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Original research

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ABSTRACT

Objective To investigate the prognostic impact of left ventricular (LV) diastolic dysfunction in patients with moderate aortic stenosis (AS) and preserved LV systolic function.

Methods Patients with a first diagnosis of moderate AS (aortic valve area >1.0 and ≤1.5 cm^2) and preserved LV systolic function (LV ejection fraction ≥50%) were identified. LV diastolic function was evaluated using echocardiographic criteria according to the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines. Clinical outcomes were defined as all-cause mortality and a composite of all-cause mortality and aortic valve replacement (AVR).

Results Of 1247 patients (age 74±10 years, 47% men), 535 (43%) had LV diastolic dysfunction at baseline. Patients with LV diastolic dysfunction showed significantly higher mortality rates at 1-year, 3-year and 5-year follow-up (13%, 30% and 41%, respectively) when compared with patients with normal LV diastolic function (6%, 17% and 29%, respectively) (p<0.001). On multivariable analysis, LV diastolic dysfunction was independently associated with all-cause mortality (HR 1.368; 95% CI 1.085 to 1.725; p=0.008) and the composite endpoint of all-cause mortality and AVR (HR 1.241; 95% CI 1.035 to 1.488; p=0.020).

Conclusions LV diastolic dysfunction is independently associated with all-cause mortality and the composite endpoint of all-cause mortality and AVR in patients with moderate AS and preserved LV systolic function. Assessment of LV diastolic function therefore contributes significantly to the risk stratification of patients with moderate AS. Future clinical trials are needed to investigate whether patients with moderate AS and LV diastolic dysfunction may benefit from earlier valve intervention.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients with severe aortic stenosis (AS) and preserved left ventricular (LV) ejection fraction (EF), LV diastolic dysfunction is associated with an unfavourable prognosis.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that LV diastolic dysfunction is independently associated with reduced event-free survival in a large cohort of patients with moderate AS and preserved LVEF, after adjustment for other important confounders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Recent studies have shown that moderate AS is associated with reduced survival.
⇒ Assessment of LV diastolic dysfunction may identify patients at an increased risk of mortality or requiring future aortic valve replacement (AVR).
⇒ The role of LV diastolic dysfunction to identify patients with moderate AS who may benefit from early AVR merits further investigation.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease in developed countries and its prevalence is increasing with ageing of the population.[1] It is well documented that severe AS is associated with significantly reduced survival if left untreated.[2] Recent studies have demonstrated that moderate AS is also associated with reduced survival.[3] Despite these findings, identifying patients with moderate AS at increased risk of adverse events has not been thoroughly investigated with only a few studies reporting worse outcome in the presence of reduced left ventricular (LV) systolic function.[4 5] In patients with severe AS and preserved LV systolic function, LV diastolic dysfunction is associated with an unfavourable prognosis.[6–8] Moreover, patients with advanced LV diastolic dysfunction may not show LV reverse remodelling after aortic valve intervention leading to worse outcomes.[9] Therefore, assessment of LV diastolic dysfunction at an earlier stage could help to risk-stratify patients with moderate AS and preserved LV systolic function, which may improve selection of patients who might benefit from surgical or transcatheter valve replacement. Accordingly, the aim of the present study was to evaluate the prognostic implications (in terms of aortic valve surgery and all-cause mortality) of LV diastolic dysfunction in patients with moderate AS and preserved LV systolic function.

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METHODS

Patient population

From the ongoing registries of patients with moderate aortic valve stenosis from three academic institutions (Leiden University Medical Center, Leiden, The Netherlands; National University Hospital, Singapore; and National Heart Center Singapore, Singapore), patients ≥18 years who presented between October 2001 and December 2019 with a first echocardiographic diagnosis of moderate AS and LV ejection fraction (EF) ≥50% were identified.[10] Moderate AS was defined as an aortic valve area between 1.0 and 1.5 cm^2.[11] The definition of moderate AS based on aortic valve area was used to avoid inclusion of patients with severe, low-flow, low-gradient AS. Patients with previous aortic valve surgery, congenital heart disease, bicuspid aortic valve, supravalvular or subvalvular AS or dynamic LV outflow tract obstruction were excluded. All patients underwent complete clinical and echocardiographic evaluation at the time of first diagnosis of moderate AS. Patient information was prospectively collected from the departmental cardiology information system and retrospectively analysed. Clinical data included demographic characteristics, cardiovascular risk factors, New York Heart Association (NYHA) functional class and comorbidities. The study complies with the Declaration of Helsinki and was approved by the institutional review boards of each centre. Due to the retrospective design of the study, the medical ethical committee of each participating centre waived the need for written informed consent.

Transthoracic echocardiography

All echocardiographic studies were performed using commercially available ultrasound systems and images were retrospectively analysed in each centre according to current guidelines.[12] In the parasternal long-axis view, LV dimensions were assessed and LV mass was calculated using Devereux's formula and indexed for body surface area.[12] LV volumes were assessed and LVEF was calculated according to Simpson's biplane method.[12] Left atrial volumes were measured by the biplane method of disks and indexed for body surface area.[12] From the apical 3-chamber or 5-chamber views, continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity.[13] Mean and peak transvalvular pressure gradients were calculated using the Bernoulli equation (13). Aortic valve area was calculated using the LV outflow tract diameter and velocity time integrals of the aortic valve and LV outflow tract.[13] Severity of mitral and tricuspid regurgitation was graded using a multiparametric approach, as recommended by current guidelines.[14] Pulsed wave-Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities.[15] Using tissue Doppler imaging of the mitral annulus on the apical 4-chamber view, the e′ was measured at both the lateral and septal side, and averaged to calculate the E/e′ ratio.[15] The right ventricular systolic pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava.[12 16] LV diastolic function was then evaluated using septal and lateral e′ velocity, average E/e′, tricuspid regurgitation velocity and left atrial volume index and categorised as normal, indeterminate or diastolic dysfunction, according to the current guidelines[15] (figure 1). Patients who could not be categorised into one of these three groups due to insufficient data were excluded. For the evaluation of right ventricular systolic function, anatomical M-mode was applied on the focused apical 4-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion.[16]

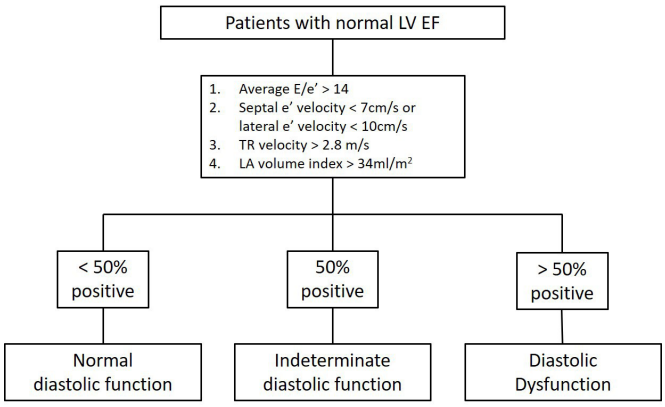

Figure 1 Assessment of left ventricular diastolic function in patients with normal LVEF. LA, left atrium; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

Clinical endpoints

All patients were followed-up for all-cause mortality and the occurrence of aortic valve replacement (AVR) (either surgical or transcatheter). The primary outcome was all-cause mortality, which was obtained by review of hospital records linked to the governmental death registry database. The secondary outcome was a composite of all-cause mortality and surgical or transcatheter AVR as well as AVR alone. Indications for AVR were based on contemporary guidelines.[11 17]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Statistical analysis

Continuous data are presented as mean±SD when normally distributed and as median (IQR) when not normally distributed. Categorical data are presented as frequencies and percentages. For comparison of continuous variables between groups, the one-way analysis of variance with Bonferroni's post hoc analysis or the Kruskal-Wallis test were used for normally and non-normally distributed variables, respectively. Categorical variables were compared using the Pearson χ^2 test. Event-free survival curves were generated using the Kaplan-Meier method, and differences between groups were analysed using the log-rank test. Univariable and multivariable Cox proportional hazard analyses were performed to assess the association of the different stages of diastolic function and the endpoints of all-cause mortality, all-cause mortality or AVR and AVR without the use of model building techniques. The following covariates, considered to have a potential prognostic impact (on the basis of epidemiological data[18]) were included: age, sex, diabetes mellitus, arterial hypertension, dyslipidaemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, NYHA functional class III to IV, LVEF and aortic valve area. The occurrence of AVR was entered as a time-dependent covariate. The entry criterium for the multivariable regression analysis was an amount of missing values that did not exceed 10% of the total study population. For both univariable and multivariable analysis, hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. The

Table 1 Baseline clinical characteristics

	Overall population (n=1247)	Normal diastolic function (n=396)	Indeterminate diastolic function (n=316)	Diastolic dysfunction (n=535)	P value
Clinical and demographic characteristics					
Age, years	73.8 (±10.3)	72.9 (±9.9)	74.9 (±9.4)*	73.9 (±11.0)	0.035
Male sex (%)	591 (47.4%)	243 (61.4%)	151 (47.8%)*	197 (36.8%)*†	<0.001
Systolic BP, mm Hg	140 (±23)	139 (±21)	140 (±21)	141 (±24)	0.345
Diastolic BP, mm Hg	71 (±12)	72 (±12)	72 (±13)	70 (±12)	0.211
Arterial hypertension (%)	1001 (80.5%)	301 (76.2%)	253 (80.1%)	447 (83.9%)*	0.014
Dyslipidaemia (%)	911 (73.4%)	278 (70.4%)	224 (71.3%)	409 (76.9%)	0.054
DM (%)	414 (33.3%)	118 (29.9%)	99 (31.3%)	197 (37.0%)	0.053
Current smoker (%)	102 (8.6%)	40 (10.7%)	23 (7.6%)	39 (7.6%)	0.218
Obesity (%)	240 (19.3%)	77 (19.4%)	70 (22.2%)	93 (17.5%)	0.260
CAD (%)	514 (41.3%)	148 (37.5%)	128 (40.5%)	238 (44.6%)	0.089
Previous MI (%)	190 (15.3%)	51 (12.9%)	47 (14.9%)	92 (17.2%)	0.196
Atrial fibrillation (%)	315 (25.3%)	58 (14.7%)	75 (23.7%)*	182 (34.1%)*†	<0.001
Previous stroke (%)	183 (14.7%)	60 (15.2%)	44 (13.9%)	79 (14.8%)	0.891
COPD (%)	83 (6.7%)	29 (7.3%)	24 (7.6%)	30 (5.6%)	0.438
NYHA class II to IV (%)	509 (41.3%)	134 (34.4%)	127 (40.6%)	248 (47.0%)*	0.001
Angina (%)	106 (8.6%)	40 (10.2%)	31 (9.9%)	35 (6.6%)	0.100
Syncope (%)	19 (1.5%)	5 (1.3%)	5 (1.6%)	9 (1.7%)	0.867
Medication					
Beta-blocker (%)	573 (46.3%)	158 (40.0%)	146 (46.6%)	269 (50.8%)*	0.005
ACEi or ARB (%)	592 (47.8%)	178 (45.1%)	154 (49.2%)	260 (49.1%)	0.413
MRA (%)	48 (3.9%)	12 (3.0%)	17 (5.4%)	19 (3.6%)	0.235
Diuretic (%)	375 (30.3%)	97 (24.6%)	87 (27.8%)	191 (36.0%)*†	<0.001
CCB (%)	514 (41.5%)	152 (38.5%)	108 (34.5%)	254 (47.9%)*†	<0.001
Statin (%)	847 (68.4%)	268 (67.8%)	209 (66.8%)	370 (69.8%)	0.629
Aspirin (%)	557 (45.0%)	172 (43.5%)	145 (46.3%)	240 (45.3%)	0.749
Oral anticoagulation (%)	217 (17.5%)	48 (12.2%)	53 (16.9%)	116 (21.9%)*	0.001
Laboratory results					
eGFR, mL/min/1.73 m^2	69.3 (48.0–89.7)	75.5 (55.6–94.0)	72.9 (52.6–89.1)	62.3 (37.8–84.0)*†	<0.001
Haemoglobin, g/L	125 (110–137)	129 (118–140)	127 (112–138)	121 (104–134)*†	<0.001

Values are presented as mean±SD, median (IQR) or n (%).
*p<0.05 vs Group I.
‡p<0.05 vs Group II.
ACEi, ACE converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

assumption of proportional hazards was tested based on the Schoenfeld residuals. A two-sided p value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, V.25.0 (IBM) and R V.4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient population

A total of 1247 patients (age 74±10 years, 47% men) were included in the study (online supplemental figure S1). Baseline characteristics are shown in table 1, while table 2 summarises the echocardiographic data for the overall population. There were 396 (32%) patients with normal LV diastolic function, 316 (25%) patients with indeterminate LV diastolic function and 535 (43%) patients with LV diastolic dysfunction.

Patients with LV diastolic dysfunction were more likely to be female, had more comorbidities (eg, hypertension, atrial fibrillation, chronic kidney disease) and were more symptomatic (NYHA functional class ≥II) compared with patients with normal LV diastolic function (table 1). In terms of echocardiographic data, patients with LV diastolic dysfunction had higher LV mass index and smaller aortic valve area compared with patients with normal LV diastolic function (table 2).

Prognostic value of diastolic dysfunction in moderate AS

During a median follow-up of 53 (IQR 26–81) months, 484 (39%) patients died. Survival rate was 91% at 1 year, 77% at 3 years and 65% at 5 years. For the composite endpoint of all-cause mortality and AVR, 770 patients (62%) underwent AVR (n=376 (49%)) or died (n=394 (51%)) during a median follow-up of 37 (IQR 15–62) months. Of the 376 patients who underwent AVR, 146 (39%) underwent transcatheter AVR and 230 (61%) underwent surgical AVR. The indication for AVR was the presence of moderate AS with concomitant coronary artery disease, requiring coronary artery bypass grafting in 127 (34%) patients and progression to severe AS in the remaining 249 (66%) patients.

Patients with LV diastolic dysfunction showed significantly higher mortality rates at 1-year, 3-year and 5-year follow-up (13%, 30% and 41%, respectively) when compared with patients with normal LV diastolic function (6%, 17% and 29%, respectively) (log rank χ^2 22.6; p<0.001) (figure 2A). Patients

Table 2 Baseline echocardiographic characteristics

	Overall population (n=1247)	Normal diastolic function (n=396)	Indeterminate diastolic function (n=316)	Diastolic dysfunction (n=535)	P value
Left ventricle and atrium					
LV EDD, mm	46.6 (±6.1)	46.1 (±5.7)	46.7 (±5.8)	47.0 (±6.5)	0.097
LV ESV, mL	34 (27–44)	32 (26–41)	35 (27–43)	36 (27–46)*	0.029
LV EDV, mL	93 (77–116)	90 (79–113)	96 (77–113)	97 (75–119)	0.117
LVEF, %	63.3 (±6.9)	64.0 (±6.4)	62.8 (±7.0)	63.0 (±7.3)	0.045
LVMI, g/m^2	110.7 (±31.3)	101.3 (±26.1)	109.7 (±29.4)*	118.4 (±33.8)*†	<0.001
LAVi, mL/m^2	35 (28–45)	28 (23–32)	33 (28–41)*	44 (38–55)*†	<0.001
E/e′	13.9 (10.5–18.9)	10.3 (8.6–12.1)	13.6 (10.5–16.9)*	19.0 (16.0–24.9)*†	<0.001
Moderate or severe MR (%)	89 (7.1%)	6 (1.5%)	19 (6.0%)*	64 (12.0%)*†	<0.001
Aortic valve					
Stroke volume index, mL/m^2	50 (±12)	47 (±12)	48 (±12)	52 (±12)*†	<0.001
Peak aortic velocity, m/s	3.1 (±0.6)	3.1 (±0.6)	3.0 (±0.6)	3.1 (±0.5)†	0.014
Aortic mean pressure gradient, mm Hg	23.2 (±8.6)	23.3 (±8.7)	22.7 (±9.1)	23.5 (±8.1)	0.445
Aortic valve area, cm	1.23 (±0.15)	1.23 (±0.14)	1.24 (±0.15)	1.20 (±0.15)*†	0.013
Moderate or severe AR, %	124 (9.9%)	28 (7.1%)	33 (10.4%)	63 (11.8%)	0.057
Right ventricle					
TAPSE, mm	22 (19–25)	22 (19–25)	22 (20–25)	21 (19–24)	0.026
PASP, mm Hg	32 (26–40)	28 (23–33)	29 (24–35)*	39 (32–47)*†	<0.001
Moderate or severe TR, %	198 (15.9%)	28 (7.1%)	29 (9.2%)	141 (26.4%)*†	<0.001

Values are presented as mean±SD, median (IQR) or n (%).
*p<0.05 vs Group I.
†p<0.05 vs Group II.
AR, aortic regurgitation; EDD, end-diastolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

with LV diastolic dysfunction also had significantly lower event-free survival for the combined endpoint of AVR and all-cause mortality (log rank χ^2 8.4; p=0.015) (figure 2B). The Kaplan-Meier curve for all-cause mortality censored for AVR, according to the different stages of diastolic function is shown in online supplemental figure S2.

Univariable and multivariable Cox proportional hazard models were built with covariates selected a priori on the basis of epidemiological data. In addition, AVR was included as a time-dependent covariate in the multivariable model evaluating the endpoint of all-cause mortality. On multivariable analysis, LV diastolic dysfunction was independently associated with all-cause mortality (HR 1.368; 95% CI 1.085 to 1.725; p=0.008), as well as with the combined endpoint of all-cause mortality and AVR (HR 1.241; 95% CI 1.035 to 1.488; p=0.020) (table 3). There was no significant association between LV diastolic dysfunction and AVR alone (HR 1.043; 95% CI 0.807 to 1.349; p=0.745), although AVR as a time-dependent covariate was independently associated with lower mortality (HR 0.737; 95% CI 0.567 to 0.957; p=0.022). There was no interaction between stages of diastolic dysfunction and gender with all-cause mortality (p value for interaction=0.122) or the combined endpoint of all-cause mortality and AVR (p value for interaction=0.098). The multivariable Cox regression analysis showing the association between each individual variable and outcome is shown in online supplemental table S1. In an additional analysis, the association between individual echocardiographic variables of LV diastolic function (ie, E/e′, tricuspid regurgitation velocity and left atrial volume index) with outcomes was also evaluated. On multivariable analysis, tricuspid regurgitation velocity (HR 1.422; 95% CI 1.171 to 1.726; p<0.001) and left atrial volume index (HR 1.008; 95% CI 1.002 to 1.013; p=0.004) were independently associated with all-cause mortality. In contrast, none of the individual variables were independently associated with the combined endpoint of all-cause mortality and AVR (online supplemental table S2).

Incremental prognostic value of diastolic dysfunction for all-cause mortality

To investigate the incremental prognostic value of LV diastolic dysfunction in addition to currently used clinical and conventional echocardiographic parameters, likelihood ratio testing was performed. The addition of the LV diastolic staging system to a clinical model (including age, sex, diabetes mellitus, arterial hypertension, dyslipidaemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, symptoms (NYHA class ≥3), LVEF and AVR as a time-dependent covariate) resulted in a significant increase in χ^2 value (from 179 to 189; p=0.018), demonstrating the incremental prognostic value of LV diastolic dysfunction in patients with moderate AS.

DISCUSSION

The main findings of this study with data obtained from a large registry of patients with moderate AS and preserved LV systolic function can be summarised as follows: (1) LV diastolic dysfunction is frequently present in patients with moderate AS; and (2) LV diastolic dysfunction is independently associated with all-cause mortality and the composite endpoint of all-cause mortality and AVR.

Prognostic implications of LV diastolic dysfunction in moderate aortic stenosis

Recently, studies have demonstrated that patients with moderate AS have worse prognosis than initially assumed.[3 19] Particularly in the presence of LV systolic dysfunction, patients with moderate AS appear to have worse outcome.[4 5] Currently, the

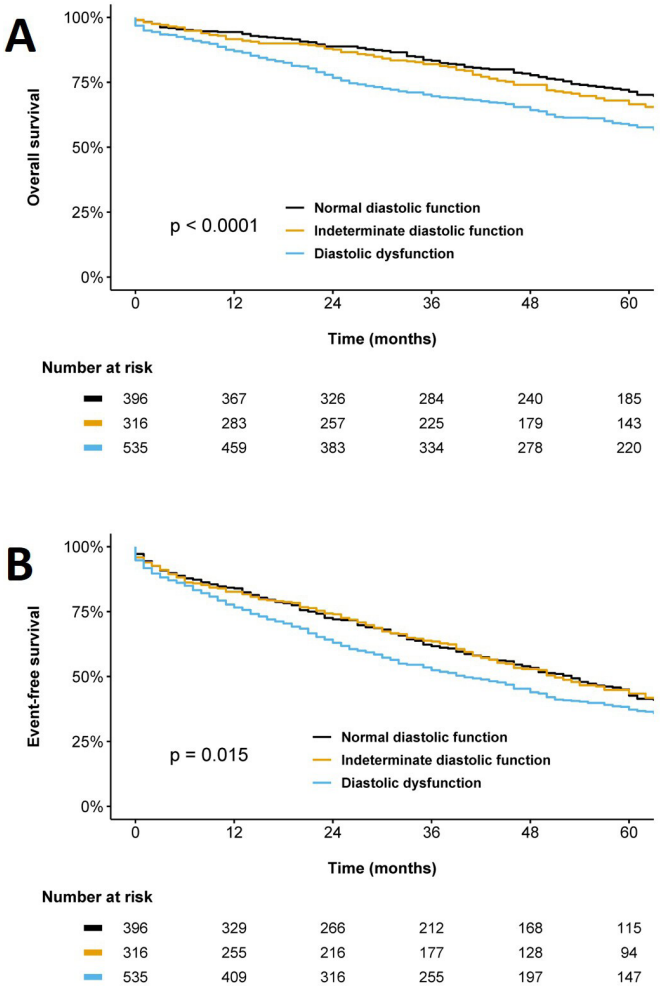

Figure 2 Kaplan-Meier survival curves for all-cause mortality (A) and the combined endpoint of all-cause mortality and AVR (B) according to the classification of LV diastolic function. AVR, aortic valve replacement; LV, left ventricular.

TAVR UNLOAD trial (NCT02661451) explores the hypothesis that transcatheter AVR may improve outcome in these patients.[20] However, even patients with moderate AS and preserved LVEF have an increased risk of mortality as shown by Delesalle *et al*, who evaluated outcomes in 508 patients with moderate AS and LVEF ≥50%, reporting mortality rates of 13% and 28% at 1 and 3 years, respectively.[21] It is well known that the compensatory mechanisms for chronic pressure overload in AS start at an early stage to reduce systolic wall stress and maintain LVEF.[22] Although initially beneficial, LV concentric remodelling can rapidly lead to LV diastolic dysfunction with formation of LV myocardial fibrosis, which is associated with an unfavourable prognosis in severe AS.[23–25] In the current study, patients with preserved LV systolic function but impaired LV diastolic function had a smaller aortic valve area and higher peak aortic jet velocity compared with patients with no or indeterminate LV diastolic dysfunction. This observation suggests that AS severity might be a continuous process with incremental increases in afterload influencing the remodelling process.

Recently, Giudicatti *et al*[26] studied the prognostic value of different indices of elevated LV filling pressures in patients with non-severe (ie, mild or moderate) AS and showed that these parameters were independently associated with increased all-cause mortality. However, this study included patients with a broad range in LVEF, with both moderate and mild AS, and only focused on echocardiographic data without comorbidity profiling. Amanullah *et al* proposed a staging model according to the extent of cardiac remodelling in patients with moderate AS, but this staging model was not focused on LV diastolic function and each of the individual parameters (ie, E/e′, left atrial volume index and tricuspid regurgitation velocity) were placed in different stages.[27] As LV diastolic function is a complex process integrating LV relaxation, restoring forces and LV chamber stiffness, it might be useful to integrate the different diastolic indices into one model, as proposed in the current guidelines on LV diastolic function.[15] The present study therefore provides additional information and demonstrates the independent prognostic value of LV diastolic dysfunction (according to the algorithm proposed by the ASE/EACVI guidelines[15]) in patients with moderate AS and preserved LV systolic function, which persists after adjusting for other factors (eg, age, sex, diabetes, arterial hypertension, dyslipidaemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, chronic kidney disease and LVEF), known to be associated with long-term prognosis. The observation that LV diastolic dysfunction was not associated with AVR alone should be interpreted carefully as these patients are at higher risk and may have died before AVR was considered according to current guidelines or they were not eligible for AVR (due to the high surgical risk). In the current study, a large group of patients (25%) had 'indeterminate LV diastolic

Table 3 Univariable and multivariable Cox regression analyses for all-cause mortality and the combined endpoint of all-cause mortality and AVR

	All-cause mortality		AVR or all-cause mortality		AVR	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
	Univariable analysis		**Univariable analysis**		**Univariable analysis**	
Normal diastolic function	*Reference group*		*Reference group*		*Reference group*	
Indeterminate diastolic function	1.268 (0.984 to 1.635)	0.066	1.048 (0.864 to 1.271)	0.633	0.870 (0.666 to 1.137)	0.308
Diastolic dysfunction	1.666 (1.340 to 2.072)	<0.001	1.256 (1.063 to 1.484)	0.007	0.933 (0.740 to 1.178)	0.562
	Multivariable analysis*		**Multivariable analysis†**		**Multivariable analysis†**	
Normal diastolic function	*Reference group*		*Reference group*		*Reference group*	
Indeterminate diastolic function	1.125 (0.863 to 1.465)	0.384	1.066 (0.868 to 1.308)	0.543	1.011 (0.758 to 1.348)	0.943
Diastolic dysfunction	1.368 (1.085 to 1.725)	0.008	1.241 (1.035 to 1.488)	0.020	1.043 (0.807 to 1.349)	0.745

*Adjusted for AVR as a time-dependent covariate, age, sex, diabetes mellitus, arterial hypertension, dyslipidaemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, New York Heart Association functional class III to IV, left ventricular ejection fraction and aortic valve area.
†Adjusted for age, sex, diabetes mellitus, arterial hypertension, dyslipidaemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, New York Heart Association functional class III to IV, left ventricular ejection fraction, and aortic valve area.
AVR, aortic valve replacement;

function' according to the current ASE/EACVI guidelines.[15] Diastolic stress testing may help to improve risk stratification in these patients and allow for an earlier diagnosis of LV diastolic dysfunction.[28] This may help to timely implement preventive strategies, although prospective trials are needed to confirm this hypothesis.

Although the presence of LV diastolic dysfunction could partially be explained by concomitant cardiovascular risk factors, the underlying moderate AS may accelerate adverse LV remodelling and aggravate LV diastolic dysfunction. This emphasises that the clinical focus should not only be on the AS severity, but rather on the integration of the LV myocardial and ventricular-valvular components of the AS disease process, to optimally risk-stratify patients with moderate AS.

Clinical implications

The present study demonstrates that regular follow-up is warranted in patients with moderate AS and LV diastolic dysfunction, even when LV systolic function is still preserved. Although current guidelines recommend a 'watchful waiting' approach for patients with moderate AS,[11 17] management strategies for AS have changed significantly since various studies reported the efficacy and safety of transcatheter AVR in severe AS.[29 30] Whether recent data demonstrating worsened outcomes in moderate AS should expand current indications for AVR before progression to severe AS occurs remain uncertain and current management of patients with moderate AS should always first focus on the recognition and adequate treatment of comorbidities (eg, arterial hypertension, diabetes mellitus) that have an impact on LV diastolic dysfunction as well. However, since moderate AS may attribute to the adverse LV remodelling process, future studies evaluating the risk-to-benefit ratio of earlier intervention in patients with moderate AS appear warranted. The use of an integrated assessment of LV diastolic function allows further risk stratification of patients with moderate AS and may identify patients who could benefit from earlier AVR. The PROGRESS Trial (A Prospective, Randomised, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement) (NCT 04889872) will start to recruit patients to explore the hypothesis that transcatheter AVR could improve outcomes in patients with moderate AS.

Limitations

This study is subject to the limitations of its retrospective, observational design. Referral bias and selection for AVR may be present, although all patients were screened by the multidisciplinary heart team in the respective centres, as per guideline recommendations. Data on cardiac amyloidosis was not available. The current study population had a high prevalence of concomitant cardiovascular comorbidities which could also have an impact on LV diastolic function. Cardiac magnetic resonance was not available to detect or exclude the presence of myocardial fibrosis. Similarly, Two-dimensional speckle tracking echocardiography was not assessed in the current study. Mortality was ascertained by review of hospital records, linked to the governmental death registry database and it was not possible to determine cardiac versus non-cardiac death.

CONCLUSIONS

LV diastolic dysfunction is strongly associated with an increased risk of adverse events in patients with moderate AS and preserved LV systolic function. Accordingly, assessment of LV diastolic function may contribute significantly to the risk stratification of patients with moderate AS. Although current guidelines recommend conservative management of patients with moderate AS, randomised controlled trials are warranted to determine whether AVR at an earlier stage would be beneficial.

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