Transoesophageal and Transthoracic Recordings of Mitral Annulus Motion

av

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Abstract

Maximal systolic and diastolic velocities recorded from four sites of the mitral annulus motion (MAM) reflect left ventricular (LV) performance. This thesis focus on factors influencing M-mode derived velocities in healthy children and adults and reference values are proposed. The usefulness of M-mode and pulsed tissue Doppler in detecting diastolic disturbances in patients with symptoms of heart failure are investigated as well. Also the reproducibility of transoesophageal (TE) recordings of long-axis movements and the difference to transthoracic (TT) recordings in anaesthetized patients are described as is the influence of respiration.

By applying tangents to M-mode echocardiography recordings from apical 2- and 4-chamber views the maximal systolic long axis velocity (MLACV) and maximal diastolic relaxation velocities (RVm) were measured. Based on stepwise multiple regression analysis concerning age, weight, height, body surface area and heart rate the following equations are suggested for calculation of reference values:

**In children and adolescents under 18:**

MLACV (mm⁻¹) = 2.5 x Age (years) + 49.0, (±20.2) (±2 SEE)
RVm (mm⁻¹) = 171 – 0.54 x Heart rate, (±37.4) (±2 SEE)

**In adults:**

MLACV (mm⁻¹) = 0.75 x Height (cm) -50.5, (±19.6) (±2 SEE)
RVm (mm⁻¹) = 163 – 1.29 x Age, (±16.8) (±2 SEE)

Intra- and inter-individual reproducibility expressed as the coefficient of variation for MLACV was 4.7% and 4.9% respectively.

In 64 patients with symptoms of heart failure the LV inflow and lung vein flow profiles were obtained by pulsed Doppler recordings and patients were classified as true cases of abnormal diastolic function by age corrected reference values. M-mode (M-RVm) and pulsed Doppler tissue imaging (TD-RVm) were used for recordings of RVm and according to Fisher’s exact test both methods can be used to detect diastolic dysfunction but velocities obtained by TD-RVm was 29.7 % (p<0.0001) higher than M-RVm. Sensitivity and specificity for M-RVm to correctly detect diastolic dysfunction were 89% and 81% respectively and for TD-RVm 81% and 78%. TD-RVm and M-RVm were highly correlated (r = 0.87).

Differences in TT and TE recordings of MAM were investigated in 24 healthy anaesthetized patients by using tissue velocity imaging. Another 10 patients were enrolled for the reproducibility study. The anterior site has low reproducibility and should be omitted when comparing TE and TT values. A TE mean value from three sites is about 15% lower than a TT mean value from four sites. Only systolic and early diastolic velocities have acceptable reproducibility values.

Respiration does not influence MLACV or RVm during anaesthesia but RVm is about 5% higher during expiration in awake individuals.

Keywords: left ventricular function, echocardiography, M-mode, tissue Doppler, mitral annulus systolic and diastolic velocities

List of papers

This thesis is based on the following original publications which will be referred to in the text by their Roman numerals:


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Abbreviations

AV: atrioventricular
BSA: body surface area
EF: ejection fraction
ccDTI: colour coded Doppler tissue imaging
C.V.: coefficient of variation
D: displacement
DTI: Doppler tissue imaging
E/A ratio: ratio between peak velocity during early (E) and atrial (A) filling phase
MA: mitral annulus
MAM-amp: amplitude of mitral annulus movement
MLACV: maximal long axis contraction velocity
M-RVm: M-mode derived maximal long axis relaxation velocity
pwDTI: pulsed wave Doppler tissue imaging
pwTD-RVm: pulsed wave tissue Doppler derived maximal long axis relaxation velocity
RVm: maximal long axis relaxation velocity
SD: standard deviation
SEE: standard error of the estimate
TE: transoesophageal
TEE: transoesophageal echocardiography
TT: transthoracic
TTE: transthoracic echocardiography
TVI: tissue velocity imaging
Va: velocity during atrial systole
Transoesophageal and Transthoracic Recordings of Mitral Annulus Motion

INTRODUCTION

Historical review

In 1953 Edler and Hertz managed to visualize parts of the heart by using ultrasound equipment and in 1965 Edler described echoes recorded from ‘the atrioventricular wall’. Two years later Zaky and co-workers (1967) performed an apical M-mode recording of the mitral annulus (MA) and described in detail the different parts of the curve, related to the different physiological events during the heart cycle and claimed: ‘In addition, if the mitral ring echo is recognized as a recording from a segment of the left ventricular wall, ultrasoundcardiography may thus provide a simple innocuous method of obtaining information concerning left ventricular activity in the intact human subject.’

Since then an enormous amount of knowledge of heart physiology has been obtained due to the development of echocardiography, computed tomography (MacMillan et al 1986, Wachspress et al 1988), magnetic resonance (Van Rossum et al. 1988, Engels et al. 1993) and radionuclide techniques (Folse & Braunwald 1962, Lewis et al. 1962, Reduto et al. 1981, Pfisterer et al. 1985) making it possible to visualize the heart during different circumstances. In assessment of left ventricular (LV) function, by these modalities, the concept ejection fraction (EF) has long been the most wide spread method. The EF however, which is the ratio between the stroke volume and the end-diastolic blood volume of the left ventricle, has its limitations and in the search for alternative methods the interest in recordings of the long axis shortening of the LV by echocardiography has increased during the last two decades. (Lundbäck 1986, Keren et al. 1988, Assmann et al. 1988, Höglund et al. 1989, Simonson & Schiller 1989, Alam et al. 1990, 1992a,b, Jones et al. 1990, Alam 1991, Pai et al. 1991, Alam & Rosenhamer 1992, Willenheimer et al. 1997, Wandt et al. 1997).

The search for reliable methods for investigation of heart function has occurred hand-in-hand with increased knowledge about the principles for LV pumping. The idea of pumping by squeezing the blood out of the ventricle, which was the predominant concept for many years, has gradually been replaced by the insight that the total heart volume is invariable during the heart cycle (Hoffman & Ritman 1985), while the atrioventricular (AV) plane
moves towards the apex during systole and away from the apex during diastole with a reciprocal relation between the blood volumes in the ventricle and the atrium (Lundbäck 1986). This concept is not quite new, however. It was described already by Leonardo da Vinci (Wandt 2000), forgotten for many years, revived by Hamilton and co-workers during the 1930s (Hamilton & Rompf 1932), thrown into the shade again by the idea of ‘the squeezing ventricle’ and finally brought back into focus by Lundbäck in the 1980s (Lundbäck 1986). Recent studies however, have shown that there is a slight systolic reduction of the outer cross sectional area of the LV (Emilsson et al. 2001a) and of the total heart volume (Carlsson et al. 2004) in healthy individuals with preserved pericardium.


In anaesthetized patients however, it is often impossible to use the transthoracic views for practical reasons, which makes it urgent to investigate the usefulness of transoesophageal (TE) recording of the amplitude and velocities of the mitral annulus. Very little has been reported so far on this issue (Simmons et al 2002), which is one of the subjects for this thesis.

LV contraction and relaxation

Systole is initiated by the depolarisation of the muscle cells creating the release of calcium ions from the sarcoplasmic reticulum, resulting in the interaction between actin and myosin filament. The architecture of the contracting myocardium is complex with subendocardial and subepicardial longitudinally oriented fibres and between these layers circular and helically oriented fibres. The contraction of these interlacing layers results in a shortening of the LV in the long axis and a synchronous thickening of the LV wall, with an inward motion of the subendocardial part of the myocardium and hardly any motion in the short axis of the outer contour of the ventricle (Lundbäck 1986, Emilsson et al. 2001a).
During the shortening of the ventricle the epicardial apex is almost stationary while the atrioventricular plane is pulled against the apex (Hoffman & Ritman 1985, Lundbäck 1986, Slager et al. 1986, Assmann et al. 1988, Jones et al. 1990). The contraction of the helical muscle fibres also results in a slight simultaneous rotational movement, around the long axis of the ventricle (McDonald 1970, Hansen et al. 1987).

Diastole is initiated when reuptake of calcium ions into the sarcoplasmic reticulum starts. This is an energy-dependent process (Nayler & Williams 1978) that allows the contractile proteins to dissociate. The intraventricular pressure declines rapidly as a result of recoil of the compressed myocardium and active relaxation. Experimentally it is shown that even negative pressure can be created if the mitral orifice is suddenly occluded which means that there is a sucking mechanism involved in early filling of the ventricle (Yellin et al. 1990).

**Echocardiographic recording of mitral annulus motion**

Ever since Höglund and co-workers in 1988 reported the usefulness of echocardiographic M-mode recording from four sites of the mitral annulus, the interest in long axis movements has increased and several studies have shown that investigation of both systolic and diastolic function can be done by measuring the MA amplitudes of movement (MAM-amp), or displacement (D), during different phases of the heart cycle (Keren et al. 1988, Höglund et al. 1989, Simonsson & Schiller 1989, Alam et al. 1990, 1992a,b, Alam 1991, Pai et al. 1991, Alam & Höglund 1992, Blomstrand et al. 1996). Furthermore the systolic and diastolic velocities of the motion have proved to be useful in assessment of LV function. Apart from M-mode recording, where the velocity can be measured as the inclination of the curve, the velocities can also be recorded by Doppler tissue imaging (DTI), either using a pulsed wave (pw DTI) technique based on spectral analysis (Isaaz et al. 1989), or colour coded (ccDTI) analysis of velocities (McDicken et al. 1992, Sutherland et al. 1994) (Figure 1). It has been shown that the maximal systolic and diastolic velocities of MA motion, detected by DTI or M-mode, can be used in the evaluation of global LV function (Gulati et al. 1996, Garcia et al. 1996a,b, Rodriguez et al. 1996, Sohn et al. 1997, Nagueh et al. 1997, Bojö et al. 1998, Lindström & Wranne 1999) and reference values for tissue Doppler measurements have been published (Alam et al. 1999, Nikitin et al. 2003). The ccDTI modality also allows thorough regional evaluation of the myocardium by strain or strain rate assessment (Heimdal et al. 1998, Brodin et al. 1998).
Assessment of LV diastolic function

Normal LV function is based on normal filling and emptying. When the actin-myosin filaments are dissociated due to the energy dependent process of reuptake of calcium ions into the sarcoplasmic reticulum, the contracted myocardium recoils and the intraventricular pressure falls rapidly and when it falls below the pressure in the left atrium the mitral valve opens and the early rapid filling of the LV begins. LV elastic recoil and the rate of relaxation are normally the predominant determinants of the filling force whereas the pressure in the left atrium plays a lesser role (Oh et al. 1997). During the early filling phase about 80% of the filling occurs in normal young individuals. (Van Dam et al. 1988, Pearson et al. 1991, Wandt
et al. 1997). The filling continues during the following period, the diastasis, but only a small part of the total filling occurs during this period (Little & Downes 1990). 15-20% of the filling occurs late in diastole during atrial contraction when a transmitral positive pressure gradient is created. In 1982 Kitabatake and co-workers introduced an echocardiographic method to measure the LV inflow velocities by pulsed Doppler during early (E) and late (A) diastole. The ratio between the maximal velocities during the early and late phases of filling (E/A ratio) has become a widespread method in the evaluation of LV diastolic properties. However, normal values are age dependent and the range for normal values is wide (Mantero et al. 1995). In addition, the transmitral pressure gradient is influenced by several complicating factors (Wigle 1990, Lewis 1996, Oh et al. 1997) making the interpretation of the LV inflow profile a challenge. Moreover, if there is a severe relaxation disturbance the atrial pressure will rise and a ‘pseudonormalized’ E/A ratio will appear, necessitating additional information by assessment of pulmonary vein flow velocities to reveal increased atrial pressure (Masuyama et al. 1992).


One of the aims of this thesis (Paper III) was to evaluate the usefulness of RVm as an index of disturbed diastolic function in consecutive patients with suspected or known heart failure, regardless of the genesis of heart disease.

Need of reference values of systolic and diastolic velocities

High intra- and inter-individual reproducibility has been reported for diastolic velocities obtained by M-mode (Bojö et al. 98). However, the reproducibility of systolic velocities has not been reported previously and one of the aims of this thesis was therefore to investigate the intra- and inter-individual reproducibility of maximal systolic velocities (Paper I).

Another advantage of M-mode, besides the expected high reproducibility, is that it is available in almost all echocardiographs, which tissue Doppler is not. But if the method is to be used in clinical routine work, there is a need for adequate reference values. Another aim of
the thesis was therefore to establish reference values for systolic (Paper I) and diastolic (Paper II) velocities, considering age and body size.

It has previously been reported that there is a significant difference between velocities recorded by different tissue Doppler methods (Kukulski et al. 2000), which means that the reference values are not interchangeable. Yet another aim of the present thesis was therefore to compare measures from M-mode and pulsed tissue Doppler (Paper III) in order to reveal if separate reference values must be used for each modality.

Influence of respiration on mitral annulus motion

Ventilation influences the filling of both right and left ventricle inducing respiratory synchronous variations in stroke volume, heart rate and blood pressure (Toska & Eriksen 1993). The filling of the right and left ventricle varies inversely and the septum is known to play an important role in this beat-to-beat regulation (Lundbäck 1986). The variation also involves the shortening of the ventricles in the long axis and it has been reported that the amplitude of MA motion varies considerably during respiration with a higher amplitude during inspiration (Wandt et al. 1998a).

During anaesthesia patients are often ventilated by positive pressure ventilation which may alter the filling conditions seen during spontaneous ventilation. One aim of the thesis was therefore to investigate the influence of the mode of ventilation and of the respiratory cycle regarding amplitudes and systolic and diastolic velocities in the LV long axis. (Papers I, II and IV).

Transoesophageal recordings in anaesthetized patients

During heart surgery transoesophageal echocardiography (TEE) has become a valuable tool in monitoring heart function. It may also be of value to use echocardiography during general surgery in patients with advanced cardiac disease, as extensive general surgery is performed in patients in advanced age and with accompanying cardiac pathologic conditions such as coronary insufficiency, myocardial diseases and cardiac valve affections. Due to practical and hygienic reasons, transthoracic echocardiography (TTE) is seldom useful when general surgery is performed.

During TEE it is often possible to visualize the septal, lateral, inferior and anterior areas of the myocardium and the corresponding parts of the mitral annulus but it can be difficult or impossible to align the echobeam fairly parallel to the direction of the long axis movement. Evaluation of LV function by recording long axis movement is a well established TTE
method but little (Simmons et al. 2002) has been done to evaluate the usefulness of transoesophageal recordings of mitral annular motion.

One aim of the current thesis was therefore to investigate the feasibility of using TEE recordings of amplitudes and systolic and diastolic velocities from four sites of the mitral annulus in anaesthetized patients without cardiac disease during general surgery. Another aim was to investigate the range of velocities and amplitudes of mitral annulus motion with TEE and to compare these values with the values obtained from transthoracic views. Yet another aim was to determine the intra- and inter-individual reproducibility of transoesophageal recordings from the septal, lateral, inferior and anterior sites of the mitral annulus as well as the angles between the observed direction of motion and the ultrasound beam. (Paper IV).
MAIN AIMS OF THE THESIS

1) To establish reference values for M-mode recordings of mitral annular velocities, considering the influence of age and body size. (Studies I and II).

2) To determine the influence of respiration on mitral annular velocities. (Studies I, II and IV).

3) To validate the clinical usefulness of echocardiographic recordings of mitral annular early diastolic velocity as an index of left ventricular diastolic function. (Study III).

4) To investigate the usefulness of transoesophageal recordings of mitral annulus motion in anaesthetized patients. (Study IV).
METHODS

Subjects

In Studies I and II fifty-seven healthy persons, 23 females and 34 males without a history of cardiac disease, mainly hospital employees and their relatives, aged 6 months to 72 years were studied. All had normal findings on physical examination and resting electrocardiograms. Individuals older than 40 years performed an exercise test without signs of heart disease. All had normal chamber dimensions and no signs of valvular dysfunction was found on the transthoracic echocardiographic examination performed before inclusion in the studies. The amplitude of the mitral annulus motion from the same population has been reported in a previous study (Wandt et al. 1997). In Study I another 10 healthy persons, aged 10 to 66 years, were recruited for the test of reproducibility.

In Study III sixty-six consecutive patients, 29 females and 35 males were included. They were all referred to echocardiography due to suspected or known heart failure. Two patients were excluded because of technical inadequate imaging. Pace-maker treatment, atrial fibrillation, bundle branch block as well as atrioventricular block of 2nd and 3rd degree precluded inclusion. Among the remaining 64 patients, aged 29 to 74 with a mean age of 59, 25 had a history of hypertension, 13 of angina pectoris and 11 a history of myocardial infarction.

In the fourth study 30 consecutive adult patients, 14 females and 16 men who were scheduled for elective general non-thoracic surgery were primarily included. There were no histories of coronary artery disease, hypertension, arrhythmias or heart failure and none had emphysema or adipositas. Two patients had partial left bundle branch blocks and were excluded as was one man with a hypertrophy of the left ventricle and one with a slightly dilated ventricle. One woman was excluded because of blurred imaging and one man due to non-reliable measurements. Among the remaining 24 patients, 13 females and 11 males, all had normal chamber dimensions in systole and diastole and there were no signs of significant valvular dysfunction. Another ten patients were enrolled, using the same inclusion and exclusion criteria, to determine intra- and inter-individual reproducibility. There were no contraindications to TEE such as swallowing problems, gastric regurgitation or known tumours or strictures of the oesophagus.
**Echocardiography and anaesthetic techniques**

An Acuson-128XP echocardiograph (Acuson Co., Mountainview, California, USA) was used for Studies I and II and an Acuson Sequoia for Study III. A combined 2 and 2.5 MHz transducer was used for adults and a combined 3 and 3.5 MHz for children. In Study IV a Vivid System Five (General Electric-Vingmed, Horten, Norway), including colour extracted Doppler tissue velocity imaging (TVI), was used together with a 2.5 MHz transducer for TTE and a 5 MHz transoesophageal multiplane probe. All persons were studied in the left lateral recumbent position and echocardiographic techniques and calculations of cardiac dimension were performed in accordance with the recommendations of the American Society of Echocardiography Committee (Sahn et al. 1978, Henry et al. 1980, Schiller et al. 1989). In Study IV, during anaesthesia, TTE was performed with patients lying flat on their back. All transthoracic recordings of the mitral annulus motion (MAM) were performed as described by Höglund and co-workers at four sites of the mitral annulus (Höglund et al. 1988). Recordings from the septal and lateral sites were obtained in the apical four chamber view and from the inferior and anterior sites in the apical two chamber view. Transoesophageal recordings in Study IV were obtained from mid oesophageal 2- and 4-chamber views of the LV.

In all studies a mean value from 3 heart cycles was used as was the average value from the four sites of the mitral annulus. In Study IV, mean values from the septal, lateral and inferior site were also calculated.

In Studies I and II the steepest portion of the M-mode recording was identified and two callipers were placed tangentially to the curves in systole and diastole respectively, or a ruler and pencil was used on printed curves after the examinations.

In Study III, M-mode recordings from the four sites of the mitral annulus were analyzed using two callipers, and the velocities obtained by pulsed tissue Doppler were measured from the outer border of the dense part of the spectral curve in accordance with the recommendations of the American Society of Echocardiography Committee (Quinones et al. 2002). The filter settings and gain were adjusted at optimal levels and a sample volume of 2 mm was used. With the sample volume located at the tip of the mitral leaflets the diastolic mitral inflow velocity was recorded by pulsed Doppler from the apical four-chamber view. The pulmonary vein flow profile was also obtained from the four chamber view with pulsed Doppler from the right upper pulmonary vein. One investigator recorded the pulmonary vein flow and E/A ratio and another investigator, who had no knowledge of the other measurements, recorded the maximal relaxation velocity by M-mode (M-RVm) and pulsed Doppler.
Doppler tissue imaging (pwTD-RVm). All patients were evaluated from measures of maximal relaxation velocity by M-RVm, pwTD-RVm and E/A ratio of mitral inflow and the pulmonary vein flow profile. Patients were classified as normal or having impaired diastolic function according to all 3 methods but abnormal E/A ratio and pulmonary vein flow profile were considered as true cases when sensitivity and specificity were calculated. Cut-off limits were determined by using the mean ± 2 SD of previously reported reference values, (Oh et al. 1997, Alam et al. 1999, Nilsson et al. 2002) and the limits for decreased E/A ratio were: 21-40 years, 0.73; 41-60 years, 0.78; and > 60 years, 0.60. To reveal the problem with pseudonormalization, in all patients with normal E/A ratio the pulmonary vein flow profiles were analyzed. The limits used for atrial reversal flow (PVa) velocity were: 21-40 years, 0.37 m/s; 41-60 years, 0.29 m/s; and > 60 years, 0.43 m/s. If the PVa duration was longer than the duration of the A-wave of the mitral inflow it was considered pathologic (Oh et al. 1997). The following cut-off limits for the ratio between maximal systolic and diastolic pulmonary vein forward flow were used: 21-40 years, 0.34; 41-60 years, 0.81 and > 60 years, 0.45.

Using the results from Study II the cut-off limits for M-RVm were given by: M-RVm (mm/s) = 146 – 1.3 x age.

pwTD-RVm limits (Alam et al. 1999) were: < 40 years, 129 mm/s; 40-59 years, 102 mm/s; and ≥ 60 years, 71 mm/s.

In Study IV echocardiography was performed when surgery was completed and patients still anaesthetized. Fentanyl and propofol or tiopentone were used for induction of anaesthesia and rocuronium was used to facilitate tracheal intubation. Supplementary doses of fentanyl and sevoflurane in an oxygen-air mixture were used to maintain anaesthesia. Echocardiographic acquisition was done when surgery was completed, during positive pressure ventilation and apnea as well as spontaneous ventilation in a steady state condition, confirmed by stable blood pressure, heart rate, transcutaneous measured oxygen saturation and a difference in inspiratory-expiratory sevoflurane concentration not exceeding 0.3 %. Spontaneous ventilation was established by just accepting an increase in end-tidal carbon dioxide value to a slightly higher level and no reversing drugs were used.

Efforts were made to get the ultrasound beam as parallel as possible to the mitral annulus long axis movement at four sites. A frame rate of at least 100/sec was used (Lind et al. 2002). Images were acquired in gray scale and colour-coded tissue Doppler during anaesthesia and stored as cine-loops in the system for later off-line analysis with extraction of myocardial long axis velocities. A first set of images was saved in a short apnoea (max 10 sec) by just disconnecting the ventilator during positive pressure ventilation and TE and TT
images were stored from each site of the mitral annulus. Other sets of images were acquired by using the respiratory tracing facility in the Vivid Five system, during positive pressure as well as spontaneous ventilation in expiration and inspiration.

All images captured for the reproducibility study were done during a short apnoea.

During the off-line analysis the image storage program with calculation facilities Echopac 6.4.1 (GE Vingmed) was used. The sampling volume was placed in such a way that the mitral annulus plane reached the sampling site at the end of systole which means that it was situated in the myocardium beneath the valve plane during the onset of contraction. The maximal velocities during systole (MLACV), early diastolic filling phase (RVm) and during the atrial contraction (Va) were determined. The displacement was calculated by integrating the velocity profile. The angle between the observed direction of total tissue motion at the sampling site and the top of the sector was measured on the screen by using a protractor and angle corrected values of velocities and displacement were calculated.

**Respiratory tracings**

In Papers I and II respiration was recorded with a nasal thermistor giving a signal displayed on the M-mode recordings classifying the beats as inspiratory or expiratory. The delay in the thermistor signal in relation to intrathoracic pressure changes is only a fraction of a second (Xiong et al. 1993). In Study IV, where a Vivid Five system was used, the respiratory tracing facility was based on variations in intrathoracic impedance. Images of the mitral annulus were captured during positive pressure as well as spontaneous ventilation and images were saved during inspiration and expiration respectively by using the direction of the respiratory signal.

**Statistics**

The Pearson product moment correlation coefficient was used for analysis of linear correlations between different variables and the two-tailed t-test was used to determine whether correlations were significant. A p-value of <0.05 was considered significant. Stepwise multiple regression analysis was performed in Studies I and II for variables with significant correlation to MLACV and RVm respectively. Differences in the velocities of the four sites of the mitral annulus was first analyzed with t-test in Study I but also by analysis of variance and Bonferroni’s method for multiple comparisons as in Study II. The paired two-tailed t-test was used in Study III to determine differences in M-RVm and pwTD-RVm and in
Study IV to determine differences between TTE and TEE values when more than 20 individuals were analyzed. The Wilcoxon signed rank test was used when fewer than 20 individuals were analyzed in Study IV. The coefficient of variation, C.V. = SD (x-y) x 100/mean x,y, was used for investigation of reproducibility in Studies I and IV. The Bland-Altman method (Bland & Altman 1986) was used to assess agreement between methods in Studies III and IV. In Study III, the Fisher’s exact test was used and sensitivity and specificity were calculated when the usefulness of two methods for detecting diastolic dysfunction was determined.

RESULTS

The influence of age and body size on mitral annular velocities obtained by the M-mode technique. (Studies I and II)

Children and adolescents up to the age of 18

MLACV had a significant positive correlation with age, height, body surface area, weight and MAM amplitude but a significant negative correlation with heart rate (table 1). The strongest correlations was with age (r=0.76) but also height was strongly correlated (r=0.74). However, in children and adolescents all tested variables which correlated with MLACV also strongly correlated with each other and when stepwise multiple regression was applied for age and height respectively, no significant additional explicatory power was found when the other variables were added. When age is used the correlation (figure 2) can be described by the equation MLACV (mm/s) = 49.0 + 2.5 x age (years), (SEE = 10.1). If height is used (figure 3) the equation MLACV (mm/s) = 24.0 + 0.34 x height (cm), (SEE = 10.5) describes the correlation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear correlation to MLACV</th>
<th>Significance of correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>r = 0.76</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Height</td>
<td>r = 0.74</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BSA</td>
<td>r = 0.73</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>r = 0.70</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>MAM-amp</td>
<td>r = 0.65</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>r = -0.46</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

*Table 1: Variables with significant linear correlation (r) to the maximal long axis contraction velocity (MLACV) in children and adolescents up to age 18 (n = 25). BSA=body surface area; MAM-amp=amplitude of mitral annulus motion.
Figure 2 and Figure 3: Correlation between maximal long axis contraction velocity (MLACV) and age and height respectively, in children and adolescents up to age 18.

RVm is significantly positive correlated with the amplitude of MAM ($r=0.59$), age ($r=0.50$) and height ($r=0.44$) but has a negative correlation with heart rate ($r=-0.55$). (Table 2). When heart rate is used the relation (figure 4) between RVm and heart rate can be described as $RVm (\text{mm/s}) = 171 - 0.54 \times \text{heart rate}$, (SEE = 18.7).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear correlation to RVm</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAM-amp</td>
<td>$r = 0.59$</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$r = -0.55$</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.50$</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Height</td>
<td>$r = 0.05$</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

**Table 2:** Variables with significant linear correlation ($r$) to long axis maximal relaxation velocity ($RVm$) in children and adolescents up to age 18 ( $n = 25$). MAM-amp=amplitude of mitral annulus motion.
**Figure 4**: Correlation between maximal long axis relaxation velocity (RVm) and heart rate in children and adolescents up to age 18.

### Adults

Height (r=0.66) and MAM amplitude (r=0.66) were strongest correlated with MLACV in adults. Also body surface area (BSA) was positively correlated (r=0.50) while age (r=-0.43) and heart rate (r=-0.40) were significantly negative correlated with MLACV (table 3). Stepwise multiple regression analysis showed that only height should be taken into account and the correlation (figure 5) can be described by the equation MLACV (mm/s) = 0.75 x height (cm) -50.5, (SEE = 9.8).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear correlation to MLACV</th>
<th>Significance of correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>$r = 0.66$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>MAM-amp</td>
<td>$r = 0.66$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>BSA</td>
<td>$r = 0.50$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = -0.43$</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$r = -0.40$</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

**Table 3**: Variables with significant linear correlation ($r$) to maximal long axis contraction velocity (MLACV) in adults over 18 ( $n = 32$ ). BSA=body surface area; MAM-amp=amplitude of mitral annulus motion.
RVm was positively correlated with MAM amplitude (r=0.63), height (r=0.54), MLACV (r=0.46), BSA (r=0.38) and negatively correlated with age (r=0.93), atrial contribution to ventricular filling (r=0.75), heart rate (r=0.67), systolic blood pressure (r=-0.61), diastolic blood pressure (r=-0.43) and ejection fraction (r=-0.37). (Table 4). Stepwise multiple regression analysis showed that RVm is best described by the equation RVm (mm/s) = 163 – 1.29 x age (years), (SEE = 8.4), (figure 6). MLACV and RVm are not correlated with weight or gender.
Table 4: Variables with significant linear correlation \((r)\) to long axis maximal relaxation velocity \((RVm)\) in adults. \(MAM\) = mitral annulus motion; \(MLACV\) = maximal long axis contraction velocity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear correlation to (RVm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(r = -0.93)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Atrial contribution to MAM</td>
<td>(r = -0.75)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>(r = -0.67)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>MAM-amp</td>
<td>(r = 0.63)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>(r = -0.61)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Height</td>
<td>(r = 0.54)</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>MLACV</td>
<td>(r = 0.46)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>(r = -0.43)</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>(r = 0.38)</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>(r = -0.37)</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

Figure 6: Correlation between maximal long axis relaxation velocity \((RVm)\) and age in adults.

**Difference between the four sites of the mitral annulus**

There are some differences in the MLACV and RVm at the different sites. When children and adults were analyzed as a common group it was found that MLACV as well as RVm at the lateral site was highest followed by the anterior, posterior and septal sites. The differences between the posterior and septal sites were not significant. The posterior site differed significantly from the anterior and lateral sites. Also the differences between the anterior and lateral sites were significant. The analysis of MLACV in Paper 1 was first performed with a repeated t-test, which can be considered as improper. However, when the test later on was performed with analysis of variance and Bonferroni’s method for multiple comparisons, as was the RVm, the results were unchanged.

**Reproducibility**

The intra- and inter-individual reproducibility for MLACV was determined, and the C.V. was calculated to 4.7 and 4.9 % respectively.

**The influence of respiration on mitral annular velocities. (Studies I, II and IV)**

In Studies I and II awake healthy individuals, children and adults were studied during spontaneous ventilation. MLACV was not affected by the respiratory cycle but RVm was about 5% higher during expiration. In Study IV anaesthetized patients were studied and when the transoesophageal recordings of the long axis movements of the mitral annulus were analyzed the anterior site was omitted because of low reproducibility. When mean values of the septal, lateral and inferior sites were compared during spontaneous as well as during positive pressure ventilation, it was not found any differences in MLACV or RVm during the inspiratory or expiratory phase of the breathing cycle. However, the integrated systolic velocity signal which expresses the amplitude of systolic motion, was higher during inspiration in spontaneously breathing patients and during expiration in positively pressure ventilated individuals.
The clinical usefulness of echocardiographic recordings of mitral annular early diastolic velocity as an index of left ventricular diastolic function. (Study III)

Age related reference values of diastolic mitral inflow velocities and pulmonary vein flow profiles were used when classifying the patients as true cases of diastolic dysfunction. According to this method 27 of the 64 patients were classified as having diastolic dysfunction, and when the systolic function was evaluated by the Simpson’s rule, 12 of these 27 patients had an EF of less than 50% which was classified as systolic dysfunction. M-RVm had a sensitivity of 89% and a specificity of 81% while pwTD-RVm had a sensitivity of 81% and a specificity of 78%. According to Fisher’s exact test both M-RVm and pwTD-RVm can be used to identify diastolic dysfunction (p<0.0001). M-RVm and pwTD-RVm were highly correlated (r=0.87) (figure 7) but pwTD-RVm was 29.7% higher than M-RVm, and there was a tendency to greater differences with higher values (figure 8). The E/A ratio was rather highly linearly correlated to both M-RVm (r=0.74) and pwTD-RVm (r=0.73). (Table 5).

Figure 7: Correlation between M-mode (M-RVm) and tissue Doppler RVm (TD-RVm).

Figure 8: Bland-Altman diagram of agreement between M-mode (M-RVm) and tissue Doppler RVm (TD-RVm).
Table 5: The linear correlation ($r$) between maximal relaxation velocity recorded by M-mode ($M-RVm$) and recorded by pulsed tissue Doppler ($TD-RVm$) and some diastolic and systolic indices of left ventricular function. $E/A$ ratio=ratio between early (E) and atrial (A) mitral inflow velocities; $MAM$=mitral annulus motion; $EF$=ejection fraction; $MLACV$=maximal long axis contraction velocity by M-mode ($M$) and tissue Doppler ($TD$).

<table>
<thead>
<tr>
<th>Diastolic:</th>
<th>$M-RVm$</th>
<th>$TD-RVm$</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A ratio of mitral inflow</td>
<td>$r = 0.74$</td>
<td>$r = 0.73$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Atrial contribution to MAM</td>
<td>$r = -0.69$</td>
<td>$r = -0.75$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Isovolumic relaxation time</td>
<td>$r = -0.40$</td>
<td>$r = -0.41$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Deceleration time of mitral inflow</td>
<td>$r = -0.18$</td>
<td>$r = -0.37$</td>
</tr>
<tr>
<td></td>
<td>$NS$</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>Systolic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAM amplitude</td>
<td>$r = 0.57$</td>
<td>$r = 0.54$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>M-MLACV</td>
<td>$r = 0.50$</td>
<td>$r = 0.54$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>TD-MLACV</td>
<td>$r = 0.54$</td>
<td>$r = 0.53$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>EF by Teichholz</td>
<td>$r = 0.32$</td>
<td>$r = 0.27$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>EF by Simpson</td>
<td>$r = 0.31$</td>
<td>$r = 0.31$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.05$</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

The usefulness of transoesophageal recordings of mitral annulus motion in anaesthetized patients. (Study IV)

Feasibility and reproducibility

In total 35 patients were investigated, 25 in the main study and 10 for the reproducibility control. The mitral region was visualized in all patients from the mid-oesophageal two- and four-chamber views and recordings from the septal, lateral, inferior and anterior sites were obtained. Analysis of TEE data was prevented by artefacts in one patient, probably due to electrical interference. Efforts were made to align the movements of the mitral annular sites as parallel as possible to the echobeams, a goal that is hardest to achieve for the anterior site (table 6). In addition, there were some problems in getting reliable diastolic values during spontaneous ventilation (Paper IV, table 2). In the reproducibility study intra- and inter-individual C.V. values varied from 6.3-24.2 % for the displacement and systolic and early diastolic velocities of the septal, lateral and inferior sites. C.V. values obtained from the anterior site for D and velocities were in the range of 17.5-35.4 %. C.V. for the maximal late diastolic velocity at the four sites varied from 17.5 to 42.7 % (table 7).

<table>
<thead>
<tr>
<th>Site of mitral annulus</th>
<th>Angle between motion and TE ultrasound beam (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal</td>
<td>17±13.3</td>
</tr>
<tr>
<td>Lateral</td>
<td>22±20.8</td>
</tr>
<tr>
<td>Inferior</td>
<td>7±6.8</td>
</tr>
<tr>
<td>Anterior</td>
<td>66±23.5</td>
</tr>
</tbody>
</table>

Table 6: The angles between observed direction of tissue motion at the four sites of the mitral annulus, and the ultrasound beam. *TE* = transoesophageal; *SD* = standard deviation.

Differences between TEE and TTE views

The comparisons between TEE and TTE values of velocities and displacement were performed using images obtained in a short apnoea during positive pressure ventilation. TTE values of mean MLACV, RVm, Va and D from four sites were significantly higher than the corresponding TEE values. If the anterior site is omitted due to low reproducibility and the difficulties in obtaining an acceptable angle, the mean differences between TTE recordings from four sites and TEE recordings were smaller (table 8). A tendency of higher differences in the higher range of velocities was shown (figures 9, 10, 11). When TTE and TEE values...
were compared using angle corrected values from all TEE sites there were no differences between TEE and TTE values but the correlation coefficient decreased indicating methodological limitations in the use of angle corrected values.

**Table 7:** Intra- and inter-individual reproducibility of systolic and diastolic velocities and displacement at four sites of the mitral annulus expressed as the coefficient of variation (C.V.) in 10 individuals (n=10).

<table>
<thead>
<tr>
<th></th>
<th>Inter-individual reproducibility (C.V.) (n=10)</th>
<th>Intra-individual reproducibility (C.V.) (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Septal site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Displacement</td>
<td>15.3</td>
<td>15.8</td>
</tr>
<tr>
<td>Max systolic velocity</td>
<td>9.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>13.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>21.0</td>
<td>35.4</td>
</tr>
<tr>
<td><strong>Lateral site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Displacement</td>
<td>23.0</td>
<td>24.2</td>
</tr>
<tr>
<td>Max systolic velocity</td>
<td>15.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>12.5</td>
<td>17.2</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>42.7</td>
<td>25.4</td>
</tr>
<tr>
<td><strong>Inferior site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Displacement</td>
<td>15.8</td>
<td>12.1</td>
</tr>
<tr>
<td>Max systolic velocity</td>
<td>8.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>11.9</td>
<td>15.0</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>21.0</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>Anterior site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Displacement</td>
<td>28.9</td>
<td>23.6</td>
</tr>
<tr>
<td>Max systolic velocity</td>
<td>24.7</td>
<td>21.7</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>21.9</td>
<td>25.7</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>35.4</td>
<td>17.5</td>
</tr>
</tbody>
</table>
Table 8: Mean values and standard deviations (SD) of transoesophageally (TE) and transthoracally (TT) recorded systolic and diastolic velocities and amplitudes from four (septal, lateral inferior and anterior) sites as well as three sites (septal, lateral and inferior) are listed. Also the differences in velocities and amplitudes in percent as well as the level of significance ($p$) are shown.

$TT-n=$ number of patients analyzed in transthoracic view; $TE-n=$ number of patients analyzed in transoesophageal view.

<table>
<thead>
<tr>
<th></th>
<th>$TT-n$</th>
<th>$TT$-recording (Mean±SD) mm, cm/sec</th>
<th>$TE-n$</th>
<th>$TE$-recording (Mean±SD) mm, cm/sec</th>
<th>Difference %</th>
<th>Significance of diff, $p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean of four sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>19</td>
<td>10.2±2.8</td>
<td>19</td>
<td>7.6±2.6</td>
<td>25.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max syst velocity</td>
<td>20</td>
<td>6.26±1.27</td>
<td>20</td>
<td>4.81±0.95</td>
<td>23.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>16</td>
<td>8.14±1.86</td>
<td>16</td>
<td>5.94±1.58</td>
<td>27.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>17</td>
<td>4.97±2.10</td>
<td>17</td>
<td>3.87±1.66</td>
<td>22.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Mean of three sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>20</td>
<td>10.7±2.5</td>
<td>20</td>
<td>9.2±2.1</td>
<td>14.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max syst velocity</td>
<td>20</td>
<td>6.30±1.34</td>
<td>20</td>
<td>5.44±0.84</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max early diastolic velocity</td>
<td>17</td>
<td>7.99±1.96</td>
<td>17</td>
<td>6.56±1.22</td>
<td>17.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Max late diastolic velocity</td>
<td>19</td>
<td>5.10±2.00</td>
<td>19</td>
<td>4.18±1.50</td>
<td>18.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
**Figure 9:** Bland-Altman plot of differences in maximal long axis contraction velocity (MLACV, cm/sec) from four transthoracic (TT) and three transoesophageal (TE) sites.

**Figure 10:** Bland-Altman plot of differences in displacement (D, mm) from four transthoracic (TT) and three transoesophageal (TE) sites.
Figure 11: Bland-Altman plot of differences in maximal long axis relaxation velocity (RVm, cm/sec) from four transthoracic and three transoesophageal sites.

Tables 7 and 8 and Figures 9, 10 and 11 are reprinted from: Nilsson, B., Henningsson, R., Brodin, L-Å. and Wandt, B. (2006) Transesophageal echocardiographic acquisition of mitral annulus motion during monitoring of left ventricular function in anesthetized patients, J Am Soc Echocardiogr, 19:00-00.
**DISCUSSION**

*Why search for other indices than EF for assessment of systolic function?*

In the beginning of the 1990s the concept of ‘isolated diastolic dysfunction’, with preserved systolic function, spread among cardiologists all over the world and it was stated that as many as about one third of patients with heart failure have normal systolic function but impaired diastolic function (Vasan RS et al. 1995). This may be a misconception due to low sensitivity of EF as an index of systolic function. In recent studies where the long axis systolic motion was used for investigation of the LV function it has been shown that the LV contraction is impaired even in many cases with normal EF (Bolognesi et al. 2001, Nikitin et al. 2002, Yip et al. 2002, Vinereanu et al. 2001, Wandt et al. 2004) and it has been questioned if ‘isolated diastolic dysfunction’ exists at all (Yip et al. 2002, Vinereanu et al. 2005).

Along with an increasing awareness of the limitations of EF, one ambition with this thesis is to contribute to the development of clinically useful measures of systolic LV function, based on the long axis motion. Hopefully the results from the studies in this thesis do their share in that respect, especially concerning the usefulness in transoesophageal echocardiography (Paper IV), but also by the presentation of reference values for TTE M-mode recordings (Paper I).

*Why search for other indices than E/A-ratio for investigation of diastolic function?*

Non-invasive evaluation of diastolic function by echo-Doppler technique has been used since the early 1980s when Kitabatake and co-workers introduced pulsed Doppler recordings of early and late transmitral blood inflow velocities during the LV filling. The E/A ratio and deceleration time of the E wave used in the evaluation of LV diastolic function is however, highly dependent upon the transmitral pressure gradient which in turn is influenced not only by the property of the LV wall, but also by several other factors as loading conditions, left atrial pressure and function.

There is also a problem with ‘pseudonormalization’ of the E/A ratio due to an increased LV filling pressure and pulsed Doppler signals from blood flow in pulmonary veins have therefore been used in order to detect elevated filling pressure. (Oh et al. 1997, Appleton et al. 1988). But even with the addition of investigation of the venous flow, the diagnostic value of the method is very limited, due to a wide range for normal values (Mantero et al. 1995).
In the struggle for developing new methods to describe the intrinsic diastolic properties of the LV, irrespective of loading conditions, the interest in the maximal diastolic long axis velocities increased and it was shown that these velocities were useful in the evaluation of diastolic function in different heart diseases (Garcia et al. 1996b, Sohn et al. 1997, Bojö et al. 1998, Ohte et al. 1998, Oki et al. 1998). It has also been claimed that this index of diastolic function was less preload dependent than the E/A value and pulmonary vein velocity profiles (Farias et al. 1999), though not totally insensitive to loading conditions (Nagueh et al. 2001).

The results presented in the present thesis hopefully contribute to the development of clinically useful alternatives to the E/A-ratio in assessment of diastolic function, specially concerning reference values for TTE M-mode recording (Paper II), the usefulness of TTE M-mode and pulsed wave tissue Doppler recordings in patients with different heart diseases (Paper III) and the usefulness in TEE investigation of the LV function (Paper IV).

**Theoretical considerations concerning relations between systolic and diastolic indices.**

A significant correlation between systolic and diastolic function is expected, as a dysfunction in either is often (or always) associated with dysfunction in the other. That is probably the main reason for the rather weak correlation between RVm and EF ($r=0.31$, $p<0.05$) in the patients in Paper III. In healthy adults in Paper II however, there was a weak negative correlation between RVm and EF ($r=-0.37$, $p<0.05$). This might be confusing but can be explained by the fact that in healthy subjects EF is constant or tends to increase by advancing age, (Pfisterer et al. 1985, Bauer et al. 1988, Wandt et al. 1998b), while as shown in the current study (Paper II), RVm decreases considerably by advancing age. The preserved or slightly increased EF by advancing age is not believed to reflect unaffected or improved LV function, but rather myocardial thickening with decreased LV lumen (Wandt et al. 1998b).

In healthy subjects (Paper II) and in patients (Paper III) there were significant positive correlations between RVm and the systolic indices MAM-amp and MLACV. This relation might be expected since all three indices reflect long axis motion, MAM-amp the total distance of motion and RVm and MLACV the velocities during diastole and systole respectively. There is probably also a mechanistic coupling between these long axis indices, however. During systole there is a deformation of the myocardium, partly due to a shortening of the LV wall in the long axis and a simultaneous thickening of the wall but partly also due
to a twisting motion around the long axis. The deformation, and perhaps particularly the twisting motion, during systole is important for the onset of the rapid filling period. By storage of potential energy which is released in early diastole the systolic deformation contributes to effective filling of the LV. In human transplant patients and animals, MR studies have shown that enhanced inotropic state increase the systolic twist and also the early diastolic untwisting, occurring during the diastolic isovolumic period, (Rademakers et al. 1992, Moon et al. 1994) probably because of higher storage of potential energy.

**Reference values for M-mode recordings of MLACV and RVm**

In order to establish reference values the correlations between MLACV and RVM respectively and age, height, body surface area, and heart rate were investigated.

In Paper I it was shown that MLACV in adults has a stronger correlation to height (r=-0.66) than to body surface area (r=0.50) or age (r=-0.43) or heart rate (r=-0.40). There was no significant correlation with weight or gender. The analysis implies that height is the variable that ought to be taken into account when reference values are given. Stepwise multiple regression analysis showed that the addition of age does not increase the explicatory power significantly. The strong correlation between MLACV and height might be explained by the relation between height and heart size. A strong correlation between the MA motion amplitude and height has been reported previously (Wandt et al. 1997) and it is plausible to believe that in a large ventricle with long diameter in the longitudinal axis, the mitral annulus has to move a longer distance during systole than in a small heart, which influences the mean velocity but may also have an impact on the maximal velocity of the motion, MLACV.

Based on the findings above the suggestion is that only height should be taken into account in adults and that the equation MLACV (mm s\(^{-1}\)) = 0.75 x height (cm) - 50.5 (±19.6) (±2 SEE) be used for calculation of normal range. The study population was only 32 adults however, and it is therefore desirable that this equation for normal range can be replaced by normal values based on a much greater study population.

In children and adolescents all tested variables with significant correlation with MLACV are also strongly correlated to each other. Stepwise multiple regression analysis showed the strongest correlations with age and height (r=0.76 and 0.74 respectively) and no significant explicatory power was gained when the other variables were added, not even when
age or height were added to each others equations. Either height or age may be used for calculation of the normal range. When height is used the equation is MLACV (mm s\(^{-1}\)) = 0.34 x height (cm) + 24.0 (±21.0)(± 2 SEE) and when age is used the equation is MLACV (mm s\(^{-1}\)) = 2.5 x age (years) + 49.0 (±20.2)(± 2 SEE). The desire for reference values based on larger study population is even more pronounced in children and adolescents as these equations are based on investigation of only 25 subjects.

Concerning RVm in adults, there was a very strong negative correlation with age (r=−0.93) and stepwise multiple regression analysis did not add any significant power when the other tested variables (height, weight, body surface area, and heart rate) were added. The reasons for the changes by increasing age are probably stiffening due to an increase in myocardial connective tissue content (Klima et al.1990) and possibly a reduced calcium ion sequestration by the sarcoplasmic reticulum, which is also seen with increasing age (Lompre et al. 1991).

For calculation of normal range of RVm in adults only age should be taken into account. The equation RVm (mm s\(^{-1}\)) = 163 - 1.29 x age (years) (±16.8)(± 2 SEE) can be used.

In children and adolescents the strongest correlation (r=−0.55) was seen for heart rate, and no significant explicatory power was gained when the other tested variables were investigated by stepwise multiple regression analysis. For calculation of reference values the equation RVm (mm s\(^{-1}\)) = 171 - 0.54 x heart rate (±37.4)(±2 SEE) may be used.

**Differences between the four sites of the mitral annulus**

The presented reference values are valid for mean velocities of all four sites of the mitral annulus. As shown in Papers I and II there are differences between the sites with the highest velocities recorded from the lateral site and the lowest from the septal site, which must be taken into account if fewer than four sites are used in the assessment. The mean of the septal and lateral sites however, probably differ very little from the mean of all four sites.
Influence of respiration

No significant difference was found in MLACV between expiratory and inspiratory beats (Paper I) while RVm was about 5% higher during expiration than during inspiration (Paper II). For practical purposes it is probably not necessary to take respiration into account, at least not if the mean of a few beats is used for the measurement. Changes during respiration are of theoretical interest however, and are dealt with in a separate section below.

Reference values for M-mode and pulsed tissue Doppler are not interchangeable

As shown in Paper III there are considerable differences between RVm recorded by M-mode and by pulsed tissue Doppler. A similar difference has appeared concerning MLACV (Wandt et al. 2004). Values from tissue Doppler recordings are almost 30% higher than those from M-mode recordings which means that reference values for these two modalities are certainly not interchangeable. The difference is probably mainly due to the fact that measures from pulsed tissue Doppler were obtained from the outer border of the dense part of the spectral curve, in accordance with recent guidelines (Quinones et al. 2002). As previously advocated by some authors (Zhou et al. 1997) concerning pulsed Doppler recording of blood flow, it is for theoretical reasons more proper to measure from the point which represents the modal velocity, which is difficult to identify on the recordings, but is expected to be in the middle of the dense part of the curve. Values of RVm by pulsed Doppler in Paper III were 18% lower when measured from the point which represents the modal velocity than measures from the outer border of the dense part of the curve. Another reason for the difference between M-mode recordings and pulsed tissue Doppler recordings might be that the endocardial part of the most basal part of the LV has lower longitudinal velocities than the epicardial part, which was recently reported from an echocardiographic and angiographic study (Emilsson et al. 2001b). M-mode recordings are usually obtained from the endocardial part, which corresponds to the fibrous part of the mitral annulus, while tissue Doppler recordings can be obtained from more epicardial parts as well. Furthermore, it was reported from a phantom study, that pulsed tissue Doppler recordings overestimate velocities even when measures from the part of the curve which represents the modal velocity is used (Kukulski et al. 2000).

However it must be remembered that during the longitudinal motion of the mitral annulus and LV basal parts, there are also radial and twisting motions which means that new
tissue is entering into the sampling site when pulsed tissue Doppler is used. Also when M-
mode is used it may be difficult to align the cursor in such a direction that a single spot is
visualized. Radial and twisting motion may bring adjacent tissue into the cursor line and a
‘wall climbing’ effect may be seen. The steepest parts of the M-mode curves can be hard to
define since the highest velocity may exist during a very short time and when placing a
tangent to the curve it may be considered more as a mean velocity.

Disturbances in the timing of contraction and relaxation in the long- and short-axis exist
during conditions as myocardial hypertrophy, mitral valve and coronary artery disease (Jones
et al. 1990, Henein et al. 1997). Time events are easily detected by the TVI technique while
M-mode recordings are less suitable (figure 1).

** Influence of respiratory cycle and mode of ventilation on displacement and velocities

The cyclic variations in intrathoracic pressure that are created during ventilation are
known to influence the filling of both right and left ventricle which varies inversely and the
interventricular septum plays a regulatory role (Lundbäck 1986) between the two ventricles,
allowing the right ventricle to receive more blood during spontaneous inspiration when blood
is pooled in the venous lung vessels and thus decreasing the LV stroke volume. It is not
obvious however, how that affects the amplitude and velocities of the long axis motions. In
TEE and TTE investigation of anaesthetized patients (Paper IV) the amplitude of motion was
higher during inspiration in spontaneous ventilation, which is also described in a previous TT
study (Wandt et al. 1998a) and when positive pressure ventilation was applied, displacement
was higher during expiration. It seems that long axis displacement and stroke volume vary
inversely. Probably there is an increased vagal tone decreasing contractility during expiration
in spontaneous ventilation (Karlocai et al.1998) and these variations in the parasympathetic-
sympathetic balance may act as a compensatory mechanism in order to decrease variations in
stroke volume and blood pressure.

During positive pressure ventilation, when the increased intrathoracic pressure during
inspiration will expel the pooled blood in the lung vessels, the filling and stroke volume of the
LV is increased during inspiration. If the compensatory mechanisms act as during
spontaneous ventilation, the findings that displacement is reduced during inspiration in
positive pressure ventilation are not surprising but emphasize the role of the interventricular
septum in the handling of ventilation synchronous variations in right and left ventricular filling.

In the anaesthetized patients there were no differences in MLACV or RVm during inspiration and expiration. However, a tendency (p=0.069) of higher MLACV during spontaneous inspiration was seen. These facts contrast with the findings in the awake patients where RVm was about 5% higher during expiration but no difference was seen in MLACV. Anaesthesia may influence the power of respiratory muscles including the diaphragm which may alter the filling rate and also the balance in the autonomous nervous system. Further studies including higher number of patients are needed to investigate these conditions more thoroughly.

Comparisons of MLACV and RVm between spontaneous and positive pressure ventilation were not performed since there was a slight difference in end-tidal carbon-dioxide value between the two modes of ventilation which may alter afterload.

**Usefulness of RVm for investigation of LV diastolic function**

Rather high sensitivity and specificity were found when M-mode and pulsed tissue Doppler recordings were used for identification of LV diastolic dysfunction in Paper III. The figures were 89% sensitivity and 81% specificity for M-mode and slightly lower for pulsed tissue Doppler where a sensitivity of 81% and a specificity of 78% was found. The results suggest that RVm, recorded by either modality can be used in assessment of diastolic function. The high sensitivity is expected for theoretical reasons, as impaired relaxation occurs very early in the development towards diastolic dysfunction. The traditional non-invasive variables, which were used to determine ‘true’ cases of dysfunction in the study, namely the combination of E/A ratio of the mitral inflow and pulmonary vein flow, are to a great extent dependent on the compliance of the LV, which is often maintained until later in the development of diastolic dysfunction. In early cases of diastolic dysfunction the RVm can therefore be expected to be decreased while the E/A ratio and pulmonary vein flow are still within normal limits.

**Why should TEE long axis recordings be used?**

Practical and hygienic reasons often make it impossible to perform TTE during surgery but by introducing a probe into the oesophagus it is possible to obtain images of the myocardium and valves, often with excellent quality since no lung tissue will interpose
between the probe and heart. TEE has been a routine method in monitoring heart and valve function during cardiac anaesthesia and in the transgastric short axis view the myocardium perfused by the three main coronary arteries is visualized. However, the longitudinal movement of the heart brings new tissue into the short axis view and in a recent study with a conic shaped phantom it was claimed that the long axis movement will create an illusion of contraction (Playford et al. 2003). The longitudinal movement is the major determinant of stroke volume (Emilsson et al. 2001a) which underlines the importance of investigating the usefulness of long axis recordings of the LV. It also seems that maximal longitudinal velocities may be more sensitive to disturbances in LV function than EF (Nikitin et al. 2002, Yip et al. 2002, Wandt et al. 2004, Vinereanu et al. 2002, 2004). However, in spite of the use of multiplane transducers it is a challenge to align the echobeams fairly parallel to the long axis movements which will result in an underestimation of the velocities.

**Feasibility and reproducibility of TEE recordings by TVI Imaging**

In all patients investigated in Study IV a clear view of the mitral region was obtained with recordings from the septal, lateral and inferior sites of the annulus, but in most patients acceptable recordings from the anterior site could not be achieved, due to wide angles between the motion in the long axis and the ultrasound beam.

**Angle errors**

During systole the contraction of the different myocardial layers causes a shortening in the long axis of the LV, a thickening of the wall with an inward motion of the endocardial part of the myocardium and a twisting motion around the long axis. In echocardiographic recording of longitudinal velocities it is very important to direct the ultrasound beam as parallel to the long axis as possible and in TEE it is often difficult to achieve angles low enough for reliable recordings, as the transducer position is limited to the oesophagus (and sometimes the ventricle). The problem could maybe be decreased by the use of angle corrections, which is a technical possibility in the program package in most echocardiographs. In the investigation presented in Paper IV however, angle correction brought mean measurements which differed less compared with TTE recordings, but also unfortunately a decreased correlation coefficient when the modalities were compared, suggesting methodological problems in angle correction. The failure is probably mainly due to the fact
that the correction by guidance from the 2-dimensional image only deals with two directions, but a true correction demands visualisation of all three dimensions.

In the current study the longitudinal movements of the inferior sub-annular region was easiest to record, with the longitudinal motion fairly parallel to the echo beams, but an increasing angle difference could be seen for the septal, lateral and anterior parts of the myocardium. At the anterior site the mean angle was as wide as 66 degrees (Table 6).

**Reproducibility**

The reproducibility for anterior displacement and velocities were unacceptably low, with C.V. in the range of 21.7-28.9%. Late diastolic velocities from all sites also had unacceptably low reproducibility with C.V. in the range of 17.5-42.7%.

Recordings of MLACV and RVm from the septal, inferior and lateral sites had acceptable reproducibility with C.V. in the range of 6.3-17.2%.

The reproducibility for displacement was also acceptable concerning the septal and inferior sites, with C.V. in the range of 12.1-15.8%, but unacceptably low for the lateral site with C.V. of 24.2% and 23.0% for intra- and inter-individual tests respectively.

Based on these findings one suggestion is that the anterior site be omitted and that the mean of the measurements from the septal, lateral and inferior sites be used in assessment of global systolic and diastolic LV function. A second suggestion is that only RVm be used in investigation of diastolic function as the late diastolic velocities have unacceptably low reproducibility.

Higher reproducibility was recently reported for TTE measures, with C.V. of 5-10% (Gaballa et al. 2001). However, the authors estimated the reproducibility (single measurement error estimated from double measurements) using Dahlberg’s formula which means that the values are divided by $\sqrt{2}$. They also performed the off line measurements from the same recordings while the TEE assessments in the current study were done from images captured by two sets of investigations, which includes difficulties in image acquisition. The studies are therefore not comparable, but a higher reproducibility in TTE recording is expected as the distance to the sampling site is longer due to the transthoracic position of the transducer in TTE investigations, which makes it easier to align the echo beams parallel to the long axis movements and thus making the radial motion of the myocardium less important.
**Differences between TTE and TEE measurements**

When TTE and TEE mean values from four sites were compared, MLACV, D, RVm and V_a were 25% higher for TTE images. A mean difference of 15% was found when the anterior site was excluded due to low reproducibility. No differences were found at the inferior site which is easiest to align parallel to the echo beams, nor did D differ at the septal site. Similar results were reported from a recent study (Simmons et al. 2002), except that in that study there was no significant difference in velocities obtained from the septal site, which was found in the current study. The different results may be explained by the somewhat greater group of patients in the present study.
CONCLUSIONS

**Reference values**

- M-mode recordings of the long axis maximal systolic velocity are highly reproducible and when reference values are calculated age or height should be taken into account in children and adolescents, and height in adults. If age is used in children the reference values can be calculated by the equation: MLACV (mm/sec) = 2.5 x Age (years) + 49.0 (±20.2) (±2 SEE). In adults the normal interval can be calculated from the equation MLACV (mm/sec) = 0.75 x Height (cm) -50.5 (±19.6) (±2 SEE).

- When M-mode recordings of the early maximal relaxation velocity is used, heart rate should be used when calculating reference values in children and adolescents and the calculation can be done from the equation RVm (mm/sec) = 171 – 0.54 x heart rate (±37.4) (±2 SEE). In adults, age should be taken into account and the normal values can be calculated from the equation RVm (mm/sec) = 163 – 1.29 x age (±16.8) (±2 SEE).

- **Influence of respiration**

  In awake healthy individuals respiration does not influence MLACV but RVm is about 5% higher during expiration.

- Respiration does not affect the systolic or early diastolic maximum velocities during anaesthesia.

- **RVm in assessment of diastolic function**

  RVm obtained by M-mode and pulsed tissue Doppler can be used to identify diastolic dysfunction.

- Pulsed tissue Doppler values are about 30% higher than M-mode values. The reference values are therefore not interchangeable.
• **Transoesophageal TVI recording**

  • Due to low reproducibility, the anterior site should be omitted when mean values of transoesophageal longitudinal systolic and diastolic velocities of the mitral annulus are used for assessment of global LV function.

  • Late diastolic longitudinal velocities have low reproducibility and should not be used.

  • When mean values from the septal, lateral and inferior sites are used TEE measures are about 15 % lower than TTE values of longitudinal systolic and early diastolic velocities.
Sammanfattning

Maximale systoliska och diastoliska hastigheter mätt på fyra punkter i mitralisklaffringen (MA) avspeglar vänster kammarbes (VK) egenskaper. I denna avhandling undersöktes vilka faktorer som påverkar M-mode registrerade hastigheter hos friska barn och vuxna och referensvärden anges. Vidare kartlades hur användbar M-mode och pulsad vävnadsdoppler är för att upptäcka diastoliska rubbningar hos patienter med hjärtsviktssymptom. Även reproducibilheten vid transesofageal (TE) avbildning av VK längsaxelrörelse och skillnaden mot transthorakal (TT) registrering hos sövda hjärtafriska patienter liksom andningens inverkan undersöktes.

Genom att anbringa tangenter till M-moderegistreringar av MA från apikal 2- och 4-kammarprojektion mättes maximala systoliska (MLACV) och tidigdiastoliska (RVm) längsaxelhastigheterna. Efter stegvis multipel regressionsanalys beträffande ålder, vikt, kroppslängd, kroppsyta och hjärtfrekvens föreslås följande ekvationer vid beräkning av referensvärden:

**Barn och ungdomar under 18 år:**
MLACV (mm/s) = 2,5 x Ålder (år) + 49,0, (±20,2) (±2 SEE)
RVm (mm/s) = 171 – 0,54 x Hjärtfrekvens, (±37,4) (±2 SEE)

**Vuxna:**
MLACV (mm/s) = 0,75 x Kroppslängd (cm) – 50,5, (±19,6) (±2 SEE)
RVm (mm/s) = 163 – 1,29 x Ålder (år), (±16,8) (±2 SEE)

Intra- och inter-individuell reproducibilitet uttryckt som variationskoeficienten för MLACV var 4,7% och 4,9%.

Hos 64 patienter med hjärtsviktssymptom registrerades inflödet till VK och lungvensflödesprofiler med pulsad Doppler och patienterna klassades som ”äkta” fall av diastolisk dysfunktion baserat på ålderskorrigerade referensvärden. RVm mättes med M-mode (M-RVm) och pulsad vävnadsdoppler (TD-RVm) och enligt Fisher’s exakta test kan båda mätmetoderna användas för att detektera diastolisk dysfunktion men TD-RVm är 29,7 % (p< 0,0001) högre än M-RVm. Sensitiviteten och specificiteten för RVm att korrekt detektera diastolisk rubbning var 89 % respektive 81 %, och för TD-RVm 81 % och 79 %. M-RVm och TD-RVm var starkt linjärt korrelerade (r = 0,87).

Skillnader i TT och TE registreringar av MA undersöktes med färgkodad vävnadsdoppler (TVI) hos 24 hjärtafriska sövda patienter. Ytterligare 10 patienter inkluderades för reproducibelhetskontrollen. Anteriora punkten har låg reproducibelbarhet och bör ej användas när TT och TE värden jämförs. Ett TE medelvärde från 3 punkter (laterala, septala och inferiora) är ca 15 % lägre än ett TT medelvärde från 4 punkter. Bara systoliska och tidigdiastoliska värden befunnna ha accepterbar reproducibelbarhet.

Andningen påverkar inte MLACV eller RVm hos sövda patienter men hos vakna är RVm ca 5 % högre under utandningen.
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