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

Maria Dons, MB[1], Tor Biering-Sørensen, MD, PhD[1,2], Jan Skov Jensen, MD, PhD, DMSc[1,2], Thomas Fritz-Hansen, MD[1], Jan Bech, MD, PhD[1], Martina Chantal de Knegt, MD[1], Jacob Sivertsen, MD[1], Flemming Javier Olsen, MB[1], Rasmus Mogelvang, MD, PhD[1]

[1]Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark. [2]Clinical Institute, Faculty of Health Sciences, University of Copenhagen, Denmark.

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[6] such as hypertension,[7] diabetes,[8] ischemic heart disease[9,10] 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
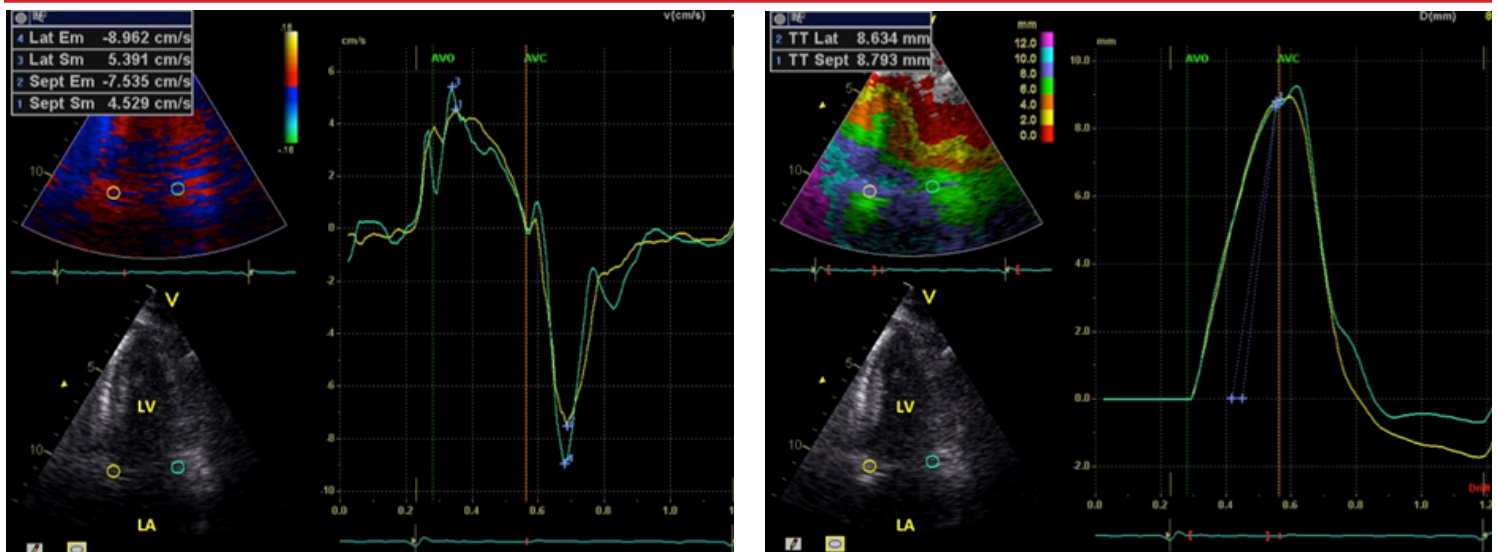
Figure 1: Color Tissue Doppler Imaging Curves
Examples of mitral annular longitudinal A) myocardial velocity curves and B) displacement curves

Table 1: Baseline clinical and echocardiographic characteristics in patients with atrial fibrillation stratified according to death

	Alive at follow-up (n = 249)	Dead at follow-up (n = 64)	P-value
Baseline characteristics			
Age (years)	71±10	79±8	<0.001
Male gender	70%	58%	0.14
Heart rate (beats/min)	88±26	95±35	0.08
Diabetes Mellitus (%)	5%	17%	0.002
Hypertension (%)	9%	17%	0.07
Thyroid toxicity/metabolic disease (%)	0%	3%	0.11
Ischaemic heart disease (%)	16%	16%	1.00
STEMI (%)	2%	5%	0.40
NSTEMI (%)	4%	8%	0.20
Valvular disease	35%	45%	0.15
Aortic stenosis (%)	12%	23%	0.027
Mitral stenosis (%)	2%	2%	1.00
Aortic insufficiency (%)	10%	9%	1.00
Mitral insufficiency (%)	19%	22%	0.60
Mitral valve prosthesis (%)	2%	2%	1.00
Aortic valve prosthesis (%)	5%	8%	0.36
Heart failure (%)	27%	34%	0.28
Conventional echocardiographic measurements			
LVEF (%)	47±8	41±10	<0.001
IVSd (cm)	1.1±0.00	1.1±0.00	0.12
LVIDd (cm)	4.9±0.01	4.8±0.01	0.32
LVPWd (cm)	1.1±0.00	1.1±0.00	0.12
Color Tissue Doppler Imaging			
s' (cm/s)	4.4 ±1.5	3.7±1.3	<0.001
e' (cm/s)	7.5±2.2	5.9±1.9	<0.001
LD (mm)	6.0±2.2	4.7±1.9	<0.001
Strain			
Global strain (%)	-11.7±3.99	-10.9±4.20	0.13
Global strain rate s' (s-1)	-0.78±0.24	-0.75±0.27	0.14
Global strain rate e' (s-1)	1.02±0.40	0.94±0.39	0.48

local hard disk since 2005.

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.
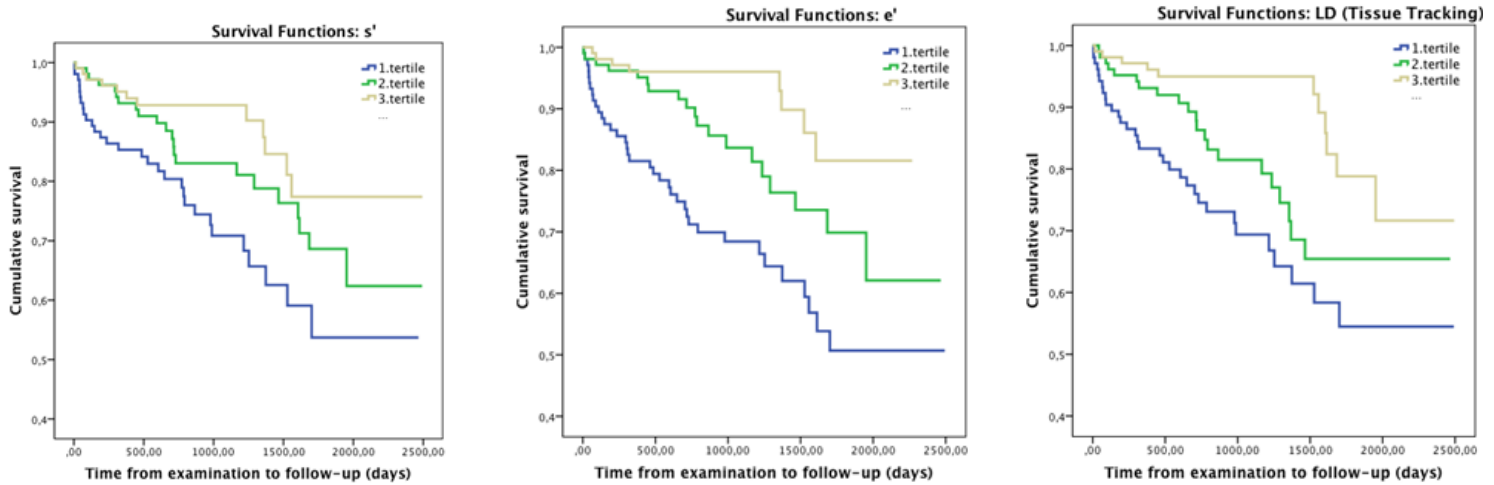
Figure 2:

Cumulative survival for patients stratified into tertiles of s', e' and LD
A) Kaplan-Meier curves depicting cumulative probability of staying event free for patients stratified into tertiles of global s', upper cutoff point being (4.8 cm/s) and lower cutoff point being (3.6 cm/s). B) Kaplan-Meier curves depicting cumulative probability of staying event free for patients stratified into tertiles of global e', upper cutoff point being (8.0 cm/s) and lower cutoff point being (6.1 cm/s). C) Kaplan-Meier curves depicting cumulative probability of staying event free for patients stratified into tertiles according to values of global LD, upper cutoff point being (6.6 mm) and lower cutoff point being (4.6 mm).

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

Table 2: Unadjusted and adjusted Cox proportional hazards regression models of global tissue Doppler velocities as predictors of outcome

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

DM = diabetes mellitus, LVEF = Left Ventricular Ejection Fraction, 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, E/E' = transmitral to mitral anular early diastolic velocity ratio

Color Tissue Doppler Imaging

Color TDI loops were obtained in the apical 4-chamber, 2-chamber and apical long-axis view. Peak longitudinal systolic (s') and early diastolic (e') velocities were measured at six mitral annular sites (Fig. 1a) obtained by dividing the LV into six segments of interest: the septal, lateral, anterior, inferior, posterior and anteroseptal myocardial wall. By averaging the myocardial velocities from the six mitral annular sites, an assessment of global longitudinal performance of the left ventricle is obtained. Inter- and intra-observer variability of mitral anular veloities estimated by color TDI have been reported to be low.[13,14,15] Also, longitudinal displacement was measured by tissue tracking in all six segments in the three apical projections and averaged to assess global longitudinal displacement (Fig. 1b).

Strain and Strain Rate Imaging

If frame rate was sufficient (i.e. ≥40 frames per second), strain and strain rate (SR) was measured by speckle tracking (n = 305, 61 events). Peak global longitudinal systolic strain and SR was measured and averaged to provide global strain and SR.

Follow-Up and Endpoint

The endpoint was defined as all-cause mortality. Data was obtained using a unique personal social security number issued by the Central Office of Civilian Registration. Follow-up was 100%.

Statistics

In Table 1, continuous Gaussian distributed variables were compared using student's t-test and χ^2-test was used for proportions.

Cumulative survival curves were established by the Kaplan–Meier method. Hazards ratios (HR) were calculated by uni- and multivariable Cox proportional hazards regression analyses. The assumption of proportional hazards was tested. Harrell's c-statistics were calculated for the conventional echocardiographic parameters (LVEF and E/e') and for the conventional echocardiographic parameters in combination with s'+e'. First order interaction was tested among valve diseases and TDI parameters and Bonferroni correction was used to exclude multiple significances.
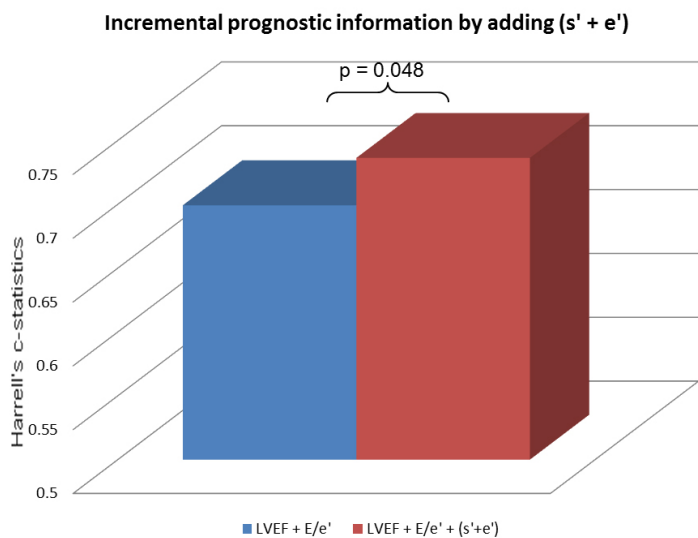
Incremental prognostic information by adding (s' + e')

Figure 3: Incremental prognostic information by adding an assessment of s'+e' to the conventional echocardiographic parameters
The Harrell's c-statistic values obtained from the multivariate Cox proportional hazards regression models. Model 1 includes LVEF and E/e'. Model 2 includes LVEF, E/e' and (s'+e')

LVEF = left ventricular ejection fraction, s'+e' = the sum of peak systolic and early diastolic mitral annular velocities by color tissue Doppler imaging, E/e' = ratio of early mitral inflow velocity divided by average septal and lateral mitral annular peak early diastolic velocity obtained by pulsed wave TDI

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[16] (Fig. 1a). Also, AF patients are often excluded in echocardiographic studies. This study is the first to illustrate that the prognostic information obtained by tissue Doppler imaging is applicable to patients with AF.

In the literature, many suggestions have been put forward with regards to risk stratification of 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.[17] 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

Table 3: Cox proportional hazardsregression model depicting the risk of reaching the combined endpoint for patients stratified according to high and low global s' and e'

	Hazard Ratio	95% CI	P-value
High s', high e' (n = 99)	-	-	-
High s', low e' (n = 47)	0.70	0.19 - 2.53	0.58
Low s', high e' (n = 41)	2.32	0.94 - 5.72	0.07
Low s', low e' (n = 126)	3.74*	1.88 - 7.46	<0.001

High and low global s' and e' refer to above or below the mean (cut-off points 4.27 cm/s for s' and 7.15 cm/s for e'). 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. * = Remained in significantly higher risk of death after adjustment for age, gender, heart rate, aortic stenosis, DM and LVEF quartiles
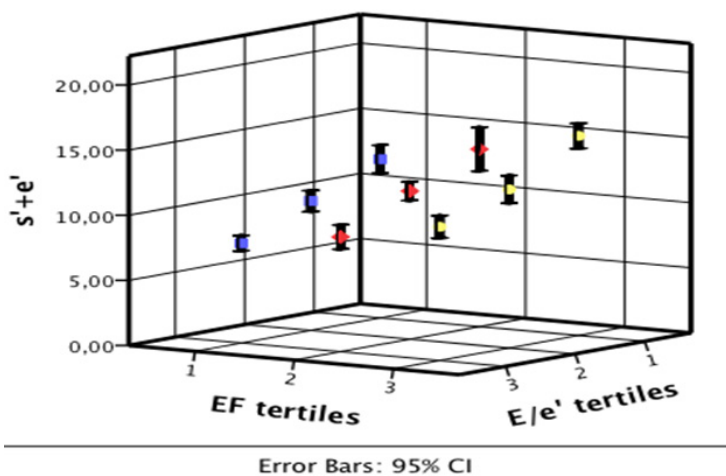
Error Bars: 95% CI

Figure 4:	**The association between s'+e', LVEF and E/e'** **The association between the combined systolic and early diastolic tissue Doppler velocities and two conventional echocardiographic measurements reflecting systolic (LVEF) and diastolic function (E/e'), showing that s'+e' correlates with both**

LVEF = left ventricular ejection fraction, s'+e' = the sum of peak systolic and early diastolic mitral annular velocities by color tissue Doppler imaging, E/e' = ratio of early mitral inflow velocity divided by average septal and lateral mitral annular peak early diastolic velocity obtained by pulsed wave TDI

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.[18] 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.[19] Strain and SR might be advantageous in the assessment of diastolic function in patients with AF.[16]

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 valid quantification of LA function in patients with LA dilatation due to AF and aging.[20] Furthermore, in patients with paroxysmal AF, decreased left atrial SR has been shown to be independently associated with paroxysmal AF.[21] Also, left atrial SR was significantly lower in patients with AF than in age-matched controls.[20]

Tops and collegues[22] demonstrated that global longitudinal strain and SR measured in the LV improved significantly in patients who maintained sinus rhythm following catheter ablation as opposed to patients with recurrent AF. The patients with a recurrence of AF had a significant decrease in LV longitudinal strain and SR. This might be due to the longitudinal fibers in the subendocardium that are be more prone to pathological changes in response to the fibrillating atria, and global longitudinal strain and SR imaging might better detect these pathological changes during diastolic filling. Nevertheless, global strain and SR did not seem to be significant prognosticators of death in the present study (Table 1). It has previously been stated that strain and SR measurements are difficult to apply in patients

with tachycardia as the optimal frame rate for speckle tracking is 50-70 frames per second (FPS).[18,23] 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.

Color Tissue Doppler Imaging

The prognostic value of TDI velocities has been validated in several studies.[6,24]

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,[25] 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 demontstrated the same pattern in patients with ST-segment elevation myocardial infarction.[26]

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

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

	Intraobserver variability (n=20)		Interobserver variability (n=20)	
	Mean±1.96SD	CV (%)	Mean±1.96SD	CV (%)
High s', high e' (n = 99)	0.03±0.15	2	-0.06±0.47	5
Low s', high e' (n = 41)	-0.09±0.30	2	0.15±0.55	4
Low s', low e' (n = 126)	0.04±0.30	2	-0.10±0.54	4

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

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285: 2370–2375.

2. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey J-Y, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europacel. 2010; 12: 1360–1420.

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22: 983–988.

4. Yu C-M, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. J. Am. Coll. Cardiol. 2007; 49: 1903–1914.

5. Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Schnohr P, Jensen JS. Tissue Doppler echocardiography in persons with hypertension, diabetes, or ischaemic heart disease: the Copenhagen City Heart Study. Eur. Heart J. 2009; 30: 731–739.

6. Wang M, Yip GWK, Wang AYM, Zhang Y, Ho PY, Tse MK, Lam PKW, Sanderson JE. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J. Am. Coll. Cardiol. 2003; 41: 820–826.

7. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, Yu C-M, Sanderson JE. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J. Hypertens. 2005; 23: 183–191.

8. Andersson C, Gislason GH, Møgelvang R, Hoffmann S, Mérie C, Køber L, Torp-Pedersen C, Søgaard P. Importance and inter-relationship of tissue Doppler variables for predicting adverse outcomes in high-risk patients: an analysis of 388 diabetic patients referred for coronary angiography. Eur. Heart J. Cardiovasc. Imaging 2012; 13: 643–649.

9. Westholm C, Johnson J, Sahlen A, Winter R, Jernberg T. Peak systolic velocity using color-coded tissue Doppler imaging, a strong and independent predictor of outcome in acute coronary syndrome patients. Cardiovasc. Ultrasound 2013; 11: 9.

10. Hoffmann S, Mogelvang R, Sogaard P, Iversen AZ, Hvelplund A, Schaadt BK, Fritz-Hansen T, Galatius S, Risum N, Biering-Sørensen T, Jensen JS. Tissue Doppler echocardiography reveals impaired cardiac function in patients with reversible ischaemia. Eur. J. Echocardiogr. 2011; 12: 628–634.

11. Lee C-H, Hung K-C, Chang S-H, Lin F-C, Hsieh M-J, Chen C-C, Chu C-M, Hsieh I-C, Wen M-S, Wu D. Reversible left ventricular diastolic dysfunction on Doppler tissue imaging predicts a more favorable prognosis in chronic heart failure. Circ. J. Soc. 2012; 76: 1145–1150.

12. Wang M, Yip G, Yu C-M, Zhang Q, Zhang Y, Tse D, Kong S-L, Sanderson JE. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. J. Am. Coll. Cardiol. 2005; 45: 272–277.

13. Olsen NT, Jons C, Fritz-Hansen T, Mogelvang R, Sogaard P. Pulsed-wave tissue Doppler and color tissue Doppler echocardiography: calibration with M-mode, agreement, and reproducibility in a clinical setting. Echocardiogr. 2009; 26: 638–644.

14. Manouras A, Shahgaldi K, Winter R, Nowak J, Brodin L-A. Comparison between colour-coded and spectral tissue Doppler measurements of systolic and diastolic myocardial velocities: effect of temporal filtering and offline gain setting. Eur. J. Echocardiogr. 2009; 10: 406–413.

15. De Knegt MC, Biering-Sorensen T, Sogaard P, Sivertsen J, Jensen JS, Mogelvang R. Concordance and reproducibility between M-mode, tissue Doppler imaging, and two-dimensional strain imaging in the assessment of mitral annular displacement and velocity in patients with various heart conditions. Eur. Heart J. Cardiovasc. Imaging 2014; 15: 62–69.

16. Kim T-S, Youn H-J. Role of echocardiography in atrial fibrillation. J. Cardiovasc. Ultrasound 2011; 19: 51–61.

17. Okura H, Takada Y, Kubo T, Iwata K, Mizoguchi S, Taguchi H, Toda I, Yoshikawa J, Yoshida K. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. Heart 2006; 92: 1248–1252.

18. Dandel M, Hetzer R. Echocardiographic strain and strain rate imaging--clinical applications. Int. J. Cardiol. 2009; 132: 11–24.

19. Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S, Smith H-J, Ihlen H, Edvardsen T. Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin. Sci. 1979 2007; 113: 287–296.

20. Inaba Y, Yuda S, Kobayashi N, Hashimoto A, Uno K, Nakata T, Tsuchihashi K, Miura T, Ura N, Shimamoto K. Strain rate imaging for noninvasive functional quantification of the left atrium: comparative studies in controls and patients with atrial fibrillation. J. Am. Soc. Echocardiogr. 2005; 18: 729–736.

21. Tsai W-C, Lee C-H, Lin C-C, Liu Y-W, Huang Y-Y, Li W-T, Chen J-Y, Lin L-J. Association of left atrial strain and strain rate assessed by speckle tracking echocardiography with paroxysmal atrial fibrillation. Echocardiogr. 2009; 26: 1188–1194.

22. Tops LF, Den Uijl DW, Delgado V, Marsan NA, Zeppenfeld K, Holman E, van der Wall EE, Schalij MJ, Bax JJ. Long-term improvement in left ventricular strain after successful catheter ablation for atrial fibrillation in patients with preserved left ventricular systolic function. Circ. Arrhythm. Electrophysiol. 2009; 2: 249–257.

23. Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, Gorissen W, Houle H. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. Echocardiogr. 2013; 30: 88–105.

24. Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Marott JL, Schnohr P, Goetze JP, Jensen JS. Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent predictor of mortality in the general population. Circulation 2009; 119: 2679–2685.

25. Shin H-W, Kim H, Son J, Yoon H-J, Park H-S, Cho Y-K, Han C-D, Nam C-W, Hur S-H, Kim Y-N, Kim K-B. Tissue Doppler imaging as a prognostic marker for cardiovascular events in heart failure with preserved ejection fraction and atrial fibrillation. J. Am. Soc. Echocardiogr. 2010; 23: 755–761.

26. Biering-Sørensen T, Jensen JS, Pedersen S, Galatius S, Hoffmann S, Jensen MT, Mogelvang R. Doppler Tissue Imaging Is an Independent Predictor of Outcome in Patients with ST-Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention. J. Am. Soc. Echocardiogr. 2014; 27: 258–267.