Systolic and Diastolic Function by Tissue Doppler Imaging Predicts Mortality in Patients with Atrial Fibrillation

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Abstract

Aim: Tissue Doppler Imaging (TDI) detects early signs of left ventricular dysfunction. The prognostic potential of TDI in patients with atrial fibrillation (AF) has, however, not yet been clarified. This study evaluates the prognostic value of TDI in patients with atrial fibrillation.

Methods and Results: In total, echocardiograms from 313 patients with AF during examination were analyzed offline. Longitudinal systolic velocity (s′), early diastolic velocity (e′) and longitudinal displacement (LD) were measured by color TDI. During a median follow-up of 891 days, 64 patients (20%) died.

TDI was significantly associated with all-cause mortality, and the risk of dying increased significantly per 1 cm/s decrease in s′ (HR of 1.31, 95% CI 1.05-1.63; p=0.018) and e′ (HR of 1.17, 95% CI 1.01-1.35; p=0.038) respectively, even after adjustment for age, gender, heart rate, aortic stenosis, DM and LVEF quartiles.

LD also proved to be a significant predictor of outcome after multivariate adjustment (HR 1.23; 95% CI 1.05-1.44; p=0.012).

The population was stratified according to high or low s′ and e′. Patients with low s′ and e′ had more than three times the risk of mortality compared to the patients with high s′ and e′ (HR 3.64; 95% CI 1.83-7.26; p<0.001) and remained in significantly higher risk after adjustment for various risk factors.

Conclusions: Both systolic and diastolic performance, as assessed by TDI, are strong predictors of mortality in patients with atrial fibrillation, and especially the combination of systolic and diastolic dysfunction is a significant prognostic marker.

Introduction

Atrial fibrillation (AF) is the most common of all cardiac arrhythmias and affects about 1-2% of the general population. It occurs in less than 4% of those under the age of 60 but in more than 9% of those over 80 years of age.1 The high prevalence makes atrial fibrillation a frequent cause of illness and hospitalisation in the western world and the prevalence is expected to double over the next 50 years.2 AF is responsible for impaired quality of life as well as more severe conditions such as heart failure, every fifth stroke, and in the worst cases, death.3

As the incidence of AF and its complications are expected to increase in the population, an increasing amount of resources in health care will be needed in the form of frequent hospitalisations, increased consumption of drugs and invasive interventions, care and other support measures. Consequently, efforts to improve risk-stratification, clarify pathophysiological mechanisms and identify targets for therapeutic intervention in AF are of the utmost importance.

Tissue Doppler Imaging (TDI) has proven to be a useful and reproducible tool for assessment of systolic and diastolic function.4,5 The prognostic role of tissue Doppler velocities has been explored and proven to have strong predictive power in various diseases such as hypertension,7 diabetes,8 ischemic heart disease9,10 and heart failure.11,12 Relatively small populations have limited current studies of TDI and AF and evaluation of longitudinal systolic and diastolic function of the left ventricle in AF determined by TDI remains to be investigated. The aim of this study was to evaluate the prognostic value of longitudinal systolic and diastolic function by TDI in patients with AF.

Methods

Data Source

The Department of Cardiology, Gentofte Hospital Copenhagen performs routine echocardiograms according to a standardised protocol. These echocardiograms have been stored in a database on a
Study Population

The study is a retrospective echocardiographic cohort study. Relevant patients (n=1,016) were identified in the database by searching for echocardiograms from patients with AF. Of the 1,016 AF patients identified, 418 patients fulfilled the inclusion criteria: 1) presence of AF during examination and 2) the echocardiographic examination included color TDI-recordings. 105 patients were excluded due to various reasons: invalid social security number (n=10), poor echocardiographic quality (n=68), and duplicates (n=27). Thus, the study sample consisted of 313 patients.

Information about co-morbidity at baseline was collected in the form of ICD-10 codes (A- and B-diagnoses) noted in the same hospitalisation as the examination was conducted. Also, information about condition and co-morbidity was noted from the report attached to the echocardiographic examination included in the study.

Echocardiography

All echocardiograms were stored digitally using Image Vault (GE Healthcare, Horten Norway) and analysed offline with commercially available software (EchoPac, BT11) by a single investigator who was blinded to all other patient data. If the examination contained more than one heart cycle, the first cycle was used. All measurements were performed in the 4-chamber, 2-chamber and apical long axis view, meaning that all parameters were calculated based on an average of three cardiac cycles to account for beat-to-beat variations.

Conventional Echocardiography

From the parasternal long-axis view, the left ventricle (LV) diameter and wall thicknesses (posterior and interventricular wall) were measured at the level of the mitral valve tips, thereby ensuring a measurement perpendicular to the long axis of the ventricle. From the apical four and two chamber positions, LV ejection fraction (LVEF) was obtained using modified biplane Simpson's method. Left atrial (LA) volume was estimated by the biplane area-length method. Pulsed wave Doppler at the apical position was used to obtain mitral inflow velocities between the tips of the mitral leaflets. E/e' was calculated as early mitral inflow velocity (E) divided by the average of septal and lateral mitral annular peak early diastolic velocity (e') obtained by pulsed wave TDI.
Unadjusted and adjusted Cox proportional hazards regression models of global tissue Doppler velocities as predictors of outcome

<table>
<thead>
<tr>
<th>Endpoint (64 events)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s' per 1 cm/s decrease</td>
<td>1.42 (1.18-1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.34 (1.19-1.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LD per 1 mm decrease</td>
<td>1.32 (1.17-1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of s' and e' per 1 cm/s decrease</td>
<td>1.22 (1.13-1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.04 (1.02-1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model adjusted for age and gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s' per 1 cm/s decrease</td>
<td>1.39 (1.14-1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.25 (1.09-1.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LD per 1 mm decrease</td>
<td>1.28 (1.12-1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of s' and e' per 1 cm/s decrease</td>
<td>1.19 (1.09-1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.03 (1.01-1.06)</td>
<td>0.014</td>
</tr>
<tr>
<td>Multivariable model adjusted for age, gender, heart rate, aortic stenosis and DM</td>
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<td></td>
</tr>
<tr>
<td>s' per 1 cm/s decrease</td>
<td>1.41 (1.16-1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.23 (1.08-1.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>LD per 1 mm decrease</td>
<td>1.29 (1.12-1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of s' and e' per 1 cm/s decrease</td>
<td>1.18 (1.08-1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.03 (1.00-1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td>Multivariable model adjusted for age, gender, heart rate, aortic stenosis, DM and LVEF quartiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s' per 1 cm/s decrease</td>
<td>1.33 (1.05-1.67)</td>
<td>0.016</td>
</tr>
<tr>
<td>e' per 1 cm/s decrease</td>
<td>1.19 (1.02-1.38)</td>
<td>0.029</td>
</tr>
<tr>
<td>LD per 1 mm decrease</td>
<td>1.23 (1.05-1.43)</td>
<td>0.010</td>
</tr>
<tr>
<td>Sum of s' and e' per 1 cm/s decrease</td>
<td>1.15 (1.03-1.27)</td>
<td>0.009</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.02 (1.00-1.05)</td>
<td>0.13</td>
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</table>

s' = global peak systolic longitudinal mitral annular velocity determined by color tissue Doppler imaging, e' = global peak early diastolic longitudinal mitral annular velocity determined by color Tissue Doppler Imaging, LD = longitudinal displacement determined by tissue tracking.
Bland Altman analysis was used to assess intra and interobserver variability of tissue Doppler measures of systolic and diastolic heart function in 20 randomly selected patients and was expressed as mean difference ± 1.96 standard deviation (SD) and as coefficient of variation (CV).

P-values ≤ 0.05 in 2-sided tests were considered statistically significant. The statistical software used was SPSS for Mac version 20.0.

**Results**

Baseline characteristics are displayed in Table 1. During a median follow-up of 891 days (range: 5-2493 days) 64 patients (20%) died.

**Myocardial Longitudinal Function**

s' and e' were significantly lower in the group of patients who died compared to the patients still alive at follow-up (Table 1). The risk of mortality increased with decreasing systolic and diastolic performance by TDI (Fig. 2a-b), even after multivariable adjustments (Table 2). No significant interaction was found between systolic and diastolic performance and valvular disease.

Longitudinal function was assessed by global strain and strain rate and although statistically insignificant (Table 1), there was a trend towards lower strain and strain rate in the patients who died at follow-up.

**Combining Tissue Doppler Velocities**

Combining the information on systolic and diastolic function by combining global s' and global e' (s'+e') provided a significant risk marker of death (Table 2). Furthermore, using the mean value of global s' and e' as cutoff, the population was stratified according to high or low s' and e' and patients were divided into four groups: patients with high s' and e', high s' and low e', low s' and high e', and low s' and e'. Isolated impaired systolic or diastolic function determined by a low value of either s' or e' did not seem to provide prognostic information (Table 3). Compared to patients with high global s' and e', patients with both low global s' and e' had more than three times the risk of death (Table 3). Even after adjustment for age, gender, heart rate, aortic stenosis, diabetes mellitus (DM) and LVEF quartiles, these patients remained in significantly higher risk of death (HR 2.21, 95% CI 1.00-4.86, p=0.049). Furthermore, the combined systolic and diastolic global tissue Doppler velocities (s'+e') provided incremental prognostic information to the conventional echocardiographic parameters of systolic and diastolic function (LVEF and E/e'), determined by a significant increase in the Harrell’s c-statistics (LVEF+E/e': 0.70 (0.62-0.66) vs. LVEF+E/e'+(s'+e'): 0.74 (0.66-0.81), p=0.048) (Fig. 3).

The cutoff values determined in the current study were 4.27 cm/s for s' and 7.15 cm/s for e', respectively and were found to be very similar to the prespecified cutoff-values of 5 cm/s for s' and 7 cm/s for e' proposed by Shin and colleagues in heart failure with preserved ejection fraction and AF.

The association between (s'+e') and conventional echocardiographic parameters of systolic and diastolic function (LVEF and E/e') are depicted in Fig. 4. s'+e' increased independently with decreasing E/e' (p<0.001) and increasing LVEF (p<0.001).

**Reproducibility**

Intraobserver and interobserver variability was low for all obtained tissue Doppler measures, as is shown by the mean difference being close to zero, a narrow standard deviation, and a low CV for each measurement (Table 4). The smallest variability was seen in intraobserver measures.

**Discussion**

So far, evaluation of systolic and diastolic function in patients with AF has been a clinical challenge, especially due to variable cycle lengths and the lack of the late diastolic velocity wave, the A and the a' wave. E/e' has been shown to be a predictor of clinical outcome in patients with AF. Among these, mitral valve deceleration time (DT), which provides information on left ventricular diastolic function, has been suggested. Matsukida and colleagues proposed a cutoff value of DT ≤ 100 ms as a predictor of pulmonary capillary wedge pressure and thus an evaluation of diastolic function in patients with AF. In the present study, however, we found no prognostic value of DT (Table 1).

E/e' has been shown to be a predictor of clinical outcome in patients with non-valvular AF. Similarly we found that E/e' predicted risk of mortality independent of age and gender. E/e' did not, however, seem to provide prognostic information after multivariable adjustments for
age, gender, heart rate, aortic stenosis, DM and LVEF (Table 2). This might be due to the varied population, as the current study included both valvular and non-valvular AF patients. However, we did not find any interaction between valve disease and echocardiographic parameters for death.

Strain and Strain Rate Imaging

Both strain and SR have proven to be associated with various diseases such as hypertension, diabetes, ischemic heart disease, mitral regurgitation and cardiomyopathies. Additionally, due to the regional myocardial changes that accompany myocardial ischemia, strain and SR have been found to have great prognostic value, especially in patients with myocardial infarction. Strain and SR might be advantageous in the assessment of diastolic function in patients with AF.

The majority of research within this area has mainly investigated strain and SR measured in the left atrium in patients with AF. SR, measured in the left atrium, has been shown to provide a new prognostic parameter for death in the present study (Table 1). It has previously been stated that strain and SR being insignificantly associated with death in patients with AF.

Color Tissue Doppler Imaging

The prognostic value of TDI velocities has been validated in several studies. In the current study, global systolic and diastolic peak velocities and longitudinal displacement was shown to provide independent prognostic information in an otherwise difficult patient population. These echocardiographic markers were shown to be highly significant in predicting outcome in patients with AF, even after adjusting for other conventional risk factors and LVEF quartiles.

In a study by Shin and colleagues, the relationship between systolic and diastolic parameters and the prognosis of patients with heart failure with preserved ejection fraction and AF was investigated. In concordance with our findings, Shin et al. found that s’ and e’ velocities had prognostic potential to predict adverse clinical outcomes. Furthermore they suggested that the combination of the two velocities would be a good marker of prognosis, and that the combined information of systolic and diastolic dysfunction may be used for risk stratification. Cutoff points at s’< 5 cm/s and e’< 7 cm/s were suggested as clinical binary cutoff-points and, according to the study, patients with values below these cutoffs had a 12-fold higher risk of cardiac events. As systole and diastole are coherent and interdependent, it may be valuable to consider assessment of both s’ and e’ in the same risk stratification strategy in patients with AF. In accordance with this, the combined information on systolic and diastolic function in the present study seems to provide valuable information about prognosis in patients with AF. Our group has previously demonstrated the same pattern in patients with ST-segment elevation myocardial infarction.

Furthermore, we found an association between the combined systolic and diastolic global tissue Doppler velocities (s’+e’) and conventional echocardiographic measurements of systolic (LVEF) and diastolic function (E/e’) (Fig. 4). Interestingly, s’+e’ seems to provide additional prognostic information as it is a significant independent predictor, even after adjustment for E/e’ and LVEF (and age, gender, heart rate, aortic stenosis and DM). Although all velocity measurements proved to have prognostic potential in the evaluation of the numeric values (Table 2), isolated with tachycardia as the optimal frame rate for speckle tracking is 50–70 frames per second (FPS). Compared to TDI which has an optimal frame rate of >180 FPS, the low frame rate of strain and SR imaging might result in undersampling in patients with tachycardia or other patients with a high heart rate, which is often the case with AF patients. This might to some extent explain our findings with regards to strain and SR being insignificantly associated with death in patients with AF.

Table 4: Intra and interobserver variability of tissue Doppler derived measures of peak systolic and diastolic velocity and maximal systolic displacement

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intraobserver variability (n=20)</th>
<th>Interobserver variability (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±1.96SD</td>
<td>CV (%)</td>
</tr>
<tr>
<td></td>
<td>Mean±1.96SD</td>
<td>CV (%)</td>
</tr>
<tr>
<td>High s’, high e’ (n = 99)</td>
<td>0.03±0.15</td>
<td>2</td>
</tr>
<tr>
<td>Low s’, high e’ (n = 41)</td>
<td>-0.09±0.30</td>
<td>2</td>
</tr>
<tr>
<td>Low s’, low e’ (n = 126)</td>
<td>0.04±0.30</td>
<td>2</td>
</tr>
</tbody>
</table>

Displaying the mean difference and the coefficient of variation. SD = standard deviation, CV = coefficient of variation, s’ = global peak systolic longitudinal mitral annular velocity determined by color Tissue Doppler Imaging, e’ = global peak early diastolic longitudinal mitral annular velocity determined by color Tissue Doppler Imaging, LD = global longitudinal displacement determined by color Tissue Doppler Imaging.
impaired systolic or diastolic dysfunction, determined by a low value of one velocity alone (Table 3), did not seem to provide statistically significant information on prognosis when the other velocity was high (Table 3). The combination of an impaired systolic and diastolic function, however, provides great prognostic value as this patient group had more than 3 times the risk of death compared to the group with high values of both s’ and e’ (p<0.001). Furthermore, (s’+e’) provided prognostic information above and beyond conventional echocardiographic parameters of systolic and diastolic function (Fig. 3).

Limitations
This retrospective study included only clinical echocardiographic examinations from the period 2005-2012 and echocardiograms were analyzed in the light of previous clinical reports, i.e. conventional echocardiographic data already noted in the downloaded examination was included in the study. This may have resulted in interobserver errors when assessing the echocardiographic examinations. Many previous studies states, that TDI is an independent predictor in sinus rhythm. We have not assessed the TDI velocities in SR as the purpose of the study was to evaluate the predictive value of TDI in AF.

Conclusion
The systolic and diastolic performances, as assessed by TDI, are strong predictors of mortality in patients with AF. The combination of systolic and diastolic dysfunction is especially a significant marker, which provides prognostic information incremental to conventional echocardiographic parameters of systolic and diastolic function.

References
