Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis

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Aims
Left ventricular (LV) hypertrophy and abnormal non-invasive measures of LV diastolic function are common in patients with severe aortic stenosis (AS) but their prognostic importance is uncertain. This study aimed to determine whether tissue Doppler measures of LV systolic and/or diastolic function or echocardiographic LV hypertrophy are useful for risk stratifying asymptomatic patients with severe calcific AS.

Methods and results
One hundred and eighty-three initially asymptomatic patients with moderate or severe AS (valve area mean 0.96 ± SD 0.3 cm²) and a normal LV ejection fraction were followed for median 31 (IQR 14–40) months. Peak systolic (S') and diastolic (E') mitral annular velocities and LV mass were measured by echocardiography at baseline and during follow-up. During follow-up 106 (58%) patients suffered symptomatic deterioration, including three sudden deaths and one resuscitated cardiac arrest. Peak aortic velocity (for 0.5 m/s increase HR = 1.43, 95% CI 1.25, 1.64, P = 0.0001) and aortic valve area (for 0.1 cm²/m² HR = 1.23, 95% CI 1.12, 1.35, P = 0.004) at baseline were most strongly associated with symptomatic deterioration. After peak aortic velocity adjustment neither LV mass index nor any measure of LV systolic or diastolic function was associated with symptomatic deterioration (P > 0.2 for all).

Conclusion
In patients with calcific AS who have a normal LV ejection fraction the severity of stenosis is the most important correlate of symptomatic deterioration. Tissue Doppler measures of LV systolic and diastolic function and LV mass provide limited predictive information after accounting for the severity of stenosis.

Keywords
Aortic stenosis ● Tissue Doppler imaging ● Left ventricular diastolic function ● Left ventricular hypertrophy

Introduction
Current guidelines recommend aortic valve replacement for severe aortic stenosis (AS) in symptomatic or asymptomatic patients when there is impairment of left ventricular (LV) function, defined as an ejection fraction <50%. Reduction in LV ejection fraction occurs late in the natural history of AS and most patients with severe AS have a normal LV ejection fraction even when symptoms are present. Conversely, LV hypertrophy and abnormal non-invasive measures of LV diastolic function are common in these patients. Decreased longitudinal contractile function measured by tissue Doppler imaging has also been reported in both symptomatic and asymptomatic patients with AS. Previous prospective cohort studies reported that higher peak aortic velocity and lower aortic valve area are associated with a higher risk of symptomatic deterioration. However, these studies did not...
include an assessment of longitudinal contractile function or a comprehensive evaluation of LV diastolic function. The aim of this study is to determine whether echocardiographic measures of LV hypertrophy and/or tissue Doppler measures of LV diastolic and LV longitudinal contractile function are associated with symptomatic deterioration and adverse clinical events in initially asymptomatic patients with moderate or severe AS.

Methods

Study population

Subjects had asymptomatic moderate or severe calcific AS defined as a peak velocity of $>3.0$ m/s measured by Doppler ultrasound, calcification of the aortic valve and LV ejection fraction $>50\%$ by echocardiography. Exclusion criteria included symptoms thought to be related to AS, previous or scheduled aortic valve replacement, another heart valve lesion of moderate or greater severity, an acute coronary syndrome during the previous 6 months, LV outflow obstruction from a cause other than AS, clinically significant respiratory disease, and serum creatinine $>0.16$ mmol/L. All subjects gave written informed consent and the study was approved by the regional ethics committee. Two hundred and 12 patients were enrolled from nine centres in New Zealand. Of these 183 met criteria for inclusion in this study (Figure 1).

Clinical assessment during follow-up

Study participants were assessed every 6 months during follow-up. At each visit patients were asked about cardiac symptoms. Dyspnoea, angina, and the occurrence of pre-syncope or syncope were noted. The clinician indicated whether symptoms were unlikely or likely to be due to AS. Cardiac medication and hospital admissions were recorded. A clinical outcomes committee reviewed clinical data to decide whether symptomatic deterioration due to AS had occurred.

Echocardiography

Echocardiography was performed at baseline, 12 and 24 months, and at the final visit up to 36 months after study entry using commercially available echocardiography machines. Images were stored digitally and analysed later blind to all other study information by an experienced echocardiographer (GW) at the Echocardiography Research Unit, University of Auckland using a commercial analysis system (EchoPac PC version 3.0 X GE Medical, Milwaukee, WI, USA).

Peak aortic velocity and aortic valve area (by the continuity equation using peak velocity) were determined using standard two-dimensional and Doppler techniques as described in the guidelines of the American Society of Echocardiography. Left ventricular volumes and LV mass (area-length) were determined utilizing standard and validated 2D and Doppler techniques. Left ventricular ejection fraction was measured using a single plane measurement from the apical four-chamber view using the modified Simpson’s method. To assess LV diastolic function, the trans-mitral early (E) and late (A) velocities and E wave deceleration time were measured by pulsed Doppler ultrasound from the mitral leaflet tips. Peak systolic ($S'$) and early ($E'$) and late ($A'$) diastolic velocities of the lateral and medial mitral annulus were measured by pulsed wave tissue Doppler imaging from the apical four-chamber view and the average used for analysis. Diastolic function was also classified as ‘impaired relaxation’ if $E/A$ was $<1.0$, ‘pseudo-normal filling’ if $E/A$ was $\geq 1.0$ and the deceleration time $>140$ ms, and ‘restrictive filling’ if $E/A$ was $\geq 1.0$ and the deceleration time $<140$ ms. Left atrial area was measured from the apical four-chamber view. Aortic valve area, LV mass, and left atrial area were normalized to body surface area.

Figure 2 Example of a recording of medial longitudinal mitral annular velocities measured by pulsed tissue Doppler ultrasound. The peak systolic ($S'$) and diastolic ($E'$) velocities are indicated. The average of the medial and lateral annular velocity was used in the analysis.
Statistical analysis
The differences in continuous measures at baseline between patients with and without symptom deterioration were assessed by the Mann–Whitney U-test; χ² or Fisher exact tests were used for categorical characteristics. Associations between pair-wise echocardiographic variables were assessed by the Spearman correlation coefficient. Time-dependent Cox regressions were used to assess relations between echocardiography variables and symptom deterioration or cardiac death. Echocardiographic variables included in the model were the tissue Doppler measurements of LV systolic and diastolic functions and LV mass, and any variables with \( P < 0.10 \) in the baseline comparison. The first used each individual value at different time points and the second used the average of all previous measurements at each time point. Only echocardiographic measurements made before the onset of symptoms were used in the analysis. Results were similar but confidence intervals narrower when the average of all measurements was used and these results are reported in Table 2. Multiple Cox regression was also used to adjust for clinical variables which may be associated with outcome. Deviance residual and Shoenfeld residuals were used to assess the assumption of proportionality. Analyses were performed with SAS software (version 9; SAS Institute, Inc., Cary, NC, USA). P-values <0.05 were considered significant and all tests were two tailed.

Results
The mean age of the study population was 70 years, 65% were male and the majority had European ancestry (84%). Half (51%) were current or previous smokers; 47% had a history of hypertension; 13%, of diabetes; and 5%, of chronic obstructive pulmonary disease. The median aortic valve area was 0.81 (IQR 0.62–1.01) cm² and median LV ejection fraction was 74% (IQR 68–81%). All patients had calcific AS. In 6%, this was a consequence of rheumatic heart disease and in 15%, a bicuspid aortic valve. At baseline 34% of patients were taking a beta-blocker; 23% an angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist; and 5% a loop diuretic.

Clinical outcomes during follow-up
The median follow-up was 31 months (inter-quartile range 14–40). One hundred and fifty-three (81%) patients completed at least 12 months follow-up. One hundred and six (58%) subjects suffered symptomatic deterioration due to AS during follow-up (Figure 1). The most common symptoms were increase in shortness of breath and/or angina on exertion. Ninety-five of these patients were referred for cardiac surgery. Three patients died suddenly and one patient was resuscitated following an out of hospital cardiac arrest.

Comparison of patients with and without symptomatic deterioration
There were no significant differences in age, gender, current smoking, diabetes, chronic obstructive pulmonary disease, serum creatinine, or haemoglobin between patients who remained symptomatic and those who suffered symptomatic deterioration during follow-up. There were also no significant differences in the proportion of patients taking a beta-blocker, angiotensin converting enzyme inhibitor, or loop diuretic. Patients who suffered symptomatic deterioration were slightly more likely to have a lower systolic (<130 mmHg, \( P = 0.05 \)) or diastolic (<70 mmHg, \( P = 0.02 \)) blood pressure at baseline (Table 1).

On average patients who suffered symptomatic deterioration had a higher peak aortic velocity and a lower aortic valve area index at the baseline assessment (Table 1). They also had a higher LV mass index and lower peak S. Trends for larger left atrial area, lower E′, and higher E/E′ in patients who became symptomatic were not statistically significant, and there was no difference in the proportion of patients with other measures of diastolic function (Table 1).

Echocardiography during follow-up
During follow-up peak aortic velocity increased and aortic valve area decreased. The average rate of increase in peak aortic velocity was greater for patients who became symptomatic compared with those who remained asymptomatic (31 ± 55 vs. 13 ± 32 cm/s/year, \( P = 0.0008 \)). In contrast, change in echocardiographic measures of LV function including S′, E′, E/E′, and LV mass during follow-up were small and not statistically significant. In addition, there was no difference in the average rate of change of these measurements between subjects who became symptomatic and those who remained asymptomatic during follow-up (\( P > 0.1 \) for all).

Associations with symptomatic deterioration
The risks of symptomatic deterioration by different echocardiographic parameters measured at baseline and during follow-up but before the onset of symptoms are presented in Table 2. The hazard ratio for symptomatic deterioration increased with higher peak aortic velocity and with smaller aortic valve area. There were weaker associations between symptomatic deterioration and lower S′, lower E′, and higher E/E′ on univariate analysis. There was no statistically significant association between symptomatic deterioration and either LV mass, LV ejection fraction, TDI A′, the ratio of E′ to A′, the ratio of mitral inflow velocities (E/A), or the deceleration time of the early mitral (E) filling wave (data not shown, \( P > 0.2 \) for all). Hazard ratios were similar when calculated from measurements at baseline only or from all baseline and follow-up measurements (Table 2), and when only the last follow-up measurement prior to onset of symptoms was used in analysis (data not shown). The Kaplan–Meier plots for symptom-free survival by peak aortic velocity, S′, and LV mass index are presented in Figure 3A–C.

There were statistically significant correlations between the peak aortic velocity and tissue Doppler measures of LV systolic function (S′, \( r = 0.29 \), \( P = 0.0002 \)) and LV diastolic function (E′, \( r = -0.28 \), \( P = 0.0002 \); E/E′, \( r = 0.25 \), \( P = 0.001 \)) and LV mass (\( r = 0.39 \), \( P < 0.001 \)). In multivariate models, the peak aortic velocity was the only significant predictor of symptomatic deterioration (\( P < 0.0001 \)). Other echocardiographic measures did not provide additional predictive information when peak velocity was included in the model (Table 2). There was also no evidence for
a statistical interaction between peak aortic velocity, other echo-Doppler measures (tissue Doppler measures of systolic or diastolic function, left atrial area or LV mass), and clinical outcome (P-value for interaction >0.2 for all).

### Discussion

In this study of initially asymptomatic patients with moderate-severe calcific AS and a normal LV ejection fraction, the peak...
Figure 3 Kaplan–Meier plots for survival free of symptoms of aortic stenosis by (A) peak aortic velocity <350 cm/s, 350–400 cm/s, and >400 cm/s (log rank \( P < 0.0001 \)); (B) peak mitral annular systolic velocity (S') < and \( \geq 6.7 \text{ cm/s} \) (\( P = 0.02 \)), and (C) LV mass < and \( \geq 133 \text{ g/m}^2 \) (\( P = 0.66 \)). Cut levels for S' and LV mass index are the median levels for the study population. For S' time from the first follow-up measurement was used in the analysis if the baseline measure was missing or of poor quality.
Tissue Doppler imaging in aortic stenosis

aortic velocity was the variable most strongly correlated symptom onset. Increase in peak aortic velocity during follow-up was also associated with a higher risk of symptomatic deterioration. These observations are consistent with previous prospective cohort studies. However, these earlier studies were undertaken before the availability of tissue Doppler imaging and did not include an assessment of LV longitudinal contractile or diastolic functions.

Because the LV ejection fraction is normal in most symptomatic patients with AS and non-invasive indices of diastolic function are often abnormal, symptoms such as dyspnoea and fatigue may be due to ‘LV diastolic dysfunction’. In a previous study of patients with severe AS and more advanced symptoms, a raised end diastolic pressure at cardiac catheterization was associated with a high E/E′. In the current study, there was a modest but statistically significant association between increasing severity of AS and lower E′ and higher E/E′ in asymptomatic patients. However, after adjusting for peak velocity in multivariate analysis there was no significant association between any measure of diastolic function at baseline or during follow-up and subsequent symptomatic deterioration. Other measures of diastolic dysfunction associated with adverse outcomes in patients with heart failure or after myocardial infarction including the left atrial area, the ratio E/E′ and the E wave deceleration time were similar in patients who did and did not suffer symptomatic deterioration. These observations suggest excessive after-load rather than LV diastolic function is the predominant determinant of symptoms for most patients with AS.

S′ was chosen to estimate global longitudinal LV contractile function in this study because it is widely available and easy to record and measure by pulsed wave tissue Doppler ultrasound. Cross-sectional studies have reported that peak mitral systolic annular velocity (S′) is lower in symptomatic compared with asymptomatic patients with AS, and that lower S′ is associated with a greater risk of LV dysfunction after aortic valve replacement. In a study by Van Pelt S′ was similar at rest for patients with AS compared with controls, but increase in S′ after exercise was lower in AS. More direct measures of regional myocardial strain, for example from speckle tracking have also been associated with risk of symptom onset on univariate analysis in patients with AS. In the current study, S′ was on average lower in patients who became symptomatic, but S′ tended to decrease as the severity of the aortic valve stenosis increased, and after adjustment for stenosis severity the association between S′ and symptomatic deterioration was not statistically significant. These observations suggest that the decrease in longitudinal LV strain is at least in part a consequence of the increase in LV after-load in these patients.

Left ventricular hypertrophy is associated with increased mortality in general population studies and in patients with hypertension. In AS LV hypertrophy is an adaptive response to increased LV after-load, which could have both favourable and adverse effects. A previous study suggested that severe LV hypertrophy is associated with poorer outcomes after aortic valve replacement. However, in the current study neither echocardiographic LV mass nor electrocardiographic LV hypertrophy predicted symptomatic deterioration after accounting for the severity of the valve stenosis.

Study limitations

In this study, the major outcome was symptomatic deterioration due to AS, and this was the indication for surgery in almost all patients. In most of these patients, symptoms were mild or moderate rather than severely limiting at the time of referral for aortic valve replacement. The study did not have sufficient statistical power to evaluate associations between LV hypertrophy and diastolic dysfunction and serious adverse events. The occurrence, despite regular monitoring, of one resuscitation from ventricular fibrillation and three sudden deaths is cause for concern. All of these patients had a peak velocity >4.0 m/s at the last assessment, a level which predicts a high rate of symptomatic deterioration. No patients developed overt heart failure or a significant decrease in the LV ejection fraction during follow-up.

While images were analysed at a core laboratory, echocardiograms were performed by different experienced sonographers at participating sites. Variability in performance of scans would decrease the statistical power of the study to evaluate modest associations. Echocardiograms were performed according to recommendations from standard guidelines and study results are likely to reflect the predictive value of these echocardiographic measurements in usual clinical practice.

Much longer follow-up including follow-up after aortic valve replacement would be needed to evaluate possible long-term adverse effects of marked LV hypertrophy and LV diastolic dysfunction in AS. In this study, over half the participants became symptomatic within 2–3 years, and for this outcome, medium-term predictors of symptom onset are most relevant. The study results support current guidelines which recommend repeat echocardiography at least yearly in patients with severe AS to detect disease progression and change in risk.

Conclusion

In asymptomatic patients with moderate to severe AS and a normal LV ejection fraction the peak aortic velocity and aortic valve area are the most important correlates of symptomatic deterioration, which may occur without progressive worsening of LV systolic or diastolic functions. Referral for surgery may be justified in asymptomatic patients with very severe AS because of the high risk of symptom deterioration and the small risk of sudden death.

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