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

Biering-Sørensen et al: Cardiac Time Intervals by TDI Predicts Outcome after pPCI

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DOI: 10.1161/CIRCIMAGING.112.000230

Abstract

Background — Color Tissue Doppler Imaging (TDI) M-mode through the mitral leaflet is an easy and precise method to estimate all cardiac time intervals from one cardiac cycle and thereby obtaining the Myocardial Performance Index (MPI). However, the prognostic value of the cardiac time intervals and the MPI assessed by color TDI M-mode through the mitral leaflet in patients with ST-segment Elevation Myocardial Infarction (STEMI) is unknown.

Methods and Results — In total 391 patients were admitted with a STEMI, treated with primary Percutaneous Coronary Intervention (pPCI) and were examined by echocardiography median 2 days after the STEMI. Outcome was assessed according to death (n=33), hospitalization with heart failure (CHF, n=53) or new myocardial infarction (re-MI, n=25). Follow-up time was median 25 months. The population was stratified according to tertiles of the MPI. The risk of a re-MI, being admitted with CHF or death, increased with increasing tertile of MPI, being approximately three times as high for the third tertile compared to the first tertile (HR 2.8, 95% CI 1.7 to 4.7, p<0.001). MPI provided independent prognostic information in a multivariable Cox regression model adjusted for age, gender, previous MI, peak troponin, systolic and diastolic echocardiographic parameters, with a HR of 1.24 (p=0.005) for the combined endpoint per each 0.1 increase in MPI.

Conclusions — MPI assessed by TDI M-mode is a simple and reproducible measure, which 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.

Key Words: tissue Doppler imaging echocardiography, myocardial performance index, cardiac time intervals, STEMI, outcome
Preservation of normal time intervals is closely associated with normal cardiac biochemistry, mechanics and physiology. Therefore cardiac time intervals have been the target for investigation as markers of cardiac dysfunction for decades. The main concern has been how to obtain these cardiac time intervals in a fast, easy, non-invasive and reproducible manner. Tei and colleagues proposed to overcome this problem by obtaining the intervals from pulsed-Doppler echocardiography of the left ventricular (LV) outflow tract and mitral valve (MV) inflow and hereby calculating the index of combined systolic and diastolic performance, the Myocardial Performance Index (MPI). Tissue Doppler Imaging (TDI) is an alternative non-invasive approach to obtain the cardiac time intervals and thereby the MPI. With this method the time intervals can be obtained from one projection and one cardiac cycle. In contrast, with the conventional method described by Tei and colleagues, the time intervals are obtained from two projections and at least two cardiac cycles, and may therefore be prone to errors caused by heart rate variability, which is not a concern using TDI. However, the time intervals obtained from the TDI velocity curves are prone to regional differences in myocardial biochemistry, mechanics and physiology, which will display regional differences in the cardiac time intervals. This can be overcome by analysing the global time intervals through evaluating the MV movement by a simple color TDI M-mode analysis instead of the regional velocity curves. Thus using color TDI M-mode through the mitral leaflet to estimate the cardiac time intervals is an improved method reflecting global cardiac time intervals and eliminating beat-to-beat variation. The advantage and validity of this method has previously been demonstrated.

Efforts to improve risk-stratification, clarify pathophysiological mechanisms and identify targets for therapeutic intervention are of the utmost importance in patients with ST-Segment Elevation Myocardial Infarction (STEMI). Echocardiography after an acute myocardial infarction (AMI) is a routine procedure for risk-stratification. The systole and the diastole are
interdependent and coherent\textsuperscript{11,12}, therefore improved risk stratification by combining the systolic and diastolic performance in one index may be possible. The aim of this study was 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 STEMI treated with Primary Percutaneous Coronary Intervention (pPCI).

**Methods**

**Study population:** 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 $\geq$2 mm in at least 2 contiguous precordial ECG-leads or $\geq$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 $\mu$g/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 $\geq$7 mmol/L or non-fasting plasma glucose concentration $\geq$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.

**Echocardiography:** Echocardiography was performed using Vivid 7 ultrasound systems (GE Healthcare, Horten Norway) with a 3.5-MHz transducer by experienced sonographers. At our institution echocardiography is performed during the initial 5 days of admission (median 2,
IQR: 1-3). All participants were examined with conventional two-dimensional echocardiography, pulsed-wave and color TDI according to standardized protocols. All echocardiograms were stored digitally and analysed off-line (EchoPac, GE Healthcare, Horten Norway) by a single investigator, who was blinded to all other patient data.

**Conventional Echocardiography:** From the parasternal long-axis view, the LV diameters and wall thickness were measured. From the apical position peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave (DT) were measured using pulsed-wave Doppler to record the mitral inflow. LV ejection fraction (LVEF) was obtained using modified biplane Simpson’s method. Left atrial volume was estimated by the area-length method and the Left Atrial Volume Index (LAVI) was calculated. The LV Mass Index (LVMI) was calculated by the formula using LV linear dimensions\(^{13}\).

**Two-Dimensional Strain Echocardiography:** Two-dimensional strain analysis was performed from the apical 4-chamber, 2-chamber and apical long-axis view (mean 86 frames/s, standard deviation 23 frames/s). Peak longitudinal systolic strain was measured in all three apical projections and was averaged to provide global estimates.

**Tissue Doppler Imaging:** 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’.

Color TDI loops were obtained in the apical 4-chamber view at the highest possible frame rate (mean 169 frames/s, standard deviation 33 frames/s). The cardiac time intervals were obtained by placing a 2-4 cm straight M-mode line through the septal half of the mitral leaflet in the color TDI 4-chamber view, and the time intervals was measured directly from the color diagram (Figure 1). The Isovolumic Contraction Time (IVCT) was defined as the time interval from the MV closure, 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 1). The Ejection Time (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 1). The Isovolumic Relaxation Time (IVRT) was defined as the time interval from the AVC to the MV opening, determined by the color shift from red-orange to yellow (Figure 1). The method has previously been validated. Both isovolumic time intervals were divided with ET creating IVRT/ET and IVCT/ET, respectively, and MPI was calculated as the sum of the two ((IVRT+IVCT)/ET).

Diastolic function was assessed using mitral inflow velocity profiles and pulsed-wave TDI tracings from the septal and lateral mitral annulus according to the present guidelines. 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'.

**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.

**Follow-Up and End Points:** The primary endpoint was the combined endpoint of all-cause mortality, a new myocardial infarction (re-MI) or admission with heart failure (CHF). Secondary endpoints were all of the above analysed separately. Follow-up was 100%. Follow-up data on re-MI and admission with CHF were obtained from the Danish National Board of Health’s National Patient Registry, using ICD-10 codes, and thoroughly validated...
using hospital source data. Follow-up data on mortality were collected from the National Person Identification Registry.

Statistics: In Tables 1 and 2 proportions were compared using χ²-test, continuous Gaussian distributed variables with Student’s t-test and Mann-Whitney test if non-Gaussian distributed. Association with MPI was tested for LVEF and e’ by multivariable regression analyses including the prespecified baseline variables age and gender.

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. First order interactions between all cardiac time intervals, including the combined indexes, and atrial fibrillation for the combined endpoint were tested.

Receiver operating characteristic (ROC) 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.

Intra- and interobserver variabilities were determined by Bland-Altman plots and coefficients of variation (CV) of repeated analyses of stored echocardiographic loops (n=25 for patients with sinus rhythm and n=14 for patients with atrial fibrillation). A p-value ≤0.05 in 2-sided tests was considered statistically significant. SPSS for Windows version 20.0 (Chicago, Ill., USA) was used.

The study was approved by the local scientific ethical committee and The Danish Data Protection Agency, furthermore it complied with the 2nd Declaration of Helsinki and all participants signed informed consent.
Results
During follow-up (median 25, IQR: 19-32 months), 25 (6.5%) were admitted with a re-MI, 53 (13.7%) were admitted to hospital due to CHF and 33 (8.5%) patients died. The combined endpoint was reached by 96 (24.9%) patients.
Baseline characteristics are displayed in Table 1 and 2.

The MPI and Conventional Echocardiography: Association between MPI and the established echocardiographic parameters of diastolic and systolic function, e’ and LVEF was tested (Figure 2). MPI increased independently with decreasing values of e’ (p<0.001) and LVEF (p<0.001) after adjusting for age and gender.

The Cardiac Time Intervals and Prognosis: The risk of a subsequent re-MI, being admitted with CHF or death, increased with increasing tertile of the IVCT (Figure 3a), being two times as high in the third tertile compared to the first tertile (hazard ratio (HR) 2.0; 95% CI=(1.2=3.3); p=0.007). When interpreting the Kaplan-Meier curves, neither the IVRT nor the ET seems to provide easily comprehensible prognostic information, since the risk of the combined endpoint did not increase incrementally with increasing or decreasing tertile respectively (Figure 3b and c). We found no interactions between cardiac time intervals (including the combined indexes) and atrial fibrillation for the combined endpoint.

The MPI and Prognosis: All the indexes obtained by combining the cardiac time intervals IVRT/ET, IVCT/ET and MPI were associated with an increased risk of reaching the combined endpoint with increasing tertile (Figure 4). The risk of a re-MI, being admitted with CHF or death, increased with increasing tertile of the combined indexes (Figure 4), being approximately two times as high for the IVRT/ET and approximately three times as
high for the IVCT/ET and MPI in the third tertile compared to the first tertile (IVRT/ET: HR 1.9, 95% CI=(1.2-3.2), p=0.010; IVCT/ET: HR 2.8, 95% CI=(1.6-4.7), p<0.001; MPI: HR 2.8, 95% CI=(1.7-4.7), p<0.001). Consequently all the combined indexes were tested as predictors of an adverse outcome using Cox regression models (Table 3). Only the IVRT/ET and the MPI remained independent predictors of the combined outcome after adjusting for age, gender, peak TnI, previous AMI, LVEF, GLS, diastolic function grade, LVIDd/BSA and LVMI (Table 3). The same result was achieved when adjusting for the presence of atrial fibrillation, heart rate, mean arterial blood pressure, BMI and e’, but in order to maintain a robust model, these variables were not included in the final multivariable Cox model (Table 3). The optimal cut-off for predicting the combined endpoint was determined from the ROC curves and was 0.14 for IVCT/ET, 0.42 for IVRT/ET and 0.52 for MPI, respectively.

The MPI in Atrial Fibrillation and Outcome: Even in patients with atrial fibrillation the MPI was significantly higher in patients with an adverse outcome (0.45, 95% CI=(0.34-0.55) vs. 0.67, 95% CI=(0.58-0.76), p=0.005) (Figure 5). 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).

Intra- and Interobserver Variability Analysis: Bland-Altman plots of intra- and interobserver differences of MPI are shown in Figure 6. The intraobserver variability analysis showed a mean difference ± SD of -0.004 ± 0.029 (CV 6%) for patients with sinus rhythm and 0.031 ± 0.055 (CV 9%) for patients with atrial fibrillation (Figure 6a). 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 6b).
Discussion
This prospective study of STEMI-patients illustrates the prognostic information that can be obtained from cardiac time intervals and emphasizes the importance of combining the evaluation of the systolic and diastolic performance. Our study is the first to demonstrate that the cardiac time intervals can be valuable in risk stratification of patients with atrial fibrillation.

We found that MPI was associated with established echocardiographic parameters of both diastolic and systolic function. MPI increased with decreasing systolic function, determined by LVEF, and increased with decreasing diastolic function, determined by e’ (Figure 2). Furthermore prolongation in the systolic time interval, IVCT, and higher values of all the combined indexes, IVCT/ET, IVRT/ET and MPI, were associated with an adverse outcome (Table 3 and Figure 3 and 4). Additionally the combined indexes of systolic and diastolic performance, the IVRT/ET and the MPI, provided independent prognostic information incremental to conventional and novel echocardiographic parameters of systolic and diastolic function and all other strong predictors in our population (Table 3).

**The MPI and Conventional Echocardiography:** Invasive measures of systolic and diastolic performance, the LVEF and LV relaxation constant (τ), have previously been illustrated to be independent predictors of MPI obtained from TDI velocity curves. We found LVEF and e’ to be independent predictors of MPI determined by color TDI M-mode through the mitral leaflet. This illustrates that an ailing systolic or diastolic performance can be detected by an increasing value of the MPI when assessed by TDI. These results are interesting when considering the potential advantages of obtaining the cardiac time intervals by color TDI M-mode through the mitral leaflet compared to the conventional method. Besides obtaining all the cardiac time intervals from one cardiac cycle, the MPI obtained by TDI M-mode is less
influenced by physical parameters compared to the conventional method\textsuperscript{10}. Hence MPI based on simple cardiac mechanisms, i.e. the passively opening and closing of the MV, is less confounded than MPI based on calculations from versatile blood flow patterns through the mitral and aorta valve. Furthermore the precision and reproducibility of the cardiac time intervals and MPI are improved when they are obtained by the TDI M-mode method compared to the conventional method\textsuperscript{9,10}. In addition, 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 1). In contrast the time intervals obtained by the conventional method\textsuperscript{4,5} are assessed from velocity curves where the signals may be scattered making it hard to accurately define the cardiac time intervals. Furthermore, when good imaging quality is difficult to obtain, e.g. in patients shortly after a pPCI who are not mobilizable, it is often possible to visualize the MV in the apical view and assess its longitudinal movement by color TDI M-mode.

\textbf{The Cardiac Time Interval, MPI and Prognosis:} The MPI obtained by the conventional method can provide prognostic information in patients with various cardiac conditions\textsuperscript{17–20} including AMI\textsuperscript{21–25}. Our study is the first to evaluate the prognostic value of the MPI assessed by TDI M-mode through the mitral leaflet in a STEMI population treated by pPCI. Previous studies on predictive power of the MPI in patients with AMI have included patients with both non-ST-segment elevation MI and STEMI patients, treated with either thrombolytic therapy or PCI. Our population is more homogeneous and less confounded by difference in therapy. We found that the cardiac time intervals when evaluated separately provided ambiguous and not easily comprehensible prognostic information (Figure 3). Only the IVCT seemed to provide prognostic information when interpreting the Kaplan-Meier curves depicting the proportion of patients staying event-free for patients stratified into tertiles of the cardiac time
intervals (Figure 3a). For the IVRT and ET the risk of the combined endpoint did not increase incrementally with increasing or decreasing tertile respectively (Figure 3b and c). However when we corrected the IVCT and the IVRT for heart rate by dividing it with ET\textsuperscript{10}, both the combined indexes provided incremental prognostic information with increasing tertile (Figure 4a and b). This result is interesting since neither the IVRT nor the ET provided incremental prognostic information when evaluating them separately (Figure 3b and c), but when combining 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 (Figure 4a and b). Only the combined indexes including information on both the systolic and diastolic performance, the MPI and the IVRT/ET, were strong prognosticators after multivariable adjustment for the conventional and novel echocardiographic parameters of systolic and diastolic function (Table 3). The index only including information on the systolic performance, the IVCT/ET, did not provide prognostic information independent of other echocardiographic parameters (Table 3). Furthermore we propose using a cut-off of 0.42 for IVRT/ET and 0.52 for MPI when using these indexes for risk stratification in STEMI patients.

The MPI has previously been demonstrated to be a superior predictor of cardiovascular mortality and congestive heart failure compared to conventional echocardiographic measures of systolic and diastolic performance in a population of elderly men\textsuperscript{17,18}. In addition this superiority of the predictive capacity of the MPI compared to conventional echocardiographic measures has also been demonstrated in an AMI population\textsuperscript{22}. 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. Additionally in accordance with our results, we have previously demonstrated that MPI obtained by the M-mode method was an independent predictor of all-cause mortality in the general population.
providing prognostic information incremental to known confounders such as age, gender, BMI, heart rate, blood pressure and ischemic heart disease. In contrast the MPI obtained by the conventional method was not an independent predictor when adjusting for the same confounders\textsuperscript{10}. The discrepancy in the predictive capacity of the MPI when obtained by the two different methods is probably due to the fact that the method by Tei and colleagues\textsuperscript{4,5} seems to be influenced by more physical parameters than the M-mode method\textsuperscript{10}. This makes the MPI obtained by TDI M-mode less complex to interpret in a clinical setting.

The MPI in Atrial Fibrillation and Outcome: 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\textsuperscript{4,5} or by the newer TDI method\textsuperscript{6,7}. This is due to the absence of the A and a’ velocity curves 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 color TDI M-mode method regardless of the presence of atrial fibrillation. Thus, in patients with atrial fibrillation, color M-mode MPI can differentiate between high and low risk patients (Figure 5), 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 6). Nevertheless the intra- and interobserver variability for TDI M-mode MPI 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\textsuperscript{10}, which provides more optimism for this new method.

Limitations

The risk of residual confounders always exists in a non-randomized study.

Furthermore we did not investigate the cause of death. However, we assume that individuals
with cardiac dysfunction determined by echocardiography following a STEMI are more likely to die due to cardiovascular causes and that, if we were able to limit our analysis to cardiovascular deaths, the prognostic impact of MPI would be even greater.

The investigator was not blinded for other echocardiographic parameters which theoretically could have a potential for bias. Nevertheless the combined indexes provide independent prognostic information after adjustment for all other systolic and diastolic parameters in our population, which would not be the case if the combined indexes only contain prognostic information gained from other echocardiographic parameters.

Echocardiography was performed median 2 days after pPCI, which is the typical timespan for echocardiographic risk-assessment in east Denmark, 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 intervention26, 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 still to be investigated.

Conclusion

MPI assessed by TDI M-mode is simple and reproducible measure, which 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.
Sources of Funding

This study was financially supported by the Faculty of Health Sciences, University of Copenhagen, Denmark. The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Disclosures

None.

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Table 1. Baseline clinical characteristics in ST-elevation myocardial infarction (STEMI) patients treated by primary Percutaneous Coronary Intervention (pPCI) stratified according to major adverse outcome

<table>
<thead>
<tr>
<th></th>
<th>No major adverse outcome (n=290)</th>
<th>Major adverse outcome (n=96)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>61±11</td>
<td>67±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>76%</td>
<td>72%</td>
<td>0.40</td>
</tr>
<tr>
<td>MAP (mmHg)*</td>
<td>100±18</td>
<td>102±22</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)*</td>
<td>76±39</td>
<td>81±25</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32%</td>
<td>33%</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8%</td>
<td>9%</td>
<td>0.66</td>
</tr>
<tr>
<td>Current smoker</td>
<td>52%</td>
<td>47%</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17%</td>
<td>19%</td>
<td>0.68</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3%</td>
<td>8%</td>
<td>0.030</td>
</tr>
<tr>
<td>BMI (kg/m^2)*</td>
<td>26.9±4.2</td>
<td>25.7±4.9</td>
<td>0.017</td>
</tr>
<tr>
<td>Peak Troponin I (μg/L)†</td>
<td>89 (26-213)</td>
<td>163 (48-310)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR*</td>
<td>74±21</td>
<td>72±24</td>
<td>0.44</td>
</tr>
<tr>
<td>Symptom-to-balloon time (min)†</td>
<td>180 (120-305)</td>
<td>201 (145-340)</td>
<td>0.10</td>
</tr>
<tr>
<td>Complex lesion</td>
<td>44%</td>
<td>53%</td>
<td>0.12</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>27%</td>
<td>31%</td>
<td>0.41</td>
</tr>
<tr>
<td>LAD-lesion</td>
<td>45%</td>
<td>48%</td>
<td>0.60</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>22%</td>
<td>29%</td>
<td>0.16</td>
</tr>
<tr>
<td>TIMI grade flow before pPCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 0 flow</td>
<td>62%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>TIMI 1 flow</td>
<td>14%</td>
<td>10%</td>
<td>0.61</td>
</tr>
<tr>
<td>TIMI 2 flow</td>
<td>10%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>TIMI 3 flow</td>
<td>15%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>TIMI grade flow after pPCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 0 flow</td>
<td>4%</td>
<td>3%</td>
<td>0.13</td>
</tr>
<tr>
<td>TIMI 1 flow</td>
<td>4%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>TIMI 2 flow</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>TIMI 3 flow</td>
<td>84%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2%</td>
<td>8%</td>
<td>0.004</td>
</tr>
</tbody>
</table>
*mean (standard deviation (SD))
†median (interquartile range)

MAP = Mean Arterial Blood Pressure, MI = Myocardial Infarction, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, LAD = Left Anterior Descending coronary artery, TIMI = Thrombolysis in Myocardial Infarction classification.
**Table 2.** Baseline echocardiographic characteristics in ST-elevation myocardial infarction (STEMI) patients treated by primary Percutaneous Coronary Intervention (pPCI) stratified according to major adverse outcome

<table>
<thead>
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<th>Major adverse outcome (n=96)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)*</td>
<td>47±8</td>
<td>41±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GLS (%)*</td>
<td>-12.8±3.7</td>
<td>-10.4±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDd/BSA (cm/m²)*</td>
<td>2.4 (2.3-2.7)</td>
<td>2.6 (2.4-2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV/BSA (mL/m²)†</td>
<td>48 (40-58)</td>
<td>50 (42-57)</td>
<td>0.23</td>
</tr>
<tr>
<td>LVESV/BSA (mL/m²)†</td>
<td>25 (21-31)</td>
<td>29 (22-37)</td>
<td>0.001</td>
</tr>
<tr>
<td>LAVI (ml/m²)*</td>
<td>25±7</td>
<td>25±7</td>
<td>0.81</td>
</tr>
<tr>
<td>E (m/s)*</td>
<td>0.77±0.18</td>
<td>0.77±0.24</td>
<td>0.83</td>
</tr>
<tr>
<td>A (m/s)*</td>
<td>0.74±0.19</td>
<td>0.75±0.23</td>
<td>0.68</td>
</tr>
<tr>
<td>E/A ratio*</td>
<td>1.09±0.37</td>
<td>1.09±0.37</td>
<td>0.95</td>
</tr>
<tr>
<td>DT (ms)*</td>
<td>199±59</td>
<td>201±75</td>
<td>0.80</td>
</tr>
<tr>
<td>e'†</td>
<td>7.6±2.2</td>
<td>6.7±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'†</td>
<td>10.3 (8.1-12.4)</td>
<td>11.4 (9.1-14.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Grade of diastolic function
- Normal: 32% 15%
- Grade I dysfunction: 23% 24%  <0.001
- Grade II dysfunction: 40% 47%
- Grade III dysfunction: 4% 15%

**Cardiac time intervals:**
- IVRT (ms)*: 101±21 105±28 0.31
- IVCT (ms)*: 30±14 35±14 0.004
- ET (ms)*: 258±30 241±42 <0.001
- IVRT/ET*: 0.40±0.10 0.44±13 <0.001
- IVCT/ET*: 0.12±0.06 0.15±0.07 <0.001
- MPI*: 0.52±0.13 0.59±0.16 <0.001
*mean (standard deviation (SD))
†median (interquartile range)

LVEF=Left Ventricular Ejection Fraction, GLS=peak Global Longitudinal systolic Strain,
LVIDd=Left Ventricular Internal Diameter in Diastole, BSA=Body Surface Area,
LVEDV=Left Ventricular End-Diastolic Volume, LVESV=Left Ventricular End-Systolic Volume,
LVMI=Left Ventricular Mass Index, LAVI=Left Atrial Volume 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 pulsed-wave TDI, IVRT=Isovolumic Relaxation Time,
IVCT=Isovolumic Contraction Time, ET=Ejection Time, MPI=Myocardial Performance Index.
Table 3. Unadjusted and adjusted Cox proportional hazards regression models depicting the combined indexes of the cardiac time intervals as predictors of outcome

<table>
<thead>
<tr>
<th>Combined endpoint (96 events)</th>
<th>CHF (53 events)</th>
<th>re-MI (25 events)</th>
<th>Mortality (33 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
</tr>
</tbody>
</table>

**Unadjusted model:**

| IVRT/ET per 0.1 increase | 1.34 (1.14-1.57) | 0.001 | 1.28 (1.03-1.59) | 0.12 | 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) | 0.09 | 1.17 (0.86-1.59) | 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 | 1.20 (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, LVMI and LVIDd/BSA: Left Ventricular Mass Index and Left Ventricular Internal Dimension/Body Surface Area.

Hazard Ratio (95% CI): The hazard ratio represents the relative risk of the event occurring in one group compared to the other, with the 95% confidence interval indicating the precision of the estimate. P-value: This indicates the statistical significance of the hazard ratio, with values less than 0.05 typically considered statistically significant.
Ventricular Mass Index, LVIDd=Left Ventricular Internal Diameter in Diastole, BSA=Body Surface Area, GLS=peak Global Longitudinal systolic Strain.
Figure Legends

Figure 1. Title: The cardiac time intervals assessed by a color TDI M-mode line through the mitral leaflet.

Caption: 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=MV Closing; AVO=Aortic Valve Opening; AVC=Aortic Valve Closure; MVO=MV Opening.

Figure 2. Title: Association between the MPI and established echocardiographic parameters of diastolic and systolic function.

Caption: Depicting the association between the MPI and the ET and e’. Error bars represents standard errors. e’=average peak early diastolic longitudinal mitral annular velocity determined by pulsed-wave TDI; MPI=Myocardial Performance Index; EF=Ejection Fraction.

Figure 3. Title: Cardiac time intervals and outcome.

Caption: Kaplan-Meier curves depicting cumulative probability of staying event free for patients stratified into tertiles of the IVCT (1.tertile <24 ms; 2.tertile ≥24 ms to <34 ms; 3.tertile ≥34 ms)(Figure 3a), of the IVRT (1.tertile <93 ms; 2.tertile ≥93 ms to <110 ms; 3.tertile ≥110 ms)(Figure 3b) and of the ET (1.tertile <244 ms; 2.tertile ≥244 ms to <271 ms; 3.tertile ≥271 ms)( Figure 3c). IVCT=Isovolumic Contraction Time; IVRT=Isovolumic Relaxation Time; ET=Ejection Time.

Figure 4. Title: The combined indexes of the cardiac time intervals and outcome.
Caption: Kaplan-Meier curves depicting cumulative probability of staying event free for patients stratified into tertiles of the combined index IVCT/ET (1.tertile <0.09; 2.tertile ≥0.09 to <0.14; 3.tertile ≥0.14) (Figure 4a), of the combined index IVRT/ET (1.tertile <0.36; 2.tertile ≥0.36 to <0.43; 3.tertile ≥0.43) (Figure 4b) and of the MPI (1.tertile <0.46; 2.tertile ≥0.46 to <0.57; 3.tertile ≥0.57) (Figure 4c). IVCT=Isovolumic Contraction Time; IVRT=Isovolumic Relaxation Time; ET=Ejection Time; MPI=Myocardial Performance Index.

Figure 5. Title: MPI in patients with atrial fibrillation stratified according to outcome.

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

Figure 6. Title: Intra- and interobserver variability analysis.

Caption: Bland-Altman plots of intra- (Figure 6a) and interobserver (Figure 6b) 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).
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

Tor Biering-Sørensen, Rasmus Mogelvang, Peter Søgaard, Sune H. Pedersen, Søren Galatius, Peter Godsk Jørgensen and Jan Skov Jensen

*Circ Cardiovasc Imaging*, published online March 27, 2013;
*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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