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QUANTITATIVE ECHOCARDIOGRAPHIC METHODS FOR PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Background:
The aim of this thesis was to evaluate two diagnostic and two prognostic quantitative echocardiographic methods for patients with acute coronary syndrome (ACS).

Methods:
Velocity tracking (VeT) presents the longitudinal tissue Doppler velocities of the left ventricle (LV) as a bull's eye plot giving an easy three dimensional understanding of both the global and regional function of the LV in regard to longitudinal velocities, systolic as well as diastolic.

The state diagram ,also derived from tissue Doppler imaging (TDI), gives a schematic view of the timing of the different phases of the cardiac cycle both on a global and segmental level, from this diagram we get the State index based on myocardial performance index (MPI) both on a global level and its intersegmental variation. Both methods were compared to wall motion score (WMS) and ejection fraction (EF) in a population with ACS without previously known heart disease. We included 20 NSTEMI patients and 10 controls for the VeT study and 49 NSTEMI patients and 21 controls for the State index study.

For prognostic evaluation we tested peak systolic velocity (PSV) and four different dyssynchrony parameters in two studies. PSV is an easy accessible parameter derived from TDI. As dyssynchrony parameters we examined septal-lateral delay, post systolic index (PSI), myocardial performance index (MPI) and time to peak systolic 2D strain both as a global mean and with the standard deviation (SD) as a measurement of intersegmental variation. We included 227 unselected patients with NSTEMI and used a combined endpoint of death, readmission due to heart failure and new MI.

Results:
Both diagnostic methods were shown to be sensitive to acute ischemia but only the state index showed significantly better diagnostic value compared to WMS with an AUC of 0.87 (WMSI 0.66 p=0.008). VeT had comparable results to that of WMS regarding both ischemia and regional information.

PSV showed a strong association with outcome in respect to our combined endpoint when compared to all other tested echo methods with a AUC of 0.74. When adjusting for known risk factors PSV remained independent when the other echo parameters did not. The dyssynchrony parameters did carry some prognostic information but were not of incremental value to that of conventional parameters such as EF and WMS.

Conclusion:
Both VeT and the State index showed a strong diagnostic value but only the State index was significantly stronger compared to EF and WMSI. Both these promising methods need to be evaluated further in a larger prospective study.

For risk stratification after ACS PSV seems to be a robust and easily obtained echocardiographic parameter that carries independent prognostic information with incremental value to that of known strong predictors such as NT pro BNP and eGFR. Mechanical LV dyssynchrony parameters seem to carry some significant prognostic information but in comparison to conventional echo parameters there was no or little incremental value of this information.

Keywords: Tissue Doppler, Quantitative Parameter, Acute Coronary Syndrome, Diagnosis, Prognosis.

LIST OF PUBLICATIONS

I. **Carl Westholm**, Anna Bjällmark, Matilda Larsson, Per Jacobsen, Lars-Åke Brodin, Reidar Winter.
Velocity Tracking (VeT), a new and user independent method for detecting regional function of the left ventricle
Clin Physiol funct imaging. 2009 Jan,29(1):24-31

II. **Carl Westholm**, Jonas Johnson, Elif Gunyeli, Tomas Jernberg, Aristomenis Manouras, Reidar Winter
The State index, a new timing based diagnostic tool for identifying patients with acute coronary syndrome
In Manuscript

III. **Carl Westholm**, Jonas Johnson, Anders Sahlén, Reidar Winter, Tomas Jernberg.
Peak systolic velocity using color-coded tissue Doppler imaging, a strong and independent predictor of outcome in acute coronary syndrome patients.
Cardiovasc Ultrasound. 2013 Apr 1;11:9

IV. **Carl Westholm,** Jonas Johnson, Tomas Jernberg, Reidar Winter.
The prognostic value of dyssynchrony parameters in patients with acute coronary syndrome.
Cardiovasc Ultrasound 2013 Oct 11;11:35

CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AUC	Area under curve
AVC	Aortic valve closure
CABG	Coronary Bypass surgery
CAD	Coronary artery disease
CCU	Coronary care unit
CV	Coefficient of variability
CSD	Cardiac State diagram
CVD	Cardiovascular disease
CW	Continuous Doppler
ECG	Electrocardiogram
ED	Emergency Department
EF	Ejection Fraction
GE	General electric
GH	GrippingHeart
HR	Hazard ratio
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
KTH	Kungliga tekniska högskolan
LBBB	Left bundle branch block
LV	Left Ventricle
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MPI	Myocardial performance index
MRI	Magnet resonance imaging
NSTEMI	Non ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PST	Post systolic thickening
PSI	Post systolic index
PSV	Peak systolic velocity
PW	Pulsed Doppler
ROC	Receiver operator or characteristic
ROI	Region of interest
SD	Standard deviation
ST	Speckle tracking
STEMI	ST-elevation myocardial infarction
TDI	Tissue Doppler imaging
TVI	Tissue Velocity imaging
UA	Unstable angina
VeT	Velocity tracking
WHO	Worlds health organization
WMS	Wall motion score
WMSI	Wall motion score index

1 INTRODUCTION

1.1 ACUTE CORONARY SYNDROME

Epidemiology

Despite a reduction in recent years in the incidence of cardiovascular disease (CVD) including coronary artery disease (CAD) and acute coronary syndrome (ACS), CVD remains the cause of 4 million deaths in Europe and 1.9 million deaths within the EU. CVD therefore accounts for 47% of all deaths in Europe and 40% in the EU [1].

Sweden is no exception to this and it is estimated that the overall total economic cost of CVD in Sweden every year is 61,5 billion SEK and accounts for 14% of the total cost for medicines [2].

Worldwide, according to the World Health Organization (WHO) in 2008 approximately 17.3 million people died because of CVD, of which 7.3 millions deaths were due to (CAD) [3] while in The United States it is estimated that every 44 seconds someone will have a myocardial infarction (MI) [4] which in 2010 resulted in 625 000 discharged patients with a diagnosis of acute coronary syndrome (ACS). [4]

In Gothenburg, the second largest city in Sweden, it has been shown that 19% of all visits to the Emergency Department (ED) are due to chest pain suggestive of ACS [5]. With that and the above stated in mind, it is evident that distinguishing ACS among all the patients with chest pain is a challenging task that requires effective tools for both diagnosis and risk stratification, considering the wide range of important differential diagnoses [6, 7] and the fact that the rate of missed ACS in patients at the ED has been reported in different studies to be between 1.9% and 2.3%. [8, 9]

Diagnosis

ACS is a clinical syndrome that basically includes three different diagnoses:

1. ST-elevation myocardial infarction (STEMI). This condition is most often due to total occlusion of a coronary artery resulting in transmural myocardial damage unless treated rapidly [6].
2. Non ST-elevation myocardial infarction (NSTEMI) usually due to a subtotal occlusion of a coronary artery that also leads to myocardial necrosis.[6]
3. Unstable angina pectoris (UA) which resembles a NSTEMI but without persistent myocardial damage.[6]

The definition and diagnostic criteria for myocardial infarction (MI) has changed over time alongside the rapid development of diagnostic tools. Presently it is based on patients history, ECG-changes consistent with myocardial ischemia, a dynamic course of values of cardiac biomarkers (cardiac troponins) and now also imaging evidence of regional wall motion abnormality consistent with myocardial ischemia [10-13] which is one of the reasons for compiling data for the first two papers in this thesis.

Prognosis

In Sweden between 2001 and 2011 the incidence of acute MI decreased by 32% in men and 30% in women [14] and the 28 day mortality decreased between 1990 and 2011 from 41% to 26% in men and from 45% to 31% in women. Despite these positive numbers, patients with CHD in both Sweden and the United states continue to have a very high morbidity and mortality [4, 14] and worldwide the number of persons living at risk or with manifestations of the disease is increasing [15] which makes risk stratification very important and is one of the reasons for writing the final two papers in this thesis.

1.2 QUANTITATIVE ECHOCARDIOGRAPHIC METHODS

1.2.1 Background

One and two-dimensional images

Since 1953, when the first echocardiographic examination was performed, the development of this technique has been remarkable. Methods that seem very modern one year are suddenly replaced by new methods (even more modern and feasible) than the previous methods. Only two decades ago, echocardiography was something clinical physiologists or highly specialized cardiologists could handle, however, today it is considered an everyday routine similar to using a stethoscope. (Fig 1)

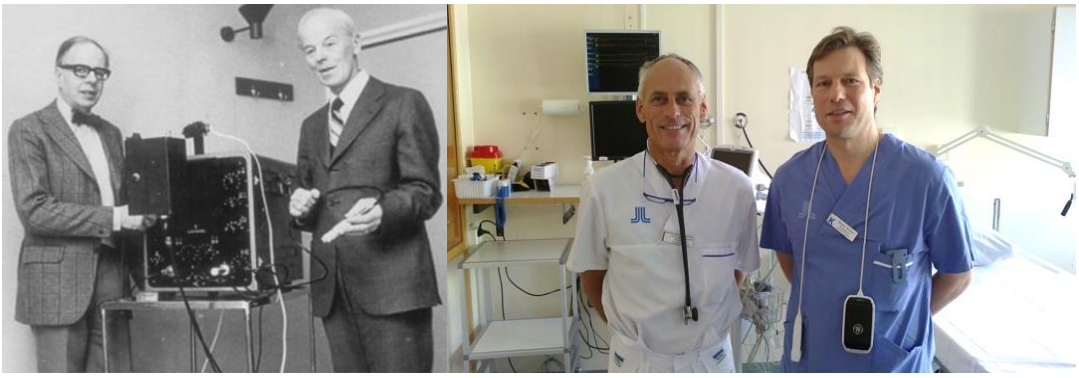

Figure 1*. To the left, Prof. Kjell Lindström and Dr.Inge Edler with the first echocardiographic machine in 1953. To the right, two cardiologists, one traditional with the conventional stethoscope beside a modern cardiologist with a handheld echocardiographic machine not much bigger than the old stethoscope with both both 2D images and color Doppler capability. Reprinted with permission from prof. K. Lindström.*

The first echocardiographic method available for clinical use was ultrasound beams that were sent out in just one direction giving a one-dimensional image of the heart, called M-mode (fig 2) Eventually the 2D technique was developed where the ultrasound is sent out successively in different directions from the probe resulting in a 2-dimensional image of a sector (fig 3). With this technique, using different projections, all parts of the

heart can be examined, with moving pictures in real time making assessment of cardiac function and dimensional measurements possible. These measurements have proved to be highly important in respect to diagnosis, management and prognosis in patients with cardiac disease [16-18].

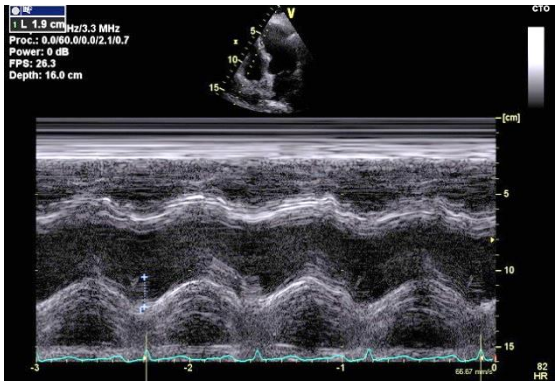

Figure 2. *Example of the modern version of M-mode. Distance from probe on the Y-axis and time on the X-axis with the corresponding ECG, and the small 2D image above showing the line along which the M-mode registration is being made. Of course, with the first machines there were no 2D images or ECG for guidance.*

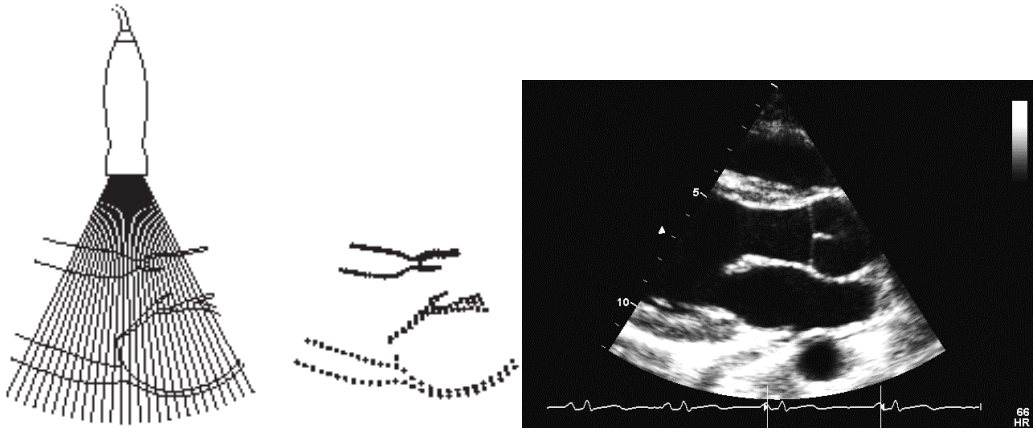

Figure 3. *Schematic image of how the different ultrasound beams form the complete image that can be seen to the right. This is a parasternal long axis view. Reprinted with permission from Arne Olsson.*

Doppler registration of blood flow

When ultrasound is reflected by a moving object its frequency will change with direction, just as the pitch of an ambulance siren will fall when the vehicle is moving away from you instead of towards you. This phenomenon is used by the Doppler technique to measure the velocity of the blood flow within the different heart chambers. With continuous Doppler (CW) the velocity is recorded along the whole reach of the beam and with pulsed Doppler (PW) the velocity will be registered at one specific point along the reach of the beam (Fig 4). With the knowledge of the dimensions together with the flow velocities and some easy physics and calculations a wide range of hemodynamic assessments can be made. With these calculations, valvular insufficiencies and stenosis can be assessed as well as the inflow pattern to the left ventricle (LV). [19-22] This technique gave us the first possibilities of non-invasive quantitative measurement of the hearts function and haemodynamics and following

this, more and more techniques for quantitative measurements have been developed using different modalities of which some will be described below.

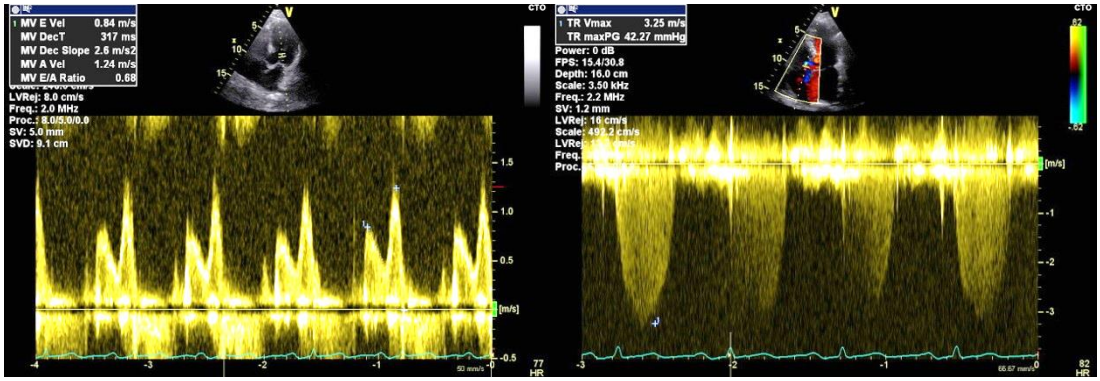

Figure 4. *To the left a pulsed Doppler registration of the inflow to the left ventricle, in the small 2D image above you see the cursor with the marking showing where the velocities are recorded. To the right a continuous Doppler registration of the regurgitation from the tricuspid valve, in this case the maximum velocity along the whole cursor is registered.*

1.2.2 Tissue Doppler

The technique for obtaining Doppler information from tissue was initially developed in the 1960's [23] but it was first in the late 1980's that the first systematic description of tissue Doppler was made [24] which in turn paved the way for a wide range of new quantitative echocardiographic analyses. Tissue Doppler is often called tissue Doppler imaging (TDI) or tissue velocity imaging (TVI) and initially pulsed tissue Doppler was used. With pulsed tissue Doppler, similar to with PW, the velocity of the myocardium is registered within a sample volume that can be moved by the examiner in real time guided by a 2D image and with the velocity curve in another display (Fig5). Later on Colour TDI was developed where the velocities from the whole myocardium are registered and can be processed in a later session from every part of the myocardium in the image (Fig 5) [25, 26]. The myocardial velocities have in many studies shown to be a very good and quantitative way to describe both LV systolic and diastolic function globally and regional differences. [26-31]

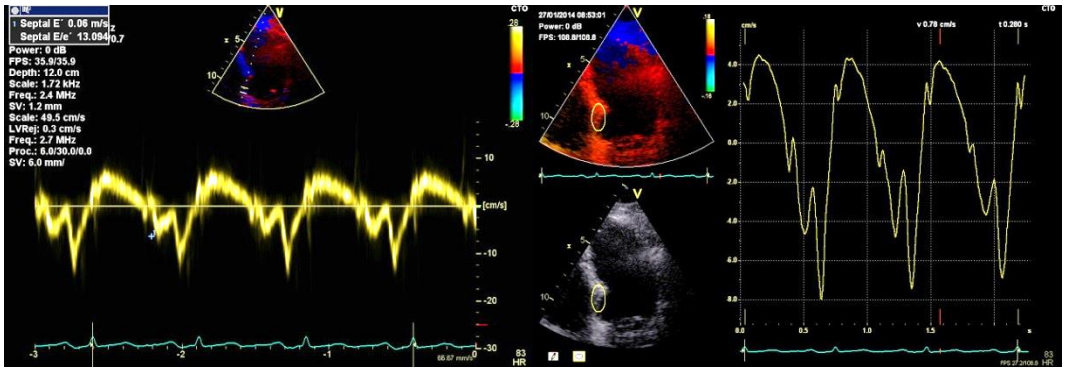

Figure 5. *To the left a pulsed tissue Doppler registration performed in real time with the cursor in the image above showing from what region of the myocardium the velocities are recorded. To the right a TVI image of a four chamber view is being analysed. In this case you can move your region of interest (ROI) to any place in the myocardia and get the corresponding velocity curve in the adjacent graph in a post processing session.*

Furthermore, and also widely used, the myocardial velocities in combination with the registered inflow to the LV recorded with PW can be used to describe the diastolic function and filling pressure of the heart [32-34] with the ratio of the maximum inflow velocity by PW, called the e-wave, divided by the maximum myocardial diastolic velocity called the É, the e/É-ratio. [32-34]. For both colour TDI and pulsed tissue Doppler there are published proposed normal values.[35-37] TDI has also showed to be a robust parameter quite insensitive to noise and poor image quality [38] compared to 2D imaging and the technique offers a higher frame rate and therefore also a higher time resolution compared to 2D echocardiography.

Deformation, or shortening of the myocardium is often called strain, and the rate of this deformation is called strain rate. Due to the high time resolution, TDI is suitable for strain and strain rate calculations. It is also known that the rate of deformation correlates better to contractility compared to just deformation indicating that TDI is a very good modality to measure the actual contractility of the LV. [39]

However, on the other hand, the registered velocities will be dependent on the angle between the probe and the myocardium which always adds some uncertainty to the measured velocity especially the closer to the LV apex you try to measure, as the angel there will be more acute compared to the basal segments of the LV.

1.2.3 Speckle tracking

2D echocardiographic images are built up by small irregular structures that can be seen if one observes the images with strong magnification .These irregularities, called speckles, shape unique patterns for every different part of the myocardium. With the speckle tracking (ST) technique the software learns to identify and recognize small portions of the myocardium and can follow them during the hearts motion from image to image. With this technique the longitudinal and radial deformation as well as thickening of the myocardium over time can be measured and the strain e.g. shortening or strain rate for a chosen segment or globally can be calculated [40, 41]. These measurements are less dependent on the angle between the probe and the myocardium

compared to tissue Doppler and can follow the motion int the image in any direction. Using modern software both strain and strain rate can be very comprehensively presented directly in the image or in a "bull´s eye plot" including information from all three apical views (fig 6). Strain as well as strain rate derived from ST and the different ways to present it, have been validated and have been shown to correlate well to the hearts motion in various medical conditions. [42-45]. Speckle tracking requires 2D images so therefore, as mentioned in the section above, the time resolution will be substantially lower compared to information derived from tissue Doppler and in addition the technique is rather sensitive to poor image quality [38]which limits its clinical applicability to some extent.

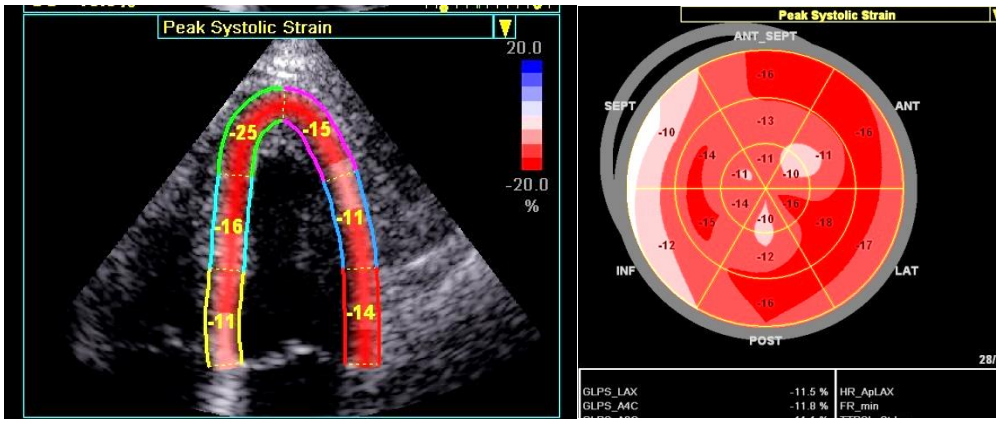

Figure 6. *To the left a four chamber apical view with the segmental strain noted in each corresponding segment, and to the right a bull´s eye plot of the LV with different strain correlating to different color, in this case lower strain in basal septal and inferior part of the LV.*

1.2.4 Function and Timing parameters

Further on in this thesis I will divide all echocardiographic parameters in two groups: 1.Function parameters and 2.Timing parameters.

Function parameters

Function parameters encompass all parameters that focus on systolic or diastolic function, pump function, myocardial velocity, deformation or displacement without regard to when it actually occurs. In this group we find both qualitative and quantitative parameters. Examples of function parameters are ejection fraction (EF), wall motion score index (WMSI), global or segmental strain and peak systolic velocity (PSV) etc.

Timing parameters

Timing parameters also measure velocities, displacement and deformation but focus on when in the cardiac cycle the registered event occurs instead of the actual magnitude. Timing parameters can be global as with Myocardial performance index (MPI) that gives information of disturbances in timing between the different phases of the cardiac

cycle or a parameter that focus on the intersegmental variation of timing of events called dyssynchrony or mechanical dispersion. An example of the latter is septal – lateral delay, time to peak systolic strain and post systolic index (PSI). All the parameters mentioned in this section will be discussed in more detail below under section 1.3.

1.2.5 Timing terminology

Dyssynchrony and mechanical dispersion

The terminology regarding intersegmental timing variation varies slightly in the literature from dyssynchrony or asynchrony to asynergy or mechanical dispersion [46-49]. They all describe the same phenomenon but the term dyssynchrony is most commonly used when the variation is significant and affects the motion and contraction patterns of the LV as seen in left bundle branch block (LBBB). When the timing differences is smaller and difficult to register with the human eye and not apparently affects the LV function, it is often called mechanical dispersion [49] but there is, to my knowledge, no consensus about this terminology. In paper II I will use the term mechanical dispersion.

Isovolumetric phases and pre or post ejection times

The isovolumetric phases, the isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) are the times between the closing and opening of the mitral and aortic valves. These phases are the same for the whole LV and therefore a global timing parameter. Traditionally this measurement is done with PW or CW images to identify when the valves are closing. If you use TDI to measure the time when the myocardium change state between relaxation and ejection in the myocardium (fig 15) the value is almost similar but can vary between the different segments of the LV and therefore the term pre ejection and post ejection times are more suitable for these measurements. We call both these phases transition phases.

1.3 ECHOCARDIOGRAPHY AND ACUTE CORONARY SYNDROME

Patients in the ED presenting with chest pain are a challenging task for the physician on duty. The majority of these patients are admitted to a Coronary care unit (CCU) for further examination and evaluation with ECG-monitoring and lab tests, but only a small portion of them are ultimately diagnosed with ACS. Many methods to sharpen the available diagnostic tools have been tested and evaluated with the aim of both improving the outcome and care for the patients in addition to increasing the cost effectiveness by excluding the less harmful diagnoses. Scintigraphy has been shown to have an extremely high negative predictive value for ACS [50] but with the downside of having limited availability in the daily clinical routine. Echocardiography is a well-established and validated method for detection of regional LV dysfunction with a high negative value for ACS [51-53] and with a higher availability but nevertheless not

routinely used which may be explained by its rather high user dependency [54-56]. Even if the diagnosis is not unclear, echocardiography has proved important to provide information regarding complications, infarction size, eventual concomitant right ventricular infarction and to monitor recent or ongoing therapy [57].

Furthermore, evaluation of the regional function of the LV following an acute MI is of the utmost importance as both morbidity and mortality are related to infarct size and location and this increases with the amount of scar shown with magnetic resonance imaging (MRI). [58-60] It has also been shown that echocardiographic findings correlate well to the findings of MRI [61, 62]. The high incidence and prevalence of ACS in combination with its associated high morbidity and mortality necessitate the need for effective risk stratification.

1.3.1 Diagnostic methods, function parameters

Echocardiography offers us a wide range of methods for evaluating LV regional and global function, both qualitatively and quantitatively. With the use of conventional 2D echocardiography the EF of the LV can be assessment visually which has been shown to correlate quite well with other objective measurements[63], however this method has a relatively high inter-observer variability and requires a long learning curve and high expertise before being usable in clinical practice. A more objective way to assess left ventricular ejection fraction (LVEF) is the modified Simpson's biplane method [64] but still this results in a global parameter regardless of regional dysfunction.
Another way of expressing LV function including the regional function is wall motion score index (WMSI) where the LV is divided into 16 or 18 segments from the three different apical views with the regional function described segment by segment in a so called "bull´s eye plot" (fig 7) giving important information especially in coronary heart disease where the dysfunction is expected to be only regional and the overall global function or EF might be considered normal [65].

This regional information can assist in identifying the culprit coronary vessel in ongoing ischemia. Figure 7 demonstrates distribution of coronary blood supply to various regions of the LV.

Tissue Doppler which offers many ways of quantitative measurements of the hearts function is today a well-established method for analysis of LV longitudinal velocities and displacement [66, 67] and it has previously been shown that the longitudinal velocities are highly sensitive to acute myocardial ischemia even when the radial velocities and global function remain normal[68-70].

Instead of myocardial velocities or displacement LV regional function can also be described with segmental or global deformation e.g. shortening which is most often called strain and can be derived with the SD technique from 2D images but also from TDI. Just as with WMSI, the segmental strain can be presented in a bull´s eye plot which gives an easy understandable image of the regional LV function (fig 7) and has also been shown to be sensitive to myocardial ischemia.[71-73]. The advantage of strain derived from 2D images compared to Tissue Doppler is that it registers myocardial motion in all directions in regard to the probe, longitudinal and radial as well as thickening or rotation of the myocardium, but on the downside it is quite sensitive to poor image quality[38] and the lower time resolution.

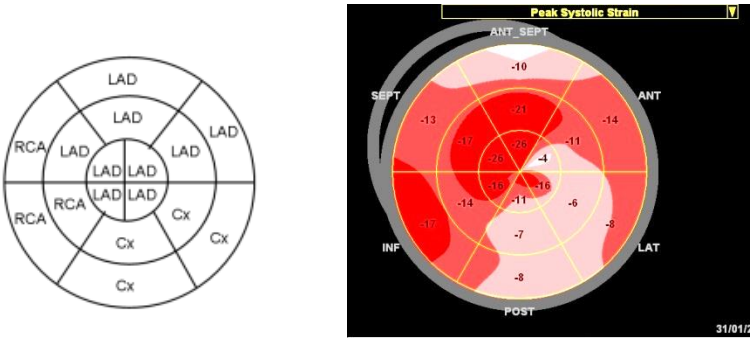

***Figure 7**. Schematic short axis view of the LV showing which coronary vessel supports which region. To the right a bull´s eye plot rendered from 2D strain showing impaired strain in the lateral and posterior region corresponding to the region supported by the circumflex artery.*

1.3.2 Diagnostic methods, Timing parameters

It is known that not only velocities, displacement and deformation are sensitive to ischemia but also the timing of events in the different segments of the LV with a delayed activation and an electromechanical delay [74, 75]. This delay results in both post-systolic contraction and prolonged isovolumetric phases and deranged relations between the different phases of the cardiac cycle. Focusing on the latter, a method called myocardial performance index (MPI) was first described by Tei et al in 1995 under the name Tei index [76] that was calculated with the formula: (IVCT+IVRT)/ejection time. At that time CW was used to determine the MPI but more recently TDI has been used creating the possibility to record the different phases from more than one segment of the LV [77-79]. Both the transition phases and the MPI has been shown to be affected by myocardial ischemia[80-83] and are very robust measurements shown to be insensitive to load conditions and heart rate [84].

Post systolic index (PSI) and post systolic thickening (PST) are two other timing parameters derived from 2D strain or tissue Doppler that describe the amount of contraction and deformation that actually occurs after the systolic phase and aortic closure. These methods have also been shown to be sensitive to both acute and chronic ischemia [31, 85, 86] even in patients without any other detectable systolic impairment of the LV [46, 87, 88] which indicates that timing might be even more crucial for detecting ischemia than the actual function, velocities and deformation.

It has been reported that even in the normal heart the contractility pattern is heterogeneous within the different segments of the LV [89] which is measured as dyssynchrony or mechanical dispersion. Furthermore we know that the intersegmental timing variation increases with both acute and chronic ischemia.[47, 48, 90, 91]

1.3.3 Velocity Tracking and the State Diagram

Velocity tracking is a method that was introduced in 2007 and was developed in cooperation with KTH Royal Institute of Technology, Stockholm, Sweden [92]. This is a quantitative method in which the different longitudinal velocities of the LV are

presented using colour coding in discrete colour bands representing different velocities (fig 8) in a bull's eye plot similar to 2D strain from SD. This bull's eye plot gives an easily understandable three dimensional map of the longitudinal velocities of the LV at any chosen time point in the cardiac cycle. In figure 8 we see two plots, the first with the peak systolic velocities (PSV), and the second with the sum of PSV and the peak diastolic velocity from the É-wave. However, this method and its diagnostic value have not previously been tested in a clinical setting and will therefore be the focus of Paper I of this thesis and will be disused in further detail below under section 3.2.1.

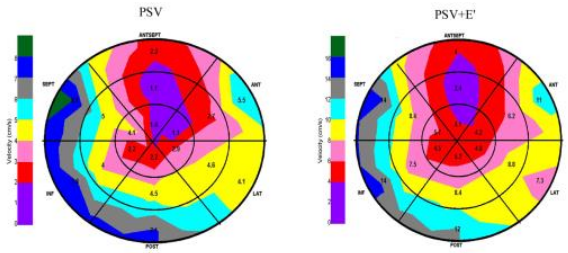

Figure 8. *An example of velocity tracking bull´s eye plot from a patient with an occlusion of the left anterior descending artery (LAD). Reprinted with permission.*

The cardiac state diagram (CSD) created by GrippingHeart (GH) is a new visualization tool that provides quantitative analysis of the timing of mechanical events in the cardiac cycle by registering the tissue velocities from the six basal segments of the LV and presenting them as seen in figure 9.[93]

This software analyses the velocity curves in respect to many parameters of which just the duration of the different cardiac phases can be seen in this version of the State Diagram but the possible varieties are numerous and will be discussed in detail in section 3.2..2. This diagram gives easy accessible information regarding the timing of the different phases of the cardiac cycle both on a global and segmental level.

From this information we can easily get the MPI automatically calculated both global (as a mean value of all the basal segments) and with the intersegmental variation of MPI as a possible mechanical dispersion parameter called MPI_SD and multiply them to get the "state index". This method, and the information and its diagnostic value in patients with ACS are yet not investigated and will be in focus in paper II of this thesis.

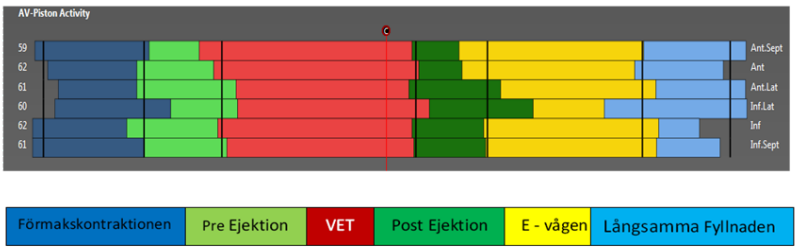

Figure 9. *An example of the state diagram showing the different phases of the heart with different colors and from the six basal segments of the LV from top to bottom with the segments noted to the far right of the picture.*

1.3.4 Prognostic methods, function parameters

Patients admitted to hospital who ultimately get diagnosed with MI or acute coronary syndrome constitute a very heterogeneous population and therefore the risk for future cardiac events will vary significantly within this population. The population with a high risk of future events may benefit from a more intensive treatment strategy and perhaps prolonged admission and monitoring, while the low risk population may benefit from a more conservative approach with early discharge. To separate these two groups adequate risk stratification is important.

Traditionally, conventional echocardiographic parameters such as EF and WMSI have been used for this purpose with good results [94, 95] however both these methods are limited due to poor reproducibility and the long required learning curve [56, 96].

The more recently developed quantitative parameter strain, derived from either 2D images or TDI, has also been shown to carry important prognostic information in addition to traditional parameters [97, 98]and they are less user dependent but also less available and feasible [99-102].

Subsequent studies introduced the diastolic parameter E/e' –ratio that reflects the LV filling pressure [34] as a prognostic parameter with incremental value to both EF and WMSI [103, 104]. This parameter has also been shown to ad complementary prognostic value to biochemical markers such as NTproBNP after ACS and MI [105-108].

1.3.5 Prognostic methods, Timing parameters

Regardless of QRS-width [47] it is known that ACS has significant impact on LV synchrony and in addition this can have a detrimental effect on the LV systolic function [90] . Furthermore it is known that LV dyssynchrony predicts LV remodeling [109, 110] and in a population selected for impaired LV function also predicts long term outcome [111]. All this implicates a possibly high prognostic value of dyssynchrony parameters in patients with ACS however whether that is applicable in an unselected ACS population has to our knowledge not as yet been tested.

Dyssynchrony or mechanical dispersion can be measured in many ways but it is always with an intention to describe intersegmental variation within the LV regarding function or timing. Just as in the case with the diagnostic parameters MPI, PSI and PST that are discussed above under 1.3.2 these parameters can be evaluated regarding their prognostic value both as the global mean value or the intersegmental variation of the parameter. Another parameter, which is perhaps the most established and commonly used, is septal –lateral delay which is derived from TDI and reflects the time difference between when the septal and lateral wall respectively reaches its peak systolic velocities.

Another method of measuring dyssynchrony or mechanical dispersion is time to peak strain and the intersegmental variation within the LV. This can be done with strain derived from both 2D images and tissue Doppler and has been shown to have prognostic value after ACS [111] where the two modalities have downsides and benefits as discussed above in section 1.2.2 and 1.2.3

1.3.6 Peak Systolic velocity (PSV) and dyssynchrony parameters

Although both systolic and diastolic LV function parameters are evaluated regarding their prognostic value in this group of patients, less is known about the systolic tissue velocities. Peak systolic velocity (PSV) is an easy accessible parameter that can be derived both online and in post processing from a TDI image and will be the focus in Paper III of this thesis and is discussed in detail below.

As mentioned above, many timing parameters have been proposed to be important when it comes to prognostic value after ACS but no comprehensive comparison between the methods is previously made in a group of unselected ACS patients which will be the focus of Paper IV of this thesis.

2 AIMS

2.1 AIMS PAPER I&II

Our aim with the first two papers was to evaluate both VeT and the state index in a bedside setting as a diagnostic tool for patients with ACS and compare it with expert WMSI and EF in regard to sensitivity and specificity with coronary angiography as the golden standard as reference.

We also intended to explore whether VeT could give us regional information regarding ischemia that was comparable or superior compared to WMSI. Furthermore, with the state index, our secondary aim was a post hoc analysis in which we examined if any other timing or dispersion parameter instead of MPI_SD could improve the diagnostic value of the State index.

2.2 AIMS PAPER III&IV

The aim of these studies was to investigate the prognostic value and feasibility of both PSV and four selected timing parameters and compare this to the prognostic value of both conventional echocardiographic methods and biochemical markers after ACS in an unselected group of patients.

3 METHODS

3.1 STUDY POPULATIONS

Study population Paper I

Twenty consecutive patients admitted to the CCU at Karolinska University Hospital Huddinge or Solna with confirmed NSTEMI without previously known heart disease were included in this study. The MI was confirmed according to current guidelines [112], the echocardiographic examination was performed within the first 24 hours after admission and always prior to the angiography which all patients underwent within the hospital stay. All patients were included during 2006 and 2007.

The control group consisted of 10 patients admitted to the CCU due to chest pain and suspected ACS but without any objective signs of ACS (e.g. normal troponins and ECG) and who did not undergo angiography. In this group also the echocardiographic examination was performed during the hospital stay.

The echocardiographic examinations were identical to the routine clinical examination all patients undergo during a hospital stay due to ACS or suspected ACS, so participation in this study had no practical consequences for either patients or controls.

All included patients and controls received written and oral information before entering the study. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Study population Paper II

The study included patients admitted to the CCU at Karolinska University Hospital Huddinge between 2011 and 2013 with the diagnosis of MI. Exclusion criteria were all previously known heart disease including arrhythmias such as ongoing atrial fibrillation (AF) or other significant arrhythmias however paroxysmal AF was not considered an exclusion criteria if the patient had sinus rhythm during the examination. The inclusion was consecutive with the limitation that there needed to be a highly specialized echocardiographer available to collect the images before the angiographic examination. All echocardiographic image acquisition was done within the first 24 hours of admission and always prior to angiography.

All patients underwent conventional clinical assessment including physical examination, clinical history, standard 12-lead ECG, ECG-monitoring and serial measurement of biochemical cardiac markers. An acute MI was defined according to current guidelines [112].

The control group consisted of patients without previously diagnosed heart disease referred for angiography for any reason with negative results. Mild atheromathosis without significant stenoses was not considered an exclusion criteria in this study. They were recruited retrospectively and the echocardiographic examination was done after their hospital stay but within 6 month of their angiography.

All patients and controls received oral and written information about the study and written informed consent was obtained before entering the study. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Study Populations Paper III&IV

The patient population in the studies in paper III and IV are the same and include patients admitted to the coronary care unit at Karolinska University Hospital, Huddinge, between August 2006 and January 2008 with a clinical diagnosis of ACS. The patients were consecutively included except for temporary interruptions of the study due to high work load at the coronary care unit. All patients underwent clinical assessment including clinical history, physical examination, standard 12-lead ECG, ECG-monitoring and serial measurement of biochemical cardiac markers up to 9-12 hours after admission and acute MI was defined according to current guidelines[112] . In this population not all patients underwent angiography and previous heart disease was not an exclusion criterion, making this an unselected population with ACS.

Echocardiographic examination were performed during the hospital stay according to the local clinical protocol at that time by the cardiac technician or cardiologist on duty that day where participation in these studies did not mean any extended echocardiographic examination compared to the normal routine.

All other clinical data were prospectively collected and entered into a database. Within this population we will also find the 20 patients from paper I which was a pilot study with more narrow inclusion criteria. The patients received written and oral information about the study that was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Endpoints paper III&IV

We used a pre specified combined endpoint consisting of death from any cause, new MI and readmission due to heart failure and the isolated endpoint of death in both Paper III&IV. In Paper IV in addition we also used the combined endpoint of death from any cause and readmission due to heart failure but not MI.

Out of hospital death and need for readmission because of MI or heart failure was obtained by merging the database with the National Death registry and the national patient registry.

3.2 ECHOCARDIOGRAPHIC METHODS

3.2.1 2D images, EF and WMSI

In the studies included in this thesis we have tested new quantitative echocardiographic methods and compared them with conventional and well established methods that most cardiologists have knowledge about and access to. For this purpose we have used

WMSI [65] for detection of regional hypokinesia and supposed regional ischemia and EF[63] for estimation of LV systolic function.

Echocardiographic acquisition and analyses

In paper I, III and IV all echocardiographic images was collected on a GE Vivid 7 (Horten, Norway) and digitally stored on a dedicated workstation (EchoPAC BT06 Horten Norway) for both clinical and scientific use. Wall motion scoring was made in a later session by an experienced cardiologist who was blinded to all other echocardiographic and clinical data.

In Paper II the image acquisition was made several years later and therefore both a GE Vivid 9 and GE Vivid 7 were used. All images were stored digitally and analysed at a later stage by two highly experience cardiologists blinded to all clinical and other echocardiographic date, using a 18-segment model.

WMS and WMSI

The scoring is done by using moving 2D images from all three apical projections and divide each image in six segments, two basal, two mid ventricular and two apical and visually assessing their function.

Wall motion score index is calculated after the visual assessment by giving each segment 1 point if it is normal, 2 if there is hypokinesia, 3 for akinesia and finally 4 points if it is dyskinetic. The sum of the points taken and is then divided by the number of segments used which are 18. This gives us an index of 1 if there are no visible abnormalities or hypokinesias indicating regional ischemia. So the higher the index is the more regional abnormalities there is.

For estimation of sensitivity and specificity for WMSI we used the established cut off of more than one hypokinetic adjacent regions as marker of ischemia and regarded as positive.

Regarding regionality the LV was divided into three regions corresponding to the three major coronary vessels according to figure 7.

EF

EF is measured in two ways, visually and by modified Simpson biplane. Visually the assessement is made using moving 2D images from any projection, most often more than one and just visually assess the EF. This is often called “Eye balling EF” and has been proven to correlate quite well to LV function [63]. In paper I as a marker of ischemia for visual EF, we used detection of any regional or global hypokinesia from the bedside 2D echo statements we could read in the patient’s records.

A more objective way to assess the EF of the LV is to use modified Simpson biplane [64]. This model is based on the assumption that the LV volume can be described as built up by a series of spherical discs in radial direction, put on top of each other from the mitral annulus and up to the apex of the LV. To make this possible in the clinical routine, most echocardiographic machines have pre-installed software with a simple algorithm for this. The examiner uses both the apical 4-chamber and 2-chamber view and marks the endocardium around the whole cavity in both end systole and end

diastole and from that the software will calculated both the end systolic and diastolic volumes and from that the EF.

An EF of 55% or more is regarded as normal.

3.2.2 Velocity Tracking

From the same echocardiographic examination session as described above, TDI images in all three apical projections was digitally stored for post processing and analysis. These images was transferred as raw data for editing in matlab 7.0.1 (mathworks, Natick, USA). The VeT images was created by creating a step by step colour coding of the longitudinal myocardial velocities of the LV giving every velocity interval a discrete colour band as described in figure 10 presented as a Bull's eye plot. The method is previously described and published [92]. In figure 11 there are examples of VeT plots from PSV, É and Á plus the sum of PSV and É in two healthy subjects. It is possible to get this plot from any given time in the cardiac cycle but from a clinical point of view, PSV and É are presumably the most important. In the PSV+É plot the two velocities in absolute values are superimposed in the same plot giving an easy understandable visual assessment of the LV function with contribution from both systole and diastole. This plot might have an incremental synergetic diagnostic value to only PSV as it is known that both systolic and diastolic velocities decrease during ischemia [70, 113].

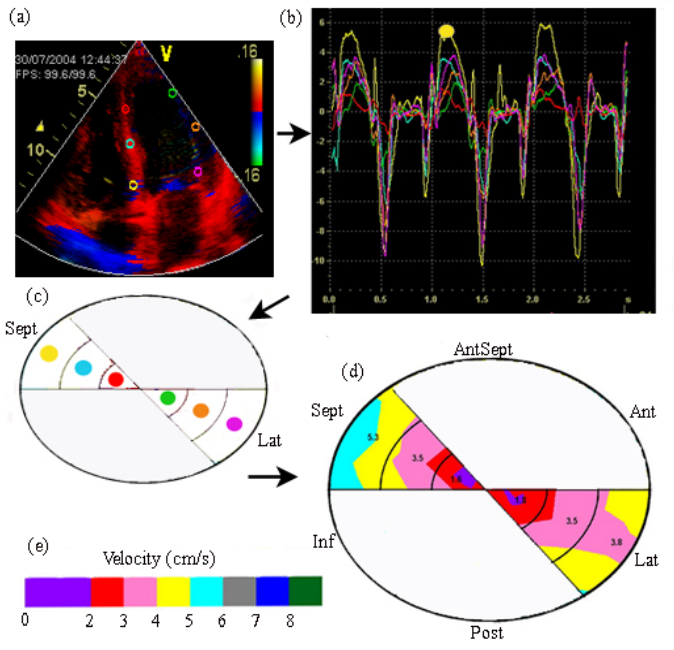

Figure 10. *Derivation of a static bull´s-eye plot (a) the apical four-chamber view (A4C) with the six regions of interest (ROI´s) in the myocardial wall marked by six circles in different colours. (b) Velocity curves from the six ROI´s in figure 1(a) presented in EchoPAC (GE Healthcare). (c) A basal lateral wall velocity curve (cm/s)) during three heart cycles with the pink marker displaying the automatically detected peak systolic velocity.(d) Demonstration of the position of different Segments from the four-chamber view in the bull´s-eye plot. (e) Bull´s-eye plot viewing the stepwise color-coding with an interpolation between the segments. The colour bar on the left side shows the range of velocities (cm/s.)Reprinted with permission.*

In figure 11 we see that the older patient to the right in the image has lower velocities (but still within the normal range) which is expected considering the higher age as we know that longitudinal velocities decrease with age partly compensated by higher radial velocities.[35] We also see that the anteroseptal velocities are lower compared with

other regions which is also expected and correlates to previously published normal values[35] and is probably due to mechanical anatomical reasons.

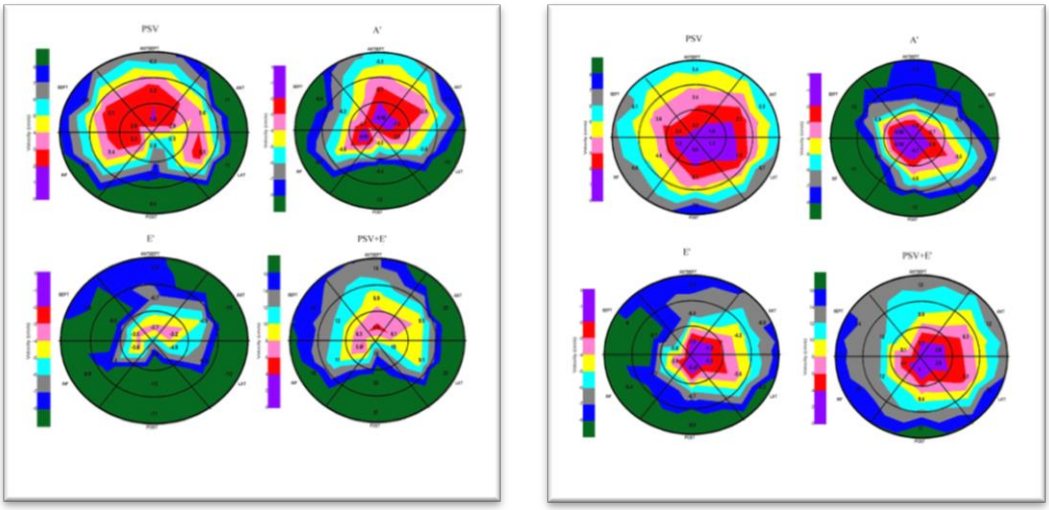

Figure 11. *To the left a 31 year old male without any known heart disease with perfectly normal longitudinal velocities.To the right a 55 year old male also without known heart disease with slightly lower longitudinal velocities which is expected due to older age. Reprinted with permission.*

Based on previously published studies and normal material [35, 114, 115] we defined ischemia as <4 cm/s(pink color) in PSV and <10 cm/s(yellow color) in PSV+E in any basal segment with the actual color reaching the outer perimeter of that segment. To assess culprit lesion we used the same division of the LV as with WMSI (fig 7).with the segments showing the most prominent impairment considered to contain the culprit lesion. In the case of globally impaired velocities and no obvious regional differences it was considered as a multi vessel disease.

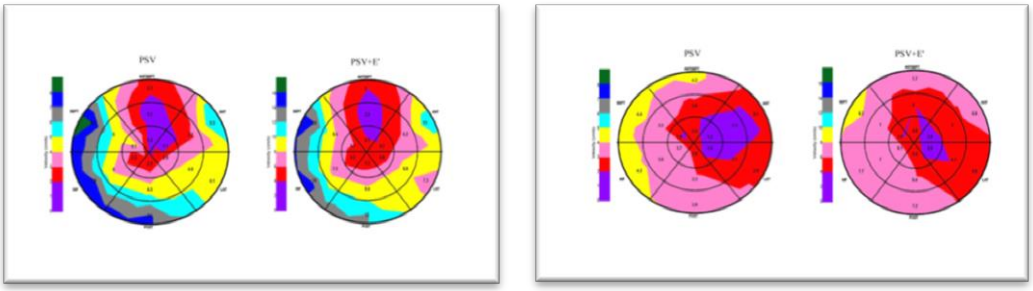

Figure 12. *To the left one image of PSV and one of PSV+E from the same patients as in fig 8 with a LAD occlusion and marked reduction of velocities in the anteroseptal region supported by LAD. Here in comparison with another patient in the images to the right with three vessel disease and culprit lesion in the circumflex artery. In these images we see globally reduced velocities, probably due to ischemic cardiomyopathy and multi vessel disease but most prominent in the region supported by the circumflex artery. Reprinted with permission.*

The regional abnormalities detected by both VeT and WMSI was compared with the interpretation of ischemic region as interpreted in a consensus session based on coronary angiography, ECG and report from the clinical echocardiography, in a session

which was blinded for the results from VeT and WMSI. ECG criteria for ischemia were ST-depression and/or negative T-waves and from angiography an estimated occlusion of more than 50% was considered significant.

As an estimation of the diagnostic value we assessed the sensitivity and specificity for each method.

3.2.3 The State diagram and state index

Echocardiographic acquisition and analyses

All echocardiography data was collected during the first 24 hours of admission by a highly specialized echocardiographer. The images, including 2D, TDI and spectral Doppler, were collected with a GE Vingmed 7or 9 ultrasound machine with a M4S transducer and standard installed software. The images were stored on EchoPAC Software for post processing and analysis.

Definition of phases

The cardiac cycle is divided into six main phases: atrial contraction , pre ejection, ventricular ejection, post ejection, rapid filling and slow filling . The time intervals of these phases were measured by identifying the changes from static to dynamic work. Thus, the definitions of the pre-ejection, ventricular ejection and post-ejection phases in the CSD are different than what is commonly used when discussing systolic isovolumetric contraction and relaxation phases [116] as described above under section 1.2.5.

Atrial contraction begins with an elevation of the AV-plane and ends as the reshaping of the ventricles prepare to move it towards the apex. There is an internal redistribution of blood between the atria and ventricles in this phase.

The pre-ejection phase starts when the forces in the ventricles begin a volumetric reshaping process to prepares to move the AV-plane towards the apex. The phase ends when the acceleration of blood starts open of the pulmonary and aortic valves and the ventricular ejection begins.

The ejection phase ends when there is no outflow from the semilunar valves and the AV-plane declines in their movement toward the apex and thus declines its sucking and volume expanding properties in relation to atrial volumes. The atria may therefore not expand at the rate that the inflow requires and thus pressures rise in the atria.

The post-ejection phase starts mechanically when there is no outflow from the aortic or pulmonary valves, which are about to be closed just before a backflow into the ventricles is generated. This phase ends with the start of rapid relaxation and when the tricuspid and the mitral valve are about to open, i.e., when the muscle tension decreases and a reverse volumetric reshaping process begins and the fast filling starts.

This phase starts as the atrioventricular valves are about to open and a reverse volumetric reshaping process begin, which enables the return of the AV-plane to its neutral position by the inflow controlled hydraulic return.

This phase ends as soon as the dynamic and resilient forces outside the heart have ceased and the slow filling begins. Static and dynamic forces generated by blood flow

into the heart are now the only forces left to keep the heart in an expanded position. Once the slow filling ends a new cardiac cycle begins.

The state diagram

After manually choosing one ROI each for the six basal segments of the left ventricle the TDI images was exported to GHLab software version 2.10 (GrippingHeart AB, Sweden). In this software the different phases are identified semi-automatically as seen in figure 13 guided by the acceleration curve that can be seen on the same screen. Traditionally the "zero" e.g. when the curve crosses the x-axis are used as the point when the heart changes state. This, however, is not entirely true as the heart moves inside the body in respect to the probe and therefore we use a prominent change in the acceleration curve as indication of change of state even if this does not occur exactly on the x-axis (figure 13). In this respect our method of registering the different phases to calculate the MPI differs from previous studies where only the velocity curve is used. This is done for each segment of the LV and is stored by the software in a database with both the timing and velocity information.

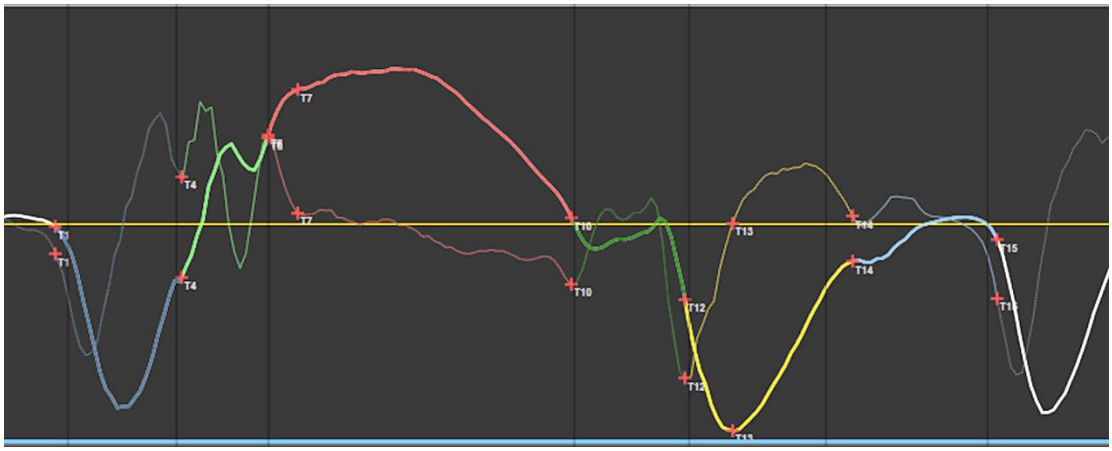

Figure 13. *The TVI curves from one heartbeat. Both the velocity and acceleration in this image (the velocity curve high-lightened). All the events manually identified guided by the acceleration curve. A prominent shift in acceleration indication a change of phase.*

The information can be visualized as an illustrative schematic color coded diagram (Figure 14) displaying the different phases of the cardiac cycle or in a table with all velocities and time measurements for each event. This is called the State Diagram because it illustrates the time relations between the different phases e.g. when the heart changes state e.g. from dynamic to static work, for any chosen parameter such as velocities or deformation in one diagram. The rows represents one basal segment each starting with the anteroseptal segment and then clockwise around the LV. From left to right every phase of the cardiac cycle starts with the atrial contraction phase (dark blue) and ends with slow filling phase (light blue). The black vertical lines indicate the global timing of the left ventricle

Figure 14*. Examples of state diagrams from two patients. Every horizontal row represents one of the basal segments of the left ventricle, and from left to right, every color represent the different phases of the cardiac cycle, atrial contraction, pre-ejection, ejection, post-ejection, and the rapid and slow filling. The diagram shows from top the following left ventricular wall: anterior-septal, anterior, anterior-lateral, inferior-lateral, inferior and inferior-septal.*
The upper panel represents a healthy subject, one of our controls with low mechanical dispersion and short transition phases. In lower panel we see a patient we ACS with obvious mechanical dispersion and prolonged transition phases.

We used a ROI of 6(w)x30(h)mm as this size has shown to give the best diagnostic value of dyssynchrony measurements compared to other ROI sizes. [117] However this ROI size will register the velocity as the mean velocity within the ROI giving a lower value of the velocity compared to a smaller ROI as the velocity decrease the closer to the apex the ROI will reach. Therefore the actual value of the velocity in these measurements will be false low compared to other studies but can still be used to compare groups.

MPI and the State index

Myocardial performance index (MPI) is the sum of the pre-ejection and post-ejection times divided by the ejection time and can be calculated both as a mean value and as a segmental value for each segment of the LV. The State index is given by the product of the global MPI for the left ventricle as a mean of the MPI for each segment and the standard deviation of the different MPI: s for each segment as we call the MPI_SD.

For our post hoc analysis we evaluated the pre-ejection and post-ejection phases isolated, and time to peak systolic velocities. All these calculations were done both global and as the standard deviation of the intersegmental variation and analysed alone and combined with MPI_mean to see if it improved the State index in comparison with the MPI_SD. Time to peak systolic velocity was calculated from onset QRS to T7 (figure 13).

When calculating time to peak systolic velocity it becomes apparent that in systole there is often more than one peak velocity and which of them has the highest value is very sensitive to where the ROI and the probe is placed and they can differ significantly in time and when they occur. Therefore we always used the first peak, or notch on the

systolic velocity curve that coincides with when the acceleration is going to zero at T7 as seen in figure 13

To evaluate the state index we compared with WMSI and visual EF as described in section 3.2.1 performed by two highly experienced echocardiographers blinded to all other echocardiographic and clinical data. The state diagram index also automatically gives us established echocardiographic parameters such as AV-plane displacement and PSV which we also compare with.

The comparison is made with Receiver operator characteristics (ROC) analyses which express the diagnostic value as Area under curve (AUC) which will be discussed in detail below under section 3.4.

3.2.4 Peak Systolic velocity (PSV)

All the images in study III and IV were collected between 2006 and 2008 and stored on an EchoPAC server for post processing and analysis. PSV was measured as described in figure 15 in all six basal segment of the LV. Global PSV was defined as the mean of the velocities from the different basal segments. To exclude velocity peaks from the isovolumetric phases we used the aortic valve closing as definition of end of systole.

These images were collected by various sonographers and physicians during the inclusion period just as with the clinical everyday routine examination without standardized frame rate which therefore varied between 100 and 150 frames/s. The image quality varied and we did not always have all three apical projections but calculated PSV if we had 2 or more acceptable measurements. And to confirm the assumption that 2 segments is sufficient we calculated the correlation between the mean of all six segments and only the mean of the septal and lateral wall.

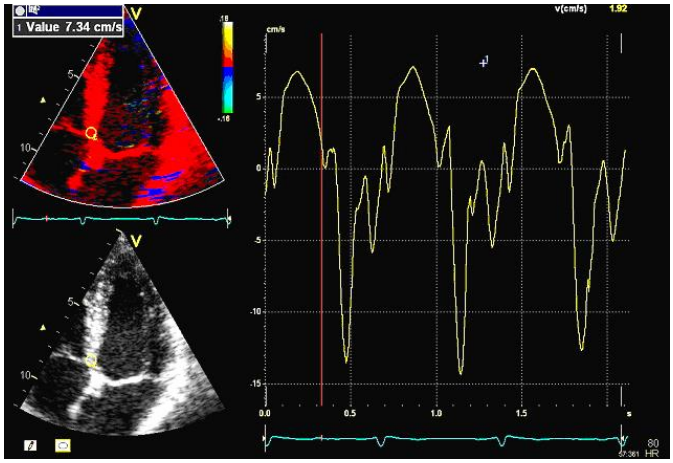

***Figure 15**. A TDI image with PSV marked with a blue cross. 4-chamber view of the LV and the region of interest (ROI) marked in the basal septal segment and the corresponding velocity curve to the right and ECG below that.*

We also investigated the inter observer variability having another well trained cardiologist examine 20 randomly chosen patients and evaluated the coefficient of variation (CV) which is described below under section 3.4.

Furthermore, we examined the sensitivity for poor image quality compared to the other methods tested in this study by comparing the amount of missing values for each parameter.

The prognostic value of PSV was compared to the prognostic value of other echocardiographic parameters with known and previously evaluated prognostic value in a population of patients with ACS such as EF, WMSI, E/e' ratio and global 2D which are described in detail below under section 3.2.6.

We also examined whether PSV had any incremental independent prognostic value compared to known risk factors such as natriuretic peptides, NTproBNP and creatinine clearances, eGFR .

3.2.5 Dyssynchrony parameters.

In Paper IV we examined the prognostic value of timing and dyssynchrony parameters compared to the prognostic value of conventional established echocardiographic parameters such as EF and WMSI as well as the global 2D strain.

All images were recorded at the same session as the images used in Paper III. For all parameters in this study we used both a global value that is a mean of all segmental measurement of the LV. Dyssynchrony or dispersion is measured as the SD of the intersegmental variation with the suffix "SD" or the difference between the lowest and the highest value called "delta".

MPI

From TDI images we assessed the different times of the cardiac cycle used to calculate MPI, we registered these times manually in EchoPAC for all the six basal segments of the LV and calculated the MPI in SPSS statistical software afterwards (fig 16). This is the established method for calculating MPI and differs slightly to the method we used in Paper II with the State Diagram and the acceleration curve (figure 13, section 3.2.3).

As a global timing parameter we used the mean MPI of the LV and for mechanical dispersion or dyssynchrony we used the SD of the six MPI: s calculated for each segment. As stated above in section 1.3.2 MPI is calculated by using the formula (pre-ejection+post-ejection)/ejection time and the SD and delta is given automatically with SPSS software.

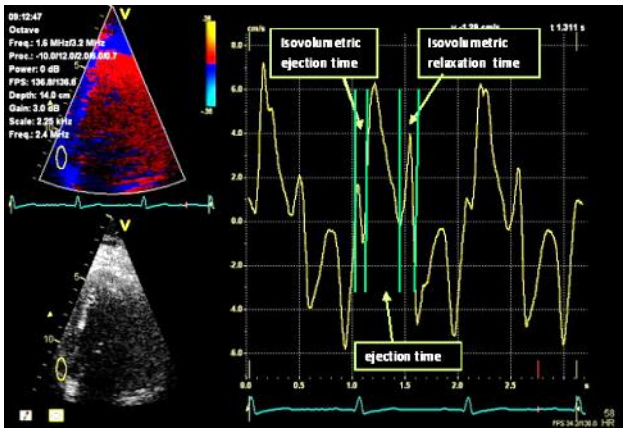

Figure 16. *Showing how the different phases of the MPI are registered from TDI in the basal septal segment in a four chamber view of the LV.*

Time to peak strain

Time to peak strain and its intersegmental variation is a previously used and established measurement for dyssynchrony or mechanical dispersion [49] and is a measurement of the time from onset QRS to peak strain. This time is measured separately for all the 18 segment of the LV from the three apical views and the SD and delta becomes the measurement of intersegmental variation. For this purpose segmental 2D strain curves was exported from GE EchoPAC and imported to GH software for analysis as seen in figure 17 and exported for further statistical analysis in SPSS software.

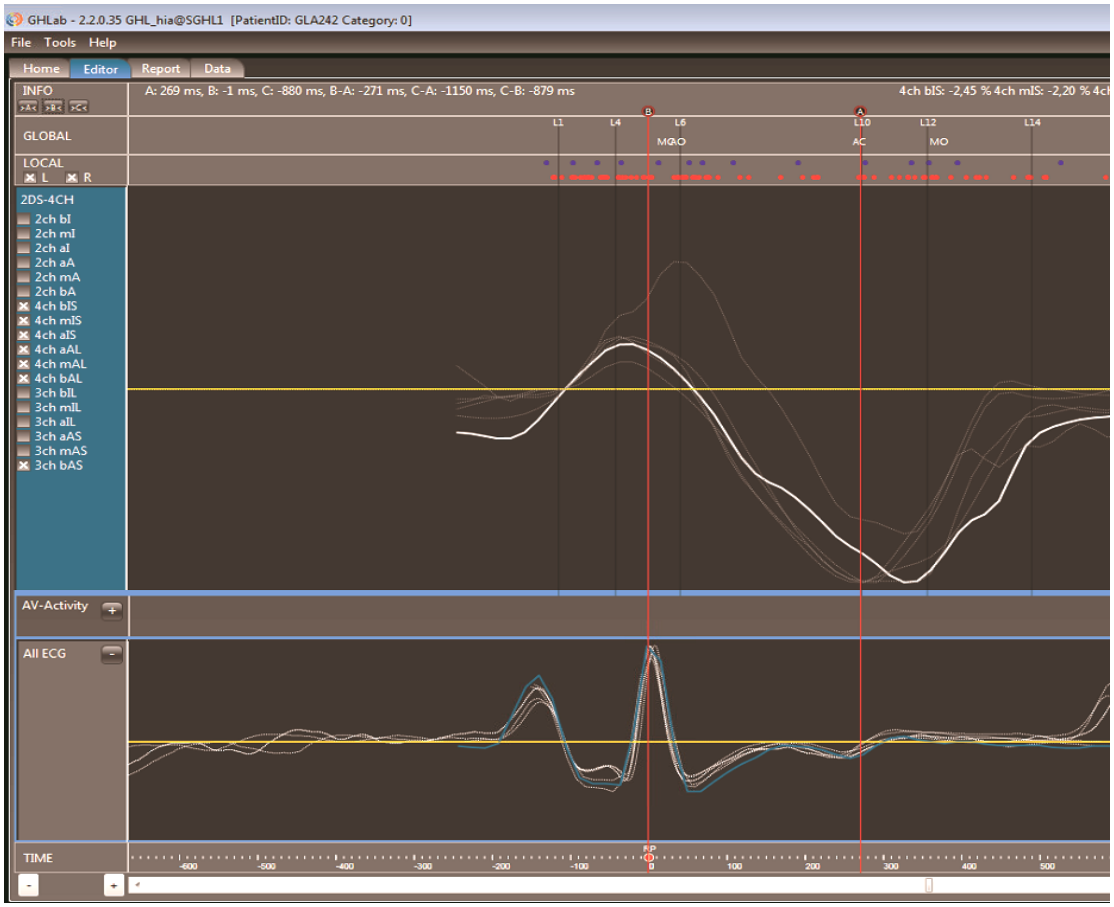

Figure 17. *2D strain curves from four chamber view, in the upper panel curves from all six segments can be seen and one of them high lightened as it is being analyzed at the moment. The first red line indicates the R-wave and the other red line the aortic valve closing. Below the corresponding ECG for each segment is seen.*

Septal lateral delay

One of the first established ways of measuring dyssynchrony with tissue Doppler is the septal lateral delay measured from TDI as seen in figure 18 [118]. For this we used TDI images and Q-analysis in the EchoPAC software. As this measurement only consists of two measurements there is no need of calculating SD or delta for septal lateral delay.

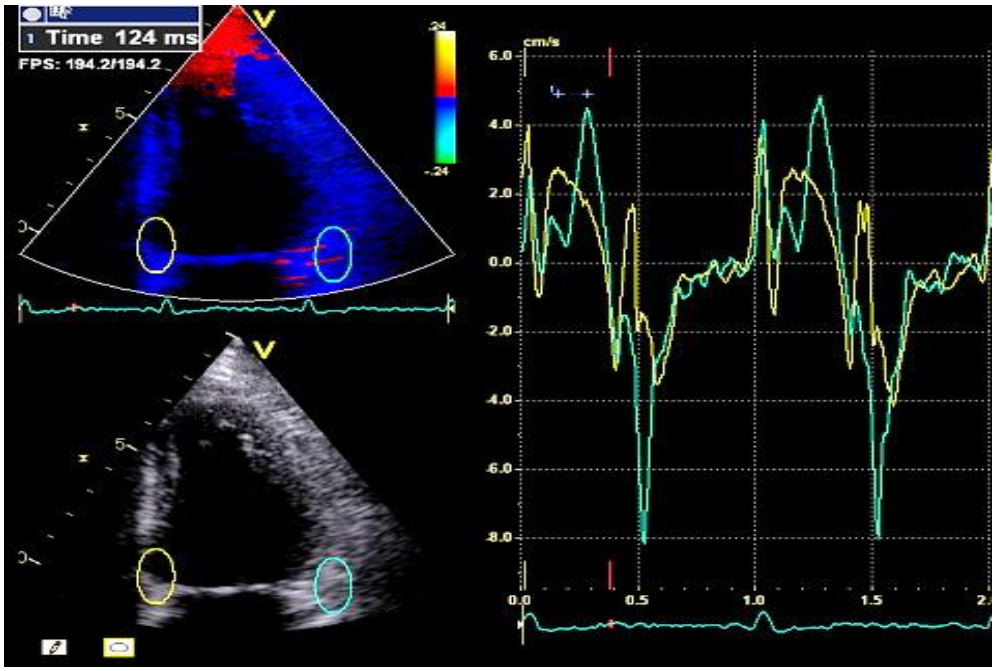

Figure 18. *TDI image of the four chamber view with two ROI: s in the septal and lateral wall respectively. To the right the corresponding velocity curves can be seen with a time delay between the peak velocities in the lateral wall compared to the septal wall marked with the two small blue crosses. Below is the corresponding ECG for guidance. In this image we also see the septal curve has a pre ejection peak with higher amplitude compared to the systolic peak which can be misinterpreted as the systolic peak if you do not know when systole starts and ends.*

Post systolic index

Post systolic index PSI is given by the formula ((peak strain- endsystolic strain)/peak strain)x100 but is given automatically by the EchoPAC workstation if the aortic valve closure (AVC) is defined as seen in figure 19. This index is describing the amount of contraction that actually occurs after systole and the AVC. In this case also the global mean can be defined as a timing parameter so we present that as one parameter and the SD and delta as measurements of dispersion.

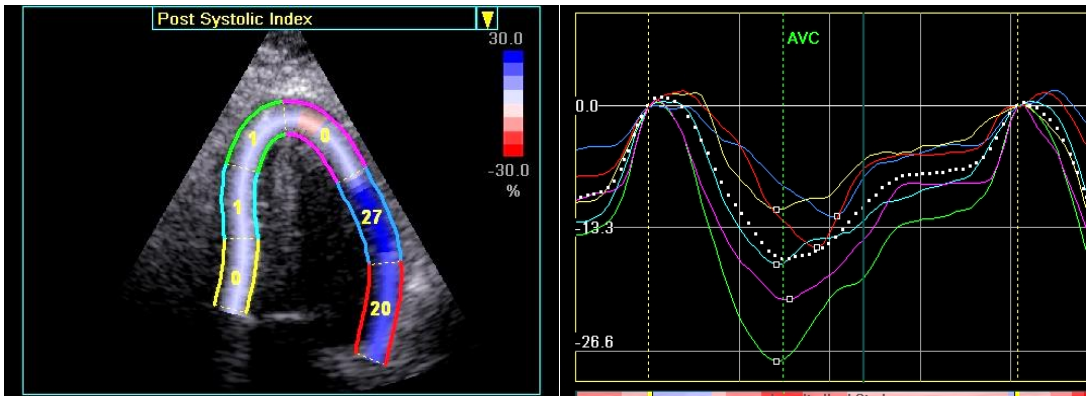

Figure 19. *To the left the PSI is given automatically for each segment of the heart. To the right is the strain curve for each corresponding segment and the white squares indicates the negative peaks that the software has identified and the dotted green line is the AVC. So in this case the mid and basal lateral segments with the blue and red curves to the right shows more strain after the AVC and therefore gets a positive PSI.*

3.2.6 Other established Non-timing echocardiographic parameters

Global 2D strain

All global strain measurements were derived from 2D images using the EchoPAC software. Global strain was calculated as the mean of all 18 segments and was calculated if the image quality admitted strain measurement in at least 12 segments.

E/e' ratio

E/e' ratio was calculated from the E-wave of the mitral inflow to the LV measured by pulsed Doppler and e' was measured from the four chamber TDI image as the mean of the septal and lateral maximum diastolic velocity.

3.3 LABORATORY MEASUREMENTS

N-terminal pro B-type natriuretic peptide (BT-proBNP) was determined 24 hours after admission for all patients in Paper I&II using the assay from Roche Diagnostics on a modular Analytics E170 with the analytic range 20 to 35000 ng/l.

Plasma clearance was analyzed on admission and the glomerular filtration rate eGFR was calculated using the Cockroft-Gault formula[119].

All troponins were measured serially after admission with a minimum of two measurements with 6 hours in between using the conventional method used by the pharmacological laboratory of the Karolinska University Hospital at that time.

3.4 STATISTICAL METHODS

Continuous data is presented as medians with interquartile range (IQR) and categorical data are presented with frequencies and percent. When analyzing statistical differences between groups Mann Whitney-test was performed for continuous data and Chi^2-test for categorical variables and P-values are presented for each variable. A p value of <0.05 was considered statistically significant.

To evaluate both diagnostic and prognostic value Receiver operator characteristic (ROC) analyses are used and the diagnostic or prognostic value are expressed with Area under Curve (AUC) with 95% confidence interval (CI) and significance testing for differences between more than one AUC was made according to Hanley and McNeil[120].

In both Paper I&II we calculated the sensitivity and specificity for each diagnostic parameter in Paper II using the ROC analysis to identify the optimal cut off value for the state index by identifying the value closest to "the upper left corner" of the graph.

Correlations in Paper III were evaluated with Spearman´s rho.

To investigate interobserver variability we calculated the coefficient of variability (CV) using the formula "CV=Standard deviation/expected return" where the expected return is the mean of all the measurements by both readers and standard deviation is between the paired readers.

Also in paper III, as an illustration of the timing of events Kaplan Meyer curves were generated after dividing the parameter into tertiles.

In paper III&IV, to identify which parameter that were independent predictors of outcome we used Cox-regression analyses both univariate and multivariate with and without adjustment for known risk factors. We used two models, one where we adjusted for age, gender, diabetes, hypertension and previous heart failure, and another model where NT-proBNP and eGFR were also included in the model.

4 RESULTS

4.1 RESULTS PAPER I, VELOCITY TRACKING

In this pilot study the number of included patients was 20 with 10 controls. Figure 12 demonstrates examples of two typical patterns in patients with NSTEMI with two different culprit lesions. Baseline data for both patients and controls are presented in table 1 below.

	All (n=30)		NSTEMI (n= 20)		Healthy controls (n=10)		
Variables	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**p**
Demographics:							
Age (median, 25th-75th perc.)	62	(52-71)	63	(53-71)	62	(45-71)	0.643
Men	22	(73)	17	(85)	5	(50)	0.041
Risk factors:							
Hypertension	13	(43)	9	(45)	4	(40)	0.794
Diabetes Mellitus	6	(20)	3	(15)	3	(30)	0.512
Hyperlipidemia	3	(10)	2	(10)	1	(10)	1.000
Current smoker	5	(17)	5	(25)	0	(0)	0.084
Laboratory measurements							
eGFR (median, 25th-75th perc.) (n=27)	1.00	(0.86-1.39)	0.97	(0.81-1.40)	1.25	(0.95-1.39)	0.407

Table 1 *Baseline characteristics for all the patients and controls included in this study. N=30.*

For detection of ischemia on global patients basis regardless of ischemic region both VeT and WMSI showed better results compared to clinical routine Echocardiography where PSV+E had the highest sensitivity (85%) with seventeen out twenty true positive, but PSV had the highest specificity (80%) with only two out of ten false positive.

The results for sensitivity and specificity for the different methods are presented in Table2 below. Due to the relatively low number of patients and controls no significance tests have been performed regarding these results.

Echocardiographic method	True positive	Sensitivity (%)	False positive	Specificity (%)
Clinical Echo	10/20	50	2/10	80
WMS	14/20	70	6/10	40
VeT (PSV+E)	17/20	85	4/10	60
VeT (PSV)	14/20	70	2/10	80

Table 2. *Results for detection of global ischemia on a patients basis regardless of ischemic region for Clinical echo, WMSI, and Vet in the NSTEMI and control groups.*

For detection of correct ischemic region VeT and WMS showed comparable results and both were superior to clinical echo with correct region in 11 out of 20 patients when comparing with ischemic region based on ECG, angiogram and clinical picture as described in section 3.2.2. The results regarding correct identified ischemic region are presented in Table 3 below.

Echocardiographic method	Detection of correct ischemic region	Detection of incorrect ischemic region	Detection of no ischemic region
Clinical Echo	8	2	10
WMS	11	3	6
VeT (PSV+E)	11	5	4
VeT (PSV)	7	7	6

Table 3*. Results for the different echocardiographic methods regaing detection of correct ischemic region.*

4.2 RESULTS PAPER II, THE STATE INDEX

A total of 49 NSTEMI patients and 21 healthy controls were included in this study. All baseline characteristics are presented in table 4.

	All (n=70)		NSTEMI (n= 49)		Healthy controls (n=21)		
Variables	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**p**
Demographics:							
Age (median, 25th-75th perc.)	63	(54-72)	62	(53-75)	65	(58-70)	0.974
Men	46	(66)	35	(71)	11	(52)	0.124
Risk factors:							
Hypertension	25	(36)	15	(31)	10	(48)	0,174
Diabetes Mellitus	12	(17)	7	(14)	5	(24)	0.333
Current smoker	15	(21)	13	(27)	2	(10)	0.098
Laboratory measurements: (median, 25th-75th perc.)							
eGFR (n=62)	1.40	(1.12-1.81)	1.44	(1.16-2.05)	1.18	(0.88-1.50)	0.184
Max troponin T (n=61)	260	(29-636)	317	(162-902)	6	(5-16)	<0.001
LDL cholesterol (n=56)	3.1	(2.1-3.9)	3.25	(2.18-4.15)	3.00	(2.34-3.1)	0.049

Table 4. *Baseline characteristics (n = 70)*

State index

Patients with NSTEMI had significantly higher MPI, MPI_SD and state index compared to the controls and the same difference could be seen for EF and AV-plane displacement but not for WMSI and PSV. When comparing AUC:s State index had the largest AUC.

	All. (n=70)		NSTEMI (n=49)		Healthy controls (n=21)		
Variables, median (25th-75th perc)							**p**
WMSI	1.00	(1.00-1.19)	1.06	(1.00-1.25)	1.00	(1.00-1.11)	0.020
EF visual (%)	60	(55-65)	60	(55-60)	65	(60-65)	0.001
AV-plane displ. (mm)	7.9	(6.6-9.4)	7.4	(6.3-9.2)	9.0	(7.3-11.3)	0.008
PSV (cm/s)	4.8	(3.7-5.9)	4.5	(3.7-5.6)	5.2	(4.5-6.2)	0.132
MPI mean	0.82	(0.74-0.91)	0.87	(0.81-0.94)	0.69	(0.66-0.76)	<0.001
MPI SD	0.083	(0.043-0.11)	0.100	(0.070-0.110)	0.036	(0.030-0.068)	<0.001
State index	0.068	(0.035-0.92)	0.084	(0.052-0.097)	0.030	(0.0230-0.051)	<0.001

Table 5. *Echocardiographic measurements*

When exploring the significance between different AUC's of State index and other parameters the difference was significant for WMSI, PSV, AV-displacement but not for visual EF (Table 6). When calculating a cut off value for the state index the value closest to the upper left corner was 0.047. All the results concerning sensitivity and specificity are presented in table 7.

Variables	AUC (95%CI)	P-value in comparison with State index
WMSI	0.66 (0.53-0.77)	0.008
EF visual	0.74 (0.62-0.87)	0.076
PSV	0.61 (0.47-0.76)	0.002
AV-plane displacement	0.70 (0.57-0.84)	0.027
MPI mean	0.84 (0.73-0.95)	
MPI SD	0.86 (0.77-0.96)	
State index	0.87 (0.77-0.97)	

***Table 6**: AUC:s for all the echocardiographic parameters and the p-value when compare to the AUC of The state index*

	True positive	False positive	True negative	False negative	Sensitivity (%)	Specificity (%)
EF	10	1	20	39	20	95
WMSI	24	6	15	25	49	71
State index	40	6	15	9	82	71

***Table 7**. Comparing the amount of false and true, positive and negative values for EF, WMSI and the State index using 55% as cut off value for EF, two adjacent hypokinetic segments for WMSI and 0.047 for The state index..*

<u>Other timing parameters, post hoc analysis</u>

When we tested the other timing parameters and their AUC: s the AUC of the pre-ejection_SD was the largest and in combination with MPI-mean also larger than State index. All the tested parameters got larger AUC: s in combination with MPI_mean than tested alone.

The AUC for pre-ejection_SD was significantly larger compared also to visual EF both with and without combination with MPI_mean (p=0.008 and p=0.001)

Variables	AUC (95%CI)	AUC (95%CI) When combined with MPI mean
Time to peak systolic velocity mean	0.53 (0.39-0.67)	0.73 (0.60-0.85)
Time to peal systolic velocity SD	0.61 (0.45-0.76)	0.65 (0.50-0.80)
Pre-ejection time mean	0.73 (0.59-0.87)	0.82 (0.67-0.94)
Pre-ejection time SD	0.92 (0.85-0.98)	**0.95 (0.91-0.99)**
Post-ejection time mean	0.68 (0.54-0.81)	0.81 (0.69-0.93)
Post ejection time SD	0.78 (0.65-0.91)	0.83 (0.72-0.95)

***Table 8**: AUC: s For the additional timing parameters and in combination with MPI mean*.

4.3 RESULTS PAPER III, PEAK SYSTOLIC VELOCITY

A total of 227 patients were included in this study between 2006 and 2008. The median follow up was 53 (48-58) months. Eighty-five (37%) patients reached the combined endpoint and among them 42 (19%) died, 48 (21%) had a new MI and 52 (23%) were readmitted due to heart failure.

All the baseline characteristics, laboratory results and final diagnosis in all patients with or without a subsequent event are listed in table 9 below. Patients with subsequent events were older, more frequently had hypertension and a history of previous heart failure. They also had higher levels of troponins and NT-proBNP. Coronary angiography was performed in 192 patients of which 109 underwent percutaneous coronary intervention (PCI) and 25 Bypass surgery (CABG). All baseline data are presented in table 9.

	All (n=227)		No Death, MI or HF (n= 142)		Death, MI or HF (n=85)		
Variables:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**p**
Demographics:							
Age (median, 25th-75th perc.)	67	(59-77)	62	(56-74)	74	(63-80)	<0,001
Men	172	(76)	111	(78)	61	(72)	0.276
Risk factors:							
Hypertension	121	(53)	63	(44)	58	(68)	<0.001
Diabetes Mellitus	51	(22)	29	(20)	22	(26)	0.340
Current smoker (missing n=6)	43	(19)	33	(23)	10	(13)	0.049
Previous cardiovascular disease:							
Myocardial infarction	56	(25)	31	(22)	25	(30)	0.200
Heart Failure	19	(8)	2	(1)	17	(20)	<0.001
Revascularization, PCI	33	(15)	23	(16)	10	(12)	0.359
Revascularization, CABG	10	(4)	4	(3)	6	(7)	0.132
Stroke	17	(7)	10	(7)	7	(8)	0.741
Laboratory measurements: (median, 25th-75th perc.)							
NTproBNP 24h (n=189)	1220	(535-3465)	724	(303-1887)	2300	(1030-26040)	<0.001
eGFR (n=220)	81	(58-110)	92	(72-116)	66	(40-96)	<0.001
Index Diagnosis:							
Myocardial infarction	188	(83)	119	(84)	69	(81	0.612

Table 9. *Baseline characteristics for all patients in Paper III and IV*.

Echocardiographic acquisition and measurements

Peak systolic velocity could be obtained in all except 3 (1%) patients in this study, whereas EF Simpson and WMS could not be assessed in 19 (8%) and 9 (4%) respectively. 2D strain could not be measured in 41 (18%) of the patients and the corresponding number for E/e' was 28 (12%).

The interobserver variability measured with CV was 5.9% and the correlation between the mean PSV from all six segment of from just the septal and lateral was 0.91.

	All. (n=227)		No Death, MI or HF (n= 142)		Death, MI or HF (n=85)		
Variables Median (25^{th}-75^{th} perc)							**p**
PSV	4.9	(4.2-5.8)	5.3	(4.7-6.0)	4.4	(3.6-5.0)	<0.001
EF	49	(41-56)	52	(45-58)	45	(35-52)	<0.001
WMS	1.0	(1.0-1.3)	1.26	(1.09-1.16)	1.29	(1.21-1.36)	<0.001
Global 2D-Strain	-14	(-18- -9.8)	-15	(-19- -11)	11	(-16.8- --5.0)	<0.001
E/e'-ratio	13.4	(10.1-17.6)	13.2	(12.3-14.2)	18.4	(16.1-20.8)	<0.001

Table 10. *Results of all the echocardiographic measurements*

Prognostic value of PSV compared to other methods

Patients reaching the combined endpoint had lower median PSV than those not reaching the combined endpoint (4,4 cm/s vs 5,3cm/s) (p<0,001). These groups differed significantly regarding all the other measured echocardiographic parameters as can be seen in table 10 where all echocardiographic measurements are presented.

When patients were divided into tertiles according to the PSV results the long term risk of subsequent cardiac events increased with decreasing PSV (Figure 20).
In ROC analysis the AUC was larger for PSV than for the other parameters with an AUC of 0,75 (0,68-0,81) where corresponding value for EF was (0,68 (0,610,76), WMS (0,64 (0,56-0,72), Global 2D strain 9,67 (0,58-0,75) and E/e'-ratio 0,70 (0,62-0,77) however the differences did not reach statistical significance.

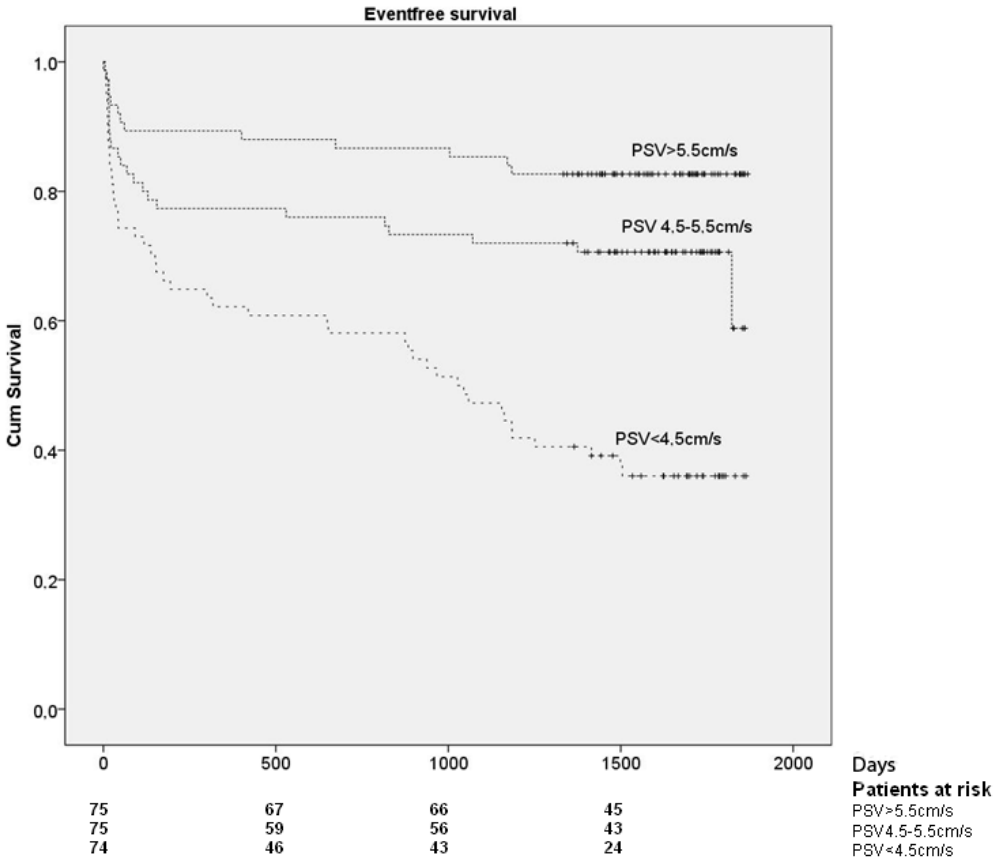

Figure 20. *Kaplan Meyer curve from the combined endpoint of death, new MI and readmission due to heart failure in relation to PSV measurements*.

Independent predictors of outcome

All tested echocardiographic parameters except 2D-strain remained independently associated with outcome when these variables one at the time were adjusted for age, gender, diabetes, hypertension and previous heart failure (table 11, model 1). In model 2 where NT-proBNP and eGFR were added to the model, only PSV, and E/e' and remained independent predictors of outcome (table 11, model 2). When including PSV in the model, PSV was the only echocardiographic parameter independently associated with outcome (table 11, model 3). When patients in the third tertile according to PSV (>5.5cm/s) were used as reference the HR(95%CI) increased to 1.65 (0.80-3.37) p=0.169, and 3.16 (1.58-6.35) p=0.001 in the second and first tertile, respectively. Furthermore, the 5-year cumulative risk of death, MI or readmission because of heart failure was 64% and 32% for the first and second tertile and 17% for the first.

Parameter	**Model 1.** Adjusted for age, gender, diabetes, hypertension and previous heart failure.		**Model 2.** Adjusted for the same factors as model 1 plus NT-proBNP 24h and eGFR		**Model 3.** Same Adjustement as model 1 plus PSV. The corresponding results for PSV is also presented for each parameter HR (95%CI)	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
PSV	0.65 (0.51-0.82)	<0.001	0.71 (0.54-0.93)	0.013	----------	

EF	0.97 (0.95-0.99)	0.006	0.98 (0.96-1.00)	0.070	0.99 (0.96-1.01)	0.227
					PSV 0.68 (0.52-0.90)	0.007
WMS	2.09 (1.06-4.15)	0.003	1.52 (0.71-3.24)	0.280	0.95 (0.41-2.22)	0.915
					PSV 0.61 (0.46-0.82)	0.001
Global 2D Strain	1.03 (0.99-1.07)	0.035	1.04 (0.96-1.05)	0.037	1.02 (0.98-1.06)	0.249
					PSV 0.67 (0.50-0.90)	0.032
E/e'	18.0 (2.24-144)	0.007	20.0 (2.31-174)	0.007	6.90 (0.74-64.3)	0.090
					PSV 0.70 (0.54-0.91)	0.008

Table 11. *Cox regression analysis of the different echocardiographic methods in three different models*.

4.4 RESULTS PAPER IV, DYSSYNCHRONY PARAMETERS

The study population, included patients and patients reaching the different endpoints was the same as in paper III presented in the section above. All the baseline characteristics are presented in Table 9 above.

Prognostic value

Patients with and without a subsequent combined endpoint differed significantly regarding both calculated SD's and delta-value for PSI and for time to peak 2D-strain and MPI but not for septal-lateral delay (table 12a and 12b). The pattern was similar when patients were divided according to the isolated endpoint death or to the composite endpoint of death from any cause or readmission due to heart failure. (Table 12a and 12b).

	Death		
	Yes n=48	No n=179	p
Dyssynchrony parameters	(median, 25th-75th perc.)	(median, 25th-75th perc.)	
Sept-lat delay	35 (12.5-105.5)	18 (0-70)	P=0.060
PSI	13.7 (8.7-22.1)	7.6 (3.1-13.7)	P<0.001
PSI SD	20.8 (14.4-28.9	12.0 (6.1-18.7)	P<0.001
PSI delta	72 (46.5-103)	36.5 (21-63.7)	P<0.001
Time to peak 2D-strain SD	0.041 (0.017-0.064)	0.017 (0.007-0.047)	P=0.003
Time to peak 2D-strain delta	0.13 (0.053-0.23)	0.058 (0.026-0.17)	P=0.003
MPI SD	0.17 (0.12-0.24)	0.13 (0.09-0.28)	P=0.003
MPI Delta	0.40 (0.31-0.63)	0.32 (0.22-0.48)	P=0.005
Non-timing Parameters			
Simpson EF	41.0 (33.0-50.0	50.0 (44.0-58.0)	P<0.001
Global 2D Strain	-10.3 (-12.5--7.6)	-14.4 (-16.4--11.9)	P<0.001
WMSI	1.33 (1.0-1.63)	1.0 (1.9-1.2)	P<0.001

Table .12a *All tested echocardiographic parameters in patients with the isolated endpoint of death (n=227)*

	Composite endpoint Death, MI and Readmission due to heartfailure		
	Yes n=85	no n=142	p
Dyssynchrony parameters	(median, 25th-75th perc.)	(median, 25th-75th perc.)	
Sept-lat delay	25 (0-84)	18.5 (0-69.3)	P=0.387
PSI	11.3 (5.1-18.7)	7.6 (3.3-13.4)	P=0.007
PSI SD	17.0 (9.3-27.7)	11.0 (6.1-17.8)	P=0.001
PSI delta	61.5 (29-97.2)	36 (21-62.5)	P=0.001
Time to peak 2D-strain SD	0.031 (0.016-0.065)	0.015 (0.008-0.045)	P=0.001
Time to peak 2D-strain delta	0.11 (0.044-0.23)	0.048 (0.026-0.14)	P=0.001
MPI SD	0.16 (0.11-0.24)	0.13 (0.09-0.18)	P=0.006
MPI Delta	0.39 (0.27-0.60)	0.31 (0.22-0.45)	P=0.004
Non-timing Parameters			
Simpson EF	45.0 (35.0-52.0)	52.0 (45.0-58.2)	P<0.001
Global 2D Strain	-11.2 (-14.5--7.8)	-14.6 (-16.7--12.3)	P<0.001
WMSI	1.13 (1.0-1.56)	1.00 (1.00-1.11)	P<0.001

Table .12b *All tested echocardiographic parameters in patients with combined endpoint of death, new MI and readmission due to heart failure(n=227*

When the associations between tested parameters and outcome were evaluated with ROC-analyses, dyssynchrony parameters based on PSI and time to peak 2D-strain were more associated with the composite endpoint than both MPI and septal-lateral delay but none of the dyssynchrony parameters had a larger AUC than EF according to Simpson regardless of endpoint (table 13). None of the differences were statistically significant. The combination of EF and the dyssynchrony parameters Time-to-peak Strain SD and PSI SD did not generate higher AUC: s than either of the parameters isolated ((EF*Time-to-peak Strain SD: 0.61) and (EF*PSI SD: 0.57)).

	AUC (95%CI) Death n=42	AUC (95%CI) Composite endpoint. Death, Heart failure and MI n=85
Dyssynchrony parameters		
Sept-lat delay	0.59 (0.49-0.79)	0.53 (0.45-0.62)
PSI	0.68 (0.60-0.77)	0.60 (0.51-0.67)
PSI SD	0.72 (0.64-0.80)	0.64 (0.56-0.72)
PSI delta	0.72 (0.63-0.80)	0.64 (0.56-0.72)
Time to peak 2D-strain-SD	0.65 (0.56-0.74)	0.64 (0.56-0.72)
Time to peak 2D-strain-delta	0.65 (0.56-0.74)	0.64 (0.56-0.72)
MPI SD	0.65 (0.56-0.74)	0.61 (0.53-0.68)
MPI Delta	0.64 (0.55-0.73)	0.61 (0.54-0.69)
Non-timing parameters		
Simpson EF	0.73 (0.65-0.81)	0.68 (0.60-0.76)
Global Strain	0.76 (0.68-0.84)	0.72 (0.64-0.79)
WMSI	0.68 (0.58-0.77)	0.65 (0.58-0.73)
PSI	0.68 (0.60-0.77)	0.60 (0.51-0.67)

Table 13. *ROC-analyses with AUC:s for all the echocardiographic measurements in respect to death and the combined combined endpoint of Death, Heart failure and MI.*

Independent prognostic value

In a Cox regression analysis when adjusting for traditional risk factors (age, gender, diabetes, hypertension, previous heart failure, creatinine clearance and troponin levels) none of the dyssynchrony parameters remained independently associated with outcome, whereas EF according to Simpson still did.

	Cox regression anlalysis Model 1 univariate. HR (95%CI)	Cox regression analysis Model 2 HR (95%CI)
Sept-lat delay	1.002 (0.997-1.006)	0.999 (0.987-1.008)
PSI SD	1.017 (1.005-1.029)	1,007 (0.989-1-026)
PSI delta	1.004 (1.001-1.008)	1.002 (0.996-1.007)
Time to peak 2D-strain SD x100	1.088 (1.027-1.151)	1.016 (0.934-1.106)
Time to peak 2D-strain delta	31.81 (4.267-237.1)	2.345 (0.160-34.45)
MPI SD	1.798 (0.602-5.370)	1.076 (0.240-4.819)
MPI Delta	1.291 (0.831-2.007)	1.004 (0.569-1-016)
Simpson EF	0.947 (0.947-0.979)	0.977 (0.955-0.999)

Table 14. *Cox regression analyses. In model 1 no adjustment was made. In Model 2 adjustment was made for age, gender, diabetes, hypertension, heart failure, creatinine clearance and troponin levels. The echocardiographic parameters are tested one by one with the risk factors and not at the same time.*

5 DISCUSSION

5.1 GENERAL DISSUSSION

All the included papers in this thesis shows that quantitative echocardiographic methods derived from Tissue Doppler are suitable and feasible for both diagnostic and prognostic evaluation of patients with ACS. All the papers will be discussed in detail below under section 5.2-5.5.

Tissue Doppler seem to be robust and insensitive to poor image quality compared to both qualitative methods and quantitative methods derived from 2D images regardless of whether it is for diagnostic or prognostic purposes.

Basically, Tissue Doppler registers tissue velocities and the timing of the measured events. From these measurements we can get displacement, acceleration and also strain and strain rate. In this thesis we have focused on velocity and timing and the results in general are somewhat contradictive. From the diagnostic methods we have examined, VeT and the state index, it would appear that timing is crucial and more important than velocities or deformation but with the prognostic methods the result were the other way around. In comparison with WMSI the state index, based on timing, had a greater diagnostic value when VeT, based on velocity, was only comparable to WMSI. Several years passed between those two studies and with that the image quality and technical methods have improved which might be one explanation. Although even with today's technique it appears that timing of events is easier to measure with high precision than the actual amplitude of the measured events.

However, both these studies are pilot studies with few included patients and must therefore be regarded as merely hypothesis generating studies which needs further evaluation.

Both the VeT Bull´s eye plot (fig 8, 11, 12) and the Cardiac State Diagram (fig 9, 14) gives us, with a quick glance at them, easy understandable information both regarding the global and regional function of the LV regarding velocities and timing respectively.

All this information is available in the Velocity-time curve generated by the Tissue Doppler images in the workstation but to acquire the same amount of information with repeated manual measurements would be extremely time consuming which makes both VeT and the State Diagram attractive in a bedside setting.

In the last two papers we explored the prognostic value of different echocardiographic methods, both quantitative and qualitative derived from both 2D images and Tissue Doppler. In this case the timing based parameters in paper IV did not have any incremental value to that of conventional methods such as EF and WMSI but in Paper III PSV did. PSV was also very robust and insensitive to poor image quality with a low number of missing values compared to all other methods.

The reasons for the different results can be many and various. Of course there can be purely physiological reasons to why timing based parameters is better for diagnostic evaluation compared to prognostic evaluation but there it might also have technical reasons like image quality, software and different quantitative techniques. All this and other issues will be discussed in detail for every paper in the next section.

5.2 VELOCITY TRACKING, PAPER I

The results from the Paper I suggest that the VeT method with a bull´s eye presentation of discrete velocities is sensitive and feasible for the detection of regional dysfunction and ischemia in a NSTEMI population. VeT in this setting seems to be comparable to expert WMS and both methods are superior to clinical echo in this particular group of NSTEMI patients even though the low number of subjects have made any significance testing impossible. However, the major advantage is that the VeT bull´s eye plot displays quantitative data and therefore does not require the same echocardiographic expertise as interpretation of grey scale 2D echo, which is subjective and requires qualified expertise for satisfactory results. Tissue Doppler data have been presented in a bull´s eye plot in an earlier study and, in that study, was shown to be helpful in the assessment of regional wall motion [121].

The results of this study furthermore suggest that there could be an incremental value in combining PSV and E'. The sensitivity for myocardial ischemia seems to be higher when looking at both the systolic and diastolic decrease in velocities in this particular patient population. (Tables 2 and 3) The suggestive improvement in sensitivity from using PSV + E' is in agreement with earlier studies showing the impairment of both diastolic and systolic velocities during myocardial ischemia. [113, 122, 123]

One thing worth mentioning is that when this thesis is being written more than eight years have passed since this study was planned. In the intervening time period a lot has happened and changed concerning available and tested methods. The 2D strain Bull´s eye plot has become easily accessible and widely used with the GE EchoPAC workstation. However presenting velocities instead of strain has an advantage as it also gives an image of the strain rate which is more correlated to contractility than strain. The radial width of the color bands in the VeT plot gives us this information, wide bands indicates low difference in velocity along the longitudinal myocardial wall and therefore must also mean low longitudinal strain rate and vice versa.

The relatively low sensitivity for detecting ischemia in this study for all echocardiographic methods, both on patient and regional basis, could be due to a number of reasons. One factor might be the relatively long time span between the actual ischemia and the echocardiographic examination, which in our study was up to 24 h after the admission of the patient. In earlier studies and as stated in guidelines for perfusion scintigraphy [50] there is a recommended time span of up to 6 hours from chest pain. Compared to this, the possible time lag of up to 24 h in the present study could have a negative impact on sensitivity and specificity.

Another important reason for the rather low sensitivity and especially specificity in detecting ischemia on regional basis is the fact that the angiography in some cases concluded “multi-vessel disease’’ without actually pointing out a culprit lesion, and the recorded comments regarding ECG were somewhat vague and often done by a physician not specialized in cardiology. Furthermore, the visual grading of the degree of coronary stenosis is an uncertain method for detecting ischemia. It was, however, not possible to measure the actual site of ischemia in this study. For that purpose, we would need an additional diagnostic imaging technique (i.e. MRI, SPECT) or thorough invasive hemodynamic measurements during coronary angiography, which is of course

not possible in clinical practice in severely multi-vessel diseased patients. Furthermore, we need to keep in mind that neither ultrasound nor angiography measures the actual ischemia. What we measure is a secondary effect on the myocardium with ultrasound and, in the case of angiography, a narrowing of the coronary vessel merely pointing out a possibility of ischemia in the distribution area of that vessel. Nevertheless, the VeT bull's eye presentation is a promising new quantitative approach for the detection of myocardial ischemia in the bedside setting with a potential of being relatively user independent.

Limitations

The major limitation of this study is of course the relatively small number of patients and the poor gender match between the case and control group which makes any conclusions drawn from this study uncertain. The results should therefore be evaluated with caution. Larger prospective studies are needed to confirm these findings and test the cut-off values. This is, however, the first clinical study using the VeT method designed as a pilot study primarily testing the feasibility of the method in a clinical bedside setting.

Another problem with the population, apart from just being small, is the fact that the controls did not undergo coronary angiography and this was the time before high sensitive troponin so it is possible that a portion of these patients would have been diagnosed with ACS today and been furthermore examined with angiography.

In the present version of VeT, the color coding does not take into account the normal variation in regional longitudinal velocity. We know that the longitudinal velocities vary significantly between segments in a normal heart and also decrease with age [35, 114, 115, 124] but have not corrected the results according to that in this study, which also can be considered as a limitation and has to be taken in consideration in further development of the VeT method. There is also some degree of uncertainty with the apical registration of tissue Doppler velocities in apical projections due to the acute angle between the probe and the myocardium.

Another limitation is the difficulty in defining which myocardial region actually corresponds to which vessel, both due to variation in the vessel anatomy and the actual position of the heart in the chest.

5.3 THE STATE INDEX, PAPER II

The results of this study indicates that an echocardiographic parameter based only on timing and mechanical dispersion is more sensitive to acute ischemic heart disease compared to conventional parameters such as WMSI, EF PSV and AV-plane displacement. It also shows that the intersegmental variation of these measurements expressed with the standard deviation seems to be more discriminative than the global mean of the parameter itself, even if it is very small measured variations.

Indeed all measurements in this study involving peak velocities, displacement or wall motion seem to be less sensitive to acute ischemia compared to timing and mechanical dispersion. Both MPI and MPI_SD isolated hade larger AUC than all the conventional parameters.

Edvardsen et al. have demonstrated that the velocities during the transition times are better markers of acute ischemia than the ejection velocities [31]and disturbed transition velocities will result in disturbed transition times. Furthermore, the aforementioned study demonstrates that TDI has an excellent ability to quantify regional myocardial dysfunction. In our present study with a population where all included patients were without previous heart disease we can expect the regions without ischemia to have normal transition velocities and transition times which indicates that the mechanical dispersion is expected to be very sensitive to ischemia in this population.

In the post hoc analysis in this study the standard deviation of the pre-ejection times showed better results compared both to the post-ejection times and the MPI_SD. One possible explanation to this is that the pre-ejection, almost similar to the isovolumetric contraction phase, is more correlated to contractility compared to the post-ejection and relaxation, and because of this more prone to be affected by acute ischemia as we know that predominantly affects the contractility.[125, 126].

The benefit of combining MPI and MPI_SD to form the state index was rather small compared to MPI_SD alone, and thus it might be reasonable to argue that the simpler measure of MPI_SD alone is not inferior to the more comprehensive state undex. . However, our study population was quite homogeneous, and before that can be concluded this needs to be evaluated in other, less homogenous patient groups in order to see whether it might be that the contribution of MPI to the state index is more important in a heterogeneous population. Furthermore, in our post hoc analysis the benefit of combining with MPI_mean was more pronounced than for the state index, indicating that the combination of two parameters is consistently better compared to the isolated parameters. The post hoc analysis also indicates that using pre-ejection_SD instead of MPI_SD for the state diagram could improve the diagnostic value quite dramatically giving significantly larger AUC compared to all conventional parameters. Nevertheless, we need to keep in mind that testing the pre-ejection times was a post hoc analysis and therefore needs to be reevaluated in prospective studies.

The fact that the standard deviation of the transition phases seem to have a much stronger diagnostic value compared to the standard deviation of time to peak velocity does not necessarily have a physiological explanation but maybe instead have a technical explanation . The velocities are dependent on the angel between the probe and the heart and the systolic velocity curve does also have a somewhat convex shape and sometimes have more than one velocity peak and different points of systole which sometimes makes the measurements uncertain. Furthermore, in this study we optimized the ROI for best results concerning timing and not velocity and therefore if we had the same technical conditions for velocities as for timing the result might have been different.

In this study visual EF showed better results than WMSI which was not expected, however these findings are hard to draw conclusions from as almost all the measured EF values were within the normal values (table 5) so when a 55% EF was used as the cut off value, the amount of false negatives was as high as 39 out of 49. (Table7)

Limitations

The study population is rather small which limits the value of some of the significance testes we performed. The most note-worthy and interesting results regarding pre-ejection times was showed in a post hoc analysis and must therefore be re-evaluated in another study.

5.4 PEAK SYSTOLIC VELOCITY, PAPER III

This study demonstrates that the tissue Doppler parameter PSV can be measured in most patients with a low interobserver variability. This parameter may even be a better predictor of outcome than both traditional echocardiographic measurements of left ventricular function, such as EF, WMS and E/e'-ratio and more recent deformation parameters, such as longitudinal myocardial strain in ACS patients.

The aim of this study was to test PSV in a real world setting outside the highly specialized research laboratory. We therefore included consecutive unselected ACS patients and all images were acquired in line with the clinical routine. As seen in table 9 the median PSV value was significantly lower in those with, compared to those without a subsequent cardiac event.

When the prognostic value of PSV was compared with that of other echocardiographic parameters in a ROC analysis, PSV had the largest AUC although the differences were not statistically significant.

Even after adjusting for differences in well-known predictors of outcome (including natriuretic peptides and estimates of kidney function), there was a strong and independent association between PSV and outcome. Furthermore, when comparing PSV with the other echocardiographic parameters one by one still adjusting for the same risk factors PSV was the only echocardiographic parameter remaining independent as seen in table 11, model 3. In the same analysis we find a HR of 0.7 which with the inversion (1/07=1.4) gives us a 1.4 fold increased risk of the combined endpoint for every unit decrease in PSV.

As demonstrated in the Kaplan Meyer curve (figure 20) when patients are divided into tertiles, there is a wide difference in eventfree survival between PSV>5.5 and PSV< 4.5 cm/s with the cumulative 5-year risk of event is 17% and 64% respectively in the first and third tertile.

The predictive value of different echocardiographic parameters may vary in different patient populations. Wang et al [103] demonstrated a better prognostic value for both é, PSV and E/e' than for EF and WMS. In that study e' was the strongest predictor of cardiac death although PSV and E/e' also were strong predictors of cardiac death. However, that study included patients with a broad spectrum of heart disease and only 16 % had ischemic heart disease. The fact that the diastolic parameter e' was demonstrated to have a higher prognostic value than PSV might be explained by a relatively small proportion of patients having ischemic heart disease and a larger proportion of patients having heart failure. In such a population the proportion of patients with high filling pressures is expected to be higher than in our study population, which included ACS patients with predominantly normal or only mildly depressed EF.

Our study does not only confirm but also extends previous findings showing that E/e' has an incremental prognostic value to that of natriuretic peptides [8, 9]. Somewhat unexpectedly 2D-strain was not better to predict outcome than traditional measurements of systolic LV function such as EF and WMS. This is in contrast to earlier studies in the field. In a cohort of 649 ACS patients Antoni and co-workers showed that both strain and strain rate were superior to the traditional parameters, EF and WMS, to predict 1-year outcome [97] and similar finding were made by Bertini and co-workers but in a population with chronic ischemic heart disease[127]. In our study, we could not confirm a superiority of deformation parameters in comparison to EF and WMS. Clearly, the operator's skills and experience, and their compliance to strict protocols are important determinants of the quality of echocardiographic examinations. It is important to note that the images in our study were collected from routine clinical echocardiography not always of highest quality, but still sufficient for analyzing PSV in a very large proportion of the patients, whereas in the study of Antoni et al. and Bertini et al., all examinations were performed within a dedicated laboratory with great experience of conducting studies and using deformation analysis. Still, even if a technique is good in the hands of experts in specialized centers, it can be problematic in the more generalized everyday clinical situation if the demand for technical skill is too high as seen in earlier studies[128].

Therefore, the simplicity of PSV must be regarded as a great advantage, which can be an important determinant in why PSV in our study is superior to the other parameters. Another advantage is the fact that the method seems robust and insensitive to poor image quality with a low interobserver variability and low number of missing values.

Furthermore the strong correlation (0.91) between global PSV from all 6 basal segments and PSV from only septal and lateral wall indicates that the use of only one projection and two measurements might be as predictive as the global PSV which would further simplify the method.

Limitations

The present study has some limitations. The sample size was rather small. Thus, lack of significant differences may still be caused by lack of power to detect such differences and our findings need to be confirmed in larger studies. Although interobserver variability was assessed for PSV in a subgroup of patients and all analyses were performed according to a protocol, only one person performed the echocardiographic analyses.

5.5 DYSSYNCHRONY PARAMETERS AND PROGNOSIS, PAPER IV

The main findings of this study are that the dyssynchrony parameters do carry prognostic information regarding long term outcome after ACS in an unselected population. However, the clinical value of this information is limited since the dyssynchrony parameters seem to have only a moderate predictive prognostic value and no incremental value to well known risk factors such as age, gender, diabetes, hypertension, previous heart failure, creatinine clearance and troponin levels. In

comparison with the prognostic value of EF, the most established and commonly used method for assessment of systolic LV function, there was no incremental value of the dyssynchrony parameters. Let us also then keep in mind that in Paper III in this thesis, in the exact same population as in this study, we could show that PSV had an even greater prognostic value than EF, both visual and Simpson Biplane.

Given the previous data of the importance of LV dyssynchrony in various clinical patients groups, the seemingly relatively weak prognostic value of LV dyssynchrony in this setting of unselected ACS patients is both somewhat surprising and not easily understandable.

One possible explanation might be that these parameters, which have consistently been shown to be very sensitive in detecting ischemia in previous studies [47, 109-111] could therefore be already significantly deranged at a relatively small ischemic burden and therefore not increase proportionally with increasing ischemic burden. The dyssynchrony could thus be relatively similar in the whole ACS population compared to the normal population and accordingly not reflect the actual size of the damaged myocardium. The dyssynchrony might therefore not be strongly associated with the subsequent loss of contractility and heart failure in long-term outcome.

Furthermore there is a lack of detailed knowledge about the time course of the different timing disturbances after ACS. It might therefore be possible that myocardial contractility actually recovers earlier than LV dyssynchrony and if this is true, dyssynchrony measured in the early phase in the recovering myocardium might give a false measure of risk. The result might in fact have been different if the images had been acquired earlier or later after the ACS episode, for example within the first hours of admission or 3-4 weeks after discharge.

Another possibility is due to the fact that dyssynchrony parameters reflect the relative intersegmental differences. We need to keep in mind that a very large myocardial infarct will affect a larger number of LV segments, which over a certain level could lead to a seemingly paradoxically lower intersegmental variation, Thus, a large myocardial infarction does not necessarily result in a high degree of dyssynchrony.

Post systolic contraction, measured with PSI, is known to be highly correlated to ischemia [86]and seem to have a higher predictive value in the present study compared to the other more electromechanical parameters and might therefore reflect the amount of remaining myocardial ischemia. If so, this observation suggests that it is the remaining ischemia at the time of examination that is the main determinant of worse prognosis rather than LV dyssynchrony regardless of origin.

One interesting finding, however, is the fact that the predictive value of these parameters seems to be better using death as an endpoint compared to the combined endpoint. The small number of events and the lack of significant results in this study allow for nothing more than speculations. Nevertheless, one possible explanation may be that death in this group to some extent is due to ventricular arrhythmias and that the dyssynchrony parameters actually predict that more than heart failure and new ischemic events. This is to some extent supported in earlier studies, although it has not been described in an ACS population [49].

Limitations:

A major limitation of this study is the lack of a standardized time between the coronary angiography and the echocardiographic examination in relation to time of admission. If all echocardiographic examinations would have been performed within the first 24 hours after diagnosis and prior to angiography the result might have been different. The result might also have been different if we had included a 3-6 months follow up echocardiographic examination to assess the amount of reverse remodeling and actual persisting damage.

Another fact that could be considered as a limitation is the image quality. All images used in this study were stored from everyday clinical examinations and not by a highly specialized research lab and it is reasonable to speculate that the image quality is more essential for timing parameters compared to conventional parameters, which again might have impacted on the results. On the other hand this can also be considered as one of the strengths of this study, pointing out the limitation of using the dyssynchrony parameters with the technique and resources we have at hand today in the daily clinical routine.

6 CONCLUSION

1. Quantitative echocardiographic methods derived from tissue Doppler are robust and are more insensitive to poor image quality compared to both qualitative and quantitative methods derived from 2D images such as WMSI, EF or 2D strain.

2. The diagnostic value in patients with ACS seems to be highest and better compared to other methods, such as WMSI and EF, when using the intersegmental variation of timing parameters as with State index. But also VeT, based on longitudinal velocities, systolic as well as diastolic, provides good information regarding ischemia both global and especially regional ischemia and dysfunction. Both these promising methods, however, need to be evaluated further in larger prospective study before clinical implementation.

3. For risk stratification in ACS patients, PSV seems to be a robust and easily obtained echocardiographic measurement that carries independent prognostic information and has incremental value to that of other strong predictors such as NT-proBNP and creatinine clearance.

4. Mechanical LV dyssynchrony seem to carry some significant prognostic information in ACS patient but in comparison to well-known risk factors and conventional parameters such as EF or PSV, mentioned above, there is little or no incremental value of this information.

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8 REFERENCES

1. http://www.escardio.org/about/what/advocacy/EuroHeart/Pages/2012-CVD-statistics.aspx.
2. http://www.ucr.uu.se/swedeheart/index.php/arsrapporter.
3. www.who.int/mediacentre/factsheet/fs317/en/index.html.
4. Go, A.S., et al., *Heart Disease and Stroke Statistics--2014 Update: A Report From the American Heart Association*. Circulation, 2013.
5. Karlson, B.W., et al., *Patients admitted to the emergency room with symptoms indicative of acute myocardial infarction*. J Intern Med, 1991. **230**(3): p. 251-8.
6. Hamm, C.W., et al., *ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)*. Eur Heart J, 2011. **32**(23): p. 2999-3054.
7. Erhardt, L., et al., *Task force on the management of chest pain*. Eur Heart J, 2002. **23**(15): p. 1153-76.
8. Pope, J.H., et al., *Missed diagnoses of acute cardiac ischemia in the emergency department*. N Engl J Med, 2000. **342**(16): p. 1163-70.
9. McCarthy, B.D., et al., *Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study*. Ann Emerg Med, 1993. **22**(3): p. 579-82.
10. Thygesen, K., et al., *Diagnostic application of the universal definition of myocardial infarction in the intensive care unit*. Curr Opin Crit Care, 2008. **14**(5): p. 543-8.
11. Thygesen, K., et al., *Third universal definition of myocardial infarction*. Circulation, 2012. **126**(16): p. 2020-35.
12. Thygesen, K., et al., *Third universal definition of myocardial infarction*. Eur Heart J, 2012. **33**(20): p. 2551-67.
13. White, H.D., et al., *Clinical implications of the Third Universal Definition of Myocardial Infarction*. Heart, 2013.
14. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18921/2012-12-21.pdf.
15. Graham, I., et al., *European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts)*. Eur J Cardiovasc Prev Rehabil, 2007. **14 Suppl 2**: p. S1-113.
16. Volpi, A., et al., *Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base*. Circulation, 1993. **88**(2): p. 416-29.
17. St John Sutton, M., et al., *Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial*. Circulation, 1997. **96**(10): p. 3294-9.
18. Benjamin, E.J., et al., *Left atrial size and the risk of stroke and death. The Framingham Heart Study*. Circulation, 1995. **92**(4): p. 835-41.
19. Appleton, C.P., et al., *Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings*. J Am Soc Echocardiogr, 1997. **10**(3): p. 271-92.
20. Baumgartner, H., et al., *Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice*. J Am Soc Echocardiogr, 2009. **22**(1): p. 1-23; quiz 101-2.
21. Lancellotti, P., et al., *European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease)*. Eur J Echocardiogr, 2010. **11**(4): p. 307-32.
22. Lancellotti, P., et al., *European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease)*. Eur J Echocardiogr, 2010. **11**(3): p. 223-44.

23. Yoshida, T., et al., *Analysis of heart motion with ultrasonic Doppler method and its clinical application*. Am Heart J, 1961. **61**: p. 61-75.
24. Isaaz, K., et al., *Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall*. Am J Cardiol, 1989. **64**(1): p. 66-75.
25. McDicken, W.N., et al., *Colour Doppler velocity imaging of the myocardium*. Ultrasound Med Biol, 1992. **18**(6-7): p. 651-4.
26. Sutherland, G.R., et al., *Color Doppler myocardial imaging: a new technique for the assessment of myocardial function*. J Am Soc Echocardiogr, 1994. **7**(5): p. 441-58.
27. Gulati, V.K., et al., *Mitral annular descent velocity by tissue Doppler echocardiography as an index of global left ventricular function*. Am J Cardiol, 1996. **77**(11): p. 979-84.
28. Alam, M., et al., *Effects of first myocardial infarction on left ventricular systolic and diastolic function with the use of mitral annular velocity determined by pulsed wave doppler tissue imaging*. J Am Soc Echocardiogr, 2000. **13**(5): p. 343-52.
29. Bartel, T., et al., *Evaluation of Hemodynamic Determinants of Quantitative Tissue Doppler Echocardiography in the Assessment of Left Ventricular Function*. Echocardiography, 1999. **16**(5): p. 481-489.
30. Yu, W.C., et al., *Evaluation of cardiac function by tissue Doppler echocardiography: hemodynamic determinants and clinical application*. Ultrasound Med Biol, 2005. **31**(1): p. 23-30.
31. Edvardsen, T., et al., *Quantification of left ventricular systolic function by tissue Doppler echocardiography: added value of measuring pre- and postejection velocities in ischemic myocardium*. Circulation, 2002. **105**(17): p. 2071-7.
32. Nagueh, S.F., et al., *Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures*. J Am Coll Cardiol, 1997. **30**(6): p. 1527-33.
33. Nagueh, S.F., et al., *Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue doppler imaging*. Circulation, 1998. **98**(16): p. 1644-50.
34. Ommen, S.R., et al., *Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study*. Circulation, 2000. **102**(15): p. 1788-94.
35. Nikitin, N.P., et al., *Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging*. J Am Soc Echocardiogr, 2003. **16**(9): p. 906-21.
36. Pai, R.G. and K.S. Gill, *Amplitudes, durations, and timings of apically directed left ventricular myocardial velocities: II. Systolic and diastolic asynchrony in patients with left ventricular hypertrophy*. J Am Soc Echocardiogr, 1998. **11**(2): p. 112-8.
37. Chahal, N.S., et al., *Normative reference values for the tissue Doppler imaging parameters of left ventricular function: a population-based study*. Eur J Echocardiogr, 2010. **11**(1): p. 51-6.
38. Westholm, C., et al., *Peak systolic velocity using color-coded tissue Doppler imaging, a strong and independent predictor of outcome in acute coronary syndrome patients*. Cardiovasc Ultrasound, 2013. **11**: p. 9.
39. Greenberg, N.L., et al., *Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility*. Circulation, 2002. **105**(1): p. 99-105.
40. Leitman, M., et al., *Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function*. J Am Soc Echocardiogr, 2004. **17**(10): p. 1021-9.
41. Stoylen, A., et al., *Strain Rate Imaging by Ultrasound in the Diagnosis of Regional Dysfunction of the Left Ventricle*. Echocardiography, 1999. **16**(4): p. 321-329.
42. Amundsen, B.H., et al., *Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging*. J Am Coll Cardiol, 2006. **47**(4): p. 789-93.
43. Nestaas, E., et al., *Feasibility and reliability of strain and strain rate measurement in neonates by optimizing the analysis parameters settings*. Ultrasound Med Biol, 2007. **33**(2): p. 270-8.
44. Risum, N., et al., *Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults*. J Am Soc Echocardiogr, 2012. **25**(11): p. 1195-203.
45. Geyer, H., et al., *Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications*. J Am Soc Echocardiogr, 2010. **23**(4): p. 351-69; quiz 453-5.

46. Onishi, T., et al., *Detection of diastolic abnormality by dyssynchrony imaging: correlation with coronary artery disease in patients presenting with visibly normal wall motion*. Circ J, 2009. **73**(1): p. 125-31.
47. Zhang, Y., et al., *Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes*. Am Heart J, 2005. **149**(3): p. 497-503.
48. Heger, J.J., et al., *Cross-sectional echocardiography in acute myocardial infarction: detection and localization of regional left ventricular asynergy*. Circulation, 1979. **60**(3): p. 531-8.
49. Haugaa, K.H., et al., *Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia*. JACC Cardiovasc Imaging, 2010. **3**(3): p. 247-56.
50. Klocke, F.J., et al., *ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging)*. J Am Coll Cardiol, 2003. **42**(7): p. 1318-33.
51. Peels, C.H., et al., *Usefulness of two-dimensional echocardiography for immediate detection of myocardial ischemia in the emergency room*. Am J Cardiol, 1990. **65**(11): p. 687-91.
52. Kontos, M.C., et al., *Comparison of 2-dimensional echocardiography and myocardial perfusion imaging for diagnosing myocardial infarction in emergency department patients*. Am Heart J, 2002. **143**(4): p. 659-67.
53. Weston, P., et al., *Hand-held echocardiographic examination of patients with symptoms of acute coronary syndromes in the emergency department: the 30-day outcome associated with normal left ventricular wall motion*. Am Heart J, 2004. **148**(6): p. 1096-101.
54. Hibberd, M.G., et al., *Accuracy of three-dimensional echocardiography with unrestricted selection of imaging planes for measurement of left ventricular volumes and ejection fraction*. Am Heart J, 2000. **140**(3): p. 469-75.
55. Schnaack, S.D., et al., *Transpulmonary contrast echocardiography: effects on delineation of endocardial border, assessment of wall motion and interobserver variability in stress echocardiograms of limited image quality*. Coron Artery Dis, 2000. **11**(7): p. 549-54.
56. Jenkins, C., et al., *Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography*. J Am Coll Cardiol, 2004. **44**(4): p. 878-86.
57. Neskovic, A.N., et al., *Emergency echocardiography: the European Association of Cardiovascular Imaging recommendations*. Eur Heart J Cardiovasc Imaging, 2013. **14**(1): p. 1-11.
58. Schuster, A., et al., *Imaging in the management of ischemic cardiomyopathy: special focus on magnetic resonance*. J Am Coll Cardiol, 2012. **59**(4): p. 359-70.
59. Kelle, S., et al., *Prognostic value of myocardial infarct size and contractile reserve using magnetic resonance imaging*. J Am Coll Cardiol, 2009. **54**(19): p. 1770-7.
60. Roes, S.D., et al., *Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction*. Am J Cardiol, 2007. **100**(6): p. 930-6.
61. Montant, P., et al., *Detection and quantification of myocardial scars by contrast-enhanced 3D echocardiography*. Circ Cardiovasc Imaging, 2010. **3**(4): p. 415-23.
62. Sjoli, B., et al., *Comparison of left ventricular ejection fraction and left ventricular global strain as determinants of infarct size in patients with acute myocardial infarction*. J Am Soc Echocardiogr, 2009. **22**(11): p. 1232-8.
63. Jensen-Urstad, K., et al., *Comparison of different echocardiographic methods with radionuclide imaging for measuring left ventricular ejection fraction during acute myocardial infarction treated by thrombolytic therapy*. Am J Cardiol, 1998. **81**(5): p. 538-44.
64. Lang, R.M., et al., *Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology*. J Am Soc Echocardiogr, 2005. **18**(12): p. 1440-63.
65. Schiller, N.B., et al., *Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms*. J Am Soc Echocardiogr, 1989. **2**(5): p. 358-67.

66. Brodin, L.A., *Tissue Doppler, a fundamental tool for parametric imaging*. Clin Physiol Funct Imaging, 2004. **24**(3): p. 147-55.
67. Schuster, P., et al., *Feasibility of color doppler tissue velocity imaging for assessment of regional timing of left ventricular longitudinal movement*. Scand Cardiovasc J, 2004. **38**(1): p. 39-45.
68. Henein, M.Y., et al., *Early changes in left ventricular subendocardial function after successful coronary angioplasty*. Br Heart J, 1993. **69**(6): p. 501-6.
69. Henein, M.Y., et al., *Effects of acute coronary occlusion and previous ischaemic injury on left ventricular wall motion in humans*. Heart, 1997. **77**(4): p. 338-45.
70. Derumeaux, G., et al., *Assessment of nonuniformity of transmural myocardial velocities by color-coded tissue Doppler imaging: characterization of normal, ischemic, and stunned myocardium*. Circulation, 2000. **101**(12): p. 1390-5.
71. Carasso, S., et al., *Left ventricular function and functional recovery early and late after myocardial infarction: a prospective pilot study comparing two-dimensional strain, conventional echocardiography, and radionuclide myocardial perfusion imaging*. J Am Soc Echocardiogr, 2013. **26**(11): p. 1235-44.
72. Shimoni, S., et al., *Differential effects of coronary artery stenosis on myocardial function: the value of myocardial strain analysis for the detection of coronary artery disease*. J Am Soc Echocardiogr, 2011. **24**(7): p. 748-57.
73. Becker, M., et al., *Analysis of myocardial deformation based on ultrasonic pixel tracking to determine transmurality in chronic myocardial infarction*. Eur Heart J, 2006. **27**(21): p. 2560-6.
74. O'Sullivan, C.A., et al., *The effect of the localization of Q wave myocardial infarction on ventricular electromechanics*. Int J Cardiol, 2002. **84**(2-3): p. 241-7.
75. O'Sullivan, C.A., et al., *The effect of the Q wave infarct on left ventricular electromechanical function*. Int J Cardiol, 2003. **92**(1): p. 71-6.
76. Tei, C., et al., *New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy*. J Cardiol, 1995. **26**(6): p. 357-66.
77. Gaibazzi, N., N. Petrucci, and V. Ziacchi, *Left ventricle myocardial performance index derived either by conventional method or mitral annulus tissue-Doppler: a comparison study in healthy subjects and subjects with heart failure*. J Am Soc Echocardiogr, 2005. **18**(12): p. 1270-6.
78. Tekten, T., et al., *Novel approach to measure myocardial performance index: pulsed-wave tissue Doppler echocardiography*. Echocardiography, 2003. **20**(6): p. 503-10.
79. Tekten, T., et al., *Value of measuring myocardial performance index by tissue Doppler echocardiography in normal and diseased heart*. Jpn Heart J, 2003. **44**(3): p. 403-16.
80. Pislaru, C., et al., *Higher myocardial strain rates during isovolumic relaxation phase than during ejection characterize acutely ischemic myocardium*. J Am Coll Cardiol, 2002. **40**(8): p. 1487-94.
81. Hayashi, S.Y., et al., *Analysis of mitral annulus motion measurements derived from M-mode, anatomic M-mode, tissue Doppler displacement, and 2-dimensional strain imaging*. J Am Soc Echocardiogr, 2006. **19**(9): p. 1092-101.
82. Karatzis, E.N., et al., *Myocardial performance index (Tei index): evaluating its application to myocardial infarction*. Hellenic J Cardiol, 2009. **50**(1): p. 60-5.
83. Sahin, D.Y., et al., *Relationship between myocardial performance index and severity of coronary artery disease assessed with SYNTAX score in stable coronary artery disease*. Echocardiography, 2013. **30**(4): p. 385-91.
84. Ozdemir, K., et al., *Effect of preload and heart rate on the doppler and tissue doppler-derived myocardial performance index*. Clin Cardiol, 2007. **30**(7): p. 342-8.
85. Jamal, F., et al., *Abnormal postsystolic thickening in acutely ischemic myocardium during coronary angioplasty: a velocity, strain, and strain rate doppler myocardial imaging study*. J Am Soc Echocardiogr, 1999. **12**(11): p. 994-6.
86. Voigt, J.U., et al., *Incidence and characteristics of segmental postsystolic longitudinal shortening in normal, acutely ischemic, and scarred myocardium*. J Am Soc Echocardiogr, 2003. **16**(5): p. 415-23.
87. Onishi, T., et al., *Positive isovolumic relaxation velocity detected by a spectral tissue Doppler mapping technique as an indicator of coronary artery disease: a prospective study*. J Am Soc Echocardiogr, 2007. **20**(2): p. 158-64.
88. T. Onoshi , T.W., M. Fujita, Y. Mizakami, Y. Sakata, S. Nkatani, S. Nanto, M Uematsu, *Risk stratification of chest pain in emergency departement usising non-provocative*

exhocardiography combined with tissue doppler dyssynchrony imaging, in *EuroEcho 2013*. 2013: Istanbul Turkey.
89. Lind, B., et al., *Longitudinal isovolumic displacement of the left ventricular myocardium assessed by tissue velocity echocardiography in healthy individuals*. J Am Soc Echocardiogr, 2006. **19**(3): p. 255-65.
90. Nucifora, G., et al., *Impact of left ventricular dyssynchrony early on left ventricular function after first acute myocardial infarction*. Am J Cardiol, 2010. **105**(3): p. 306-11.
91. Chen, C.C., et al., *Stress-induced myocardial ischemia is associated with early post-stress left ventricular mechanical dyssynchrony as assessed by phase analysis of 201Tl gated SPECT myocardial perfusion imaging*. Eur J Nucl Med Mol Imaging, 2012. **39**(12): p. 1904-9.
92. Bjallmark, A., et al., *Velocity tracking--a novel method for quantitative analysis of longitudinal myocardial function*. J Am Soc Echocardiogr, 2007. **20**(7): p. 847-56.
93. Larsson, M., et al., *State diagrams of the heart--a new approach to describing cardiac mechanics*. Cardiovasc Ultrasound, 2009. **7**: p. 22.
94. Burns, R.J., et al., *The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis*. J Am Coll Cardiol, 2002. **39**(1): p. 30-6.
95. Moller, J.E., et al., *Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction*. Am Heart J, 2006. **151**(2): p. 419-25.
96. Burianova, L., et al., *Assessment of left ventricular function in non-dilated and dilated hearts: comparison of contrast-enhanced 2-dimensional echocardiography with multi-detector row CT angiography*. Acta Cardiol, 2009. **64**(6): p. 787-94.
97. Antoni, M.L., et al., *Prognostic importance of strain and strain rate after acute myocardial infarction*. Eur Heart J, 2010. **31**(13): p. 1640-7.
98. Sjoli, B., et al., *The advantage of global strain compared to left ventricular ejection fraction to predict outcome after acute myocardial infarction*. Echocardiography, 2011. **28**(5): p. 556-63.
99. Dandel, M., et al., *Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability*. Curr Cardiol Rev, 2009. **5**(2): p. 133-48.
100. Stanton, T., R. Leano, and T.H. Marwick, *Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring*. Circ Cardiovasc Imaging, 2009. **2**(5): p. 356-64.
101. Hung, C.L., et al., *Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction*. J Am Coll Cardiol, 2010. **56**(22): p. 1812-22.
102. Leung, D.Y. and A.C. Ng, *Emerging clinical role of strain imaging in echocardiography*. Heart Lung Circ, 2010. **19**(3): p. 161-74.
103. Wang, M., et al., *Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value*. J Am Coll Cardiol, 2003. **41**(5): p. 820-6.
104. Hillis, G.S., et al., *Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction*. J Am Coll Cardiol, 2004. **43**(3): p. 360-7.
105. Morrow, D.A., et al., *Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18*. J Am Coll Cardiol, 2003. **41**(8): p. 1264-72.
106. Jernberg, T., et al., *Natriuretic peptides in unstable coronary artery disease*. Eur Heart J, 2004. **25**(17): p. 1486-93.
107. Lorgis, L., et al., *Prognostic value of N-terminal pro-brain natriuretic peptide in elderly people with acute myocardial infarction: prospective observational study*. BMJ, 2009. **338**: p. b1605.
108. Kruszewski, K., et al., *Noninvasive assessment of left ventricular filling pressure after acute myocardial infarction: a prospective study of the relative prognostic utility of clinical assessment, echocardiography, and B-type natriuretic peptide*. Am Heart J, 2010. **159**(1): p. 47-54.
109. Mollema, S.A., et al., *Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling*. J Am Coll Cardiol, 2007. **50**(16): p. 1532-40.
110. Ng, A.C., et al., *Prognostic implications of left ventricular dyssynchrony early after non-ST elevation myocardial infarction without congestive heart failure*. Eur Heart J, 2010. **31**(3): p. 298-308.
111. Shin, S.H., et al., *Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both*. Circulation, 2010. **121**(9): p. 1096-103.

112. *Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction*. Eur Heart J, 2000. **21**(18): p. 1502-13.
113. Labovitz, A.J., et al., *Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty*. J Am Coll Cardiol, 1987. **10**(4): p. 748-55.
114. Cain, P., et al., *Application of tissue Doppler to interpretation of dobutamine echocardiography and comparison with quantitative coronary angiography*. Am J Cardiol, 2001. **87**(5): p. 525-31.
115. Madler, C.F., et al., *Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study*. Eur Heart J, 2003. **24**(17): p. 1584-94.
116. Lundback, S., *Cardiac pumping and function of the ventricular septum*. Acta Physiol Scand Suppl, 1986. **550**: p. 1-101.
117. Fornwalt, B.K., et al., *Variability in tissue Doppler echocardiographic measures of dyssynchrony is reduced with use of a larger region of interest*. J Am Soc Echocardiogr, 2009. **22**(5): p. 478-85 e3.
118. Sadeghian, H., et al., *Ventricular asynchrony of time-to-peak systolic velocity in structurally normal heart by tissue Doppler imaging*. Echocardiography, 2010. **27**(7): p. 823-30.
119. Cockcroft, D.W. and M.H. Gault, *Prediction of creatinine clearance from serum creatinine*. Nephron, 1976. **16**(1): p. 31-41.
120. Hanley, J.A. and B.J. McNeil, *The meaning and use of the area under a receiver operating characteristic (ROC) curve*. Radiology, 1982. **143**(1): p. 29-36.
121. Hunziker, P.R., et al., *Regional wall motion assessment in stress echocardiography by tissue Doppler bull's-eyes*. J Am Soc Echocardiogr, 1999. **12**(3): p. 196-202.
122. Witt, N., et al., *Detection of left ventricular dysfunction by Doppler tissue imaging in patients with complete recovery of visual wall motion abnormalities 6 months after a first ST-elevation myocardial infarction*. Clin Physiol Funct Imaging, 2007. **27**(5): p. 305-8.
123. Palmes, P.P., et al., *Myocardial longitudinal motion by tissue velocity imaging in the evaluation of patients with myocardial infarction*. J Am Soc Echocardiogr, 2000. **13**(9): p. 818-26.
124. Marwick, T.H., et al., *Use of tissue Doppler imaging to facilitate the prediction of events in patients with abnormal left ventricular function by dobutamine echocardiography*. Am J Cardiol, 2004. **93**(2): p. 142-6.
125. Rhee, H. and L. Tyler, *Effects of myocardial ischemia on cardiac contractility and ion transport in working and Langendorff rabbit heart*. Adv Exp Med Biol, 1984. **180**: p. 477-87.
126. Lee, J.A. and D.G. Allen, *Mechanisms of acute ischemic contractile failure of the heart. Role of intracellular calcium*. J Clin Invest, 1991. **88**(2): p. 361-7.
127. Bertini, M., et al., *Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy*. Circ Cardiovasc Imaging, 2012. **5**(3): p. 383-91.
128. Chung, E.S., et al., *Results of the Predictors of Response to CRT (PROSPECT) trial*. Circulation, 2008. **117**(20): p. 2608-16.