E against pre 'a' end-diastolic pressure

n = 50
r = 0.42
p = 0.002

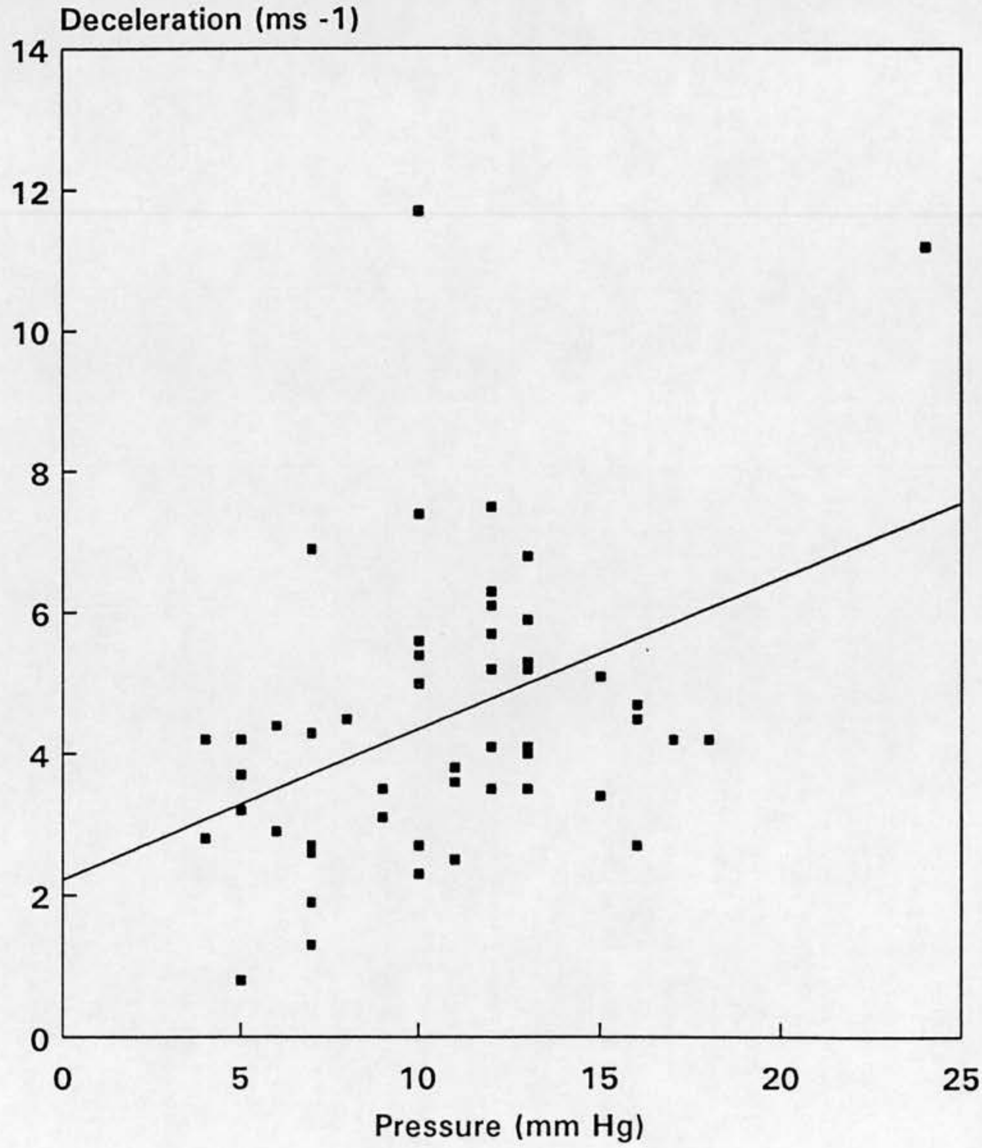


Figure 8.5

<u>Plot of slope of initial deceleration from peak E against post 'a' end-diastolic pressure</u>

n = 50
r = 0.47
$p < 0.001$

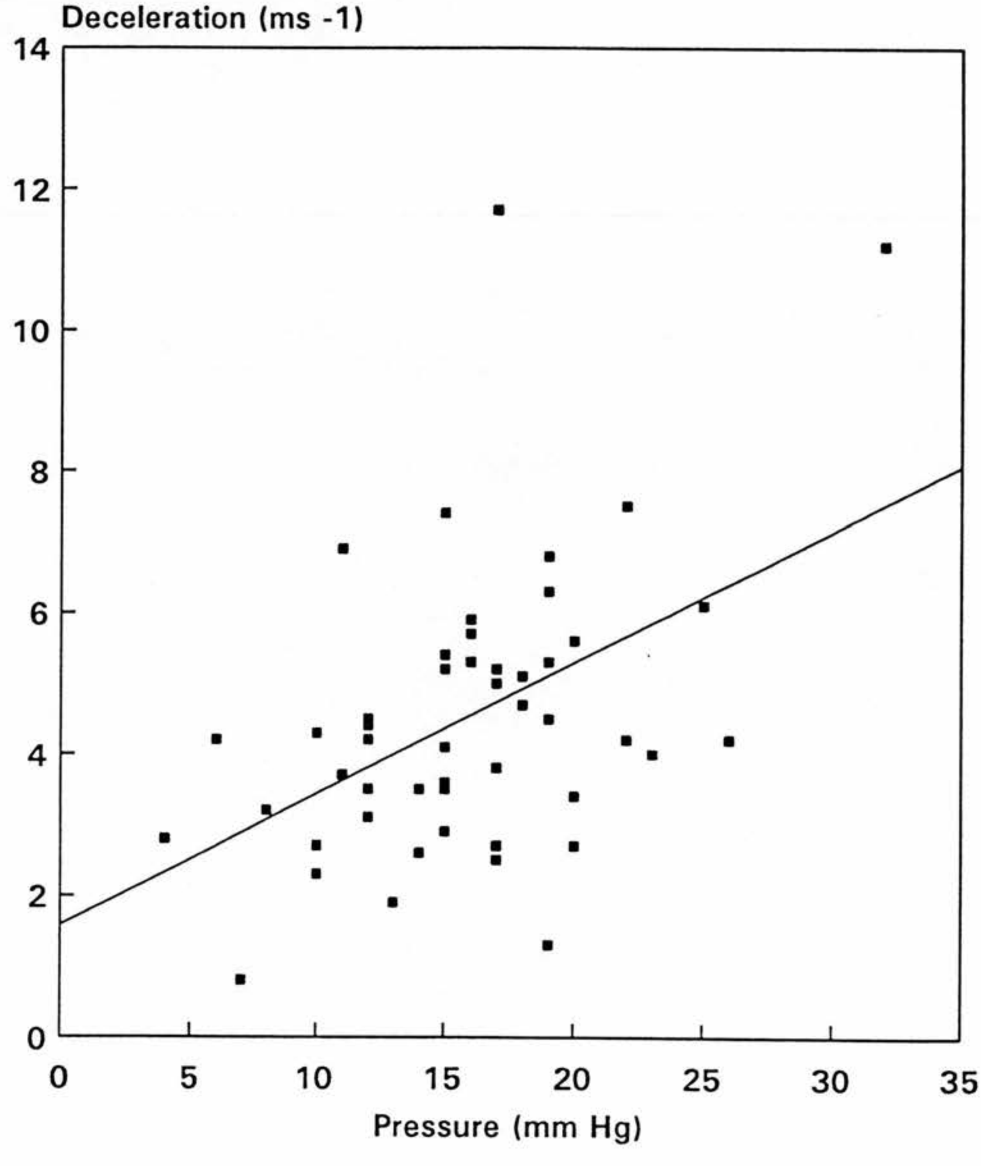


Figure 8.6

<u>Plot of mean slope of deceleration from peak E against pre 'a' end-diastolic pressure</u>

n = 50
r = 0.41
p = 0.003

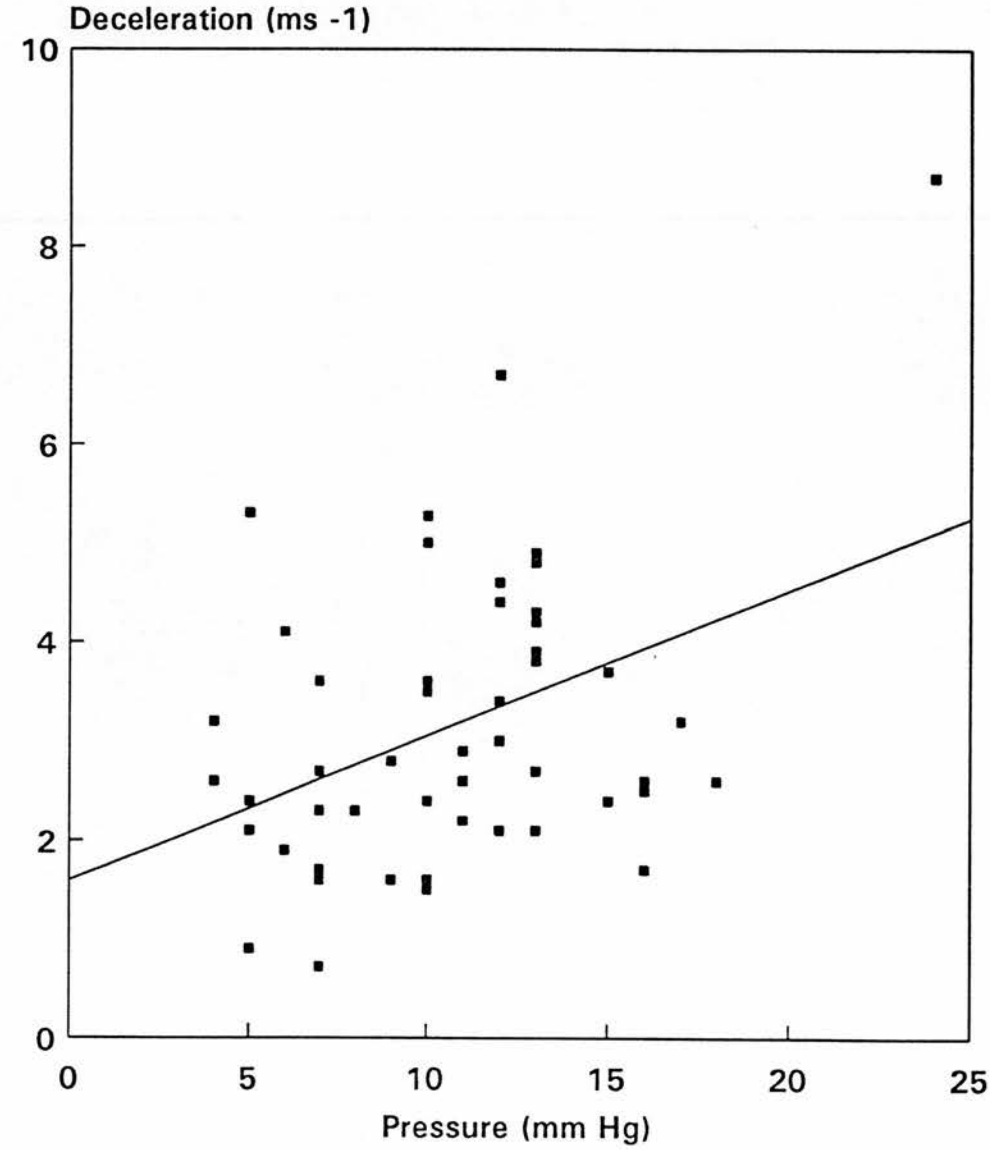


Figure 8.7

<u>Plot of mean slope of deceleration from peak E against post 'a' end-diastolic pressure</u>

n = 50
r = 0.5
$p < 0.001$

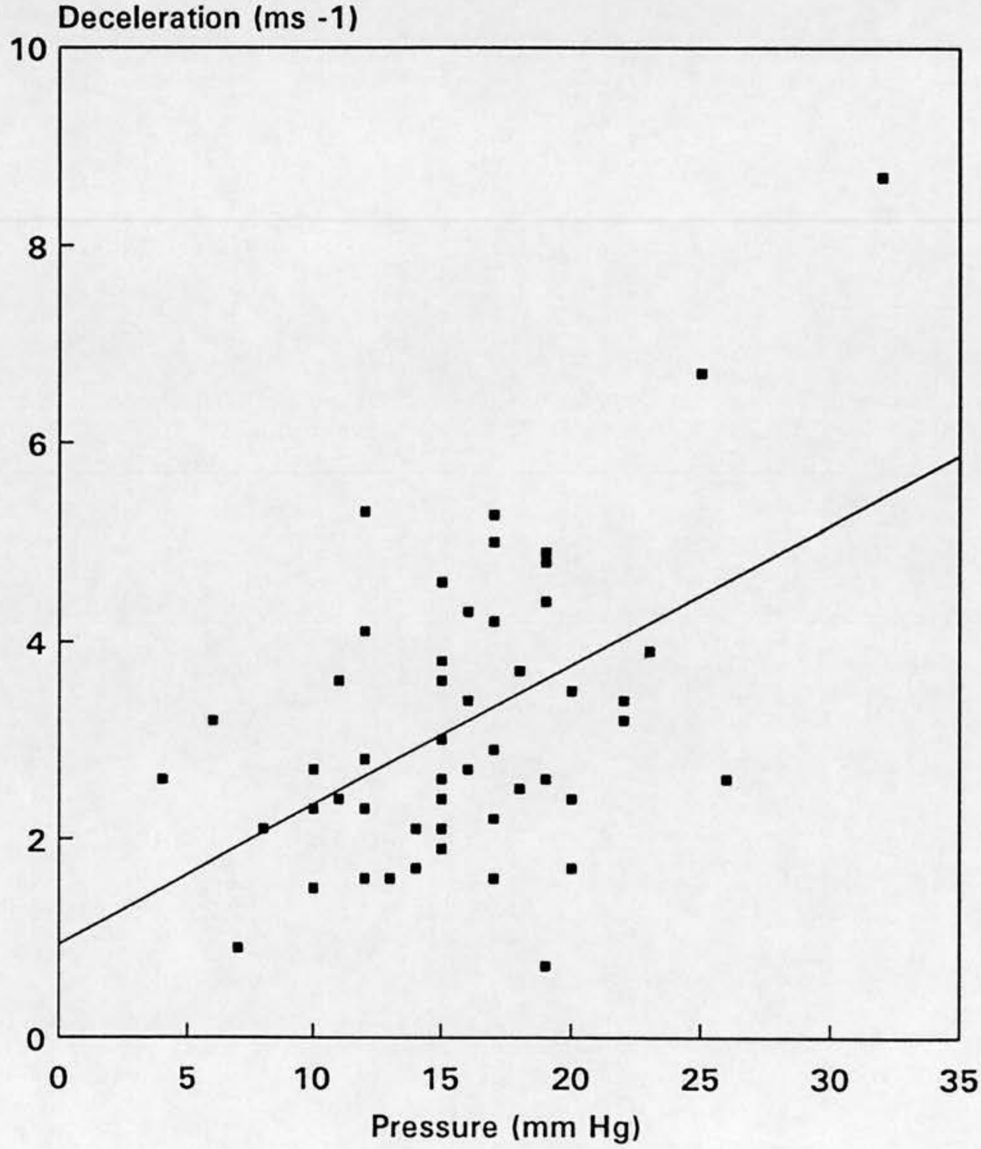
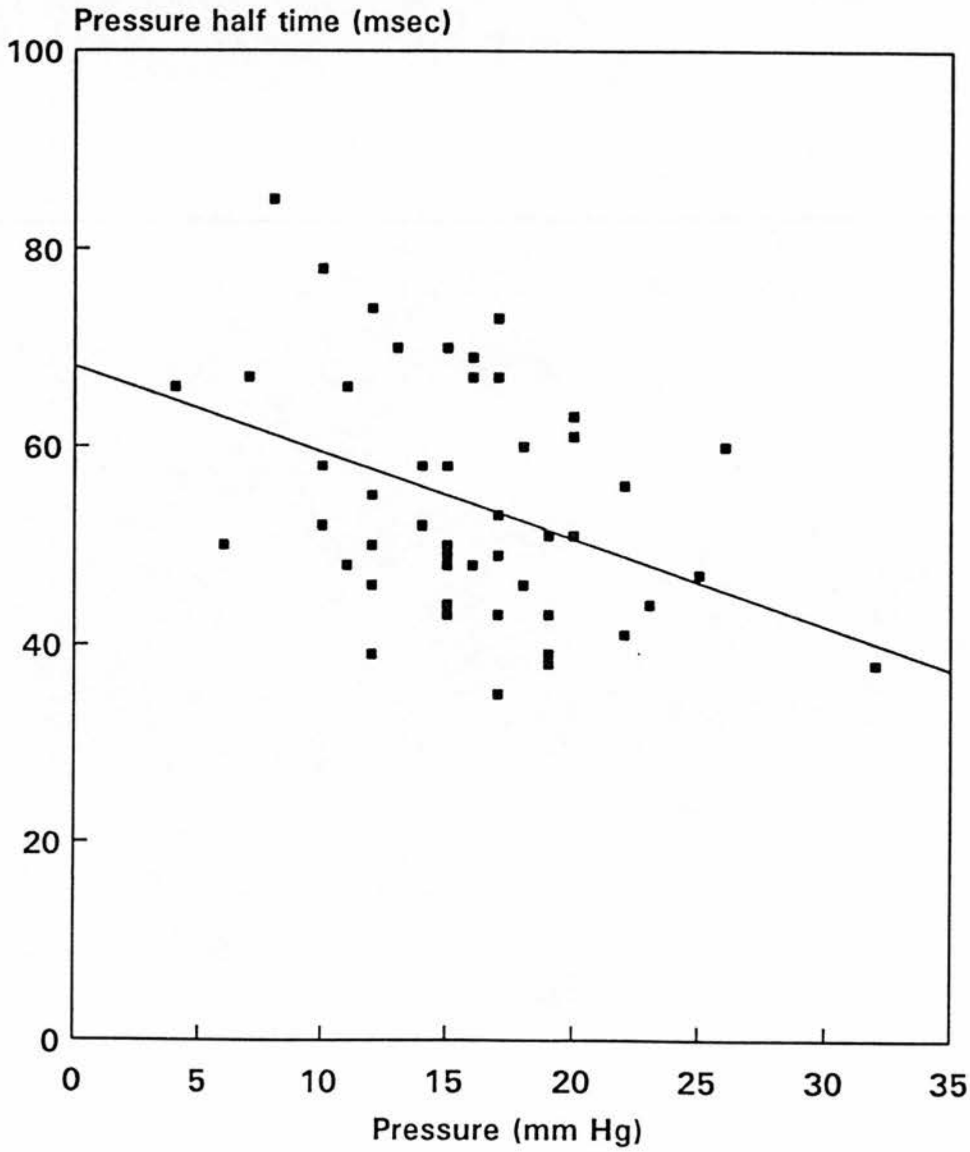


Figure 8.8

Plot of atrioventricular pressure half-time against post 'a' end-diastolic pressure

n = 50
r = - 0.4
p = 0.004



Summary of results

1) Analysis of the relationship between pulsed Doppler transmitral flow velocity spectra and end-diastolic pressure measurements revealed that peak early flow velocity, slope of deceleration from peak E and pressure half-time showed statistically significant correlation with simultaneous measurement of left ventricular end-diastolic pressure.

2) No significant relationship was found to exist between the ratio of either the peak transmitral flow velocities or the ratio of time velocity integrals and end-diastolic pressure.

3) Patients with end-diastolic pressures of 20mm Hg or greater show statistically significant differences in the slope of deceleration from peak early velocity and the ratio of time-velocity integrals compared to those patients with pressures below 20mm Hg.

4) No parameter derived from pulsed Doppler flow velocity spectra allows accurate prediction of end-diastolic pressure.

5) No parameter derived from pulsed Doppler flow velocity spectra allows reliable differentiation between patients with end-diastolic pressure measurements above and below 20mm Hg.

Discussion

The results of this investigation indicate that no simple relationship exists between left ventricular end-diastolic pressure, measured either before or after atrial contraction and the derived Doppler measurements described, which allows the accurate prediction of end-diastolic pressure in a given individual. While statistically significant correlations exist between peak early ventricular filling velocity and the slope of deceleration from peak E velocity and transmitral pressure half-time, the wide scatter of results means that clinical estimates of end-diastolic presure at the bedside are not possible. As the study group is heterogeneous with respect to age, severity and distribution of lesions, conclusions regarding the possible prediction of pressure trends within a given individual cannot be derived from this data.

Relationship between peak early filling velocity and end-diastolic pressure

In the absence of mitral valve obstruction, the peak early diastolic flow velocity (E) represents the maximum instantaneous atrioventricular pressure difference at the onset of left ventricular filling. The statistically significant correlation found between peak E velocity and end-diastolic pressure measured pre and post atrial contraction suggests that the maximum atrioventricular pressure gradient may increase in patients with elevated end-diastolic pressure. Elevation of the initial atrioventricular pressure gradient may in turn relate to the presence of left atrial hypertension due to incomplete atrial emptying in abnormal compliance states (Noble 1969, Mann 1977), but the possible effects of other variables such as myocardial stiffness and chamber geometry are unknown. The exact mechanism of elevation of the atrioventricular pressure gradient remains unknown in a given subject. Reference to figures 8.3 and 8.4 confirms however that the height of the E peak cannot be used for the prediction of left ventricular end-diastolic pressure. No statistically significant difference in peak E velocity was demonstrated between patients with end-diastolic pressures above and below 20mm Hg. This is in contrast to the findings of Kuecherer who demonstrated a significant difference between early filling velocity for the two groups (Kuecherer 1988a). The values for peak E velocity found by Kuecherer in both groups were considerably lower than in this study population which may relate both to methodological differences and intrinsic population differences.

Relationship between initial and mean rates of deceleration from peak early velocity and end-diastolic pressure

In the abscence of mitral valve obstruction, the slope of descent from peak early velocity to the baseline relates directly to the rate of pressure equalisation between the left atrium and ventricle. Highly significant positive correlations were shown between the initial and mean deceleration slopes and both pre and post 'a' end-diastolic pressure. These results indicate increasingly rapid atrioventricular pressure equalisation as end-diastolic pressure rises. Factors which might contribute to this include abnormal myocardial stiffness and chamber compliance. The rates of deceleration from E were found to differ significantly in patients with end-diastolic pressures above and below 20mm Hg suggesting that early filling is abbreviated in those patients with greatly elevated end-diastolic pressure. Despite significant differences in the slope of deceleration from peak E, no correlation was found between end-diastolic pressure and the early time-velocity integral. This may partly relate to the effect of the concurrent increase in peak early flow velocity which would tend to compensate for any reduction in area beneath the E wave. From the plots of rate of deceleration against EDP in figures 8.5, 8.6, 8.7 and 8.8 it is apparent that prediction of end-diastolic pressure in the individual is not possible. The finding of abnormal rates of relaxation in patients with elevated end-diastolic pressure is in keeping with the report by Appleton who found that a similar measurement of the deceleration slope, the deceleration half time, correlated inversely with end-diastolic pressure. Deceleration rate was also found to indicate abnormal isovolumic relaxation of the left ventricle by Lin et al (Appleton 1988a, Lin 1988). The quantitative influence of heart rate on the slope of deceleration from peak E velocity is not established and was not addressed in this present study or by those of previous authors.

Relationship between pressure half-time and end-diastolic pressure

The atrioventricular pressure half-time is defined as the time taken for the initial atrioventricular pressure to fall to half its original value (Hatle 1985). It is therefore closely related to the slope of deceleration from peak E but unlike the former can be easily measured without the need for computer assisted planimetry. Therefore it might serve as a more clinically useful "bedside" measurement. With increasing rates of atrioventricular pressure equalisation, the pressure half-time can be expected to shorten. Statistically significant negative correlations were found between pressure half-time and pre and post 'a' end-diastolic pressure but prediction of pressure in the individual was not possible.

Relationship between time-velocity integral ratio and end-diastolic pressure

No relationship was demonstrated between either the ratio of peak early and late velocities or the ratio of the time-velocity integrals beneath their respective filling waves. However, statistically significant differences were obtained by comparison of the values obtained for both ratios between patients with end-diastolic pressures above 20 mm Hg and those below. While it is possible that those individuals with end-diastolic pressures of 20mm Hg or greater, represent a specific subpopulation this is of no practical value as even a semi-quantitative pressure estimation based on transmitral flow velocity spectra does not appear feasible. These conclusions are in contrast with those of Channer and Kuecherer who proposed that the correlation demonstrated between the ratio of the early and late filling time-velocity integrals could provide a reliable means of end-diastolic pressure estimation (Channer 1986, Kuecherer 1988a). While both of these authors demonstrate similar statistical relationships between end-diastolic pressure and the ratio of time-velocity integrals, examination of their data plots confirms that prediction of end-diastolic pressure in individual cases is not feasible. In Channer's study, a ratio for the time-velocity integrals of 2:1 was associated with end-diastolic pressure ranging between 8 and 35mm Hg and in Kuecherer's report a ratio between the early and late time-velocity waves of 2 was associated with end-diastolic pressures ranging from 10 to 35mm Hg. Similarly, the claim that a ratio of greater than 2 between the early and late filling waves is always associated with end-diastolic pressure of 20mm Hg or greater is not justified. The results of this present study appear to corroborate those of Channer and Kuecherer and suggest that in the presence of significantly elevated end-diastolic pressure, a shift towards filling in early diastole may occur. This finding is supported by the work of Greenberg who showed that with increasing ventricular diastolic pressure, atrial augmentation becomes less effective (Greenberg 1979). However, there is conficting data from the work of Rahimtoola et al who demonstrated an increase in atrial augmentation in the presence of ischaemic heart disease (Rahimtoola 1975). While the relationship between time-velocity integrals and end-diastolic pressure may differ significantly in patients with end-diastolic pressures above 20 mm Hg, there is an important limitation to the application of this ratio in clinical work. The great majority of healthy individuals in the age group of these study populations can be expected to have time-velocity integral ratios equal to or greater than 2:1. Therefore, the ratio of flow velocities or time-velocity integrals cannot be applied clinically for screening or haemodynamic assessment. The findings of Stork et al were of an increasing ratio of atrial to early time-velocity integrals with increasing end-diastolic pressure (Stork 1989). The results of my own investigation and those of Channer, Kuecherer, Lin and Appleton fail to corroborate this finding (Channer 1986, Kuecherer 1988a, Lin 1988, Appleton 1988a). As only minor differences in methodology appear to exist between these studies, population differences must be largely responsible for this discrepancy.

Methodological considerations

Certain methodological differences may account for some of the discrepancies between results obtained in previous studies and this investigation. Non-simultaneous recording of Doppler and intracardiac pressure was used in the study by Kuecherer and colleagues (Kuecherer 1988a). In some cases patients were catheterised up to 48 hours after Doppler recordings of transmitral flow were made. Analysis of transmitral Doppler flow velocity spectra by both Channer and Kuecherer employed a technique of triangulation rather than formal planimetry for the measurement of early and late time-velocity integrals. This measurement was assumed to provide an acceptable approximation to flow, but transmitral flow velocity patterns rarely exhibit true geometric shapes and are often complex in outline favouring formal planimetry. Stork chose the mitral annulus plane for placement of the pulsed Doppler sample volume rather the point of maximal separation of the mitral leaflets (Stork 1989).

Limitations of pulsed Doppler in measurement of left ventricular end diastolic pressure

Transmitral flow velocity spectra can be reliably and reproducibly obtained in the majority of patients (Kitabatake 1982, Spirito 1988b, Fast 1988). If reliable estimation of end-diastolic pressure was feasible by pulsed Doppler ultrasound, then the technique would find wide ranging clinical and research applications. The fundamental difficulty in applying transmitral flow velocity spectra to estimation of ventricular pressure relates to the absence of a measurable reference pressure. Transmitral diastolic flow velocities represent the instantaneous pressure difference driving blood flow across the mitral valve at a preselected range from the transducer. Thus while the atrioventricular pressure difference may be accurately reflected, no indication of absolute chamber pressures can be obtained. From the results of this and other studies (Channer 1988, Kuecherer 1988a) there seems little doubt that the relationship between early and late filling is often altered in the presence of elevated left ventricular diastolic pressure. However, the apparently heterogeneous nature of disturbed diastolic regulation means that widely differing sets of circumstances may lead to similar effects on the transmitral flow velocity pattern (Appleton 1988a). The finding that atrial compensatory mechanisms can mask the effect of altered ventricular compliance means, for instance, that we cannot always rely on simple peak velocity measurements to indicate abnormal pressure-volume relationships. The presence of mitral regurgitation may further complicate the interpretation of the transmitral flow pattern (Takenaka 1986a Shaikh 1988). The wide scatter of pulsed Doppler echocardiographic parameters in relation to end-diastolic pressure suggests that the detection of small variations in pressure would not be possible.

Possible effects of regional wall asynchrony and drug therapy

It cannot be assumed that the ventricular wall behaves in a uniform manner in the presence of ischaemic damage. Gibson et al have comprehensively described the effects of coronary artery disease in producing regional wall motion disturbances (Gibson 1977) and pulsed Doppler studies of transmitral flow during dynamic coronary occlusion show that transmitral flow velocity patterns may alter dramatically without significant change in diastolic pressure (Labovitz 1987, Bowman 1988). The effect of regional asynchrony cannot be independently assessed from pressure changes using the currently available techniques. Subclinical ischaemia at the time of pulsed Doppler and pressure recordings may have contributed in an unpredictable manner to the results obtained. While the majority of patients were taking no vasoactive medication at the time of the combined recordings, a proportion were receiving beta-blockers plus nitrate or calcium antagonist for clinical reasons. All these agents have been shown to affect the transmitral waveform (Choong 1987a, Myreng 1988, Iwase 1987)) and their possible effects on the relationship between pressure and transmitral flow cannot be assessed. It is arguable, however, that any clinically useful relationship between these measurements would have to apply regardless of concomitant therapy.

Summary

Statistically significant relationships were demonstrated between left ventricular end-diastolic pressure and both the peak early flow velocity and the rate of deceleration from peak E. No single parameter derived from transmitral flow velocity spectra allowed confident clinical prediction of end-diastolic pressure. The ratio of the early and late time-velocity integrals and the mean rate of deceleration from peak E velocity differed significantly from the rest of the group in those patients with end-diastolic pressures above 20 mm Hg but neither parameter allowed distinction of these groups clinically. With increasing end-diastolic pressure an increase in the early filling velocity, increased slope of deceleration and increase in the ratio of early to late time-velocity integrals was found. While these results provide further insights into disturbances of the relationship between passive and active ventricular filling in the presence of elevated end-diastolic pressures, pulsed Doppler ultrasound cannot yet be used at the bedside for estimation of left ventricular end-diastolic pressure.

Chapter 9

Summary and Clinical Implications

The results of this dissertation confirm that pulsed Doppler recording of transmitral flow velocity spectra can be obtained with ease in the great majority of patients. In healthy adults, technically satisfactory recordings were obtained in all cases while in unselected patients technically unsatisfactory recordings occurred in 12%. In this respect, the pulsed Doppler technique offers an important advantage over M-mode echocardiography in the assessment of diastolic performance. Patients may be unsuitable for the assessment of diastolic left ventricular function by the pulsed Doppler method for other reasons which include the presence of arrhythmias and profound tachycardias, because of the loss of clearly definable passive and atrial filling phases and in the presence of mitral stenosis, due to the abnormal transmitral waveform caused by the presence of valvular obstruction and associated arrhythmias. It has been suggested that the presence of mitral regurgitation can mask abnormalities of the transmitral waveform (Takenaka 1986a) making this a further restriction to the clinical application of pulsed Doppler for assessment of diastolic left ventricular function. The non-invasive nature of pulsed Doppler velocimetry and its ease of repeatability make it suitable for population screening for the detection of abnormalities of left ventricular diastolic behaviour. No adverse side effects of the technique have been demonstrated in vivo giving pulsed Doppler velocimetry clear advantages over contrast ventriculography and radionuclide angiography for the serial assessment of diastolic ventricular function. This latter consideration has particular relevance to the investigation of paediatric cardiac problems. The small inter-operator variation observed in recording peak transmitral flow velocities confirms that strict adherence to a specified methodology allows comparative studies to be reliably performed by different ultrasonographers.

When technically adequate recordings were presented for analysis, only small and clinically acceptable intra and interobserver variation was observed for values obtained for peak early and atrial filling velocities and the time velocity integrals beneath each component filling wave. Larger variability was found for the measurement of the slopes of acceleration and deceleration of the early filling wave which was likely to have related to the degree of spectral dispersion of these portions of the trace, to perceptual factors influencing the choice of modal velocity for planimetry and occasional difficulties of manipulation of the trackerball cursor where the slopes were very steep or complex. None of the calculated coefficients of variation was, however, in excess of 8.5% and most were appreciably smaller.

While planimetry of the transmitral complex is required in order to obtain values for the slopes of acceleration and deceleration and for time-velocity integrals, values for peak modal flow velocity can be obtained by simple direct measurement from the transmitral trace. In addition, a qualitative assessment of the relative heights of the peak early and late flow velocities can be made. In a young adult, for instance, a ratio for the early to late velocities of less than one would be clearly abnormal and alert the operator to the possible presence of ventricular dysfunction. While others have reported the effect of respiration on the ratio of early and late flow velocities to be negligible, the results from my own study of normal volunteers show that all of the specified derived parameters of diastolic filling vary significantly with respiration. Therefore averaging of derived values from as many consecutive complexes during the respiratory cycle is recommended.

If satisfactory transmitral flow recordings were obtained in a given individual, technically acceptable repeat recordings were found to be possible in all cases. Furthermore, in apparently haemodynamically stable individuals restudied after a mean interval of three weeks, no statistically significant changes were observed for values of peak early flow velocity, early time-velocity integral, mean rate of deceleration from peak early flow velocity and the ratio of peak early and atrial flow velocities. These results confirm the suitability of pulsed Doppler transmitral velocimetry for serial clinical assessment of left ventricular diastolic function, the study of disease progression over relatively short periods of time and the effects of therapeutic intervention on diastolic ventricular behaviour. Because of the known effects of ageing on the transmitral waveform (Gardin 1987, Miyatake 1984, Kuo 1984) it is not possible to extrapolate these results to the assessment of left ventricular diastolic function over longer time intervals. However, in the patient with changing symptoms in whom frequent changes in drug therapy and dosage are neccessary, the pulsed Doppler technique might offer a reliable and simple method for the documentation of any consequent changes in diastolic ventricular behaviour without the need for more invasive studies. It is equally clear, that the interaction between inherent changes in ventricular diastolic function and the effects of therapy cannot yet be easily predicted (Appleton 1988a) and great caution is needed in the conclusions which can be drawn from transmitral flow velocity data.

The results of my own study confirm the conclusion of Spirito that simultaneous recording of transmitral flow and phonocardiogram allows clinically acceptable measurement of left ventricular isovolumic relaxation time (Spirito 1986b). Comparison of transmitral velocity data to digitised M-mode recordings of diastolic left ventricular minor axis dimension also revealed close correlation between the early time-velocity integral and peak rate of increase of left ventricular dimension. A similarly close statistical agreement was found to exist between peak early flow velocity and the normalised rate of chamber enlargement. While it is likely that these observed relationships reflect differing expressions of left ventricular relaxation, the study population was relatively small and highly selected, thus limiting the conclusions which can be drawn with regard to the constancy of this relationship with advancing age and the presence of ventricular disease.

In attempting to relate derived measurements of transmitral diastolic blood flow to intracavitary left ventricular pressure, the results of my investigation show like those of Channer (1986) and Kuecherer (1988a), that changes in the relative contributions of passive and active left ventricular filling show a close relationship to left ventricular end-diastolic pressure. Despite this, it is not feasible to predict left ventricular diastolic pressure in a given individual. The transmitral spectral waveform is an expression of global left ventricular diastolic performance and as such must be subject to a complex combination of influences at any given point during diastole. Whether integration of pulsed Doppler measurements with other noninvasive parameters of diastolic function could allow prediction of diastolic pressure remains to be clarified.

Despite the widespread application of pulsed Doppler velocimetry to the study of ventricular diastolic behaviour, its precise contribution to the care of the patient with myocardial disease remains elusive. Experimental studies have largely concentrated on attempts to resolve the complex mechanics and haemodynamics of left ventricular diastole. Clinical studies have documented the disturbances of transmitral flow velocity spectra that occur in a variety of disease processes and an increasing amount of information has become available regarding the effects of therapy on transmitral flow. In order to rationalise the place of pulsed Doppler velocimetry amongst the numerous investigative modalities available to the clinician, further work is clearly required to relate changes in transmitral flow velocity waveforms to symptomatology and prognosis in myocardial disease.

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APPENDIX

Part of the work presented in this dissertation has already appeared in published form. Reprints of these publications are appended. Permission for this has been obtained from Elsevier Science Publishers (Biomedical Division).

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Can left ventricular end-diastolic pressure be estimated non-invasively?

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Ettles DF, Davies J, Williams GJ. Can left ventricular end-diastolic pressure be estimated non-invasively? Int J Cardiol 1988;20:239–245.

The relationship between the velocity waveforms due to the early and late phases of ventricular filling recorded by pulsed Doppler changes with abnormalities of left ventricular diastolic function and it has previously been suggested that quantitative assessment of these changes may provide a clinically useful estimate of left ventricular end-diastolic pressure.

Pulsed Doppler ultrasound was used to record transmitral blood flow velocities simultaneously and on the same recorder as left ventricular pressure measurements in 30 patients undergoing cardiac catheterisation for the investigation of ischaemic heart disease. Contrary to previous reports we found no relationship between transmitral flow and left ventricular end-diastolic pressure.

Caution is required in the conclusions drawn from transmitral flow velocity patterns whose relationship to left ventricular end-diastolic pressure remains uncertain.

Key words: Transmitral flow velocity pattern: Left ventricular end-diastolic pressure

Introduction

In healthy adults, pulsed Doppler recordings of transmitral diastolic blood flow show an early or "E" wave due to the passive phase of ventricular filling and a late or "A" wave due to atrial systole. The ratio of the early and late velocity peaks (E/A ratio) is normally greater than unity in adults but varies with heart rate and

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age [1,2]. Abnormal transmitral flow velocity patterns with changes in the ratio of the early and late velocity peaks, reflecting alterations in the pattern of ventricular diastolic filling, have been reported in association with ischaemic heart disease [3]. More recently, it has been claimed that simple parameters derived from transmitral flow recordings allow reliable estimates of left ventricular end-diastolic pressure in ischaemic heart disease [4]. However, while abnormal diastolic flow characteristics are often present in ischaemic heart disease, controversy remains over their use in estimating left ventricular end-diastolic pressure [5].

This study was undertaken to determine whether the measurement of Doppler derived parameters of transmitral flow would allow a simple "bedside" method of left ventricular end-diastolic pressure estimation in chronic ischaemic heart disease.

Patients and Methods

Thirty-six patients undergoing elective cardiac chateterisation for the investigation of ischaemic heart disease were studied. Satisfactory pulsed Doppler recordings were obtained in 30 patients. These 24 males and 6 females comprised the study group with a mean age of 62 years and mean heart rate at the time of recordings of 69 ± 8 beats per minute in sinus rhythm. Valvar abnormalities were excluded by

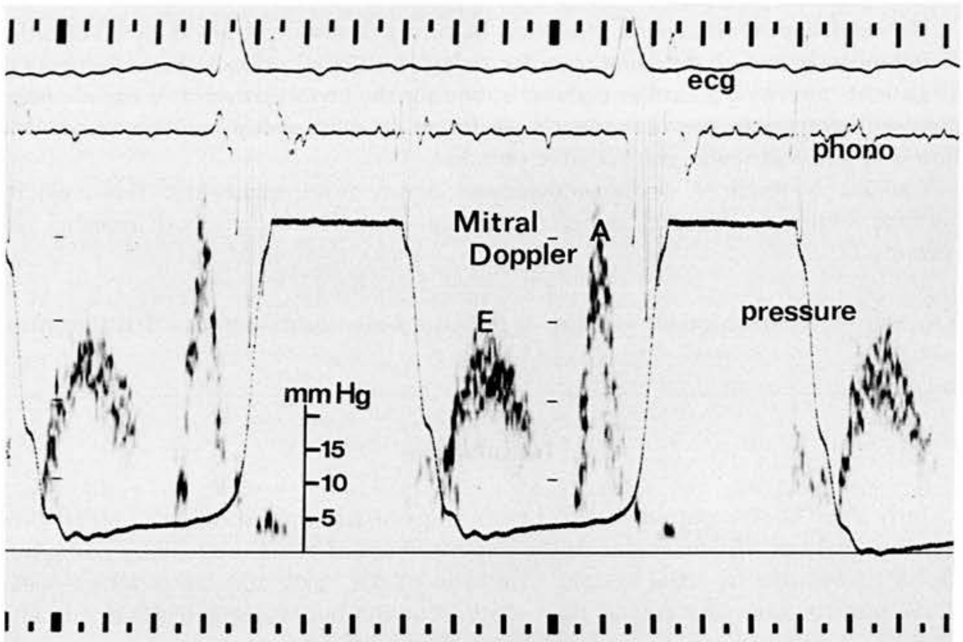

Fig. 1. Hard copy trace showing simultaneously recorded pulsed Doppler and diastolic pressure with electrocardiogram (ecg) and phonocardiogram (phono). E and A denote the early and late flow velocity peaks respectively.

echocardiography and left ventricular angiography prior to the Doppler and pressure recordings.

2.25 MHz or 3.5 MHz transducers and a Honeywell Ultra Imager were used to conduct combined cross-sectional and pulsed Doppler examinations. With the patient in a supine or left lateral position, an apical four-chamber view was obtained and the Doppler sample volume placed at the point of maximum separation of the mitral leaflets. The axial length of the sample volume can be varied between 1 mm and 7 mm. By then making small adjustments in the third plane, the best "pure tone" audio signal was obtained.

Left ventricular end-diastolic pressure was recorded using a French gauge 8 fluid-filled pigtail catheter. Initial studies using manometer-tipped catheters established that a time delay of less than 20 msec was introduced by using a fluid-filled pressure recording system. The Honeywell Ultra Imager is equipped with a multichannel input that allows simultaneous recording of electrocardiogram, phonocardiogram, pressure and pulsed Doppler on the same hard copy at a paper speed of 100 mm/sec giving both accurate timing and unambiguous identification of the events during each diastolic period.

An example recording is shown in Fig. 1.

Using a microcomputer based digitising system, hard copy recordings of five consecutive flow velocity waveforms were analysed for each patient. The peak E velocity, peak A velocity and the area under each of the velocity waves were calculated and the means of these five sets of values used for subsequent statistical analysis.

Left ventricular end-diastolic pressure was measured at the point of onset of the QRS complex on the electrocardiogram for the same five consecutive cardiac cycles and the mean of the values calculated.

Statistical Analysis

The relationship between left ventricular end-diastolic pressure and Doppler derived parameters of transmitral flow was subjected to regression analysis.

Results

No relationship was found to exist between left ventricular end-diastolic pressure and the ratio of peak early and late flow velocities (E/A ratio, Fig. 2) or the ratio of the areas beneath each of the velocity waves (E area/A area ratio, Fig. 3). Furthermore, it was not possible to distinguish raised from normal values of end-diastolic pressure using these measurements.

Discussion

Raised values of end-diastolic pressure recorded immediately before or after atrial systole (pre-a and post-a) are commonly used as an index of impaired ventricular diastolic function although correlation with other manifestations of

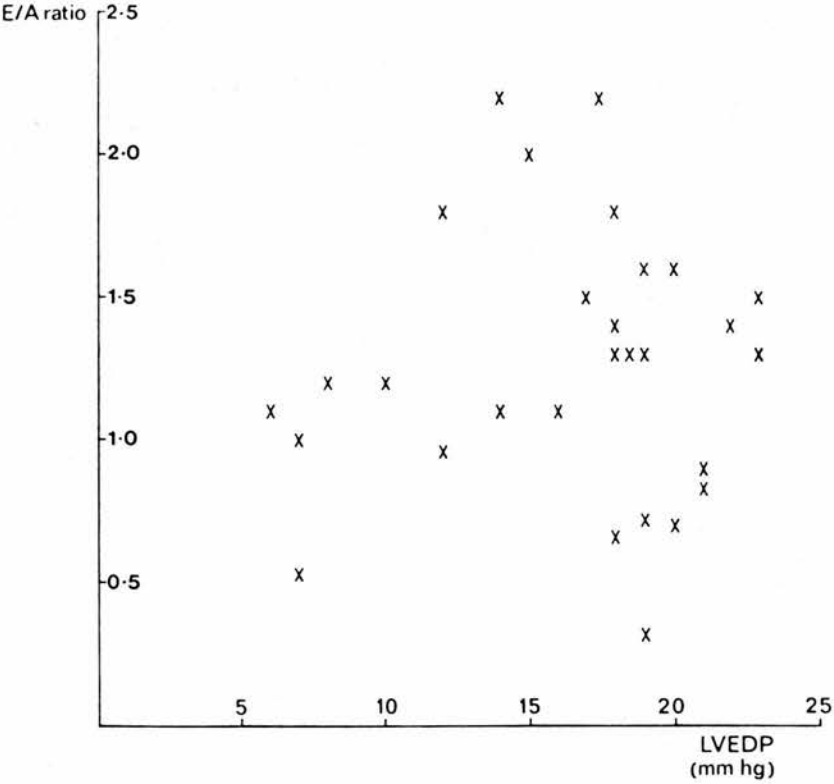

Fig. 2. Relation between left ventricular end-diastolic pressure and the ratio of peak E to peak A velocity (E/A ratio).

ventricular dysfunction, such as ejection fraction, is poor [6]. Ventricular wall stiffness, intrathoracic tension and intravascular volume exert influences on end-diastolic pressure. The effect of diuretic therapy in lowering end-diastolic pressure by volume reduction in the presence of significant ventricular dysfunction is one example of these interactions. Nevertheless, raised end-diastolic pressure remains a clinically useful indicator of chronic ventricular disease and a reliable non-invasive means of ventricular diastolic pressure measurement would be of value in the management of acute and chronic left ventricular disease.

Earlier attempts to estimate end-diastolic pressure by ultrasound used M-mode to detect altered patterns of closure of the mitral valve [7]. Subsequent investigation showed these abnormalities to be non-specific and relatively insensitive, reducing the reliability of the technique [8]. Further limitations of M-mode include inter-observer variability [9] and the reduced resolution of traces due to digital scan conversion in most modern equipment.

Satisfactory pulsed Doppler examinations can be performed in most patients with good inter-observer correlation [10] but the results of this study demonstrate that no simple relationship exists between transmitral Doppler flow velocities and

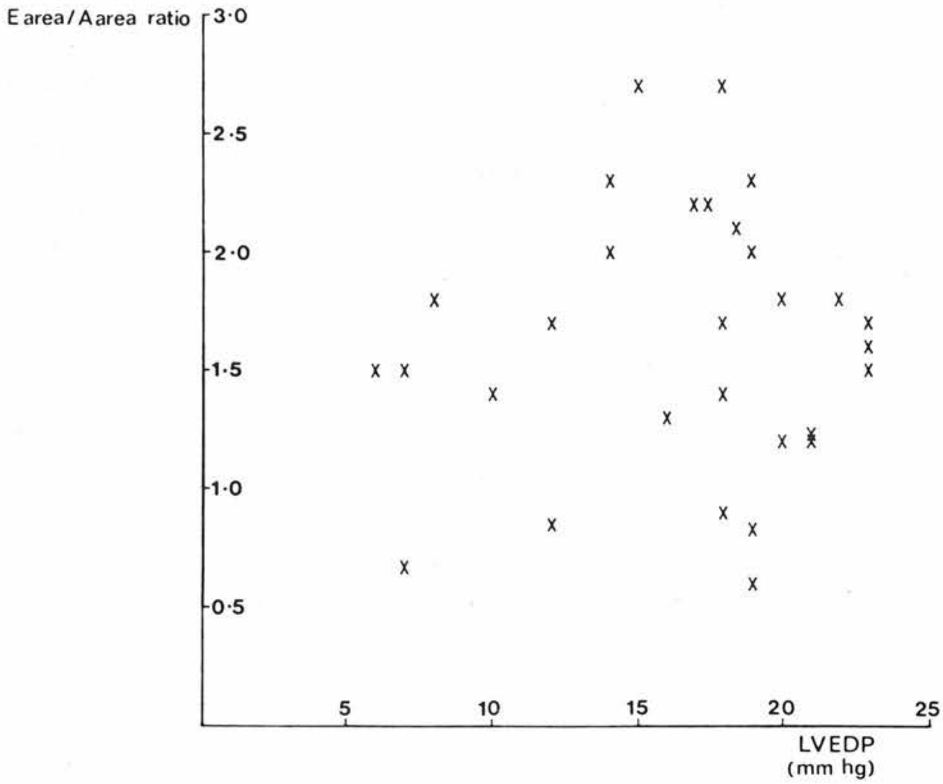

Fig. 3. Relation between end-diastolic pressure in the left ventricle and the ratio of the area beneath each of the velocity waves (E area/A area ratio).

left ventricular end-diastolic pressure in patients with ischaemic heart disease. No correlation was found between left ventricular end-diastolic pressure and either the ratio of peak early and late flow velocities or the ratio of the areas beneath each of the velocity waves.

These findings are in direct contrast with one previous study of patients with ischaemic heart disease, by Channer and colleagues [4], which claimed that pulsed Doppler could reliably differentiate raised from normal values of end-diastolic pressure and accurately predict end-diastolic pressure in individual cases. While the authors found a statistical correlation between transmitral Doppler and end-diastolic pressure, the claim that individual pressure estimation is possible is not supported by their data which shows similar Doppler derived parameters from patients whose recorded end-diastolic pressures ranged between 8 and 35 mm Hg. They also state that a ratio exceeding 2 to 1 for the areas beneath the early and late velocity waves always indicates an end-diastolic pressure greater than 20 mm Hg. Since only four of their patients fell into this category, few conclusions can be drawn from this data. In the study of Channer et al. [4] a triangulation method was used to calculate approximate values for the areas beneath each of the flow velocity waves in this previous study. We have employed formal planimetry rather than triangulation as transmitral Doppler flow velocity patterns are rarely regular in outline.

Increased peak atrial flow velocities with reversal of the normal ratio of early and late components flow velocities have been reported in association with ventricular diastolic dysfunction due to ischaemic heart disease and reflect the need for an increased atrial "kick" where passive ventricular filling is abnormal [3,11]. Of 23 patients in whom we recorded elevated end-diastolic pressures only six showed reversal of the ratio of early and late flow velocity peaks, making it impossible to even qualitatively distinguish those patients with significantly raised end-diastolic pressures.

The application of pulsed Doppler to the study of left ventricular diastolic dysfunction is of considerable potential value. Pulsed Doppler is a sensitive method for the detection of early diastolic dysfunction [12] and correlates well with cineangiography and radionuclide techniques for the assessment of peak ventricular filling rate [13,14]. Transmitral flow velocity patterns persist unchanged in haemodynamically stable patients [10] and reflect changes in diastolic function following the introduction of drug therapy [15].

While it is not yet possible to derive end-diastolic pressure from transmitral flow recordings using simple formulae, further investigation of the relationship between diastolic flow velocities and pressure should be persued.

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Reproducibility and persistence of abnormal transmitral flow velocity patterns detected by pulsed Doppler ultrasound

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This prospective study examines the reproducibility and persistence of abnormal transmitral flow detected using pulsed Doppler ultrasound on 2 separate occasions between 2 days and 6 weeks apart. The 22 patients included were accepted consecutively from those having an abnormal diastolic flow pattern at initial examination. Abnormal flow velocity patterns were defined as those exhibiting reversal of the ratio of the passive filling velocity (E) and active atrial transport velocity (A).

There was no significant difference between the separately recorded values for the ratio of the peak E and A velocities or of the ratio of the planimetered areas beneath each of the velocity waves, with positive correlations for both sets of values ($r = 0.68$, $r = 0.67$). Significant positive correlation also existed between the mean rates of acceleration to each of the E and A velocity peaks of the transmitral waveform recorded on separate occasions ($r = 0.68$, $r = 0.95$). Interobserver variation for the analysis of hard-copy pulsed Doppler recordings between two trained observers was less than 5% and intraobserver error for recording analysis was less than 2% for both observers.

Abnormal transmitral flow velocity patterns persist unchanged in the absence of therapeutic intervention and the acceptably small observer error in the recording and analysis of such flow patterns allows consistent and clinically reliable data to be obtained.

Key words: E/A ratio; Pulsed Doppler; Transmitral flow velocity

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Introduction

In normal adults, diastolic blood flow through the mitral valve detected by pulsed Doppler ultrasound shows an initial (E) peak due to passive flow into the left ventricle and a second (A) peak due to atrial contraction. The ratio of the peak E and A velocities is usually greater than unity [1].

Reversal of the E/A ratio has been described in association with left ventricular dysfunction [2], but it is not clear if this ever occurs in healthy adults. Furthermore, while this abnormality may be a marker of left ventricular dysfunction, it is possible to demonstrate normal transmitral blood flow velocity patterns in patients where clear angiocardiographic or echocardiographic evidence of impaired ventricular function exists. Examples of transmitral flow velocity patterns showing normal and reversed E/A ratios are shown in Fig. 1.

The possible relationships between these observed flow velocity patterns and disease states affecting the left ventricle have been the subject of a number of recent reports [3–5] including correlations with left ventricular end-diastolic pressure

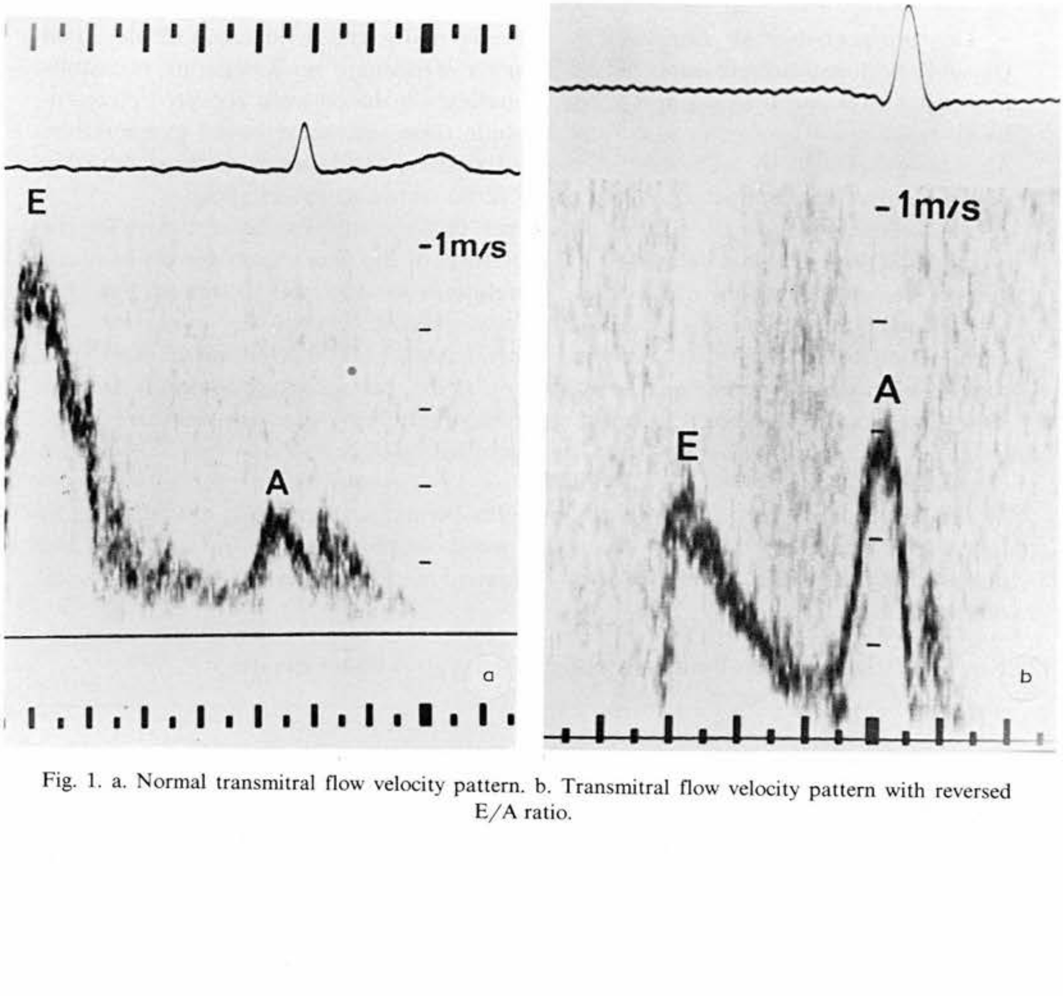

Fig. 1. a. Normal transmitral flow velocity pattern. b. Transmitral flow velocity pattern with reversed E/A ratio.

measurements [6]. However, there are no data regarding either the reproducibility of pulsed Doppler recordings of abnormal transmitral flow patterns or the stability of such observed flow abnormalities over time.

The significance of inter- and intraobserver variation in the analysis of such data is equally important and should be established prior to studies of the clinical application of this technique.

This article reports the prospective findings in 29 patients who were found to have abnormal transmitral flow velocity patterns at an initial cardiac ultrasound examination and who were subsequently recalled for a repeat Doppler study.

Materials and Methods

Patient Selection

Twenty-nine consecutive patients in whom the ratio of the early and late flow velocity peaks (E/A ratio) was less than unity at routine diagnostic ultrasound examination comprised the study group. Seven patients were excluded from follow-up because the quality of mitral flow recordings was considered to be unacceptable for later analysis. The study group comprised 8 male and 14 female patients with a median age of 69 years (range 1 to 80 years). The mean heart rate was 73/min (range 52 to 110) and in no patient varied by more than 8 beats per minute between attendances (mean $\pm$ 4 beats per minute). Of the 22 patients restudied, 13 had echocardiographic evidence of left ventricular hypertrophy associated in 11 cases with aortic stenosis with a mean value for the peak instantaneous pressure drop of 42 mm Hg (range 20 to 80 mm Hg). The remainder had clinical evidence of ischaemic heart disease. All patients were in sinus rhythm and no patient in whom there was echocardiographic evidence of mitral valve disease was included.

Medical therapy was unchanged within the study period which varied from 2 days to 6 weeks with a mean interval of 2 weeks between Doppler examinations.

Recording Techniques

Doppler examinations were conducted using Honeywell Ultra-Imager or Biosound ND 256 ultrasound machines. Both instruments use 2.5 MHz or 3.5 MHz transducers to give combined cross-sectional imaging with a variable pulsed Doppler sample volume size and steerable Doppler cursor with adjustable depth.

All patients were examined at rest in quiet respiration in a left lateral decubitus position and transmitral flow velocities were recorded with simultaneous electrocardiography at a paper speed of 100 mm per sec.

The Doppler examinations were performed by any one of five experienced technical or medical staff within the department. Staff members making the recordings were "blind" to the results of the original studies when making the follow-up recordings. Eight of the patients were studied by the same observer at both attendances, the remainder being randomly allocated.

The Doppler sample volume was placed at the point of maximum separation of the mitral leaflets shown on the cross-sectional image and the best audio signal then obtained by making small adjustments in the third plane. The "pure tone" signal of greatest amplitude was then recorded for at least twenty consecutive beats.

Hard-copy traces were only considered to be suitable for later analysis if they showed a low signal-to-noise ratio and if at least four consecutive mitral complexes were of sufficient quality to allow accurate determination of the beginning and end-points of each complex as well as clear peak E and A velocities.

Analysis of Doppler Traces

The hard copy traces were analysed using a microcomputer based digitising system with the observer blind to the results of analysis of previous transmitral waveforms. Peak E velocity, peak A velocity, the areas under the E and A velocity waves and the mean acceleration to the E and A peaks were recorded. The mean of each of these values from 4 consecutive complexes were used for later statistical analyses.

The modal peak velocity was chosen for digitisation of the hard copy traces. This is defined as the most dense area of the waveform produced by spectral analysis. The use of modal peak velocity for the analysis of pulsed Doppler recordings has been reported previously [7]. The traces were digitised by one of two observers (D.F.E. and G.A.W.).

To test interobserver variation, 4 randomly selected Doppler traces were digitised 10 times by each observer. To test intraobserver variation, 10 pulsed Doppler recordings were digitised on two separate occasions by each observer "blind" to previous results.

Statistical Analysis

The values obtained for the various parameters of transmitral flow were analysed by Student's *t*-test and a linear correlation was calculated for the paired observations.

The coefficient of variance was calculated to test the inter- and intraobserver variation.

Results

In all but one of the patients studied, the ratio of the E and A velocities gave a value of less than unity on both occasions. There was a mean difference of 12% between the value obtained for the E/A ratio on the first and second occasions.

A significant positive linear correlation existed for E/A ratio recorded on separate occasions with an r value of 0.68 ($P = 0.0004$) and a similar correlation found for the ratio of the areas under the peak E and A velocities with an r value of 0.67 ($P = 0.0004$). The mean rates of acceleration to the E and A velocity peaks showed good correlations between the values obtained at the initial and follow-up examinations with r values of 0.67 and 0.95, respectively ($P = 0.001$, $P = 0.0001$).

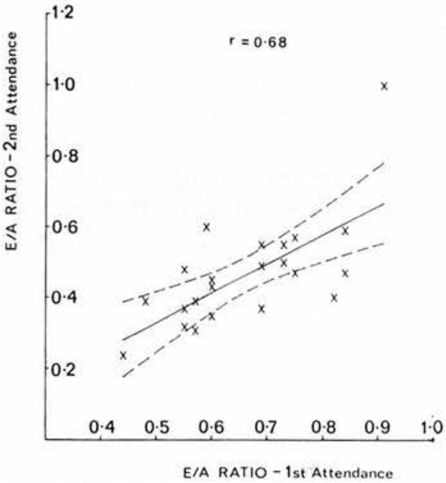

Fig. 2. Scatter plot showing the E/A ratios of all patients at both attendances. The regression line is plotted with 95% confidence bands for the regression.

The intraobserver variation for repeated measurements of peak E and A velocities from hard-copy traces gave a coefficient of variance of less than 2% for both observers (1.2% for G.A.W. and 1.5% for D.F.E.).

Interobserver variation for measurements of peak E and A velocities from hard-copy traces was 4.2% for peak E velocity and 4.8% for peak A velocity.

Fig. 2 shows a scatter plot of the E/A ratios recorded at both attendances.

Discussion

Abnormalities of diastolic relaxation are known to occur early in the development of left ventricular dysfunction [8,9]. Pulsed Doppler ultrasound being a relatively easily applied and non-invasive technique could be a clinically valuable adjunct in the recognition of diastolic abnormalities and in this respect has already been claimed, in one study, to be superior to angiocardiographic and other echocardiographic parameters [5]. The importance of correct alignment of the pulsed Doppler sample volume with blood flow when making recordings is generally recognised, as are the significant recording errors which can be introduced by even small changes in transducer angulation. The reproducibility and variability of the recording and analysis of abnormal transmitral velocities must, therefore, be established prior to the widespread acceptance of transmitral flow velocity patterns for correlative clinical work.

Equally, whilst left ventricular dysfunction will almost invariably progress with time, it is of importance to establish whether transmitral flow reflecting left ventricular diastolic filling remains unchanged over a relatively short time interval providing the patient's clinical status and medications are unchanged.

The results of this communication reveal that if the described quality control is applied before subjecting recorded material to analysis, then with unselected patients attending a routine echo service satisfactory data may not be obtained in almost one-quarter. This reduces the clinical application of the technique.

Five different staff members produced recordings which revealed similar values in the 22 patients progressing to the second part of the study. This suggests that for a recording to be acceptable by the criteria applied, very close alignment with flow must have been achieved on both occasions and that the technique is reproducible between recording operators if the conditions set out in the "methods" section are applied.

Recognising starting and finishing points on the Doppler trace and planimetering the modal velocity are all potential areas of analysis error. However, with a well-defined technique, the inter- and intraobserver errors are small and in keeping with a previous study where these measurements were used for calculating cardiac output [19]. Such observer errors are small enough to allow clinically reliable results to be obtained and used for other correlative work.

Our findings also indicate that no statistically significant change occurs in an abnormal transmitral flow velocity pattern studied on two separate occasions in haemodynamically stable patients.

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