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Characteristics of pulmonary hypertension in adults with left ventricular diastolic dysfunction

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ABSTRACT

Background and objectives Left ventricular diastolic dysfunction (LVDD) is commonly associated with pulmonary hypertension (PHT); however, the factors associated with the presence and severity of PHT in patients with LVDD have not been well characterised.

Methods We analysed the profiles and echo characteristics of 16 058 adults with LVDD and preserved left ventricular ejection fraction (LVEF, >50%) from the National Echocardiography Database of Australia. Peak tricuspid regurgitation velocity (TRV) was used to determine the presence of PHT. Univariate and multivariate analyses were performed to evaluate the parameters associated with the presence/increasing severity of PHT.

Results Mean age was 73±12 years and 9216 (57.4%) were women. 2503 (15.6%) subjects had atrial fibrillation (AF) and 13 555 (84.4%) were in sinus rhythm. Overall, 9976 (62.1%) had PHT (TRV >2.9 m/s). There was a progressive increase in indexed left atrial volume with rising TRV levels. AF and right ventricular (RV) dilation were strongly associated with the presence of PHT (adjusted OR (aOR) 1.27 (95% CI 1.12 to 1.43) and aOR 4.99 (95% CI 4.44 to 5.62), respectively). Increased age, LVEF and body mass index were also independently associated with PHT ($p<0.001$). On multivariate analysis, older age, female sex, AF, lower E/e' and LVEF were independently associated with the severity of PHT ($p<0.001$). The presence of AF increased the TRV by an average of 0.32 m/s, RV dilation by 1.82 m/s, female sex by 0.32 m/s and age (per decade) by 0.3 m/s.

Conclusion In this large study, PHT was common in LVDD and was strongly associated with the presence of enlarged left atrium, AF and older age, in particular.

Trial registration number ACTRN12617001387314.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary hypertension (PHT) is commonly found in adults with left ventricular diastolic dysfunction (LVDD) and preserved ejection fraction (pEF) and its presence is known to have a negative prognostic impact on clinical outcomes. Prior studies do not discern which adults with LVDD and pEF will develop PHT.

WHAT THIS STUDY ADDS

⇒ This large study shows that in adults with LVDD, increased age, left ventricular ejection fraction, body mass index and atrial fibrillation are all significantly and independently associated with the presence of PHT. The factors which are independently associated with increasing severity of PHT include increased age, female sex and atrial fibrillation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study has identified demographic, clinical and echocardiographic factors which are associated with the presence and severity of PHT in LVDD and pEF. This provides clinicians with a framework for risk classification and long-term monitoring for patients.

INTRODUCTION

Pulmonary hypertension (PHT) is commonly found in adults with left ventricular diastolic dysfunction (LVDD) and preserved ejection fraction (pEF) and its presence is known to have a negative prognostic impact on clinical outcomes.[1–4] Prior studies, however, do not discern which adults with LVDD and pEF will develop PHT, only that it is a common occurrence.[5]

Many adults with LVDD with pEF develop raised pulmonary pressures as a direct consequence of impaired left ventricular (LV) relaxation and hence raised left atrial (LA) pressure.[6–8] PHT in this setting has adverse consequences.[3 9] Cardiovascular risk factors such as atrial fibrillation (AF) and obesity are postulated to be important in the pathophysiology of this complication.[5 7 8] The characteristics of PHT in left heart disease (LHD) may be complex. In studies focused on other LHDs such as mitral or aortic valve disease, the degree of PHT is independent of the severity of the valvular disease.[7 10–12] The characteristics of PHT in adults with LVDD have not been well characterised in a large, contemporary clinical cohort.

Using data from the large National Echo Database of Australia (NEDA), we performed further analyses on our previously defined cohort of adults with LVDD and pEF,[4] aiming (1) to identify the factors which are significantly associated with the presence of PHT in patients with LVDD and (2) to determine which factors are significantly associated with the severity of PHT.

METHODS

Study design and data

This is a retrospective cohort study derived from the NEDA, a multicentre database that captured basic demographic and detailed echocardiographic data from all participating centres Australia-wide.[13 14] In the current iteration, this includes >25 clinical centres. All echocardiographic measurements and basic demographic profiling were transferred into a central database via an automated data extraction process. All data were then cleaned to generate uniform echo profile data with duplicate, inconsistent or impossible measurements removed.

The core echo database is then linked to the National Death Index to obtain mortality data for each individual. At the time of analysis, NEDA contained >1 million echo reports from >600 000 subjects from January 2000 to June 2019. Median follow-up was 6.2 years, IQR 3.8–9.8 years. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314).

Study cohort

As per recent guidelines, PHT was defined as a tricuspid regurgitation velocity (TRV) >2.9 m/s.[15] LVDD was determined via the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines.[16 17] LVDD was defined as those meeting three or more (>50%) of the following parameters being positive: (1) E/e' >14, (2) septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, (3) TRV >2.8 m/s and (4) left atrial volume index (LAVi) >34 mL/m^2. Left ventricular ejection fraction (LVEF) values had to be quantified and consistent with guidelines.[18] AF and atrial arrhythmia were determined by text extraction or mitral inflow pattern, as previously described.[16] Right ventricular (RV) size was described qualitatively using text extraction from echo reports.

We have previously published our study flow diagram (figure 1).[4] To summarise, to be included in the analysis, subjects were >18 years, with at least one echocardiogram recorded including measurements to determine LVEF, TRV and diastolic function. Where subjects had multiple studies, only the last study was analysed. Subjects were included if they had LVDD and preserved LVEF (>50%). Subjects with documented mitral and aortic valve replacements were excluded, as were subjects with moderate or greater left-sided valvular pathology.

Statistical analyses

All categorical data are expressed as frequency and percentages, unless otherwise stated, and continuous variables are expressed as mean±SD. X^2 test was used to determine if there was a trend in the change in proportions across groups for binary variables. For continuous variables, linear regression using analysis of variance was used to test the trend of the mean across the categorical groups. Univariate association between the parameters of LVDD and the severity of PHT was determined by assessing the median and IQR for each parameter at each decile distribution of TRV. The decile distribution for the total cohort (n=16 058) was 1st decile 0.00–2.36 m/s, 2nd decile 2.37–2.55 m/s, 3rd decile 2.56–2.70 m/s, 4th decile 2.71–2.87 m/s, 5th decile 2.88–2.90 m/s, 6th decile 2.91–3.00 m/s, 7th decile 3.01–3.10 m/s, 8th decile 3.11–3.20 m/s, 9th decile 3.21–3.40 m/s and 10th decile >3.40 m/s. The decile distribution for the AF cohort (n=2503) was 1st decile 0.00–2.40 m/s, 2nd decile 2.41–2.60 m/s, 3rd decile 2.61–2.80 m/s, 4th decile 2.81–2.90 m/s, 5th decile 2.91–2.97 m/s, 6th decile 2.98–3.00 m/s, 7th decile 3.01–3.10 m/s, 8th decile 3.11–3.24 m/s, 9th decile 3.25–3.50 m/s and 10th decile >3.50 m/s. Correlation between echo parameters was determined using Spearman correlation.

Multiple logistic regression was performed to determine the variables associated with the presence of PHT using entry models with variables determined by an 'a priori' approach. Clinically significant variables included age, sex, LVEF, AF, E/e', LAVi, RV dilation and body mass index (BMI). Sensitivity analyses were performed on the cohort with LAVi documented (n=9872). As there was significant collinearity between LAVi and AF, these two variables were not included together in the same models. Sensitivity analyses were performed analysing the AF and sinus rhythm cohorts separately. Given the non-linear distribution of TRV, the categorical decile distribution of TRV was used in multivariate linear regression models to determine if the above 'a priori' selected variables could predict the severity of PHT in patients with LVDD. Further sensitivity analyses were performed on the cohort with LAVi documented (n=9872). All analyses were performed with SPSS software V.25.0 (IBM), and statistical significance was inferred at a two-tailed p value of <0.05.

RESULTS

Study cohort

There were 16 058 subjects with LVDD and pEF; 9216 (57.4%) were female. When rhythm was assessed at the time of echocardiogram, 2503 (15.6%) were in AF and 13 555 (84.4%) were in sinus rhythm. Mean BMI was 28.9 kg/m^2. Table 1 shows the demographics and echo characteristics of the cohort stratified by the presence of PHT. The cohort with PHT had a significantly higher BMI, LVEF and LAVi (p<0.0001) and higher proportions of AF (16.3% vs 14.4%) and RV dilation (36.5% vs 7.9%) compared with the subjects without PHT.

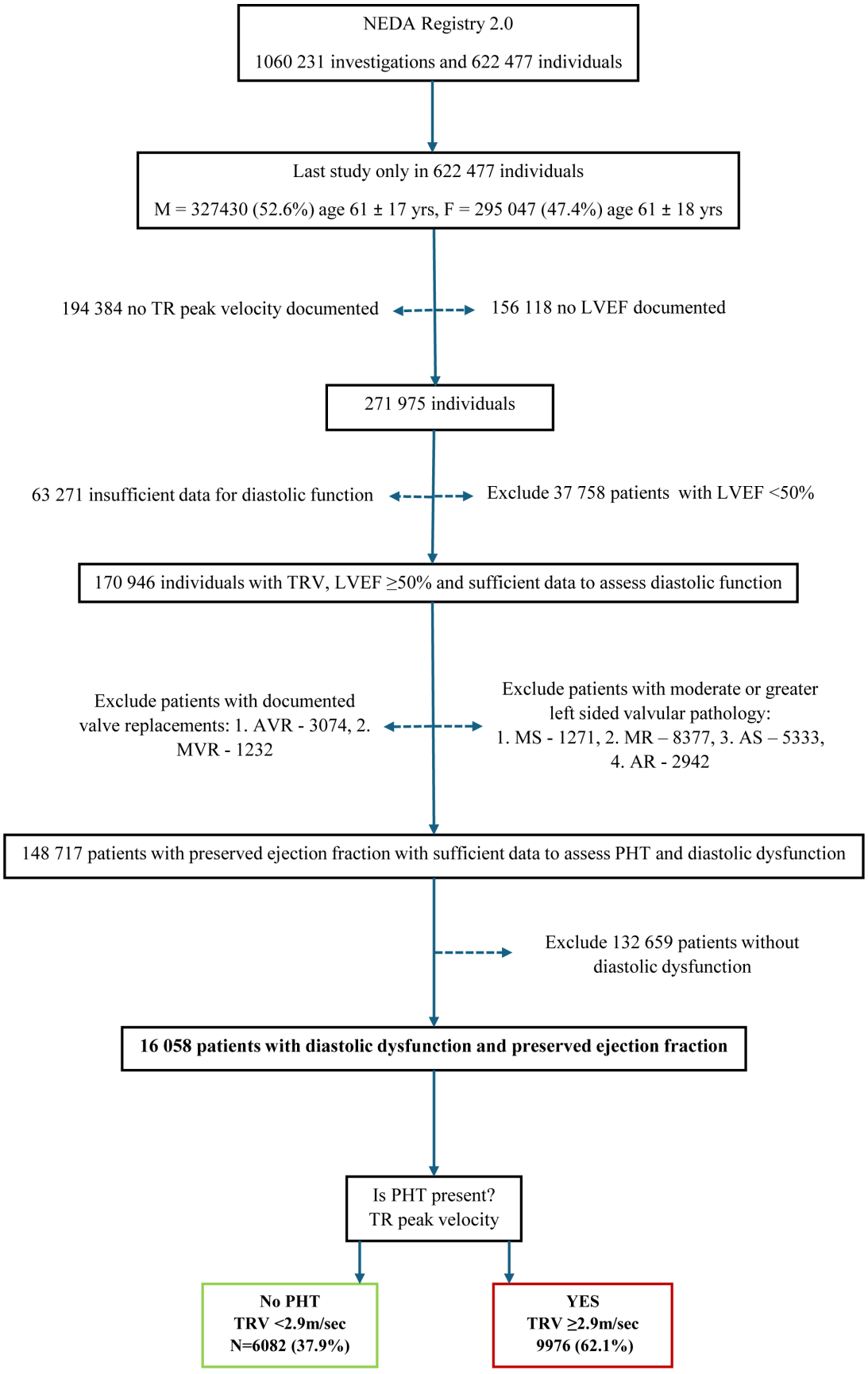

Figure 1 Study flow chart. Analysis flow chart performed in this study. AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; MVR, mitral valve replacement; NEDA, National Echo Database Australia; PHT, pulmonary hypertension; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity.

Table 1 Baseline characteristics of patients with left ventricular diastolic dysfunction stratified by presence of pulmonary hypertension

	LVDD without PHT TRV <2.9 m/s n=6082	LVDD with PHT TRV ≥2.9 m/s n=9976	P value
Demographics			
Age, years	73±12	73±12	0.40
Female (%)	3694 (60.7)	5522 (55.4)	<0.0001
Anthropometrics			
BMI	28.02±6.07	29.38±7.18	<0.0001
BSA	1.85±0.25	1.90±0.27	<0.0001
Rhythm			
Atrial fibrillation/atrial arrhythmia	875 (14.4)	1628 (16.3)	0.001
LV dimensions and functions			
LVEF %	65.40±8.42	70.51±10.38	<0.0001
E/E' ratio	17.70±4.07	14.76±4.78	<0.0001
LVEDD	4.51±0.68	4.86±0.73	0.002
LVESD	2.82±0.62	2.76±0.70	0.001
Stroke volume index (mL/m^2)	44.33±11.46	43.45±13.50	<0.0001
Mitral E/A ratio	1.00±0.52	1.01±0.71	<0.0001
Lateral e' velocity	6.96±2.34	8.03±2.59	<0.0001
Septal e' velocity	5.13±1.13	5.82±1.46	<0.0001
Atrial dimensions			
LA volume index, mL/m^2	52.25±23.33	75.60±33.92	<0.0001
RA area, cm^2	21.19±7.39	28.24±6.79	<0.0001
Right heart dimensions and function			
eRVSP, mm Hg	33.82±5.88	50.31±10.22	<0.0001
Peak TR velocity, m/s	2.50±0.25	3.17±0.34	<0.0001
Dilated RV*	482 (7.9)	3638 (36.5)	<0.0001

Values are n (%) unless otherwise indicated.
*Qualitative assessments based on text extraction from echo reports.
BMI, body mass index; BSA, body surface area; eRVSP, estimated right ventricular systolic pressure; LA, left atrial; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PHT, pulmonary hypertension; RA, right atrial; RV, right ventricular; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity.

Association between parameters of LVDD and the severity of PHT

Overall, LAVi was recorded in 9872 (65.1%), E/e' in 13 427 (83.6%) and septal E' in 15 961 (99.4%) subjects, respectively. Figure 2A shows the association between LAVi and TRV in the total, AF and sinus rhythm cohorts, respectively. There was a progressive increase in indexed LA volume with rising TRV levels, with a plateau noted in the 9th and 10th deciles. The median LAVi values at each decile point were higher in the AF cohort (figure 2B) compared with the sinus rhythm (figure 2C) cohort, though the overall trends mirrored those of the total cohort. Figure 3A shows that there was no clear association between worsening E/e' and increasing TRV. There was a similar lack of clear association seen between age and increasing TRV shown in figure 4A. These trends were present in both the AF and sinus rhythm cohorts (figures 3B,C and 4B,C, respectively), though the AF cohort had a higher median age at each decile compared with those in sinus rhythm.

Online supplemental figure 1 shows the distribution of LAVi against E/e'. The Spearman correlation coefficient was −0.180 (p<0.0001).

Factors associated with the presence of PHT in LVDD

Among the 16 058 subjects with LVDD and pEF, 9976 (62.1%) had PHT. Table 2 shows the univariate and multivariate predictors of PHT. The presence of AF and RV dilation were the factors most strongly associated with the presence of PHT (adjusted OR (aOR) 1.27 (95% CI 1.12 to 1.43) and aOR 4.99 (95% CI 4.44 to 5.62), respectively), while increased age, LVEF and BMI were

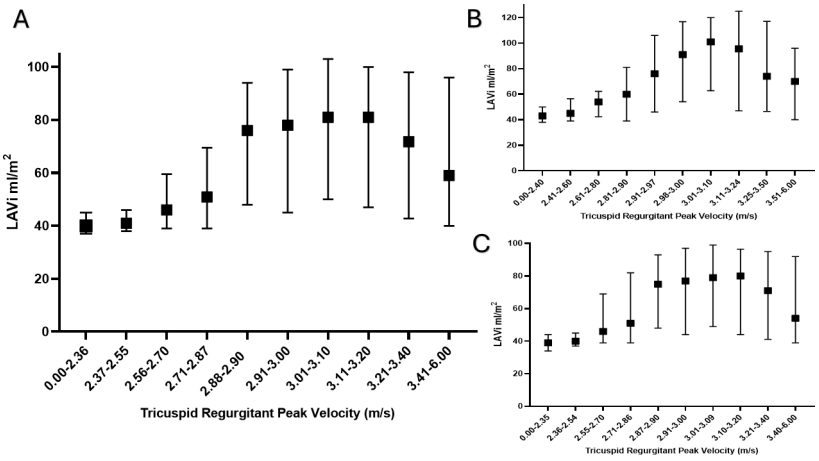

Figure 2 Univariate correlation between left atrial volume index (LAVi) and tricuspid regurgitation velocity (TRV). Correlation between LAVi and TRV deciles showing a progressive increase in LAVi as TRV decile increases before a plateau is noted in (A) total cohort, (B) atrial fibrillation (AF) cohort and (C) sinus rhythm cohort.

also independently associated with PHT. Lower E/e' reduced the odds of PHT development. These trends were maintained in a sensitivity analysis including only those subjects with a documented LAVi (n=9872), shown in online supplemental table 1. Online supplemental table 2 shows that when LAVi was included as a predictive variable in place of AF, similar trends were seen. However, increasing LAVi was less strongly predictive of PHT than the presence of AF (aOR 1.01, 95% CI 1.01 to 1.02), and female sex was a predictive variable.

Online supplemental tables 3 and 4 show the association of these variables to the presence of PHT when the AF and sinus rhythm cohorts were assessed separately. There was a significant association between age, LAVi, LVEF, RV dilation and BMI and the development of PHT, with lower E/e' decreasing the odds of PHT in both cohorts. Female sex was associated with the presence of PHT in the sinus rhythm but not the AF cohort.

Factors predicting the severity of PHT in adults with LVDD

A multiple regression model was performed to predict the severity of PHT using the decile distribution of TRV using age, gender, AF (or LAVi), E/e', LVEF, BMI and RV dilation as independent variables in the models (table 3). All were strongly and independently associated with the severity of PHT in adults with LVDD and pEF ($p<0.001$) with the exception of BMI ($p=0.11$). The presence of AF increased the TRV by an average of 0.32 m/s, the presence of RV dilation increased the TRV by 1.82 m/s and female sex increased the TRV by 0.32 m/s. For every 10 years of increase in age, there was a 0.3 m/s increase in TRV, while for every 10% increase in LVEF, there was a 0.3 m/s increase in TRV. In contrast, lower E/e' reduced the TRV. Similar trends were seen when the base model included LAVi instead of AF (online supplemental table 5) and in the sensitivity analysis of the cohort with complete LAVi data (online supplemental table 6).

DISCUSSION

In this 'real-world' observational study using echocardiography data from a large group of adults with LVDD, we document those variables which are associated with the common and serious complication of PHT. Given

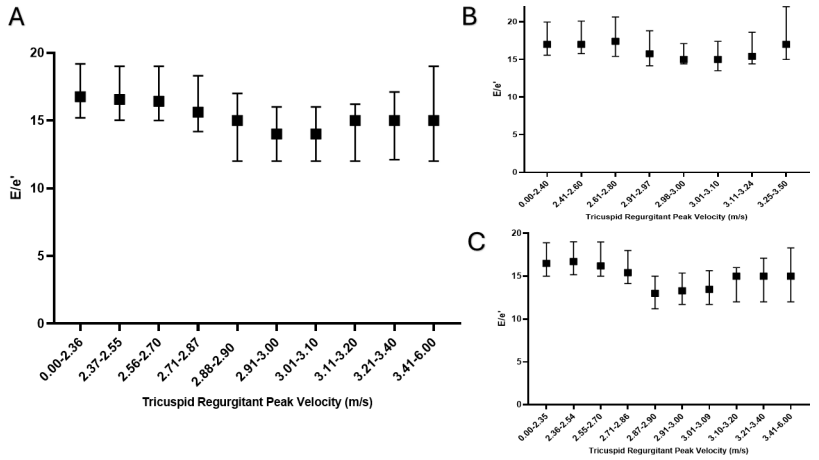

Figure 3 Univariate correlation between E/e' and tricuspid regurgitation velocity (TRV). No clear correlation noted between E/e' and TRV deciles noted in (A) total cohort, (B) atrial fibrillation (AF) cohort and (C) sinus rhythm cohort.

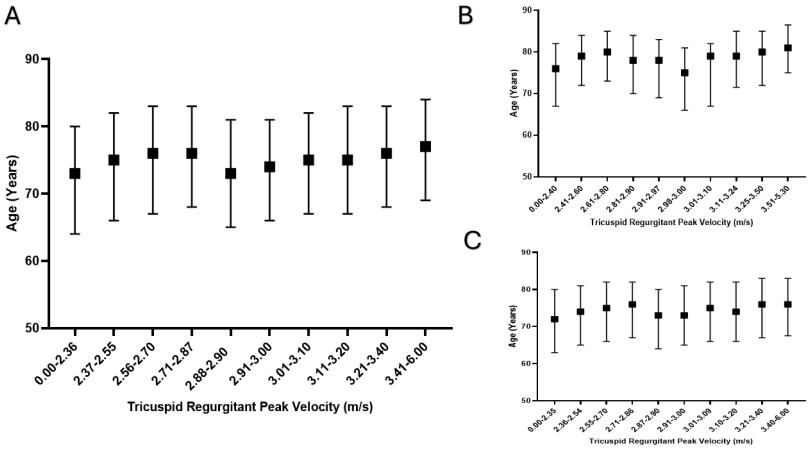

Figure 4 Univariate correlation between age and tricuspid regurgitation velocity (TRV). No clear correlation noted between age and TRV deciles noted in (A) total cohort, (B) atrial fibrillation (AF) cohort and (C) sinus rhythm cohort.

this investigation was conducted in >16 000 cases, this represents the largest study of its kind (to the best of our knowledge). We found that LAVi is the parameter with the strongest univariate association with increasing TRV. In addition, we identified key factors including older age, higher LVEF, lower E/e' and AF, which are independently associated with both the presence and severity of PHT. Female sex was associated with only the severity of PHT, especially in those with sinus rhythm, while BMI was associated with the presence but not the severity of PHT (figure 5).

Prior, smaller population-based trials have reported conflicting data regarding the demographic, clinical and echo characteristics of patients with LVDD, with and without PHT.[3 19] The largest previous cohort (n=455) identified advanced age (>80 years), obesity and atrial arrhythmias as being strong, independent predictors of PHT.[7] Two even smaller studies confirmed advanced age as a predictor of PHT but differed on the key echo parameters associated with PHT.[3 20] Lam *et al* identified increased LA size as a predictor, while Thenappan *et al* identified right atrial and ventricular enlargement.[3 20] While early studies documented a positive correlation between the magnitude of pulmonary pressure elevation and the degree of diastolic dysfunction as assessed on echo,[21] more recent studies have suggested that this correlation is weak, possibly suggesting an additional precapillary component driving the raised pulmonary pressures.[3 19]

The increase in LAVi with each decile of TRV noted in our study is likely a result of the progressive increase in LA filling pressures caused by the increased LV diastolic stiffness and impaired relaxation seen in LVDD.[7 8] The plateau in LAVi values from the 9th decile onwards may reflect the subset of patients with 'out of proportion' PHT, where intrinsic pulmonary vascular disease has developed.[5 7 22] Similar to other studies, we showed that increasing LAVi and AF were both key predictors of PHT within this cohort,[3 19] although they are closely associated with each other.[16 23]

Age has been shown to have an important influence on both the worsening of diastolic dysfunction and the development of PHT[24 25]; our findings reinforce this observation with the demonstration of an independent association between age and both the presence and severity of PHT. Similar to other studies, we show that BMI is an independent predictor of PHT; however, it did not predict the severity of PHT within our cohort.[19]

Table 2 Parameters associated with pulmonary hypertension

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value
Age	1.0001 (0.998 to 1.004)	1.01 (1.01 to 1.01)	<0.0001
Gender	0.80 (0.75 to 0.86)	1.02 (0.93 to 1.11)	0.78
AF	1.16 (1.06 to 1.27)	1.27 (1.12 to 1.43)	<0.0001
E/e'	0.87 (0.86 to 0.88)	0.89 (0.88 to 0.90)	<0.0001
LVEF	1.06 (1.05 to 1.06)	1.05 (1.04 to 1.05)	<0.0001
BMI	1.03 (1.02 to 1.04)	1.01 (1.00 to 1.02)	0.01
RV dilation	6.67 (6.03 to 7.38)	4.99 (4.44 to 5.62)	<0.0001

AF, atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; RV, right ventricular.

Table 3 Predictors of the severity of pulmonary hypertension

	B	SE	T statistic	95% CI	P value
Age	0.03	0.002	13.07	(0.02 to 0.03)	<0.0001
Gender	0.16	0.05	3.28	(0.06 to 0.26)	0.001
AF	0.32	0.07	4.88	(0.19 to 0.45)	<0.0001
E/e'	−0.06	0.005	−12.09	(−0.07 to −0.05)	<0.0001
LVEF	0.03	0.002	10.75	(0.02 to 0.03)	<0.0001
BMI	−0.006	0.004	−1.59	(−0.01 to 0.001)	0.11
RV dilation	1.82	0.06	33.28	(1.71 to 1.93)	<0.0001

AF, atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; RV, right ventricular.

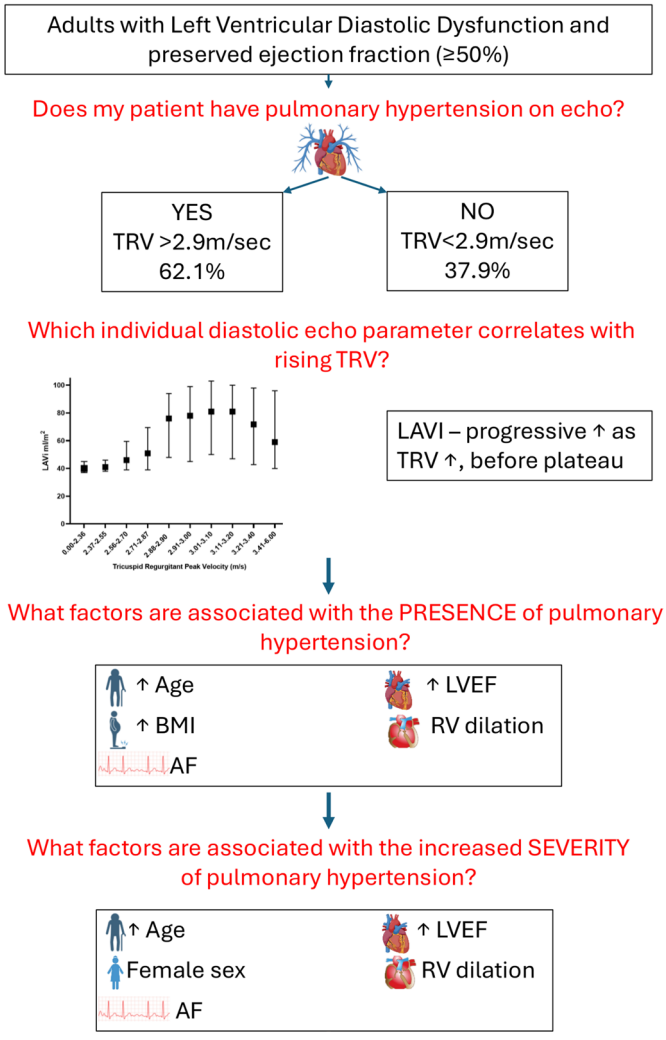

Figure 5 Illustration of the factors associated with the presence and severity of pulmonary hypertension in adults with left ventricular diastolic dysfunction. AF, atrial fibrillation; BMI, body mass index; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; RV, right ventricular; TRV, tricuspid regurgitation velocity.

Interestingly, animal and human studies have shown that myocardial fat deposition seen in obesity is a predictor of LVDD.[26 27] Our findings regarding BMI are in contrast to previous studies which established an association between increasing BMI class and PHT severity, though differences in cohorts (all-cause PHT vs group 2 only) may explain varying results.[28] Sustained 'backward' transmission of elevated left heart filling pressures into the pulmonary vasculature in patients with LVDD can lead to increased RV afterload, resulting in right atrial and ventricular remodelling, dilation and fibrosis.[7]

Our findings regarding RV dilation and its significant association with PHT probably reflect that this is a consequence rather than a cause of PHT, as this is more likely in a pathophysiological sense, but causality cannot be confidently inferred in a cross-sectional study such as this. This study reported a lower E/e' in the cohort with raised pulmonary pressures compared with those without raised pulmonary pressures, which differs from the expected finding of E/e' being higher in those with PHT and LVDD reflecting increased LA pressure. There may be clinical factors including medications and treatments not captured in this study influencing this measurement, and thus this finding should be interpreted with caution.

The findings from our study have several potential clinical implications. We have shown the important role for LAVi as the individual diastolic parameter that has the clearest univariate correlation to raised TRV. We have also identified demographic, clinical and echocardiographic factors which are associated with the presence and severity of PHT in LVDD and pEF. This provides clinicians with a framework for risk classification and long-term monitoring for patients, which is significant given the growing burden of patients with this condition. Also, the identification of these key factors within the cohort allows future studies to use these as potential therapeutic targets.

Study limitations

NEDA provides detailed echocardiographic data and linkage to mortality; it does not yet, however, provide granular clinical data such as symptoms, important comorbidities such as hypertension, diabetes, obstructive sleep apnoea or coronary disease, or pharmacological treatments. We also cannot determine whether individuals developed clinical symptoms of heart failure, nor their functional class. These can all impact each individual's health outcomes and thereby cause residual confounding in our models. Furthermore, without clinical symptoms or biomarkers, we cannot determine whether individuals had a clinical syndrome of heart failure with pEF. A proportion of patients in the study cohort had AF, making the definition of LVDD more difficult in this subset.

Consistent with our previous studies,[10 13 29] data concerning PHT in NEDA are based on echocardiography-based measures, rather than the gold standard haemodynamic assessment at right heart catheterisation. This means that we cannot definitively separate those PHT caused by LVDD or PHT due to another cause where LVDD happens to also be present. We also cannot determine those with isolated postcapillary PHT from those with mixed precapillary and postcapillary PHT. However, prior studies have correlated estimated right ventricular systolic pressure with invasive pulmonary artery systolic pressure,[30 31] supporting the broad validity of our approach. Our study also did not report on advanced imaging techniques such as LA strain, which can further characterise LVDD as these measurements were not routinely performed in the 25 echo labs contributing to the NEDA. We also note that the absence of a tricuspid regurgitation (TR) jet does not exclude PHT risk, and there may be subjects with LVDD and pEF at risk of PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR. Our data are lacking in quantitative RV measurements, with only a small minority of patients having recorded RV functional

parameters. Thus, we are unable to fully assess the impact of raised pulmonary pressures on the right heart. Finally, 'cause and effect' between LVDD and PHT are difficult to deduce with confidence from a cross-sectional study such as this.

CONCLUSIONS

In this large clinical cohort study, we identify the key factors associated with the presence and severity of PHT in adults with LVDD. LAVi is the parameter most closely correlated to progressively rising pulmonary pressures.

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Contributors All the named authors have contributed significant amounts to this manuscript. DSC (senior author professor) is the guarantor that all authors have contributed.

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Competing interests SS, DP and GS have previously received consultancy/speaking fees from Edwards Lifesciences. DP and GS have received consultancy fees from Medtronic, Edwards Lifesciences, Abbott Laboratories and ECHO IQ Pty Ltd. DSC is on the editorial board of BMJ HEART.

Patient and public involvement statement Patients and/or the public were not in involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Human ethics approval has been obtained (protocol SLHD X15-0387 and 2019/ETH069899). As a part of this ethics protocol, a retrospective waiver of consent was authorised.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The NEDA collaboration encourages use of the NEDA data with the cooperation of participating sites and responsible NEDA investigators—a full list is available (with contact details for advice on accessing data) via NEDA's home website (https://www.neda.net.au/).

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