Cardiac Time Intervals by Tissue Doppler Imaging M-mode Echocardiography: Reproducibility, Reference Values, Association with Clinical Characteristics and Prognostic Implications

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List of Papers

I. Biering-Sørensen T, Mogelvang R, Pedersen S, Schnohr P, Sogaard P, Jensen JS. Usefulness of the Myocardial Performance Index Determined by Tissue Doppler Imaging M-Mode for Predicting Mortality in the General Population. Am J Cardiol. 2011 Feb 1;107(3):478-83.

II. Biering-Sørensen T, Mogelvang R, de Knegt MC, Olsen FJ, Galatius S, Jensen JS. Cardiac Time Intervals by Tissue Doppler Imaging M-mode: Normal Values and association with established Echocardiographic and Invasive measures of Systolic and Diastolic function. PLoS One. 2016 Apr 19;11(4):e0153636.

III. Biering-Sørensen T, Mogelvang R, Søgaard P, Pedersen SH, Galatius S, Jørgensen PG, Jensen JS. Prognostic value of cardiac time intervals by tissue Doppler imaging M-mode in patients with acute ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. Circ Cardiovasc Imaging. 2013 May 1;6(3):457-65.

IV. Biering-Sørensen T, Mogelvang R, Schnohr P, Jensen JS. The Cardiac Time Intervals measured by Tissue Doppler Imaging M-mode: Association to Hypertension, Left Ventricular Geometry and Future Ischemic Cardiovascular Diseases. J Am Heart Assoc. 2016 Jan 19;5(1). Pii: e002687.

V. Biering-Sørensen T, Mogelvang R, Jensen JS. Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode in the General Population. Heart. 2015 Jun;101(12):954-60.

Abbreviations

a' = Peak late longitudinal diastolic myocardial velocity by Tissue Doppler Imaging
AMI = Acute Myocardial Infarction
A-wave = Atrial diastolic filling by pulsed-wave Doppler
AVC = Aortic Valve Closing
AVO = Aortic Valve Opening
BMI = Body Mass Index
BP = Blood Pressure
CHF = Heart Failure
CI = Confidence Interval
CV = Coefficient of variation
dP/dt max = The rate of LV pressure rise in early systole
dP/dt min = The rate of LV pressure decline in early diastole
DT = Deceleration Time of the E-wave
e' = Peak early longitudinal diastolic myocardial velocity by Tissue Doppler Imaging
eGFR = Estimated Glomerular Filtration Rate
E-wave = Early diastolic filling by pulsed-wave Doppler
ECG = Electrocardiogram
ESH/ESC = European Society of Hypertension/European Society of Cardiology
ET = Ejection Time
GLS = Global Longitudinal Strain
GL SR s = Global Longitudinal systolic strain rate
GL SR e = Global Longitudinal early diastolic strain rate
HR = Hazard Ratio
ICVD = Ischemic Cardiovascular Disease
IHD = Ischemic Heart Disease
IS = previous Ischemic Stroke
IVCT = Isovolumic Contraction Time
IVRT = Isovolumic Relaxation Time
LA = Left Atrium
LAD = Left Atrium Diameter in end-systole
LV = Left Ventricle
LVEF = LV Ejection Fraction
LVH = LV Hypertrophy
LVIDd = LV diameter in end-diastole
LVMI = LV Mass Index

MACE = Major Adverse Cardiovascular Events
M-mode = Motion mode
MPI = Myocardial Performance Index
MPI_{Conv} = MPI obtained by the conventional method
MPI_{TDI} = MPI obtained by using TDI M-mode through the mitral valve
MV = Mitral Valve
MVC = Mitral Valve Closing
MVO = Mitral Valve Opening
NRI = Net Reclassification Index
PEP = Pre Ejection Period
pPCI = Primary Percutaneous Coronary Intervention
re-MI = New Myocardial Infarction
RWT = Relative Wall Thickness
SERCA2a = Sarco/Endoplasmic Reticulum Ca2+-ATPase 2a
SHR = Subdistribution Hazard Ratios
STEMI = ST-Segment Elevation Myocardial Infarction
TDI = Tissue Doppler Imaging
TnI = Troponin I

Introduction

The cardiac time intervals are defined by the opening and closing of the valves of the heart, which in turn is determined by pressure differences across the valves. All clinicians are familiar with audible assessing the cardiac time intervals. By using their stethoscope, audible changes in the cardiac time intervals can be assessed. Just by auscultating the first (S1) and second (S2) heart sound the clinician can evaluate the total systolic time (isovolumic contraction time (IVCT) + ejection time (ET)), which is the time difference between the mitral valve closing (MVC) and the aortic valve closing (AVC). Additionally, the time difference from the S2 to the S1 is the total diastolic time (isovolumic relaxation time (IVRT) + the diastolic filling period), which is the time difference between the AVC and the MVC. The cardiac time intervals have therefore been accessible for the clinician to evaluate since the beginning of the 19th century where the stethoscope was invented. Thus researchers have for more than a century investigated the usability of theses for diagnostic and predictive purposes [1–7]. However, the methods of assessing the cardiac time intervals have changed significantly through the last century. From using sphygmographic recording of the arterial pulse initiated in the 19th century [1] to using simultaneous photographic recordings of the electrocardiogram, phonocardiogram, and the central arterial pulse [4,5] in the beginning of the 20th century, to simultaneous recordings of the electrocardiogram, the central arterial pulse, and M-mode echocardiography in the late 20th century [6], to Doppler echocardiography in the mid-1990th [7–9], and finally tissue Doppler imaging (TDI) velocity traces of the ventricular myocardium in the beginning of the 21th century [10–12]. The progress in how to obtain the cardiac time intervals has made them easily accessible to attain. Therefore, the evaluation of the usefulness of cardiac time intervals as diagnostic and prognostic markers in the clinical setting has become increasingly meaningful.

A decade ago, yet another echocardiographic method of obtaining the cardiac time intervals evolved. Using this method, the cardiac time intervals are obtained by evaluating the mitral valve (MV) movement through the cardiac cycle using a simple color TDI M-mode analysis [13,14]. This novel echocardiographic method seemed to have several advantages compared to the conventional echocardiographic methods of obtaining the cardiac time intervals. However, in order to assess the usability of this method of obtaining the cardiac time intervals in clinical practice, future studies are necessary.

Objectives

The aims of the present thesis were:

1) To compare the reproducibility, association with clinical characteristics and the usefulness in predicting all-cause mortality in the general population, for the Myocardial Performance Index (MPI) obtained by the conventional method of obtaining the MPI (MPI_{Conv}), as described by Tei and colleagues [7,9] and by the novel method of obtaining the MPI (MPI_{TDI}), using TDI M-mode.

2) To define normal values of the cardiac time intervals obtained by TDI M-mode through the MV, and to evaluate the association of the novel MPI_{TDI} and the conventional method of obtaining the MPI (MPI_{Conv}), with established echocardiographic and invasive measures of systolic and diastolic function.

3) To evaluate the prognostic value of the cardiac time intervals and the combined index of systolic and diastolic performance, the MPI, obtained by TDI M-mode method in patients with ST-Segment Elevation Myocardial Infarction (STEMI) treated with Primary Percutaneous Coronary Intervention (pPCI).

4) To investigate if the cardiac time intervals are able to identify miniscule cardiac impairments in individuals with hypertension, which are unrecognized by conventional echocardiography, and if these time intervals are affected according to blood pressure (BP) severity and left ventricular geometry. Additionally, to investigate if these cardiac time intervals can be used to predict hypertension related diseases such as ischemic cardiovascular diseases.

5) To investigate whether the combined indexes containing information on both systolic and diastolic function (the IVRT/ET and the MPI), provide prognostic information regarding the risk of future cardiovascular disease and cardiovascular mortality in the general population, incremental to clinical predictors and conventional echocardiographic measures of systolic and diastolic function.

Background

Cardiac Time Intervals at Cellular Level.

The preservation of normal cardiac time intervals is intimately related to normal cardiac physiology and function. Both contraction and relaxation of the heart is orchestrated by the recycling of calcium in the myocardial cells. This recycling of calcium ions is initiated when the action potential, origination from the sinus node, propagating from myocyte to myocyte through the gap junctions, depolarizes the plasma membrane. This activates the voltage-gated L-type Ca2+ channels in the sarcolemma. The ensuing Ca2+ influx then triggers a much greater Ca2+ release from the sarcoplasmic reticulum via ryanodine receptors (RyR2) in a

process called Ca2+-induced Ca2+ release [15]. The Ca2+-induced Ca2+ release results in a tenfold increase in cytoplasmic Ca2+ concentrations. The Ca2+-ions bind to troponin C which in turn results in actin-myosin cross-bridge formation. ATP fuels the subsequent cross-bridge cycling which translocates the myosin heads along the actin filaments, which results in the contraction of the myocyte. The contraction will proceed as long Ca2+ (and ATP) is available in the cytosol, why relaxation is initiated by the removal of Ca2+. Cytosolic Ca2+ is pumped back into the sarcoplasmic reticulum by a Ca2+ pump (SERCA2a) [16,17], and extruded into the extracellular fluid from the cardiomyocyte via the sarcolemmal Na-Ca exchanger [18]. This recycling of Ca2+ happens approximately once every second and is, as long as normal cardiac physiology is maintained, orchestrated with a precision of millisecond intervals. However, in the ailing heart, maladaptive changes result in depressed intracellular Ca2+ cycling and lower Ca2+ concentrations in the sarcoplasmic reticulum such that any given action potential leads to less Ca2+ influx to the cytosol and produces slower and less force during contraction [19–21]. Additionally, a reduced synchrony of sarcoplasmic reticulum Ca2+ release and prolonged Ca2+ release in failing cardiomyocytes from human hearts has been ducumented [22]. Also the SERCA2a pump has been demonstrated to be impaired in the failing heart leading to delayed reuptake of the Ca2+ to the sarcoplasmic reticulum causing diastolic dysfunction [23–25]. Therefore, the rate of calcium recycling and therefore also the amount of time the heart remains in different phases of the cardiac cycle will indeed change in the progression of heart disease.

Cardiac Time Intervals at Organ Level

In the ailing myocardium, the cardiac time intervals will change during disease progression [26–29]. As left ventricular (LV) systolic function deteriorates, the time it takes for myocardial myocytes to achieve an LV pressure equal to that of aorta increases, resulting in a prolongation of IVCT [29]. Furthermore, the ability of myocardial myocytes to maintain the LV pressure decreases, resulting in reduction in the ET [29]. As LV diastolic function declines further, early diastolic relaxation proceeds more slowly, explaining the prolongation of IVRT. Consequently, the IVRT/ET and the MPI, defined as (IVCT + IVRT)/ET, will detect cardiac dysfunction with an increase, irrespective of whether the LV is suffering from impaired systolic or diastolic function [30,31]. The MPI increases even in patients with severe diastolic dysfunction with a restrictive filling pattern, which is seen as a short IVRT time [32]. This is attributable to the increase in IVCT or decrease in ET, illustrating the subtle impaired systolic function identified by novel echocardiographic parameters which is found in patients with severe diastolic dysfunction, even though they display a preserved LV ejection fraction [33,34]. Therefore, the cardiac time intervals, especially the combined indexes containing information on both systolic and diastolic performance (the IVRT/ET and the MPI), may be useful to identify subtle impairments in the cardiac function (both systolic and diastolic) in the general population, which are unnoticed by conventional echocardiography [35,36].These echocardiographic parameters may thus identify patients in high risk of future fulminant cardiovascular disease.

Methods of obtaining the cardiac time intervals

Cardiac intervals have been suggested and investigated as potential markers of cardiac dysfunction for several decades [5–7,9]. In 1964, Weissler and colleagues derived an index of systolic function defined as the preejection period (PEP = defined as the Q-wave of the electrocardiogram – the ET from the central artery pulse) divided by the ET (PEP/ET), using simultaneous photographic recordings of the electrocardiogram, phonocardiogram, and the central arterial pulse [5]. This index was significantly impaired in patients with heart failure compared to normal individuals, despite no difference in electromechanical systole, defined as the time from beginning of the QRS to the end of the T-wave. However, this index was only a measure of systolic function, why Mancini and colleagues6 in 1982 incorporated IVRT into an index which they named the isovolumic index (IVCT + IVRT)/ET in the attempt to capture both the systolic and diastolic function in one measure. The sum of IVCT and IVRT was determined by subtracting the ET (obtained from the central artery pulse) from the peak of the R wave on the electrocardiogram to the onset of mitral valve opening, determined from M-mode echocardiography [6]. However, the interval from the peak of the R wave to the onset of mitral valve opening contains an interval of electromechanical delay, which can be pronounced in patients with left bundle branch block. However, a main concern has always been that these cardiac time intervals were very difficult to obtain in a fast, easy, non-invasive and reproducible manner.

Tei and colleagues proposed in 1995 to overcome this problem by obtaining the cardiac time intervals from the velocity curves obtained from pulsed-Doppler echocardiography of the LV MV inflow and outflow tract and hereby calculating the index of combined systolic and diastolic performance, the MPI [7,9]. The method suggested by Tei and colleagues unfortunately also has several limitations. Firstly, the time intervals are obtained from two projections and at least two cardiac cycles [7,9], and may therefore be prone to changes in the cardiac time intervals caused by heart rate variations in-between obtaining the two projections. Secondly, the IVRT and IVCT are not obtained when using this method, only the sum of the IVRT and the IVCT [7,9]. Using TDI and the velocity curves from the myocardium is an alternative non-invasive approach to obtain the cardiac time intervals [10–12,26,27]. With this method the time intervals can be obtained from one projection and one cardiac cycle. However, the time intervals obtained from the TDI velocity curves are prone to regional differences in myocardial activation, mechanics and physiology [37]. These regional differences in the cardiac time intervals will be attenuated in persons suffering from, e.g. bundle branch blocks, ischemic heart disease or LV dyssynchrony. However, we can overcome this problem by analysing the global time intervals through evaluating the MV movement by a simple color TDI M-mode analysis [13], instead of the regional velocity curves. Thus, using color TDI M-mode through the mitral leaflet to estimate the cardiac time intervals may be an improved method reflecting global cardiac time intervals and eliminating beat-to-beat variation and regional differences. Furthermore, the precision and reproducibility of the cardiac time intervals and MPI seem to be improved when using the TDI M-mode method compared to the conventional method as described by Tei and colleagues [14]. Additionally, it is not possible to obtain the cardiac time intervals from velocity curves in patients with atrial fibrillation regardless if they are obtained by the conventional method as describe by Tei and colleagues [7,9] or by the newer regional TDI velocity curve method [10,11]. This is due to the absence of the atrial diastolic filling wave (A-wave) and late diastolic myocardial velocity (a' curve) in patients with atrial fibrillation, which are needed to obtain the time intervals by both methods. In contrast, all cardiac time intervals can be obtained by the novel color TDI M-mode method regardless of the presence of atrial fibrillation.

Also, the time intervals achieved by clear color shifts marking minimal changes in direction in the MV by the color TDI M-mode method are very easy to identify (Figure 2.1). In contrast the time intervals obtained by the conventional method [7,9] or the newer regional TDI velocity curve method [10,11] are assessed from velocity curves where the signals may be scattered making it hard to accurately define the cardiac time intervals. Finally, when good imaging quality is difficult to obtain, it is often possible to visualize the MV in the apical view, due to the perpendicular nature between the ultrasound beam and the MV, why assessing its longitudinal movement by color TDI M-mode nearly always is manageable.

Methods

Study population (The Copenhagen City Heart Study) paper I+II+IV+V

Within the Copenhagen City Heart Study, a longitudinal cohort study of cardiovascular disease and risk factors, an echocardiographic sub study was performed [38,39]. The present thesis includes all participants from the fourth Copenhagen City Heart Study examination 2001-2003, who had an echocardiographic examination, including TDI, performed. We were able to obtain the cardiac time intervals from 1,915 participants aged 20 to 93 years. In paper I only the 1,100 first analysed participants were included. Whether a participant underwent echocardiography as part of the fourth Copenhagen City Heart Study examination was independent of his or her health status and other risk factors.

Health Examination

All participants answered a self-administered questionnaire and underwent thorough physical examinations. BP of all participants was measured with the London School of Hygiene sphygmomanometer. Hypertension was defined as systolic BP of 140 mm Hg or above, diastolic BP of 90 mm Hg or above, or use of antihypertensive medication [40]. A 12-lead electrocardiogram (ECG) was recorded at rest in a supine position and coded according to the Minnesota code. Plasma cholesterol and glucose values were measured on non-fasting venous blood samples [41]. Diabetes mellitus was defined as plasma glucose concentration of 11.1 mmol/L or above, use of insulin or other antidiabetic medicine, self-reported disease, or hemoglobin A1c level of 7.0% or above [42,43]. Ischemic heart disease (IHD) was defined as a history of hospital admission for acute coronary artery occlusion, percutaneous coronary intervention or coronary artery bypass grafting, or major ischemic alterations on the ECG as defined by Minnesota codes 1.1 to 3.

Study population (Prognosis After Percutaneous Coronary Intervention) paper III

From September 2006 to December 2008 a total of 391 patients were admitted with a STEMI, treated with pPCI, and underwent a detailed echocardiographic examination at Gentofte University Hospital, Denmark. Five patients were excluded due to inadequate quality of the echocardiographic examination in regard to obtaining the cardiac time intervals.
The definition of a STEMI was: Presence of chest pain for >30 minutes and <12 hours, persistent ST-segment elevation ≥2 mm in at least 2 contiguous precordial ECG-leads or ≥1 mm in at least two contiguous limb ECG-leads (or a newly developed Left Bundle Branch Block) combined with a Troponin I (TnI) increase >0.5 µg/L.
Baseline data were collected prospectively. Hypertension was defined as use of blood pressure-lowering drugs on admission. Diabetes was defined as fasting plasma glucose concentration ≥7 mmol/L or non-fasting plasma glucose concentration ≥11.1 mmol/L or the use of glucose-lowering drugs on admission.
TnI was measured immediately upon admission and after 6 and 12 hours.

Primary PCI procedure: pPCI was performed according to contemporary interventional guidelines using pre-treatment with 300 mg acetyl salicylic acid, 600 mg clopidogrel and 10,000 IU of unfractionated heparin. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Multivessel disease was defined as 2- or 3 vessel disease and complex lesions as type C-lesions. Subsequent medical treatment included anti-ischemic, lipid-lowering and anti-thrombotic drugs.

Study population (INVASIVE study) paper II

This study population consists of patients suspected of ischemic heart disease that underwent coronary angiography, left heart ventricle catheterization and echocardiography (n = 44) at Department of Cardiology, Gentofte Hospital, University of Copenhagen between April 2009 and February 2011.

Invasive Measurements: LV pressures were measured, and an echocardiogram was preformed according to a standardized protocol. Invasively obtained pressure curves were obtained using 5 French pigtail catheters which were placed in the LV chamber and the pressure set and transducer was calibrated. Measurements were obtained over at least three cardiac cycles and saved as hard copies and digitalized in relation to this study. The LV pressure curves were digitalized using Dagra Version 2.0.12.35924. In all cardiac cycles the rate of LV pressure rise in early systole (dP/dt max) and the rate of LV pressure decline in early diastole (dP/dt min) were measured and averaged over all the cardiac cycles.

Conventional and novel echocardiography

All echocardiograms were obtained using Vivid ultrasound systems (GE Healthcare, Horten, Norway). All participants were examined with conventional two-dimensional echocardiography and color TDI. All echocardiograms were stored and analyzed offline with commercially available software (EchoPac, GE Medical, Horten, Norway).
In the echocardiographic sub study of the Copenhagen City Heart Study, regional function was evaluated by the 16 standard segments model, as suggested by the American Society of Echocardiography [44]. Left ventricular ejection fraction (LVEF) was evaluated by one observer on the basis of the wall motion index score. LV systolic dysfunction was defined as LVEF below 50%.
From the parasternal long-axis view, the LV diameter in end-diastole (LVIDd), wall thickness and the left atrium diameter in end-systole (LAD) were measured. LV mass index (LVMI) was calculated as the anatomic mass [44] divided by body surface area [45. Pulsed wave Doppler at the apical view was utilized to record mitral inflow between the tips of the mitral leaflets. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave (DT) were measured and the E/A-ratio was calculated.
In paper IV left ventricular hypertrophy (LVH) was defined as LVMI ≥ 96 g/m2 for women and ≥ 116 g/m2 for men [44]. Left

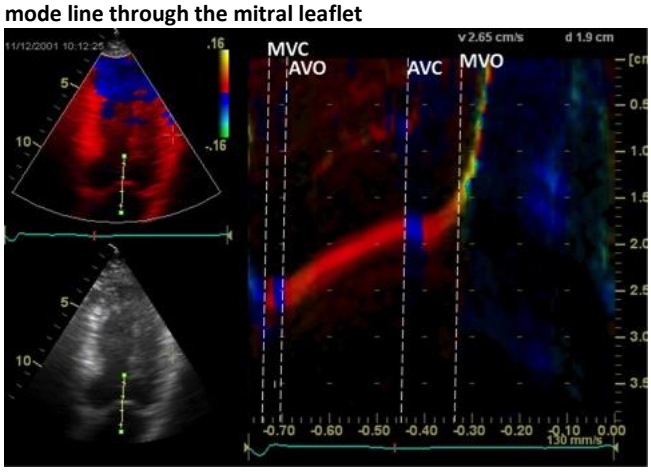
ventricular dilatation was considered present if LVIDd/height ≥ 3.3 cm/m [44]. Furthermore, diastolic dysfunction was defined as DT < 140 ms and E/A<50 years > 2.5, E/A50–70 years > 2, or E/A>70 years > 1.5, respectively. Participants were stratified according to left ventricular geometry. Normal geometry was defined as a relative wall thickness (RWT) ≤ 0.42 and absence of LVH, concentric remodeling was defined as a RWT > 0.42 and absence of LVH, eccentric hypertrophy was defined as a RWT ≤ 0.42 and the presence of LVH and concentric hypertrophy was defined as a RWT > 0.42 and the presence of LVH[44]. A normal conventional echocardiographic examination was defined as the absence of LVH, dilatation, LVEF < 50%, and diastolic dysfunction.

In the "Prognosis After Percutaneous Coronary Intervention" study and "INVASIVE" study the LV and left atrium (LA) volumes and LVEF were obtained using modified biplane Simpson's method [44]. Pulsed-wave TDI tracings were obtained with the range gate placed at the septal and lateral mitral annular segments in the 4-chamber view. The peak longitudinal early diastolic (e') velocity was measured and the average was calculated from the lateral and septal velocities and used to obtain the E/e'. Also, two-dimensional strain echocardiography was performed from the apical 4-chamber, 2-chamber and apical long-axis view. By speckle tracking, the endocardial border was traced in end systole. The integrity of speckle tracking was automatically detected and visually ascertained. In case of poor tracking, the region of interest tracing was readjusted. Global longitudinal strain (GLS) was measured in all three apical views and averaged to provide GLS. Furthermore, in each three apical views global longitudinal systolic strain rate (GL SR s) and global longitudinal early diastolic strain rate (GL SR e) were measured, and averaged to provide global estimates.
Lastly, in paper III diastolic function was assessed using mitral inflow velocity profiles and pulsed-wave TDI tracings from the septal and lateral mitral annulus [46]. Patients with atrial fibrillation were defined as having diastolic dysfunction, and were graded as 1, 2 or 3 according to the value of E/e' [47].

Cardiac Time Intervals obtained by the conventional method (paper I & II)
In paper I & II the time intervals were measured using the method described by Tei and colleagues [7,9]. The interval from MV closing to opening was determined as the period from the end to onset of mitral inflow (A to E time) obtained from the pulsed-wave Doppler at the apical position. LV ET was determined as the period from onset to end of LV outflow. MPI_{Conv} was calculated as: (A to E time – ET)/ET [7,9].

Cardiac Time Intervals obtained by color TDI M-mode (paper I-V)
In all the papers included in the present thesis the cardiac time intervals were obtained by the novel color TDI M-mode method. By this method, the cardiac time intervals were obtained by placing a 2-4 cm straight M-mode line through the septal half of the MV in the color TDI 4-chamber view, whereby the cardiac time intervals were measured directly from the color diagram [13,14] (Figure 2.1). The IVCT was defined as the time interval from the MV closure (MVC), determined by the color shift from blue/turquoise to red at end-diastole, to the aortic valve opening (AVO) determined by the color shift from blue to red (Figure 2.1). The ET was defined as the time interval from the AVO to the aortic valve closing (AVC), determined by the color shift from red to blue at end systole (Figure 2.1). The IVRT was defined as the time interval from the AVC to the MV opening (MVO), determined by the color shift from red-orange to yellow (Figure 2.1).

Figure 2.1 The cardiac time intervals assessed by a color TDI M-mode line through the mitral leaflet



Left: Four-chamber gray-scale (bottom) and color TDI (top) views in end-systole displaying the position of the M-mode line used for measuring the cardiac time intervals. Right: Color diagram of the TDI M-mode line through the mitral leaflet.
MVC = Mitral Valve (MV) Closing; AVO = Aortic Valve Opening; AVC = Aortic Valve Closure; MVO = MV Opening.

Follow-up (paper I & III-V)
In papers investigating outcome, follow-up data on diseases were obtained from the Danish National Board of Health's National Patient Registry, using ICD-10 codes. Additionally, follow-up data on mortality were collected from the National Person Identification Registry. Follow-up was 100% in all the papers in this thesis.

Statistics (paper I-V)
Proportions were compared using $\chi 2$-test, continuous Gaussian distributed variables with Student's t-test and Mann-Whitney test if non-Gaussian distributed.
The association between the cardiac time intervals and clinical parameters were tested by univariable and multivariable regression analyses including significant confounders. Linearity, variance homogeneity, and the assumption of normality were tested with plots of residuals. Trends were analyzed by linear regression analyses and departure from linearity was assessed by simultaneous assessment of linear and quadratic effects.
In paper III receiver operating characteristic curves were constructed for the IVCT/ET, IVRT/ET and MPI in effort to find the optimal cut-off value with the highest sensitivity and specificity for predicting the risk of the combined endpoint.
In paper I and III intra- and interobserver variabilities were determined by Bland-Altman plots of repeated analyses of stored echocardiographic loops (n=25 for patients with sinus rhythm in both paper I and III and also performed in 14 patients with atrial fibrillation in paper III).

Additionally, in paper I and III, the cumulative survival curves were established by the Kaplan–Meier method and compared by the log-rank test. Hazards ratios were calculated by Cox proportional hazards regression analyses. The assumptions of linearity

and proportional hazards in the models were tested graphically and tested based on the Schoenfeld residuals.
In paper III and V, cumulative incidence curves of future cardiovascular events were obtained by competing risk Cox proportional hazards regression models. Subdistribution Hazard Ratios (SHR) were calculated by competing risk Cox proportional hazards regression analyses. Additionally, for paper V, Harrell's c-statistics48 obtained from univariable Cox proportional hazards regression models were calculated in order to test the prognostic performance of all the cardiac time intervals. Harrell's c-statistics were obtained from multivariable Cox proportional hazards regression models including all the conventional echocardiographic parameters and compared with Harrell's c-statistics obtained from multivariable Cox proportional hazards regression models including all the conventional echocardiographic parameters and the IVRT/ET or MPI, respectively. Predictive models, using logistic regression models, predicting the risk of future cardiovascular diseases, were constructed to assess the integrated diagnostic improvement and net reclassification index (NRI) when adding the IVRT/ET and the MPI, to models already including significant predictors of the cardiovascular outcomes. A p-value ≤ 0.05 in 2-sided test was considered statistically significant. All analyses were performed with STATA Statistics/Data analysis, SE 12.0 (StataCorp, Texas,USA).

Summary of main results

Paper I

The aim of this paper was to compare the reproducibility, association with clinical characteristics and the usefulness in predicting all-cause mortality in the general population, for MPI_{Conv} and MPI_{TDI}.

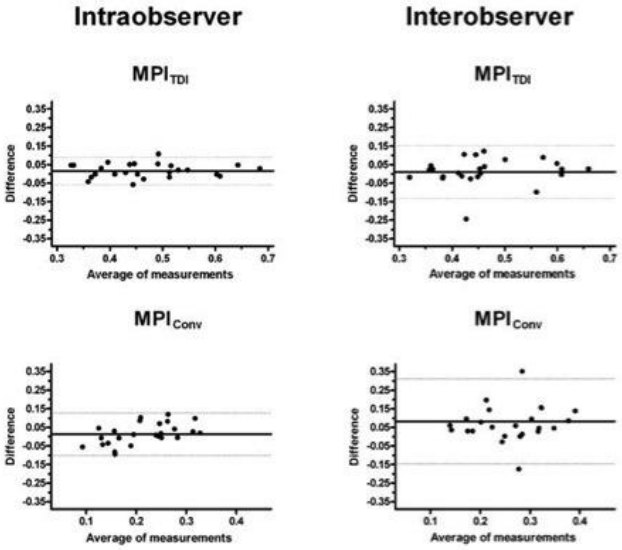
Cardiac function remained significantly impaired in the IHD group determined by significantly higher MPI_{Conv} and MPI_{TDI} after multivariable adjustment for age, gender, body mass index, heart rate, and mean arterial blood pressure (MPI_{Conv}: 0.44 (95% CI 0.41-0.48) vs. 0.39 (95% CI 0.38-0.40), p<0.002; MPI_{TDI}: 0.56 (95% CI 0.53-0.59) vs. 0.51 (0.50-0.52), p<0.002. Besides being associated with the presence of IHD, MPI_{TDI} increased independently with increasing age and mean arterial blood pressure, whereas MPI_{Conv} increased independently with increasing age, mean arterial blood pressure, decreasing body mass index and heart rate (Table 3.1). MPI_{TDI}, but not MPI_{Conv}, remained independently associated with overall mortality after multivariable adjustment for age, gender, body mass index, heart rate, mean arterial blood pressure, and IHD (MPI_{Conv}, pr 0.1 increase: Hazard Ratio (HR) 1.11 (95% CI 0.96-1.27), p=0.15; MPI_{TDI}, pr 0.1 increase: HR 1.18 (95% CI 1.04-1.34), p=0.010.
For MPI_{TDI} intraobserver variability analysis showed a mean difference ± SD of 0.016 ± 0.038 and interobserver variability analysis showed a mean difference of 0.010 ± 0.073 (Figure 3.1). For MPI_{Conv} intraobserver variability analysis showed a mean difference of 0.013 ± 0.057 and interobserver variability analysis showed a mean difference of 0.082 ± 0.114 (Figure 3.1).

Table 3.1 Multiple Regression Models with Myocardial Performance index obtained by the convention method (MPI_{Conv}) and by the TDI M-mode method (MPI_{TDI}) as Dependent Variables.

	MPI_{Conv}		MPI_{TDI}	
	β	*P-value*	*β*	*P-value*
Age, per 10 year	0.010 (0.003 to 0.017)	*P=0.006*	0.025 (0.019 to 0.031)	*P<0.0001*
Male Sex	0.019 (-0.001 to 0.040)	*P=0.06*	0.004 (-0.013 to 0.021)	*P=0.64*
Body mass index, per 5 kg/m^2	-0.015 (-0.028 to -0.001)	*P=0.033*	0.002 (-0.009 to 0.013)	*P=0.77*
Heart Rate, per 10 beats per minute	-0.015 (-0.024 to -0.005)	*P=0.002*	0.006 (-0.001 to 0.014)	*P=0.11*
Mean arterial blood pressure, per 10 mmHg	0.013 (0.005 to 0.021)	*P=0.002*	0.018 (0.011 to 0.025)	*P<.0001*

Two Multiple regression models with MPI_{Conv} and MPI_{TDI} as Dependent Variables, and the mentioned parameters as independent variables. 95 % confidence intervals are cited in parentheses.

Figure 3.1 Bland-Altman plots of the Intra- and Interobserver Difference of MPI_{TDI} and MPI_{Conv}.



Solid lines indicate mean difference and dotted lines the 95% limits of agreement.

Paper II

The aim of this paper was to define normal values of the cardiac time intervals obtained by TDI M-mode through the MV, and to evaluate the association of MPI_{TDI} and MPI_{Conv}, with established echocardiographic and invasive measures of systolic and diastolic function.

In participants from the echocardiographic sub study of the Copenhagen City Heart Study without hypertension, diabetes, IHD, heart failure (CHF) or atrial fibrillation (n=989), normal values of the cardiac time intervals were assessed (Table 3.2). IVRT, IVRT/ET and MPI all increased significantly with increasing age in both genders (p<0.001 for all). IVCT, ET, IVRT/ET, and MPI differed significantly between male and female gender (Table 3.2).
In our invasive validation population (n=44), MPI_{TDI} was significantly associated with invasive (dP/dt max) and echocardiographic measures of systolic (LVEF, GLS and GL SR s) and diastolic function (e', GL SR e), whereas MPI_{Conv} was significantly associated with LVEF, e' and GL SR e (Table 3.3).

Table 3.2 Normal values of the cardiac time intervals in healthy participants stratified according to age category and gender

	Women (n=553)					Men (n=421)					
	Overall (n=553)	Age category 20 to 39 (n=150)	Age category 40 to 59 (n=252)	Age category 60 or above (n=151)	*p-value for age category difference*	Overall (n=421)	Age category 20 to 39 (n=101)	Age category 40 to 59 (n=210)	Age category 60 or above (n=110)	*p-value for age category difference*	*p-value for gender difference*
IVRT (ms)	92 (20)	78 (16)	93 (16)	106 (20)	*<0.001*	94 (20)	78 (15)	95 (16)	109 (18)	*<0.001*	*0.13*
IVCT (ms)	36 (13)	32 (12)	37 (12)	38 (14)	*<0.001*	34 (11)	35 (11)	33 (11)	36 (12)	*0.07*	*0.012**
ET (ms)	293 (21)	291 (19)	296 (20)	289 (23)	*0.001*	281 (24)	284 (19)	280 (23)	279 (28)	*0.34*	*<0.001**
IVRT/ET	0.32 (0.07)	0.27 (0.05)	0.31 (0.06)	0.37 (0.07)	*<0.001*	0.34 (0.08)	0.28 (0.06)	0.34 (0.06)	0.40 (0.08)	*<0.001*	*<0.001**
IVCT/ET	0.12 (0.05)	0.11 (0.04)	0.13 (0.04)	0.13 (0.05)	*<0.001*	0.12 (0.04)	0.13 (0.04)	0.12 (0.04)	0.13 (0.05)	*0.10*	*0.61*
MPI	0.44 (0.10)	0.38 (0.08)	0.44 (0.08)	0.51 (0.10)	*<0.001*	0.46 (0.10)	0.40 (0.08)	0.46 (0.09)	0.53 (0.10)	*<0.001*	*0.002**

*BMI=Body Mass Index; LVMI=Left Ventricular Mass Index; LVIDd= left ventricular dimension in end-diastole; LAD=Left atrium diameter in end-systole; DT=deceleration time of early diastolic inflow; IVCT=Isovolumic Contraction Time; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI = Myocardial Performance Index. Numbers in parenthesis indicates standard deviation. * remained statistical significantly different between the genders after multivariable adjustment for age, BMI, heart rate, systolic and diastolic blood pressure, LVMI, LVIDd, LAD, and DT*

Table 3.3 Regression Models with Myocardial Performance index obtaines by the convention method (MPI_{Conv}) and by the TDI M.mode method (MPI_{TDI}) as Dependent Variables (n=44)

	MPI_{TDI}		$MPI_{Conv.}$	
	Beta (95% CI)	*p-value*	Beta (95% CI)	*p-value*
Invasive measures of systolic and diastolic function:				
dP/dt max, per 100 mmHg/sec increase	-0.015 (-0.029 to -0.000)	*0.047*	0.011 (-0.005 to 0.0263)	*0.18*
dP/dt min, per 100 mmHg/sec decrease	0.012 (-0.003 to 0.027)	*0.12*	-0.001 (-0.017 to 0.016)	*0.94*
Conventional and novel echocardiographic measures of systolic and diastolic function:				
LVEF, per 1 % increase	-0.743 (-1.338 to -0.148)	*0.016*	-0.613 (-1.220 to -0.007)	*0.048*
e', per 1 cm/sec decrease	0.035 (0.018 to 0.053)	*<0.001*	0.021 (0.001 to 0.040)	*0.026*
E/e', per 1 increase	0.003 (-0.007 to 0.013)	*0.56*	0.002 (-0.008 to 0.011)	*0.74*
GLS (%), per 1 % decrease	0.021 (0.010 to 0.033)	*0.001*	0.009 (-0.004 to 0.022)	*0.16*
GL SR s, per 1 sec^{-1} decrease	0.525 (0.306 to 0.745)	*<0.001*	0.240 (-0.002 to 0.482)	*0.051*
GL SR e, per 1 sec^{-1} increase	-0.481 (-0.618 to -0.343)	*<0.001*	-0.361 (-0.511 to -0.210)	*<0.001*

dP/dt max= the rate of LV pressure rise in early systole; dP/dt min= the rate of LV pressure decline in early diastole; LVEF=Left Ventricular Ejection Fraction; E=peak transmitral early diastolic inflow velocity; e'=average peak early diastolic longitudinal mitral, GLS = Global Longitudinal Strain; GL SR s = Global Longitudinal systolic strain rate; GL SR e = Global Longitudinal early diastolic strain rate

Paper III

The aim of this paper was to evaluate the prognostic value of the cardiac time intervals and MPI, obtained by TDI M-mode method in patients with ST-Segment Elevation Myocardial Infarction (STEMI) treated with Primary Percutaneous Coronary Intervention (pPCI).

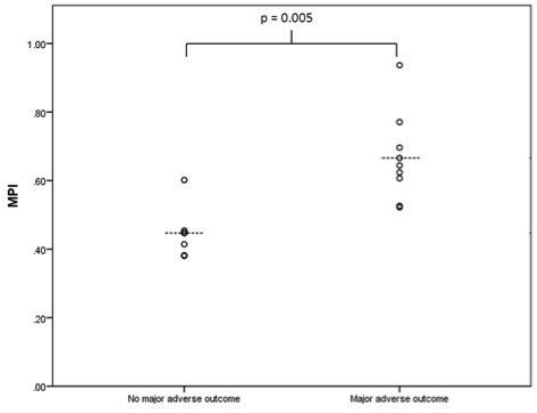
Only the IVRT/ET and the MPI remained independent predictors of the combined outcome after adjusting for age, gender, peak TnI, previous acute myocardial infarction (AMI), LVEF, GLS, diastolic function grade, LVIDd/BSA and LVMI in patients with STEMI undergoing pPCI (Table 3.4). Even in patients with atrial fibrillation the MPI was significantly higher in patients with an adverse outcome (0.45 (95% confidence interval (CI) 0.34-0.55) vs. 0.67 (95% CI 0.58-0.76), p=0.005) (Figure 3.2). Even after adjusting for age, gender and LVEF the MPI remained significantly higher in the group with an adverse outcome (0.44, 95% CI=(0.29-0.58) vs. 0.67, 95% CI=(0.56-0.79), p=0.026). The intraobserver variability analysis showed a mean difference ± SD of -0.004 ± 0.029 (Coefficient of variation (CV) 6%) for patients with sinus rhythm and 0.031 ± 0.055 (CV 9%) for patients with atrial fibrillation (Figure 3.3). The interobserver variability analysis showed a mean difference of ± SD of -0.022 ± 0.084 (CV 16%) for patients with sinus rhythm and 0.017 ± 0.096 (CV 16%) for patients with atrial fibrillation (Figure 3.3).

Table 3.4 Unadjusted and adjusted Cox proportional hazards regression models depicting the combined indexes of the cardiac time intervals as predictors of outcome

	Combined endpoint (96 events)		CHF (53 events)		re-MI (25 events)		Mortality (33 events)	
	Hazard Ratio (95% CI)	*P-value*	Hazard Ratio (95% CI)	*P-value*	Hazard Ratio (95% CI)	*P-value*	Hazard Ratio (95% CI)	*P-value*
Unadjusted model:								
IVRT/ET per 0.1 increase	1.34 (1.14-1.57)	*<0.001*	1.28 (1.03-1.59)	*0.028*	1.40 (1.04-1.89)	*0.025*	1.12 (0.84-1.50)	*0.44*
IVCT/ET per 0.1 increase	1.53 (1.26-1.86)	*<0.001*	1.68 (1.34-2.11)	*<0.001*	1.39 (0.94-2.08)	*0.10*	1.41 (0.99-2.00)	*0.06*
MPI per 0.1 increase	1.30 (1.16-1.46)	*<0.001*	1.32 (1.14-1.54)	*<0.001*	1.31 (1.05-1.63)	*0.015*	1.17 (0.95-1.43)	*0.15*
Multivariable model adjusted for age, gender, peak TnI, pre-MI, LVEF, diastolic function grade, LVMI and LVIDd/BSA:								
IVRT/ET per 0.1 increase	1.29 (1.08-1.54)	*0.005*	1.21 (0.94-1.56)	*0.15*	1.18 (0.81-1.72)	*0.40*	1.20 (0.89-1.60)	*0.23*
IVCT/ET per 0.1 increase	1.42 (1.00-2.02)	*0.053*	1.43 (0.90-2.26)	*0.13*	1.34 (0.63-2.89)	*0.45*	1.42 (0.77-2.60)	*0.26*
MPI per 0.1 increase	1.26 (1.09-1.46)	*0.002*	1.22 (0.99-1.50)	*0.06*	1.17 (0.86-1.60)	*0.32*	1.20 (0.94-1.52)	*0.15*
Multivariable model adjusted for age, gender, peak TnI, pre-MI, GLS, diastolic function grade, LVMI and LVIDd/BSA:								
IVRT/ET per 0.1 increase	1.30 (1.08-1.56)	*0.005*	1.22 (0.94-1.58)	*0.14*	1.26 (0.86-1.84)	*0.23*	1.20 (0.88-1.64)	*0.26*
IVCT/ET per 0.1 increase	1.43 (0.98-2.08)	*0.06*	1.53 (0.93-2.49)	*0.09*	1.54 (0.70-3.38)	*0.28*	1.16 (0.59-2.28)	*0.66*
MPI per 0.1 increase	1.27 (1.09-1.48)	*0.002*	1.25 (1.00-1.55)	*0.046*	1.25 (0.92-1.71)	*0.16*	1.16 (0.89-1.52)	*0.26*
Multivariable model adjusted for age, gender, peak TnI, pre-MI, LVEF, GLS, diastolic function grade, LVMI and LVIDd/BSA:								
IVRT/ET per 0.1 increase	1.28 (1.07-1.53)	*0.008*	1.22 (0.94-1.57)	*0.14*	1.14 (0.77-1.68)	*0.51*	1.18 (0.87-1.61)	*0.29*
IVCT/ET per 0.1 increase	1.30 (0.89-1.90)	*0.18*	1.36 (0.83-2.24)	*0.23*	1.25 (0.56-2.75)	*0.59*	1.13 (0.58-2.20)	*0.72*
MPI per 0.1 increase	1.24 (1.07-1.45)	*0.005*	1.22 (0.98-1.51)	*0.08*	1.14 (0.82-1.57)	*0.44*	1.15 (0.88-1.49)	*0.30*

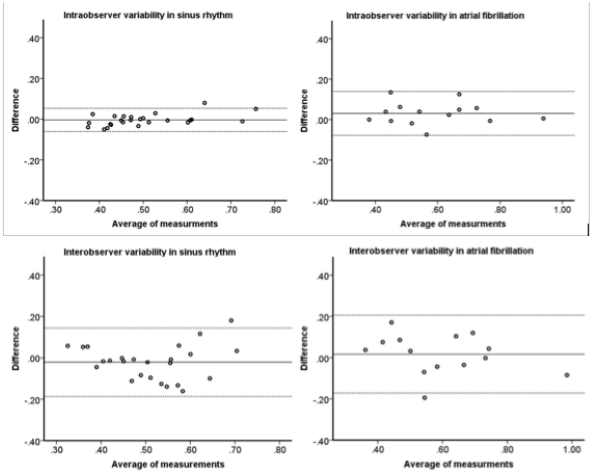
IVRT=Isovolumic Relaxation Time; IVCT=Isovolumic Contraction Time; ET=Ejection Time; MPI=Myocardial Performance Index; peak TnI=Peak Troponin I; Pre-MI=Previous Acute Myocardial Infarction; LVEF=Left Ventricular Ejection Fraction; LVMI=Left Ventricular Mass Index; LVIDd=Left Ventricular Internal Diameter in Diastole; BSA=Body Surface Area, GLS=peak Global Longitudinal systolic Strain; CHF=Heart Failure; re-MI= new myocardial infarction

Figure 3.2 MPI in patients with atrial fibrillation stratified according to outcome



The MPI for patients with atrial fibrillation divided according to outcome. Circles indicate absolute values, dotted lines indicate means. MPI = Myocardial Performance Index.

Figure 3.3 Intra- and interobserver variability analysis



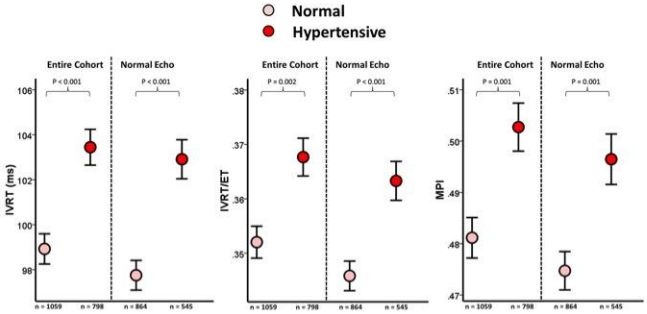
Bland-Altman plots of intra- and interobserver differences of myocardial performance index assessed by color tissue Doppler imaging M-mode through the mitral leaflet for patients with sinus rhythm (n=25) and for patients with atrial fibrillation (n=14) showing mean difference (solid lines) and 95% limits of agreement (dotted lines).

Paper IV

The aim of this paper was to investigate if the cardiac time intervals were able to identify miniscule cardiac impairments in individuals with hypertension, and if the time intervals were affected according to BP severity and left ventricular geometry. Additionally, to investigate if cardiac time intervals can be used to predict hypertension related diseases such as ischemic cardiovascular diseases.

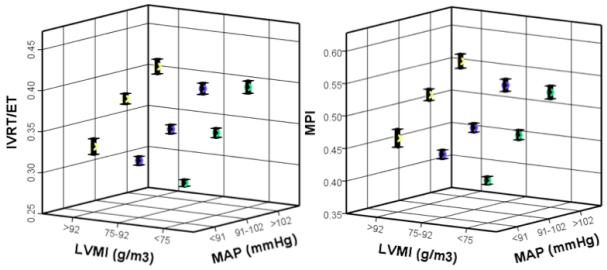
After multivariable adjustment for clinical variables the IVRT, IVRT/ET and MPI, remained significantly impaired in persons with hypertension compared to participants without (Figure 3.4). Furthermore, the IVRT, the IVRT/ET, and the MPI, remained significantly impaired after multivariable adjustment when the analysis was confined to persons with a normal conventional echocardiography (Figure 3.4). Additionally, they displayed a significant dose-response relationship, with increasing severity of elevated BP and increasing LVMI (p<0.001 for all)(Figure 3.5). The IVRT/ET and MPI were powerful and independent predictors of future ischemic cardiovascular disease (ICVD) especially in participants with known hypertension (Figure 3.6). In addition, reclassification analysis demonstrated, that adding IVRT/ET or MPI, to the clinical predictors from the Framingham Risk score [49] and the SCORE risk chart [50] (age, gender, cholesterol, smoking status and systolic BP), yielded better predicting models with significant increase in the categorical NRI of 2.27% (95% CI 0.17-4.37%, p=0.034) for IVRT/ET and 4.02% (95% CI 1.50-6.53%, p=0.002) for the MPI, respectively. Additionally, reclassification analysis demonstrated, that adding IVRT/ET or MPI, to a model also including the clinical predictors from the newer European Society of Hypertension/European Society of Cardiology (ESH/ESC) risk chart [51] (age, gender, smoking status, cholesterol, diabetes, systolic BP, diastolic BP, LVH, chronic kidney disease (defined as estimated Glomerular Filtration Rate (eGFR)≤60 mL/min/1,73 m2), IHD and previous ischemic stroke (IS)), yielded better predicting models with significant increase in the categorical NRI of 3.41% (95% CI 0.79-6.03%, p=0.011) for IVRT/ET and 3.44% (95% CI 0.39-6.48%, p=0.027) for the MPI, respectively.

Figure 3.4 Systolic and diastolic function determined by the cardiac time intervals in participants with and without hypertension after multivariable adjustment



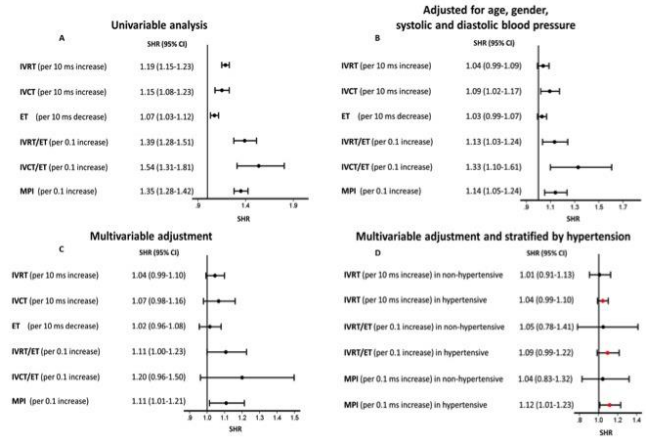
Multivariable adjusted means are depicted for the cardiac time intervals in participants with and without hypertension for both the entire study cohort and the subgroup with a normal conventional echocardiographic examination. Multivariable adjustment designates adjustment for age, gender, body mass index, estimated glomerular filtration rate, heart rate, diabetes, cholesterol, atrial fibrillation, ischemic heart disease and previous ischemic stroke. Normal echo designates the absence of left ventricular hypertrophy, dilatation and ejection fraction<50%, and severe diastolic dysfunction. Bars indicate standard error. IVRT=Isovolumic Relaxation Time; ET=Ejection Time.

Figure 3.5 The association between the cardiac time intervals and LVMI and MAP



The association between the combines cardiac time intervals (VRT/ET and MPI) and the left ventricular mass index and mean arterial blood pressure. Participants were stratified into tertiles of the LVMI and MAP. Bars indicate standard error. LVMI=Left Ventricular Mass Index; MAP=Mean Arterial Blood Pressure; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI=Myocardial Performance Index.

Figure 3.6 The cardiac time intervals as predictors of future ischemic cardiovascular disease



Depicting the subdistribution hazard ratios (SHR) obtained from univariable analysis (Figure 3.6A), adjusted for age, gender, systolic and diastolic blood pressure (Figure 3.6B), and multivariable (Figure 3.6C) competing risk Cox proportional hazards regression models describing the cardiac time intervals as predictors of future hypertension related ICVD. The IVRT, IVRT/ET and the MPI are also stratified according to hypertension status (Figure 3.6D). Multivariable adjustment indicates adjustment for age, gender, BMI, eGFR, heart rate, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, cholesterol, smoking status, atrial fibrillation, IHD, previous ischemic stroke, LVEF<50%, diastolic dysfunction and LV hypertrophy. Depicting the SHR and the 95% confidence intervals. BMI=Body Mass Index; eGFR= estimated Glomerular Filtration Rate; LVEF=Left Ventricular Ejection Fraction; IVCT=Isovolumic Contraction Time; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI=Myocardial Performance Index. IHD= Ischemic Heart Disease.

Paper V

The aim of this paper was to investigate whether the combined indexes containing information on both systolic and diastolic function (IVRT/ET and MPI), provides prognostic information regarding the risk of future cardiovascular disease and cardiovascular mortality in the general population, incremental to clinical predictors and conventional echocardiographic measures of systolic and diastolic function.

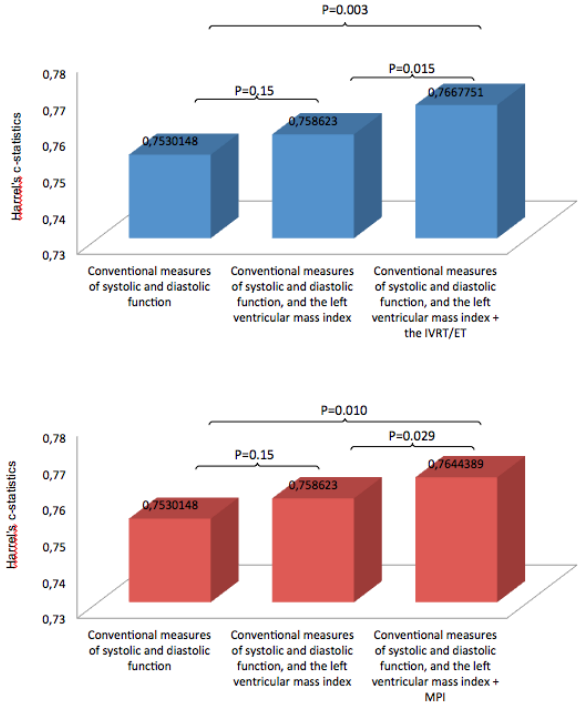
After multivariable adjustment for clinical predictors and conventional echocardiography, only the combined indexes, including information on both the systolic and diastolic performance (IVRT/ET and MPI), remained significant prognosticators (Table 3.5). Adding IVRT/ET or MPI to a model already including all other echocardiographic parameters resulted in a significant increase in the Harrell's c-statistics (Figure 3.7). Finally, reclassification analysis when adding the combined indexes (IVRT/ET or MPI), to clinical predictors (age, gender, body mass index (BMI), eGFR, heart rate, hypertension, diabetes, smoking status and atrial fibrillation), yielded better predicting models with a significant increase in the categorical NRI of 3.052% (95% CI 0.957-5.145%, p=0.004) for the IVRT/ET and 3.058% (95% CI 0.159-5.957%, p=0.039) for the MPI, respectively. In addition, when using continuous NRI, without using arbitrary risk categories, the predicting models were improved even further, with an increase in the continuous NRI of 19.2% (95% CI 3.2-33.0%) for the IVRT/ET and of 16.0% (95% CI 5.5-33.5%) for the MPI, respectively.

Table 3.5 Unadjusted and adjusted a competing risk Cox proportional hazards regression models depicting the cardiac time intervals as predictors of future major adverse cardiovascular ourcome (MACE).

	Harrell's c-statistics	Univariable		Model 1 Multivariable Adjustment		Model 2 Multivariable Adjustment	
		SHR (95% CI)	P-value	SHR (95% CI)	P-value	SHR (95% CI)	P-value
IVRT per 10 ms increase	0.62	1.20 (1.16-1.25)	<0.001	1.06 (1.02-1.12)	0.004	1.07 (1.00-1.14)	0.051
IVCT per 10 ms increase	0.57	1.19 (1.11-1.27)	<0.001	1.10 (1.02-1.19)	0.010	1.07 (0.98-1.17)	0.14
ET per 10 ms decrease	0.57	1.13 (1.08-1.18)	<0.001	1.05 (0.99-1.11)	0.12	1.01 (0.94-1.07)	0.84
IVRT/ET per 0.1 increase	0.64	1.44 (1.31-1.58)	<0.001	1.17 (1.08-1.27)	<0.001	1.16 (1.00-1.34)	0.047
IVCT/ET per 0.1 increase	0.59	1.71 (1.46-2.02)	<0.001	1.33 (1.10-1.60)	0.003	1.18 (0.96-1.45)	0.11
MPI per 0.1 increase	0.64	1.41 (1.33-1.50)	<0.001	1.17 (1.09-1.25)	<0.001	1.11 (1.03-1.23)	0.024

Model 1 is adjusted for age, gender, BMI, eGFR=Estimates Glomerular Filtration Rate; LVEF=Left Ventricular Ejection Fraction; LVMI=Left Ventricular Mass Index; E=peak transmitral early diastolic inflow velocity; A=peak transmitral late diastolic inflow velocity; DT=Deceleration Time of early diastolic inflow; e'=average peak early diastolic longitudinal mitral annular velocity determined by color TDI; IVCT=Isovolumic Contraction Time; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI=Myocardial Performance Index.

Figure 3.7 Incremental prognostic information by adding an assessment of the combined cardiac time intervals (the IVRT/ET and the MPI) to the conventional echocardiographic measures



The Harrell's c-statistic values obtained from the multivariable Cox proportional hazards regression models. Conventional measures of systolic and diastolic function includes: LVEF<50%, E/e', E/A-ratio, Dec time, LA dimension. Conventional measures of systolic and diastolic function, and the left ventricular mass index in-

cludes: LVEF<50%, E/e', E/A-ratio, Dec time, LA dimension and LVMI. LVEF = Left Ventricular Ejection Fraction; LVMI = Left Ventricular Mass Index; E = peak transmitral early diastolic inflow velocity; A = peak transmitral late diastolic inflow velocity; DT = deceleration time of early diastolic inflow; e' = average peak early diastolic longitudinal mitral annular velocity determined by color TDI; LA dimension = Left Atrium end-systolic diameter; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI = Myocardial Performance Index.

Discussion

Normal values of the cardiac time intervals obtained by TDI M-mode

This thesis is the first to assess the normal values of the cardiac time intervals obtained by TDI M-mode in a sample from the general population without cardiovascular disease and cardiovascular risk factors. We found that LV function as assessed by IVRT, IVRT/ET, and MPI all decreased with increasing age in both genders (Table 3.2). The decrease in LV cardiac function with increasing age as assessed by IVCT and IVCT/ET, was statistically significant in females but not in males (Table 3.2). ET decreased with increasing age in both genders; however this decrease was not statistically significant (Table 3.2). Other novel echocardiographic parameters detecting subtle myocardial impairments like two-dimensional strain echocardiography [52] and TDI [38], have previously, in accordance with our results, been demonstrated to detect miniscule LV dysfunction with increasing age despite the absence of any cardiovascular disease or risk factor.

IVCT, ET, IVRT/ET, and MPI all differed significantly between male and female genders (Table 3.2). Gender differences exist both in novel echocardiographic parameters like two-dimensional strain echocardiography [52] and TDI [38], but also in the cardiac dimensions obtained by conventional echocardiography [44], and in conventional measures of systolic [53] and diastolic function [38,44]. The discrepancy we found, that woman in general display better cardiac function than men, appears to be physiologically plausible and in accordance with previous studies [38,44,52,53].

Comparison between MP_{Conv} and MPI_{TDI}

We found that the absolute values of MPI_{Conv} and MPI_{TDI} were different [54]. The same result was seen in previous studies comparing MPI_{Conv} to MPI obtained from regional TDI velocity curves of the ventricular myocardium [12,26,27]. Additionally, MPI_{Conv} was influenced by several physical parameters compared to MPI_{TDI} (Table 3.1). MPI_{TDI} is based on analysis of the mitral leaflet moving passively depending on shifts in pressure and blood flow in the left ventricle and left atrium, whereas MPI_{Conv} is derived purely from blood flow. Hence, the difference in physical parameters that define the two methods may explain the discrepancy between the absolute values. Furthermore, it seems as if MPI based on simple cardiac mechanics are less confounded than MPI based on calculations from versatile blood flow patterns around the mitral valve, which may make the interpretation of MPI_{TDI} less complex.

Our results demonstrated that MPI_{TDI} (but not MPI_{Conv}) was significantly correlated with the invasive measure of contractility and systolic function dP/dt max (Table 3.3). The only other echocardiographic measure which was significantly correlated with dP/dt max was GL SR s, which previously has been demonstrated to be the most accurate marker of myocardial contractile function [55]. Therefore, MPI_{TDI} may be an accurate marker of myocardial contractile function as well.

Furthermore, MPI_{TDI} increased significantly with worsening systolic function determined by all the echocardiographic measures of systolic function (LVEF, GLS or GL SR s), whereas MPI_{Conv} only increased significantly with worsening LVEF (Table 3.3). Likewise, MPI_{TDI} increased with worsening diastolic function determined by the measures of diastolic function (e' or GL SR e), whereas MPI_{Conv} only increased significantly with worsening e' and GL SR e (Table 3.3). Our results illustrate that an ailing systolic or diastolic performance can be detected by an increasing value of the MPI when assessed by TDI M-mode. Furthermore, MPI_{TDI} seem superior to MPI_{Conv} in detecting an ailing systolic or diastolic performance regardless if evaluated with conventional echocardiographic, novel echocardiographic or invasive measures.

In the present thesis we also compared the reproducibility of the MPI_{Conv} and MPI_{TDI}. We found that the precision of the measurement of MPI improved when measured with the M-mode TDI method compared to the conventional method (Figure 3.1). These findings are in line with a previous study which showed that the time intervals obtained with the color TDI M-mode through the mitral leaflet was an accurate and reproducible method, especially when intervals were used to calculate MPI_{TDI} [14]. In contrast to our results, Tei and colleagues previously demonstrated good correlation between MPI_{Conv} and dP/dt max in a smaller study of patients with IHD [56]. However, like our results, several studies performed during the last decade, comparing MPI obtained by the conventional method as described by Tei and collegues [7,9] and by TDI, has demonstrated MPI obtained by TDI to be a superior method [14,27,57], both when comparing the reproducibility [14] and when comparing their diagnostic and prognostic utilities [27,57]. Likewise, we found that MPI_{TDI}, but not MPI_{Conv}, remained independently associated with overall mortality after multivariable adjustment. Additionally it is not possible to obtain cardiac time intervals from velocity curves in patients with atrial fibrillation regardless if they are obtained by the conventional method [7,9] or by the newer TDI method using regional myocardial velocity curves [10,11]. This is due to the absence of the A and a' velocity curves in patients with atrial fibrillation, which are needed to accurately obtain the time intervals by both methods. In contrast all cardiac time intervals can easily be obtained by the color TDI M-mode method regardless of the presence of atrial fibrillation. Thus, in patients with atrial fibrillation suffering from a STEMI, MPI_{TDI} can differentiate between high and low risk patients (Figure 3.2), even after adjustment for age, gender and LVEF. However, the reproducibility seems lower in patients with atrial fibrillation than in patients with sinus rhythm (Figure 3.3). Nevertheless the intra- and interobserver variability for MPI_{TDI} in patients with atrial fibrillation seems superior to the variability found for the conventional method described by Tei and colleagues in patients with sinus rhythm (Figure 3.1) [54], which provides more optimism for this new method.

Cardiac time intervals obtained by TDI M-mode in hypertension

In the present thesis we found that after multivariable adjustment, and when confining the analysis to participants with a normal conventional echocardiographic examination, only IVRT, IVRT/ET, and MPI remained significantly impaired in participants with hypertension (Figure 3.4). These results were expected, since it is well known that patients with hypertension primarily suffer from an impaired diastolic function and not an impaired systolic

function [58,59], why only the time intervals containing information about the diastolic function remained impaired after multivariable adjustment.

However, the pivotal finding in Figure 3.4 was that the cardiac time intervals were capable of identifying subtle impairments in the cardiac function in participants with hypertension, which were unnoticed by conventional echocardiography (Figure 3.4). Therefore, the cardiac time intervals, containing information about diastolic function, seem capable of identifying participants in the risk of hypertension related asymptomatic organ damage of the heart, despite of a normal conventional echocardiography. In accordance with our results, a previous small scale study including 62 hypertensive patients and 15 controls, also found IVRT and MPI to be the only cardiac time intervals demonstrating impaired cardiac function in patients with hypertension, despite of a normal systolic function [60]. Unfortunately, Cacciapuoti and colleagues did not evaluate the diagnostic utility of IVRT/ET in their study [60].

We found a significant linear dose-response relationship, between increasing severity of elevated blood pressure and incremental impairment in cardiac function determined by IVRT/ET and MPI (Figure 3.5). Likewise, a previous study demonstrated that MPI increased with increasing severity of hypertension according to left ventricular geometry [61]. Accordingly, we found that IVRT/ET and MPI displayed impaired cardiac function with increasing values of the LVMI (Figure 3.5) even after multivariable adjustment. These findings of incremental impairment of the cardiac time intervals (especially the IVRT/ET and MPI) with increasing BP and LVMI (Figure 3.5), are very important, because a potential future echocardiographic parameter for risk stratification in hypertension, should display incremental impairment in the measure with increasing BP, LVMI and in all types of pathological left ventricular geometry, since the risk of cardiovascular diseases increases continuously with increasing BP [62] and LVH [63,64].

In addition, another central observation in our study was that IVRT and MPI were capable in detecting miniscule cardiac dysfunction in participants with high normal BP compared to participants with normal BP, when confining our analysis to participants without hypertension and after adjustment for clinical variables. This is very important because it has previously been demonstrated that persons with high normal BP have increased risk of developing future hypertension [65] and increased risk of ICVD [66]. Thus, IVRT and MPI reveal impaired cardiac function in persons with high normal BP, why these time intervals may aid in the early identification of persons in high risk of future fulminant hypertension and ICVD.

Prognostic utility of cardiac time intervals obtained by TDI M-mode

Previous studies have already evaluated the prognostic value of the MPI either obtained by the conventional method as proposed by Tei and colleagues [7,9] or by using the regional TDI velocity curves [10,11], in various populations, e.g., patients after acute myocardial infarction [67,68], elderly men [69,70], patients with cardiac amyloidosis [8], with idiopathic-dilated cardiomyopathy [71], with isolated diastolic dysfunction [34], and in patients with systolic heart failure [72]. The present thesis is the first to evaluate the prognostic value of all the cardiac time intervals and the MPI assessed by TDI M-mode through the mitral leaflet in a STEMI population treated by pPCI and a low risk general population.

We found that impairment in all the cardiac time intervals was individually associated with increased risk of MACE (Table 3.5) and ICVD (Figure 3.6) in the general population. In our smaller study of STEMI patients we found that the cardiac time intervals when evaluated separately provided ambiguous and not easily comprehensible prognostic information. However when we corrected the IVCT and the IVRT for heart rate by dividing them with ET30, both of the combined indexes provided incremental prognostic information with increasing tertile [73]. This result is interesting since neither the IVRT nor the ET provided incremental prognostic information when evaluating them separately, but when combing the information about the systolic and the diastolic performance in one index (and thereby also indirectly adjusting for heart rate), the prognostic information becomes evident [73]. However, after multivariable adjustment for other clinical and echocardiographic predictors, only the combined indexes containing information on both the systolic and diastolic performance (IVRT/ET and MPI) remained independent predictors of future cardiovascular outcomes regardless which population and outcomes were examined (Table 3.4, 3.5 and Figure 3.6). The superiority of the IVRT/ET and the MPI compared to the remaining cardiac time intervals in predicting outcomes, regardless of population, may reflect that they detect myocardial dysfunction, irrespective of myocardial sufferings from an ailing systolic or diastolic function [73]. In contrast, the remaining cardiac time intervals only detect isolated diastolic (IVRT) or systolic (IVCT, ET and IVCT/ET) dysfunction, respectively. Similarly, when using TDI velocities in predicting outcome, studies have demonstrated that when combining the information on systolic (s') and diastolic function (e' and a') in one risk stratification strategy, the prognostic information obtained improves [39,74,75]. These and our results emphasize the prognostic information gained by combining the interdependent and coherent relations of systolic and diastolic function in a simple and feasible index.

Incremental prognostic value of adding an assessment of the IVRT/ET and the MPI obtained by TDI M-mode

We found that the combined indexes containing information on both the systolic and diastolic performance (IVRT/ET and MPI) remained not only independent predictors of future MACE in the general population, but provided incremental prognostic value to all other echocardiographic predictors of MACE (Figure 3.7). In addition, reclassification analysis, using arbitrary risk categories, when adding the combined indexes (IVRT/ET or MPI) to our clinical predictors, yielded better predicting models with significant increases in the categorical NRI of approximately 3.1% for both IVRT/ET and MPI. In addition, when using continuous NRI, without using arbitrary risk categories, the predicting models were improved even further, corresponding with an increase in the continuous NRI of 19.2% for the IVRT/ET and of 16.0% for the MPI, respectively. In comparison, neither of the conventional echocardiographic parameters evaluating systolic or diastolic function (LVEF<50%, E/e', LAD or E/A-ratio) or the LVMI yielded better predicting models when added to our clinical predictors. Additionally, when evaluating the risk of ICVD, adding IVRT/ET or MPI, to the clinical predictors from the Framingham Risk Score [49], the SCORE risk chart [50] and the ESH/ESC risk chart [51] yielded better predicting models with significant increases in the categorical NRIs. However, we found that hypertension significantly modified the relationship between all the cardiac time intervals containing information about diastolic function (IVRT, IVRT/ET and MPI) and the risk of future ICVD. These cardiac time intervals

primarily predicted hypertension related ICVD in participants with hypertension but not in participants without hypertension (Figure 3.6). Similarly, a previous study demonstrated that the presence of diastolic dysfunction, determined by a short deceleration time, only predicted all-cause mortality in hypertensive heart failure patients and not in heart failure patients without hypertension [76]. Therefore, in participants suffering from hypertension, who are in particularly high risk of future ICVD [77], the IVRT/ET and MPI may be useful cardiac measures for risk stratification. They are simple to obtain, have high reproducibility (Figure 3.1 and 3.3) [14] and encompasses information on both BP severity, left ventricular geometry and risk of future ICVD. The superiority of the IVRT/ET and the MPI to all the conventional echocardiographic parameters evaluating systolic or diastolic function, may again reflect that they detect very miniscule impairment in the myocardial function, irrespective if the myocardium suffers from an ailing systolic or diastolic function [73]. Therefore, the IVRT/ET and MPI identify subtle impairments in the cardiac function (both systolic and diastolic), that may be unnoticed by conventional echocardiography [35,36], and can improve risk stratification strategies evaluating future risk of fulminant cardiovascular disease over and above the traditional predictors, in the low risk general population. In contrast, it seems that adding an assessment of the conventional echocardiographic parameters to the clinical risk factors, does not improve the risk stratification strategy to identify high risk people in the general population.

Limitations

Certain limitations have to be taken into account in relation to the reported results.

In paper I and III we did not investigate the cause of death. However, we assume that individuals with cardiac dysfunction determined by echocardiography are more likely to die due to cardiovascular causes and that, if we were able to limit our analysis to cardiovascular deaths in paper I and III, the prognostic impact of MPI (and the other time intervals) would be even greater. This assumption is supported by our results found in paper V where cardiac mortality was included in the combined endpoint of MACE.

In paper III and in the INVASIVE study (part of paper II) I was not blinded for other echocardiographic parameters, in the sense that I also measured other echocardiographic parameters when measuring the cardiac time intervals, which theoretically could be a potential for bias. Nevertheless the combined indexes provide independent prognostic information after adjustment for all other systolic and diastolic parameters in our study population of paper III, which would not be the case if the combined indexes only contain prognostic information gained from other echocardiographic parameters. In addition, this potential bias should affect the association between MPI_{TDI} and MPI_{Conv} with established echocardiographic and invasive measures of systolic and diastolic function equally in the INVASIVE population, and cannot explain why the MPI_{TDI}, but not MPI_{Conv}, is associated with most invasive and established echocardiographic measures of systolic and diastolic function. Furthermore, we were blinded to other echocardiographic parameters, in the sense that we did not measure other echocardiographic parameters but only TDI velocities and the cardiac time intervals in the echocardiographic sub study of the Copenhagen City Heart Study.

In paper III echocardiography was performed median 2 days after pPCI, which was the typical timespan for echocardiographic risk-assessment at our institution, where various degree of myocardial stunning might be present and may impact the cardiac time intervals. However myocardial function can be affected for as long as 2 weeks after the intervention [78], at which point the myocardial function could be influenced by long-term compensatory mechanisms and the effects of additional therapeutic interventions, so the optimal time for risk assessment after pPCI is to be investigated.

In the echocardiographic sub study of the Copenhagen City Heart study (paper I, II, IV and V), pulsed-wave TDI, pulmonary venous flow or Valsalva maneuver were not performed. In paper IV we therefore only defined diastolic dysfunction as the presence of severe diastolic dysfunction as determined from the DT and E/A-ratio [79]. Participants with milder degrees of diastolic dysfunction might have been overlooked in paper IV where a normal conventional echocardiography was defined as the absence of LVH, dilatation and ejection fraction<50%, and severe diastolic dysfunction. However, it is unlikely that many of our participants had mild or pseudonormal diastolic dysfunction without concomitant structural heart disease or reduced LVEF. In addition, in paper III (the "Prognosis After Percutaneous Coronary Intervention" population) where pulsed-wave TDI was performed and we therefore were able to grade the diastolic function, we found that the time intervals provided independent prognostic information after adjustment for diastolic function grade.

Our study population undergoing heart catheterization and invasive measures of systolic and diastolic function in paper II was small, only comprising 44 individuals, which limits our study. However, the previous studies evaluating the association of the cardiac time intervals with invasive measures of systolic and diastolic function have included a lower number of individuals [56,80], which makes the validity of our results greater.

Lastly, results reported in this thesis do not demonstrate causal mechanisms, but only associations. By adjusting for known confounders we tried to scrutinize our results. Additionally, since this thesis only includes prospective non-randomized observational studies, the risk of residual confounders always exists.

Conclusion

Based on the findings in the present thesis the following conclusions are drawn:

1) MPI_{TDI} is a measure of combined cardiac time intervals with superior reproducibility, less confounded by association with clinical characteristics, and provides superior prognostic information in a low-risk population when compared to MPI_{Conv}.

2) The normal values of the cardiac time intervals differ between genders, displaying that women in general exhibit better cardiac function. Furthermore, they deteriorated with increasing age. The MPI_{TDI} (but not MPI_{Conv}) is significantly associated with most invasive and established echocardiographic measures of systolic and diastolic function.

3) The combined cardiac time intervals which include information on both the systolic and diastolic function in one index (IVRT/ET and MPI) provides independent prognostic information, regardless of rhythm, incremental to conventional and novel echocardiographic

parameters of systolic and diastolic function in patients with STEMI treated with pPCI.

4) The cardiac time intervals display a significant dose-response relationship, with increasing severity of elevated BP and increasing left ventricular mass index. Furthermore, they identify impaired cardiac function in participants with hypertension, not only independently of conventional risk factors, but also in participants with a normal conventional echocardiographic examination. Additionally, in the general population, the IVRT/ET and MPI, are powerful and independent predictors of future hypertension related ICVD especially in participants with known hypertension. They provide prognostic information incremental to clinical variables from the Framingham Risk Score, the SCORE risk chart and the ESH/ESC risk chart.

5) In the general population, the combined cardiac time intervals which include information on both the systolic and diastolic function in one index (IVRT/ET and MPI) are powerful and independent predictors of future major cardiovascular events. In addition, they provide prognostic information incremental to clinical variables and conventional echocardiographic measures of systolic and diastolic function.

Perspectives

The results in the present thesis demonstrate that a novel, simple and reproducible method of obtaining the cardiac time intervals and the index of combined systolic and diastolic function, the MPI, may be useful to identify high risk persons both in the general population and in patients suffering a STEMI. Additionally, this novel method seem superior to the conventional method of obtaining the cardiac time intervals. These results motivate to include an assessment of the cardiac time intervals by TDI M-mode when preforming echocardiography. However, our results do not indicate that an assessment of the cardiac time intervals should replace conventional echocardiography, but rather that the time intervals provide additional information, incremental to the information we can gain from conventional echocardiography.

Several results from the present thesis need to be investigated further. Firstly, we are the first to investigate this method, why additional validation in other populations is necessary. We found that it was possible to obtaining the cardiac time intervals and the MPI with reasonable reproducibility in patients with atrial fibrillation. Furthermore, it seems to be a prognostic marker in this patient category. The potential to use this index in patients with atrial fibrillation is promising and has to be investigated further in prospective studies. Especially in this patient category where heart rate variability is present and often limits the usability of the conventional echocardiographic measures, the MPI, which is corrected for heart rate by the division with ET [30], might be a fast, accurate and superior measure of systolic and diastolic function in one index.

The association between ailing cardiac time intervals and adverse outcome also has to be investigated in intervention studies. Does intervention improve the cardiac time intervals and if so do these improvements result in a significant better prognosis.

It seems as if the cardiac time intervals (IVRT/ET and MPI) are especially useful in patients with hypertension. It would be of interest to test the usability of the time intervals to risk stratify patients in an actual hypertension study.

In general, especially the prognostic capabilities of the MPI obtained by TDI M-mode would be of interest to validate in various patient populations, which might pave the way for the cardiac time intervals to be used in the clinical setting in the future?

Summary

Background: The preservation of normal cardiac time intervals is intimately related to normal cardiac physiology and function. In the ailing myocardium, the cardiac time intervals will change during disease progression. As left ventricular (LV) systolic function deteriorates, the time it takes for myocardial myocytes to achieve an LV pressure equal to that of aorta increases, resulting in a prolongation of the isovolumic contraction time (IVCT). Furthermore, the ability of myocardial myocytes to maintain the LV pressure decreases, resulting in reduction in the ejection time (ET). As LV diastolic function declines further, early diastolic relaxation proceeds more slowly, explaining the prolongation of isovolumic relaxation time (IVRT). Consequently, the IVRT/ET and the myocardial performance index (MPI), defined as (IVCT + IVRT)/ET, will detect cardiac dysfunction with an increase, irrespective of whether the LV is suffering from impaired systolic or diastolic function. A novel method of evaluating the cardiac time intervals has recently evolved. Using Tissue Doppler Imaging (TDI) M-mode through the mitral valve (MV) to estimate the cardiac time intervals may be an improved method reflecting global cardiac time intervals and eliminating beat-to-beat variation and regional differences. However, little is known about the usability of the cardiac time intervals obtained by this novel method.

Objective: To compare the reproducibility, association with clinical characteristics, association with established echocardiographic and invasive measures of systolic and diastolic function, and the usefulness in predicting all-cause mortality in the general population, for the MPI obtained by the conventional method (MPI_{Conv}) and by the novel method of obtaining the MPI (MPI_{TDI}). Furthermore, to define normal values of the cardiac time intervals obtained by TDI M-mode through the MV. In addition, to investigate if the cardiac time intervals are able to identify miniscule cardiac impairments in individuals with hypertension, which are unrecognized by conventional echocardiography. Lastly, to evaluate the prognostic value of the cardiac time intervals and the combined indexes of systolic and diastolic performance, IVRT/ET and MPI, obtained by TDI M-mode method in low risk participants from the general population and in high risk patients with ST-Segment Elevation Myocardial Infarction (STEMI) treated with Primary Percutaneous Coronary Intervention (pPCI).

Method: The research involved three prospective observational studies. Within the Copenhagen City Heart Study, a large community based study of cardiovascular risk factors, the cardiac time intervals were obtained by TDI M-mode in 1,915 participants. Additionally, in the present thesis the cardiac time intervals were also obtained in 391 patients who were admitted with a STEMI and treated with pPCI at Gentofte Hospital. All patients were examined by echocardiography median 2 days (IQR 1-3) after the STEMI. Lastly, we also included a population (n=44) of patients who underwent left heart ventricular catheterization and had the MPI_{TDI} and MPI_{Conv} measured. In all cohorts baseline data and an assessment of cardiac function were obtained by conventional

echocardiography. Follow-up data on admission were obtained from the Danish National Board of Health's National Patient Registry and from the national Danish Causes of Death Registry.
Results: MPI_{TDI} had superior reproducibility, was less confounded by association with clinical characteristics, and provided superior prognostic information in a low-risk population as compared to MPI_{Conv}. Additionally, the MPI_{TDI} (but not MPI_{Conv}) was significantly associated with most invasive and established echocardiographic measures of systolic and diastolic function.
The cardiac time intervals displayed a significant dose-response relationship, with increasing severity of elevated blood pressure and increasing left ventricular mass index. They identified impaired cardiac function in participants with hypertension, not only independent of conventional risk factors, but also in participants with a normal conventional echocardiographic examination. The combined cardiac time intervals which include information on both the systolic and diastolic function in one index (IVRT/ET and MPI) provided independent prognostic information, regardless of rhythm, incremental to conventional and novel echocardiographic parameters of systolic and diastolic function both in the general population and in patients with STEMI treated with pPCI.
Conclusion: The novel TDI M-mode method is superior to the conventional method of obtaining the MPI, both when comparing reproducibility, validity, prognostic power and the ability to display both the systolic and diastolic function in one index. The cardiac time intervals obtained by TDI M-mode reveal impaired cardiac function in persons with hypertension even when conventional echocardiography gives the impression of normal cardiac function. The combined cardiac time intervals which include information on both the systolic and diastolic function in one index (IVRT/ET and MPI) provide prognostic information incremental to conventional and novel echocardiographic parameters of systolic and diastolic function both in the general population and in patients with STEMI treated with pPCI.

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