The prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure due to left ventricular systolic dysfunction

Nikolay P. Nikitin, Poay Huan Loh, Ramesh de Silva, Justin Ghosh, Olga Y. Khaleva, Kevin Goode, Alan S Rigby, Farqad Alamgir, Andrew L. Clark, John G.F. Cleland

Institutional Affiliation for all authors: Department of Cardiology, Academic Unit, The University of Hull, Kingston-upon-Hull, HU16 5JQ, UK

Corresponding Author: N.P. Nikitin
E-mail: N.P.Nikitin@hull.ac.uk Tel: +44-1482-624144 (business), fax: +44-1482-624073

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Abstract

Objective. This study was designed to assess the prognostic value of various conventional and novel echocardiographic indices in patients with chronic heart failure (CHF) due to left ventricular (LV) systolic dysfunction.

Methods. We prospectively enrolled 185 patients aged 67 (11) years with CHF and LV ejection fraction < 45% despite optimal pharmacological treatment. The patients underwent 2D echocardiography with tissue harmonic imaging to assess global LV systolic function and obtain volumetric data. Transmitral flow was assessed with conventional pulse wave Doppler. Systolic ($S_m$), early and late diastolic mitral annular velocities were measured with the use of colour-coded Doppler tissue imaging (DTI).

Results. During a median follow-up of 32 months (range 24 to 38 months in survivors), 34 patients died and one underwent heart transplantation. $S_m$ velocity (p=0.011), diastolic arterial pressure (p=0.015), serum creatinine (p=0.023), LV ejection fraction (p=0.024), age (p=0.052), LV end-systolic volume index (p=0.067), and restrictive pattern of transmitral flow (p=0.074) predicted the outcome of death or transplantation on univariate analysis. On multivariate analysis, only $S_m$ velocity (HR=0.648, 95%CI (0.460-0.912), p=0.013) and diastolic arterial pressure (HR=0.966, 95%CI (0.938-0.994), p=0.016) emerged as independent predictors of outcome.

Conclusions. In patients with CHF and LV systolic dysfunction despite optimal pharmacological treatment, the strongest independent echocardiographic predictor of prognosis was systolic mitral annular $S_m$ velocity measured with quantitative colour-coded DTI.
Introduction

Despite recent advances in management, chronic heart failure (CHF) is still associated with a high morbidity and mortality.[1] Risk stratification can help gauge which patients are most in need of further treatment or who remain at high risk of future events, and who should therefore be considered for clinical trials of new interventions.

Both the ESC [2] and ACC/AHA [3] guidelines recommend the use of echocardiography as the preferred diagnostic imaging tool. Echocardiographic techniques provide the cardiologist with numerous indices reflecting left ventricular (LV) systolic and diastolic function and ventricular remodelling. Many of these indices have been shown to predict outcome in patients with CHF,[4] but, surprisingly, controversy exists around one of the most popular measures, left ventricular ejection fraction (LVEF). Although LVEF measured by radionuclide ventriculography [5] [6] appears a consistent independent predictor of risk, this is less certain when LVEF is measured by echocardiography.[7] [8] [9] [10] [11] [12] The failure of echocardiographic LVEF to predict risk in some studies may reflect outmoded technology leading to poor quality data, the competing prognostic value of many other echocardiographic measurements that may eliminate LVEF on multivariate analysis and differences in patient samples.

Recent advances in echocardiography, such as the introduction of contrast and of tissue harmonic imaging, have improved the accuracy and reproducibility of echocardiographic imaging [13] and could enhance the value of LVEF measured by echocardiography for risk stratification in CHF. However, other echocardiographic techniques, such as Doppler tissue imaging (DTI), provide alternative, potentially more robust methods for risk stratification that are less dependent on the quality of images.

Few studies [14] [15] [16] have addressed the prognostic importance of novel tissue Doppler derived indices of LV systolic and diastolic function. The aim of this study was to assess the prognostic value of a range of conventional and novel indices of LV systolic and diastolic function obtained with the use of two-dimensional echocardiography with second harmonic imaging, conventional Doppler and quantitative colour-coded DTI in patients with CHF due to LV systolic dysfunction. Our intention was to identify those echocardiographic variables that provide independent prognostic value in addition to basic clinical information such as age, sex, aetiology of CHF, New York Heart Association (NYHA) functional class, heart rate, blood pressure, serum sodium and creatinine in order to generate a minimum prognostic data-set feasible for routine clinical use.

Methods

Study subjects. We prospectively enrolled 185 consecutive patients aged 67 (11) years (range 27 to 89 years) with clinical signs and symptoms of CHF. Exclusion criteria were preserved LV systolic function (LVEF ≥ 45%), atrial fibrillation, recent myocardial infarction (during the previous 6 months) and significant primary valvular heart disease. The aetiology of LV dysfunction was ischaemic heart disease in 153 patients and nonischemic cardiomyopathy in 32 patients. Informed consent was obtained in all study patients. The study complies with the Declaration of Helsinki and was approved by the local research ethics committee.
**Echocardiography.** The study subjects underwent full echocardiographic examination using commercially available equipment (GE Vingmed Vivid Five, Horten, Norway) equipped with a 2.5 MHz phased array transducer. Imaging was performed in the tissue harmonic imaging mode (Coded Octave Harmonic Imaging) with optimised gain settings.

LV end-diastolic volume and end-systolic volumes were calculated using the modified Simpson’s rule,[17] and the standard formula was applied to obtain LVEF. LV end-diastolic volume and end-systolic volume indices were obtained by correcting for body surface area.

**Doppler echocardiography.** Doppler studies were performed in the pulsed wave mode. Recordings of transmitral flow velocities were made from an apical 4-chamber view with the sample volume positioned at the tips of mitral leaflets in diastole. Care was taken to obtain the smallest possible angle between the direction of transmitral flow and the ultrasound beam.

Peak velocity of the E-wave (E), peak velocity of the A-wave (A), deceleration time of early filling and isovolumic relaxation time were measured from the transmitral Doppler spectrum. Deceleration time was calculated as the time between peak E wave and the upper deceleration slope extrapolated to the baseline, and isovolumic relaxation time was measured as the interval between the aortic valve closure click and the beginning of the E wave by placing the sample volume between the anterior mitral leaflet and LV outflow tract. The E/A ratio was also calculated.

According to Doppler-derived indices, patients were classified as having a restrictive (E/A ratio ≥ 2, or 1 < E/A ratio < 2 with deceleration time ≤ 140 ms) or non-restrictive (E/A ratio ≤ 1, or 1 < E/A ratio < 2 with deceleration time > 140 ms) pattern of LV diastolic filling.[18]

**Doppler tissue imaging.** Raw images were acquired with the use of real time two-dimensional colour-coded DTI in three apical views (4-chamber, 2-chamber, and apical long-axis view) and stored digitally on magnetic optical disks. A commercially available software package (Echopac 6.3, GE Vingmed) running on a Power Macintosh personal computer was used for off-line analysis of the data.

Longitudinal mitral annular systolic velocities (Sm), as assessed during true ventricular systole ignoring peaks that are observed during isometric ventricular contraction or post-systolic waves, early diastolic (Em) and late diastolic (Am) velocities were measured from 6 positions (at the lateral, septal, anterior, inferior, posterior and antero-septal sites of the mitral annulus) and averaged. The Em/Am ratio was then calculated. As an example, Fig. 1 illustrates a de-coded trace from a study patient obtained with quantitative TDI at the septal site of the mitral annulus.

The echocardiographic study was performed by the same experienced investigator (N.P.N). All measurements were done as the mean of two or three consecutive cardiac cycles.

**Clinical Variables Recorded.** The following clinical variables were recorded and included in the prognostic model: age, sex, body mass index, systolic, diastolic and pulse arterial pressure, heart rate, aetiology of CHF (ischaemic vs. non-ischaemic), NYHA functional class, serum sodium and creatinine.
Statistical analysis. Results are presented as mean (SD) or as number/percentage of patients. Univariate Cox proportional hazards analysis was performed to assess the significance of various variables as predictors of cardiac death or transplantation. Variables predictive of the outcome (p < 0.1) were then entered into a multivariate Cox proportional hazards regression model (forward selection) to identify independent predictors of cardiac death or transplantation. The output from the Cox regression analysis is given as hazard ratios with 95% confidence intervals. Cumulative mortality curves were obtained using the Kaplan-Meier method. The SPSS software (version 12.0 for Windows) was used for analysing data.

Results

Baseline characteristics of the study patients are shown in Table 1. The majority of patients were men and had ischaemic heart disease. All the patients were in class II (n=122) or III (n=63) of the NYHA functional classification at the time of entry into the study. Prior to recruitment, patients were followed for at least 6 months in a specialised heart failure clinic to ensure continued optimization of pharmacological therapy. Most patients were on beta-blockers (92%), of whom 72% were taking target doses. Every patient was either on an ACE inhibitor (84%) or an angiotensin receptor antagonist (16%), of whom 78% and 70% accordingly, were taking target doses. As for other heart failure medications, 84% of patients were taking diuretics, 35% taking spironolactone and 12% taking digoxin.

Thirty-four patients died and 1 patient underwent cardiac transplantation during a median follow-up of 32 months (range, 3 to 38 months). All surviving patients were followed for minimum of 24 months (range, 24 to 38 months). Table 2 shows the variables that predicted the combined outcome of death or cardiac transplantation on univariate Cox regression analysis (p<0.1). Systolic mitral annular S_m velocity, diastolic arterial pressure, serum creatinine, LVEF, age, LV end-systolic volume index (corrected for the body size) and restrictive pattern of transmital flow emerged as predictors of outcome in the study patients.

Sex, body mass index, systolic and pulse arterial pressure, heart rate, NYHA functional class, aetiology of CHF, serum sodium, LV end-diastolic volume index (corrected for the body size), individual Doppler indices of transmital flow (E, A, E/A ratio, isovolumic relaxation time and deceleration time), diastolic mitral annular velocities (E_m and A_m velocities, and their ratio E_m/A_m) and the E/E_m ratio did not show significant association with death and cardiac transplantation on univariate analysis in this study.

After all the variables that predicted the combined outcome of death or cardiac transplantation on univariate Cox regression analysis (p<0.1) were entered into a forward multivariate Cox regression analysis, only systolic mitral annular S_m velocity and diastolic arterial pressure emerged as independent predictors of outcome in patients with CHF. The final multivariate Cox model is shown in Table 2.

Two-year mortality (including 1 case of cardiac transplantation) in the study patients was 18%. Kaplan-Meier curves showing survival of the patients categorised according to S_m velocity of higher or less than 2.8 cm/s (median value) are shown in Fig. 2.
Table 1. Clinical and echocardiographic characteristics of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Study group (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 (11)</td>
</tr>
<tr>
<td>Male sex (n / %)</td>
<td>146 / 79</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 (4.1)</td>
</tr>
<tr>
<td>Systolic AP (mm Hg)</td>
<td>133 (22)</td>
</tr>
<tr>
<td>Diastolic AP (mm Hg)</td>
<td>81 (13)</td>
</tr>
<tr>
<td>Pulse AP (mm Hg)</td>
<td>52 (17)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71 (14)</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>139 (3)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>120 (44)</td>
</tr>
<tr>
<td>Ischemic aetiology (n / %)</td>
<td>153 / 83</td>
</tr>
<tr>
<td>EDV index (ml/m²)</td>
<td>116 (37)</td>
</tr>
<tr>
<td>ESV index (ml/m²)</td>
<td>76 (29)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>Peak E (cm/s)</td>
<td>81 (30)</td>
</tr>
<tr>
<td>Peak A (cm/s)</td>
<td>71 (32)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.62 (1.39)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>93 (33)</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>183 (69)</td>
</tr>
<tr>
<td>Restrictive TMF pattern (n / %)</td>
<td>56 / 30</td>
</tr>
<tr>
<td>S_m (cm/s)</td>
<td>2.9 (1.2)</td>
</tr>
<tr>
<td>E_m (cm/s)</td>
<td>3.1 (1.5)</td>
</tr>
<tr>
<td>A_m (cm/s)</td>
<td>4.0 (1.8)</td>
</tr>
<tr>
<td>E_m/A_m ratio</td>
<td>1.0 (1.1)</td>
</tr>
<tr>
<td>E/E_m ratio</td>
<td>31 (18)</td>
</tr>
</tbody>
</table>

Table footnote. Data are expressed as mean (SD) or as number/percentage of patients.
BMI, body mass index; AP, arterial pressure; HR, heart rate; NYHA, New York Heart Association; EDV, end-diastolic volume; ESV, end-systolic volume; E, peak velocity of early transmitral flow; A, peak velocity of atrial transmitral flow; IVRT, isovolumic relaxation time; DT, deceleration time of early transmitral flow; TMF, transmitral flow; S_m, systolic mitral velocity; E_m, early diastolic mitral velocity; A_m, late diastolic mitral velocity.
Table 2. Univariate and multivariate predictors of death and cardiac transplantation among patients with chronic heart failure

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Sm velocity</td>
<td>0.648 (0.463-0.907)</td>
<td>0.011</td>
<td>0.648 (0.460-0.912)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diastolic AP</td>
<td>0.965 (0.938-0.993)</td>
<td>0.015</td>
<td>0.966 (0.938-0.994)</td>
<td>0.016</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.006 (1.001-1.011)</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.945 (0.899-0.992)</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.035 (1.000-1.071)</td>
<td>0.052</td>
<td></td>
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</tr>
<tr>
<td>ESV index</td>
<td>1.009 (0.999-1.019)</td>
<td>0.067</td>
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<td></td>
</tr>
<tr>
<td>Restrictive TMF pattern</td>
<td>0.543 (0.278-1.061)</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table footnote. HR, hazard ratio; CI, confidence interval; Sm, systolic mitral velocity; AP, arterial pressure; ESV, end-systolic volume; TMF, transmitral flow

Discussion

This analysis suggests that a great array of echocardiographic measures adds little to a single, relatively simple marker of cardiac function in patients with CHF due to LV systolic dysfunction already receiving optimal medical therapy. To our knowledge, this is the first study demonstrating that systolic mitral annular Sm velocity is a powerful predictor of outcome in patients with CHF due to LV systolic dysfunction and is more strongly related to outcome than other echo-derived variables. It retains its prognostic value after adjusting for clinical data and other echocardiographic, conventional Doppler and tissue Doppler indices. The inter- and intraobserver variability of measurements of Sm velocity with the use of quantitative colour two-dimensional DTI is within 4-8%,[19] which compares favourably with assessment of LVEF [20] and the technique is now widely available on echocardiographic equipment of various manufacturers. The prognostic value of Sm velocity now requires replication in other cohorts and by other investigators.

Several previous studies using echocardiographic imaging have suggested that LVEF and/or LV volumes indices, which were probably measured less accurately in some studies before the era of harmonic imaging, were strong predictors of outcome in the setting of CHF [7][8][9] and after myocardial infarction.[21] However, other studies failed to show that these measures had independent predictive value even in relatively large cohorts of patients.[10][11][12] Univariate analysis of our data supports the observation that echocardiographic LVEF and volumetric data have prognostic value but are inferior to a tissue Doppler-derived index of LV systolic function (Sm velocity) which eliminated these conventional indices from a multivariate model.

Differences in predictive variables between studies may reflect differences in study samples, which variables were entered into the prognostic model and the accuracy of measurements, such as LV volumes, and their derivatives, such as LVEF. Importantly, changes in echocardiographic technology will have improved the accuracy of some measurements and added new variables. New technology is often rapidly adopted into clinical practice but this frequently leads to new
measurements being added to rather than replacing traditional ones. Whilst this may often be appropriate, it is not always so. Research should seek to rationalise clinical practice to identify the smallest amount of useful information and not just increase the number of things that can be measured.

Measures of LV diastolic filling obtained with the use of conventional Doppler have also been shown to be of prognostic significance. The restrictive pattern of transmitral flow was associated with an adverse prognosis in patients with dilated cardiomyopathy [22] and CHF due to LV systolic dysfunction.[18] However, the use of conventional Doppler indices of transmitral flow is associated with well recognised limitations. The pattern of transmitral flow is dependent on loading conditions, interpretation of the Doppler spectrum in the presence of severe mitral regurgitation is difficult, and measurements of the Doppler spectrum of pulmonary venous flow to improve interpretation are often difficult to obtain using the transthoracic approach. The restrictive pattern of transmitral flow, a predictor of outcome on univariate analysis in this study, was eliminated on multivariate analysis.

DTI is a relatively new echocardiographic technique, which enables measurement of atrioventricular annular and segmental myocardial velocities. Several DTI modes including pulsed wave DTI, colour M-mode DTI and colour two-dimensional DTI are currently available. DTI is less dependent on the quality of echocardiographic images and does not require tracing of endocardial contours unlike LV volumes and LVEF. The technique can also overcome some limitations of conventional Doppler studies (dependence on loading conditions).[23] The assessment of mitral annular motion has been recognised as an accurate method to quantify both systolic [24][25] and diastolic [23] [26] longitudinal LV function and normal values obtained with the use of pulsed wave DTI [27] and colour-coded two-dimensional DTI have been reported.[19]

Although not directly comparable, this study lends support to a few previous reports on prognostic significance of quantitative tissue Doppler indices reported in other cohorts of cardiac patients. Wang et al [16] demonstrated, in a group of patients with a variety of cardiac diseases, that both systolic Sm and early diastolic E_m mitral annular velocities were predictors of cardiac mortality on univariate analysis, but E_m velocity was marginally superior on multivariate analysis. In patients with LV dysfunction due to various causes, Yamamoto et al [15] found that late diastolic A_m mitral annular velocity (assessed as a single measurement at the posterior wall site of the mitral annulus) and E_m velocity in combination with mitral peak E-wave velocity (E/E_m ratio) were the strongest predictors of cardiac mortality. However, systolic S_m mitral annular velocity was not included in the analysis. Møller et al [14] studied a group of patients after first myocardial infarction and reported that the E/E_m ratio was an independent predictor of death or readmission to the hospital as the result of worsening of CHF. However, mitral annular velocities were measured at only one site (at the lateral site of the mitral annulus with the use of pulsed wave DTI) and no measurements of systolic S_m mitral annular velocity were reported.

Although most of the above studies focussed on diastolic measurements, it should be noted that there is a significant correlation between systolic and diastolic mitral annular velocities (both early and late) due to the close physiological interaction between systolic shortening and diastolic lengthening. The descent of the mitral annulus from its equilibrium position leads to storage and subsequent release of potential energy in a reciprocal fashion between atrium and ventricle.[28]
Low diastolic arterial pressure was another important predictor of outcome in this study. The prognostic significance of arterial pressure in patients with CHF has been previously reported.[29][30] Arterial pulse pressure, which was found to be of additional value in one study on post-infarction patients,[29] did not emerge as a predictor of outcome in this study.

**Limitations**
These data should be extrapolated to other groups of patients with care. It is not clear what effect chronic treatment with ACE inhibitors and beta-blockers has on the predictive accuracy of most variables and so our data should not be extrapolated to ACE inhibitor or beta-blocker naïve patients. We did not adjust for the known age-related decrease in $S_m$ velocity,[19] although age was included in the multivariate model, which could affect its predictive capacity.

Despite optimal pharmacological treatment, two-year mortality in this study was 18%. It is higher than rates suggested by large clinical trials. Several potential explanations exist for this discrepancy. Our patients were older and had more co-morbidity that would have excluded many from clinical trials. There was also a higher prevalence of ischaemic heart disease in our group of patients, which is associated with a worse outcome.[4]

Mitral annular velocities in this study were measured using two-dimensional colour-coded tissue DTI, and are lower than velocities measured with pulsed wave DTI. Further studies are required to elucidate whether the 2 techniques provide data of similar prognostic importance. However, we believe that colour-coded DTI is a more advanced method and has emerged as the leading method of investigating mitral annular motion.

**Conclusion**
In patients with CHF and LV systolic dysfunction despite optimal pharmacological treatment, the strongest independent echocardiographic predictor of prognosis was systolic mitral annular $S_m$ velocity measured with quantitative colour-coded DTI, a simple measure of LV systolic function.
Acknowledgements
We wish to thank the team of physicians and nurses in the Academic Unit of Cardiology in Hull for assistance with conducting the study, Elena Lukaschuk for research assistance, and Elaine Allison and Hanka Remblence for secretarial support.

Competing interest statement
There are no competing interests to report

Ethics Approval
Informed consent was obtained in all study patients. The study complies with the Declaration of Helsinki and was approved by the local (Hull and East Riding) research ethics committee.
References
Figure legends

Figure 1. Example of the measurement of systolic ($S_m$), early diastolic ($E_m$) and late diastolic ($A_m$) velocities at the septal site of the mitral annulus using color-coded tissue Doppler imaging. Note low mitral annular velocities suggestive of left ventricular dysfunction in a patient with chronic heart failure.

Figure 2. Survival curves categorised according to $S_m$ velocity, greater (upper curve) or less (lower curve) than 2.8 cm/s (median value), $p=0.01$. Vertical bars represent censored observations.