Markers of Elevated Left Ventricular Filling Pressure Are Associated with Increased Mortality in Nonsevere Aortic Stenosis

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Background: Echocardiographic measures of elevated left ventricular filling pressures are associated with an adverse prognosis. The aim of this study was to determine the relationship between acute (ratio of early transmitral flow to mitral annular velocity [E/e′]) and chronic (indexed left atrial volume) markers of left ventricular filling pressure and mortality in patients with nonsevere aortic stenosis (AS), within the National Echo Database Australia cohort, testing the hypothesis that they would reflect the early hemodynamic consequences of AS and be associated with increased mortality in this setting.

Methods: The first record for patients ≥18 years of age showing hemodynamically significant but nonsevere (mild or moderate) AS (mean pressure gradient ≥ 10 to <40 mm Hg and aortic valve area > 1 cm^2) was analyzed. Baseline demographics and echocardiographic variables were compared with those among patients without AS (mean pressure gradient < 10 mm Hg). Mortality linkage data were available for all patients.

Results: Of 78,886 patients with aortic valve mean pressure gradients < 40 mm Hg and aortic valve areas > 1 cm^2, 13,768 (17%) were identified with nonsevere AS (aortic valve mean pressure gradient 10–40 mm Hg), of whom 57% were men (mean age, 73 ± 13.4 years) with a median follow-up of 3.4 years (interquartile range, 1.7–6.1 years). In unadjusted time-varying coefficient models, nonsevere AS and indexed left atrial volume > 34 mL/m^2 (hazard ratio [HR], 2.29; 95% CI, 2.03–2.58), E/e′ ratio > 14 (HR, 2.27; 95% CI, 2.08–2.49), left ventricular ejection fraction < 50% (HR, 2.82; 95% CI, 2.50–3.19), and tricuspid regurgitation peak velocity > 280 cm/sec (HR, 2.54; 95% CI, 2.30–2.80) were associated with increased mortality hazard at the time of echocardiography. All markers were significant when combined in a multivariate model.

Conclusions: Indices of elevated left ventricular filling pressure are independently associated with death in patients with nonsevere AS. Risk stratification models incorporating these variables may identify patients at risk for complications, warranting closer surveillance and possibly earlier intervention. (J Am Soc Echocardiogr 2021;34:465-71.)

Keywords: Echocardiography, Observational, Aortic stenosis, Left ventricular filling pressure, Mortality

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Aortic stenosis (AS) is an increasingly prevalent condition, affecting 4% to 5% of those >65 years of age and associated with high mortality.[1] Recent data from the National Echo Database Australia (NEDA) demonstrated poor long-term survival in patients with moderate AS, challenging traditional definitions of severity and timing of invasive intervention in this population.[2] Although patients with moderate AS do not currently meet criteria for valve intervention, some studies suggest that a significant proportion will progress to severe stenosis within the current recommended window for echocardiographic follow-up.[3,4] Furthermore, there is mounting evidence that patients with chronically elevated left ventricular filling pressures (LVFPs) may not remodel following aortic valve replacement (AVR).[5] Identifying patients in the presevere range at higher mortality risk, who may benefit from closer surveillance and potentially from earlier intervention, may therefore be important.

Data for echocardiographic predictors of survival in patients with AS are currently limited predominantly to indices reflecting systolic function and stenosis severity.[6] However, diastolic parameters,

Abbreviations

AS = Aortic stenosis

AV = Aortic valve

AVA = Aortic valve area

AVR = Aortic valve replacement

HR = Hazard ratio

LAVI = Indexed left atrial volume

LVEF = Left ventricular ejection fraction

LVFP = Left ventricular filling pressure

NEDA = National Echo Database Australia

TR = Tricuspid regurgitation

reflecting acute and chronic elevation in LVFP, confer a worse prognosis in many conditions[7-12] and are frequently abnormal in patients with AS as a consequence of increased myocardial stiffness. An elevated ratio of early mitral inflow E-wave peak velocity to peak early relaxation mitral annular tissue Doppler velocity (E/e′) remains the most robust echocardiographic surrogate of acutely elevated LVFP and is a reliable marker of LVFP in patients with AS.[13] Indexed left atrial volume (LAVI), which reflects medium to long-term LVFP, is also required to accurately diagnose and quantify diastolic dysfunction.[14-16] We anticipate that these parameters might reflect the hemodynamic consequences of AS and be useful predictors of outcomes in this setting.

Our aim was to determine the relationship between markers of increased LVFP (measured primarily by LAVI and the mitral E/e′ ratio) and mortality in patients with nonsevere (mild and moderate) AS using the extensive NEDA. We hypothesized that these markers would be independently associated with mortality in this cohort.

METHODS

Study Setting and Design

The NEDA data set was first described in the original NEDA report[17] and more recently in an analysis of mortality in patients with moderate AS.[2] NEDA is a very large observational registry that captures individual echocardiographic data (combined with basic demographic profiling) on a retrospective and prospective basis from participating centers throughout Australia. At the time of study census, a total of 12 centers had contributed >500,000 investigations (approximately 20 million measurements) from approximately 350,000 individuals undergoing echocardiography. NEDA is also registered with the publicly accessible Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval has been obtained from all relevant human research ethics committees.

Study Data

All echocardiographic measurements and text report data contained in the echocardiographic database of a participating center are collected (study period April 11, 2000, to June 13, 2017). Each database is remotely transferred into a central database using a "vendor-agnostic," automated data extraction process that transfers every measurement for each echocardiogram obtained in an entire echocardiography database into a standard NEDA data format. Precise definitions for each echocardiographic variable are applied. Variables with the same names as the NEDA standard are automatically matched. Variables with different names are manually matched with the NEDA standard by the principal investigator. Duplicate measurements with different naming conventions are combined. Units are transformed to the single NEDA standard, and repeated measures for the same variable are converted to a single variable according to the NEDA study protocol. Additional text recognition software captures free text, clinical comments, and conclusions. A continuously updated NEDA data dictionary is maintained through a master NEDA database that forms the basis for all subsequent analyses. To address the prespecified hypotheses, individual NEDA data were linked to Australia's National Death Index.[18] With enhanced probability matching, this linkage provided reliable data on the survival status and primary cause of death of individuals up to the study census date of October 20, 2017. If an individual had died, the listed causes of death were categorized according to ICD-10 coding. Subsequently, consistent with previous reports of this type,[19] all ICD-10 (Australian Modification) chapter codes in the range of 100 to 199 were considered to refer to cardiovascular disease–related deaths.

Study Cohort

NEDA data collected up to June 13, 2017, were used to identify the following: (1) men and women ≥18 years of age with (2) at least one echocardiographic investigation. We included the first echocardiogram per patient showing hemodynamically significant but nonsevere AS, defined as aortic valve (AV) mean pressure gradient ≥ 10 mm Hg and <40 mm Hg and AV area (AVA) > 1 cm^2, where present. When patients had more than one echocardiogram, with none of these indicating AS, the first echocardiogram was included. Patients who had undergone AVR were identified through text extraction and excluded from the analysis. We identified separately a group without hemodynamically significant AS (AV mean pressure gradient < 10 mm Hg, also with AVA > 1 cm^2) as a comparator for baseline echocardiographic characteristics.

Study Measures

Echocardiographic markers reflecting elevated LVFP included (1) LAVI (mL/m^2) and (2) E/e′ ratio (unitless). Important prognostic indicators reflecting both pulmonary hypertension, represented by maximum tricuspid regurgitation (TR) velocity (cm/sec), and left heart disease, represented by left ventricular ejection fraction (LVEF), were incorporated in the analysis.[17]

LAVI and E/e′ ratio were recorded from raw data and, where absent, populated from text comment fields. LVEF was measured using primarily the percentage chosen by the reporting physician, followed by the Simpson biplane, four- and two-chamber values and followed lastly by Teichholz method if none of the aforementioned variables were populated.

Echocardiographic variables were represented as continuous variables and also dichotomized using cutoff ranges identified by the American Society of Echocardiography 2016 recommendations for the evaluation of diastolic function: LAVI > 34 mL/m^2, average E/e′ > 14, and TR velocity > 280 cm/sec.[16] The normal cutoff for LVEF was defined as ≥50%.

Statistical Analysis

No formal calculations of study power were performed given the large number of cases, fatal events, and patient-years of follow-up. Data were analyzed using Stata version 15 (StataCorp, College Station, TX) and SPSS version 23.0 (SPSS, Chicago, IL). Normally distributed continuous data are presented as mean ± SD and skewed

HIGHLIGHTS

- Patients with nonsevere AS have elevated echocardiographic markers of LVFP.
- These markers are independently associated with increased mortality in these patients.
- This may help identify high-risk subgroups that may benefit from closer surveillance.

data as median (interquartile range). Categorical data are expressed as frequencies and proportions (with 95% CIs as appropriate). The "nonsevere AS" and "no AS" groups were compared with respect to demographics and echocardiographic variables to establish baseline differences between the populations, particularly with respect to patterns of abnormal LVFP. Between-group comparisons were made using Student's two-sided *t* test or χ^2 tests. The remainder of the analysis focused on the nonsevere AS cohort. The associations between echocardiographic variables and all-cause mortality were initially investigated using Cox proportional-hazard models. The proportional-hazards assumption was assessed by visual examination of smoothed plots of Schoenfeld residuals versus time. Suspected violations were confirmed by testing interactions of all echocardiographic variables with time in a Cox regression model (time-varying coefficient model). Univariate analysis was performed on dichotomized forms of the echocardiographic variables. All statistically significant variables were included in the multivariate time-varying coefficient models, along with age and sex. Interactions between echocardiographic markers were tested. Only patients with all multivariate variables populated were included in the final multivariate analysis. Variations in the hazard ratios (HRs) over time were plotted for each variable, incorporating the effect of sex and age (fixed at the sample average) on the risk for death. A test of the Cox proportional-hazards assumption for the included variables revealed nonproportionality for all variables except LAVI, indicating a time-varying effect. This was likely contributed to by the prolonged duration of follow-up. Kaplan-Meier survival curves were used to demonstrate mortality differences between subgroups. Statistical significance was accepted as a two-sided *P* value of <.05.

RESULTS

There were 78,886 patients ≥18 years of age with AV mean pressure gradients < 40 mm Hg, AVAs > 1 cm^2, and no histories of AVR. Of these, 13,768 patients (17%) were identified with AV mean gradients ≥10 to 40 mm Hg; 57% were men, with a mean age of 74 years and median follow-up duration of 3.4 years [interquartile range, 1.7–6.1 years). In total, 4,848 fatal events were recorded in the nonsevere AS group (35% of the nonsevere AS cohort). The final cohort included in the multivariate model comprised patients with populated data for all variables of interest and consisted of 3,777 patients.

Baseline demographic and echocardiographic characteristics of interest are summarized in Table 1. Patients in the nonsevere AS cohort were older, with a higher proportion of men, compared with those without AS. Unadjusted baseline echocardiographic markers of LVFP were higher in the nonsevere AS cohort compared with those with no AS (LAVI, 38.4 vs 32.4 mL/m^2 [$P < .001$]; E/e′ ratio, 13.2 vs 12.0 [$P < .001$]). There was a statistical but not clinically significant difference in LVEF between groups (62.5% in patients with nonsevere AS vs 60.0% in those with no AS, $P < .001$). Furthermore, patients with nonsevere AS demonstrated elevated pulmonary pressure, reflected by increased peak TR velocities (277 vs 256 cm/sec, $P < .001$). Nonsevere AS was associated with an unadjusted twofold risk for death compared with no AS, with median survival of 8.7 versus 14.8 years, respectively (HR, 2.02; 95% CI, 1.95–2.10; $P < .001$). The excess mortality in the nonsevere AS group largely reflected the older population. After adjusting for age and sex, the remaining risk for mortality in patients with nonsevere AS was 7% (HR, 1.07; 95% CI, 1.03–1.10; $P < .001$). Adjusting for the absence

Table 1 Baseline characteristics of study cohort (*n* = 78,886)

Characteristic	No AS (*n* = 65,118)	Nonsevere AS (*n* = 13,768)	*P*
Demographic profile			
Gender, male, %	50.8	57.2	<.001
Age at echocardiography, y (%)	60.8 ± 17.8	73.7 ± 13.4	<.001
Anthropometrics			
Body mass index, kg/m^2	28.4 ± 6.8	28.6 ± 6.5	<.001
Median time to death, y (95% CI)	14.8 (14.6–.)*	8.7 (8.5–8.9)	<.001
Mean AV gradient, mm Hg	4.4 ± 1.8	16.0 ± 6.2	<.001
Echocardiographic characteristics			
LVEF, %	60.0 ± 12.2 (*n* = 41,542)	62.5 ± 11.4 (*n* = 9,939)	<.001
LAVI, mL/m^2	32.4 ± 15.3 (*n* = 22,995)	38.4 ± 16.3 (*n* = 7,968)	<.001
E/e′ ratio	12.0 ± 5.2 (*n* = 22,360)	13.2 ± 5.9 (*n* = 6,560)	<.001
TR peak velocity, cm/sec	255.9 ± 51.3 (*n* = 33,266)	277.3 ± 49.2 (*n* = 9,200)	<.001

Data are expressed as mean ± SD or as median (interquartile range) except as indicated. Available data for echocardiographic characteristics are displayed in parentheses.
*The upper bound of the CI does not drop below 0.5.

Table 2 Variables associated with increased all-cause mortality in patients with nonsevere AS (n = 13,768)

Characteristic	Alive (n = 8,920)	Dead (n = 4,848)	Univariate (n as indicated)	P	Multivariate* (n = 3,777)	P
Age at echocardiography, y	70.6 ± 14.1	79.6 ± 9.9	1.06† (1.06–1.07)	<.001	1.08† (1.07–1.08)	<.001
Gender, male	4,977/8,920 (55.8)	2,903/4,848 (59.9)	1.11† (1.05–1.18)	<.001	1.36† (1.21–1.53)	<.001
LAVI > 34 mL/m^2 (at baseline)	2,265/5,021 (45.1)	1,865/2,947 (63.3)	2.29 (2.03–2.58)	<.001	1.18† (1.05–1.34)	.006
LAVI > 34 mL/m^2 × time (variation per year)			0.96 (0.94–0.99)	.002	NA†	
LVEF < 50% (at baseline)	520/6,361 (8.2)	640/3,578 (17.9)	2.82 (2.50–3.19)	<.001	2.38 (1.79–3.17)	<.001
LVEF < 50% × time (variation per year)			0.91 (0.88–0.94)	<.001	0.87 (0.81–0.94)	<.001
TR peak velocity > 280 cm/sec (at baseline)	1,796/5,528 (32.5)	1,883/3,672 (51.3)	2.54 (2.31–2.80)	<.001	1.65 (1.35–2.01)	<.001
TR peak velocity > 280 cm/sec × time (variation per year)			0.94 (0.92–0.96)	<.001	0.96 (0.92–1.00)	.042
E/e′ ratio > 14 (at baseline)	1,229/4,597 (26.3)	838/1,963 (42.7)	2.27† (2.08–2.49)	<.001	1.17 (0.96–1.43)	.12
E/e′ ratio > 14 × time (variation per year)			NA†		1.05 (1.01–1.09)	.023

NA, Not applicable.
Data are expressed as mean ± SD or as proportion (percentage) of available records.
*Multivariate HR is based on a final sample of 3,777 patients in the proportional-hazards model with time-varying coefficients at baseline (time of echocardiography), adjusted for age, sex, and all other echocardiographic variables tested.
†Constant hazard across all follow-up years.

of sinus rhythm had minimal effect on the observed hazard (HR, 1.06; 95% CI, 1.02–1.10; $P = .002$).

Among patients with nonsevere AS, all echocardiographic parameters were associated with increased mortality in a univariate model (Table 2). The proportional-hazards assumption was violated in either univariate or multivariate analysis for all echocardiographic variables, indicating varying hazard over time. For some parameters, the violation was minor and likely detected because of the power of the sample. However, the effect in LVEF < 50% was more substantial over time. When incorporated in a time-varying coefficients multivariate model and adjusted for age and sex, all variables remained independently associated with death over time. No significant interactions between echocardiographic markers were detected. Table 2 displays the HRs for each variable in the multivariate analysis at baseline as well as

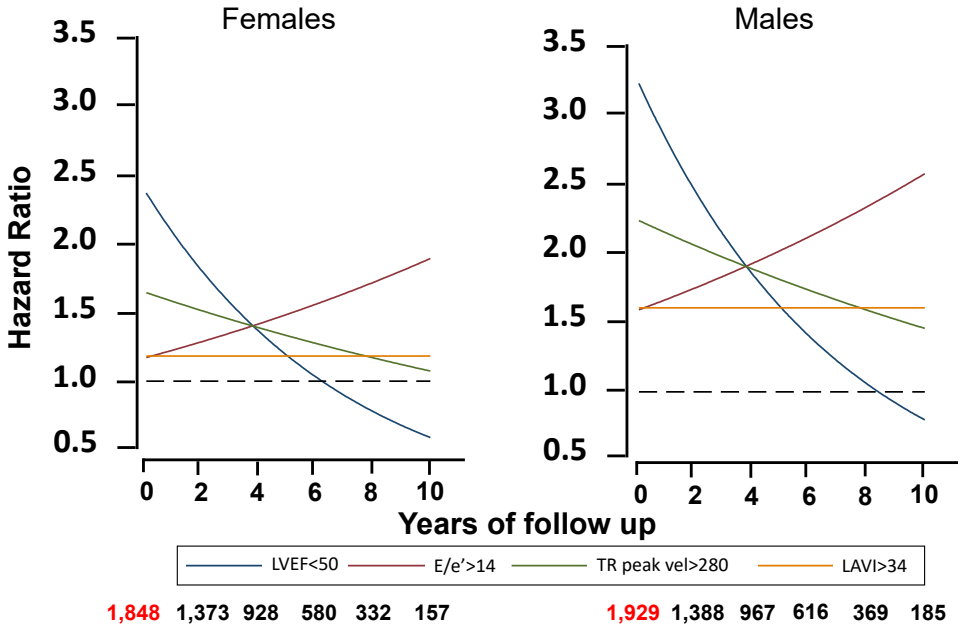

Figure 1 HRs over time derived from a time-varying coefficient Cox regression model in men and women with nonsevere AS, stratified by LAVI cutoff of 34 mL/m^2, E/e′ ratio cutoff of 14, LVEF cutoff of 50%, and TR peak velocity cutoff of 280 cm/sec. LAVI demonstrates nonproportionality with fixed risk over time, while hazard associated with E/e′ increases over the follow-up period.

Table 3 Mortality risk by cumulative echocardiographic markers of systolic and diastolic function in patients with nonsevere AS

Number of abnormal echocardiographic features*	Proportion, *n* (%)	HR (95% CI)	*P*
0	1,270 (33.6)	Reference	
1	1,264 (33.5)	1.29 (1.11–1.52)	<.001
2	780 (20.7)	1.69 (1.43–2.00)	<.001
3	396 (10.5)	2.67 (2.21–3.21)	<.001
4	68 (1.8)	2.88 (2.10–3.96)	<.001

HRs are age and sex adjusted.
*LAVI > 34 mL/m^2, E/e′ ratio > 14, TR peak velocity > 280 cm/sec, and LVEF < 50%.

the change over time per year where relevant. For patients with LVEFs < 50%, the risk for death was estimated to be more than double the risk for death in those with LVEFs ≥ 50% at the time of echocardiography (HR, 2.38; 95% CI, 1.79–3.17; $P < .001$), but this risk decreased by 13% per year over the follow-up period (HR, 0.87; 95% CI, 0.81–0.94; $P < .001$). The change in mortality risk over time from the baseline echocardiogram is displayed in Figure 1 and was generated using estimates from the time-varying coefficients multivariate model, assuming the average age of the sample. The pattern over time in men appears slightly different from that in women, but this is due to the increased risk for mortality associated with being male (HR, 1.36; 95% CI, 1.21–1.53; $P < .001$), not a variation in the change over time in the echocardiographic parameters between genders. LAVI demonstrated a stable risk for death over the follow-up period, while the risk associated with elevated E/e′ ratio increased over time (E/e′ > 14 became significant by 1 year follow-up and conferred 5% increased risk per year thereafter). Conversely, the prognostic impact

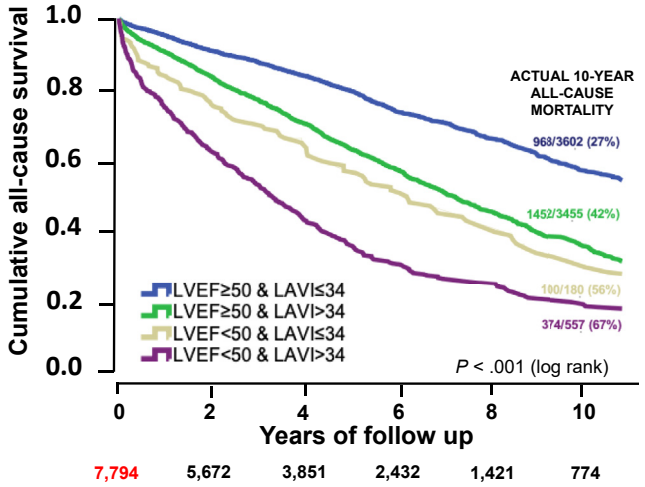

Figure 2 Kaplan-Meier 10-year survival in patients with nonsevere AS with and without reduced LVEF, as stratified by LAVI cutoff of 34 ml/m^2. This graph compares survival curves of patients with different categories of LAVI and LVEF. Values per line represent the number and percentage deceased at 10 years as a proportion of the initial number per category.

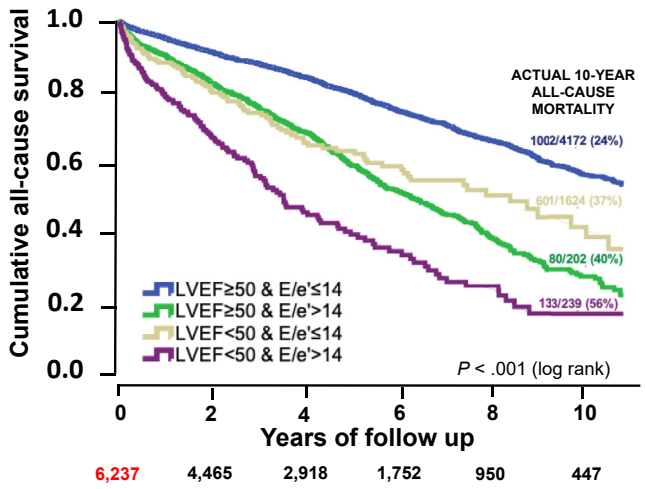

Figure 3 Kaplan-Meier 10-year survival in patients with nonsevere AS with and without reduced LVEF as stratified by E/e′ ratio cutoff of 14. This graph compares survival curves of patients with different categories of E/e′ ratio and LVEF. Values per line represent the number and percentage deceased at 10 years as a proportion of the initial number per category.

of LVEF < 50% and TR peak velocity > 280 cm/sec decreased with time. The risk associated with elevated E/e′ surpassed that of having a reduced LVEF after approximately 4 years of follow-up.

Table 3 demonstrates the incremental effect on mortality with one or more markers of elevated LVFP and/or reduced LVEF, adjusted for age and sex. Patients who exhibited LAVI > 34 mL/m^2, E/e′ ratio > 14, TR velocity > 280 msec, and LVEF < 50% had almost threefold risk for mortality (HR, 2.88; 95% CI, 2.10–3.96; $P < .0001$) compared with those with values below each of these thresholds. The unadjusted prognostic impact of markers of elevated LVFP in the presence of both normal and low LVEF is demonstrated in Kaplan-Meier curves in Figure 2 (LAVI > 34 mL/m^2) and Figure 3 (E/e′ > 14).

DISCUSSION

The results of our analysis of this large multicenter echocardiography database support the hypothesis that markers of acute and chronic elevated LVFP, namely, E/e′ ratio and LAVI, are associated with increased all-cause mortality in the nonsevere AS population independent of age, sex, LVEF, and pulmonary hypertension.

We observed the presence of higher LVFP in patients with nonsevere AS (AV mean gradient ≥ 10 to <40 mm Hg) compared with those without hemodynamically significant AS (AV mean gradient < 10 mm Hg). We postulate two mechanisms for this. First, it seems likely that this reflects, at least in part, the hemodynamic consequences of AS, which result in early left ventricular remodeling and diastolic dysfunction. Second, elevated LVFP likely represents the final common pathway of multiple factors that increase myocardial stiffness and determine outcome, including blood pressure, atrial fibrillation, and age. Although this relationship is not specific to AS, it is clinically useful to know that patients with elevated LVFP are at increased risk within this group, particularly as we know that even if this abnormality is not exclusively, or even primarily, related to the AS, it would be expected that AS will exacerbate it over time.

Although the hemodynamic sequelae of elevated LVFP in patients with severe AS are widely appreciated, the significance in patients with nonsevere AS has been previously underrecognized. Our findings are consistent with those of former studies in other settings that demonstrate the prognostic importance of elevated LVFP and markers of diastolic dysfunction.[7-12] Recent data from the NEDA cohort demonstrated an association between markers of diastolic dysfunction (including LAVI and septal E/e′ ratio) and death in patients with AS using an artificial intelligence model.[20] A second study showed that impaired valvular hemodynamics in the setting of AVR were associated with the same trajectory as in native AS.[12] Within the nonsevere AS cohort, other studies outside the NEDA population have shown markers of myocardial dysfunction to be associated with poor outcomes. Levy-Neuman *et al.*[21] demonstrated the relationship between peak and postexercise basal longitudinal strain and increased rate of future cardiovascular events in asymptomatic patients with moderate AS. Other parameters, including pressure recovery–adjusted AVA and the ratio of AV acceleration to ejection time, have also been found to be useful in risk-stratifying patients with moderate to severe AS.[22,23] There are, however, few previous data addressing the prognostic value of E/e′ ratio, LAVI, and other echocardiographic indices of elevated LVFP in the nonsevere AS cohort over time. Biner *et al.*[24] described E/e′ as the single most predictive clinical and Doppler echocardiographic marker of overall prognosis among a small cohort ($n = 125$) of patients with unoperated severe AS. Rusinaru *et al.*[25] demonstrated an association between increased left atrial volume and mortality in patients with AS of at least mild severity, although again in a small population.

Although LAVI and E/e′ ratio are routinely measured in echocardiographic assessment of diastolic dysfunction, they remain underrepresented in guidelines for echocardiography-based risk stratifications of AS, which focus on stenosis severity and LVEF in guiding intervention.[1] We therefore propose that the incorporation of LAVI and particularly E/e′ ratio in risk stratification models for patients with nonsevere AS, in addition to traditional markers of stenosis severity and left ventricular function, may be useful in guiding future clinical decision-making, though currently there are no data supporting valve replacement in patients with nonsevere AS. However, this issue is currently being explored in the Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure trial (NCT02661451), which is testing the hypothesis that transcatheter AVR plus optimal medical therapy improves outcomes in patients with moderate AS and heart failure with reduced LVEF compared with optimal medical therapy alone.

Limitations

There were a few limitations to this study. The NEDA cohort typically comprises individuals being investigated for possible or preexisting cardiovascular disease. NEDA does not (yet) capture important clinical details pivotal to outcomes relevant to AS and conditions such as coronary artery disease, hypertension, and diabetes. We did identify patients with "nonsinus" rhythm by the presence of a documented E wave without a documented A wave. However, on an adjusted basis, the absence of sinus rhythm did not significantly influence the threshold for increased mortality and had had little impact on the model overall (data not shown). Furthermore, the echocardiographic variables contained within NEDA rely on the reports of individual laboratories and hence contain a significant proportion of missing values, which may have introduced bias. Finally, these data were derived largely from specialist centers or clinics in Australia, and care should be exercised when extrapolating these results to the rest of the world. Since this study, NEDA has continued to extend the number of contributing centers to improve applicability of these data to the entire population.

CONCLUSION

These data describe the prognostic implications of markers of LVFP in a very large cohort of adults over a prolonged period. Markers of raised LVFP were shown to be independently associated with increased mortality in this population. These easily measured and routinely available echocardiographic parameters might therefore be useful to identify high-risk subgroups that may benefit from closer surveillance and potentially earlier intervention. However, this is an area requiring further prospective evaluation.

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