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Ventricular Long Axis Function: Amplitudes and Timings

Echocardiographic Studies in Health and Disease

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To my family
Frida, Anthony, Arnold and Maria

Time brings wisdom to the mind
and healing to the heart.

Anonymous

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Abstract

Background: The ageing process not only increases the risk of coronary artery disease (CAD) but also complicates its diagnosis and treatment. It is therefore important to understand the newer concepts of cardiovascular ageing physiology as well as methods of predicting the outcomes of therapeutic options available for the elderly with severe CAD. Studies of atrioventricular (AV) ring or plane motion have attracted considerable interest in the last few years as a means of assessing ventricular and atrial function. As the displacement of AV rings towards the ventricular apex is a direct reflection of longitudinal fibre contraction, its measurement by echocardiography provides additional information regarding global and regional systolic and diastolic function. Left ventricular (LV) long axis amplitude of motion, referred to as mitral valve annular (MA) motion, is reduced in CAD and to some extent in the elderly as part of the normal ageing process. **Objectives & Methods:** The aim of the present study was two-fold. First, to investigate the relationship between the timing of MA motion and transmitral and pulmonary venous flow in healthy subjects, and to define the physiological significance of that relationship including its potential diagnostic utility. Second, to investigate the relationship between the clinical outcome and the behaviour of long axis function in patients with severe ischaemic LV dysfunction (SLVD) after percutaneous coronary angioplasty (PTCA). Transmitral early (E) and late (A) filling, and pulmonary venous flow reversal (Ar) were studied by Doppler echocardiography, while at the left lateral AV ring, the MA motion in early (E_m) and late (A_m) diastole were recorded by Doppler tissue imaging (DTI) and M-mode echocardiography. **Results:** *Healthy subjects* – In early diastole the onsets of LV filling (E) and relaxation (E_m) were simultaneous, and peak E_m preceded peak E by 26 msec in all age groups, constituting a time interval referred to as early diastolic temporal discordance (EDTD). Similarly, the onsets of A_m, A and Ar were simultaneous at onset and began approximately 84 msec after the electrocardiographic P wave. Peak A_m preceded peak A by 23 msec in the young and by 13 msec in the elderly, a time interval referred to as late diastolic temporal discordance (LDTD). Peak Ar, on the other hand, coincided with peak A_m in all age groups. With increasing age and sequential prolongation of isovolumic relaxation time, the peaks of A_m, Ar and A converged. This point of convergence is described as atrial mechanical alignment (AMA). *Patients* – MA total amplitude of motion, rates of shortening and lengthening were all reduced in patients with SLVD. At mid-term, 3-6 months after PTCA, there was improvement in all these variables. A pre-procedure long axis cut off value of ≥5 mm was associated with favourable symptomatic outcome. Overall angiographic success was 95.2%, and event-free survival was 78.4% at one month and declined steadily to 62.3% at one year with 2.5% mortality. **Conclusions:** EDTD, which reflects ventricular restoring forces (suction) is age independent while the narrowing of LDTD leading to AMA provides a novel method to identify healthy subjects at increased dependency on left atrial contraction for late diastolic filling. Peak atrial contraction (A_m) coincides with peak Ar, thus the timing of regional atrial contraction by DTI can be used to estimate corresponding measurements of Ar, which is often difficult to image by transthoracic echocardiography. In patients with SLVD long axis total amplitude of at least 5 mm at the left MA suggests a significant potential for segmental function recovery after PTCA.

Keywords: Echocardiography, Doppler tissue imaging, ageing, coronary disease, left ventricular dysfunction, atrial contraction, electromechanical function, coronary angioplasty.

List of original studies

This thesis is based on the following original studies, which are referred to in the text by their Roman numerals:

I. Bukachi F, Kazzam E, Mörner S, Lindqvist P, Henein MY, Waldenström A. Age-dependency in the timing of mitral annular motion in relation to ventricular filling in healthy subjects – a pulsed and tissue Doppler study. (submitted)

II. Bukachi F, Waldenström A, Lindqvist P, Mörner S, Henein MY, Kazzam E. Pulmonary venous flow reversal and its relationship to atrial mechanical function in normal subjects. (submitted)

III. Bukachi F, Clague JR, Waldenström A, Kazzam E, Henein MY. Clinical outcome of coronary angioplasty in patients with ischaemic cardiomyopathy. *Int J Cardiol* 2003;88:167-74.

IV. Bukachi F, Kazzam E, Clague JR, Waldenström A, Henein MY. Severe ischaemic left ventricular dysfunction: segmental ventricular function recovery and symptomatic improvement after percutaneous coronary intervention. (submitted)

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Abbreviations

A	Doppler late diastolic flow
Ar	Doppler pulmonary venous retrograde flow
AMA	Atrial mechanical alignment
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
A_m	Atrial contraction using Doppler tissue imaging
AV	Atrioventricular
CAD	Coronary artery disease
EDT	Mitral E-wave deceleration time
DTI	Doppler tissue imaging
E	Doppler early diastolic flow
ECG	Electrocardiogram
EDTD	Early diastolic temporal discordance
EDTDc	Early diastolic temporal discordance (corrected)
E_m	Velocity of basal LV motion in early diastole using DTI
HR	Heart rate
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
LA	Left atrial
LBBB	Left bundle branch block
LDTD	Late diastolic temporal discordance
LDTDc	Late diastolic temporal discordance (corrected)
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVET	Left ventricular ejection time
LVH	Left ventricular hypertrophy
MA	Mitral valve annulus
MPI	Myocardial performance index
PCG	Phonocardiogram
PCWP	Pulmonary capillary wedge pressure
PTCA	Percutaneous transluminal coronary angioplasty
PEP	Pre-ejection period
PVF	Pulmonary venous flow
SLVD	Severe left ventricular dysfunction
TA	Total amplitude
TFT	Total filling time
TTE	Transthoracic echocardiography

1. Introduction

The burden of cardiovascular diseases will increase substantially in the most affluent nations of the world as more people live longer [1]. The ageing process and coronary artery disease (CAD) have a synergistic effect on the human heart. At the extremes of both conditions are two profoundly unique clinical challenges. First, making a clear distinction between the effects of normal ageing and those of underlying coronary disease on the heart is often difficult. Second, among those with severe left ventricular dysfunction (SLVD) secondary to CAD, the ability to select appropriate therapeutic interventions and predict early and late outcomes is often limited due to lack of objective markers. To overcome these challenges, however, there is urgent need to investigate newer concepts of ageing cardiovascular physiology as well as define other potential markers of ventricular function recovery after interventions. Using both well-established and newer echocardiographic techniques, the movement of the base of the heart in the longitudinal (long axis) direction was studied, particularly the timing of its amplitude of motion in relation to blood flow in healthy volunteers and in patients with SLVD. This thesis discusses the background principles and the theoretical basis of ventricular long axis function, and further highlights the potential clinical applications of the results from these studies.

2. Ventricular long axis

2.1. General overview and historical perspective

The importance of longitudinal (long axis) motion of the ventricles to the overall cardiac pump function has been known since the time of Leonardo da Vinci [2, 3]. Much later, Hamilton and Rompf [4] working with animal experiments observed that the base of the heart, referred to us the atrioventricular (AV) plane or ring moved towards the apex during systole and the apex made very slight movements. That novel observation has been confirmed in humans, where the left ventricle performs its pump function by coordinated movements, which involve shortening in the longitudinal axis in systole with concomitant reduction in intracavitary diameter [5, 6], and slight rotational movement around its longitudinal axis [7]. In diastole, however, early ventricular relaxation returns the mitral valve annulus (MA) back to its original position in a motion that is predominantly cephalad. This annular displacement, its velocities and timings in relation to blood flow are altered in disease conditions and also by the normal ageing process. Imaging the MA, therefore, provides an approach by which non-invasive techniques can be used to evaluate both regional and global left ventricular (LV) function.

2.2. Anatomy of the long axis

The relationships between the MA, the ventricular apex, ventricular myocardium, subendocardial fibres and the left atrial (LA) muscles constitute the major components of the functional anatomy of the LV long axis. By definition, long axis is measured as the distance between the MA and the apex of the left ventricle. The MA is elliptical or nearly elliptical in shape [8], and from gross dissection it is not a clearly defined structure because most of its circumference is continuous with only the most superficial muscle fibres of the left ventricle [9]. The MA separates and gives attachment to the muscles of the left atrium and left ventricle and to the mitral valve leaflets. It is not a rigid circumferential fibrous ring but is pliable and incomplete anteriorly [10], and has been shown to change in size and shape during the cardiac cycle [11]. The annulus includes two main collagenous structures, the right and left trigones. The right fibrous trigone, or central fibrous body, lies in the midline of the heart and represents the confluence of fibrous tissue from the mitral valve, tricuspid valve, membranous septum and posterior aspect of the root of the aorta. The left fibrous trigone is composed of fibrous tissue at the confluence of the left margin of the aortic and the mitral valves.

Ventricular myocardial fibre architecture is complex and has been a subject of investigation by anatomists for many centuries; all proposing different morphological patterns [9, 12]. One thing in common, however, was the early recognition that the LV wall was composed of different muscle layers oriented at different angles to each other. More recent anatomical studies have clearly shown that the human left ventricle comprises three major myocardial layers: longitudinal (subendocardial), circumferential (middle) and oblique (superficial) [9]. Each one of these layers serves a specific and unique function. Based on anatomical fibre alignment, subendocardial fibres control ventricular long axis function [9, 13]. These fibres arise from the apex and course in three different directions: towards the origin of the papillary muscles, towards the lower edge of the membranous portion of the interventricular septum and towards the fibrous AV rings. The papillary muscles run longitudinally into the left ventricle from the apex and free wall into the mitral leaflets and annulus. The vast majority of the subendocardial fibres, directly or indirectly, insert into one or the other of the two trigones [13]. The subendocardial layer is continuous with subepicardial fibres at the apex [9]. It is also worth noting that the ventricular specialised conduction system runs within the subendocardial layer [14] at the anteroseptal part.

Circumferential fibres form the middle layer, and its greatest thickness is found at the LV base where they encircle the inlet and outlet portions. Towards the apex, the middle layer becomes gradually thinner until the apical part of the free wall, distal to the insertion of the papillary muscle, becomes formed only of superficial and subendocardial fibres [9]. Superficial fibres in general, are highly organised and vary

greatly in position in the ventricular mass. From an imaging viewpoint, circumferential fibre shortening has formed the dominant basis for the conventional analysis of LV function by echocardiography with measurement of ventricular dimensions, ejection fraction, and fractional shortening. Usually, the apex is clearly defined anatomically but the exact point used to locate the base has varied in different studies; the most convenient is the AV rings, tricuspid on the right and mitral on the left.

2.3. LV physiology and long axis function

The role of the AV ring motion in the volume changes in the ventricles and atria was pointed out almost 100 years ago [15]. As noted above, long axis motion of the AV rings reflects the function of longitudinally oriented ventricular myocardial fibres. In early systole shortening of the longitudinal fibres occurs before shortening of circumferential fibres [16-18]. As a result, the LV dimensions along the short-axis transiently increase during isovolumic contraction, and the LV cavity becomes more spherical – a conformational change, which if impaired causes loss of mechanical efficiency of the LV pump function [19]. During systole there is shortening of the longitudinal fibres and annular descent, which corresponds to pulmonary venous flow into the left atrium [20] and to systemic venous inflow down into the right atrium from the superior vena cava [21]. In diastole, lengthening of the long axis begins immediately after mitral valve opening, at which point the annulus ascends rapidly towards the atrium away from the apex. This rapid motion of the mitral annulus, is dependent on stored energy from the previous systole, and contributes significantly to LV [suction and early] filling in normal hearts. This systo-diastolic interdependence implies that impairment of systolic function may influence the extent of MA motion [22]. During the intervening diastasis period filling is very slow and no significant change of annular motion occurs, until at atrial contraction when the ring is pulled up with farther lengthening before the next cardiac cycle. This final displacement in late diastole contributes further to LV filling and is preceded by the P wave of the electrocardiogram. This sequence of events that ensures efficient emptying and filling of the human heart underpins the functional importance of the ventricular long axis. Accordingly, more recent studies [17] have supported the need for preservation of papillary muscles (longitudinal fibres) during surgical repair of the mitral valve.

2.4. Long axis and atrial mechanical function

The relationship between atrial contraction and AV ring motion is intriguing. Previously it was thought that the atria performed the reservoir and conduit functions passively throughout the cardiac cycle until at atrial contraction [23]. Functional anatomy of the atrial musculature, however, provides a better understanding of the overall atrial active performance. The pectinate muscles, which insert into the common AV ring, are a mirror image of the LV longitudinal fibres [24]. Therefore, the

respective lengthening and shortening of these atrial muscles is the main opponent to the LV long axis motion. Furthermore, left atrial distensibility in all planes is restricted by the fusion of its lateral walls and the back wall with the mediastinum. In this setting, therefore, the dominant atrial wall motion is in the longitudinal direction. This is thought to begin in early diastole with acceleration of blood flow, which implies a positive pressure gradient from the atrium to the ventricle. It has therefore been proposed that the backward motion of the MA which, occurs at the same time, cannot be a passive consequence of distension of the LV cavity by incoming blood, but must represent the effect of retraction by the atrium itself [25]. In late diastole, however, the dominant mechanism by which atrial volume falls in (atrial) systole is by motion of the AV rings away from the ventricular apex [25], with the addition of backward motion of the aorta contributing to the left atrium. AV ring motion therefore appears to be the earliest mechanical consequence of atrial contraction that can be detected non-invasively. Unlike transmitral Doppler, AV valve motion, or pressure measurements, ring motion reflects local function more precisely [26]. This final motion is related to the P wave of the ECG and has been used to study atrial electromechanical function in health and disease [27, 28].

2.5. Long axis function in normal ageing

Because a significant proportion of the population is and will be elderly and the morbidity and mortality of cardiovascular disease is so profound in this population, it is important to understand the current concepts of ageing physiology. As part of the ventricle, long axis function is known to be affected by age [29-31], which partly explains some of the ventricular filling patterns seen in the elderly. The normal mean MA total amplitude of motion in healthy adults ranges from 14 to 15 mm [32, 33]. These values may be higher in younger subjects and have been reported to decline from 15 mm at 20–40 years to about 10 mm at 61–80 years [33]. It is therefore important to determine ageing changes of long axis function before considering any abnormality as significant, especially in the elderly.

In general, age slows down myocyte's contraction and relaxation velocities [34] and the cell itself tends to hypertrophy [35]. The sum of these individual cellular changes in a myocardial segment could be demonstrated in the form of slow shortening and lengthening rates [30, 36]. Previous studies have already shown that in healthy individuals significant fibrosis occurs only in the longitudinal fibres of the endocardial and epicardial portions of the LV wall with increasing age [37]. Consequently, selective imaging of myocardial fibres by echocardiography, particularly DTI has clearly shown a decline in peak longitudinal muscle contraction velocities with ageing, while the circumferential fibre peak velocities remain essentially unchanged [38]. In spite of these changes, several studies have shown that indices of global LV systolic function such as LV ejection fraction (LVEF) determined by ventriculography, percent

LV fractional shortening determined by M-mode echocardiography [39] and myocardial velocity gradients determined by DTI [40] are not affected by ageing in healthy individuals. A few studies, however, showed a slight decline in cardiac output and LV myocardial systolic function with age [41, 42]. Overall, maintained indices of LV systolic function with ageing emphasizes the predominant role of circumferential fibres in the traditional assessment of ventricular function.

2.6. Long axis function and in CAD

Anatomical location of a substantial proportion of the longitudinal fibres in the subendocardial region of the heart makes them amenable to ischaemia. It is therefore not surprising that necropsy studies in patients with CAD have shown that subendocardial fibres are more susceptible to diffuse ischaemic damage [43]. Thus, subendocardial dysfunction is likely to selectively affect the longitudinally directed fibres and manifest itself as abnormal long axis shortening. Indeed several studies have already shown variable degrees of wall motion abnormalities in patients with CAD. For instance, in chronic stable CAD, asynchronous LV long axis function is common and is segmental in distribution [44, 45]. In the affected areas, onset of contraction is delayed and may be replaced by abnormal lengthening during isovolumic contraction and early ejection. In spite of these, peak-shortening velocity is usually maintained but shortening continues after A_2 (closure of aortic valve), so that the onset of lengthening may be delayed until the onset of atrial systole [44]; a phenomenon described as ‘incoordination’ or ‘post-ejection shortening’. The overall effect of this asynchrony is to reduce or even suppress the early diastolic E wave of the transmitral Doppler, and to increase the amplitude of the A-wave – an abnormality commonly referred to as ‘abnormal relaxation pattern’ [46]. Asynchrony of this type has been described as the most common cause of peak E wave velocity below age-related normal value [26], and may be related directly to coronary stenosis. Interestingly, asynchrony occurs in the absence of symptoms or ECG changes, and thus provides the most sensitive non-invasive evidence for ischaemic dysfunction [26]. Coronary angioplasty, however, resolves this wall asynchrony within 48 hours [47], although transient aggravation has been observed during balloon inflation [48].

After myocardial infarction, regional reduction in the extent and velocity of long axis shortening is common. In non-Q wave myocardial infarction long axis amplitude of motion is maintained, whereas in Q-wave infarctions there is reduction in amplitude consistent with significant segmental loss of myocardial function along the longitudinal component [49]. Thus, anterior Q-waves correlate with septal involvement, and inferior Q waves correlate with posterior infarction with or without a right ventricular component. Furthermore, these disturbances have been shown to correlate closely with the presence of a fixed defect on myocardial perfusion scanning [50]. In other studies, however, mean MA (long axis) total amplitude has clearly been

shown to be an independent strong predictor of mortality in patients with stable CAD [51]. Again all these evidence underscore the fact that long axis reflects the functional status of subendocardial fibres, and is likely to be reduced even in mild CAD prior to any measurable reduction in LVEF.

With permanent myocyte loss following myocardial infarctions and scar formation, in some patients the left ventricle undergoes remodelling characterised by regional myocyte hypertrophy and change in LV cavity size [52]. Increased LV cavity size as seen in dilated cardiomyopathy with or without heart failure, long axis function is always reduced. Characteristically when the overall LV MA (long axis) amplitude is low, peak shortening and lengthening rates are reduced, and global ejection fraction is reduced or may be absent [20]. These findings are consistent in severe LV dysfunction, and coupled with a well-established correlation between MA (long axis) amplitude of motion and ejection fraction [33, 53, 54] provides a basis for the use of MA motion as a prognostic marker in patients with heart failure. Indeed, it has already been demonstrated in a single non-randomised study that MA (long axis) mean total amplitude <10 mm is associated with a mortality of approximately 25% at one year follow-up [55] in patients with chronic heart failure.

3. Current echocardiographic assessment of ventricular function

3.1. General overview and historical perspective

Non-invasive assessment of ventricular function by echocardiography has truly been a story of remarkable success. In 1954, Edler and Hertz [56] of Sweden were the first to record movements of cardiac structures, in particular, the mitral valve with ultrasound. A decade after that novel achievement, echocardiography became established as a diagnostic technique [57], which has so far undergone enormous advances. Presently the available tools are not only able to quantify LV function, but also have the ability to characterise the myocardium. Therefore, any future innovations in these diagnostic techniques that will allow simultaneous imaging of the changes in the LV wall motion especially the timing, synchrony and coordination of different myocardial layers will undoubtedly be of wider application in research and clinical practice. Recent advances in echocardiography, however, provide a greater window of opportunity to examine all these areas of altered ventricular function. Notably, the diagnostic ability of M-mode, 2-D, Doppler and DTI combined with electrocardiogram and phonocardiogram provide a multifaceted and seamless tool for studying normal and abnormal ventricular physiology, particularly the timings, amplitudes and velocities.

3.2. Assessment of long axis by echocardiography

Because the quantification of LV systolic and diastolic function has been shown to be a reliable indicator of mortality [58, 59], assessment of LV dysfunction is the most frequent indication for echocardiographic request in clinical practice. Nevertheless, ejection fraction and parameters of diastolic assessment are dependent on loading conditions and may therefore provide inaccurate results. Furthermore, fractional shortening and Teichholz techniques are not reliable when ventricular contraction is asymmetrical [60, 61]. On the other hand, cross-sectional echocardiography that tolerates ventricular asymmetry requires good image quality for adequate tracing of endocardial borders, which is not always obtainable. Thus, there has been a concerted research effort to define other more reliable measures of systolic and diastolic function based on mitral annular motion.

The potential clinical use of the motion of the MA studied by ultrasound for the assessment of ventricular performance was first suggested by Zaky *et al* [62]. Thereafter several studies have used the mitral annular motion ultrasound measurements combined with ventricular dimensions for estimating LV stroke volume [63-65]. Although traditionally, the LV pump function has been attributed mainly to the circumferentially oriented fibres [18], the contribution of longitudinal fibres to LV ejection is well described [6, 17, 32, 64, 66, 67]. Anatomically, the distance between the apex of the heart and the chest wall is constant during the cardiac cycle [6, 17, 67]. Therefore, the AV ring displacement measured from the surface of the thorax, using two-dimensionally guided M-mode echocardiography, equals intraventricular displacement [66]. Thus, AV plane displacement reflects global LV function despite LV asymmetry, since it is determined in four different regions of the LV – the lateral, septal, posterior and anterior regions – which, evaluates the total shortening along the LV long axis in the respective regions. In addition, measurements obtained by this method have a significant correlation with LVEF obtained by cross-sectional echocardiography using area-length method, LV wall motion index, radionuclide ventriculography, and contrast cineangiography [31, 68-70]. More importantly, the mitral annulus is highly echogenic and therefore the procedure does not depend on high quality images and can be performed rapidly.

4. Cardiac cycle time intervals

4.1. Historic background

The precision with which the heart performs its pump function, provides another basis for analysing cardiac performance, and has attracted interest amongst cardiovascular physiologists for a long time. As early as more than 100 years ago, Marrey, Garrod and others were able to record the arterial pulse [71]. Wiggers [72] in 1921defined the phases of systole. Subsequently, cardiac cycle time intervals were measured non-invasively using sphygmography (peripheral recording of arterial pulses), phonocardiography, carotid pulse recording, apexcardiography, and echocardiography. In the 1960s there was extensive work to describe systolic function based on cardiac time intervals, particularly isovolumic contraction time (IVCT) and pre-ejection period (PEP). Moreover, LV ejection time (LVET) was used as a measure of LV stroke volume. Hopes of finding a non-invasive index based on these timings faded upon the realization that these variables were not only influenced by many haemodynamic and electrical variables but also myocardial dysfunction prolonged PEP and shortened LVET. Weisller *et al* [73] derived an index (PEP/LVET) called "systolic time interval", which was less heart rate dependent as a measure of LV systolic function. However, the variability of this index as a measure of LV systolic dysfunction was significant and a lengthening of the systolic time interval was found to occur after LV function deteriorated. Because isovolumic relaxation time (IVRT) is also affected by LV function, Mancini *et al* [74] incorporated IVRT into an index called " isovolumic index" derived as (IVCT + IVRT)/LVET. The sum of IVRT and IVCT was measured by subtracting the LVET from the peak of R wave on the ECG to the onset of mitral valve opening. The isovolumic index was considered more sensitive for cardiac dysfunction than the systolic time interval because it contains IVCT as well as IVRT. However, the interval from R wave peak to onset of mitral valve opening contains an interval of electromechanical delay, which can be pronounced in patients with LBBB [75]. With a series of disappointing work on cardiac cycle time intervals, there was a hiatus of several years until the advent of Doppler echocardiography.

As noninvasive imaging and Doppler technology has improved, measuring cardiac time intervals has become easier, more precise and reliable. Tei *et al* [76] proposed a " myocardial performance index" (or Tei Index) that is independent of electromechanical delay, (IVCT + IVRT)/LVET, using Doppler echocardiography to identify the exact onset of isovolumic contraction. The Tei index has been shown to have prognostic value for various cardiac conditions [77, 78]. More recently Zhou *et al* [79] have described the Z-ratio, which is taken as the sum of LVET and total filling time (TFT) divided by the RR interval [(LVET + TFT/RR], expressed as a percentage. It represents the fraction of the total cardiac cycle when blood is either entering or

leaving the left ventricle, and has the potential to separate effects of abnormal ventricular activation (LBBB) from those of ventricular disease.

4.2. Timing of mitral annulus in relation to blood flow

Since the cardiac base motion plays an important role in the filling and emptying of the heart, attempts have been made to define the timing relationship between, MA motion and blood flow [80-82]. These relationships were previously recorded by M-mode echocardiography [17, 20] and later reproduced by DTI [81, 82], in small groups of patients. It has already been shown that during the IVCT, long axis contraction precedes that of the minor axis by approximately 20 msec [17]. At the LV base, Pai *et al* [83] described characteristic features of amplitudes, durations and timings of myocardial velocities in the long axis direction in 20 normal healthy volunteers aged 25–72 years. The onsets of systolic waves (S_m) were simultaneous, and measured 62 msec from the electrocardiographic q, which is shorter than the electromechanical delay of 90 msec reported in other studies [20, 75]; their durations and timings in the cardiac cycle were similar in all four walls (lateral, anterior, posterior and septum). However, the onsets of early (E_m) and late (A_m) myocardial relaxation were variable at the different ventricular sites, reflecting regional heterogeneity of LV wall motion which has also been described in healthy subjects by digitised cineangiograms [84], MRI studies [85, 86] and DTI [87]. Similar functional heterogeneity has also been demonstrated in the longitudinal contraction and relaxation velocities, which are greatest in the basal segments and decrease progressively towards the apex, where in fact velocities, may be reversed [88]. In another small study of 12 normal subjects aged 26–49 years, Keren *et al* [20] demonstrated that the onset of mitral flow coincided with the onset of MA relaxation, an observation that was later reproduced by DTI studies [80-82]. Although these two events begin simultaneously, peak annular relaxation velocity has been shown to precede peak mitral flow velocity by 20 msec in adults studied by DTI [82], and by 50 msec in children studied by digitised M-mode [89]. These phase differences between LV wall motion and transmitral flow in humans provides evidence for involvement of ventricular restoring forces, and hence suction in normal rapid filling.

Late diastolic time intervals, particularly at the left MA base, have been described and show consistency despite the use of different echocardiographic methods [20, 80, 83]. The onset of transmitral A wave, however, was found to be simultaneous with the onset of atrial contraction in one study [80], but delayed by approximately 30–40 msec [83] and by 20 msec [27] in others. Atrial electromechanical delay (the time from the onset of P wave on ECG to onset of atrial contraction) is approximately 90 msec at the same site [27]. Peak inter-atrial septum contraction velocity has been shown to coincide with pulmonary venous flow reversal peak velocity [90]. On the other hand, overall pulmonary flow starts only when the mitral valve cusps separate and occurs in

spite of motion of the annulus in the reverse direction [20]. In patients with dilated cardiomyopathy, loss of atrial contraction and hence of immobilisation of the MA due to reduced ventricular systolic function reduces pulmonary systolic flow into the left atrium. It has been suggested that reduction in mitral annular motion may itself reduce or even abolish the systolic component of pulmonary venous flow [20]. Evidently knowledge of the mitral annular motion is likely to be essential in interpreting clinical disturbances of pulmonary venous flow. However, in all these studies, the effects of ageing on the timing of diastolic events have not been described, although there is sufficient evidence that diastolic time intervals can be measured in patients and normal subjects at rest, and have a practical application.

4.3. MA motion velocities and timings: current clinical applications

Measurements of the durations, velocities and timings of transmitral and pulmonary venous flow patterns are an indirect measure of the integrity of the MA. The mitral annular velocity profile in diastole reflects the rate of changes in the long axis dimension and LV volume, since filling of the heart is partly dependent of the ventricular long axis function. Transmitral and pulmonary flow waveforms are influenced by filling pressures in disease and in ageing, thus respective waveform durations, velocities and timings are gaining increasing application as noninvasive indices for the estimation of filling pressures [91, 92]. For instance, the deceleration time of the early diastolic mitral inflow velocity (E) has been well correlated with pulmonary capillary wedge pressure (PCWP) [93]. In another study, Rossvoll and Hatle [94] almost ten years ago demonstrated that the duration of pulmonary venous reversal flow (Ar) exceeding that of mitral A-wave predicted LV end-diastolic pressure >15 mmHg with a sensitivity of 0.85 and specificity of 0.79. More significantly the difference between Ar and A-wave durations was shown to be age independent [94, 95]. Subsequently other studies showed that increased Ar to A velocity ratio was a useful marker for detecting elevated PCWP [96]. Widespread application of these measurements has been hampered by the load dependency of diastolic flow parameters [97, 98] as well as the inherent pitfalls in transthoracic echocardiography especially in the imaging of pulmonary flow reversal [99].

With the advent of newer echocardiographic techniques, particularly DTI, that can record velocities of myocardial tissues more precisely, recent studies have focused on the validation of mitral annular velocities in the determination of cardiac filling pressures [100, 101]. An important observation made with tissue velocity recorded by DTI was that the early diastolic velocity of the mitral annulus (E_m) is relatively independent of preload [101, 102] and closely related to the rate of myocardial relaxation as determined by tau [101]. Thus, the ratio of $E/E_m < 8$ accurately predicts normal mean PCWP, and if >15, reliably estimates PCWP at 20 mmHg or higher [46, 103]. More recently in an animal model, Rivas-Gotz *et al* [104] have clearly shown

that when LV myocardial relaxation is normal, E begins with LV diastolic suction induced by rapid relaxation resulting in simultaneous onset of E and E_m. However, if myocardial relaxation is impaired, early diastolic filling is initiated by LA pressure at the time of mitral valve opening, and E_m velocity starts later as a result of delayed myocardial relaxation. Thus demonstrating that the timing of E is regulated by LV filling pressure whereas that of E_m by myocardial relaxation. The difference between the timing of E_m and E, therefore, was found to correlate well with tau, and a ratio of IVRT to that time difference <2 predicted PCWP of >15 mmHg.

5. Aims

This thesis investigates the physiological significance and diagnostic utility of some aspects of ventricular long axis amplitude of motion and its timing in the cardiac cycle. The specific objectives of the studies are:

- To describe the relationship between the timing of mitral annular motion and left ventricular filling in early and late diastole, and to examine the effects of normal aging on these time intervals.

- To investigate the clinical significance of the relationship between the timing of left atrial contraction and ventricular filling in late diastole.

- To determine the relationship between pulmonary venous flow reversal (Ar) and left atrial mechanical function, and to define surrogate measurements for Ar with a view to improving the diagnostic ability of transthoracic echocardiography.

- To assess the clinical outcome of successful percutaneous transluminal coronary angioplasty (PTCA) in patients with poor left ventricular (LV) function.

- To determine the relationship between LV long axis function and clinical recovery after PTCA in patients with severe LV dysfunction.

6. Methods

6.1. Study populations

6.1.1. Umeå General population Heart Study

Study subjects for Studies I and II were selected from participants in the Umeå General Population Heart Study (UGPHS), which is a cross-sectional study designed to investigate cardiovascular effects of normal ageing in both men and women. UGPHS participants were drawn from a Population Register using a unique personal identification system. Every permanent resident in Sweden has a national registration number that includes the date of birth. These numbers are registered and controlled by the Census Bureau (Swedish Tax Authority) in a Population Register, which includes vital statistics, and which by law must be kept up to date. Besides the date of birth, the registration number contains information about gender.

After Umeå University Ethics Committee approved the study protocol, one thousand subjects living in the Umeå area, and equally distributed by gender, were randomly selected from the Register based on their dates of birth. A total of 15 age categories covering a wide age range (20–90 years) were drawn at a five-year interval sequence (1905, 1910, 1915 up 1975). Summary information about the project and invitations to participate were sent to those selected. Willing volunteers were then sent a specially designed questionnaire to assess their general state of health before enrolment. At that stage, subjects with confirmed diabetes, hypertension, hyperlipidaemia, history of rheumatic fever, transient ischaemic attacks, stroke and intermittent claudication were excluded. Those on any cardioactive medications were also excluded. Three hundred subjects (ten from each group with equal sex distribution) were selected (Fig. 1) and invited to undergo a series of investigations to exclude any silent cardiopulmonary disease.

Informed consent was obtained from each subject before thorough physical examination (including blood pressure) and a 12-lead electrocardiogram (ECG) were performed. A complete echocardiographic examination was also performed at the same sitting or on the same hospital visit. Basic lung function tests were carried out and blood samples taken for neurohormonal studies.

6.1.2. Normal subjects (Studies I and II)

All echo, ECG and clinical data from the 300 subjects were inspected and subjects with significant valvular heart disease, ECG abnormalities, and elevated blood pressure were excluded from subsequent measurements and analysis. Only subjects with complete echocardiographic studies with clear analysable pulmonary venous flow profiles on Doppler echocardiography, and accompanying clear P waves on superimposed ECG were studied.

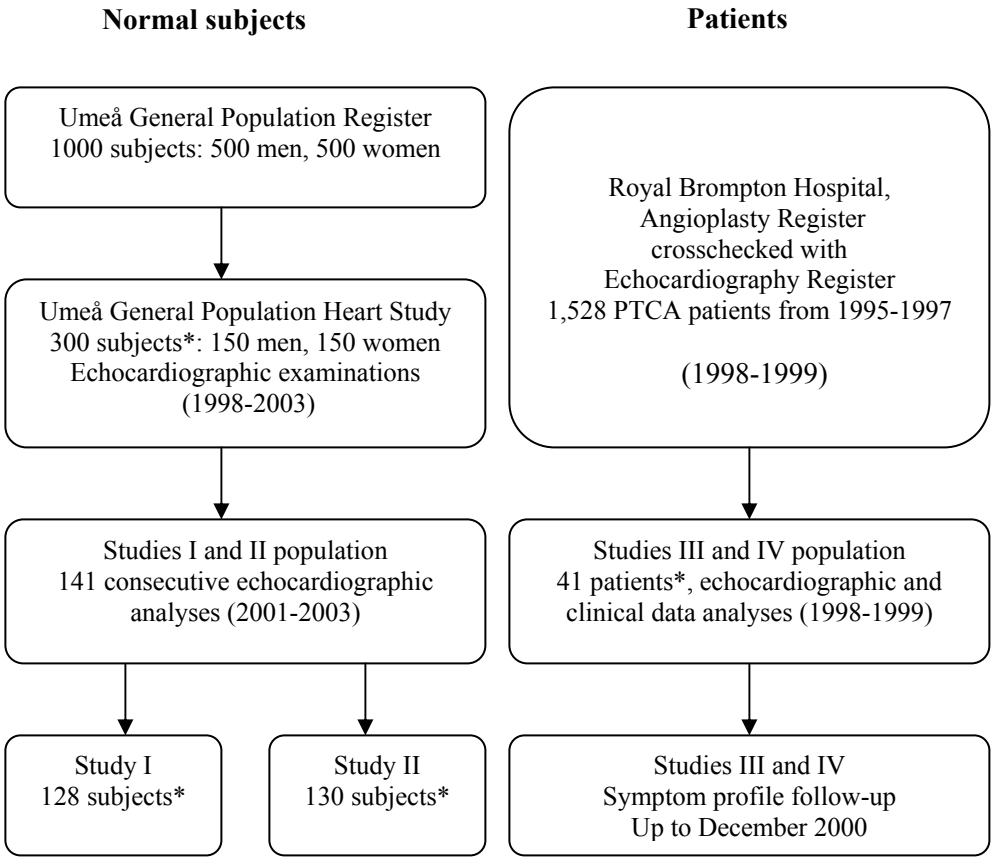

Figure 1 Selection of the study populations (Studies I-IV). Inclusion* criteria as explained in the text.

At the time of writing Studies I and II only 141 consecutive studies, out of the 300, had been performed by the author. Thus, from that number 130 (Study I) and 128 (Study II) participants (mean age 54 ± 18 years, range 25 to 88 years, 62 women) who met the inclusion criteria were selected. They were arbitrarily classified into three groups: Y (young), M (middle age) and E (elderly). For Study I Group Y (25–44 years) consisted of 44 subjects; Group M (45–64 years) and Group E (≥65 years) each consisted of 43 subjects. Study II had only one subject less in groups M and E.

6.1.3. Patients (Studies III and IV)

Forty-one patients, age 63 ± 10 years, 36 men, with CAD and poor LV function who fulfilled the inclusion criteria were studied and followed up. They were among the 1,528 adult patients who underwent PTCA at the Royal Brompton Hospital (London, UK) within a period of three years, from January 1995 to December 1997. From the date of the procedure each study patient was followed-up for 36 months, ending in December 2000 (Fig. 1).

To select the study group, all patient data for the three year period was obtained from the Angioplasty Register in the Cardiac Catheterisation Laboratory. This data was cross-checked with the Echocardiography Register to confirm whether the patients had undergone a complete echo study before and after the procedure. All patients with significant impairment of LV systolic function by echocardiography, Fractional Shortening (FS) of ≤20% or Ejection Fraction (EF) of ≤35% were selected. A complete echocardiographic follow-up study within 30 days prior to PTCA and at 3-6 months and 12 months afterwards was a mandatory inclusion criterion. Patients with previous revascularisation procedures, CABG (coronary artery bypass graft) surgery and PTCA, were also included. However, none of the patients with previous revascularisation had CABG surgery 36 months prior to PTCA. Patients who had suffered an acute myocardial infarction (AMI) a week before the echo study, or were in cardiogenic shock or had prosthetic valves or valvular heart disease were also excluded. After PTCA, patients who suffered major cardiac events (AMI, additional PTCA procedures, CABG surgery, cardiac transplant) or death were excluded from subsequent echocardiographic and symptom profile data analysis. Baseline data from patients were compared with those from 21 controls with a mean age of 51 ± 11 years, 14 male, none of whom had a history of cardiac disease, hypertension, or diabetes mellitus. All patients and controls were in sinus rhythm.

6.2. Echocardiography procedures and data

6.2.1. General procedure (all studies)

A complete M-mode, two-dimensional and Doppler examination was performed in each subject while lying in a left lateral decubitus position. Commercially available ultrasound systems (Acuson Sequoia, Mountain View Calf. USA) equipped with multi-frequency (2-3.5 MHz) imaging transducer (Studies 1 and II) and a HP Sonos 2500 (Andover, MA, USA) with 2.5 MHz imaging transducer (Studies III and IV) were used. All studies were performed according to the recommendations of the American Society of Echocardiography using conventional views and measurements [105]. To minimise cardiac movement resulting from respiration, all echocardiographic data were obtained at end-expiration. M-mode (Figs. 2 and 3) and Doppler images (Figs. 4 and 5) were all recorded with simultaneous lead II of the ECG and phonocardiogram

(PCG) at sweep speeds of 50 and 100 mm/sec (Studies 1 and II) and at only 100 mm/sec (Studies III and IV). The data (Studies I and II) were recorded on Magneto Optical Disks (Maxell Corp., New Jersey, USA) and later analysed off-line using the same ultrasound machine, while M-mode and Doppler traces (Studies III and IV) were all recorded on a strip chart recorder and analysed manually.

6.2.2. M-mode studies (all studies)

Standard M-mode echocardiograms of left ventricular minor axis were recorded at the tips of mitral valve leaflets. In addition, M-mode echocardiograms of the ventricular long axis were obtained with the cursor longitudinally placed through the left, central fibrous body (septal) and the right sites of the atrioventricular ring (Fig. 2). Anterior and posterior AV ring imaging was also performed for Studies I and II. Images recorded on strip charts (Studies III and IV) were digitised as described below using the method described by Gibson and Brown [106]

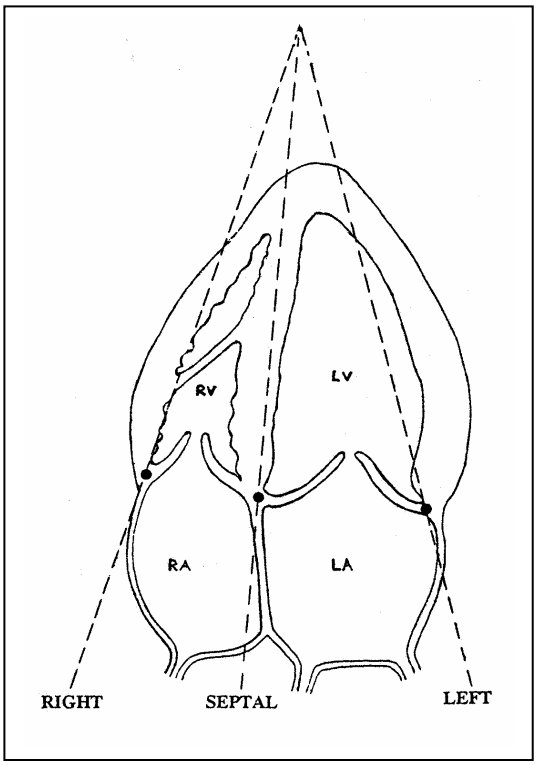

Figure 2 Diagram of apical four chamber cross sectional view showing the M-mode cursor positioned through the lateral tricuspid ring, the central fibrous body, and the lateral mitral ring.

6.2.3. Doppler studies (all studies)

Transmitral and transaortic flow velocities were recorded using pulsed-wave Doppler technique from the apical four and five chamber views with the sample volume placed at the tips of each respective valve. Doppler pulmonary venous flow (PVF) was obtained from the same view with the sample volume placed in the right superior pulmonary vein proximal to the LA.

6.2.4. Doppler tissue imaging (Studies I and II)

In Studies I and II, myocardial DTI was performed with the sample volume placed at the endocardial border of the base of the LV lateral wall from the apical four-chamber view. The wall motion velocity pattern was recorded and expressed as: systolic wave (S_m), early diastolic wave (E_m) and late diastolic wave (A_m) (Fig 4, lower panel).

6.3. Coronary angioplasty procedure and data (Studies III and IV)

Coronary angioplasty was the preferred therapeutic option in these patients, and was performed for standard indications using conventional techniques. The procedure was attempted on all major coronary arteries that had >70 percent diameter narrowing with favourable anatomy. Similarly, significant stenoses affecting vein and arterial grafts were also dilated. Major arteries were defined as the left anterior descending and its large diagonal branches, the circumflex and its large obtuse marginal branches and the right coronary system. In most cases attempts were made to achieve complete revascularisation including chronic occlusions with favourable characteristics. When haemodynamic conditions were unstable, an intra-aortic balloon pump (IABP) was inserted at the beginning or during the procedure. Surgical back up was available for all the patients.

Coronary stents were used electively and also following abrupt or threatened vessel closure. In the catheterisation laboratory all patients were given 10,000 units of Heparin at the beginning of the procedure with an additional dose of 5,000 units if the procedure was prolonged for more than one hour. All patients who received intra-coronary stents were commenced on Ticlopidine 250 mg twice daily for 3 weeks. Prior to January 1997, patients were anticoagulated with Warfarin. Patients were also given Aspirin 75 mg daily to continue indefinitely.

6.4. Electrocardiography: measurements (Studies I and II)

The onset of the P wave on the ECG was first derived by manually measuring the PR interval on the standard 12 lead ECG, using an Electronic Digimetric Calliper (Mitutoga). To maintain the same PR interval in all the measurements performed on every subject, individual measurements were made in reference to R wave of the ECG, which is a more reproducible landmark. Hence, the distance from the peak of R wave

to the onset of the preceding P wave (PR′ on Fig. 5, middle panel) was determined and used throughout all measurements for each individual subject. This ensured a universal onset point of the P wave on every set of images studied thus eliminating possible errors associated with determination of the nadir point of the P waves. At least measurements were obtained from different cardiac cycles and a mean calculated.

6.5. Echocardiography: measurements and calculations

All measurements and calculations were carried out by the author, unless where specified. An average of at least three measurements from different cardiac cycles were taken for every measurement.

6.5.1. General measurements (all studies)

1. From standard transverse M-mode echocardiograms LV and LA dimensions were measured. LV minor-axis dimensions were measured using the leading edge methodology. End-diastolic dimension (EDD) was determined at the onset of the q wave of the ECG, and end-systolic dimension (ESD) at A_2 (aortic component of the second heart sound) (Fig. 3). LV FS was calculated using the equation: FS = (EDD – ESD)/EDD and expressed as a percentage.
2. From transmitral Doppler recordings, peak early 'E' and late 'A' wave flow velocities were measured and E/A ratio calculated (Figs. 4 and 5, upper panels)
3. The time interval from A_2 to the onset and peak of 'E' was also measured as well as total LV total filling time (TFT), from the onset of E-wave to end of A-wave (Fig. 4, upper panel).
4. RR intervals and heart rate (HR) were measured from every image examined and a mean value obtained.

6.5.2. Doppler transmitral and pulmonary venous flow

1. Time duration from peak R on the ECG to peak E-wave (R-E) (Fig. 4)
2. Isovolumic relaxation time (IVRT) as the time interval from A_2 (aortic component of the second heart sound) on the PCG to the onset of transmitral E-wave (Fig. 4).
3. The time interval from the onset of P wave on the ECG to onset and then to the peak of:
   - A-wave of the TMF (P-A and P-pA, respectively) (Fig. 5).
   - Ar-wave on the PVF (P-Ar and P-pAr, respectively)
4. Duration, acceleration, deceleration times of A-wave and Ar.
5. Peak A-wave and Ar velocities and their respective velocity-time integrals.
6. PVF systolic (S) and diastolic (D), velocities, time-integrals and systolic fraction were derived (Fig. 5, lower panel).

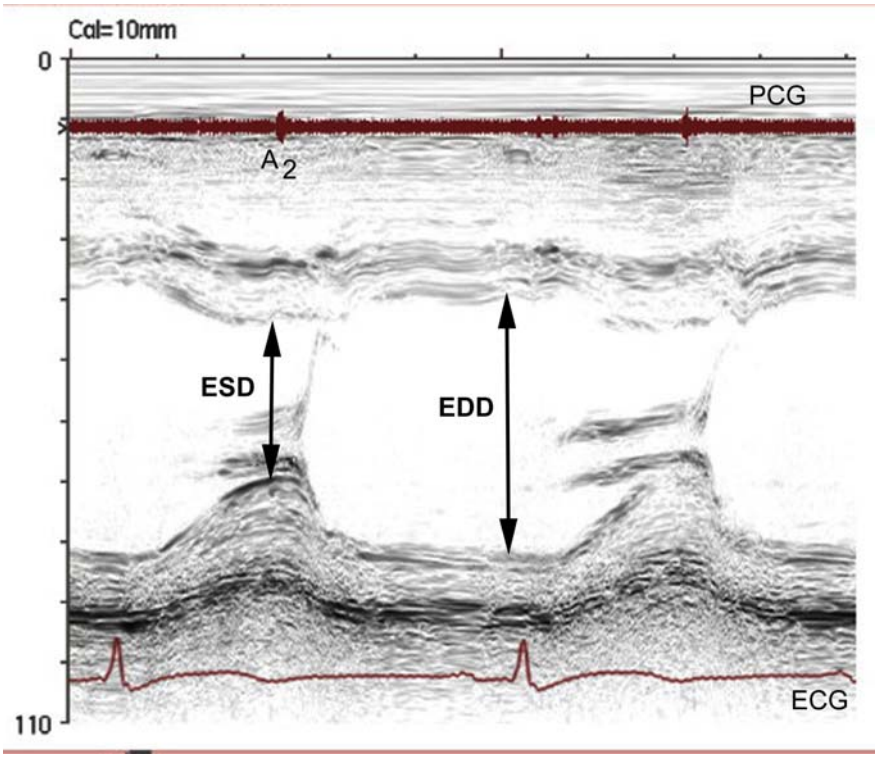

Figure 3 M-mode echocardiogram of left ventricular short axis. Calibration scale: 10 mm vertical (distance), and 200 msec horizontal (time). A_2, aortic component of the second heart sound; EDD, End-diastolic dimension, and ESD, End-systolic dimension.

6.5.3. Doppler transmitral and aortic flow (Studies III and IV)

1. From the aortic flow trace, LV ejection time was measured from the onset of ejection to the end of the velocity decline at the point hitting the baseline.
2. Total isovolumic time was measured as the R-R interval minus the sum of total filling and ejection times.
3. Thus, myocardial performance index (MPI) was derived as the ratio of total isovolumic time divided by the ejection time.
4. Cardiac output was calculated from the measured aortic stroke distance, aortic valve area and heart rate. Stroke distance was calculated as the time integral of aortic velocity, and stroke volume as the product of stroke distance and subaortic area, derived from aortic root diameter.

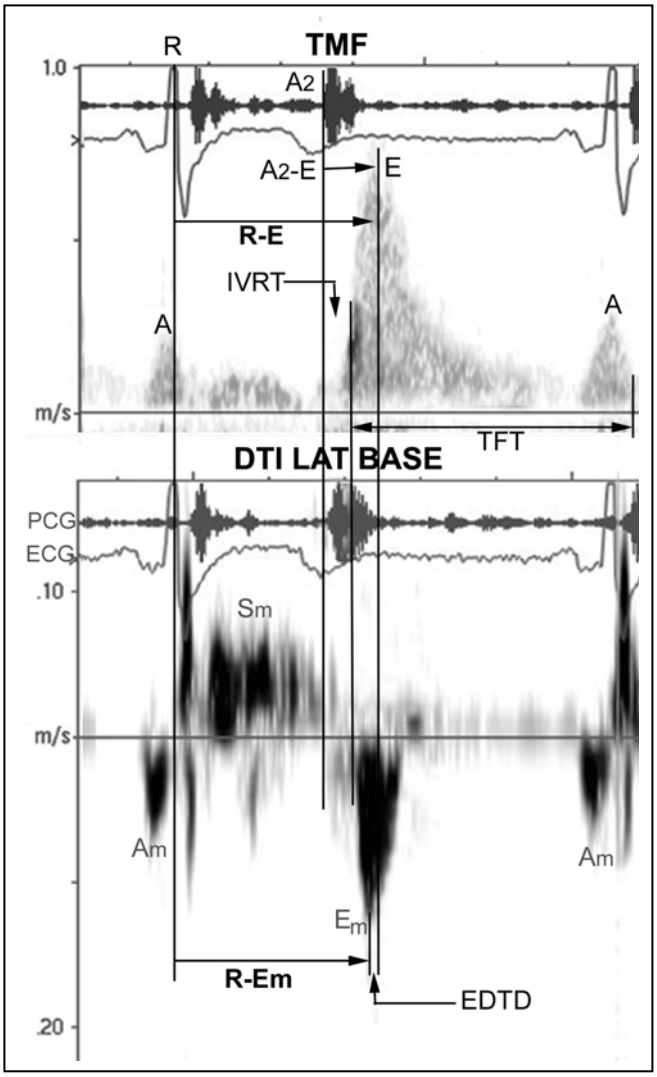

Figure 4 Vertical lines show specific landmarks for time measurements in the cardiac cycle. Early diastolic timing differences between peak early mitral flow (E) and peak mitral annular velocity (E_m) in a 28-year-old healthy subject. E and E_m began simultaneously but E_m preceded E, defining early diastolic temporal discordance (EDTD). TMF, transmitral flow; TFT, mitral total filling time; IVRT, isovolumic relaxation time; A_2, aortic component of the second heart sound; DTI LAT BASE, Doppler tissue imaging of the lateral annular base; and S_m, E_m, A_m, E, A, PCG, ECG as in the text.

6.5.4. Doppler tissue imaging (Studies I and II)

1. Duration from peak R on the ECG to peak E_m (R- E_m) was measured. Thus, early diastolic temporal discordance (EDTD) was computed as the difference between (R-E) and (R-E_m) (Fig. 4, upper panel).
2. The time interval from the onset of P wave on the ECG to the onset and the peak of A_m (P-A_m and P-pA_m, respectively) (Fig. 5).
3. Duration, acceleration, deceleration times, and peak velocity of A_m.
4. Late diastolic temporal discordance (LDTD) was calculated as the difference between (P-pA) and (P-pA_m) (Fig. 5)
5. Peak E_m velocity was measured and the E_m to A_m ratio calculated.

6.5.5. Two-dimensional apical 2 and 4 chamber (Studies I and II)

1. LV end-diastolic and end-systolic volumes were determined using modified Simpson's formula and the LV ejection fraction (LVEF) was derived from these volumes.

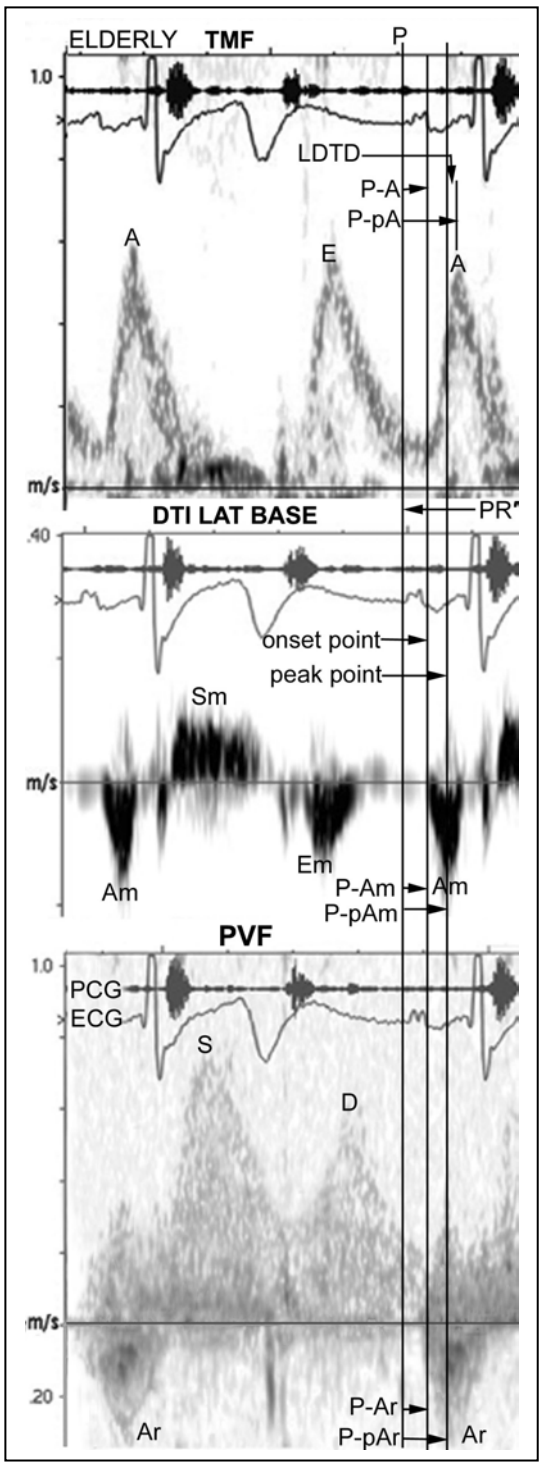

Figure 5 Vertical lines show specific landmarks for time measurements in the cardiac cycle. Late diastolic timing relationships between A_m, Ar and A-wave with respect to the onset of P wave on the ECG in a healthy elderly subject. All begin immediately after atrial contraction (**onset point**). A_m peaks at the same time as pulmonary reversal flow (Ar) (**peak point**), while A peaks later (late diastolic temporal discordance [LDTD]). PR′**,** interval from peak R on the ECG to the onset of the preceding P wave; P-A/P-Ar/P-A_m, from the onset of P wave to the onset of A-wave/Ar/A_m; P-pA/P-pAr/P-pA_m, from the onset of P wave to the peak of A-wave/Ar/A_m; and PCG, PVF, TMF, DTI, S_m, E_m, S, D, as described in the text.

6.5.6. M-mode long axis amplitudes and digitisation (III and IV)
From LV long-axis M-mode recordings both free-wall and septal traces were analysed. Long-axis total amplitude (TA) of motion was measured from the innermost point (at A_2) in systole to peak outward point (at q wave) in late diastole (Fig. 6).

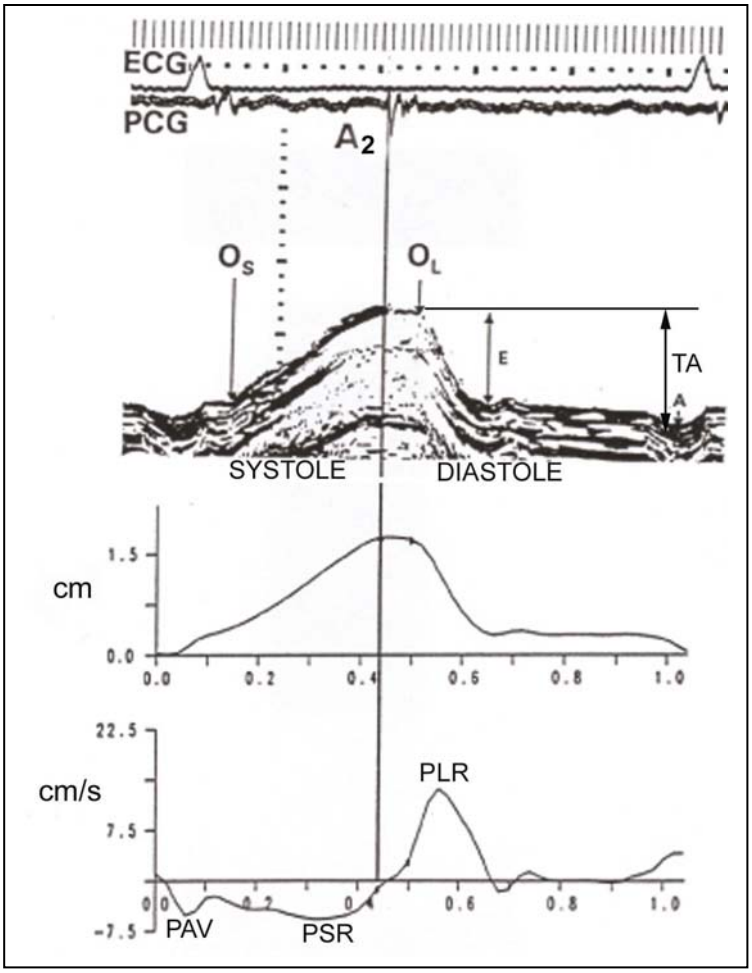

Figure 6 Digitised trace of the M-mode left lateral mitral annulus showing peak shortening rate (PSR), peak lengthening rate (PLR) and peak atrial contraction velocity (PAV). Specific landmarks of long axis (mitral annular) motion are shown: OL, onset of lengthening; OS, onset of shortening; E, early diastolic excursion (EDE); A, atrial systolic amplitude, and TA, long axis total amplitude.

Also, measured was the overall amplitude of atrioventricular ring motion (cm), early diastolic excursion (cm); from peak inward motion to the position at onset of diastasis, that during atrial systole was measured as the A-wave, occurring after the P wave in the electrocardiogram. Peak rate of early diastolic lengthening was measured from digitised traces and onset of rapid outward motion was the shoulder angling point between shortening and lengthening. Peak rates of long-axis shortening (PSR) and lengthening (PLR) were obtained from the digitised traces (Fig. 6). Briefly, the digitisation process involved three steps: (1). The echocardiogram to be digitised was positioned on the digitising table (DMAC) connected to a PC with dedicated software (2) the beat to be studied was identified and calibration corresponding to 1 cm, half a second, and the RR interval. This was performed by moving a crosswire cursor along the echoes and pressing the interrupt button at the beginning and end of each of the measurements in sequence. (3). Finally, the crosswire cursor was moved along the septum and posterior wall endocardial borders and the interrupt button pressed appropriately to allow for transition from one endocardial line to another.

Since the cursor emits low frequency radio waves, its position can be sensed by detection coils in the gantry below the digitising table, and converted into electrical signals representing the x and y coordinates with a resolution of 0.01 cm each time an interrupt button is pressed. This information together with calibration signals was stored directly onto the computer, which converted it into typical output curves (Fig. 6). These curves were then printed out and velocity measurements taken manually.

6.6. Symptom profile and follow-up (III and IV)

Patients' symptoms were documented before and after PTCA. Angina was graded according to the Canadian Cardiovascular Society (CCS) classification, and the degree of dyspnoea according the New York Heart Association (NYHA) classification. These data were obtained at: (1) end of the first week (at the time of discharge from hospital); (2) end of the first month; (3) after 6 months, and at the end of the first year. Thereafter data were collected at scheduled follow-up visits at least twice a year. At the beginning of the study, however, all patients' case notes were reviewed. At that point of the study, those who had not fulfilled complete 36 months follow-up since the date of the PTCA were prospectively followed up either through routine outpatient clinics or by a simple questionnaire administered to their General Practitioners. Clinical data obtained during this period included, cardiac events since the last PTCA (history of AMI, need for additional PTCA procedures, CABG or cardiac transplant); death (cardiac or non-cardiac); hospitalisations and any change in the medications. This study presents data only for the first 12 months. Data collection adhered to the guidelines of the local ethics committee, which approved the study protocol.

6.7. Statistical analyses

6.7.1. Calculations and analysis

Standard statistical methods were used with SPSS 11.0 for PC (SPSS, Chicago, Illinois, USA) for Studies I and II, while Statview Software package (version 4.5; Abacus Space Concepts, Berkeley California) for Studies III and IV. A probability of less than 5% was taken as significant in all the studies. All tests were two-tailed.

Studies I and II

All values are expressed as mean ± standard deviation. Comparisons between age groups were carried out by one-way analysis of variance (ANOVA) with Bonferroni post-hoc tests, and associations between variables by simple linear regression analysis. Multivariate analyses were performed with enter method to identify the factors affecting LDTD such as age, PR interval and IVRT.

Studies III and IV

All baseline characteristics are presented as frequencies and percentages for discrete variables. Echocardiographic values represent mean ± standard deviation. Controls were compared with patients before PTCA using ANOVA. Patients' data before and after PTCA were compared using paired Student *t* test for continuous variables and Wilcoxon matched-pairs rank for change in symptoms. Fisher's exact probability test was used to demonstrate the relationship between improvement in LV free-wall amplitude and change in symptoms, and Pearson's product-moment correlation coefficient was used where appropriate. Kaplan-Meier event-free survival curves (Study III) were plotted for data defined by absence of myocardial infarction, repeat revascularisation, cardiac transplant and death at follow-up starting at the baseline PTCA procedure.

6.7.2. Reproducibility

Studies I and II

Intraobserver and interobserver variabilities were tested in 22 subjects selected randomly from the three groups. Measurements, particularly timings upon which our conclusions are based, were repeated by one investigator and independently by a second at different times to determine both intra- and inter-observer variability. Results were analysed using the method of agreement as described by Bland and Altman [107] and presented as the coefficient of variation. There were no significant variations in the duplicate measurements. All measurements from DTI images and Doppler derived peak velocities had the best intra- and interobserver variability of 2% to 3%. All time intervals used to calculate early and late diastolic temporal discordance had an intraobserver and interobserver variability ranging from 1% to 3.3% and 1.1%

to 4.3%, respectively. However, the intra- and interobserver variability for the duration of Ar and A-wave were within the range of 4% to 6%.

Studies III and IV

From a total of 16 randomly selected echo studies, measurements of long axis total amplitudes at the left free wall and septum were repeated by the author on two different occasions and by one other investigator who was unaware of the initial measurements. Interobserver and intraobserver variability for left and septal long axis were 4.1% and 2.9%, and 2.6% and 2.3%, respectively; values that are consistent with data recently reported from the same laboratory [108].

7. Summary of results

7.1. Normal subjects (Studies I and II)

7.1.1. General and echocardiographic features

Studies I and II had a total of 128 and 130 participants respectively. Both study groups had similar general and echocardiographic features and gender balance was maintained with an almost equal ratio of men to women in both groups. There were no significant differences in the study participants with regard to diastolic blood pressure (BP), HR, RR interval and LV end-diastolic cavity size. LV systolic function assessed by ejection fraction was normal across all age groups. However, early abnormal relaxation pattern characterised by E to A ratio <1 was present in group E compared to Y ($p < 0.001$). In addition, the LA anteroposterior diameter was larger ($p < 0.001$) and the PR interval longer ($p < 0.001$) in the elderly compared to the young. Other important demographic, clinical, Doppler and echocardiographic data are presented in Table 1 (Study II).

7.1.2. Diastolic time intervals and the effect of age (Study I)

Early diastolic temporal discordance (EDTD)

The onset of E_m coincided with the onset of transmitral flow E (Figs. 4 and 7). However, the time interval (R-E_m) was longer in group E ($p = 0.014$) as was (R-E) ($p = 0.012$) compared to group Y. IVRT was longer in the E group with respect to the Y group ($p < 0.001$). Peak E_m preceded peak E in all age groups by approximately 26 msec. After correcting this time interval as a ratio of the RR interval expressed as a percentage, there were still no significant differences between the groups. The corrected EDTD (EDTDc) accounted for approximately 3% of the cardiac cycle (Fig. 8). Furthermore, in univariate analysis this ratio correlated poorly with factors associated with diastolic dysfunction: age ($r = 0.05$), mitral EDT ($r = –0.10$), E/A ratio ($r = –0.19$) and corrected IVRT (IVRTc) ($r = 0.13$)

Late diastolic temporal discordance (LDTD)

Unlike the temporal discordance in early diastole, the corresponding discordance in late diastole had very distinct characteristics on univariate analysis. First, it correlated inversely with age ($r = –0.35$, $p < 0.001$) and with IVRT ($r = –0.34$, $p < 0.001$). Second, peak A_m coincided with peak Ar ($r = 0.97$, $p < 0.001$) and generally preceded peak A in all age groups. Therefore, progressive prolongation of (P-pA_m) with aging diminished the time difference between the peaks of A_m and A. In this respect, LDTD decreased from 23 ± 10 msec in the young to 13 ± 10 msec in the elderly ($p < 0.001$) Moreover, 24 (18.8%) subjects [one young, 8 middle-aged and 15 elderly] had a LDTD approximating zero (≤7 msec), implying that peak A_m coincided with peak A.

At this point of coincidence, all the peaks of A, A_m and Ar would be aligned. Thus, this point of convergence is described as atrial mechanical alignment (AMA) (Fig. 7). Finally, LDTD corrected for RR interval (LDTDc) accounted for approximately 2.5% of the cardiac cycle in the young and progressively declined to approximately 1.5% in the elderly ($p < 0.001$). Conversely, IVRTc increased with age ($p < 0.001$) while EDTDc remained unchanged (p = NS) (Fig. 8).

Table 1. General and echocardiographic characteristics (mean ± SD)

	Group Y (n = 44)	**Group M (n = 42)**	**Group E (n = 42)**
General			
Age (years)	33.4 ± 5.8	54.0 ± 7.2	75.2 ± 5.5
Sex (male: female)	19:25	28:14	19:23
Systolic BP (mm Hg)	116 ±11	127 ± 13‡	142 ± 12‡
Diastolic BP (mm Hg)	73 ± 9	76 ± 10	76 ± 8
Heart rate (beats/min)	66 ± 12	66 ± 8	68 ± 11
RR interval (msec)	939 ± 175	929 ± 113	904 ± 152
PR interval (msec)	161 ± 16	174 ± 20‡	173 ± 15‡
Echocardiographic			
LA dimension (mm)	32.9 ± 3.6	36.3 ± 4.3†	37.7 ± 4.7‡
LV end-diastolic dimension (mm)	47.6 ± 5.4	48.8 ± 4.2	47.2 ± 5.0
LV end-systolic dimension (mm)	28.3 ± 4.2	28.7 ± 3.7	25.4 ± 4.2†
LV ejection fraction (%)	65.1 ± 5.6	62.8 ± 4.8	63.8 ± 5.7
E velocity (cm/sec)	71.0 ± 13.7	62.9 ± 16.6*	58.3 ± 15.0†
A velocity (cm/sec)	43.7 ± 11.9	52.6 ± 13.8†	75.4 ± 14.2‡
E/A ratio	1.74 ± 0.58	1.24 ± 0.34‡	0.79 ± 0.17‡
IVRT (msec)	56 ± 13	72 ± 11‡	83 ± 18‡
EDT (msec)	168 ± 37	192 ± 36*	228 ± 50‡
E_m velocity (cm/sec)	18.9 ± 4.1	15.3 ± 3.6‡	10.7 ± 2.3‡
A_m velocity (cm/sec)	10.8 ± 3.0	14.0 ± 3.1‡	15.5 ± 2.5‡
E_m / A_m ratio	1.87 ± 0.64	1.15 ± 0.39‡	0.70 ± 0.15‡

A, late diastolic flow; A_m, atrial contraction using Doppler tissue imaging; BP, blood pressure; EDT, mitral E-wave deceleration time; E, early diastolic flow; IVRT, isovolumic relaxation time; E_m, velocity of basal LV motion in early diastole using Doppler tissue imaging; LA, left atrial; and LV, left ventricular.

*$p < 0.05$, †$p < 0.01$ and ‡$p < 0.001$ vs. Group Y.

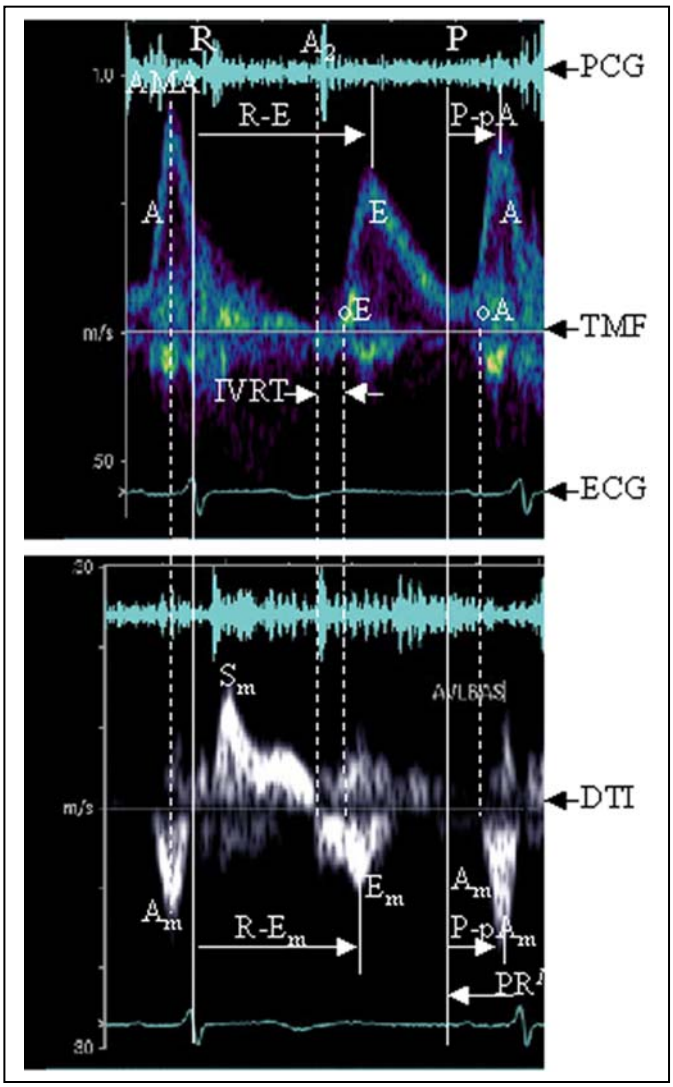

Figure 7 Relationship between Doppler transmitral flow (TMF) (upper panel), and Doppler tissue imaging (DTI) of the LV basal free wall motion (lower panel) in an 84-year-old healthy man. Vertical lines (R) and (P) refer to electrocardiographic (ECG) peak of R and the onset of P, used as reference points for measurements of early diastolic temporal discordance (EDTD) and late diastolic temporal discordance (LDTD) respectively. Mitral in-flow is biphasic, early diastolic (E) and atrial contraction (A). DTI wall motion profile is triphasic – systolic (S_m), early diastolic (E_m) and atrial contraction (A_m). E and E_m began simultaneously (oE) as did A and A_m (oA). R to peak E (R-E) was longer than R to peak E_m (R-E_m). Peak A coincided with peak A_m (AMA) – atrial mechanical alignment. Isovolumic relaxation time (IVRT) was determined from aortic valve closure (A_2) on the phonocardiogram (PCG) to the onset of E (global) and E_m (regional). PR′ refers to the interval from the peak of R to the onset of P of the preceding cycle. In this particular case EDTD was 14 msec while LDTD was zero.

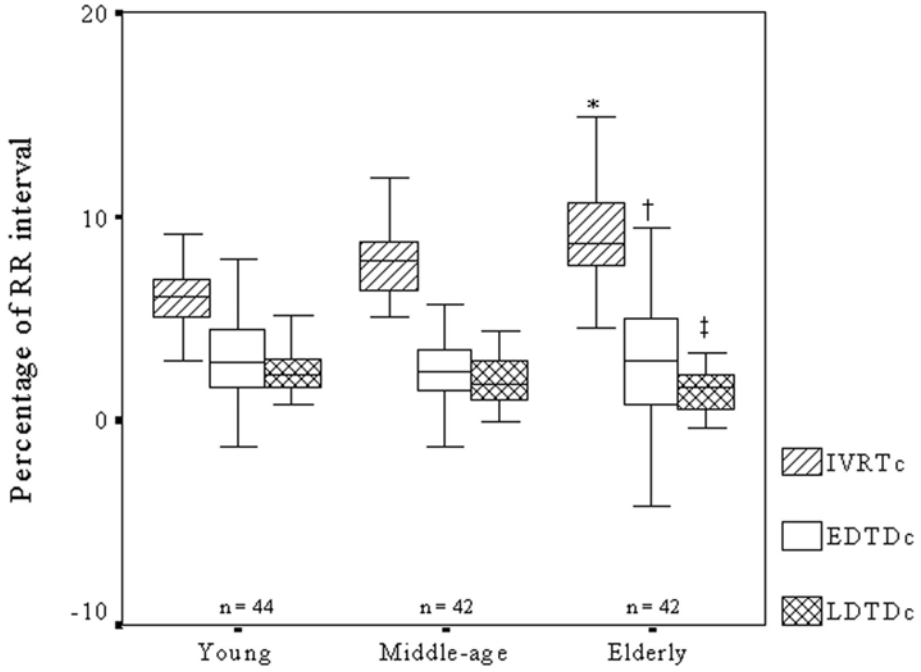

Figure 8 Box plots showing the pattern of change in IVRTc, EDTDc and LDTDc with increasing age. In the young versus the elderly, there is an increase in IVRTc (*$p < 0.001$); a decrease in LDTD (‡$p < 0.001$), while EDTD remains unchanged (†p = NS). The lowest, second lowest, middle, second highest and highest box points represent the minimum, 25th percentile, median, 75th percentile, and the maximum, respectively.

On multivariate analysis with LDTD as dependent variable, multiple linear regression analysis was performed to weigh the independent associations between LDTD and other variables, particularly those conventionally used to define diastolic dysfunction (age, E/A ratio, mitral EDT and IVRT). By this model, after adjusting for potential determinants such as sex, HR, PR interval, LA dimensions and systolic BP the independent inverse correlation between LDTD with age ($p = 0.01$) and with IVRT ($p = 0.03$) was confirmed. However, age lost its ability to predict LDTD in the presence of IVRT.

7.1.3. Left atrial physiology and the effect of age (Study II)

Left atrial contraction: forward versus reversal flow
Comparisons were made mainly between Group Y (age <45 years) and Group E (age ≥65 years) to reflect LA contraction, corresponding timings and the effect of age. During atrial contraction the duration of A_m, forward flow (A-wave) and pulmonary reversal flow (Ar-wave) were all prolonged in the elderly compared to the young (114 ± 14 vs. 92 ± 13 msec; $p < 0.001$, 156 ± 16 vs. 143 ± 18 msec; $p = 0.001$ and, 118 ± 12 vs. 106 ± 16 $p < 0.001$, respectively). Similarly, deceleration time (DT) was significantly prolonged (elderly vs. young) with respect to A_m (57 ± 11 vs. 45 ± 9 msec; $p < 0.001$) but had a modest change in the transmitral A-wave (83 ± 16 vs. 73 ± 16 msec; $p = 0.003$) and none in the pulmonary Ar (57 ± 9 vs. 54 ± 8 msec; p = NS). Ar DT, however, showed a tendency to increase with age but did not achieve any level of significance. Overall, Ar DT was equal to the corresponding acceleration time (AT) (56 ± 10 vs. 57 ± 8; p = NS). The difference between Ar and A-wave durations had no correlation with age ($r = –0.18$; p = NS).

With advancing age there was a consistent increase in the corresponding peak velocities related to atrial contraction, (elderly vs. young): A_m (15.6 ± 2.5 vs. 11.0 ± 2.9 cm/sec; $p < 0.001$), A-wave (75.1 ± 14.3 vs. 44.9 ± 12.5 cm/sec; $p < 0.001$) and Ar-wave (28.1 ± 4.4 vs. 19.9 ± 4.7 cm/sec; $p < 0.001$). Ar to A velocity ratio was ≈0.47 in the young and the middle-aged but significantly declined to ≈0.39 in the elderly ($p = 0.005$). Ar to A_m velocity ratio, however, was not affected by age ($r = –0.04$, p = NS) and remained ≈1.8 across all the age groups.

Atrial electromechanical timings
The onset of atrial forward and reversal blood flow was synchronous with mechanical wall motion and all started approximately 84 msec after the onset of the P wave. This electromechanical time interval tended to prolong with age ($p = 0.02$). Similarly, the time intervals from the same landmark to the peaks of Ar, A-wave and A_m were consistently prolonged as age increased ($p < 0.001$). In spite of this characteristic prolongation, peak atrial velocity coincided with peak reversal flow in every age group with an excellent correlation ($r = 0.97$, $p < 0.001$). Peak A-wave, however, appeared approximately 20 msec after peak A_m in the young and the middle-aged, and this difference was significantly lower in the elderly ($p = 0.002$).

7.2. Patients (Studies III and IV)

7.2.1. Baseline clinical and angiographic characteristics

In this study, clinical and angiographic features were characterised in patients with SLVD before and after PTCA. Forty-one (2.6%) adult patients who fulfilled the criteria were selected out of the 1,528 consecutive patients who had undergone PTCA over a period of three years at the study institution. The age range of the study population was 40 to 76 years with a mean of 63 ± 10 years, and 36 (87.8%) were males.

Baseline clinical characteristics

The study population was elderly; predominantly men (87.8%) and 18 patients (43.9%) had comorbid systemic illnesses. A total of 34 (82.9)% patients, had at least one or more established risk factors for coronary artery disease – hypertension, 20 (48.8%); diabetes mellitus, 9 (22.0%); hypercholesterolaemia, 20 (48.8%); current smokers, 12 (29.3%) and 19 (46.3%) had previously smoked. Thirty one (75.6%) patients had a prior myocardial infarction and 27 (65.9%) had undergone previous revascularisation procedures; 23 (56.1%) CABG surgery and 16 (39.0%) PTCA (Table 2).

At the time of PTCA, 12 patients (29.3%) presented with unstable angina; 35 (85.4%) had Canadian Cardiovascular Society (CCS) Class III–IV angina pectoris and 32 (78.0%) were in New York Heart Association (NYHA) class III–IV functional status. Thirty two (78.0%) were taking angiotensin converting enzyme inhibitors (ACE-I) or beta-blockers alone or in combination.

Angiographic characteristics

Thirty-three (80.4%) patients had three-vessel disease. The remaining were divided equally in the one and two-vessel disease groups. Significant coronary artery disease was present in LAD, 39 (95.1%); RCA, 37 (90.2%) and left Circumflex (Cx), 34 (83.0%) patients respectively. The graft vessels were also involved in patients with previous CABG surgery. Three patients (7.3%) had disease of the left internal mammary artery (LIMA) graft to LAD and seven (17.1%) had stenoses in saphenous vein grafts to the left circumflex. Similarly, 22 patients (53.6%), divided equally, had significant disease in the vein grafts to the RCA and the LAD (Table 3).

A total of 112 lesions were identified in the entire study population with 13 (11.6%) being chronic total occlusions. Native vessel lesions were distributed as follows: 21 (18.7%) in the LAD, 20 (17.8%) in the RCA and 19 (17.0%) in the Cx. The distribution of lesions in the graft vessels followed this pattern: LIMA and vein graft

to LAD, 4 (3.6%) and 14 (12.5%) lesions respectively whereas saphenous vein grafts to RCA had 14 (12.5%) and to Cx 7 (6.3%) lesions each.

Table 2 Baseline clinical characteristics

Characteristic		Number	(%)
Total number of patients		41	-
Age range (years)		40 - 76	-
Mean age (SD) (years)		63±10	
Sex (men/women)		36/5	88/12
Diabetes mellitus		9	22
Hypertension		20	48.8
Current smoker		12	29.3
Previous history of smoking		19	46.3
Treatment for hypercholesterolaemia		20	48.8
Previous myocardial infarction		31	75.6
Previous coronary bypass surgery		23	56.1
Previous coronary angioplasty		16	39
Unstable angina		12	29.3
Angina pectoris CCS Class -	II	6	14.6
	III	13	31.7
	IV	22	53.7
Functional Status – NYHA Class	II	9	22
	III	20	48.8
	IV	12	29.2
Current major systemic illness		18	43.9
Treatment (ACE-I+BB) or BB, ACE-I alone		32	78

CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; ACE-I, Angiotensin Converting Enzyme Inhibitor; and BB, β- blockers

Table 3 Angiographic characteristics

Characteristic		**Patients**	(%)
Extent of CAD	- one vessel	4	9.8
	- two vessels	4	9.8
	- three vessels	33	80.4
Native vessels involved	- LAD	39	95.1
	- Cx	34	83.0
	- RCA	37	90.2
Grafted vessels involved	- LIMA→ LAD	3	7.3
	- VG → LAD	11	26.8
	- VG → Cx	7	17.1
	- VG → RCA	11	26.8

CAD, coronary artery disease; LAD, left anterior descending; Cx, left circumflex RCA, right coronary artery; LIMA, left internal mammary artery; and VG, vein graft

7.2.2. Early outcomes after coronary angioplasty (Study III)

Angiographic success was achieved in 60 lesions constituting 95.2%. Five patients (12.2%), all of whom had a single culprit lesion, achieved complete revascularisation. The remaining 36 (87.8%) patients had incomplete revascularisation. Endoluminal stents were implanted in 29 (70.1%) patients. Two patients had unsuccessful procedures - one had emergency CABG surgery whereas the other was treated medically. The remainder with incomplete revascularisation had multiple narrowings in other vessels despite good angiographic outcomes in the dilated vessels.

Complications were documented in 23 (56.1%) patients including one death (2.4%), which occurred 48 hours after the procedure. Major complications occurred in 8 (19.5%) patients; 6 (14.6%) Q-wave myocardial infarctions, and one abrupt vessel closure immediately after the procedure, requiring stent insertion. Two others received emergency CABG surgery while the rest were treated conventionally. Overall, emergency CABG surgery was performed in 3 patients. Two had suffered AMI secondary to stent occlusion. The third had circumflex vessel dissection with consequent myocardial infarction, pulmonary oedema and cardiogenic shock requiring IABP insertion. Other complications noted included angiographic evidence of minor vessel dissection, arrhythmias, hypotension, infections, entry site haematoma and distal emboli from a saphenous vein graft.

7.2.3. Follow-up results late outcomes (Study III)

Apart from the one death and 3 patients who underwent post-procedure CABG surgery, data of the remaining 37 patients was analysed reflecting events only in the first 12 months. At four weeks post-procedure, 21 (56.8%) patients showed symptomatic improvement in their angina status. Six months later 17 (46%) patients showed a significant improvement in the NYHA functional class ($p< 0.001$). A similar number of patients still showed evidence of sustained clinical improvement with a change in at least one class of angina or their cardiac functional status at twelve months. At the same time, Fractional Shortening (FS) had increased from $15.9 \pm 3.4\%$ to $19.6 \pm 6.6\%$, $p = 0.02$ and consequently cardiac output from 4.28 ± 0.98 to 5.34 ± 1.77 L/min, $p<0.01$. One patient was lost to follow-up and two (5.4%) died of cardiac causes, namely, cardiogenic shock secondary to early stent occlusion and intractable heart failure, respectively.

In general, patients who had shown improvement in their functional status by the end of the first month had maintained this improvement by the end of the year. Recurrence of symptoms necessitating a repeat angiographic study was noted in eight patients, four (10.8%) of whom required repeat angioplasty. There were no repeat procedures for new disease.

During follow-up period, non-fatal Q-wave AMI occurred in four patients and CABG surgery was performed in seven others. One patient developed cardiogenic shock requiring LV assist device as a bridge to transplantation. The rate of hospitalisation in this population tended to occur mid term post procedure. Twenty (54.1%) patients had been re-admitted at least once for worsening cardiac symptoms or for re-evaluation. No major change was observed in the types and dosages of the medications after angioplasty. Overall, event-free survival was 78.4% at one month and declined steadily to 62.3% by the end of the first year as depicted in the event-free survival curve (Fig. 9).

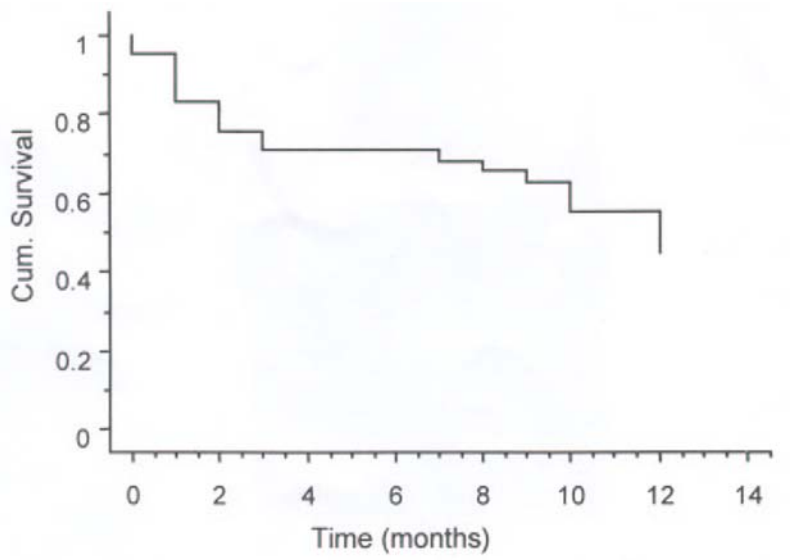

Figure 9 Kaplan-Meier event-free survival curve.

7.2.4. Changes in symptom profile (Study IV)

Symptom relief, especially angina, was achieved in 21 (56.8%) patients in the immediate post-procedure period. Thereafter, at 3–6 months assessment, 17 (46%) and 18 (48.7%) patients still experienced significant improvement in NYHA functional class and angina, ($p < 0.001$) respectively (Fig.10). Patients who were relatively symptom-free during this period maintained that status with change in at least one class of angina or cardiac functional class at 12 months

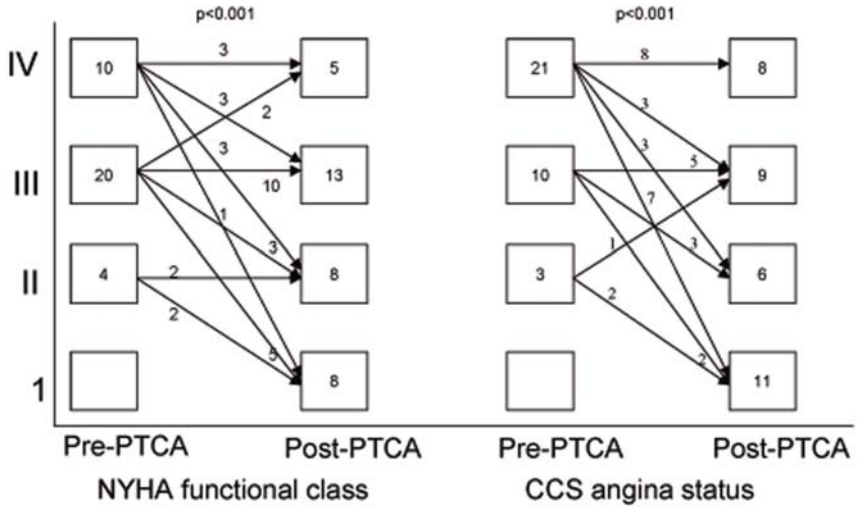

Figure 10 Change in levels of symptoms 3-6 months after PTCA (n = 34). NYHA, New York Heart Association; and CCS, Canadian Cardiovascular Society.

7.2.5. Changes in LV function after PTCA (Study IV)

Complete echocardiographic data was available for only 30 patients at mid-term analysis. Before PTCA, LV cavity dimensions were increased with a mean ±SD minor-axis diameter of 6.5 ± 0.5 cm at end-diastole and 5.5 ± 0.4 cm at end-systole hence FS was reduced, 15.9 ± 3.4% ($p < 0.001$), with respect to normal. After PTCA, ESD fell by 4 mm and consequently FS increased to 19.6 ± 6.6%, $p = 0.02$. This functional improvement, in spite of being significant, was still well below the lower 95% confidence limit of normal.

Compared with controls, LV free-wall and septal long axis TA was markedly reduced in patients ($p < 0.001$). Similarly, PSR and PLR were significantly reduced ($p < 0.001$). After PTCA, free-wall amplitude significantly increased from 1.03 ± 0.41 cm to 1.17 ± 0.34 cm, $p = 0.02$, as did its early diastolic component at the septal site, from 0.4 ± 0.2 cm to 0.6 ± 0.3 cm, $p = 0.004$. PLR also increased at the left free-wall from 5.4 ±2.2 cm/s to 6.4 ± 2.2 cm/s, $p = 0.02$, and the septum from 3.4 ±1.6 cm/s to 4.2 ± 1.8 cm/s, $p = 0.01$.

In general, there was a tendency towards prolongation of Doppler IVRT and the time interval between A_2 and the peak E-wave. There was, however, a modest fall in the E:A ratio from 1.6 ±1.2 to 1.3 ± 0.8, $p < 0.05$ up to 3 to 6 months later. Resting cardiac output increased from 4.28 ± 0.98 to 5.34 ± 1.77 L/min, $p < 0.01$, and MPI (Tei Index) decreased from 0.70 ± 0.24 to 0.58 ± 0.19 ($p < 0.01$). In the twenty-three patients who received isolated LAD angioplasty, similar results were found in addition to a significant prolongation of IVRT ($p = 0.03$).

7.2.6. Changes in LV long-axis function *versus* symptoms after PTCA

LV free-wall amplitude increased in 18 (60%) patients after PTCA, of whom improvement in at least one class of angina and NYHA functional class occurred in 16 and 12 patients respectively. Overall absolute change in free-wall LTA was 1.4 mm (95% CI –5 to +8 mm), $p = 0.02$, and a positive change in amplitude was significantly associated with a similar reduction in angina ($p < 0.001$) and improvement in functional status ($p = 0.03$)

Although the outcomes are presented in a dichotomous format – improved or not improved, the procedure did not affect free-wall long-axis amplitude in 5 patients, while the remainder worsened. In general, patients with resting pre-procedure long-axis amplitude of ≥ 5 mm and <13 mm either improved or remained unchanged (Fig. 11). Furthermore, the lower the pre-procedure free-wall long axis TA, the higher the absolute change in amplitude after PTCA ($r = –0.44$, $p = 0.01$). However, among those in whom long-axis remained unchanged, angina improved in 2 while a better

functional class was recorded in 3. Conversely, none of the patients in whom long-axis fell after PTCA showed improvement in symptoms.

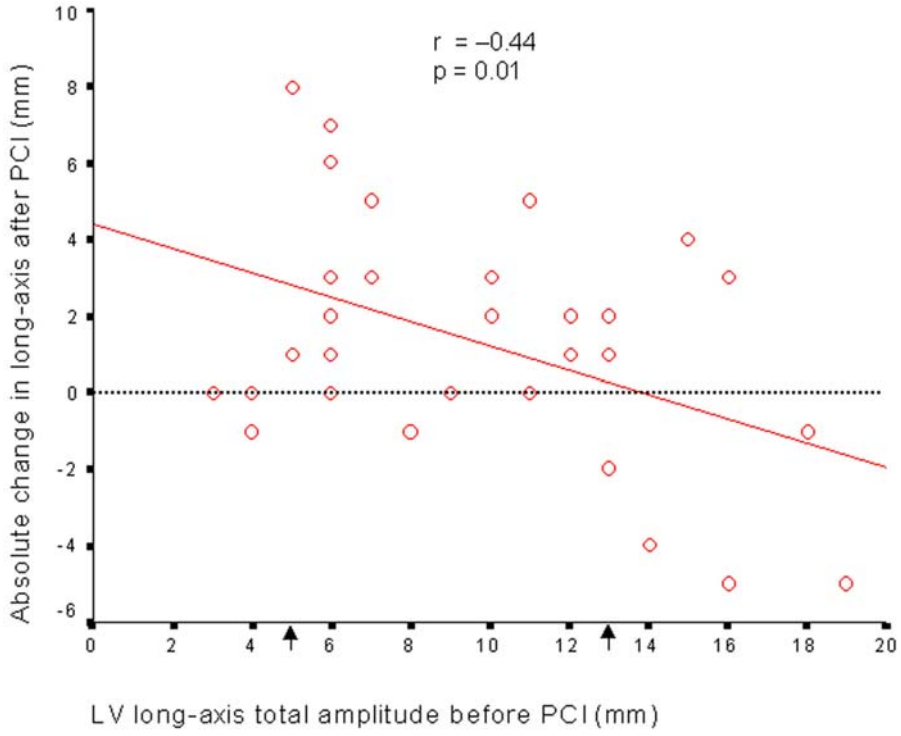

Figure 11 LV free-wall long-axis amplitude before and absolute change after PTCA or PCI, for percutaneous coronary intervention. Significant correlation between the two variables ($r = –0.44$, $p = 0.01$) suggests that patients with a lower pre-procedure long-axis amplitude achieved a higher absolute change in amplitude after PCI. Horizontal **broken line** separates improvers (above the line) from non-improvers (on the line) and those who deteriorated (below the line). Most improvers and non-improvers lie within 5 to 13 mm interval (**X-axis, Arrows)**.

8. Discussion

8.1. LV assessment beyond ejection fraction

Anatomical and physiological basis of the cardiac pump function in humans has been a subject of study for many decades. Current non-invasive methods based on the detection of change in the ventricular physiological mechanisms not only provide the best chance for early cardiovascular diagnosis and intervention, but also the estimation of long-term prognosis. In this respect, the value of echocardiography in the assessment of LV dysfunction is unquestionable, especially its success in highlighting the importance of asymptomatic LV systolic dysfunction [109] and in the quantification of LV systolic and diastolic function as being reliable indicators of mortality [58, 59]. In addition, the traditional value of LVEF as a prognostic marker in patients with LV dysfunction with and without heart failure has made it one of the most popular parameters in the assessment of LV systolic function [110, 111]. In spite of these advantages, however, LVEF is not sensitive in defining early ventricular changes in normal ageing [29, 30] and in early CAD [51], and its diagnostic ability is severely limited in ischaemic cardiomyopathy where ventricular morphology is significantly altered [112]. Furthermore in a recent review [113] it was found that LVEF measured by echocardiography failed to stratify risk in most studies of chronic heart failure. These shortcomings coupled with rapid advances in echocardiographic techniques and technology have motivated a search for alternative and complementary non-invasive parameters, particularly those that can provide information about regional myocardial function as well as global LV function. Accordingly, studies of the ventricular long axis, which represents longitudinal myocardial fibres, have shown that its amplitude of motion correlates well with LVEF [53, 54], is reduced or absent in CAD [20], and is a prognostic marker in patients with heart failure [55]. More importantly, the central role of the relationship between the timing of the MA, and thus the cardiac base motion, and filling of the heart can be recorded by M-mode echocardiography [20] and DTI [81, 82], providing an excellent opportunity to study the relationships myocardial motion and concomitant blood flow. To extend this knowledge further, this thesis uses the timing of the mitral annular motion in the cardiac cycle to enhance our understanding of alterations in ventricular physiology during the ageing process; it also examines the potential value of MA amplitude of motion as a marker of LV recovery in patients with poor LV function after percutaneous revascularisation.

8.2. Physiology of the ageing heart

Although the ageing heart shares common functional changes with other cardiovascular conditions that coexist in the elderly, there are alterations that are now believed to be intrinsic to the ageing process. The LV early diastolic filling rate is known to progressively slow after the age of 20 years, so that by 80 years, the rate is reduced, on average, up to 50% [114]. In contrast, LVEF is preserved during normal ageing [114]. Thus, Studies I and II conclusively confirm what several other investigators have demonstrated, that the pattern of transmitral diastolic flow measured by Doppler echocardiography is altered by advancing age, such that early flow is reduced and atrial flow is increased [115-119]. Similar findings have been reported with other non-invasive techniques like radionuclide angiography [120], suggesting the possibility of specific age-related alteration in LV diastolic function. However, Doppler filling indices are known to be altered in early systemic and pulmonary hypertension, as well as CAD [115, 121, 122], all of which are common in the elderly and may be undetected [123]. Furthermore, other studies have demonstrated that Doppler and other noninvasive indices of LV diastolic filling are influenced by heart rate, preload, afterload, contractility and LV mass, all of which have been reported to be altered in elderly subjects [117]. In Studies I and II, however, a wide age range of healthy volunteers both men and women were recruited from the community and rigorously screened for cardiovascular, hypertensive, pulmonary and other diseases. Although it was not possible to exclude all possible potential confounding physiologic factors that influence transmitral flow, it is now known from other studies that healthy elderly subjects still exhibit markedly altered filling patterns compared to the young even in the presence of these factors in both groups when studied at rest [117, 124]. Although results from these previous studies recognise the existence of reduced LV wall relaxation with ageing, they also seem to emphasize that altered diastolic filling may be due to intrinsic property of the normal aged human left ventricle. Furthermore, whether these alterations in the Doppler mitral flow patterns, either physiologic or associated with disease, reflect actual changes in the myocardial relaxation or compliance remains controversial [125].

8.3.Timing the mitral annular motion and LV filling

Another less investigated aspect of the transmitral flow with ageing is the timing of the diastolic mitral annular descend in relation to LV filling. In early diastole, LV filling results from a cascade of well-synchronized mechanical events that begin in the systolic phase of the cardiac cycle. During ejection period the LV undergoes counterclockwise torsion, and clockwise recoil of torsion or untwisting before mitral valve opening, especially during isovolumic relaxation period [126, 127]. This recoil is associated with release of restoring forces that had been accumulated during systole and is thought to contribute to diastolic suction and hence LV filling [126, 128]. Since

early diastolic annular motion is a potential marker of LV recoil [16, 82], peak annular velocity (E_m) should precede peak mitral flow velocity (E). Indeed this phenomenon has been demonstrated by temporal discordance between these two events using DTI combined with Doppler echocardiography [16, 81, 82]; and is altered or lost in patients with left ventricular hypertrophy (LVH) and diastolic dysfunction [82]. By applying similar methods, Study I also confirmed the presence of early diastolic temporal discordance (EDTD) with the peak of annular velocity preceding that of the mitral flow. This time interval was also age independent, a finding, which to the best of our knowledge, has not previously been reported. This observation gives further insight into the presence of ventricular restoring forces and the possibility of preservation of the LV suction properties of the heart in normal ageing. These findings seem to concur with earlier invasive studies by Yamakado *et al* [39] which demonstrated that negative dP/dt, a measure of LV relaxation, was preserved in healthy people from the age of 20 to 70 years. Again, suggesting that other factors may be responsible for altered filling seen with ageing.

8.4. Quantification of atrial contribution to LV filling

Alterations in the transmitral flow patterns that accompany the ageing process signify the increasing dependency of LV filling on atrial systole. Previous studies have estimated that the contribution of atrial contraction to LV stroke volume rises from 12% in the young to 46% in the elderly [116]. These observations are also reflected in the increase in atrial Doppler LV filling velocities, which have also been shown to correlate well with increased long axis atrial shortening velocity [129, 130]. Overall atrial size, on the other hand, has been reported to progressively increase with ageing [131]. This also increases the propensity for atrial fibrillation in elderly people [132] with consequent potential significant haemodynamic disturbances; thus underscoring the importance of understanding the change in atrial physiology with the ageing process. Studies 1 and II sought to define late diastolic timings in relation to mitral annular motion as a means to identify healthy persons at increased dependency on atrial contraction for late diastolic filling. Since pulmonary venous reversal flow is dependent on atrial contraction, peak inter-atrial septum contraction velocity has been shown to coincide with peak reversal flow velocity [90]. The current study therefore tested the hypothesis that if the timing of both peak forward flow velocity (A-wave) coincided with that of Ar (pulmonary reversal flow), then the two events must be dependent on atrial contraction. Unlike previous studies [20, 80] where electrocardiographic QRS complex was used as a reference point to study late diastolic time intervals, the onset of the P wave was used in this study for two reasons. First, it has been shown that late AV ring displacement in late diastole is related to the P wave [27, 28]. Second, the AV ring motion, which appears to be the earliest mechanical consequence of atrial contraction, can be detected non-invasively, and also reflects local function more precisely [26, 28]. Thus, the results demonstrated that both A-

wave and Ar began simultaneously after the onset of the P wave and were all synchronous with atrial contraction, and that this observation was consistent across all age groups. The tendency, however, for these time intervals to prolong with advancing age reflected the corresponding increase in the LA size and, probably the PR interval.

Results from Studies I and II further showed that peak atrial contraction strikingly coincides with peak reversal flow from the young to the elderly. This implies that in normal hearts, irrespective of age, reversal flow into the pulmonary veins is solely dependent on atrial contraction, an observation consistent with previous studies that showed absent Ar in patients with atrial fibrillation [90, 133, 134]. The same pattern was, however, not observed in the forward flow (A-wave), where peak A_m preceded peak A-wave in the young, thus defining a time interval referred to in these studies as LDTD (late diastolic temporal discordance). With increasing age, it was observed that LDTD progressively narrowed until the peaks of A and A_m coincided in some subjects (Fig. 7). This point of convergence of the peaks of A_m, A-wave and Ar was described AMA (as atrial mechanical alignment), which should potentially identify individuals at increased dependency on atrial systolic function and late diastolic LV filling. Interestingly, AMA was not only present in the elderly alone, but also in other age groups, implying the presence of other determinants besides advancing age. On multivariate analysis, however, sequential prolongation of IVRT with ageing was the best independent predictor of AMA. Thus, it is proposed that AMA may be found in other conditions where IVRT is prolonged and could be an additional echocardiographic sign for detecting increased dependency on atrial systole for late diastolic filling.

8.5. Cardiac cycle time intervals: current clinical applications

With renewed interest in the use of cardiac time intervals as a measure of cardiac function, a wide range of indices have been defined especially those that can estimate ventricular filling pressures non-invasively [135]. Most of these indices are founded on the premise that mitral inflow patterns depend on multiple factors such as LV relaxation, chamber stiffness, and loading conditions; knowledge that previous studies have exploited to establish significant relationships between the pulmonary vein Doppler pattern and mean left atrial, pulmonary wedge artery, and LV end-diastolic pressures [91]. For instance, Rossvoll and Hatle [94] demonstrated that the difference between Ar and transmitral A-wave (A) durations is a useful measure of LV end-diastolic pressure [94, 136]; which has also been shown to be age independent [95, 137]. Despite these reports, imaging Ar remains difficult in some adults. Transthoracic echocardiography a commonly used method is less reliable in quantifying Ar [138, 139]; its success rate in obtaining quality PVF recordings varies in some reports from 30–60% [138, 140, 141]. Further, the method overestimates Ar duration [142] and, to some extent, is equipment and operator dependent [99]. Study II therefore elected to

characterise Ar timings in relation to A_m (atrial contraction) as reflected by late diastolic longitudinal motion of the mitral annulus imaged by DTI. In addition to demonstrating that peak Ar velocity consistently coincided with peak A_m velocity, the Ar acceleration time was similar to the corresponding deceleration time. Since, Ar and A_m were simultaneous at onset, determination of the time to peak A_m would be used to determine corresponding time to peak Ar. Thus, the study conclusively showed that DTI measurements, which are easier to obtain irrespective of image quality [143], can be used to estimate corresponding measurements of Ar.

Another well documented cardiac cycle time interval is the IVRT (isovolumic relaxation time), which as defined earlier represents the time period from closure of the aortic valve to the opening of the mitral valve. The IVRT (normal range 60–90 msec; could be lower in the young) reflects the rate of myocardial relaxation but is dependent on afterload and heart rate [144]. It is probably the most sensitive Doppler-index to detect impaired relaxation because it is first become abnormal [93], and has therefore gained significant clinical application in the evaluation of ventricular function.

Cardiac resynchronisation and dual chamber pacing as modalities of treatment in patients with chronic heart failure, have undergone significant progress in the last few years, and therefore merit special mention. Many patients with chronic heart failure have abnormal ventricular activation [75, 79], AV conduction and interventricular delay [145], all of which are associated with significant disturbances in ventricular filling and ejection. Cardiac resynchronisation restores optimal AV mechanical timing [146], and thus improves ventricular remodelling, ejection fraction and exercise tolerance in these patients [147, 148]. On the other hand, since preserved left atrial contraction contributes significantly to cardiac output in patients with diastolic dysfunction, dual chamber pacing has been used to optimise atrial output in patients with conduction abnormalities and severe LV systolic dysfunction [149]. Both Doppler echocardiography and DTI provide non-invasive measurements of timings and cardiac output and are essential in pacemaker optimisation as well as objective assessment of improvement. More significantly, the reference values for the time intervals used in these previous reports were obtained from healthy control groups [150], thereby bringing into focus the essence of Studies I and II presented in this thesis.

8.6. Monitoring therapy in elderly patients with CAD

8.6.1. Medical versus surgical therapy

While the study and understanding of ventricular physiology in the healthy elderly is important, there are profound challenges in selecting and monitoring appropriate therapies especially among those with severe LV dysfunction (SLVD) secondary to CAD. These patients tend to be elderly and usually present with a dilated LV cavity size with reduced segmental wall motion and global impairment of LV systolic

function. At this stage, clinical outcome is usually poor despite advanced medical therapy [151], and other management options are limited. The ability to restore blood flow to ischaemic myocardium provides the best chance for symptomatic and functional improvement [152, 153]. Although this policy has previously been demonstrated in patients with preserved LV function [152], there is a paucity of evidence from the literature to support a similar approach in patients with SLVD. Nevertheless, recent extensive review of Registry data on PTCA application in this population continues to show its preference, efficacy and safety [154, 155].

In Study III, retrospective analysis of Registry data confirmed well-known trends: the study population was predominantly elderly; had multiple vessel coronary disease, with previous AMI, CABG surgery and PTCA procedures, all on a background of multiple other systemic diseases – hypertension, diabetes mellitus and hypercholesterolaemia. The study, however, provided an insight into the relationships between PTCA, LV function, and complications on the one hand, and symptomatic improvement on the other. Despite a high rate of procedure related complications, early mortality was lower than historical data [156] emphasizing improved management of major complications, and therefore supporting the safety of the procedure in this high-risk group. This achievement in improved outcomes has been attributed partly to the widespread use of intracoronary stenting in the management of potentially fatal complications during PTCA [157, 158]. In this study, 70% of patients received stents – a figure that is consistent with practice in other centres [156]. These devices have also been shown to reduce the likelihood of restenosis, which plays a major role in late outcomes [159, 160]. Another major observation in Study III was that LV function assessed by LV fractional shortening improved marginally after PTCA. Although this measurement still remained well below the 95% confidence interval of normal, patients still showed symptomatic improvement not only soon after the procedure but several months later. Accordingly, it was hypothesized that this change in symptoms could only have been brought about predominantly by regional or segmental improvement rather than global. Thus, Study IV was designed to examine further the relationship between improvement in LV segmental function, assessed by long axis function, and symptomatic improvement – an area with very scarce knowledge.

8.6.2. Predicting LV recovery after revascularisation

To date the value of long axis function as a marker of LV recovery as well as prognosis in patients with heart failure on medical therapy has been described [55, 161]. Patients with cardiomyopathy (ischaemic or non-ischaemic) are known to have a reduced or absent long axis function [20, 108], and a reduction in total amplitude of motion <10 mm has been associated with significant mortality at one year follow up [55]. More recently, early recovery of LV long axis motion was shown to occur in patients with heart failure on beta-blocker therapy, and this improvement was strongly associated

with future global recovery of LV function [161, 162]. Although revascularisation therapy, surgical and transcatheter, has been shown to improve symptoms, LV function, and the quality of life in patients with heart failure [163, 164], it remains unclear whether these favourable outcomes translate into long-term survival benefit [165]. Similarly, the relationship between improvement in LV function and symptoms has not been well documented. In addition, the threshold of viable myocardium, particularly the longitudinal component, required to improve LV function after revascularisation has not been determined thus making it difficult to objectively predict LV recovery.

Results in Study IV showed improvement in LV free wall long axis amplitude, peak velocities and myocardial performance index, signifying improvement in both regional as well as global LV function after PTCA. Increased ventricular segmental wall motion amplitude following angioplasty confirms a partial normalisation of viable myocardial function after improving its blood supply. In principle, these findings are in agreement with evidence from surgical revascularisation that clearly show improvement in LV function only in the presence of viable myocardium [166]. To quantify the level of ventricular improvement after PTCA, previous studies used angiographic studies [167], where LVEF was shown to improve. Later, perfusion studies have been shown to be accurate enough in identifying hibernating myocardium and its successful response to revascularisation [168]. However, repeat perfusion studies for myocardial recovery and repeat angiographic assessment for overall LV function have obvious limitations. In contrast, echocardiography, a non-invasive method can be used to assess and follow up both segmental and global ventricular function response in these patients.

The results in Study IV were also instructive. Although symptomatic improvement was associated with improvement in LV function, in about half the patients, there was no observable change in functional status at one month following PTCA. A similar proportion of patients showed no observable change in angina symptoms at medium-term, suggesting that the procedure may not be beneficial, at least in relieving symptoms, consequently raising the important question of how to predict clinical outcome. Based however, on a cut off value of at least 5 mm MA (long axis) amplitude, it was possible to separate patients who improved from those who deteriorated or failed to improve, thus providing a possible marker for myocardial viability at rest. Similar markers to predict recovery based on resting echocardiography alone or in combination with other viability techniques have not been adequately investigated. La Canna *et al* [169] recently demonstrated that diastolic wall thickness less than 5 mm used alone in a selected group of patients was a strong predictor of failure to recover after surgical revascularisation. Prior to that study, Baer and colleagues [170] by using MRI had also demonstrated that diastolic

wall thinning of <5.5 mm and systolic thickening <1 mm indicated the absence of viable myocardium.

In Study IV, two other key observations were made. First, patients with severe LV dysfunction with relatively lower pre-operative LV long axis amplitude achieved the highest absolute change in amplitude after PTCA. This finding supports the hypothesis that relatively lower amplitude at rest could suggest a more severe reduction in regional coronary perfusion, since long axis motion reflects the function of ventricular subendocardial fibres, which are sensitive to ischaemia. Second, improvement in LV long axis amplitude was associated with a better clinical outcome, again providing a conceptual link between potential areas of myocardial viability reflected by long axis motion and symptomatic improvement. In addition, a pre-procedure resting LV long axis amplitude of at least 5 mm was not only related to functional recovery but also a favourable clinical outcome.

Reflecting on experience from surgical revascularisation puts results from Study IV into perspective. These previous studies have shown that recovery of function and outcome in general is influenced by multiple factors that include the extent of dysfunctional but viable myocardium; the degree of LV remodelling; the success of revascularisation procedures and the time after revascularisation the LV assessment is performed [171]. In addition, the extent of transmural scar [172] and increased LV volumes and cavity size are also important predictors of functional outcome [173]. Thus, predicting LV recovery in patients with SLVD still remains one of the most challenging clinical tasks, and any single test applied is unlikely to be adequate. Furthermore, it must be borne in mind that improvement in long axis function, like the presence of hibernation alone, does not guarantee recovery of LV function suggesting that there may be other intrinsic ventricular factors that determine overall functional outcome in patients with severe LV dysfunction.

In conclusion, these two sets of studies give an insight into the behaviour of ventricular long axis in health and disease. Both the total amplitude and the timing of MA motion in the cardiac cycle have additional potential diagnostic and clinical applications. Further, Studies III and IV clearly demonstrated that PTCA as a therapeutic option can be performed safely in patients with SLVD with both favourable early and late outcomes. In addition, functional cardiac improvement further supports the indication of PTCA in symptomatic patients and therefore the ability to predict recovery is critical. Accordingly, a cut-off value based on long axis amplitude is an objective and reproducible measurement, which can easily be obtained from the mitral ring echo even in suboptimal images. This simple measurement could provide a baseline screening test for patients with severe LV dysfunction awaiting further viability studies, and could also be used in patient recruitment for revascularisation therapy.

8.7. Methodological considerations

8.7.1. Selecting subjects for normal population studies

Studies of healthy individuals frequently recruit subjects on an ad-hoc basis for reasons of organisational simplicity [130]. The disadvantage of such a recruitment policy is that the age distribution will not be even across the age spectrum studied, but instead typically sparse at both extremes. This has two inter-related adverse consequences. First, the degree of precision with which the normal ranges can be quoted at both extremes of age is poorer. Second, age-dependencies of physiological measurements can easily be missed because of relatively few data points are available at the extremes assuming that age dependence is linear. These factors, singularly or in combination, constitute a major shortcoming in the reference values presently available in the literature.

In Studies I and II echocardiographic parameters were obtained from a sample of randomly selected healthy subjects whose ages ranged widely and were equally distributed. The selection process involved stratified sampling based on the date of birth, which was only possible by the use a unique personal identification system in Sweden. Besides, this information was readily available at the local Population Register making accessibility easier.

8.7.2. Echocardiographic methods

Echocardiography allows the assessment of myocardial structure in real time and is well suited to evaluate global and regional ventricular function. M-mode measurements became popular 30 years ago [174] and have since been used extensively without significant advancement in the techniques. Nevertheless, the technique is presently used to study ventricular and atrial chamber size; LV wall motion; mitral valve motion; aortic valve and aortic wall motion. A major advantage of M-mode, is the sheer simplicity of image acquisition and the high reproducibility of measurements, especially those related to the mitral ring motion [29, 55]. In addition, the technique has proved highly sensitive in detecting long axis motion timing abnormalities [45]. In spite of these advantages, off-line measurements of mitral annular motion, particularly digitisation, is time-consuming and therefore not frequently used in clinical practice. Another major shortcoming of M-mode relates to the estimation of LV volume and LVEF. The technique relies on a single dimension of LV short axis to derive or extrapolate information about a three-dimensional structure. When the ventricle is uniformly shaped with long axis to short axis ratio of 2:1, M-mode measurements are relatively reliable. However, most pathological conditions introduce regional asymmetry; alter the axes ratio towards unity, or both [174]. Since the estimation of volume is a cube function of dimension, errors are compounded in proportion to the extend of the existing pathology [175].

Doppler tissue imaging, a relatively new addition to echocardiographic techniques calculates and displays cardiac velocities on-line [176, 177]. Pulsed wave DTI provides instantaneous temporal display of Doppler spectral information and offers an objective assessment of regional LV function. This technique has also been validated against digitised M-mode velocities with an excellent correlation (r = 0.95) [16], and thus promises to resolve some of the limitations inherent in the M-mode technique like measurement of myocardial velocities and acceleration [80]. In fact the velocity in m/s by DTI is the first derivative of the amplitude changes (m) recorded by M-mode. Nonetheless, as already mentioned in this thesis, it still remains easy to obtain images of the mitral annulus with both techniques, although pulsed DTI has a better temporal resolution, and has been shown to be superior to M-mode for timing ventricular filling events [16]. Like other Doppler based techniques, DTI has some limitations. First, angle dependency remains an important factor leading to the potential for error when trying to accurately quantify myocardial motion [178]. Second, there is no correction for normal cardiac rotation and translational motion in the thorax, especially with septal and posterior wall interrogation in the parasternal views. This may partly explain the relatively poor reproducibility of this aspect of the technique [179]. Translational motion of the heart, however, becomes much less significant when images are acquired from the cardiac apex. Through this imaging window, the Doppler beam is at right angles with circumferential myocardial thickening and therefore cannot be reliably measured with tissue velocity imaging. On the other hand, longitudinal shortening velocities are reliably measured from this window. In all our studies, longitudinal velocities were obtained through the apical window.

8.7.3. Phonocardiography

Phonocardiography records vibrations from cardiac structures especially heart valves. Although much less used in clinical practice today, it is a useful method to study heart sounds and is generally of great indirect use in the evaluation of ventricular function. Furthermore, echocardiographic methods may become more accurate in defining cardiac time intervals when used in conjunction with phonocardiography – a practice that was used in all earlier studies on systolic time intervals [73]. Presently, recording echocardiographic images with background phonocardiogram is thought to be the most accurate method for the determination of IVRT [82], because the technique helps to define the precise timing of (A_2), the aortic component of the second heart sound. Phonocardiogram was used in all studies presented in this thesis.

8.7.4. Electrocardiography

Electrocardiography is the process of recording potential changes at the skin surface resulting from depolarisation and repolarisation of heart muscle. It is the most commonly used method in the non-invasive assessment of ventricular function, and its various technical and clinical modalities include: routine 12-lead; tape recording for 24 h (Holter method); oscilloscopic monitoring; monitoring in stress testing. Subjects in

all the studies in this thesis underwent a 12-lead ECG either to exclude any evidence of arrhythmia, CAD, and LVH (normal subjects) or as part of the management strategy (patients). Ventricular function is modified by either extremely rapid or slow ventricular rates which can be precisely recorded on the ECG; and some studies, have suggested that optimal contractile action occurs between rates of 75 and 85/min [180]. All echocardiographic recordings in the four studies were performed at rest with a background lead II of the ECG, which provides important landmarks, QRS complex and the P wave, to study ventricular and atrial electromechanical function respectively [17, 20, 28, 75, 80]. Similar landmarks were used in Studies I and II, with specific modifications as explained in the relevant parts of this thesis. Based upon the same principles, the author has introduced and tested the reproducibility and the potential diagnostic utility of new time intervals, namely the onset of the P wave to the peaks of the respective atrial mechanical events Ar, A_m and A-wave (Studies I and II).

8.8. In Summary (limitations)

Studies of ventricular function are complex since ventricular function, especially diastolic function, is affected by several variables both intrinsic and extrinsic to the left ventricle. These factors, singularly or in combination have the potential to influence the timing of mitral annular motion and both atrial and ventricular filling. This forms a widely acknowledged limitation in Studies I and II. Performing ventricular function studies at rest, however, minimises this potential source of error. Furthermore, combining phonocardiography, electrocardiography and echocardiography improves the accuracy of detecting any possible alterations. It should be borne in mind, however, that signals from all these in-puts must be synchronous and accurate especially for measurements where the starting point is set in one signal and the end-point is another [181]. Furthermore, it is also vitally important to study and group subjects with similar physiologic or pathologic characteristics separately in order to observe subtle but significant changes in the timing of ventricular and atrial mechanical events – an undertaking that was attempted in this thesis. A major limitation in the patient studies (III and IV) was the small group of pathologically heterogenous patients. This, to some extent, limits a wider generalisation of the results. Finally, whether long axis amplitudes and timings are modified by gender and common pathologic conditions was, however, not studied, though these are regarded as potential areas for future investigation.

9. Conclusions

1. In healthy subjects, peak mitral annulus lengthening velocity (E_m) preceded peak mitral flow velocity (E) and the corresponding peak annulus velocity in late diastole (A_m) also preceded that of transmitral flow A-wave (A). The two time intervals are described as early diastolic temporal discordance (EDTD) and late diastolic temporal discordance (LDTD), respectively. With advancing age, EDTD which reflects ventricular restoring forces (suction) remains unchanged while LDTD narrows progressively until the peaks of A_m and A converge. This point of convergence is described as 'atrial mechanical alignment', which is potentially a novel method to identify healthy persons at increased dependency on left atrial contraction for late diastolic filling.

2. Peak left atrial contraction coincides with the peak of atrial reversal flow into the pulmonary veins and this is consistent in all age groups from the young to the elderly. Thus, the timing of regional atrial contraction by Doppler tissue imaging can be used to accurately estimate corresponding measurements of pulmonary flow reversal, which is often difficult to image by transthoracic echocardiography in adult subjects.

3. Despite high procedure-related complications, symptomatic, functional and LV function improvement can be achieved in patients with severe LV dysfunction undergoing PTCA. Comparing with 'historical data' our results suggest that both early and late outcomes have improved. This new trend, perhaps, reflects a change in the angioplasty procedure in the last two decades, with the widespread use of intracoronary stenting for the management of potentially fatal early and late complications.

4. Long axis total amplitude of at least 5 mm suggests a significant potential for LV segmental recovery of function after PTCA. Although values for overall ventricular performance may remain subnormal after the procedure, applying such a simple long axis measurement in a larger prospective study should emphasize its important use in patient recruitment for revascularisation therapy.

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