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PROGNOSTIC AND DIAGNOSTIC VALUE OF TISSUE DOPPLER IN PATIENTS WITH SYSTOLIC HEART FAILURE

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ABSTRACT

Heart failure (HF) is a condition where the heart fails to meet the need of delivery of oxygen and energy to the tissues. In spite of advances in the recent decades, the prognosis is still serious with a mortality risk comparable to severe cancer. The most common heart imaging method today is ultrasound of the heart, or echocardiography. The prognosis in HF is affected by several factors. In the last two decades, the diastolic function and the function of the right ventricle (RV) have been shown to be important for the prognosis in HF.

The purpose of the present thesis was to evaluate the diagnostic and prognostic properties of a relatively new echocardiographic method, tissue Doppler imaging (TDI). TDI measures the velocities of the myocardial tissue throughout the cardiac cycle. It has been shown to be a simple, sensitive and reproducible method to evaluate systolic and diastolic function of the left ventricle (LV) and the RV. Another aim was to examine the prognostic power of myocardial performance index (MPI), a Doppler based index, calculated as the sum of isovolumic time intervals divided by the ejection time. 173 patients admitted to the Department of Cardiology at Södersjukhuset (Stockholm General South Hospital) due to acute HF and reduced systolic function (LV ejection fraction, LVEF \leq 40%) were included in the study. Echocardiography was performed and TDI velocities were measured at 4 sites of the LV and at RV free wall. We performed two diagnostic studies (Papers I and V), and three prognostic studies (Paper II-IV). **In Study I** the diastolic function of 126 patients with sinus rhythm was evaluated with TDI and conventional methods, so called transmitral Doppler blood flow. Almost one third of the patients had a pattern on transmitral blood flow that could not be distinguished from normal diastolic function, but TDI showed that the vast majority of these patients had diastolic dysfunction. With TDI, the diastolic function could be assessed in all patients. **In Paper V**, 41 patients with newly diagnosed HF were examined again after 3-6 months when HF medication was titrated to adequate doses. At follow-up, all conventional echocardiographic parameters were improved, but the TDI parameters hardly changed at all. **In Paper II-III**, the prognostic value of TDI parameters was studied. With a shorter follow-up period, the variable E/e', a non-invasive measure of left sided filling pressure, was shown to be an independent predictor of cardiovascular (CV) mortality during the study period (HR 3.8, p 0.014). **In Paper III**, the follow-up period was longer, and a new TDI parameter from the RV (the sum of RV systolic and diastolic velocities) was found to be the only variable associated with a combined end-point of CV mortality and HF hospitalization. **In Study IV**, we showed that TDI-derived MPI was an extremely powerful tool to predict the prognosis in the longer term. Having MPI > 0.67 indicated a 13-fold increased risk of CV mortality.

In conclusion, TDI is a highly feasible method to assess cardiac function in patients with HF, and a better method to evaluate diastolic function. In the shorter term E/e' is a moderately strong and independent predictor of CV mortality, and in the longer term, MPI is a powerful marker of prognosis. TDI-derived expressions of RV function are also of some importance. TDI seems to be more stable than conventional echo parameters after treatment with HF medication.

Key words: Heart failure, Echocardiography, tissue Doppler, prognosis

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- III. Olson J, Samad B, Alam M. The prognostic significance of right ventricular tissue Doppler parameters in patients with left ventricular systolic heart failure: an observational cohort study. *Heart* 2012;98:1142-1145
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LIST OF ABBREVIATIONS

HF	Heart failure
RAAS	Renin-angiotensin-aldosterone system
CO	Cardiac output
LVEDP	Left ventricular end-diastolic pressure
HF-PEF	Heart failure with preserved ejection fraction
ESC	European Society of Cardiology
LV	Left ventricle
EF	Ejection fraction
IDCM	Idiopathic dilated cardiomyopathy
RCT	Randomized controlled trial
LVAD	Left ventricular assist device
BiVAD	Biventricular assist device
CRT	Cardiac resynchronization therapy
ICD	Implantable cardioverter defibrillator
LA	Left atrium
RV	Right ventricle
WMSI	Wall motion score index
AVPD	Atrioventricular plane displacement
E	Early diastolic peak transmitral Doppler flow
A	Late diastolic peak transmitral Doppler flow
FAC	Fractional area change
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging
s'	Systolic myocardial velocity
e'	Early diastolic velocity
a'	Late diastolic velocity
MPI	Myocardial performance index
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time

INTRODUCTION

HEART FAILURE

The symptoms of heart failure (HF) have been described in ancient documents in Egypt (e.g Papyrus Ebers)(1), India and Greece. Romans were known to use foxglove as a cure for heart failure symptoms. The mechanisms remained obscure until 1668, when some insight was rendered by Harvey's description of the circulation. In 1785 century, William Withering described the use of digitalis in patients with dropsy (swollen legs)(2). In late 19th century, it was common to treat edema with Southey's tubes (Fig 1), a medical instrument which was inserted in subcutaneous tissue to drain excess fluid from the legs(3).

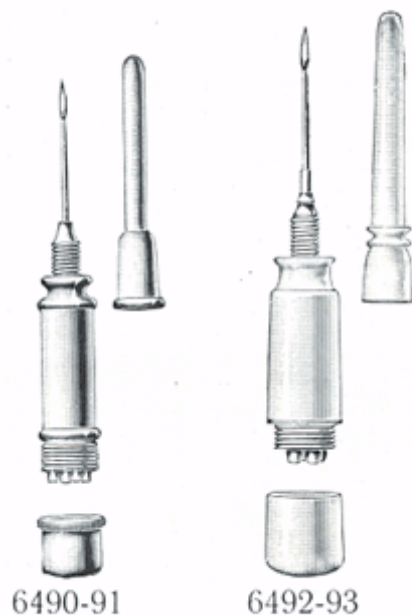


Figure 1 Southey's tubes. Reprinted with permission from Boston Medical Library.

Pathophysiology

HF is defined as a state where the heart's performance cannot meet the metabolic demands of the tissue, or can only do so with the cost of elevated filling pressure. This is often, but not always due to impaired myocardial contractility. The low output as a result of decreased systolic function causes adaptive reactions from other organs, e.g. the kidneys, with activation of the renin-angiotensin-aldosterone (RAAS) and adrenergic systems, with effects both on the circulation and the heart. This results in fluid retention, afterload increase by vasoconstriction, and has also positive inotropic and chronotropic effects. The increased energy demand of the failing heart may

accelerate myocardial cell death and the adaptive process becomes maladaptive and detrimental for the heart. The increased levels of calcium ions in the cytosol impair relaxation, and can also cause arrhythmias and sudden death.

In mild HF, cardiac output (CO) is often normal at rest but fails to increase adequately during exercise. With worsening HF, CO is reduced and symptoms can develop at rest. HF can be life-threatening when the CO is lower than the metabolic needs of the organs, or when LV end-diastolic pressure (LVEDP) rises above the threshold to cause pulmonary edema.

The decreased CO and the raised filling pressures lead to exertion dyspnea or even dyspnea during rest. The activation of RAAS leads to fluid retention which causes peripheral edema and sometimes congestion of the lungs. Other common symptoms of HF are orthopnea, palpitations and paroxysmal nocturnal dyspnea. Clinical signs of HF are also related to low-output, high filling pressure and fluid retention and include rales, jugular vein distension, peripheral edema, 3d heart sound and hepatomegaly.

HF is often secondary to impaired myocardial contractility, but can also be due to pressure or volume overload as in valvular heart disease. Isolated diastolic dysfunction (HF with preserved ejection fraction, HF-PEF) has been more recognized as a cause of HF during the last decade.

Epidemiology and prognosis

Estimating HF incidence accurately is difficult because of its insidious debut and the high proportion of comorbidities. It is appreciated that about 150 000-250 000 persons in Sweden today suffer from symptomatic HF, and for persons > 65 years, it is the most common cause of hospitalization(4). In the western world, the prevalence is estimated 1.5-2% for the total population, and about 10% in patients > 70 years. In the Framingham study, the lifetime risk to develop HF was about 20%, with a clear rise in incidence with increasing age (5). The more recent EuroHeart failure survey (6) estimated the incidence of symptomatic HF in ESC member countries to about 10 millions, and the same number for persons with asymptomatic and undiagnosed LV dysfunction.

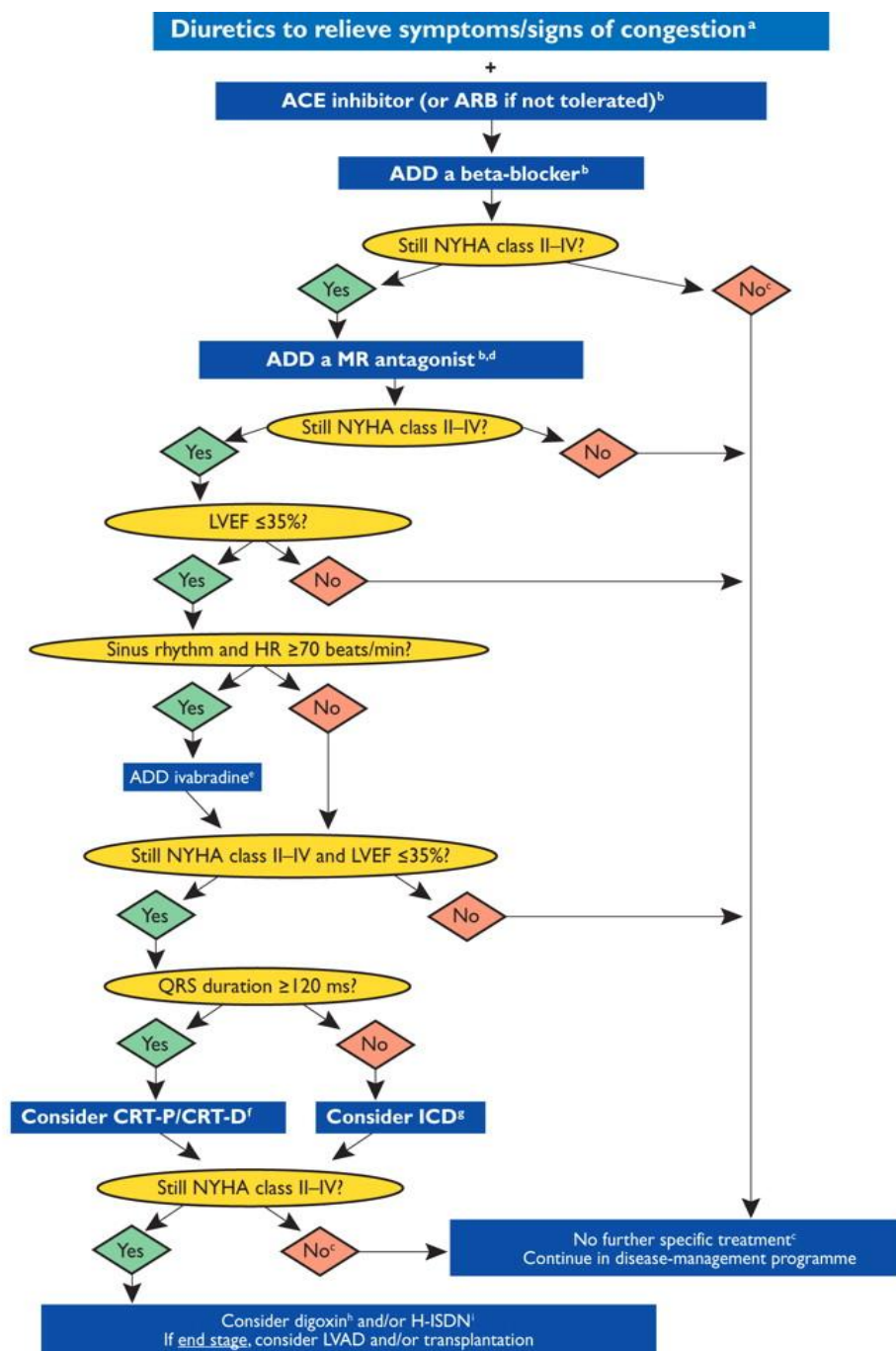
The prognosis of HF has always been severe. In the Framingham study, the median survival for patients who developed HF 1948-88, was 1.7 years for men and 3.2 years for women. After 5 years, only 25% of the men and 38% of the women were alive. No significant improvement in survival was seen during these four decades.

Since the mid-eighties, the prognosis has improved gradually and significantly. In a Swedish population with 150 000 participants the mortality fell with 5-10% per year between 1988 and 2000(7). In recent clinical HF trials the 1-year mortality is about 10-20 % and 3-year mortality about 20-30% (8-10). It is however probably fair to guess that these mortality rates do not translate to the general HF population.

The leading cause of HF is ischemic heart disease, which alone stands for more than 50% of HF. Hypertension and idiopathic dilated cardiomyopathy (IDCM) are the second and third most common etiologies. Other, less common causes are valvular heart disease, arrhythmias and cardiomyopathies other than IDCM.

Medical therapy

Until late 1980s, the only medicines available for HF were Digoxin, nitrates and diuretics. Digoxin, as mentioned above, is our oldest effective HF medication. In the middle of the 20th century, diuretics (thiazides and loop diuretics) were added, agents that were very efficient in relieving symptoms related to fluid retention, but that did not affect prognosis. In 1987, the first clinical landmark trial proving the effect of Enalapril(11), an angiotensin-converting enzyme inhibitor (ACEinhibitor, ACE-i) on survival and symptoms in a population with heart failure was published. Since then, many large randomized clinical trials (RCTs) has been published and the treatment of HF has become highly evidence based (12-20). Four groups of pharmacological agents have been proven to improve outcome in terms of morbidity and mortality in HF. These are ACE-inhibitors, beta-blockers, mineral corticoid receptor antagonists (MRAs) and angiotensin receptor antagonists (ARB). The mechanisms of action are through inhibition of the RAAS (ACE-I, ARB and MRA), and the adrenergic system (beta-blockers), thereby reducing the harmful effects of the neurohormonal response. The latest addition in modern medical treatment is ivabradine, a negative chronotropic agent that acts as a selective inhibitor of the sinus node, and has been showed to decrease the risk of HF hospitalization (8). Figure 2 shows the treatment algorithm for HF according to the latest guidelines from the European Society of Cardiology (ESC).



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR antagonist = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

^a Diuretics may be used as needed to relieve the signs and symptoms of congestion (see Section 7.5) but they have not been shown to reduce hospitalization or death.

^b Should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose.

^c Asymptomatic patients with an LVEF ≤ 35% and a history of myocardial infarction should be considered for an ICD.

^d If mineralocorticoid receptor antagonist not tolerated, an ARB may be added to an ACE inhibitor as an alternative.

^e European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥ 75 b.p.m. May also be considered in patients with a contraindication to a beta-blocker or beta-blocker intolerance.

^f See Section 9.2 for details—indication differs according to heart rhythm, NYHA class, QRS duration, QRS morphology and LVEF.

^g Not indicated in NYHA class IV.

^h Digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation—usually in conjunction with a beta-blocker.

ⁱ The combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACE inhibitor or an ARB.

Figure 2. Treatment algorithm according to European Society of Cardiology. Eur Heart J (2012) 33 (14): 1787-1847. doi: 10.1093/eurheartj/ehs104 First published online: May 19, 2012. Reprinted with permission from Oxford university press © on behalf of the European Society of Cardiology.

Surgical therapy

Surgical treatment of HF has traditionally focused on correction of causes of LV dysfunction, such as revascularization of the coronary circulation, and valvular surgery. More uncommon LV reconstruction surgery is performed. In selected patients with severe HF, a heart transplant or implantation of a ventricular assist device (LVAD or BiVAD) can be performed. In the last decades, device treatment with implantable defibrillators (ICDs) and cardiac resynchronization therapy (CRT) has been proven to increase survival (9,10,21).

LEFT VENTRICULAR FUNCTION

The left ventricle (LV) must be able to alter between two phases: (1) the diastolic phase, where the chamber has to be compliant to allow rapid filling from the left atrium in spite of a low pressure gradient and (2) the systolic phase, in which the LV must evoke power enough to create a pressure that is sufficient to expel adequate amounts of blood into the systemic circulation. Both of these phases are highly interdependent and equally energy consuming. It is now well known that both these aspects of cardiac function must be considered to determine diagnosis, treatment and prognosis.

Systolic function

The systolic phase begins with closure of the mitral valve. During the isovolumic contraction period, the LV builds up a rising intraventricular pressure without any change in volume. When the intraventricular pressure exceeds that in the aorta, the aortic valve opens and blood is ejected into the systemic circulation, representing the ejection period. During this period, the different layers of muscle fibers makes the LV rotate and twist as well as contract radially and shorten longitudinally. The systolic performance of the LV depends on contractility, preload, afterload, heart rate and several other factors. The most commonly used measure of systolic function is the LV ejection fraction (LVEF), i.e. the fractional volume of blood that is pushed out into the circulation with every single heartbeat. Echocardiography is now by far the most common method to measure LVEF, but LV angiography, magnetic resonance imaging (MRI) and radionuclide imaging can also be used. Other echocardiographic expressions of LV systolic function include atrio-ventricular plane displacement and systolic myocardial velocity. Echocardiographic methods of assessing LV systolic function are discussed more in detail below.

Diastolic function

The diastolic phase starts with the closure of the aortic valve. During the isovolumic relaxation period the intraventricular pressure now falls rapidly without volume change. When the pressure is lower than that in the left atrium (LA), the mitral valve opens and the chamber fills with blood. At the end of diastole, the LA contracts which contributes

with the last portion of filling, which is about 15% of total diastolic volume in a healthy person.

Diastolic function can be measured invasively and is then expressed as the velocity of fall in pressure, dp/dT_{min} . The time constant Tau (τ) is an accepted invasive measure of LV relaxation, derived from the curve of LV pressure fall during early diastole. After 3.5τ , the process of relaxation is 97 % complete. Diastolic dysfunction can be defined as $\tau > 48$ ms (22,23). Diastolic function can also be assessed by echocardiography, as discussed more in detail below. The filling properties of the LV can be described with the terms “stiffness” ($\Delta P / \Delta V$), or the inverse “compliance” ($\Delta V / \Delta P$) (24). These properties of the LV are influenced by several factors, such as myocardial wall thickness, chamber geometry and pericardial restraint.

The main consequence of diastolic dysfunction is elevated filling pressure.

RIGHT VENTRICULAR FUNCTION

The right ventricle (RV) has a thinner muscular wall than the LV since it pumps blood into a low-resistance circulation and thus needs to create a lower systolic pressure. The RV systolic contraction consists mainly of longitudinal shortening and radial contraction of the free wall (25,26). LV contraction also contributes to RV systole, since the two chambers are interlinked and share a common septum. The filling of the RV is affected mainly by right atrial pressure, heart rate and myocardial compliance. RV stroke volume is highly dependent on preload, and a decrease in preload, as in vasodilation or dehydration, can cause significant reductions in CO.

Assessment of RV function is more difficult than that of LV, due to the asymmetrical geometry of the RV. The historical gold standard method of RVEF determination has been radionuclide imaging (27). During the past decade, magnetic resonance imaging (MRI) has become the reference standard for assessing RV systolic function (27). $RVEF > 44\%$ is considered normal. Echocardiographic methods are discussed in a subsequent section.

ECHOCARDIOGRAPHY

Background

In the first half of 20th century, several attempts were made to use ultrasound to picture the body's inner organs. In the early 1950s, the Swedish cardiologist Inge Edler and the physicist Helmut Hertz started their work to envisage the heart with this method. In 1953, the first echocardiographic picture of the heart was recorded. In the beginning, echocardiography was used mainly to evaluate patients with mitral stenosis, due to the limits of invasive catheterization(28). The method was also suitable to discover pericardial fluid. Initially, only M-mode recordings were available. Echocardiography was not widely spread until the 1970s, when 2-dimensional real-time echocardiography was developed. Since then progress has been extensive.

Left ventricular systolic function

There are several methods to determine LV systolic function with echocardiography. Different ways to determine LVEF are the most commonly used. Most echocardiographic methods for LVEF assessment are based on assumptions of LV geometry. Single-plane methods, such as Teicholz's (29) are subject to limitations by not taking in account LV asymmetry and regional dysfunction. The method recommended by the American Society of Echocardiography (ASE) is the so called modified Simpson's biplane method (30). From the apical 4-chamber and 2-chamber views, LV volumes are estimated in end-systole and end-diastole, and LVEF can be calculated. This method is dependent on high image quality and visualization of the endocardial border. Experienced examiners often use visual assessment of LVEF ("eye-balling"), a method that is shown to correlate well with more objective means (31). However, this method has obvious limitations in its subjectivity and low interobserver reproducibility. LVEF has since long been known to have strong prognostic implications.(32-36)

Other echocardiographic expressions of LV systolic function than LVEF can be used. Wall motion score index (WMSI), a model where the LV is divided into 16 segments (37), is often used as an objective mean to describe regional LV systolic function, which is important in patients with coronary artery disease.

Using 2-D guided M-mode, atrioventricular plane displacement describes the longitudinal movement of the heart throughout the cardiac cycle. This method correlates with EF (38), is reproducible and easy to use even when image quality is suboptimal (39). AV-plane displacement (AVPD) has also been shown to be of prognostic significance (40-44). Since atrial contraction contributes to AVPD, LVEF is often underestimated in subjects with atrial fibrillation (45). M-mode determination of APVD may also be affected by angle-dependent errors.

Assessment of LV systolic function with techniques using myocardial velocity parameters can also be used, and is discussed below.

Left ventricular diastolic function

LV diastolic function is a complex process, involving several identifiable components; relaxation, filling pressure and compliance/stiffness. The multiple means of determining diastolic function with echocardiography are focused on one or more of these factors. LA dimension, area or volume, often reflects a chronic rise in left sided filling pressure. Traditionally, pulsed-wave Doppler recordings of the transmitral diastolic blood flow have been used, with tracings of early rapid filling (E) and the late contribution of atrial contraction (A) (46). The deceleration time of the E wave and the IVRT can also be measured. In normal diastolic function, with normal (low) filling pressures, the ratio between E and A is > 1 and the deceleration time of the E wave is normal. In the earliest stages of diastolic function, characterized by abnormal relaxation, the LV fills during the early phase to a lesser extent and the atrial contribution is more prominent. This results in a lower E/A-ratio, longer deceleration time and prolonged IVRT. With more advanced diastolic dysfunction and rising filling

pressure in the LV and LA, filling by atrial contraction decreases, and the E/A-ratio tends to normalize (so called “pseudonormalization”). In the most advanced cases of diastolic dysfunction, the filling pattern is restrictive with a high peak E-wave and short deceleration time. The E/A-ratio is thus high in these cases. There are some limitations of this method. Cases with pseudonormalization pattern can be difficult to separate from those with normal diastolic function. To combine transmitral flow recordings with tracings of pulmonary venous flow can be helpful, as the addition of recordings while the patient performs the Valsalva maneuver which reveals some cases of diastolic dysfunction. Secondly, this method is sensitive to changes in load and heart rate. Thirdly, it cannot be used to assess diastolic function in patients with atrial fibrillation, a condition that often co-exists with diastolic dysfunction.

During the last two decades, the above mentioned methods usually have been used in combination with measurements of myocardial tissue velocities, so called tissue Doppler imaging (TDI). Diastolic velocity of the mitral annulus (e') is a sensitive measure of diastolic function, in particular relaxation. Used together with peak early mitral flow, in the ratio E/e' , it gives an estimate of left atrial/ventricular filling pressure. An $E/e' > 15$ indicates a pulmonary capillary wedge pressure (PCWP) of > 15 mm Hg, while an $E/e' < 8$ indicates normal PCWP (47-49).

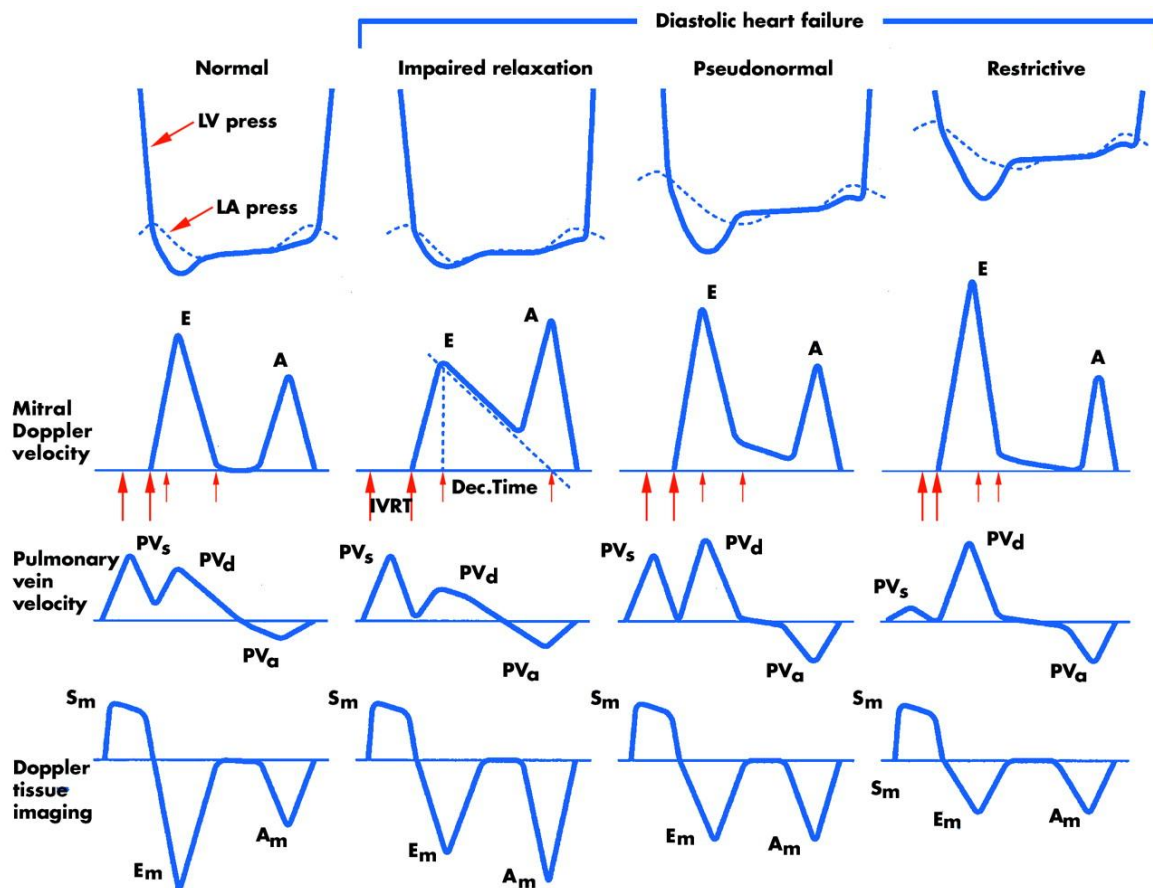


Figure 3. LV=left ventricle, LA=left atrium, E=early diastolic transmitral Doppler flow, A=late diastolic transmitral Doppler flow, PVs=systolic pulmonary vein flow, PVd=diastolic pulmonary vein flow, PVa= atrial reverse pulmonary vein flow, Sm=systolic myocardial velocity, Em=early diastolic myocardial velocity, Am=late diastolic myocardial velocity. Leite-moreira AF, Heart 2006;92:712-718 Reprinted with permission from the BMJ Publishing Group Ltd

Figure 3 and 4 show schematically how diastolic function is assessed with echocardiography.

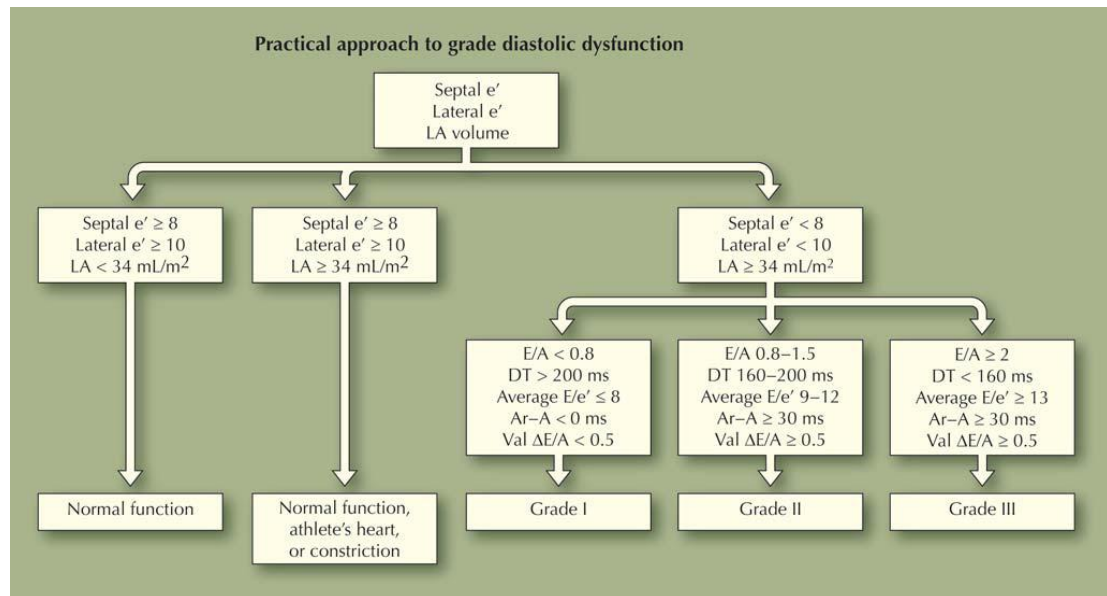


Figure 4. Proposed strategy for the diagnosis and grading of diastolic dysfunction. Nagueh et al. Current Heart Failure Reports 2009;6(3):154-159. Reprinted with permission from Springer.

Right ventricular function

Due to the asymmetric geometry of the RV, volume and EF determination with echocardiography has been unreliable. Three-dimensional echocardiography is a promising method, with improved reproducibility, but at present the data is too limited to evaluate its clinical value, and the method is still rather time consuming. Therefore, other echocardiographic measures of RV systolic function are used. The fractional area change (FAC) is the percentage of change in the RV area during the cardiac cycle, in the apical 4-chamber view. A value below 35% is considered abnormal (27). It is important to include the entire RV when calculating FAC. FAC correlates to outcome in patients with previous myocardial infarction (50,51). A simpler, less time consuming method is the tricuspid annular plane systolic excursion (TAPSE), the RV counterpart of AVPD. Using M-mode, it is a measure of RV longitudinal function, and is easily obtainable with a high level of reproducibility. In spite of measuring only longitudinal function it has shown good correlation with reference methods of RV systolic function (52). A value < 16 mm indicates abnormal RV systolic function. Several studies have shown prognostic implications of TAPSE alterations in patients with heart disease (53-55). As APVD, TAPSE is also angle-dependent.

The measurement of RV tissue velocity, especially the tricuspid annular velocity is also a reproducible and simple method, frequently used the last decade, and discussed more in detail below.

Tissue Doppler Imaging

Recordings of myocardial tissue velocity using Doppler technique was discussed relatively early in the evolution of echocardiography. However, clinical applications of TDI did not arrive until the 1990s (56-59). A rapid development of the method has taken place since then. There are three main velocities during the cardiac cycle; one systolic velocity (s') when the base of the heart moves towards the apex, and two diastolic velocities, early (e') and late (a'), when the annulus moves away from the apex. The late velocity is secondary to contraction of the LA, and is thus absent in patients with atrial fibrillation.

TDI measures myocardial velocities either by pulsed wave (PW) Doppler for on-line use, measuring velocities at a specific segment along a line (i.e. where the sample volume is placed), or off-line, using color coded TDI, where velocities can be measured anywhere in the scanning sector. Color coded TDI also allows determination of other, velocity-derived parameters, for example deformation variables such as strain and strain rate. For clinical purposes, PW-TDI is the recommended method, since validation studies have been performed with this method (24), and this thesis focuses solely on PW-TDI.

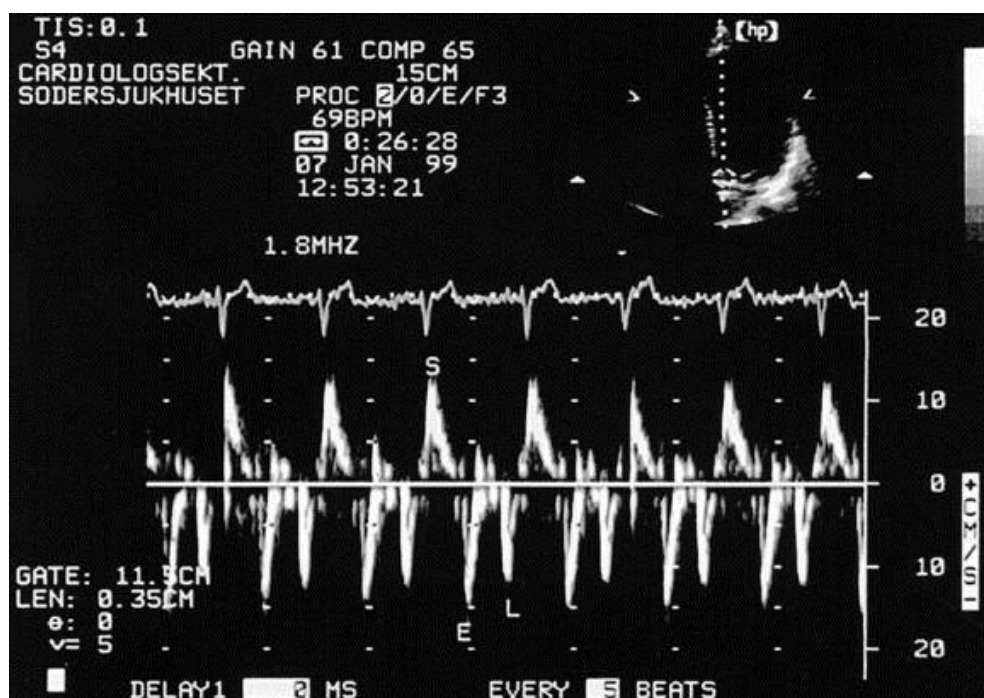


Figure 5 . Example of tissue Doppler recording from the septal side of the mitral annulus.
S=systolic velocity, E=early diastolic velocity, L=late diastolic velocity

Myocardial velocity can be recorded from any site of the heart, but the standard is PW-TDI of the AV-plane level (mitral or tricuspid annular velocities). The method is angle dependent, and it is important to set filters and gain correct to optimize the quality of the signal (60). Myocardial velocities are age dependent and velocities decrease with increasing age, this is especially true for diastolic LV velocities (61). Furthermore, mitral annular velocities differ depending on which side of the mitral annulus they are

obtained, being highest in the lateral wall, and lowest in the septal wall. Normal values are shown in Tables 1 and 2.

Table 1. Systolic and early (E) and late (L) diastolic mitral annular velocities (cm/s) at different sites in healthy subjects in a study mentioned below (n=62) (results expressed as mean \pm SD)				
	Systolic	E-diastolic	L-diastolic	E/L-diastolic
Septum	9.5 \pm 1.4	12.9 \pm 3.1	11.3 \pm 2.3	1.2 \pm 0.5
Anterior	10.2 \pm 2*	14.8 \pm 3.9 [†]	10.8 \pm 3.1	1.5 \pm 0.7 [†]
Lateral	11 \pm 1.9 [†]	16.5 \pm 4 [†]	11.5 \pm 2.9	1.5 \pm 0.6 [†]
Inferior	10.5 \pm 1.4 [†]	14.5 \pm 3.8 [†]	12.2 \pm 2.7 [†]	1.3 \pm 0.6
Mean	10.3 \pm 1.4	14.7 \pm 3.4	11.5 \pm 2.3	1.4 \pm 0.5
Mean = mean value from 4 different sites on the mitral annulus.*P < .01 compared with septum within the same parameter. [†] P < .001 compared with septum within the same parameter.Characteristics of Mitral and Tricuspid Annular Velocities Determined by Pulsed Wave Doppler Tissue Imaging in Healthy Subjects. <i>J Am Soc Echocardiogr</i> 1999;12(8):618-628) Reprinted with permission from Elsevier.				

Myocardial velocities have been shown to correlate well with other methods of measuring systolic and diastolic function, non-invasive (62-64) as well as invasive (65-67). Similarly, tricuspid annular velocities have also showed to agree with other indices of RV function (61,68).

TDI velocities are very sensitive expressions of cardiac function, and can be used to grade systolic and diastolic dysfunction, as well as detecting subclinical heart disease, e.g. in patients with diabetes, hypertension, and hypertrophic cardiomyopathy (HCM) (69-72). More specific examples are the distinction between HCM and athlete's heart (73), and between restrictive cardiomyopathy and constrictive pericarditis (74).

Table 2. Systolic and early (E) and late (L) diastolic mitral annular velocities (cm/s) at different sites in different age-groups in healthy subjects, same study as table 2. (results expressed as mean \pm SD)

	<40 years	40-59 years	≥ 60 years
Septum			
Systolic	9.9 \pm 1.2	9.2 \pm 1.5	9 \pm 1.4
E-diastolic	15.5 \pm 2.7	12.2 \pm 2.3	10.4 \pm 2.1
L-diastolic	10.5 \pm 2.4	11.2 \pm 2.1	12.4 \pm 2.1
E/L-diastolic	1.6 \pm 0.5	1.1 \pm 0.3	0.85 \pm 0.2
Anterior			
Systolic	11 \pm 2	10.2 \pm 1.8	9.1 \pm 1.6
E-diastolic	17.6 \pm 2.9	15 \pm 3.3	10.8 \pm 2.1
L-diastolic	9.5 \pm 3	11.4 \pm 3.4	11.8 \pm 2.2
E/L-diastolic	1.8 \pm 0.7	1.4 \pm 0.6	0.93 \pm 0.2
Lateral			
Systolic	11.5 \pm 2	10.6 \pm 2	10.6 \pm 1.5
E-diastolic	19.8 \pm 2.9	16.1 \pm 2.3	12.9 \pm 3.5
L-diastolic	10.5 \pm 2.5	10.8 \pm 2.2	13.5 \pm 3.3
E/L-diastolic ratio	1.9 \pm 0.6	1.5 \pm 0.5	0.9 \pm 0.4
Inferior			
Systolic	10.9 \pm 1.5	10.5 \pm 1.2	9.8 \pm 1.4
E-diastolic	17.7 \pm 2.9	14.2 \pm 2.7	10.7 \pm 2.1
L-diastolic	11 \pm 2.7	12.4 \pm 2.7	13.4 \pm 2
E/L-diastolic ratio	1.7 \pm 0.6	1.2 \pm 0.3	0.8 \pm 0.2
Mean			
Systolic	10.8 \pm 1.4	10.1 \pm 1.3	9.6 \pm 1.2 [†]
E-diastolic	17.7 \pm 2.4	14.4 \pm 2.1 [†]	11.3 \pm 2.1 [†]
L-diastolic	10.4 \pm 2.3	11.5 \pm 2	12.8 \pm 1.9 [†]
E/L-diastolic ratio	1.8 \pm 0.5	1.3 \pm 0.4*	0.89 \pm 0.2 [†]

Characteristics of Mitral and Tricuspid Annular Velocities Determined by Pulsed Wave Doppler Tissue Imaging in Healthy Subjects. *J Am Soc Echocardiogr* 1999;12(8):618-628. Reprinted with permission from Elsevier.

In clinical practice, the most common application is evaluation of diastolic function. Early diastolic velocity is a sensitive marker of diastolic dysfunction and measures specifically relaxation. It is an excellent tool to distinguish between normal and pseudonormal transmitral filling patterns (75). As mentioned before, E/e' is probably the best echocardiographic variable for the assessment of LV filling pressure, where a value of < 8 indicates normal PCWP and a value of > 15 is predictive of an elevated filling pressure. High E/e' has shown to have negative prognostic impact and is also a predictor of HF symptoms and exercise capability (76-78). In the last decade, several studies have shown the prognostic importance of TDI parameters of both the LV and the RV in a variety of cardiac conditions (79-88).

Myocardial performance index

Myocardial performance index (MPI), first described by Tei et al in 1995 (89), is an index that combines systolic and diastolic function in the same value. The index is calculated according to the formula: $(IVRT+IVCT)/ejection\ time$. MPI correlates well with systolic and diastolic dysfunction (90,91), and is also shown to be a significant predictor of prognosis in heart disease (92-94). Tei used continuous wave Doppler echocardiography to determine MPI. However, in the last years, several groups have used TDI to calculate MPI (95-100). Figure 6 shows how MPI is calculated using CW Doppler, and Figure 7 how TDI-derived MPI is calculated. One of the advantages of TDI is that all information necessary to determine MPI is present in the same picture, and during the same cardiac cycle, without the need to tilt the probe during the recording. Another factor favoring TDI is the simplicity and reproducibility of the method. Doppler-derived and TDI-derived MPI agree well in most studies, though absolute values differ, with higher values for the TDI method (95-97,100). TDI-derived MPI, however, seems to be less affected by load conditions and heart rate (100,101). TDI-derived MPI is commonly calculated from a single site (septal or lateral), and sometimes as a mean of 2 different sites (most often septal and lateral).

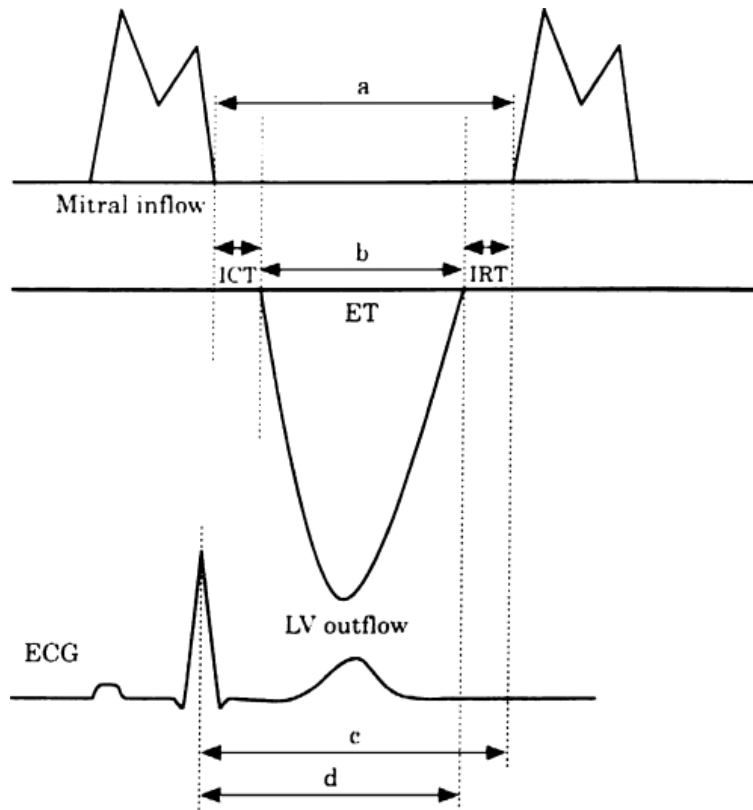


Figure 6 . Calculation of MPI from Doppler mitral inflow and LV outflow recordings. $MPI = (ICT + IRT) / ET = (a - b) / b$. MPI=myocardial performance index, LV= left ventricle, ICT=isovolumic contraction time, IRT=isovolumic relaxation time, ET=ejection time. Tekten T. *Echocardiography* 2003;20:503-10. Reprinted with permission from John Wiley and sons

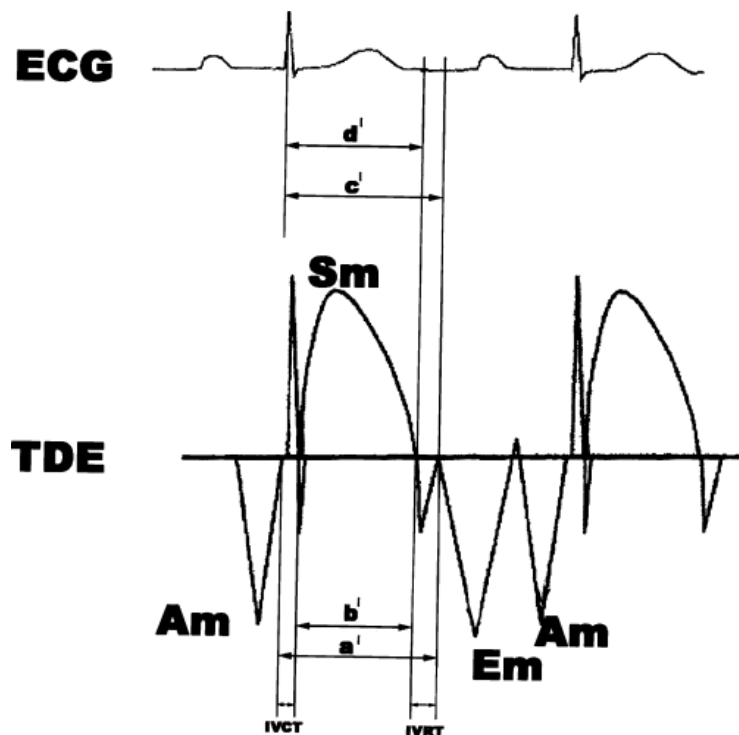


Figure 7. Calculation of MPI from tissue Doppler imaging recordings. $MPI = (a - b) / b$. MPI=myocardial performance index, Am=late diastolic velocity, Sm=systolic velocity, Em=early diastolic velocity. (Tekten T. *Echocardiography* 2003;20:503-10) Reprinted with permission from John Wiley and sons.

AIMS OF THE THESIS

The general aim of this thesis was to investigate the usefulness of tissue Doppler imaging as a diagnostic tool and as a predictor of outcome in patients with symptomatic systolic heart failure. The specific aims were:

- To investigate the overall feasibility of TDI in patients with systolic HF.
- To investigate whether TDI is superior to conventional echocardiographical methods in assessing diastolic function in patients with systolic heart failure.
- To evaluate if established TDI parameters are independent predictors of outcome in a common population with heart failure.
- To evaluate the methodology of assessing MPI as a mean of several sites, so called “global MPI”
- To investigate global MPI measured with TDI as a prognosticator in systolic heart failure.
- To evaluate the effect of HF medication on TDI parameters in patients with newly diagnosed HF.

PATIENTS AND METHODS

Patients

Patients with signs and symptoms related to HF and who were admitted to the Department of Cardiology at Södersjukhuset (Stockholm South General Hospital) between September 1999 and April 2004 were screened for participation in this study. Inclusion criteria were LVEF $\leq 40\%$. Exclusion criteria were severe valvular heart disease. Patients with atrial fibrillation were included. Eventually, 173 patients were included in the study population. Before discharge and in a reasonably stable clinical condition (within 1 week but after iv diuretics had been stopped in most cases), the patients underwent an echocardiographic examination in which conventional and TDI parameters were recorded. The patients were then followed up, with the follow-up period depending upon substudy. The Study flow chart is shown below. In Study II-IV, data from the National Registry of Deaths and in Study II-III hospital records were collected at the end of the follow-up period. In the prognostic studies, the study end-points were cardiovascular death and/or hospitalisation for decompensated heart failure, depending of substudy. No subject was lost to follow-up. The patients were not monitored clinically, and treatment was at the discretion of the physicians responsible for the patients. In Study V, 41 patients with newly diagnosed HF and with insufficient HF medication were taken back within 3-6 months (mean 130 days), after adequate titration of ACE-inhibitors and beta blockers, and a new echocardiogram was performed. The study was approved by the Regional Committee of Research Ethics. Informed consent was obtained from all patients.

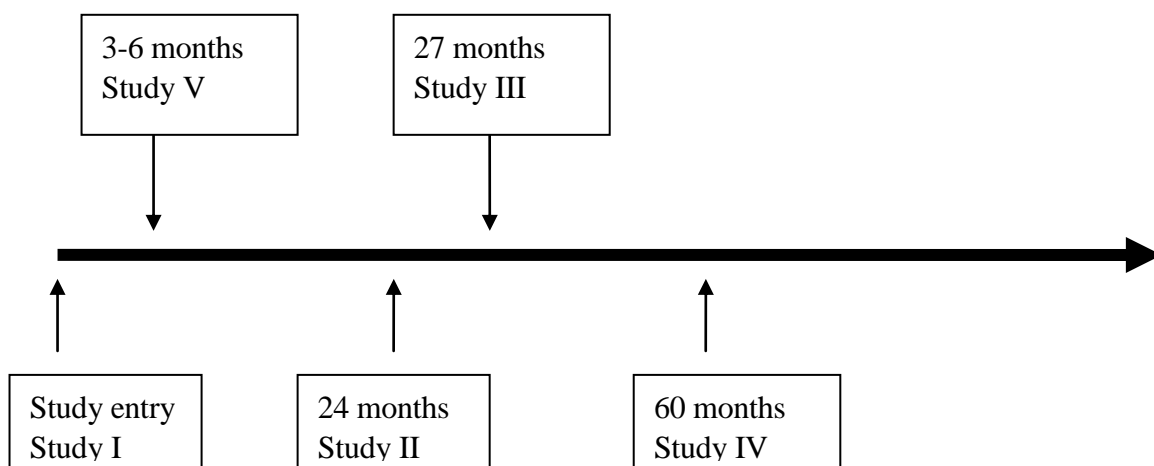


Figure 8 Time chart for the different studies in this thesis

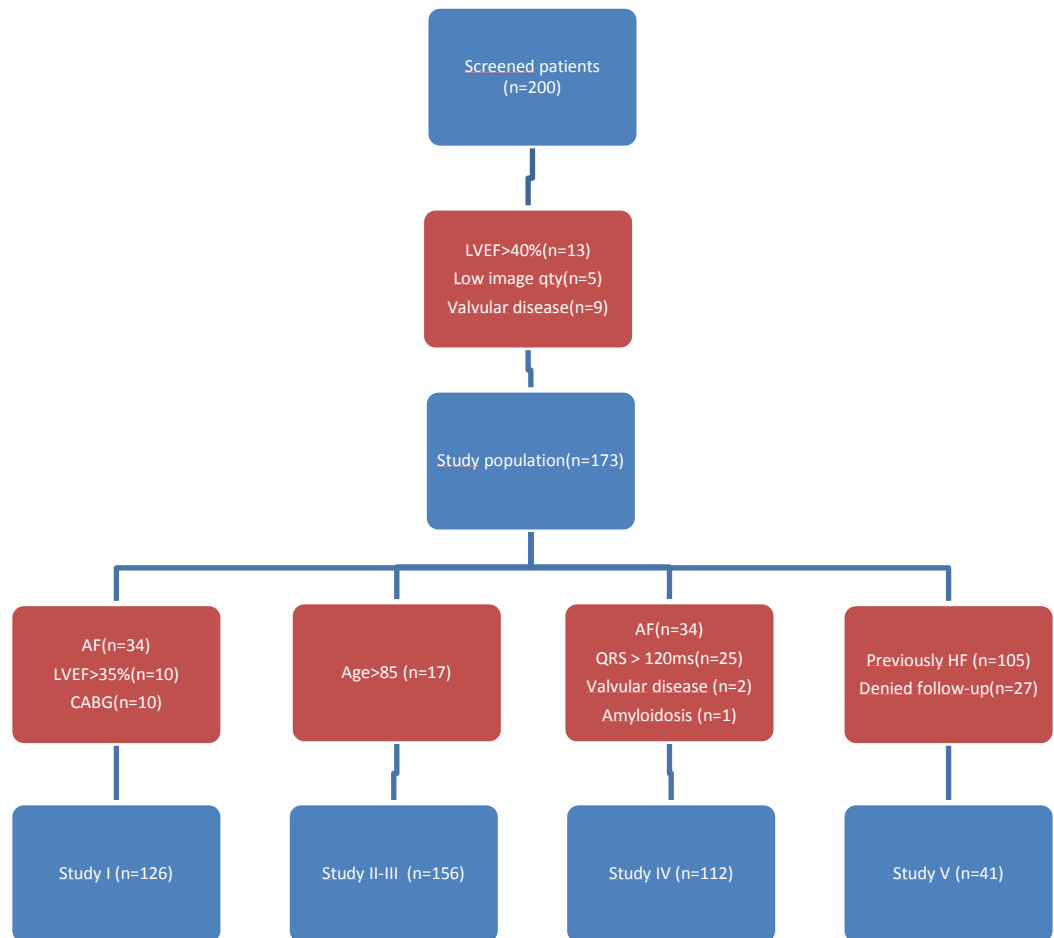


Figure 9. Study flow chart for the substudies. Red boxes=excluded patients.

Control group subjects

In Study I there were 2 control groups. One group consisted of 28 age-matched healthy individuals without a history of cardiovascular disease, hypertension, diabetes mellitus, and having normal resting electrocardiogram (ECG) and echocardiogram. The other control group was 36 patients with acute myocardial infarction and with an EF of 35 % or more.

ECHOCARDIOGRAPHY

A Hewlett-Packard Sonos 5500 was used to produce echocardiograms. The LV dimensions and LVEF were measured according to the recommendations of the American Society of Echocardiography (23). To measure LVEF we used the Simpson's biplane method. Transmitral flow was recorded by pulsed-wave Doppler placed between the mitral leaflet tips in the apical four-chamber view. Early (E) and late (A) transmitral flow velocities were recorded. The ratio of early to late flow (E/A ratio) was calculated when possible. The pulsed-wave TDI was performed by activating the TDI function of the same echocardiography machine. Images were acquired by using a

variable frequency phased array transducer (2-4 MHz). The filter settings were kept low (50 Hz), and gains were adjusted at the lowest possible level to minimize noise and eliminate the signals produced by the transmitral flow. A 1.7-mm sample volume was used. Four different sites around the mitral annulus were selected. In the apical four-chamber view, the cursor was placed at the septal and lateral sides of the mitral annulus in such a way that the annulus moved along the sample volume line. In the apical two-chamber view, the cursor was placed at the inferior and anterior sites of the mitral annulus. A Doppler velocity range of -20 to 20 cm/s was selected. Three major velocities were recorded: the positive systolic velocity when the mitral annulus moves toward the apex (s') and two negative diastolic velocities when the annulus moves away from the apex. One diastolic velocity occurs in the early phase of diastole (e'), and one in the late phase of diastole (a'). A mean value for the above four sites was used to assess global systolic and diastolic function. In patients with atrial fibrillation, A and a' are absent due to a lack of atrial contractions. The other parameters were obtained by calculating the mean for 5 consecutive cycles in these patients. The ratio of E to e' was calculated as an estimate of LV filling pressure (47,48).

Myocardial Performance Index

MPI at each site was calculated as follows: (duration of isovolumic contraction time + ejection time + isovolumic relaxation time – ejection time)/ejection time. In figure 10 the method of calculating the MPI in our study is shown. To avoid to great impact from regional impairment of contractility, a mean value from the 4 sites was used to describe the global MPI of the LV. Myocardial performance index was calculated without any knowledge of the clinical and other echocardiographic parameters.

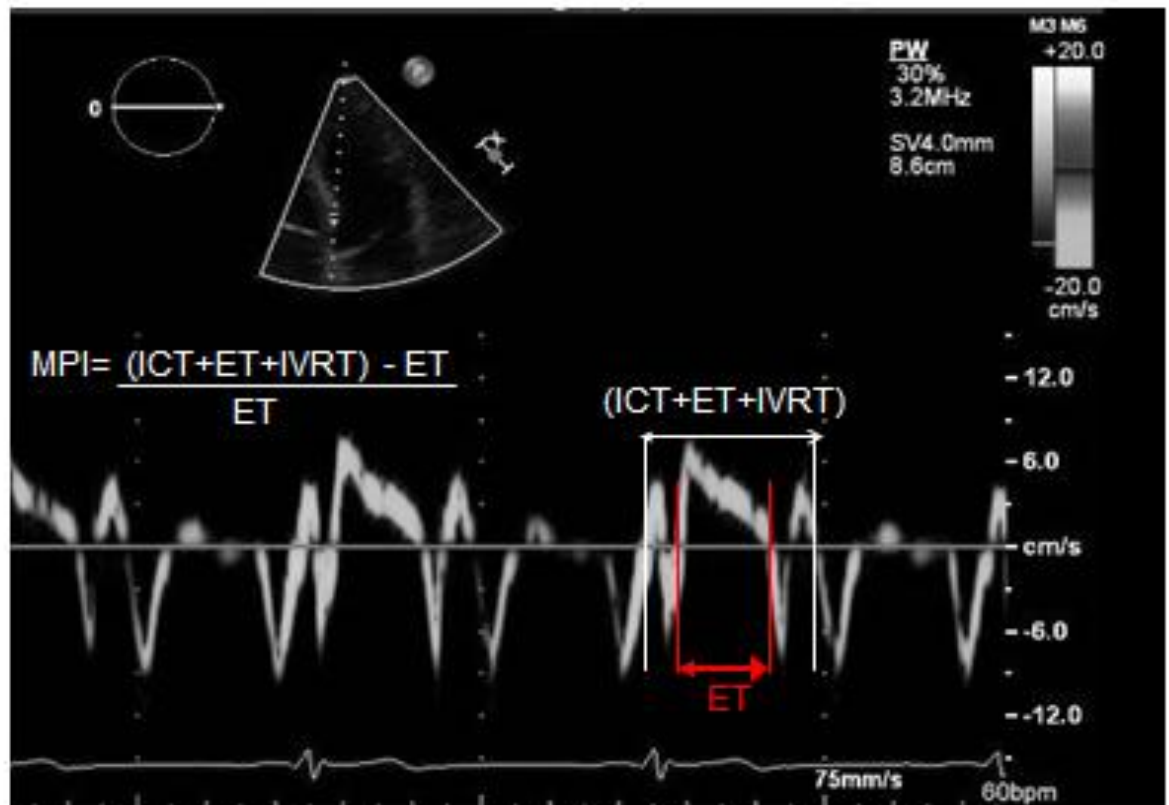


Figure 10. Recording of MPI using pulsed wave tissue Doppler imaging at septal site of the left ventricle from an apical 4-chamber view. MPI=myocardial performance index, ICT=isovolumic contraction time, ET=ejection time, IVRT=isovolumic relaxation time

Statistical analysis

The data analyses were performed with the Statistical Package for Social Science software (SPSS for Windows 17.0-19.0; SPSS Inc., Chicago, IL). All values are presented as the mean \pm standard deviation for continuous variables and frequencies for discrete variables. The student's T-test was used to compare means between groups (independent T-test, study I) or mean changes in parameters between examinations in individuals (paired-samples T-test, study V). Receiver-operating characteristic (ROC) curves and area under the curves (AUC) were obtained to discriminate cut-off values of continuous variables that were possible predictors of outcome (study II-IV). In the prognostic studies (study II-IV), univariate Cox proportional regression analysis of possible predictors of prognosis was performed. Variables with a p-value of < 0.10 were then put into a multivariate Cox analysis. The Cox models were tested with Log minus Log curves, where parallel logarithmic curves indicate a good fit of the model for the variable analyzed. An example of such a curve is shown in Figure 11.

Cumulative survival curves were constituted by the Kaplan-Meier method. The log-rank test was used to compare survival according to the cut-off value of predictors of outcome. P-values were 2-sided and $p < 0.05$ was considered statistically significant.

Reproducibility

Interobserver variability in TDI measurements was tested by picking a sample ($n=40$) that was analyzed by two observers blinded for each other's results. Variability analysis with Crombach's alpha was performed. This showed very low interobserver variability with an alpha value of 0.96

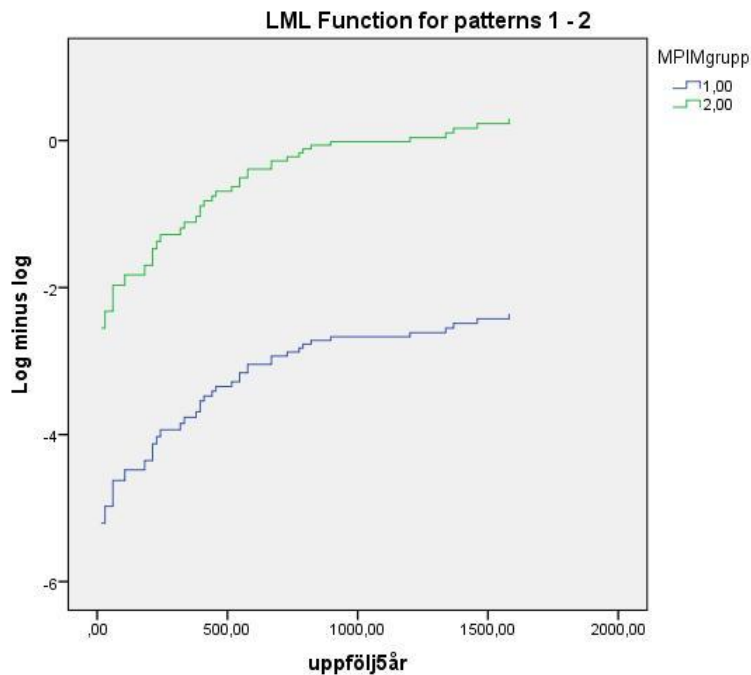


Figure 11. Example of logarithmic hazard curves to test goodness of fit of Cox model.

RESULTS

Clinical characteristics and outcome

Baseline clinical characteristics of the study population are shown in Table 3. More than half of the patients had ischemic origin of HF. Only 22 % were female. None of the patients were lost to follow up. The study flow chart shown above (Figures 8 and 9) presents the time course and subpopulations in the different substudies.

During the total study period of 5 years there were 89 deaths (54% of the patients). During the first 4 years 60 (35%) patients were hospitalized due to decompensated heart failure and 78 (45%) patients died. Fifty-five (55) of these deaths were classified as cardiovascular: Progressive heart failure (n=25), sudden death (n=23), stroke (n=6), and ruptured abdominal aortic aneurysm (n=1). Non-cardiovascular cause of death included cancer (n=16), end-stage renal failure (n=3), pneumonia (n=3), and chronic alcoholism (n=1).

Table 3. Clinical characteristics of the study population. Mean±standard deviation or number (percentage)

Age	69±13
HF duration months	7.3±12
Male gender	134(78%)
Ischemic cause of HF	104(60%)
Diabetes	45(26%)
Hypertension	37(21%)
COPD	14(8%)
Atrial fibrillation	34(20%)
Left bundle branch block	22(13%)
Heart rate (beats per minute)	79±13
Systolic blood pressure mm Hg	130±24
Diastolic blood pressure mm Hg	80±14
Medication	
Beta blockers	159(92%)
ACE-inhibitor	159(92%)
Spironolactone	50(29%)

HF=heart failure, COPD = chronic obstructive pulmonary disease

Echocardiographic characteristics

Baseline echocardiographic features are presented in Table 4. The mean LVEF was severely depressed at only 25%. As expected, mean myocardial velocities were decreased and mean E/e' was high. Mean RV velocities were also decreased compared

to normal subjects, but to a lesser degree, reflecting the fact that the study subjects mainly suffered from LV disease. In fact, the mean RV systolic velocity is above 10 cm/s, which is the proposed cut-off for abnormality proposed by the American Society of Echocardiography (30).

Table 4. Echocardiographic characteristics of study population (n=173)

LVEF (%)	25±7
LVED (mm)	59±8
Left atrium (mm)	44±6
Septum (mm)	11±2
Deceleration time (ms)	175±60
E/A (n=140)	1.7±1.0
Myocardial velocities	
s' (mean)	5.0±1.0
e' (mean)	6.1±1.9
E/e' (mean)	14.6±5.9
RV s'	10.2±2.8
RV e'	8.9±3.7
Global myocardial performance index (n=110)	0.67±0.18

LVEF=left ventricular ejection fraction, LVED=left ventricular end-diastolic diameter, E/A= ratio of transmitral early and late peak flow velocity, s'=systolic mitral annular velocity, e'= early diastolic mitral annular velocity, E/e'= ratio of transmitral early peak flow and early mitral annular velocity, RV s'=systolic tricuspid annular velocity, RV e'= early diastolic tricuspid annular velocity.

Diastolic function in patients with systolic HF (Study I)

In study I, we divided the patients into three groups according to the transmitral flow pattern; 1) abnormal relaxation 2) normal/pseudonormal pattern 3) restrictive. There were very little differences in early diastolic velocities (e') between the groups (Figure 12), where the abnormal relaxation group had the lowest values. No subject in group 1 had a normal e', while 4 of 36 had e' > 8 cm/s in group 2.

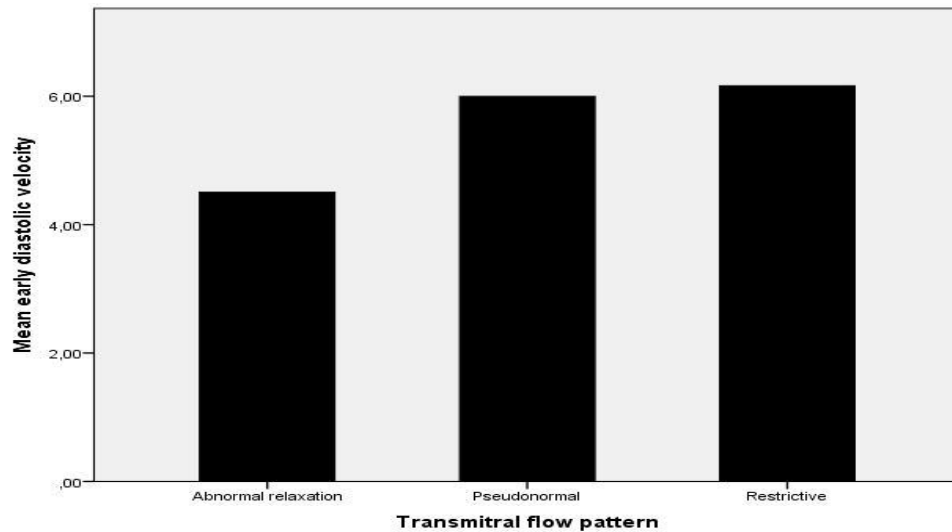


Figure 12. Mean early diastolic myocardial velocities in groups according to transmitral flow pattern.

Compared to a control group with known coronary artery disease, LVEF > 35%, and a normal/pseudonormal transmitral flow pattern, the study population had markedly lower early diastolic velocities (Figure 13).

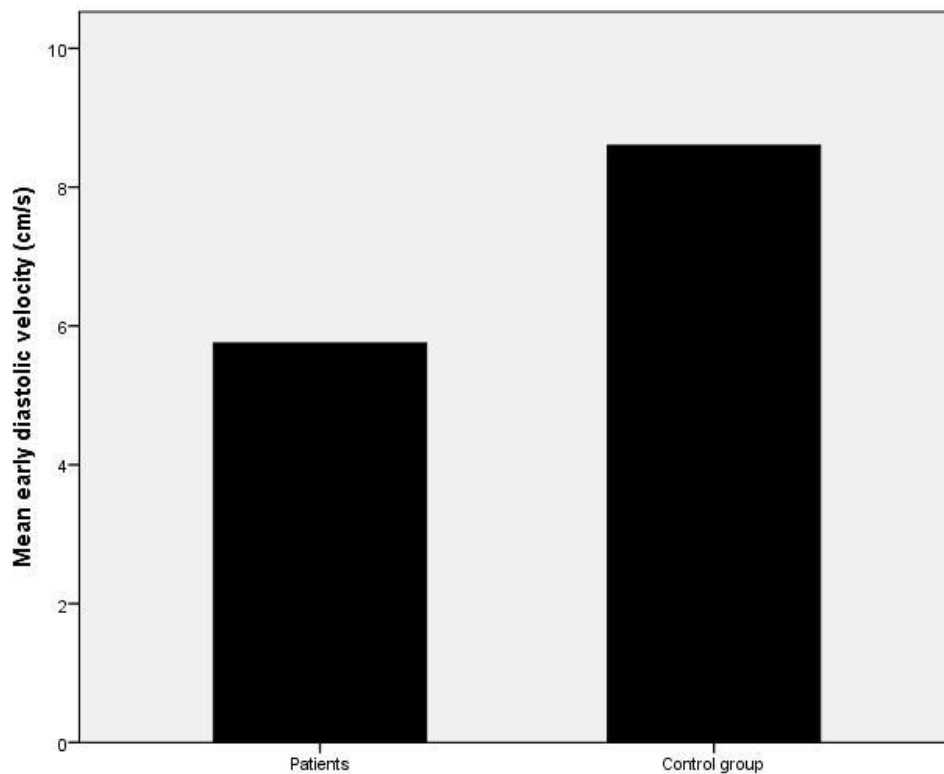


Figure 13. Mean early diastolic myocardial velocities for patients and control group with suspected diastolic dysfunction. $P < 0.001$

E/e' was, not surprisingly, highest in the group with restrictive pattern, and lowest in the group with abnormal relaxation (17 ± 5 vs. 12 ± 4 , $p < 0.001$).

TDI-recordings in patients with newly diagnosed HF before and after medication

In study V, 41 patients with newly diagnosed HF and without previous adequate HF medication were scheduled for a revisit in 3-6 months, after ACE-inhibitors (or angiotensin receptor blocker, ARB) and beta blockers had been titrated to adequate doses according to the specific agents. Physicians not involved in the study treated all the patients, and the researchers had no impact on the treatment. In Table 5, the different generic medications used are shown, with recommended target dose, number of patients for each agent, and the mean dose at the time of study entry and at the follow up visit. The mean percentage of target dose was after titration 87.5% for ACE-inhibitors/ARB, and 75 % for beta blockers.

The results of this study showed that conventional echocardiographic parameters (LVEF, LVED, LA diameter and deceleration time) improved significantly and substantially, particularly LVEF and deceleration time, while none of the TDI parameters increased or decreased significantly (Figures 14-16).

Table 5. Doses of angiotensin converting enzyme inhibitors (ACE), angiotensinogen receptor blockers (ARB), and betablockers used. Mean dose at the time echocardiogram 1 and 2. Doses are shown in mg. n=number of patients receiving specific agents.

Generic name(n)	Target dose	Mean dose1	Mean dose2
<i>ACE/ARB</i>			
Enalapril(11)	20	1,5	17.5
Ramipril(22)	10	1.0	8.75
Captopril(2)	150	50	100
Lisinopril(1)	35	10	20
Losartan(5)	50	0	50
<i>β-blocker</i>			
Metoprolol (25)	200	20	150
Bisoprolol (10)	10	1.5	7.5
Carvedilol (6)	50	0	37.5

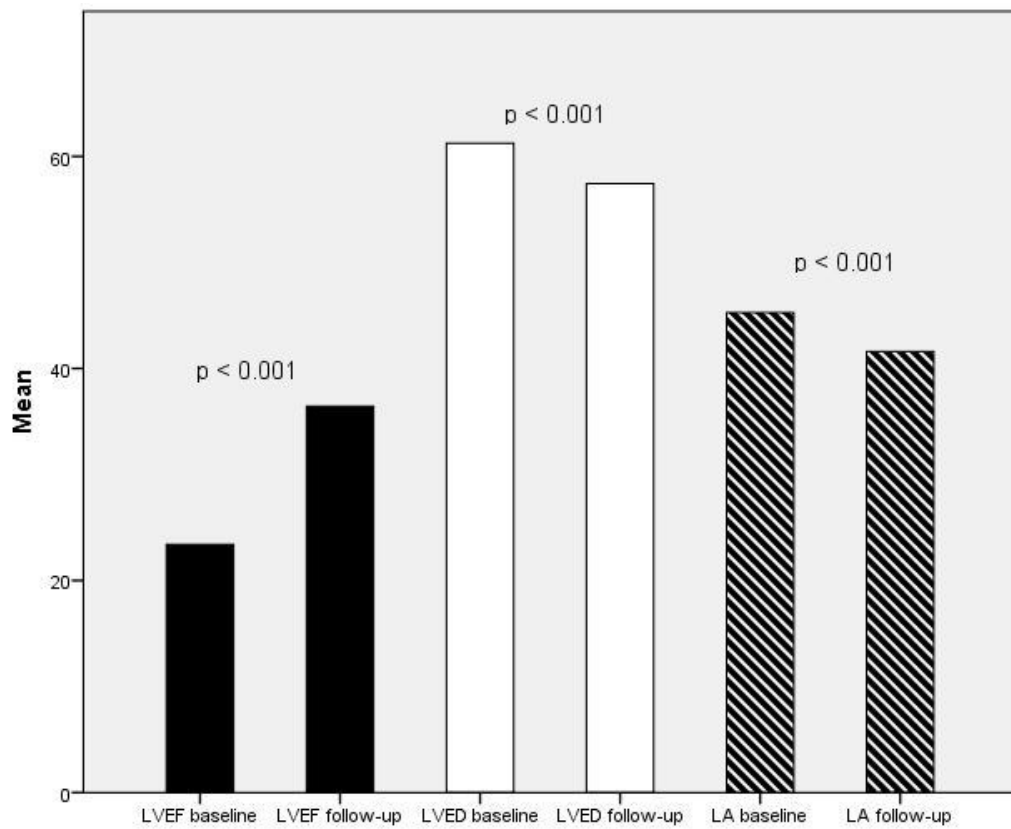


Figure 14. Mean conventional echocardiographic parameters before and after titration of heart failure medication. LVEF=left ventricular ejection fraction, LVED=left ventricular end-diastolic diameter, LA=left atrium

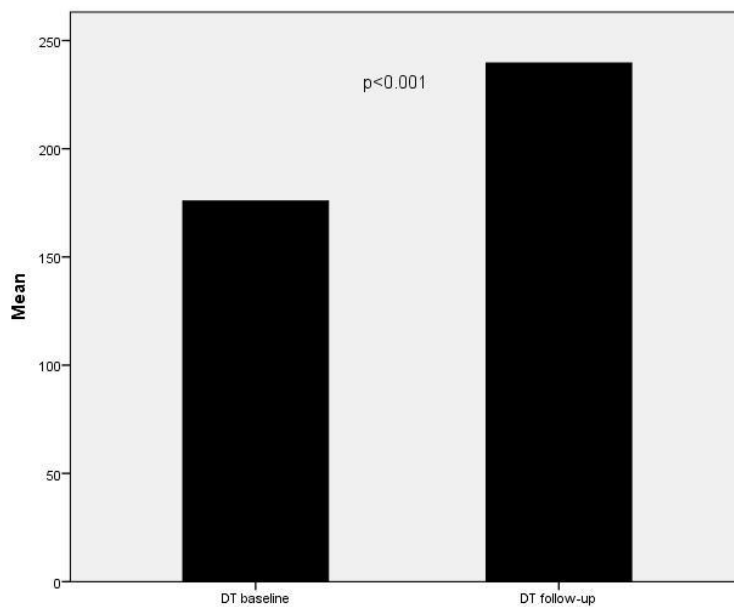


Figure 15. Mean deceleration time (DT) in patients at study entry and follow-up.

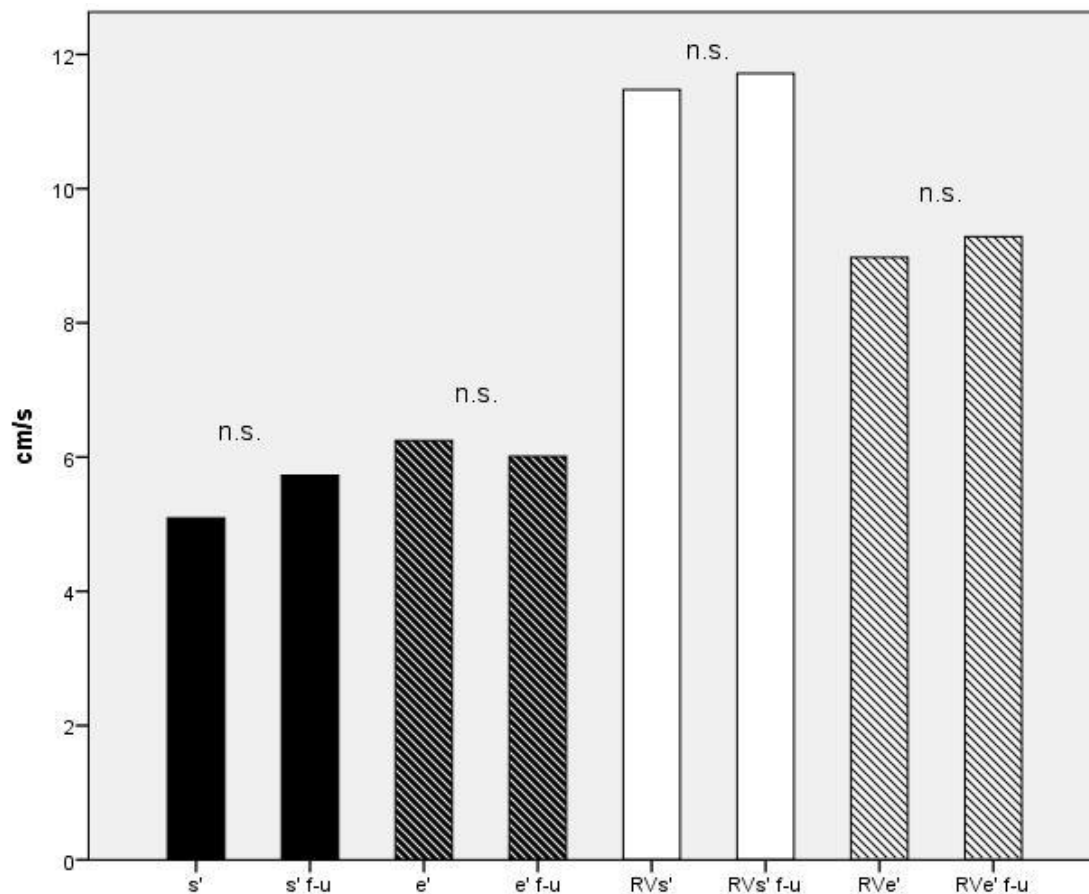


Figure 14. Mean tissue Doppler velocities at baseline and follow-up. s'=mitral annular systolic velocity, f-u=follow-up, e'=early mitral annular diastolic velocity, RVs'=tricuspid annular systolic velocity, RVe'=tricuspid annular early diastolic velocity, n.s.=not significant

Prognostic Studies (Study II-IV)

In Study II-IV we examined the prognostic importance of TDI parameters. The patients were followed for up to five years with the shortest follow-up period for Study II and the longest for Study IV. Study II-III included the same patients (n=156), while in study IV patients with LBBB and AF were excluded. The details are shown in the study flow charts (Figures 8 and 9). LVEF did not carry any prognostic information in any of these studies.

LV parameters

In paper II, only LV parameters were examined. The follow up was up to 24 months for all patients (sum of patient years 274). 27 patients (17%) died from a cardiovascular cause during this period. The result of this study was that only age and the variable E/e' were independently associated with the endpoint cardiovascular mortality. From receiver operating characteristics (ROC) analysis (Figure 17) a cut-off of 13 was determined for E/e'. Using this cut-off, non-survivors were separated from survivors with a sensitivity of 84 % and a rather low specificity of 45 %. Hazard Ratio (HR) for E/e' > 13 was 3.8, indicating a near four-fold risk of dying from a cardiovascular cause during the follow up period. Using the recommended cut-off for E/e' yielded a more balanced sensitivity/specificity, 60 % and 63 % respectively (Tables 6 and 7).

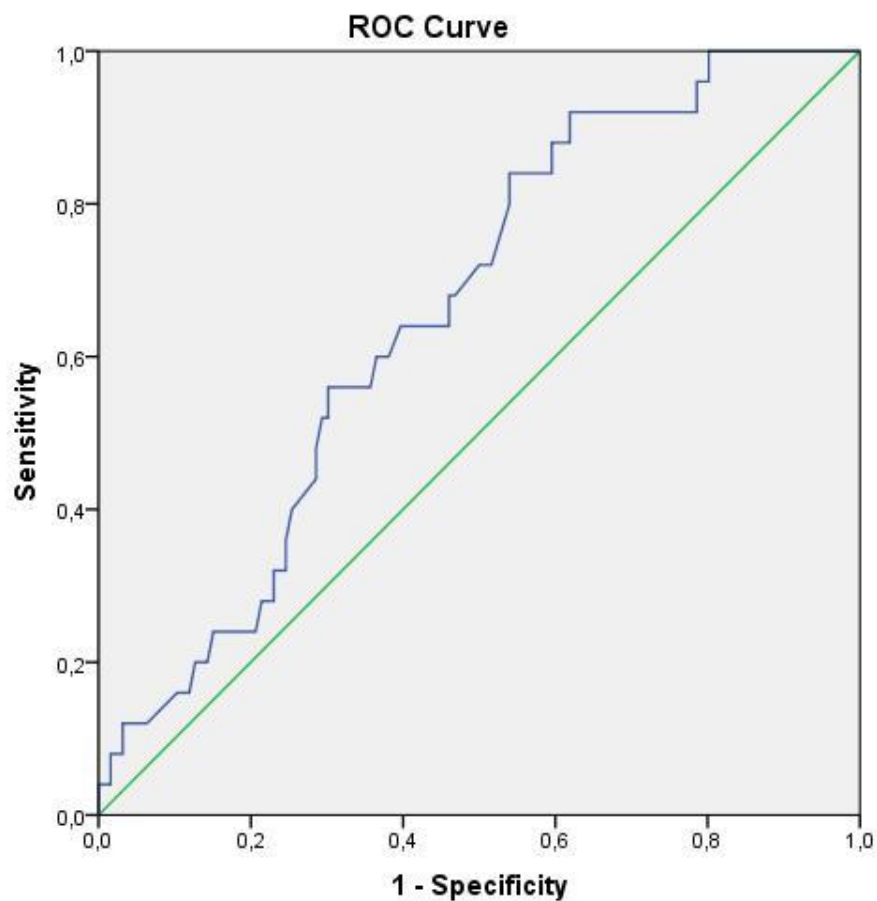


Figure 17. ROC-analysis for the parameter E/e' and the outcome cardiovascular mortality.

Table 6

Cross tabulation for $E/e' < 13$ and $E/e' > 13$ and the endpoint cardiovascular mortality within 24 months (n=156, missing values 5)

	Non-survivors	Survivors
$E/e' > 13$	21	69
$E/e' < 13$	4	57

Sensitivity $21/25 = 84\%$, specificity $57/126 = 45\%$.

Table 7

Cross tabulation for $E/e' < 15$ and $E/e' > 15$ and the endpoint cardiovascular mortality within 24 months (n=156, missing values 5)

	Non-survivors	Survivors
$E/e' > 15$	15	46
$E/e' < 15$	10	80

Sensitivity $15/25 = 60\%$, specificity $80/126 = 63\%$.

RV parameters

In Paper III TDI parameters from the RV was included in the survival analysis. The median follow up was 829 days (sum of patient years 352). During this period 43 (28%) patients died from cardiovascular causes and 55 (35%) patients were hospitalized due to acute decompensated heart failure (ADHF). In the multivariate analysis, only age and the sum of RV systolic and diastolic velocities ($RVs' + RVe'$) emerged as independent predictors of the combined end-point of cardiovascular mortality and HF hospitalization. No parameter was identified as a predictor of mortality. A value of $RVs' + RVe'$ of < 18.5 cm/s (n=35, 22%) indicated a two-fold risk of reaching the combined end-point compared to patients with $RVs' + RVe' > 18.5$ cm/s (HR=1.99).

MPI

In the third prognostic study (Paper IV) we excluded patients with atrial fibrillation (n=34), QRS-width > 120 ms (n=25), severe valvular disease (n=2). Finally, 112 patients were included in the analysis. Global MPI was calculated as described in the methods section, and the patients were followed for a median of 1474 days. The endpoints were all-cause mortality and cardiovascular mortality. During the follow-up period a total of 61 (55%) patients died, and 38 (34%) died from cardiovascular causes. Only MPI was associated with outcome. ROC-analysis yielded an ideal cut-off of 0.67 for MPI, to identify high risk individuals. Being above this cut-off, indicated a 5-fold increased risk of dying, and a 13-fold increased risk of cardiovascular death during the study period. Global MPI was better than septal MPI, in terms of Chi-square contribution and sensitivity/specificity calculation. E/e' and RV TDI parameters were not independent predictors in this setting.

Summary prognostic studies

Two post-hoc Cox analyses of the three separate variables that were shown to be associated with outcome were performed. The first was done to study the possible additive effect in predicting cardiovascular mortality by adding the $RVs' + RVe'$ -parameter to E/e' , during the shorter follow-up period described in Paper II (Table 8). This adds information, since RV parameters were not included in the survival analysis in this paper. As shown, the RV parameters do not add prognostic value. The second post-hoc analysis was to include MPI to the model (Table 9). This analysis has serious

statistical limitations, since study populations differ quite a lot in Paper II-III compared to Paper IV. Nevertheless, MPI seems to add significant prognostic information.

Table 8.

Post-hoc multivariate analysis of E/e' and the sum of RV velocities (RVs'+RVe'). And their association with cardiovascular mortality, same follow-up period as paper II.

Variable	HR(95%CI)	p value
E/e' > 13	3.0(1.01-8.91)	0.048*
RVs'+RVe' < 18.5 cm/s	1.04(0.42-2.53)	0.94

HR=Hazard Ratio, 95%CI=95% confidence intervals, *=statistically significant

Table 9.

Post hoc multivariate analysis as table 8, with the addition of MPI > 0.67 to the model.

Variable	HR(95%CI)	p value
E/e'	2.83(0.81-9.97)	0.10
RVs'+RVe' < 18.5 cm/s	1.22(0.47-3.19)	0.63
MPI > 0.67	24.3(3.22-182.3)	0.002*

GENERAL DISCUSSION

In this study we followed a population with systolic HF resembling that seen in clinical practice, and evaluated the diagnostic and prognostic value of different TDI-derived parameters. In this particular population, all had LV systolic dysfunction. Therefore, other parameters than LVEF must be used to separate groups with respect to diagnosis and prognosis. The substudies address several separate and interlinked questions. Some of the questions are answered, but the majority remains and quite a few have been added.

Is TDI the method of choice to evaluate diastolic function in patients with systolic heart failure?

In Paper I, we demonstrated that TDI revealed diastolic dysfunction in cases with pseudonormal pattern on transmitral flow recordings. Furthermore, we showed that in this population almost all patients had signs of diastolic dysfunction expressed as decreased early diastolic annular velocity (e'). This is an important finding, because we know that symptoms and prognosis in patients with HF partly depend on degree of diastolic function (102-104). In our study, we categorized groups according to transmitral flow pattern. We found that the groups with pseudonormal and restrictive pattern had similar diastolic velocities. Only about 10 % of patients with pseudonormal pattern had normal e' . The sample size may be small to draw extensive conclusions, but these findings indicate that when E/A-ratio is normal in patients with LV systolic impairment, this suggests diastolic dysfunction in most cases. At least, pseudonormalization may be defined as the combination of a normal E/A-ratio and subnormal early diastolic velocity.

A limitation of this study is the lack of invasive data limiting the validity of our findings.

Our belief is that diastolic velocity is a better estimate than transmitral flow to assess diastolic function in patients with systolic heart failure. The reasons being; the superior reproducibility, the simplicity to interpret findings and the lesser dependency on load and heart rate (48,105-108). Another major advantage is that it can be used regardless if the patient is in sinus rhythm or atrial fibrillation.

Should we stop using transmitral flow recordings in patients with HF?

No, the recommendation today is to use a combination of several methods to evaluate diastolic function in all patients (24). TDI early diastolic velocities may be used as a first screening method to assess whether diastolic dysfunction is present or not. If this is the case, transmitral flow pattern can be used to grade diastolic dysfunction according to severity. To assess other aspects of diastolic function, such as filling pressure, the ratio of E/ e' is still the best noninvasive estimate (47,48,109), in spite of its limitations (110,111). LA volume should also be documented as a measure of chronically elevated filling pressure.

Why did not myocardial velocities change after treatment with common HF medication?

In paper V, a follow-up echocardiography examination was performed in 41 patients with newly diagnosed HF and none/insufficient treatment with ACE-inhibitors/ARB

and beta blockers. The purpose was to investigate the effect of HF treatment on TDI parameters. The principal finding was that none of the recorded LV myocardial velocities changed significantly. The opposite was found for all conventional parameters recorded (LVEF, LVED, LA diameter, DT), that all changed significantly. In particular, LVEF and DT changed substantially (Figures 14-16). Thus, tissue velocities seem to be more stable. There may be several explanations for this. Previous studies have shown that HF therapy improves common echocardiographic expressions of systolic and diastolic function, such as LVEF, LVED and transmitral Doppler flow (112-120). Maybe these indices are more sensitive than tissue velocities for rapid hemodynamic changes secondary to treatment with ACE-inhibitors and beta blockers. In fact, TDI parameters are considered to be fairly insensitive to changes in load (121). Furthermore, TDI parameters are known to be sensitive, and are often subnormal even in cases of subclinical disease. Thus, the unchanged myocardial velocities might be a marker of remaining myocardial disease. A longer follow-up period, allowing the process of reverse remodeling to proceed, may have given different results. RV dysfunction in LV systolic heart failure is a well-known negative prognostic factor (50,53,122-125), also shown in this thesis (Paper III). It is our belief that RV impairment represents a more severe and less reversible stage of the disease. This could partly explain why tricuspid annular velocities hardly changed at all during follow-up in our study. The possibility to draw extensive conclusions is of course limited by the small sample size and the rather short follow-up.

Predictors of outcome, what are they good for?

It is easy to find studies on the prognostic importance of numerous different variables in heart disease. These studies are important as they render knowledge about pathophysiological aspects of the actual disease, and can hopefully help us to identify high-risk patients in need of more intense supervision and treatment. However, in a clinical context it is not always easy to understand what to do with all this information. In what way should we act in front of a patient with an unalterable factor, which a handful studies have showed means a small to moderate increase in the risk of being hospitalized for HF in the nearest 18-24 months? The answer is probably not much in most cases. Having said this, much of the research about prognostic factors has changed clinical practice, and there is still room for more.

The ideal prognostic marker should have at least the following three features:

- 1) It should be able to separate high-risk from low-risk individuals with a high sensitivity and specificity.
- 2) The increased risk pinpointed by the marker should be possible to reduce by therapeutic intervention.
- 3) It should be clinically applicable.

Why are different TDI parameters independent predictors of outcome in Study II and III?

In Paper II-IV, we investigated the prognostic importance of different TDI parameters compared to clinical and established echocardiographic parameters. Study II and III had identical populations, while in Study IV patients with atrial fibrillation and LBBB were excluded. Study II had the shortest follow-up period, and Study IV the longest. In study II, the noninvasive surrogate marker of LV filling pressure E/e' , emerged as a moderately strong, independent predictor of cardiovascular mortality. This is in line

with several previous and following studies (81,83,86-88,126-131). The cut-off for E/e' used in this study was decided by ROC-analysis and set to 13. This value is relatively close to the recommended cut-off of 15 (24), and in line with what other studies have shown.

In Study III, no individual variable was proven to be independently associated with mortality in multivariate analysis. With a combined end-point of cardiovascular mortality and HF hospitalization, a merged variable with the sum of tricuspid systolic and diastolic velocities (RVs'+RVe') was found to be the sole variable predicting outcome. E/e' was significantly associated with prognosis in univariate analysis but failed to reach significance on the multivariate analysis. This is somewhat surprising, since E/e' is an established marker of mortality and morbidity. There are some possible explanations. The only difference between the two studies is the follow-up period, and the explanation could partly lie in this factor. RV dysfunction probably reflects HF in a more advanced stage, while elevated filling pressure could be a more transient state of congestion. If this is the case, RV function could be more relevant for prognosis in the longer run. Of course, RV function might in fact be a better marker for prognosis in this study, regardless of follow-up time. However, in a post-hoc analysis performed for this thesis (Table 8), E/e' still was the best predictor of cardiovascular mortality in the shorter term, even when (RVs'+RVe') was added to the multivariate analysis.

One important matter, potentially introducing bias, is the timing of acquisition of the echocardiographic examination. Our intention was to perform this study when the acute phase of decompensation was over, but we cannot be sure that this was the case for all patients. Another possible explanation is lack of power, but this is somewhat contradicted by the high event rate.

Why is LVEF lacking prognostic value in the studies of this thesis?

Impaired systolic function is a well known negative prognostic factor, especially compared to subjects with normal cardiac function (34,35,132,133). Most of these studies have been performed before the era of modern HF treatment, contain relatively small number of patients, and have dealt with LVEF in a dichotomous way. However, in populations with reduced LVEF, the degree of reduction is not as clearly related to symptoms and prognosis. The patients in the present study had all depressed LVEF, and the prognostic value of LVEF was close to zero in Paper II-IV. This can serve as a good illustration why it is important to find other variables than LVEF in order to predict prognosis in patients with systolic heart failure.

Why is MPI such a strong prognostic predictor of outcome?

In paper IV, which had the longest follow up period, we examined the prognostic value of MPI, derived from TDI, and calculated as a mean from four different sites of the LV, so called "global" MPI. The principal finding was that global MPI was a very strong predictor of cardiovascular mortality, but also of all-cause mortality. In MPI, there is information about both systolic and diastolic function in the same value.

There are several studies proving the prognostic importance of MPI derived from Doppler flow recordings (92-94). The advantages of using TDI recordings to calculate MPI are the lesser dependency of load (101), and the possibility to calculate MPI in the same cardiac cycle, thereby avoiding heart rate variations to affect the result. With global MPI, these advantages are combined with the benefit of evaluating the whole

LV. This probably explains why global, TDI-derived MPI seems to be such an excellent prognostic tool in this population.

The population in Paper IV is a little less heterogenic than in the other studies, since patients with atrial fibrillation and LBBB were excluded. This could possibly affect the result. Study IV investigates long-term prognosis, but MPI seems to be as good with a shorter follow-up (Table 9).

A major limitation of MPI as a method is that it is not possible to calculate in patients with atrial fibrillation, since a' or A is needed to analyze MPI (Figures 6, 7 and 10).

Recently, a new method was described by Su et al (134), where IVCT was replaced by the pre-ejection period, i.e. the time interval between the start of the QRS-complex to the beginning of the systolic myocardial velocity. This might be a useful parameter in patients without atrial contraction, but has to be validated.

Furthermore, in patients with LBBB, MPI values become disproportionally high, due to late electromechanical activation of the ventricle.

To assess diastolic function in these patients, crude TDI-derived diastolic velocities are excellent, and to estimate LV filling pressure, E/e' is a validated parameter with prognostic information, even in these patients (87,135-137). However, time seems to be better than speed when it comes to prognostic information.

CONCLUSIONS

- Pulsed Tissue Doppler is an easily obtained and reproducible method in a “real world” population of patients with systolic HF.
- Tissue Doppler is better than transmitral flow recordings in determining diastolic function in patients with systolic heart failure
- Diastolic dysfunction is present in some degree in almost all patients in our study population consisting of patients with systolic HF.
- E/e' is a moderately strong independent predictor of cardiovascular mortality in patients with systolic heart failure, and a combination of right ventricular diastolic and systolic velocities is an independent predictor of longer-term mortality/morbidity in the same population.
- Myocardial performance index derived from tissue Doppler recordings is a very strong predictor of cardiovascular mortality as well as of all-cause mortality in patients with systolic heart failure in sinus rhythm and with normal QRS-width.
- Tissue Doppler parameters do not change significantly in the short term after titration of modern heart failure medication, in spite of clear improvement in LV ejection fraction, decrease in LV end-diastolic diameter and increase of deceleration time.

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