Tissue Doppler echocardiography reveals impaired cardiac function in patients with reversible ischaemia

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Aims
To determine if echocardiographic tissue Doppler imaging (TDI) performed at rest detects reduced myocardial function in patients with reversible ischaemia.

Methods and results
Eighty-four patients with angina pectoris, no previous history of ischaemic heart disease and normal left ventricular ejection fraction were examined with colour TDI, single-photon emission computed tomography (SPECT), and coronary angiography (CAG). Patients with a normal SPECT (n = 42) constituted the control group and patients with a positive SPECT (n = 42) were divided into patients with (true-positive SPECT, n = 30) or without (false-positive SPECT, n = 12) significant coronary stenoses assessed by CAG. Regional longitudinal systolic (s’), early diastolic (e’), and late diastolic (a’) myocardial velocities were measured by colour TDI at six mitral annular sites and averaged to provide global estimates. In patients with reversible ischaemia both global systolic and diastolic function were impaired in terms of reduced average s’ (5.6 ± 0.9 vs. 6.1 ± 1.1 cm/s; P < 0.05), reduced average e’ (5.9 ± 1.8 vs. 7.0 ± 1.7 cm/s; P < 0.01) and increased average E/e’ (14.2 ± 5.0 vs. 11.5 ± 3.9; P < 0.01). This impairment of the cardiac function was even more evident in patients with a true-positive SPECT with reduced average s’ (5.5 ± 0.8 vs. 6.1 ± 1.1 cm/s; P < 0.01), reduced average e’ (5.2 ± 1.5 vs. 7.0 ± 1.7 cm/s; P < 0.001), and increased average E/e’ (15.5 ± 5.2 vs. 11.5 ± 3.9; P < 0.001), whereas no difference in myocardial velocities could be demonstrated in patients with a false-positive SPECT compared with controls.

Conclusion
In patients with stable angina pectoris, preserved ejection fraction, and reversible ischaemia assessed by SPECT, echocardiographic colour TDI performed at rest reveals impaired cardiac function. The impairment of the cardiac function seems to be evident only in patients with a true-positive SPECT and colour TDI may therefore increase its diagnostic value.

Keywords
Tissue Doppler imaging • Ischaemia • Stable angina • SPECT • CAG

Introduction
Early detection of coronary artery disease (CAD) is essential to initiate treatment and improve the prognosis of CAD. Tissue Doppler imaging (TDI) is a rapid, inexpensive and non-invasive method for the assessment of the cardiac function and it has proved to be a useful prognostic tool both in the general population and in persons with known cardiovascular disease. Previous studies have demonstrated that both the longitudinal systolic and diastolic myocardial velocities are impaired in segments supplied by arteries with significant stenoses assessed by coronary angiography (CAG). However, CAG primarily evaluates the

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anatomy of the coronary arteries and do not provide information regarding myocardial perfusion. Hence the presence of stenoses assessed by CAG is not necessarily associated with myocardial ischaemia and myocardial ischaemia may occur in patients without angiographically significant stenoses.14–19

Single-photon emission computed tomography (SPECT) is a well-established technique providing information on regional myocardial perfusion. Our group has previously shown that measurements of myocardial velocities at the six mitral annular areas by colour TDI provides a thorough and clinically applicable examination of both the global and the regional cardiac function.3,4,13,20 However, it is unknown if reversible ischaemia assessed by SPECT affects the wall motion of the myocardium even at rest. Therefore the aim of this study was to determine if the longitudinal velocities of the left ventricle (LV), assessed by simple colour TDI technique, are affected at rest in patients with known stress induced reversible ischaemia assessed by SPECT.

Methods

Study population
At Gentofte University Hospital, a tertiary high-volume referral centre, data from each coronary artery catheterization and data from any related SPECT examination has been registered consecutively in a central database since 1999. The database also includes medical history and clinical information, such as risk profile and co-morbidity.

Since mid-2005, all echocardiographic examinations were digitally stored on a central server. All examinations were performed by dedicated sonographers according to a standardized protocol.

Only patients with suspected stable angina pectoris, who had been examined by SPECT and Colour TDI prior to any coronary intervention, were included. Patients with left ventricular ejection fraction (LVEF) <50%, prior myocardial infarction, congestive heart failure, heart valve disease, pacemaker, intraventricular conduction disturbances, and ongoing arrhythmias were excluded. Forty-two patients with reversible ischaemia assessed by SPECT (the study group) and 42 patients with a normal SPECT (controls) fulfilled the above stated criteria. The study patients were divided into patients with (true-positive SPECT, n = 30) or without (false-positive SPECT, n = 12) significant stenoses assessed by CAG. Both patients with significant reversible ischaemia and controls had suspected symptoms of stable angina pectoris. Five controls had a normal CAG. The remaining controls had never been examined by CAG, presumably because their SPECT was normal.

Echocardiography and colour tissue doppler imaging
Echocardiographic images were obtained using Vivid 7 (GE Healthcare, Horton, Norway) with a 3.5-MHz transducer. All subjects were examined with conventional two-dimensional echocardiography and colour TDI. All analyses were done off-line with commercially available software (EchoPac, GE Healthcare, Horton, Norway) with the investigator blinded to the results of the SPECT, the CAG and clinical information.

M-mode in the parasternal long axis was used to determine the dimensions and wall thickness of left chambers. If the correct angle could not be obtained two-dimensional images were used instead. Pulsed wave Doppler at the apical position was used to record mitral inflow between the tips of the mitral leaflets. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time (DT) of the E-wave were measured and the E/A-ratio was calculated. LVEF was determined using modified biplane Simpson’s method.

Colour TDI loops were obtained in the apical four-chamber, two-chamber, and apical long-axis view at the highest possible frame rate. Smoothing was set to 30 ms. Peak longitudinal systolic (s′), early diastolic (e′), and late diastolic (a′) velocities were measured at the six mitral annular sites dividing the left ventricle into six segments of interest: the septal, lateral, inferior, anterior, posterior, and anteroseptal myocardial walls. Inter- and intra-observer variability of mitral annular velocities estimated by colour TDI has been reported low.20,21

Regional longitudinal performance of the left ventricle was assessed by comparing each segment from patients in the ischaemic group with the corresponding segment of the matched control. Global longitudinal performance of the left ventricle was assessed by averaging the velocities from the six segments. One cardiac cycle with the best possible image quality was used for each measurement.

Single-photon emission computed tomography
Myocardial perfusion imaging by SPECT, using technetium 99 m-radiolabelled perfusion agents, was performed both at rest and during stress. Peak stress was obtained by either bicycle exercise or pharmacology stress. Images were interpreted by an experienced clinical observer without knowledge of the findings by CAG or echocardiography. The location of perfusion defects corresponding to the territory of the left anterior descending artery (LAD), the circumflex artery (Cx), or the right coronary artery (RCA) was registered in a central database. SPECT data used in this study was collected from this database. Patients with irreversible ischaemia were excluded. Patients with stress induced reversible ischaemia constituted the study group (n = 42) and patients without reversible ischaemia constituted the control group (n = 42).

 Coronary angiography
CAG was performed by the percutaneous femoral approach. Coronary angiograms were obtained in at least two projections and stenoses with ≥70% reduction of the arterial lumen area were considered significant. The analysis of the coronary angiograms was performed visually by an experienced observer.

Statistical analysis
Comparison between groups was performed by student’s t-test and χ² test. All continuous variables are expressed as mean values ± standard deviation and categorical variables as frequencies (percentages). Multi-variable linear regression was used in order to adjust conventional diastolic and TDI parameters for hypertension and gender in Figure 1. These variables were adjusted for because they have been suggested in the literature to influence the TDI parameter and because they were found to be significantly different from controls in the subgroup analysis in Table 1. A P-value of ≤0.05 was considered statistically significant. All analyses were performed by SPSS software (SPSS system for windows, release 16.0.1, 15 November 2007, SPSS Inc. Headquarters, Chicago, IL, USA).

Optimal cut-off value of e′, E/e′, and s′ for discrimination of controls and patients with a true-positive SPECT were obtained from receiver operating characteristic (ROC) curves.

Ethics
The study was approved by the Danish Data Protection Agency, journal number 2007-41-1667.
transmitral late diastolic inflow velocity (tional diastolic parameters was found, apart from increased peak lower compared with controls. No difference regarding conven- gender in patients with a false-negative SPECT was significantly SPECT was significantly higher, whereas the prevalence of male chambers in any of the of the groups compared with controls. Diabetes, body mass index (BMI), LVEF, or dimensions of the left heart hypertension no significant difference could be demonstrated (as determined by ROC analysis) were found to be 6.4, 5.7, and 11.4 cm/s, respectively. The corresponding sensitivity and specificity of e′, E/e′, and s′ were found to be (80 and 69%), (67 and 52%), and (83 and 57%), respectively.

Global myocardial performance
As mentioned above no differences were observed with regard to LVEF, left atrial diameter or conventional diastolic parameters. In contrast both global systolic and diastolic myocardial performance was impaired in patients with a positive SPECT, with significantly reduced average s′, reduced average e′, and increased average E/e′ (Table 1). Furthermore these reductions of s′, e′, and E/e′ were found to be even more evident in patients with a true-positive SPECT, whereas no significant differences were found in patients with a false-positive SPECT. This pattern remained significant after adjusting for hypertension and gender (Figure 1).

A cut-off level of average e′, s′, and E/e′ (as determined by ROC analysis) were found to be 6.4, 5.7, and 11.4 cm/s, respectively. The regional longitudinal LV wall motion in patients with a true-positive SPECT is displayed in Figure 2. The patients were stratified based on which coronary territory was suffering from reversible ischaemia assessed by SPECT.

### Results

#### Baseline characteristics

Clinical and echocardiographic characteristics for controls, all patients with reversible ischaemia (positive SPECT), patients with both reversible ischaemia and significant coronary stenoses (true-positive SPECT) and patients with reversible ischaemia without significant coronary stenoses (false-positive SPECT) are presented in Table 1.

Notably, no differences were observed with regards to age, diabetes, body mass index (BMI), LVEF, or dimensions of the left heart chambers in any of the of the groups compared with controls.

The prevalence of hypertension in patients with a true-positive SPECT was significantly higher, whereas the prevalence of male gender in patients with a false-negative SPECT was significantly lower compared with controls. No difference regarding conventional diastolic parameters was found, apart from increased peak transmittal late diastolic inflow velocity (A) and increased DT in patients with true-positive SPECT. However, when adjusted for hypertension no significant difference could be demonstrated regarding A (0.87 ± 0.27 vs. 0.78 ± 0.19 m/s; P = 0.10) or DT (260 ± 71 vs. 237 ± 55 ms; P = 0.14).

### Table 1  Baseline characteristics for controls, all patients with reversible ischaemia (positive SPECT), patients with both reversible ischaemia and significant coronary stenoses (true-positive SPECT) and patients with reversible ischaemia without significant coronary stenoses (false-positive SPECT)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Positive SPECT</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>True positive</td>
</tr>
<tr>
<td>n</td>
<td>42</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>62.5 ± 12</td>
<td>62.6 ± 11</td>
<td>64.8 ± 10</td>
</tr>
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<td>Male, n (%)</td>
<td>24 (57%)</td>
<td>24 (57%)</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (55%)</td>
<td>31 (74%)</td>
<td>26 (87%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (14%)</td>
<td>9 (21%)</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.8 ± 4.6</td>
<td>29.0 ± 5.2</td>
<td>29.9 ± 4.6</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>57.0 ± 3.5</td>
<td>55.8 ± 3.8</td>
<td>55.6 ± 4.0</td>
</tr>
<tr>
<td>LVd, cm</td>
<td>4.47 ± 0.35</td>
<td>4.60 ± 0.46</td>
<td>4.54 ± 0.50</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>3.59 ± 0.75</td>
<td>3.68 ± 0.34</td>
<td>3.67 ± 0.31</td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.76 ± 0.19</td>
<td>0.77 ± 0.17</td>
<td>0.76 ± 0.18</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.77 ± 0.22</td>
<td>0.84 ± 0.23</td>
<td>0.89 ± 0.22†</td>
</tr>
<tr>
<td>E/A</td>
<td>1.03 ± 0.29</td>
<td>0.97 ± 0.28</td>
<td>0.89 ± 0.25</td>
</tr>
<tr>
<td>DT, ms</td>
<td>235 ± 68</td>
<td>250 ± 51</td>
<td>262 ± 47†</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean ± SD and categorical data are presented as frequency (percentage). Values significantly different from controls are marked in bold.

BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; LVd, Left Ventricular Internal Diameter in Diastole; LA, Left Atrial; E, peak transmittal early diastolic inflow velocity; A, peak transmittal late diastolic inflow velocity; DT, decelerations time of early diastolic transmittal inflow; s′, average peak systolic longitudinal mitral annular velocity; e′, average peak early diastolic longitudinal mitral annular velocity; s′, average peak late diastolic longitudinal mitral annular velocity.

†P ≤ 0.05 and ‡P < 0.01 compared with controls.
The regional systolic and diastolic function seemed to be impaired in all myocardial segments in terms of relative reduction of $s'$ and $e'$ in all six segments when all three coronary territories potentially were suffering from reversible ischaemia (though not statistically significant in all segments). In patients with reversible ischaemia limited to the territory of the LAD, $e'$ was significantly reduced in the anterior myocardial segment. In patients suffering from reversible ischaemia in either the territory of the RCA or the Cx, $e'$ was significantly reduced in the inferior and posterior segments and $s'$ was significantly reduced in the inferior, posterior, and lateral segments. Hence only myocardial segments suffering from reversible ischaemia assessed by SPECT had significantly reduced TDI velocities.

**Discussion**

To our knowledge, the present study is the first to investigate if reversible ischaemia detected by SPECT affects colour TDI parameters, in patients with stable angina pectoris and preserved ejection fraction.

TDI performed at rest in patients with reversible ischaemia reveals a pronounced both diastolic and systolic global impairment of the myocardium in terms of reduced average $e'$, reduced average $s'$, and increased average $E/e'$. However, when patients were stratified based on the findings by CAG into patients with true or false-positive SPECT, only the myocardial function in patients with a true-positive SPECT were impaired, whereas patients with a false-positive SPECT showed no impairment of the myocardial function. This pattern remained significant after adjusting for hypertension and gender (Figure 1). Adjustment was made because hypertension and male gender were found to be significantly different from controls (Table 1). It is much debated whether patients with a normal CAG and a positive SPECT are suffering from ischaemia. Several investigators have questioned the existence of myocardial ischaemia in these patients, mainly based on the fact that the prognosis is good in these patients and that studies with stress echocardiography have consistently failed to show the presence of wall motions abnormalities during stress.22 – 25 Our results support this point of view and suggest that TDI may even improve the diagnostic value of SPECT in identifying patients with ischaemic heart disease.

It has been demonstrated by pulsed wave TDI that $E/e'$ reflects global diastolic function and is associated to LV preload.26,27 We found that $E/e'$ measured by colour TDI was increased only in patients with a true-positive SPECT implying that LV preload is increased in this patients due to global diastolic dysfunction.
Regional diastolic and systolic myocardial function was found to be impaired only in regions with reversible ischaemia in terms of a significantly reduced $e'$ and $s'$ (Figure 2). The impairment of the early diastolic function in regions with ischaemia confirms previous studies both in animals and humans.\textsuperscript{12,13,28–30} This is probably due to the fact that the early diastolic myocardial relaxation is an active and energy demanding process, which makes this part of the cardiac cycle particularly vulnerable to ischaemia.\textsuperscript{31} Furthermore, it has been demonstrated that recurrent ischaemia can induce structural changes of the myocardium leading to impaired early diastolic wall motion, which might explain why TDI detects ischaemia even at rest.\textsuperscript{32,33} Despite preserved ejection fraction as assessed by conventional echocardiography, regional longitudinal contraction of the left ventricle in term of $s'$ was impaired in patients with reversible ischaemia. Longitudinal systolic dysfunction might be compensated by an increase of the radial function, which might explain why the ejection fraction is preserved. However, our results demonstrate, in accordance with other studies, that systolic dysfunction assessed by longitudinal contraction might be detected at an earlier stage before a reduction of the ejection fraction is visible.\textsuperscript{11,13}

Since TDI reveals both diastolic and systolic dysfunction in terms of reduced $s'$, reduced $e'$, and increased $E/e'$ in patients with reversible ischaemia one may suggest that TDI could be a useful diagnostic test in patients under suspicion of having CAD. In our study $e'$ seems to be the most accurate in discriminating controls from patients with a true-positive SPECT with a sensitivity and specificity of 80 and 69%, respectively. This is perfectly in line with previous studies were $e'$ also were found to be particularly valuable to ischaemia.\textsuperscript{12,13,28–30}

**Limitations**

LV wall motion abnormalities may be due to other conditions than ischaemia, such as age, gender hypertension, diabetes, intraventricular conduction disturbance, loading conditions among others. However, in order to avoid confounding from the most important of these conditions, adjusted analysis was made if there was any significant difference between the study group and the control group.

**Figure 2** Regional analyses in patients with a true-positive single-photon emission computed tomography. The left ventricle is divided into six wall segments corresponding to the six mitral annular sampling areas. The relative difference from controls regarding peak early diastolic velocity ($e'$) and peak early systolic velocity ($s'$) are shown at each of the six mitral annular segments. LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery. Reversible Ischaemia LAD + Cx + RCA = regional analyses including all patients. Reversible Ischaemia LAD, regional analyses including only patients with reversible ischaemia corresponding to the territory of LAD. Reversible Ischaemia RCA + Cx = regional analyses including only patients with reversible ischaemia corresponding to the territory of RCA or Cx. Segments possibly affected by reversible ischaemia are coloured dark orange. Segments $s'$ or $e'$ significantly different ($P \leq 0.05$) from controls are marked by *. Antsept, anteroseptal; ant, anterior; lat, lateral; post, posterior; inf, inferior; sept, septal.
regarding age, gender, hypertension or diabetes, and patients with interventricular conduction disturbance were excluded.

There is a lack of angiographic results among the controls, and some of the controls might have angiographically significant stenoses despite a normal SPECT. However, despite the possible impact this may have on the myocardial function among the controls, patients with reversible ischaemia still have an impaired cardiac function assessed by colour TDI compared with controls.

SPECT data in this study was collected retrospectively from a database holding only information about the location (either LAD, Cx, or RCA) and not the extent of the perfusion defects. Unfortunately we did not have access to the SPECT raw data, why a more thorough and quantitative analysis of the SPECT studies was not possible.

Since all data were collected and evaluated retrospectively, selection may have occurred. Only patients referred to SPECT and patients without a history of heart disease and with a normal conventional echocardiography were included. Since the number of patients is limited the risk of making a type 2 error is increased. However, despite of this limitation we were able to demonstrate reduced myocardial velocities in patients with reversible ischaemia assessed by SPECT and we believe that these results would be even more evident in a larger population. Studies in an unselected population with a large number of consecutive patients are necessary to determine if TDI is a useful diagnostic tool among patients with suspected CAD.

Clinical implications
Measurement of tissue velocities at the six mitral annular areas by colour TDI provides a thorough examination of both the global and regional LV function. Our study demonstrates that if both diastolic and systolic parameters are measured by TDI one might be able to detect potentially ischaemic myocardial segments even at rest. Furthermore TDI may improve the diagnostic value of SPECT in identifying patients with ischaemic heart disease. Therefore the potential of TDI as a diagnostic test seems promising. One clinical approach could be that if the diastolic (e’) or systolic longitudinal velocities (s’) assessed by colour TDI are reduced in at least one segment (either during rest or stress), one should suspect ischaemia. Further studies are needed to validate our cut-off values and consecutive studies are needed to evaluate the diagnostic value of colour TDI in patient with stable angina pectoris.

Conclusion
In patients with stable angina pectoris, preserved ejection fraction, and reversible ischaemia assessed by SPECT, echocardiographic colour TDI performed at rest reveals impaired cardiac function. The impairment of the cardiac function seems to be evident only in patients with a true-positive SPECT suggesting that in patients suffering from angina pectoris, the diagnostic value of a positive SPECT may be increased by TDI.

Conflict of interest: none declared.

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