Pulmonary Hypertension complicating Left Heart Disease – Common and Difficult to Treat

Seshika Dinali Ratwatte

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Thesis Statement of Originality

The work in this thesis was conducted at Royal Prince Alfred Hospital, Department of Cardiology, under the supervision of Professor David S. Celermajer, Associate Professor Rachael Cordina, and Associate Professor Edmund Lau.

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis have been acknowledged. Artificial Intelligence was not used in the conduct of research, for preparing text images or other content or copy editing.

Dr Seshika Ratwatte (B.Med, FRACP)

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Abstract

Pulmonary hypertension due to left heart disease (PHT-LHD) is the most prevalent sub-type of PHT worldwide. Despite being common, this heterogenous group of patients (including those with left sided valvular pathology, reduced left ventricular ejection fraction (LVEF) and left ventricular diastolic dysfunction (LVDD)) is underrepresented in contemporary literature. With a lack of in-depth phenotyping, standardised diagnostic techniques and no clear treatment options despite an adverse prognosis, these patients represent a major unsolved problem in cardiology. The relationships between PHT and the various types of LHDs, in isolation or together, have not been well studied, and even then, only in relatively small patient numbers. This is the major focus of this thesis.

Chapter 1 critically reviews the literature and reports on the updated haemodynamic definitions and classifications of PHT. The pathophysiology of PHT secondary to LHD is described with emphasis placed on the role of left atrial hypertension and the subsequent back pressure into the pulmonary vasculature leading to a raised pulmonary arterial wedge pressure. There are varying reports of prevalence across the spectrum of LHD subtypes highlighting the unanswered questions regarding how common these conditions truly are. The current diagnostic pathway including non-invasive techniques such as echocardiography and the 'gold standard' of invasive haemodynamics are described. There is growing acknowledgement that patient specific factors including fluid status may influence baseline haemodynamics and that provocation challenges may be needed to identify 'occult' disease. However, with a lack of standardised techniques, a streamline approach to diagnosis is lacking.

The theme of the next part of this thesis is defining phenotypes within PHT-LHD. Chapters 2, 3 and 4 describe the demographic and echocardiographic phenotype of PHT in patients with valvular heart disease and the prognostic significance of raised pulmonary pressures within each cohort. This was described in distinct cohorts with moderate-severe aortic regurgitation, aortic stenosis and mitral regurgitation respectively, using data from the National Echo Database of Australia (NEDA). At the time of undertaking these studies there were > 1 million echo studies for > 600 000 individual patients, making each study the largest reported cohort to date. A similar trend in echo phenotype was noted across the cohorts; as pulmonary pressures increased there was progressive increase in E/e', right atrial (RA) size and indexed left atrial volumes (LAVi). Prospective exclusion of concomitant left heart disease allowed assessment of the impact of pulmonary hypertension *per se* on each cohorts outcomes. There was a progressively increased risk of mortality as pulmonary pressures increased, even at mild elevations in pulmonary pressure, with the threshold for mortality seen in borderline elevations in the aortic stenosis and mitral regurgitation cohorts and mild elevations in the aortic regurgitation cohort.

Chapter 5 builds on the literature of detailed phenotyping for patients with raised pulmonary pressures and reduced LVEF, another important sub-type of PHT-LHD. Again, using data from the NEDA a cohort of >23 000 patients was analysed with specific emphasis placed on assessing whether sex-based differences in echo phenotype or outcomes could be identified. There was a greater proportion of males compared with females in the total cohort (68.3% versus 31.7% respectfully). The risk of all-cause mortality significantly increased as pulmonary pressures increased in the total cohort and also when the male and female cohorts were assessed separately. However, whilst the risk of cardiovascular mortality increased progressively as PHT risk increased in the male cohort, the mortality risk only became significant in the high-risk PHT cohort, amongst females.

Chapters 6 and 7 focuses on another common and important sub-type of PHT-LHD – those with LVDD and preserved ejection fraction (pEF). A cohort of >16 000 patients with LVDD and pEF were defined from within the NEDA with prospective exclusion of other forms of LHD. Chapter 6 identified a predominantly female cohort (57.4%) with a similar echo phenotype to the previously discussed cohorts including a progressive increase in right atrial size, indexed left atrial volume and right ventricular size as pulmonary pressures increased. This study confirmed a graded, inverse relationship between worsening PHT risk and survival. A more granular analysis was performed to demonstrate the threshold of mortality; there was a perceptible increase within the 'borderline' elevations in pulmonary pressures, with a marked increase from those with a mild increase onwards. Chapter 7 directly follows on from this with the aim of addressing why some patients with LVDD and pEF develop raised pulmonary pressures and others don't. LAVi was the parameter with the strongest univariate association with increasing pulmonary pressures. Key factors including older age, higher LVEF, lower E/e' and atrial fibrillation were found to be independently associated with both the presence and severity of PHT.

Attention was then turned to whether PHT as a result of 'isolated LHD' leads to identifiable / important changes in the right ventricle (RV) as assessed by cardiac imaging. Whilst prior research has reported on the prognostic impact of the presence of RV dysfunction pre- transcatheter aortic valve implantation (TAVI), detailed phenotyping of changes to the RV post TAVI (when the LHD is ameliorated) have not been reported. Chapter 8 investigates the prevalence and predictors of RV dysfunction in cohort of patients with severe AS who were undergoing TAVI. Baseline RV dysfunction was identified in 28.8% of the cohort but did not normalise at short-term follow up, in greater than two-thirds of these patients. Clear thresholds for each RV functional parameter where recovery was unlikely were identified.

Finally, focus was shifted to the importance of accurate diagnosis of PHT-LHD. There is increasing acknowledgement that traditional haemodynamic measurements may be insufficient to identify early stages of LHD. Provocation techniques, including 'acute' fluid challenges, have been proposed, however, there is no standardised approach, and current methods do not account for important

individual factors, such as weight, duration of fasting or, importantly, volume status. Chapter 9 is a prospective, pilot study where a standardised approach to right heart catheterisation is proposed for patients with suspected PHT-LHD. Using a non-invasive finger probe patient's volume status and fluid responsiveness were assessed and if necessary corrected prior to RHC. Passive leg raising was investigated as a novel provocation technique and found to be equivalent to a standard 500-mL fluid bolus in identifying patients with occult PHT-LHD.

Taken together, the studies described in this thesis will contribute to our understanding of the demographic, imaging and haemodynamic characteristics of this highly prevalent, but under diagnosed and difficult to treat group of patients.

Authorship Attribution Statement

Part of Chapter 1 of this thesis is published as:

Ratwatte S and Celermajer D. The latest definition and classification of pulmonary hypertension. Int J Cardiol Congenital Heart Disease. 2024 Jun;17(1). DOI:10.1016/j.ijcchd.2024.100534.

I contributed to the conceptualisation of the review with DSC and wrote the drafts of the manuscript.

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Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Prevalence of pulmonary hypertension in aortic stenosis and its influence on outcomes. HEART. Publish online- 03 April 2023. doi: 10.1136/heartjnl-2022-322184.

Ratwatte S, Strange G, Playford D et al. Prevalence of pulmonary hypertension in mitral regurgitation and its influence on outcomes. OpenHeart. 2023.10(1):e002268. doi: 10.1136/openhrt-2023-002268.

I designed these studies under the supervision of DSC. DP and GS assisted with utilisation of the database. I designed and coded the study flow diagram to create the unique cohorts, analysed the data and wrote the drafts of the manuscript. I conducted all statistical analysis with methodological guidance from SS. All co-authors were involved in revisions and approved of the final manuscript.

Chapters 5, 6 and 7 of this thesis is published as:

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Ratwatte S, Playford D, Strange G, et al. Prevalence and prognostic significance of pulmonary hypertension in adults with left ventricular diastolic dysfunction. Open Heart 2024;11:e003049. doi:10.1136/ openhrt-2024-003049

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For all three publications I designed the studies under the supervision and guidance of DSC and SS. I designed and coded the study flow diagram to create the unique cohorts, analysed the data and wrote the drafts of the manuscript. I conducted all statistical analysis with methodological guidance from SS. All co-authors were involved in revisions and approved of the final manuscript.

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I designed the study under the supervision of DSC. MN assisted with utilising the Macquarie University TAVI database for patient recruitment. I reanalysed the echo data of patients within this database with the assistance of BC. I performed all data extraction and analysis and wrote the draft of the manuscript. All authors were involved in revisions and approval of the final manuscripts.

Chapter 9 of this thesis is published as:

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I designed the study under the supervision of DSC. I negotiated the use of the ClearSight Device directly with Edwards LifeSciences. EL assisted with patient recruitment and I performed patient selection. DB, RC and DSC supervised me performing the procedures for this study. I collected study data, performed data analysis and wrote the drafts of the manuscript. All co-authors were involved in the revisions.

I am the first author of all of the above listed publications.

Dr Seshika Ratwatte (B.Med, FRACP)

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor David Celermajer

10th September 2025

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Awards Arising from this Thesis

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Ratwatte S, Cordina RL, Baker D, Lau E, Celermajer DS. The importance of assessing and correcting hydration status prior to right heart catheterisation: a pilot study. Intern Med J. 2024 Nov 22. doi: 10.1111/imj.16577. PMID: 39575768.

Ratwatte S, Playford D, Strange G, Celermajer DS and Stewart S. Prevalence and prognostic significance of pulmonary hypertension in adults with left ventricular diastolic dysfunction. Open Heart 2024;11:e003049. doi:10.1136/ openhrt-2024-003049

Ratwatte S and Celermajer D. The latest definition and classification of pulmonary hypertension. Int J Cardiol Congenital Heart Disease. 2024 Jun;17(1). DOI:10.1016/j.ijcchd.2024.100534.

Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Association of Pulmonary Artery Pressures With Mortality in Adults With Reduced Left Ventricular Ejection Fraction. JACC Heart Fail. 2024 May;12(5):936-945. doi: 10.1016/j.jchf.2024.01.016.

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Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Prevalence of pulmonary hypertension in aortic stenosis and its influence on outcomes. HEART. Publish online- 03 April 2023. doi: 10.1136/heartjnl-2022-322184.

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Other Publications Arising from this Thesis

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Cordina R, **Ratwatte S,** Khor L et al. Transcatheter Edge-to-Edge Repair of Common Atrioventricular Valve Regurgitation in the Setting of a Lateral Tunnel Fontan CirculationStructural Heart. 2024 Jun. DOI: 10.1016/j.shj.2024.100348.

Burton A, **Ratwatte S**, Zalcberg D et al. Cardiac arrest in pregnancy with successful stabilisation and delivery on veno-arterial extracorporeal membrane oxygenation: a case report. Eur Heart J: case reports. 2024 Oct. DOI: 10.1093/ehjcr/ytae551.

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Abbreviations

AR	Aortic regurgitation
AS	Aortic stenosis
AF	Atrial fibrillation
BMI	Body mass index
CKD	Chronic kidney disease
CpC-PH	Combined pre- and post-capillary pulmonary hypertension
DM	Diabetes mellitus
Ersvp	estimated Right Ventricular Systolic Pressure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
IHD	Ischemic heart disease
IpC-PH	Isolated post capillary pulmonary hypertension
LAVi	Left atrial volume index
LA	Left atrium
LHD	Left heart disease
LV	Left ventricle
LVDD	Left ventricular diastolic dysfunction
LVEF	Left ventricular ejection fraction
Mpap	Mean pulmonary arterial pressure
MR	Mitral regurgitation
MS	Mitral stenosis
NEDA	National Echo Database of Australia
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PHT	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Right atrium
RHC	Right heart catheterisation
RV	Right ventricle
TTE	Transthoracic echo
TRV	Tricuspid regurgitant velocity
TR	Tricuspid regurgitation
VHD	Valvular heart disease

Chapter 1 – Introduction

Part of this chapter is based on the publication:

Ratwatte S and Celermajer D. The latest definition and classification of pulmonary hypertension. Int J Cardiol Congenital Heart Disease. 2024 Jun;17(1). DOI:10.1016/j.ijcchd.2024.100534.

Clinical Definition and Classification of Pulmonary Hypertension

Pulmonary hypertension (PHT) refers to any condition where the mean pulmonary artery pressure (mPAP) is elevated to ≥20mmHg on right heart catheterisation. Whilst previously considered a disease which primarily affected young women, there is now a greater understanding that PHT encompasses a range of diseases which may be idiopathic or inherited, or secondary to cardiac, respiratory, systemic and/or thromboembolic conditions, amongst others[1]. The clinical classification of PHT is divided into 5 key groups according to their aetiology, pathophysiology, haemodynamics and therapeutic targets. **Table 1.1** outlines the clinical classification from the 2022 Pulmonary Hypertension Guidelines[1].

The three key haemodynamic values needed for to diagnose the presence and subtype of PHT are mPAP, pulmonary arterial wedge pressure (PAWP) and pulmonary vascular resistance (PVR), with right heart catheterisation (RHC) considered the 'gold standard' diagnostic technique to determine these values[1]. To clarify the nomenclature used in this area, PHT is any condition where the mPAP is elevated. PHT can be divided into two broad hemodynamic groups according to PAWP (a surrogate measurement for the left atrial (LA) pressure): pre-capillary PHT and post-capillary PHT. PAH (Group 1) is the subset of PHT with a normal LA pressure (PAWP <15mmHg). This is also referred to as "precapillary" PHT[1] and refers to that subset with pulmonary arteriopathy causing elevated pulmonary vascular resistance. Post-capillary PHT (Group 2) is thought to be due to the backward transmission of elevated LA pressure into the pulmonary vasculature (PAWP≥15mmHg)[2]. The PVR is derived as the ratio of the transpulmonary gradient (TPG) to the cardiac output (CO)[3]. Patients with PAH are haemodynamically characterised by as Group 1, if they have neither lung disease (Group 3 PHT) or chronic thromboembolic pulmonary hypertension (CTEPH) (Group 4 PHT)[1, 3]. **Table 1.2** summarises the current hemodynamic definitions for PHT according to the 2022 Clinical Guidelines[1]. Accurate haemodynamic confirmation of diagnosis is imperative in determining suitability and response to treatment with PAH-specific medications, as well as to guide prognosis[3]. It is now widely accepted that early treatment of PAH is associated with improved outcomes[4-6].

Table 1.1 Clinical Classification of Pulmonary Hypertension

	Group 1 PAH	**Group 2** PHT associated with left heart disease	**Group 3** PHT associated with lung disease	**Group 4** PHT associated with pulmonary artery obstructions	**Group 5** PHT with unclear and / or multifactorial mechanisms
Types	• Idiopathic -Non-responders at vasoreactivity testing -Acute responders at vasoreactivity testing • Heritable • Associated with drugs and toxins • Associated with -Connective tissue disease -HIV infection -Portal hypertension -Congenital heart disease -Schistomiasis • PAH with feature of venous / capillary involvement	• HFrEF • HFpEF • Valvular pathology • Congenital / acquired cardiac condition leading to post-capillary PHT	• Obstructive lung diseases or hypoxia • Restrictive lung disease • Lung disease with mixed restrictive / obstructive pattern • Hypoventilation syndromes • Hypoxia without lung disease • Developmental lung disorders	• Chronic thromboembolic PHT • Other pulmonary artery obstruction	• Haematological disorders • Systemic disorders • Metabolic disorders • Chronic renal failure with or without haemodialysis • Pulmonary tumour thrombotic microangiopathy • Fibrosing mediastinitis
Prevalence	Rare	Very common	Common	Rare	Rare
Haemodynamics	mPAP >20mmHg, PAWP ≤15mmHg, PVR >2WU	mPAP >20mmHg, PAWP 15mmHg	mPAP >20mmHg, PAWP ≤15mmHg, PVR >2WU	mPAP >20mmHg, PAWP ≤15mmHg, PVR >2WU	mPAP >20mmHg, PAWP ≤15mmHg, PVR >2WU

PAH = pulmonary arterial hypertension; PHT = pulmonary hypertension, HFrEF = heart failure reduced ejection fraction; HFpEF = heart failure preserved ejection fraction; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; pulmonary vascular resistance
Modified from Humbert et al. 2022.[1]

Recent Updates to Haemodynamic Definitions

Up until recently a mPAP ≥25mmHg was considered abnormal. At the 6th World Symposium on Pulmonary Hypertension (WSPH) (2018, Nice, France), it was recognised that the original haemodynamic definition of PAH was somewhat arbitrary and did not reflect the evidence base for "normal" pulmonary haemodynamics[7]. Invasive RHC studies have demonstrated that in healthy subjects, normal mPAP averages 14 mmHg with an upper limit of approximately 20 mmHg[8]. Prior studies also showed that patients with mildly elevated mPAP, between 21 mmHg and 24 mmHg, experience functional limitation and poorer outcomes, compared to those with strictly normal mean PAP ⩽20 mmHg[9-11]. These findings have been further confirmed in data from large cohorts based on RHC or estimates from transthoracic echocardiography[12, 13]. Thus, the mPAP threshold for "upper limit of normal" was lowered to 20 mmHg (from 25mmHg), whilst the cut-off values of PAWP ⩽15 mmHg and PVR >3 WU remained unchanged[7].

In the recently published 2022 Pulmonary Hypertension guidelines these definitions were endorsed and expanded upon[1]. A meta-analysis of all published data on healthy controls showed that the upper normal PVR was 2 Wood units[8]. The normal threshold in the elderly remains unclear, however, given PVR is dependent on both body surface area and age, higher values are likely to be noted in healthy elderly patients[1]. Several recent studies have also demonstrated that the lowest prognostically relevant threshold for PVR, and the threshold where medication is potentially beneficial, is approximately 2WU[14-16]. To reflect these findings, the threshold for abnormally elevated PVR was reduced to <2WU (from 3WU) in the most recent PHT guidelines[1].

Haemodynamic Classification of PHT-LHD

The raised LA pressure in Group 2 PHT arises secondary to problems with the 'left heart' and is known collectively as PHT due to left heart disease (LHD). Whilst the majority of PHT research focuses patients with PAH, PHT-LHD is by far the commonest type of PHT representing 65-80% of PHT cases[17] and may be associated with worsening severity and poor prognosis. This has been acknowledged in the most recent PH guidelines[1].

The classification of PHT due to LHD falls into 3 broad sub-groups: PHT secondary to heart failure with reduced ejection fraction (HFrEF), PHT secondary to heart failure with preserved ejection fraction (HFpEF) and PHT secondary to left sided valvular pathologies[2] such as aortic stenosis or regurgitation and mitral stenosis or regurgitation (or one or more of these LHDs). These conditions are thought to cause a passive "back pressure" from an elevated LA pressure into the pulmonary vasculature. However, some patients have PHT that is "out of proportion" to their LA pressure elevation and exhibit

pulmonary arteriolar remodelling. This is known as combined pre- and post-capillary PHT. To delineate these patients from those with isolated LHD, additional hemodynamic criteria have been proposed: 1) isolated post-capillary PHT (Ipc-PH) (PVR≤2, 2) combined post- and pre-capillary PHT (Cpc-PH) (PVR>2)[18]. This is further outlined in **Table 1.2**.

Despite being recognised as an increasingly common disease, the detailed phenotypes, consequences and outcomes of PHT-LHD remain relatively poorly characterised[19]. This is likely attributable to several factors including current data being taken from small community heart failure populations, the definition of PHT being based on echo findings with a variety of cut offs and populations being heterogenous in terms of basic demographics and underlying pathologies[19]. Accurate phenotyping and diagnosis is imperative as patients with PAH who are incorrectly classified as PHT-LHD may be denied PAH-specific therapy which has been shown to be of prognostic benefit in these patients. On the other hand, if patients with PHT-LHD are misclassified as having PAH and are commenced on PAH-specific therapy there may be little prognostic benefit or even harm.

Table 1.2 Haemodynamic Definitions of Pulmonary Hypertension

Definition	**Haemodynamic Characteristics**
Pulmonary Hypertension	mPAP >20mmHg
Pre-Capillary Pulmonary Hypertension	mPAP >20mmHg, PAWP ≤15mmHg, PVR >2WU
Post-Capillary Pulmonary Hypertension	mPAP >20mmHg, PAWP >15mmHg
• Ipc-PH	• DPG <7mmHg and/or PVR<2WU
• Cpc-PH	• DPG >7mmHg and PVR>2WU

mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; pulmonary vascular resistance; Ipc-PH = isolated post-capillary pulmonary hypertension; Cpc-PH = combined pre- and post- capillary pulmonary hypertension; DPG = diastolic pulmonary gradient.
Reproduced from Humbert et al. 2022[1].

Epidemiology of Pulmonary Hypertension and Left Heart Disease

Worldwide:

The prevalence of PHT-LHD worldwide remains unclear with the majority of data coming from community heart failure populations with varying study design and diagnostic criteria. Many of these studies incorporate echocardiography parameters rather than hemodynamic measures on RHC[19]. To compound this issue, where registry data has been used it is important to note that the majority of PHT registry's focus on patients with PAH, thus patients with PHT-LHD are under-represented[20, 21]. Thus, the prevalence of PHT in patients with LHD varies between 23-80% depending on the population being studied and diagnostic criteria used[19, 22, 23].

In a community heart failure study of >1000 patients in the USA PHT diagnosed based on echocardiographic parameters was 79%[23]. Further community studies have shown a high prevalence of PHT in patients with HFpEF. Lam et al. reported a prevalence of PHT of 83% amongst a cohort of 244 patients with HFpEF using echocardiographic parameters (systolic P_{pa} >35 mmHg)[22]. Leung et al. used mean P_{pa} >25 mmHg on echocardiography and reported a prevalence of 53% in 455 patient with HFpEF[24]. In patients with chronic HFrEF, a wide range of prevalence figures have been reports (16-63%) dependent on the population[25-27]. The populations studied are often those with severe or end stage heart failure rather than chronic, stable patients who make up the majority of this population. A large single centre study in Austria (n = 2351) showed 53% of patients who underwent RHC after having raised pulmonary artery systolic pressure (PASP) on echo had PHT, and of these, 86% had PHT-LHD[28].

The largest PHT registry in the UK, ASPIRE, reported the prevalence of PHT-LHD as 11.7%[29]. The Dutch PulmoCor registry with >1500 patients from 6 tertiary referral centres reports a prevalence of PHT-LHD of 20%[30], with the Swiss PHT registry only reporting a prevalence of 3.6%[31]. It is difficult to interpret these data knowing that these registries have a strong PAH focus.

PHT can complicate patients with left sided valvular pathology with those with mitral valve disease the most commonly affected (73%)[32, 33]. Patients with aortic valve disease are less commonly affected, but still have a high prevalence of 30-50%[34, 35]. Reported prevalence varies greatly depending on the thresholds and definitions used and are further limited by small cohorts (often pre-surgical) which limits the understanding of the true community prevalence of this group of diseases. None-the-less, it has become widely acknowledged that PHT-LHD is the most common sub-type of PHT with this heterogenous group estimated as making up 65-80% of all PHT cases.

Australia:

Data on prevalence of PHT-LHD within Australia shares similar problems to that seen around the rest of the world. There is a paucity of community based data and the Pulmonary Hypertension Society of Australia and New Zealand's registry (the largest PHT registry in Australia with > 3000 patients) contains only a small portion of patients with PHT-LHD[36]. In 2012 the Armadale Echo Study was published and showed that in a large cohort (>10 000) 9.1% of patients were diagnosed as having pulmonary hypertension (defined as PASP>40mmHg), with 70% of these patients having PHT-LHD[37]. More recently the use of 'big data' from the National Echo Database of Australia (NEDA) has been used to showed that 18.7% patients from the cohort of 74 405 patients who underwent a transthoracic echo in the study period had some degree of PHT reported (estimated right ventricular systolic pressure (eRVSP) >40mmHg)[12]. However, the prevalence of PHT in patients with LHD has yet to be reported utilising big data.

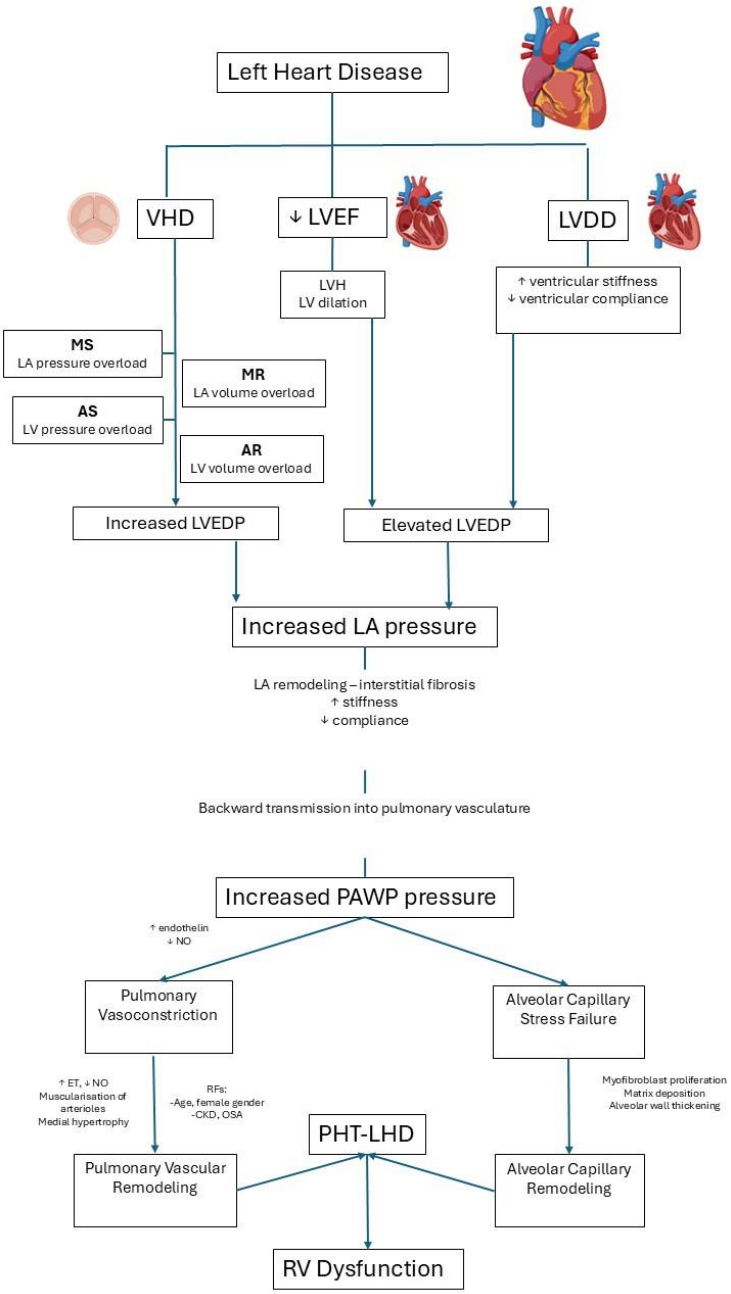
Pathophysiology of Pulmonary Hypertension and Left Heart Disease

The pathophysiology of PHT-LHD is multifactorial but is likely a result of hydrostatic pressure causing pulmonary vasculature remodelling[38]. The left atrium is an important structure which can act as a barrier between raised left ventricular filling pressures and the pulmonary vasculature. LHD (regardless of underlying cause) can lead to an increase in left atrial (LA) pressure with a reduction in LA and contractility[39]. Over time this can lead to LA remodelling evidenced by interstitial fibrosis and increased LA stiffness and reduced compliance[40]. This causes a rise in LA pressures and volumes leading to a passive increase in backwards pressure into the pulmonary vasculature. Persistent elevation of pulmonary pressures can result in alveolar capillary stress failure[41, 42] causing capillary leakage and oedema. Whilst initially reversible, the activation of chemical mediators such as endothelin I and angiotensin II, and inhibition of nitric oxide, with the release of metalloproteinases and inflammatory mediators leads to irreversible remodelling characterised by excessive collagen deposition within the intima and media of the pulmonary vessels as well as impaired smooth muscle function[43, 44]. These structural changes can lead to impairment of gas transfer and a reduction in lung diffusion capacity[45]. Pathologic changes such as lung myofibroblast proliferation leads to muscularisation of the arterioles, neointimal formation of distal pulmonary arteries; this causes lasting elevation in the PVR[44, 46].

In the initial 'passive' phase which results from a backwards pressure from raised pressures in the left atrial or ventricle there is an increase in PAWP. However, the PVR are within normal limits. This phase is generally considered reversible and is known as Ipc-PH[2, 21]. When the pathological changes to the distal pulmonary vasculature occurs there is an increase PVR. This introduces a 'pre-capillary' component and thus represents Cpc-PH which is less likely to be reversible[2, 21].

The obstructive effects on the pulmonary vasculature and the increase in pulmonary artery pressure leads to an increase in RV afterload[38]. This causes RV hypertrophy and then dilation to a spherical shape which leads to functional tricuspid regurgitation (TR) and raised RA pressures[20, 38]. There may be a reduction in RV contractility and development of RV dysfunction which pertains a poor prognosis[26]. The pathophysiology is summarised in **Figure 1.1**.

Figure 1.1 Pathophysiology of Pulmonary Hypertension due to Left Heart Disease



Depicts the pathophysiology of pulmonary hypertension due to left heart disease.

LVEF = left ventricular ejection fraction, LVDD = left ventricular diastolic dysfunction, VHD = valvular heart disease, LVH = left ventricular hypertrophy, LV = left ventricle, MS = mitral stenosis, MR = mitral regurgitation, AS = aortic stenosis, AR = aortic regurgitation, LVEDP = left ventricular end diastolic pressure, LA = left atrial, PAWP = pulmonary arterial wedge

pressure, NO = nitric oxide, ET = endothelin, RF = risk factors, CKD = chronic kidney disease, OSA = obstructive slee apnoea, PHT-LHD = pulmonary hypertension due to left heart disease, RV = right ventricle
Reproduced and modified from Ramu et al. 2016[47]

Underlying Causes of PHT-LHD

There is a growing need to identify and understand the underlying PHT-LHD substrate since the prevalence, pathophysiology, clinical profile, management approach and prognosis differs between groups[48].

PHT is known to complicate left-sided valvular pathology, with 15-60% of patients estimated to experience this complication[49].

Mitral regurgitation:

PHT in mitral regurgitation (MR) is common and varies according to the aetiology and severity of MR and the presence of LV dysfunction. In this cohort PHT is thought to be due to the direct effect of systolic backflow into the LA leading to a combination of pressure and volume overload and may develop before patients experience symptoms or left ventricular (LV) systolic dysfunction[2, 50, 51].

- Primary MR: refers to primary mitral valvular pathology e.g. mitral valve prolapse resulting in MR. In symptomatic patients the prevalence of PHT is estimated at 20-30% and decreases to <20% if asymptomatic[49]. In symptomatic patients with severe MR the prevalence has been noted to be as high as 64%[52].
- Secondary MR: refers to MR that occurs as a result of multifactorial LA and LV dilation and remodelling results to annular dilation. In patients with concomitant reduced LVEF prevalence is approximately 40%[53]

The presence of PHT is not a factor considered in guidelines in determining the timing of valvular intervention. Whilst pulmonary pressures have been noted to improve following mitral valve intervention residual PHT remains in a significant number of patients and those with severe PHT consistently had worse outcomes[54, 55].

Mitral stenosis:

The most common cause of mitral stenosis (MS) worldwide is rheumatic heart disease secondary to post-streptococcal rheumatic fever[56]. Post-infection inflammatory changes lead thickening, retraction and fusion of the mitral valve leaflets. Outside of these regions aging and the calcific valvular remodelling associated is the most common cause of MS. The obstruction which occurs at the mitral valve in MS results in sustained pressure overload on the LA[49] which is directly transmitted into the pulmonary vasculature[51]. This results in IpcPH or CpcPH in a significant proportion of patients. It is

estimated that >40% patients with MS develop PHT and that this increases with the severity of the valvular pathology[49].

The presence of PHT is known to have an impact on outcomes and has been incorporated into treatment guidelines. A non-invasive measurement of pulmonary artery systolic pressure (PASP) >50mmHg is considered an indication for percutaneous or surgical intervention in asymptomatic patients with severe MS[57]. However, clear data on phenotyping, risk stratification (particularly in light of new hemodynamic definitions), management of PHT pre-intervention and residual PHT post-intervention remains unclear.

Aortic regurgitation:

In aortic regurgitation (AR) PHT is postulated to develop via pressure and volume overload leading to indirect increases in LA pressure and the development of post-capillary PHT[49, 51]. The prevalence of PHT in patients with aortic regurgitation is approximately 27-37%[58].

The presence of severe PHT in patients with severe is known to cause greater LV enlargement and eventually LV dysfunction. Thus, PASP>60mmhg is an indicator for aortic valve intervention in asymptomatic patients in this cohort[57]. There is a paucity of data on the phenotype, management options and prognostic outcomes in this group of patients.

Aortic stenosis:

Aortic stenosis (AS) leads to concentric LV hypertrophy, this leads to myocardial fibrosis and diastolic dysfunction. This can cause an indirect increase in LA pressure and thus lead to PHT[49, 51]. There are varied reports on the prevalence of PHT in patients with AS. Older studies approximate that 15-32% patients with symptomatic AS have PHT with reduced LVEF, increased LVEDP, LA dilation and concomitant MR all contributing[49]. Whilst a recent study of patients with severe AS referred for transcatheter aortic valve intervention (TAVI) showed 20% of patients had IpcPH and 32% had CpcPH[59].

The clinical phenotype of PHT in AS and impact of the presence and severity of PHT on outcomes remains unclear. Furthermore, it is not known whether the presence of PHT should be an indication for aortic valve intervention, or whether it should preclude it[48].

Reduced Left Ventricular Ejection Fraction:

Left ventricular dysfunction, regardless of its etiology is the most common LHD causing PHT[2]. The common underlying etiologies are ischemic cardiomyopathy and dilated cardiomyopathy[17]. Regardless of underlying cause the cellular and phenotypic changes that occur in patients with reduced

LVEF result in LV hypertrophy and dilation which leads to an increase in LV end diastolic pressure, raised LA pressure, and, then a backward transmission of this increased pressure to the pulmonary vasculature causing PHT[17, 60]. These changes may interact with patient specific risk factors or characteristics and lead to the progression from IpcPH to CpcPH[61].

The treatment of PHT in patients with LVEF is focused on addressing the underlying cause of systolic dysfunction such as coronary artery disease. The prognostic impact of PHT in patients with reduced LVEF has not been thoroughly described in the literature though the PHT itself has been proposed as a modifiable target in this cohort[48]. Studies looking at the use of PAH specific therapies in this cohort are small with variable results[62].

Left Ventricular Diastolic Dysfunction, with Preserved Ejection Fraction:
Left ventricular diastolic dysfunction (LVDD) in preserved ejection fraction (pEF) and PHT is becoming increasingly recognised as a common entity[2]. Risk factors include older age, ischemic heart disease (IHD), hypertension (HTN) and obesity. PHT in patients with LVDD with pEF is thought to develop as a direct result of reduced ventricular compliance and impaired LV relaxation and thence raised LA pressure[2, 44, 60]. PHT is prevalent in this population however, reported rates have varied significantly from 36-83%[22, 24, 63].

Phenotype of Patients with PHT-LHD

Understanding the demographic and clinical phenotype of patients with PHT-LHD is crucial for clinicians to identify ‘at risk’ patients and aid early diagnosis. The general phenotype described is older age, female patients with systemic hypertension and other metabolic risk factors[2]. Of course, in clinical practice patients with pure / isolated PHT-LHD are rare. Rather, there is overlap between LHD and other diseases that may increase the risk of developing PHT[48]. Thus, clinicians are faced with the challenge of determining whether a patient has PAH with LHD co-morbidities or PHT-LHD. This difference has significant implications on treatment and highlights the importance of accurate phenotyping.

Several studies have sought to better clarify these comorbidities and better understand the presence of ‘overlap syndromes’. A recent registry study identified that the presence of ≥ 3 comorbidities – HTN, IHD, obesity or diabetes mellitus in patients with PAH suggested shared features with PHT-LHD[64]. Similarly, when trying to more accurately phenotype patients with HFpEF older age, chronic kidney disease (CKD) and IHD were more commonly related to the presence of PHT[65]. In patients with moderate to severe left sided valvular pathology, LV hypertrophy on ECG and LA enlargement on TTE were identified as predictors of PHT-LHD[66]. The identification of these significant co-morbidities

has already helped guide diagnostic testing in 'at risk' patients with Robbins et al. using clinical predictors of older age, obesity, HTN and LA enlargement to identify patients to perform provocation fluid challenges on during RHC[67].

There has been little guidance on the methodologies to address overlapping phenotypes in clinical practice resulting in delays in diagnosis and incomplete diagnostic assessment in 'at risk' patients. This issue was highlighted at the 7th World Symposium in Pulmonary Hypertension (WSPH) held in 2024 with a simplified approach for clinicians to distinguish common LHD co-morbidities from risk factors proposed **(Table 1.3)**[48]. The Taskforce reporting on PHT-LHD also noted that the extent to which a co-morbidity determines the likelihood of PHT-LHD compared with PAH with co-morbidities is probably graded and proposed a 'co-morbidity staging system' to further clarify this[48] **(Table 1.4).**

Table 1.3 Common left heart disease comorbidities and risk factors

Common LHD Comorbidities	Common LHD Risk Factors
Obesity	Hypercholestrolemia
Systemic hypertension	Tobacco use and second hand smoke exposure
Coronary artery disease	Sedentary lifestyle
Diabetes mellitus	Illicit drug use
Valvular heart disease	Chronic alcohol use
Arrhythmia	Infectious exposures in endemic regions
Reduction in left ventricular systolic function	
Peripheral artery disease	

LHD = left heart disease

Reproduced from Maron et al. 2024[48]

Table 1.4 Left Heart Disease comorbidity staging

	Mild	Moderate	Severe
Obesity (BMI)	30-35	35-40	>40
Systemic hypertension	Treated ≤ 2 drugs	Treated >3 drugs	Uncontrolled
Diabetes	Insulin resistance / prediabetes	Type 2 DM	Type 2 DM with vascular complications
Coronary artery disease	Single vessel disease	NSTEMI Multivessel disease Multiple percutaneous interventions Single episode of SCA	CABG Repeated SCA STEMI Symptomatic persistent ischemia Diffuse disease
Arrhythmia	Single episode of atrial arrhythmia Absence of AF at diagnosis	Repeated episodes of AF ≥1 treatment for arrhythmia	Permanent AF Ventricular arrhythmias Repeated ablation Implantation of pacemaker / ICD CRT
Peripheral arterial disease	Asymptomatic large vessels atheromatosis	Non-significant stenosis (carotid, temporal) Previous single percutaneous intervention	Previous surgery for large vessel disease Stage 2b PAD
	Low	**Intermediate**	**High**
Combined LHD comorbidities	≥1 mild-stage LHD comorbidity	Moderate-stage LHD comorbidity Or ≥3 mild-stage LHD co-morbidities	>1 severe-stage LHD comorbidity

BMI = body mass index, DM = diabetes mellitus, NSTEMI = non-ST segment elevation myocardial infarction, SCA = sudden cardiac arrest, CABG = coronary artery bypass grafting, AF = atrial fibrillation, ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronisation therapy, PAD = peripheral artery disease, LHD = left heart disease

Reproduced from Maron et al.2024[48]

Diagnosis of PHT-LHD

Whilst PHT-LHD is prevalent there are often delays in diagnosis given the non-specific clinical presentation, variable findings on baseline investigations and a lack of standardised diagnostic criteria. Thus, treating clinicians must have a high degree of clinical suspicion and understand the clinical diagnostic phenotype of these patients to accurately identify patients who need further invasive testing and determine treatment approach.

Clinical Presentation

Clinical presentation is non-specific and includes symptoms such as dyspnoea (sometimes exercise induced), oedema, fatigue and when more severe can lead to symptoms of right heart failure.[68] The non-specific symptoms contribute to delays in diagnosis. Each individual sub-type of LHD will have specific examination findings. For example, auscultation of the heart may reveal typical murmurs consistent with left-sided valvular pathology including AS, AR and MR.

ECG, Chest Radiograph, and Cardiac Bio-Markers

The typical electrocardiogram (ECG) abnormalities noted in patients with PHT are noted in **Table 1.5**. However, it is important to note that the ECG of a patient with PHT-LHD is likely to be different and represent structural changes related to LHD including LA dilation or LVH[1]. Likewise, the findings seen on chest x-ray (CXR) consistent with PHT include right heart and PA enlargement but there may be additional finding consistent with LHD and pulmonary congestion including LA enlargement, central air space opacification and pleural effusions[1]. **Table 1.5** summarises the typical findings in PHT patients and abnormalities seen in those with LHD.

Cardiac biomarkers such as B-type natriuretic peptide (BNP) or NT-proBNP may be elevated in patients with PHT-LHD. In patients with reduced LVEF these biomarkers are often elevated and there are consensus thresholds to grade the degree of abnormality with clinical presentation and prognosis. In LVDD, these biomarkers are more difficult to interpret. Firstly, a normal BNP or NT-proBNP does not exclude the presence of LVDD, whilst the stretch of myocardial fibres should lead to a rise in biomarkers, there is lower end diastolic wall stress thus values are often lower than patients with reduced LVEF[69]. Secondly, there are no agreed upon thresholds to determine an abnormal result. Thirdly, key co-morbidities including atrial fibrillation (AF), CKD and obesity impact these results[69, 70]. In significant valvular disease these biomarkers may also be raised, but again thresholds of clinical and prognostic significance have not been determined.

Table 1.5. Typical findings of PHT on ECG and CXR, compared with characteristics of LHD

ECG		CXR	
Signs of PHT and commitment abnormalities	**Signs of LHD**	**Signs of PHT and commitment abnormalities**	**Signs of LHD / pulmonary congestion**
-P pulmonale (p>0.25 mV in lead II) -Right axis deviation -RBBB -RV strain pattern	-Bifid P wave / increased P wave duration (LA enlargement) -LVH -LBBB	-Right heart enlargement -PA enlargement -Pruning of peripheral vessels -'Water-bottle' shaped of cardiac silouette	-Central airspace opacification -Interlobular septal thickening 'Kerly B' lines -Pleural effusions -LA enlargement -LV dilatation

ECG = electrocardiograph, CXR = chest x-ray, LHD = left heart disease, PHT = pulmonary hypertension, RBBB = right bundle branch block, RV = right ventricle, LVH = left ventricular hypertrophy, LBBB = left bundle branch block, PA = pulmonary artery, LA = left atrium, LV = left ventricle
Reproduced and modified from Humbert et al. 2022[1]

Transthoracic echocardiography

Transthoracic echocardiography (TTE) is often the simplest, most accessible non-invasive investigation that it is often the initial screening test for PHT-LHD amongst patients in whom there is a clinical suspicion of this diagnosis. PAP can be estimated on TTE through doppler measurements of ePASP, a method which is both reproducible and validated[71]. ePASP is derived using the Bernoulli equation (4x[(tricuspid regurgitation velocity) TRV]^2 + right atrial pressure (RAP)[72]. The limitations of this method include a potential for underestimation in patients with severe TR in whom the pressure difference between the right atrium and ventricle is small, and potential overestimation in patients with moderate (or lower) TR[73].

In the most recent PHT guidelines there has been shift towards using the TRV (as opposed to ePSAP) to risk stratify patients with potential PHT. TRV >3.4 m/sec suggests a high probability of PHT, TRV 2.9-3.4 m/sec are associated with an intermediate risk of PHT with a TRV ≤2.8 m/sec associated with a low probability of PHT[1]. Further echocardiographic signs suggestive of PHT, as outlined in Table 1.6, have been proposed[1]. When present, these signs increase the probability of PHT.

Identifying the cause of the LHD is also often first delineated on TTE. There are well protocolised international guidelines on the assessment of LV systolic and diastolic function, as well as left sided valvular pathology[57, 74, 75]. As such echo remains the most accessible screening and monitoring diagnostic method and provides opportunity to better phenotype and risk stratify these patients.

Table 1.6 Additional echocardiographic signs suggestive of pulmonary hypertension

Ventricles	-RV/LV basal diameter / ratio >1.0 -Flattening of interventricular septum (LVEI >1.1 in systole or diastole) -TAPSE/sPAP ratio <0.55mm.mmHg
PA	-RVOT AT <105 m/sec and / or mid-systolic notching -Early pulmonary regurgitation velocity >2.2 m/sec -PA diameter > AR diameter; PA diameter >25mm
IVC and RA	-IVC diameter >21mm with decreased inspiratory collapse -RA area (end systole) >18cm^2

PA = pulmonary artery, IVC = inferior vena cava, RA = right atrium, RV = right ventricle, LV = left ventricle, LVEI = left ventricular eccentricity index, TAPSE = tricuspid annular plane systolic excursion, sPAP = systolic pulmonary arterial pressure, RVOT AT = right ventricular outflow tract acceleration time, AR = aortic root
Reproduced from Humbert et al (2022) and Maron et al (2024)[1, 48]

Right heart catheterisation

The "gold standard" for diagnosing PHT and differentiating pre- and post- capillary PHT is RHC[76]. Patients are defined as having PHT with a mPAP >20mmHg. The left sided pressure measurement (PAWP) is important to discriminate between pre- and post- capillary PHT (PHT-LHD), with pre-capillary being defined as having a normal PAWP (<15mmHg) and post capillary being defined as elevated (>15mmHg).

Approximately 13% of cases of PHT-LHD have an increase in mPAP that is "disproportionate" to raised LAP and is likely secondary to additional pre-capillary pulmonary vascular disease[18]. These patients generally have poorer prognosis. To delineate these patients from those with isolated LHD, additional hemodynamic criteria have been proposed: 1) Ipc-PH (PVR<2 WU), 2) Cpc-PH (PVR>2 WU)[18]. The PVR is calculated with the following formula – [TPG/ CO], with the TPG being calculated by [mPAP – PAWP]. Thus, a normal PVR in patients with mPAP >20mmHg and PAWP >15mmHg represents elevated LA pressure in the absence of intrinsic pulmonary vasculopathy, as seen in IpcPH[1, 18, 48]. Whilst an elevated PVR with these haemodynamics represents an element of pulmonary vascular disease and thus patients are considered to have CpcPH[1, 18, 48]. It is important to note that with the lowered threshold of PVR seen in the 2022 PHT guidelines there has been a shift of patients from the IpcPH to the CpcPH sub-group[77]. Haemodynamic phenotyping of these patients may be crucial in identifying a subset of patients who may respond favourably to PHT therapy.

Provocation testing

There is increasing acknowledgment, however, that traditional haemodynamic measurements may be insufficient to identify early stages of LHD; thus, delineating pre- versus post- capillary PHT (or a combination) and subsequently guiding treatment is critical and unresolved. Patients with suspected PHT-LHD are almost always "fasting" prior to their RHC and may already be on diuretic therapy. These factors may "artificially" decrease PAWP as measured at fasting RHC, which may in turn lead to incorrect diagnosis[2, 3, 48, 67].

Certain provocation techniques have been proposed to better characterise patients with PHT-LHD. These include (acute) fluid challenges which can reveal occult post-capillary PHT and exercise challenges which can reveal early left ventricular diastolic dysfunction[67]. Fluid challenges have been shown to help diagnose post-capillary PHT with Robbins et al showing that 22% patients with PAH were re-classified as having PHT-LHD following a fluid challenge in a cohort of 207 patients[67]. Whilst D'Alto et al showed a reclassification of 6-8% of patients with precapillary or normal hemodynamic characteristics at baseline following a fluid challenge during RHC[78]. The literature suggests a 500mL fluid bolus over 5-10mins is an effective fluid challenge[2], though D'Alto et al used 7mL/kg to determine their fluid challenge, however there is no standardised methodology and individual patient factors such as weight and duration of fasting are not routinely taken into account. Furthermore, until recently there was no consensus on the threshold to define an abnormal response post fluid challenge. Recent studies suggest that in healthy subject a PAWP <15mmHg is able to be maintained after 500mL and an abnormal reading is considered PAWP>18mmHg[2, 76]. Clarity was given at the 6th WSPH with a post-fluid PAWP >18mmHg being determined as the threshold for an abnormal response[48]. Recent studies using this threshold have shown that 10-21% of patients were re-classified as having occult LHD following a fluid challenge and that these patients were more likely to have clinical and echo characteristics (including higher E/e') consistent with LHD[79, 80].

Exercise provocation tests have been postulated to add diagnostic and prognostic value when added to baseline hemodynamics. However, there is no standardised approach or protocol even in expert centres; use of a supine erogometer in the cardiac catheterisation lab is the most commonly reported technique, with ramp or step protocols described in the literature. Exercise challenges have been shown to diagnose occult HFpEF, with Maor et al reporting that in a cohort of 63 patients presenting with shortness of breath on exertion, normal LVEF and PAWP <15mmHg at baseline approximately a third had a rise in PAWP to >18mmHg following moderate exercise[81]. There is a lack of consensus as to what constitutes an abnormal PAWP response to exercise in the literature. It has been suggested that an abnormal increase of mPAP during exercise defined as mPAP/ CO slope >3mmHg/L/min between rest and exercise represents exercise PHT. The PAWP/CO slope >2mmHg/L/min and a PAWP threshold have proposed as ways to distinguish between pre- and post- capillary causes of exercise PHT.

However, it is unclear what an abnormal exercise PHT threshold is with some studies using 18mmHg and others using 25mmHg.

Currently there is no standardised approach to perform RHC procedures in patients with suspected PHT-LHD[2]. Provocation testing is not routinely performed and when performed there is no standardised protocol, nor a standardised approach to interpretation of results thus further research is needed in this area.

Treatment Options

The mainstay of treatment in PHT-LHD is to optimise the underlying cardiac pathology and the use of diuretic therapy to reduce pulmonary venous congestion[1]. Recently there has been suggestion that the use of remote PA monitoring which can be a surrogate of left sided filling pressures may help to optimise and titrate medications in these patients – particularly diuretics[82, 83]. However, particularly in patients with CpcPH where the pathophysiologic consequence of LHD has resulted in pulmonary vascular disease and at times RV dysfunction, PAH specific therapies have also been considered as targets[1]. Treatment options for patients with PHT-LHD are limited, with standard PAH therapy not showing benefit in unselected patients with predominantly post-capillary PHT (and even potentially showing harm). Since 2013 there have been several clinical trials targeting the three traditional PAH treatment pathways.

Phosphodiesterase-5 inhibitors (PDE-5i) and guanylate cyclase stimulators (sGC) represent one class of PAH medications which acts through inhibiting the negative feedback loop which promotes the degradation of cyclic guansine monophosphate (cGMP), and thus leads to vasodilation. The results of PDE5i use (such as sildenafil and tadalafil) and sGC (riociguat) are variable even accounting for differences in underlying LHD pathology. There have been small studies to suggest that sildenafil may improve hemodynamics, exercise capacity and RV function in patients with reduced LVEF and LVDD, particularly when their hemodynamic profile was CpcPH[84-87]. In contrast, the LEPHT trial[62] investigating the use of riociguat in patients with HFrEF and the HOENDERMIS trial looking at the use of sildenafil in patients with HFpEF found no difference in the primary outcome which was reduction in mPAP[88]. Whilst when used in patients with valvular heart disease sildenafil showed worse clinical outcomes[89].

Endothelin receptor antagonists (ERA) such as bosentan, ambrisentan and macicentan act on endothelin A and B receptors which promote vasoconstriction and proliferation of smooth muscle. ERA's have been consistently shown to have no efficacy in treating PHT-LHD across a spectrum of sub-types,

including reduced LVEF and LVDD, and, have been linked to greater adverse effects particularly with regards to worsened fluid retention[90-92].

Given the variability of the utility of these drugs in the literature there is no guideline recommended approach for PHT medications in this cohort. This further emphasises the need for accurate diagnosis to prevent potentially harmful outcomes from inappropriate treatment. It also highlights the need to accurately identify those patients with pre-capillary disease who are potential responders to PAH-specific treatment.

Thesis Aims

PHT is a common and devastating complication of LHD, with PHT-LHD representing the most prevalent sub-type of PHT across the world. This is a major and unsolved problem in cardiology, as this complication carries an adverse prognosis and currently there is no specific treatment. Despite being common and serious, PHT-LHD presents unsolved challenges in disease phenotyping, diagnosis and treatment. The relationships between PHT and the various types of LHDs, in isolation or together, have only been poorly studied, in relatively small patient numbers, and this is the major focus of this thesis.

The aims of this thesis are to:

1. Characterise PHT-LHD phenotypes by evaluating the prevalence and severity of PHT, including demographics, echocardiographic phenotype and outcomes of PHT complicating different LHD types (AR, AS, MR, reduced LVEF and LVDD).
2. Identify the consequences of PHT on the RV in patients with severe aortic stenosis and assess the RV response when the LHD is ameliorated through treatment of the AS with TAVI.
3. Develop and optimise a standardised protocol for right heart catheterisation (RHC) in patients with PHT and known or suspected LHD.

Taken together the studies within this thesis will provide valuable information on the demographic, imaging and haemodynamic characteristics of this highly prevalent, but under diagnosed and difficult to treat group of patients.

Chapter 2 – Prevalence of Pulmonary Hypertension in Aortic Regurgitation and its Influence on Outcome

This chapter is based on the publication: Ratwatte S, Playford D, Stewart S, Strange G, Celermajer DS. Prevalence of pulmonary hypertension in aortic regurgitation and its influence on outcomes. HEART. Published online- 03 April 2023. doi: 10.1136/heartjnl-2022-322187.

Abstract

Objective: Aortic regurgitation (AR) can lead to pulmonary hypertension (PHT). There is a paucity of data on the prognostic importance of PHT in these patients. We therefore aimed to describe the prevalence and prognostic importance of PHT in such patients.

Methods: In this retrospective study, we analysed the National Echocardiography Database of Australia (data from 2000-2019). Adults with an estimated right ventricular systolic pressure (eRVSP), left ventricular ejection fraction (LVEF) >50% and with moderate or greater AR were included (n= 8392). These subjects were then categorised according to their eRVSP. The relationship between PHT severity and mortality outcomes were evaluated (median follow-up of 3.1years, interquartile range 1.5-5.7years).

Results: Subjects were aged 74±14years and 58.4% (4901) were female. Overall, 1417 (16.9%) had no PHT; and 3253 (38.8%), 2249 (26.9%), 893 (10.6%) and 580 (6.9%) patients had borderline, mild, moderate and severe PHT respectively. Mean eRVSP was slightly higher in females than males (41±13 vs 39±12mmHg, p<0.0001) and increased with age in both sexes. After adjustment for age and sex, the risk of long-term mortality increased as eRVSP increased (adjusted hazard ratio 1.20, 95% confidence interval 1.06-1.36 in borderline PHT, to aHR3.32, 95%CI 2.85-3.86 in severe PHT, p<0.0001). There was a mortality threshold seen from mild PHT onwards (eRVSP 41.36-44.15mmHg; aHR1.41, 95%CI1.17-1.68).

Conclusions: In this large cohort study, we characterise the relationship between AR and PHT in adults. In patients with ≥moderate AR, PHT is associated with a progressive risk of mortality, even at mildly elevated levels.

Introduction

Aortic regurgitation is a common left-sided valvular pathology, with a lifetime risk of 13% in men and 8.5% in women[93]. Significant AR is associated with an increased mortality risk[94], even in the absence of symptoms[95]. Thus, the identification of features predictive of adverse outcomes is important for risk stratification and may help guide management decisions. Despite this, there is a paucity of data on the prevalence and prognostic impact of PHT in those adults with significant AR[19, 49, 51, 58, 96].

PHT is known to complicate LHD including left-sided valvular pathologies[2] such as AR. PHT due to LHD is thought to develop secondary to an elevated LA pressure leading to back pressure into the pulmonary vasculature and this represents the most common cause of PHT[2]. In AR specifically, PHT is postulated to develop via LV volume overload, leading eventually to increases in LA pressure and the development of post-capillary PHT[49, 51].

The relationship between PHT and AR is poorly understood, with gaps in the literature surrounding prevalence[49, 96], detailed echocardiographic phenotype[51, 97] and mortality trends[58, 96, 98]. It is within this context that we examined data from the National Echo Database of Australia (NEDA), with the aim of exploring the independent prognostic value of pulmonary pressures in patients with moderate or greater aortic regurgitation.

Methods

NEDA Database and Study Design

The NEDA is a multi-centre nationwide echocardiography Registry, previously described, in detail [12, 99, 100]. NEDA contains basic demographic and detailed echocardiographic data of adults from >25 centres across Australia. The database is linked with the comprehensive National Death Index (NDI). The study period included >1million echo reports from >600 000 individuals, studied between January 2000 and June 2019. Vital status was determined as of 21st May 2019 (median follow-up 6.2years, interquartile range (IQR) 3.8-9.8years); patients alive at this date were censored alive. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and human ethics approval was obtained, protocol SLHD X15-0387 and 2019/ETH069899. A retrospective waiver of consent was authorised as part of this ethics protocol.

Study cohort

Figure 2.1 shows our study flow diagram; data at study census were used to identify patients with significant AR in order to characterise their relationship to PHT: 1) adults ≥ 18 years of age, 2) with at least one echocardiogram recorded (where patients had multiple studies only the last study was

analysed), 3) with a recorded LVEF, eRVSP and with 4) moderate or greater AR. A combination of qualitative and quantitative measures were used to determine the presence of moderate or greater AR. Text extraction from the conclusion and body of each report was used to identify patients with moderate or severe AR, qualitatively. Aortic valve (AV) pressure ½ time <500m/sec (as per American Society of Echocardiography guidelines[101]) was the main quantitative measure. Patients with aortic valve replacements (AVR) were excluded from this analysis, as were patients with evidence of severe aortic stenosis (AV mean gradient >40mmHg, and / or peak velocity >4m/sec, and / or AVA <1cm^2)[102], LVEF < 50% and/or those with less than moderate aortic regurgitation. eRVSP was conservatively derived using the Bernoulli equation (4x[(tricuspid regurgitation velocity) TRV]^2 + assumed RA pressure of 5mmHg)[72]. RV size and function were described qualitatively using text extraction from echo reports[12]. Cardiac rhythm information was derived, as in previous NEDA reports[103].

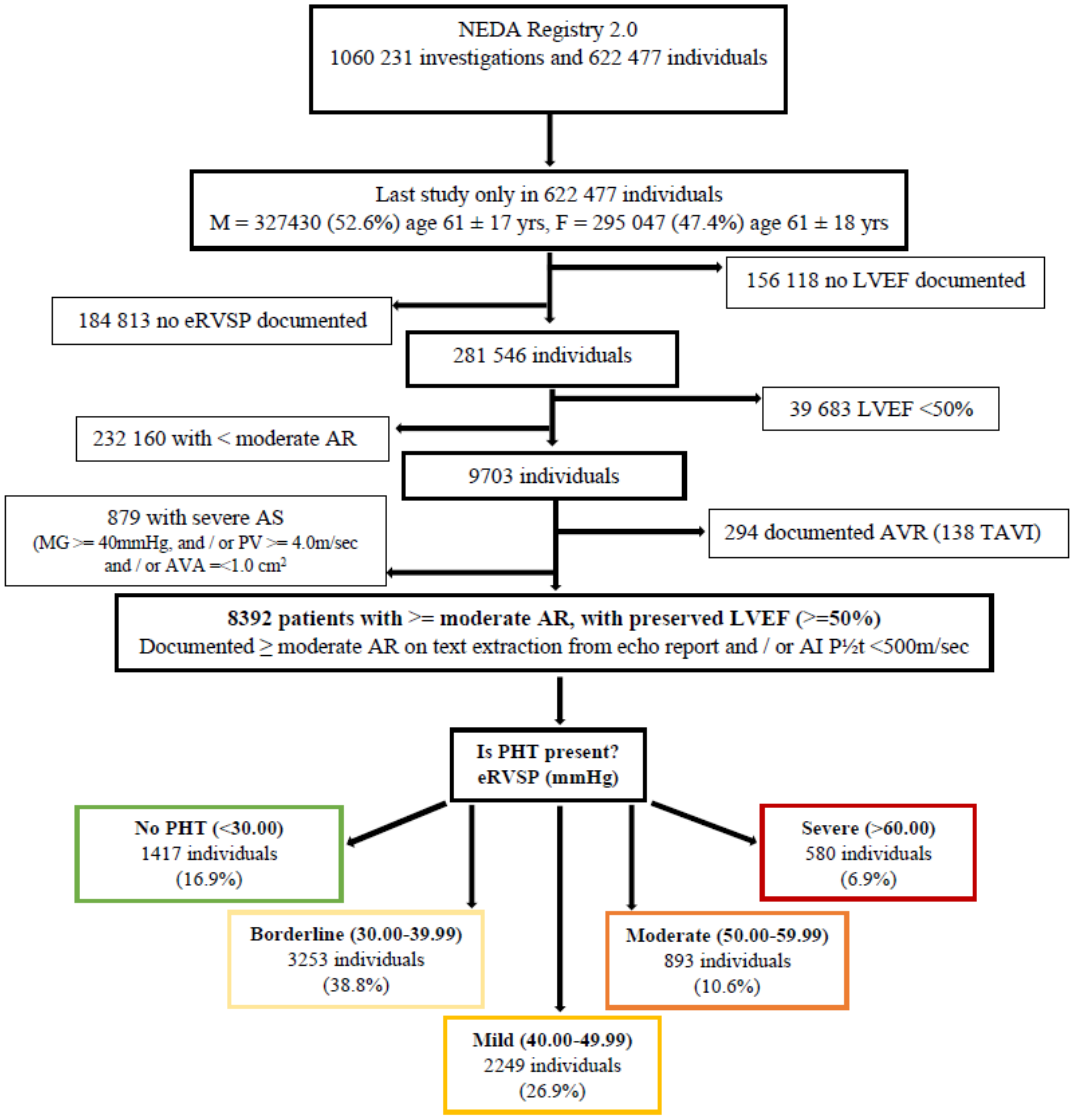
Study methods

Once the cohort of patients with moderate or greater AR was established, subjects were categorised according to their eRVSP, according to clinical guidelines[21, 37] to document the distribution of eRVSP and thence PHT severities. A "borderline PHT" group which has previously been determined as potentially significant in both NEDA papers and other recent prospective publications[12, 13, 104] was included. Defined categories were: 1) normal (eRVSP <30mmHg), 2) borderline (30.00-39.99mmHg), 3) mildly elevated (40.00-49.99mmHg), 4) moderately elevated (50.00-59.99mmHg) and, 5) severely elevated (eRVSP ≥60mmHg)[12].

We also analysed the eRVSP data according to decile distribution: 1st decile- 5.00-27.00mmHg, 2nd- 27.01-31.00mmHg, 3rd- 31.01-33.35mmHg, 4th- 33.36-36.01mmHg, 5th- 36.02-39.00mmHg, 6th- 39.01-41.35mmHg, 7th- 41.36-44.15mmHg, 8th- 44.16-48.44mmHg, 9th- 48.45-56.00mmHg and 10th- >56.00mmHg.

All-cause mortality was determined during a median follow up of 3.1 years (IQR 1.5-5.7years). We explored the relationship between eRVSP level and survival, looking at both clinically defined groups (as above) and the eRVSP decile.

Figure 2.1. Study Flow Chart



This flowchart shows the points of analysis performed in this study. NEDA = National Echo Database Australia; left ventricular ejection fraction (LVEF); eRVSP = estimated right ventricular systolic pressure; AR = aortic regurgitation; AVR = aortic valve replacement; TAVI = transcatheter aortic valve implantation; MG = mean gradient; PV = peak velocity; AVA = aortic valve area; AI P1/2t = aortic insufficiency pressure half time; PHT = pulmonary hypertension.

Statistical Analyses

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis using ANOVA was used to test whether the trend of the mean across the categorical groups of eRVSP levels was linear. For binary variables, the chi-squared test was used to determine if there was a trend in the change in proportions across the groups.

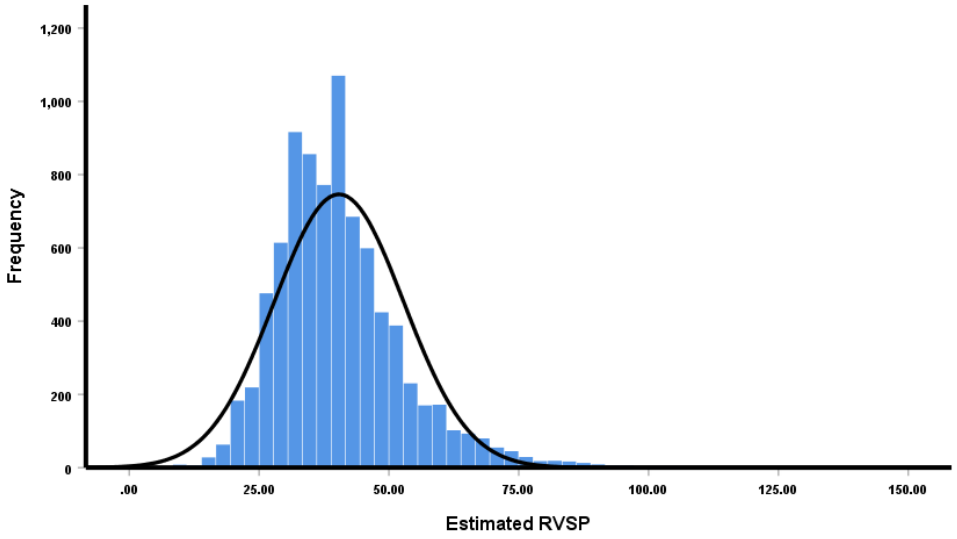
Actuarial 1- and 5- year survival rates for all-cause mortality were calculated from the 8043 (95.8%) and 5235 (62.4%) subjects with complete follow up for those time points. Multiple logistic regression models (entry at univariate p-value <0.05) were used to derive adjusted odds ratios (OR) for mortality models at fixed time points. Models were adjusted for te key demographic variables age and sex, to ensure that subject numbers remained large and reduce bias in the models. Cox regression hazard models were used to derive adjusted hazard ratios (HR) for mortality outcomes during follow up (entry model at a uni-variate p-value <0.05). Proportional hazards were confirmed by visual inspection of the log-to-log survival curves. Adjusted analyses included age and sex. A sensitivity analysis was performed excluding patients with concurrent ≥ moderate mitral regurgitation. Patients with moderate and severe AR were also assessed separately to determine if there were differences between these two groups. Severe AR, was defined as 'severe aortic regurgitation' on text extraction and / or AV pressure ½ time <200m/sec[101]. All analyses were performed with SPSS software version 22.0 (IBM Corp, Armonk, New York), and statistical significance was accepted at a 2-tailed p-value of <0.05.

Results

Prevalence of PHT and Distribution of eRVSP

A total of 8392 patients with moderate or greater aortic regurgitation, normal left ventricular systolic function and eRVSP data were identified. Mean age was 74±14years and 4901 (58.4%) were female. **Figure 2.2** shows the frequency distribution of eRSVP levels (median 39.00mmHg, IQR 32.00-46.00mmHg). The number of patients in each sub-group were: No PHT (eRVSP <30mmHg)- 1417 (16.9%), borderline PHT (eRVSP 30.00-39.99mmHg)- 3253 (38.8%), mild (eRVSP 40.00-49.99)- 2249 (26.9%), moderate (eRVSP 50.00-59.99)- 893 (10.6%) and severe (eRVSP>60mmHg)- 580 (6.9%).

Figure 2.2. *Frequency Distribution of Estimated Right Ventricular Systolic Pressure within the Cohort*



These data show the statistical distribution of estimated right ventricular systolic pressure (RVSP) levels.

As expected, there was a positive association between higher eRVSP group and older age (p<0.0001) **(Table 2.1).** Female patients were older than the males (75±14 years vs. 73±14 years, p<0.0001) but there were no clinically meaningful differences in eRVSP level (41±13 vs 39±12mmHg, p<0.0001) **(Table 2.2).** Men showed a higher burden of remodeling with greater increases in right atrial area, indexed LA volume and a greater proportion of patients with RV dilation, compared with female patients (p<0.0001, for all).

Cohort Profile

Table 2.1 summarises the demographic and echocardiographic characteristics of the study cohort divided into sub-groups, based on eRVSP levels. A typical pattern of worsening "left heart disease" phenotypic response was evident, with increasingly severe PHT. E:e' increased progressively with increased severity of PHT (11.08±4.44 vs. 16.84±7.11, no PHT vs severe PHT respectively, p<0.0001 for all). A progressive increase in right atrial area and indexed left atrial volume was noted from no PHT to moderate PHT (17.09±6.20cm^2 to 30.14±9.10cm^2 and, 34.45±13.60 mL/m^2 to 94.83±49.55mL/m^2 , respectively, p< 0.0001 for all), with a plateau noted in those with severe PHT (30.96±9.71 cm^2 and 94.99±50.33 mL/m^2 respectively). There was an increased proportion of patients with increased RV dilation and functional impairments as eRVSP level increased (7.3% vs. 43.3% and 0.8% vs. 6.4%, respectively, p<0.0001).

Table 2.1. Baseline Characteristics of Study Cohort (n = 8392)

	eRSVP 0.00-29.99 N= 1417	**eRSVP 30.00-39.99 N= 3253**	**eRVSP 40.00-49.99 N= 2249**	**eRVSP 50.00-59.99 N = 893**	**eRVSP >60.00 N = 580**	**P value**
Demographics						
Age, years	68 ± 17	73 ± 14	77 ±12	79 ± 12	78 ±14	<0.0001
Female (%)	775 (54.7)	1842 (56.6)	1339 (59.5)	546 (61.1)	399 (68.8)	<0.0001
Anthropometrics						
BMI	25.76 ± 4.98	26.11 ± 5.23	26.56 ± 5.59	26.47 ± 6.01	25.88 ± 6.40	0.02
BSA	1.81 ± 0.25	1.80 ± 0.24	1.80 ±0.25	1.79 ±0.25	1.74 ±0.25	<0.0001
Rhythm						
Atrial fibrillation / arrhythmia	232 (16.4)	684 (21.0)	639 (28.4)	339 (38.0)	246 (42.4)	<0.0001
LV dimensions and function						
LVEF %	62.03 ± 7.13	64.43 ± 8.36	66.67 ± 9.89	66.02 ± 9.58	65.72 ± 9.36	<0.0001
E:e' ratio	11.08 ± 4.44	12.39 ± 5.75	13.62 ± 5.23	15.03 ± 5.81	16.84 ± 7.11	<0.0001
LVEDD	4.58 ± 0.67	4.69 ± 0.70	4.87 ± 0.76	4.88 ± 0.81	4.72 ± 0.79	<0.0001
LVESD	3.00 ± 0.57	2.95 ± 0.61	2.95 ± 0.70	2.99 ± 0.69	2.87 ± 0.70	0.06
Atrial dimensions						
LA volume index, mL/m^2	34.45 ± 13.60	52.93 ± 31.75	83.39 ± 42.95	94.83 ± 49.55	94.99 ± 50.33	<0.0001
RA area, cm^2	17.09 ± 6.20	22.48 ± 7.95	27.50 ± 7.90	30.14 ± 9.10	30.96 ± 9.71	<0.0001
Right heart dimensions and function						
eRSVP, mmHg	25.24 ± 3.69	35.11 ± 2.89	44.36 ± 2.77	53.80 ±2.95	70.88 ± 11.73	<0.0001
TR peak velocity, m/s	2.16 ± 0.23	2.54 ± 16.68	2.93 ±0.15	3.29 ±0.14	3.84 ± 0.4	<0.0001
RV basal diameter	3.50 ± 0.56	3.30 ± 0.44	3.33 ± 0.40	3.43 ±0.43	3.55 ± 0.49	<0.0001
Dilated RV	12 (0.8)	29 (0.9)	31 (1.4)	33 (3.7)	37 (6.4)	<0.0001
Impaired RV function	103 (7.3)	349 (10.7)	568 (25.3)	306 (34.3)	251 (43.3)	<0.0001
Aortic valve dimensions and function						

Mean aortic gradient, mmHg	7.86 ± 6.45	9.14 ± 6.94	11.61 ± 8.27	11.44 ± 8.46	11.77 ± 8.33	<0.0001
Peak aortic velocity, m/s	1.73 ± 0.61	1.83 ± 0.58	1.95 ± 0.64	1.95 ± 0.65	2.04 ± 0.71	<0.0001
AV area (VTI), cm^2	2.52 ± 0.88	2.31 ± 0.82	2.17 ± 0.80	2.16 ± 0.77	1.96 ± 0.70	<0.0001
Aortic root diameter	3.47 ± 0.57	3.55 ± 0.57	3.63 ± 0.57	3.63 ± 0.57	3.39 ± 0.53	
Aortic valve pressure ½ time	480 ± 143	449 ± 110	424 ± 99	411 ± 104	404 ± 113	
Concomitant valvular pathology						
≥ moderate mitral regurgitation	170 (12.0)	439 (13.5)	536 (23.8)	292 (32.7)	202 (34.8)	<0.0001

Values are n (%) unless otherwise indicated. eRVSP = estimated right ventricular systolic pressure (mmHg); BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; TR = tricuspid regurgitant; RV = right ventricle; AV = aortic valve; VTI = velocity time integral.

Table 2.2. Baseline Characteristics of Study Cohort stratified by sex (n = 8392)

	Male (N= 3491)	Female (N= 4901)	P value
Demographics			
Age, years	73 ± 14	75 ± 14	<0.0001
Anthropometrics			
BMI	26.48 ± 4.69	25.96 ± 5.96	<0.0001
BSA	1.94 ± 0.21	1.69 ± 0.22	<0.0001
Rhythm			
Atrial fibrillation / arrhythmia	930 (26.6)	1210 (24.7)	<0.0001
LV dimensions and function			
LVEF %	63.39 ± 8.71	65.88 ± 9.00	<0.0001
E:e' ratio	12.19 ± 4.94	13.66 ± 6.10	<0.0001
LVEDD	5.07 ± 0.73	4.50 ± 0.65	<0.0001
LVESD	3.22 ± 0.64	2.77 ± 0.58	<0.0001
Atrial dimensions			
LA volume index, mL/m^2	71.42 ± 45.87	66.57 ± 40.65	0.004
RA area, cm^2	27.56 ± 9.48	23.23 ± 8.21	<0.0001
Right heart dimensions and function			
eRSVP, mmHg	39.43 ± 11.73	41.06 ± 12.91	<0.0001
TR peak velocity, m/s	2.71 ± 0.47	2.79 ± 0.49	<0.0001
RV basal diameter	3.46 ± 0.40	3.27 ± 0.44	<0.0001
Dilated RV	69 (2.0)	73 (1.5)	0.003
Impaired RV function	907 (26.0)	670 (13.7)	<0.0001
Aortic valve dimensions and function			
Peak aortic velocity, m/s	1.89 ± 0.67	1.87 ± 0.60	<0.0001
Mean aortic gradient, mmHg	10.59 ± 8.18	9.63 ± 7.17	<0.0001
AV area (VTI), cm^2	2.55 ± 0.95	2.12 ± 0.70	<0.0001
Aortic root diameter	3.89 ± 0.53	3.32 ± 0.47	<0.0001
Aortic valve pressure ½ time	445 ± 126	435 ± 107	<0.0001
Concomitant valvular pathology			
≥ moderate mitral regurgitation	636 (18.2)	1003 (20.5)	<0.0001

Values are n (%) unless otherwise indicated. eRVSP = estimated right ventricular systolic pressure (mmHg); BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; TR = tricuspid regurgitant; RV = right ventricle; AV = aortic valve; VTI = velocity time integral.

Survival data

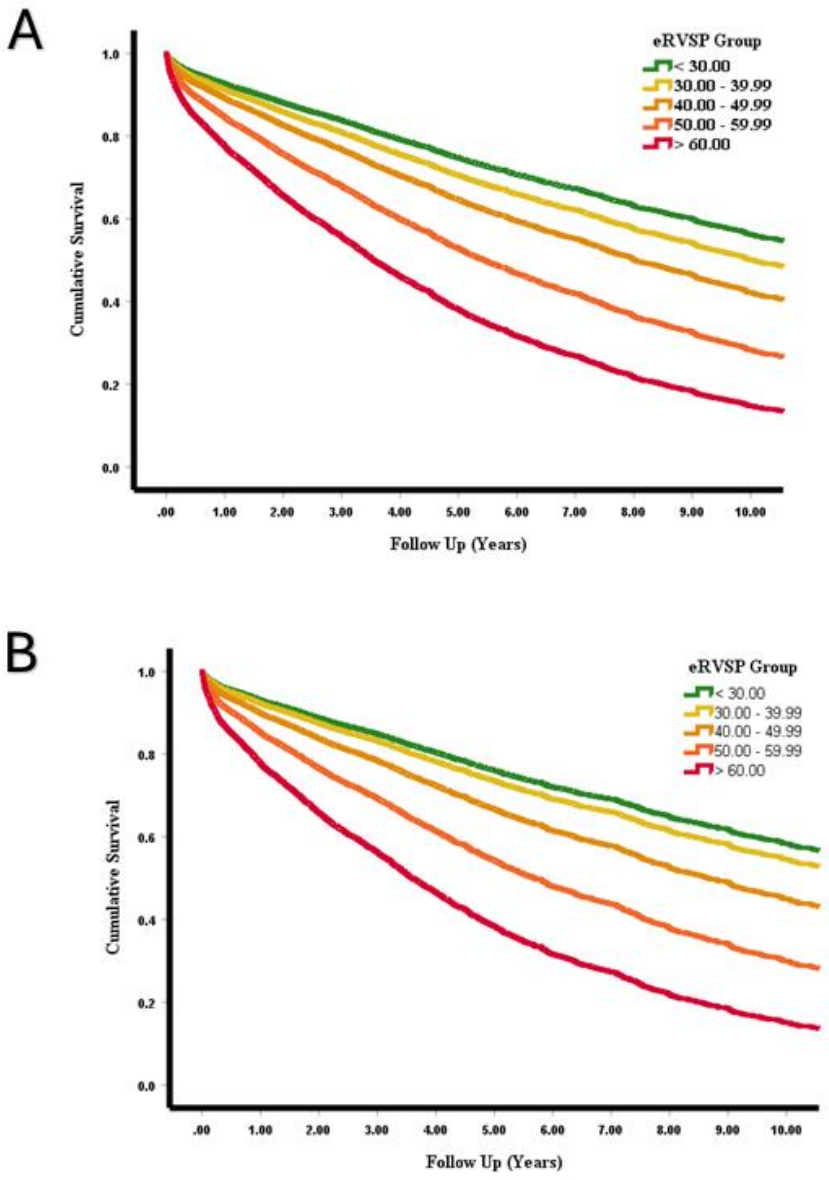
All-cause long-term survival (**Table 2.3, Figure 2.3A**) and actuarial mortality at 1 and 5 years (**Figure 2.4**) (all adjusted for age and gender) are shown for those with eRVSPs <30.00mmHg and the 4 categories of progressively higher eRSVP. Median follow up was 3.1 years (IQR 1.5-5.7years). The risk of mortality progressively increased as eRVSP level increased as evidenced in adjusted long-term mortality results which showed a 1.20-fold increase in risk in those with borderline PHT compared a 3.32-fold increase in those with severe PHT (p<0.0001 for all) (**Figure 2.3A**). When assessing cardiovascular mortality, those with moderate and severe PHT still had significantly higher risk of dying (**Table 2.3**). Trends were less clear in milder elevations of eRVSP with smaller numbers and possible wrong cause of death contributing. These trends were maintained in sensitivity analyses performed excluding patients with ≥moderate MR (**Table 2.4, Figure 2.3b**), although only became statistically significant from "mild PHT" onwards. Similarly, a sensitivity analysis only including patients without left ventricular dilation (defined as a documented left ventricular end systolic diameter ≤50mm[105]) mirrored these trends (**Table 2.5**). In all models, increasing age and male sex were also associated with increased mortality (p<0.0001, for all).

Table 2.3. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels

	Normal eRVSP (<30mmHg) n = 1417	**Borderline PHT (eRVSP 30.00-39.99) N = 3253**	**Mild PHT (eRVSP 40.00-49.99) N = 2249**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 893**	**Severe PHT (eRVSP >60) N = 580**
All-Cause Mortality N (%) HR (95% CI)	305 (21.5) Reference	1090 (33.5) HR 1.20 (1.06-1.36)	1007 (44.8) HR 1.50 (1.31–1.71)	500 (56.0) HR 2.19 (1.90-2.53)	395 (68.1) HR 3.32 (2.85-3.86)
Cardiovascular mortality	88 (6.2) Reference	348 (10.7) HR 0.86 (0.68-1.08) P =0.20	344 (15.3) HR 0.99 (0.78-1.25) P=0.99	184 (20.6) HR 1.50 (1.16-1.93)	161 (27.8) HR 1.97 (1.52–2.56)

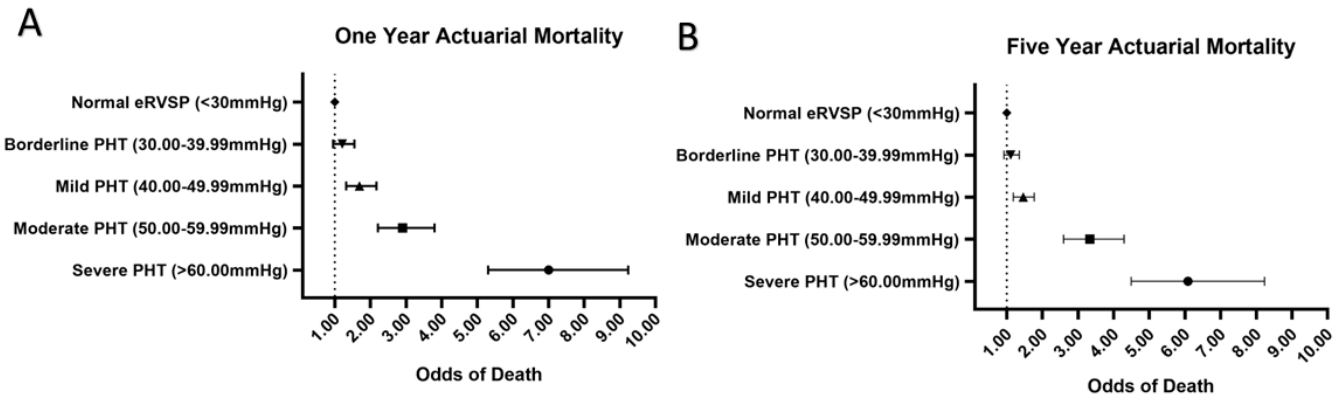
Cox Regression Analyses for total cohort (n = 8392) adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 2.3. Adjusted Risk for All-Cause Mortality



Adjusted risk for all-cause mortality using Cox proportional hazards showing as eRVSP level increases based on clinical severity, risk of mortality increases in, a) the total cohort (LR χ^2 (1) = 700.4, $p<0.0001$), and, b) the cohort excluding patients with ≥ moderate mitral regurgitation (LR χ^2 (1) = 552.1, $p<0.0001$).

Figure 2.4. One and Five Year Actuarial Mortality for the Total Cohort



Actuarial all-cause mortality using logistic regression, adjusted for age and sex, for the total cohort showing increased odds of death as pulmonary pressures increase for A) 1-year actuarial mortality (p value for trend <0.0001) and B) 5-year actuarial mortality (p value for trend <0.0001). PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Table 2.4. Sensitivity analysis – Survival Profile and Adjusted Risk for Mortality (excluding patients with moderate or greater mitral regurgitation, n = 6753)

	Normal eRVSP (<30mmHg) n = 1247	Borderline (eRVSP 30.00-39.99) N = 2814	Mild PHT (eRVSP 40.00-49.99) N = 1713	Moderate PHT (eRSVP 50.00 - 59.99) N = 601	Severe PHT (eRVSP >60) N = 378
N (%) HR (95% CI)					
All-Cause Mortality	252 (20.2) Reference	875 (31.1) HR1.13 (0.98-1.30)	740 (43.2) HR 1.48 (1.28–1.71)	332 (55.2) HR 2.24 (1.90-2.64)	256 (67.7) HR 3.51 (2.94-4.18)
Cardiovascular mortality	70 (5.6) Reference	267 (9.5) HR 0.78 (0.60-1.01)	237 (13.8) HR 0.90 (0.70-1.18)	112 (18.6) HR 1.37(1.02-1.86)	104 (27.5) HR 1.93 (1.42–2.61)

Cox Regression sensitivity analyses excluding patients with moderate or greater mitral regurgitation (n = 6753) adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Table 2.5. Sensitivity analysis – Survival Profile and Adjusted Risk for Mortality (including patients without left ventricular dilation, LVESD ≤50mm, n = 5975)

	Normal eRVSP (<30mmHg) n = 889	Borderline (eRVSP 30.00-39.99) N = 2330	Mild PHT (eRVSP 40.00-49.99) N = 1703	Moderate PHT (eRSVP 50.00 - 59.99) N = 659	Severe PHT (eRVSP >60) N = 394
N (%) HR (95% CI)					
All-Cause Mortality	168 (18.9) Reference	701 (30.1) HR1.21 (1.02 – 1.43)	690 (40.5) HR 1.46 (1.23–1.74)	348 (52.8) HR 2.31 (1.91-2.78)	246 (62.4) HR 3.19 (2.61-3.8)
Cardiovascular mortality	47 (5.3) Reference	216 (9.3) HR 0.77 (0.56-1.05)	238 (14.0) HR 0.91 (0.66-1.24)	118 (17.9) HR 1.23 (0.88-1.73)	99 (25.1) HR 2.05 (1.45–2.90)

Cox Regression sensitivity analyses including patients without left ventricular dilatation (n = 5975) adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

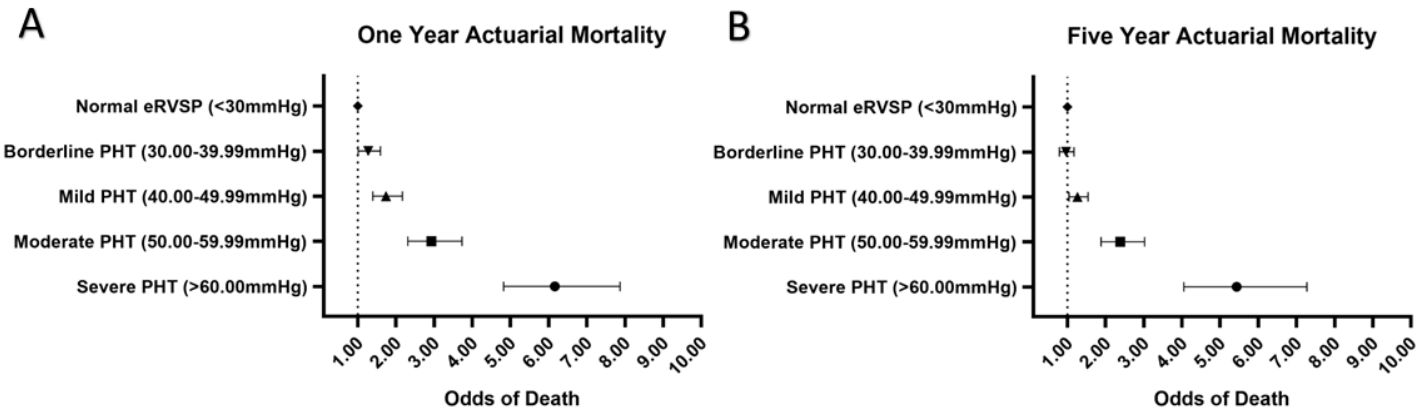
Mortality was also assessed when the cohort was divided into 2 groups based on AR severity (moderate AR- 7839 patients, severe AR- 553 patients). In the larger "moderate AR" cohort, mortality outcomes mirrored those of the total cohort, with adjusted long-term mortality increasing progressively as eRVSP increased (HR1.22, 95%CI 1.07-1.40 for borderline PHT vs. HR3.32, 95%CI 2.83-3.89 for severe PHT) (**Table 2.6, Figure 2.5**). The "severe AR" group was a much smaller cohort (6.4% of total), adjusted long-term all-cause mortality outcome had a similar trend, though statistical significance was not reached at milder elevations of eRVSP level, likely due to low subject numbers (**Table 2.7, Figure 2.6**).

Table 2.6. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with moderate aortic regurgitation (n = 10 085)

	Normal eRVSP (<30mmHg) n = 1526	**Borderline (eRVSP 30.00-39.99) N = 3540**	**Mild PHT (eRVSP 40.00-49.99) N = 2962**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 1195**	**Severe PHT (eRVSP >60) N = 862**
All-Cause Mortality N (%) HR (95% CI)	363 (23.8) Reference	1311 (37.0) HR 1.13 (1.01-1.27)	1484 (50.1) HR 1.45 (1.29-1.63)	741 (62.0) HR 2.00 (1.76–2.27)	625 (72.5) HR 3.28 (2.87-3.73)
Cardiovascular mortality N (%) HR (95% CI)	110 (7.2) Reference	439 (12.4) HR 0.82 (0.66-1.01) P=0.06	508 (17.2) HR 0.91 (0.74-1.12) P=0.40	282 (23.6) HR 1.29 (1.03-1.61)	263 (30.5) HR 2.01 (1.61–2.52)

Cox Regression analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 2.5. One and Five Year Actuarial Mortality for Moderate Aortic Regurgitation Cohort



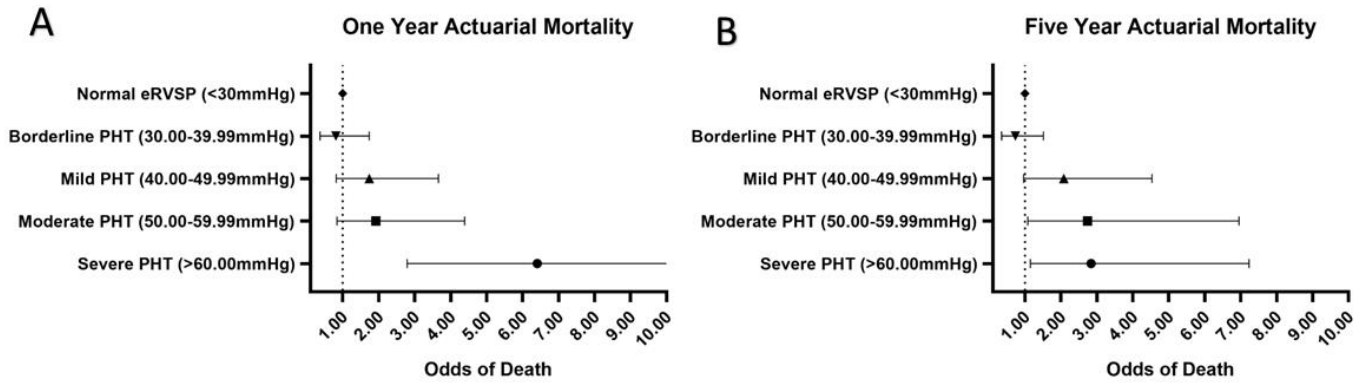
Actuarial all-cause mortality using logistic regression, adjusted for age and sex, for patients with moderate aortic regurgitation showing increased odds of death as pulmonary pressures increase for A) 1-year actuarial mortality (p value for trend <0.0001) and B) 5-year actuarial mortality (p value for trend <0.0001). PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Table 2.7. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with severe aortic regurgitation (n = 553)

	Normal eRVSP (<30mmHg) n = 105	**Borderline (eRVSP 30.00-39.99) N = 186**	**Mild PHT (eRVSP 40.00-49.99) N = 137**	**Moderate PHT (eRSVP 50.00 -59.99) N = 73**	**Severe PHT (eRVSP >60) N = 52**
All-Cause Mortality N (%) HR (95% CI)	27 (25.7) Reference	71 (38.2) HR1.003 (0.64-1.57) P=0.99	72 (52.6) HR 1.58 (1.004–2.48) P=0.04	38 (52.1) HR 1.81 (1.10-2.99) P=0.02	38 (73.1) HR 2.72 (1.65-4.50)
Cardiovascular mortality N (%) HR (95% CI)	5 (4.8) Reference	24 (12.9) HR 1.16 (0.45-3.07) P=0.77	35 (25.5) HR 2.62 (1.02-6.71) P=0.04	23 (31.5) HR 2.96 (1.12-7.83) P=0.03	20 (38.5) HR 2.76 (1.02-7.46) P=0.04

Cox regression analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 2.6. One and Five Year Actuarial Mortality for Severe Aortic Regurgitation Cohort



Actuarial all-cause mortality using logistic regression, adjusted for age and sex, for patients with severe aortic regurgitation showing increased odds of death as pulmonary pressures increase for A) 1-year actuarial mortality (p value for trend <0.0001) and B) 5-year actuarial mortality (p value for trend <0.0001). PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Mortality outcomes amongst females (n=4901) matched those in the total cohort (HR1.28, 95%CI 1.08-1.52 for borderline PHT vs. HR3.41, 95%CI 2.81-4.15 for severe PHT) (Table 2.8, Figure 2.7). The male cohort (n=3491) had similar trends, though significance was only reached when pulmonary pressures were mildly elevated **(Table 2.9, Figure 2.8).**

Table 2.8. Survival Profile and Adjusted Risk for Mortality in female patients, n = 4901

	Normal eRVSP (<30mmHg) n = 775	**Borderline (eRVSP 30.00-39.99) N = 1842**	**Mild PHT (eRVSP 40.00-49.99) N = 1339**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 546**	**Severe PHT (eRVSP >60) N = 546**
All-Cause Mortality N (%) HR (95% CI)	163 (21.0) Reference	616 (33.4) HR 1.28 (1.08-1.52)	593 (44.3) HR 1.53 (1.28–1.82)	303 (55.5) HR 2.29 (1.89-2.78)	264 (66.2) HR 3.41 (2.81-4.15)
Cardiovascular mortality N (%) HR (95% CI)	51 (6.6) Reference	205 (11.1) HR 0.96 (0.71-1.31) P =0.80	200 (14.9) HR 0.95 (0.70-1.29) P=0.74	116 (44.6) HR 1.55 (1.11-2.15) P=0.01	117 (21.4) HR 2.19 (1.57–3.05)

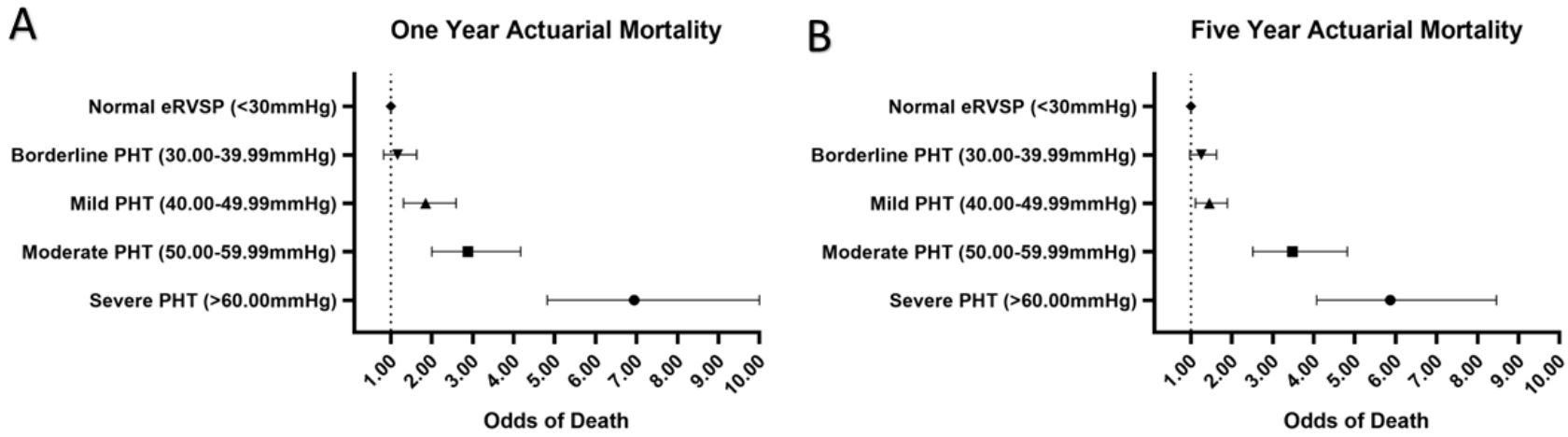
Cox regression analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Table 2.9. Survival Profile and Adjusted Risk for Mortality in male patients, n = 3491

	Normal eRVSP (<30mmHg) n = 642	**Borderline (eRVSP 30.00-39.99) N = 1411**	**Mild PHT (eRVSP 40.00-49.99) N = 910**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 347**	**Severe PHT (eRVSP >60) N = 181**
All-Cause Mortality N (%) HR (95% CI)	142 (22.1) Reference	474 (33.6) HR 1.11 (0.92-1.34)	414 (45.5) HR 1.46 (1.21–1.78)	197 (56.8) HR 2.06 (1.66-2.56)	131 (72.4) HR 3.20 (2.51-4.08)
Cardiovascular mortality N (%) HR (95% CI)	37 (5.8) Reference	143 (10.1) HR 0.86 (0.68-1.08) P =0.20	144 (15.3) HR 0.99 (0.78-1.25) P=0.99	68 (15.8) HR 1.50 (1.16-1.93)	44 (24.3) HR 1.97 (1.52–2.56)

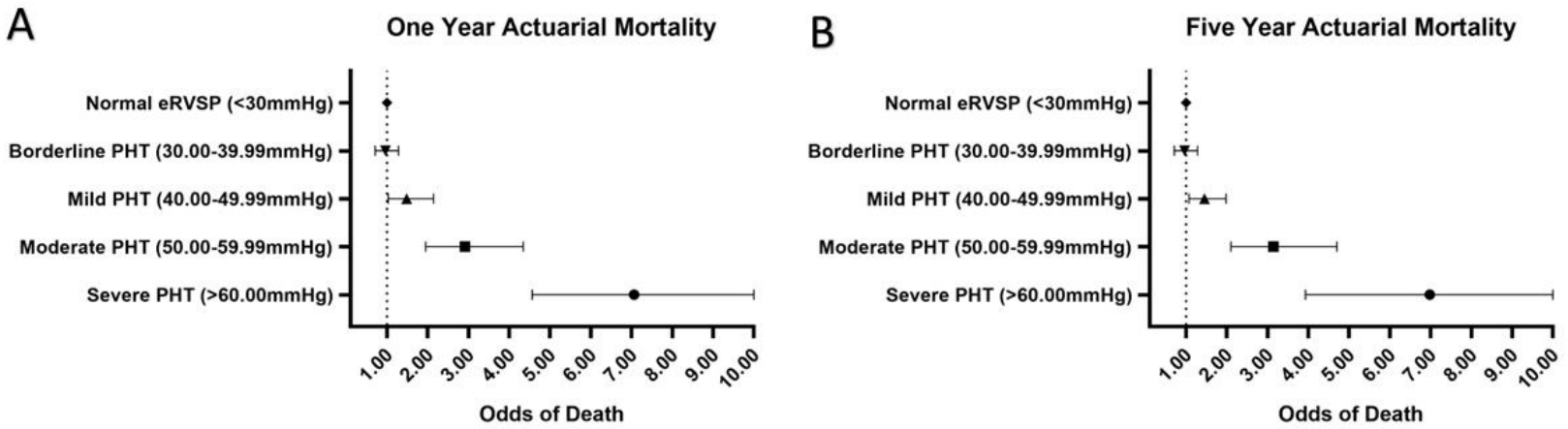
Cox regression analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 2.7. One and Five Year Actuarial Mortality in Female patients



Actuarial all-cause mortality using logistic regression, adjusted for age, for female patients showing increased odds of death as pulmonary pressures increase for A) 1-year actuarial mortality (p value for trend <0.0001) and B) 5-year actuarial mortality (p value for trend <0.0001). PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Figure 2.8. One and Five Year Actuarial Mortality in Male patients



Actuarial all-cause mortality using logistic regression, adjusted for age, for the male population showing increased odds of death as pulmonary pressures increase for A) 1-year actuarial mortality (p value for trend <0.0001) and B) 5-year actuarial mortality (p value for trend <0.0001). PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Threshold for mortality

A Cox regression model was constructed using the decile distribution of eRVSP and adjusted for age and sex. There was a signal towards a threshold of increased risk from the 5th decile, eRVSP 36.02-39.00mmHg, (HR1.20, CI1.02-1.43mmHg, P=0.048). The 6th decile had a signal towards increased risk but this was not statistically significant. The 7th decile showed increased risk (eRVSP 41.36-44.15; HR1.48, p<0.0001) and became progressively higher through to the 10th decile (eRVSP >56.01; HR2.42, CI2.42-3.36 p <0.0001) (**Table 2.10**). Hence, there was a signal towards increased risk in those with borderline PHT, with a clear threshold seen in those with mild PHT and above, regardless of age or sex.

Table 2.10. Adjusted Risk for Mortality according to decile distribution of Estimated Right Ventricular Systolic Pressure Levels

eRSVP decile distribution (mmHg)	All Fatal Events (n= 14980) HR (95% CI), p value
0.00-27.00	Reference
27.01-31.00	1.05 (0.87-1.27), p = 0.60
31.01-33.35	1.02 (0.84-1.24), p = 0.84
33.36-36.01	1.14 (0.95-1.36), p = 0.17
36.02-39.00	1.20 (1.002-1.43), p = 0.04
39.01-41.36	1.10 (0.92-1.31), p = 0.29
41.36-44.15	1.41 (1.17-1.68), p<0.0001
44.15-48.44	1.48 (1.25-1.75), p<0.0001
48.45-56.00	1.98 (1.67-2.35), p<0.0001
56.01-150.00	2.85 (2.42-3.36), p<0.0001

Analyses adjusted for age and sex. eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; CI = confidence interval

Discussion

This contemporary, "real world" cohort study, including over 8000 adults with ≥ moderate AR and normal LVEF examines the interplay between AR and PHT. The utilisation of 'big data' for the NEDA, of over 1 million echoes in over 600 000 adults, afforded us the ability to report on the prevalence and echocardiographic phenotype of these patients in substantially greater numbers, than in previous studies. We confirmed that even mild PHT imposes additional risk of short and long-term mortality, in patients with ≥ moderate AR.

PHT likely develops in patients with significant AR via the following mechanism; as the severity of AR worsens, LV pressure and volume overload develops, resulting in LV dilation, eccentric hypertrophy and eventually diastolic and systolic dysfunction[51]. In advanced stages LA dysfunction and secondary MR can contribute to raised LA pressure which leads to post-capillary PHT[49].

Prevalence and Phenotype of PHT with AR

There is little prior data on the prevalence of pulmonary hypertension in patients with aortic regurgitation. Previous studies have varied in their definition of both PHT and AR severity and are limited by relatively small population sizes; they report a prevalence of PHT as 27% (PHT defined as RVSP >40mmHg[58]), 26% (defined as RVSP>50mmHg[98]) and 16-24% (defined as RVSP >60mmHg[96, 97]). A prior catheterisation study[49] with a cohort of 802 patients and varying degrees of AR reported mild PHT in 23%, moderate PHT in 9% and severe PHT in 5% of their cohort. Our study, from community and hospital based echo labs around Australia, showed a higher burden of clinically defined PHT (almost 45%) in patients with significant AR and normal LVEF (mild PHT-26.9%, moderate- 10.6%, severe- 6.9%). Significantly, the sub-group with the highest proportion of patients was those with "borderline PHT", with eRVSP 30-39mmHg (38.8%).

The echocardiographic phenotype of patients with PHT and AR has been poorly defined, with LV dilation and eventually LV systolic dysfunction considered markers of the remodeling process[97]. We confirm that the impact of worsening PHT in patients with significant AR is similar to PHT secondary to other left-sided valvular pathologies. The resultant phenotypic pattern is that of increased LA volume and E:e', with higher proportions of RV dilation and dysfunction and RA dilatation. The progressive remodeling plateaued when PHT became severe, suggesting that the threshold for these changes occurs when PHT is in the moderate range. This study extends our understanding of the phenotypic risk profile for patients with suspected PHT-LHD proposed in the recent PHT guidelines[1] and is important, as it allows clinicians to monitor risk and prognosticate such patients, more accurately.

Outcomes in AR patients by PHT severity

Early papers are conflicted on the prognostic impact of PHT in patients with significant AR; one study of patients with severe AR (n= 139) found that the presence of PHT did not significantly change all-cause mortality[96], whilst another (n= 88), found patients with AR and concomitant PHT had reduced survival at both 1- and 4- years[58]. More recent studies, of up to 1156 patients, have suggested that moderate or greater PHT confers an almost 2-fold increased risk of long-term all-cause mortality[98]. Our current much larger study has more robustly confirmed the additional risk worsening PHT has on patients with significant AR, with the 44.4% of patients with eRVSP>40.00mmHg having a 1.50-3.32-fold adjusted increased risk of long-term all-cause mortality (dependent on PHT severity), compared with those with no PHT. Even borderline PHT (eRVSP 30.00-39.99), conferred a 1.22-fold increased risk in long-term all-cause mortality compared to normal eRVSP. Whilst the threshold for mortality is not as clear in this cohort (with 2 inflection points seen), "borderline PHT" in the presence of significant AR is not benign. These results were independent of age and gender and our sensitivity analysis showed that they did not appear to be confounded by the presence of concomitant mitral regurgitation or by LV dilation. We had also prospectively excluded patients with severe AS and/or impaired LV systolic function, to focus our attention on the influence of PHT *per se*, on outcomes in AR patients.

Clinical Implications

The presence of PHT is not an indication for 'early' procedural management of asymptomatic patients with significant AR, in current guidelines[105, 106]. This is likely due to relative lack of clinical data within this cohort of patients[51]. Previous studies have shown an independent survival benefit in patients with severe AR and concomitant PHT undergoing AVR, over a 5-year follow-up period[106]. This latter study reported pulmonary pressures almost normalised post-procedure, in the majority of these patients. Whilst we do not report on treatment effects in the current report, we do demonstrate even mildly elevated pulmonary pressures is associated with increased risk. With no medical therapy available for PHT in patients with AR, prudent monitoring and pro-active investigation into the presence of symptoms may be needed to identify 'guideline endorsed' indications for early procedural management[105]. Further study is required to understand any possible benefits of earlier treatment of AR, in the presence of PHT.

Limitations

NEDA provides detailed echocardiographic data and linkage to mortality, NEDA is however, a retrospective de-identified electronic record interface which means that we were unable to directly review echocardiographic images with regards to pressure estimates or other parameters. Furthermore, NEDA does not (yet) provide granular clinical data such as symptoms, co-morbidities or

pharmacological treatments. Thus, we were unable to adjust our models for a full range of clinical factors or potential confounders and our findings should be interpreted in this context. Most patients included the database have undergone an echocardiogram for investigation of confirmed or suspected cardiac disease and should not be taken to reflect the population prevalence.

As noted in our previous studies[12], the data concerning PHT in NEDA is based on echocardiography-based measures, rather than haemodynamic assessment at right heart catheterisation. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107, 108], supporting the broad validity of our approach. Furthermore, echocardiography remains the first-line screening tool to detect PHT and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow up. We also note that the absence of a tricuspid regurgitation jet does not preclude the presence of PHT and there may be a number of patients with AR and PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR.

Whilst we presented a cohort defined with a combined qualitative and quantitative approach to the definition of AR severity, the database did not routinely include further qualitative measures including effective regurgitant orifice area (EROA) and regurgitant volume, a reflection on real-world practice within Australia. Our data is lacking in quantitative RV measurements and so we are unable to fully assess the impact of PHT on the right heart, nor can we determine impact of RV abnormalities on mortality, in this cohort. This is a key theoretical question when assessing PHT and outcomes and is thus a limitation of this current study. Future studies should address the role of RV size and function in the relationship between AR and PHT. The prevalence and survival associated with PHT after AV replacement is not addressed in this Chapter. Further studies are needed to establish these findings in this distinct cohort.

These studies were primarily derived from specialist centres or clinics across Australia, so some caution should be applied when applying these findings to other populations. However, Australia is a diverse and multi-ethnic population with universal health coverage, aspects captured within the NEDA database.

Conclusion

In this large, “real-world” cohort study we characterise the relationship between aortic regurgitation and pulmonary hypertension. We find PHT to be more prevalent than previously reported and that a pattern of echocardiographic remodeling with worsening PHT is evident in these patients. PHT imposes an additional, progressive risk of mortality in patients with ≥moderate AR, even in the mild PHT range.

Chapter 3 – Prevalence of Pulmonary Hypertension in Aortic Stenosis and its Influence on Outcome

This chapter is based on the publication: Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Prevalence of pulmonary hypertension in aortic stenosis and its influence on outcomes. HEART. Publish online- 03 April 2023. doi: 10.1136/heartjnl-2022-322184.

Abstract

Objective: The significance of Pulmonary Hypertension (PHT) complicating Aortic Stenosis (AS) is poorly characterised. In a large cohort of adults with at least moderate AS, we aimed to describe the prevalence and prognostic importance of PHT in such patients.

Methods: In this retrospective study, we analysed the National Echocardiography Database of Australia (data from 2000-2019). Adults with an estimated right ventricular systolic pressure (eRVSP), left ventricular ejection fraction (LVEF) >50% and with moderate or greater AS were included (n=14980). These subjects were then categorised according to their eRVSP. The relationship between PHT severity and mortality outcomes were evaluated (median follow-up of 2.6 years, interquartile range 1.0-4.6years).

Results: Subjects were aged 77±13years and 57.4% were female. Overall, 2049 (13.7%), 5085 (33.9%), 4380 (29.3%), 1956 (13.1%) and 1510 (10.1%) patients had no (eRVSP<30.00mmHg), borderline (30.00-39.99mmHg), mild (40.00-49.99mmHg), moderate (50.00-59.99mmHg) and severe PHT (>60.00mmHg), respectively. A echocardiographic phenotype was evident with worsening PHT, showing rising E:e' ratio and right and left atrial sizes($p<0.0001$, for all). Adjusted analyses showed the risk of long-term mortality progressively rose as eRVSP level increased (hazard ratio 1.14-2.94, borderline to severe PHT, $p<0.0001$ for all). A mortality threshold was identified in the 4th decile of eRVSP categories (35.01–38.00mmHg; HR1.19, 95%CI 1.04-1.35), with risk progressively increasing through to the 10th decile (HR2.86, 95%CI 2.54-3.21).

Conclusions: In this large cohort study we find that PHT is common in ≥moderate AS and mortality increases as PHT becomes more severe. A threshold for higher mortality lies within the range of "borderline-mild" PHT.

Introduction

Aortic stenosis is the commonest valve abnormality in developed countries with an increasing prevalence and a long pre-symptomatic phase[109]. Measurable demographic, baseline and imaging characteristics are likely important in stratifying risk and potentially guiding treatment decisions. A cardiac damage score has been proposed and validated in AS, this includes extra variables related to left and right heart structure and function[110, 111]. The prevalence and prognostic importance of PHT in patients with AS, however, has been poorly characterised[35, 112-115].

PHT secondary to LHD, also known as post-capillary PHT, is the commonest type of PHT (65-80% of all PHT cases, in most reported series[2, 17] [37]). It refers to patients who develop PHT secondary to LHD, such as left ventricular systolic or diastolic dysfunction or left-sided valvular pathologies. In these patients, PHT is thought due to "back pressure" from an elevated LA pressure. In AS specifically, PHT likely arises from left ventricular hypertrophy and diastolic dysfunction, thence an increase in LA pressure[116]. PHT has been previously documented as an important prognostic factor in other LHD, such as left ventricular failure[2, 17].

In AS, however, a clear picture of the prevalence of PHT and its prognostic importance has not yet emerged. In relatively small series, there have been inconsistent data concerning PHT prevalence, phenotype and mortality trends in these patients[35, 112-115]. Utilising data from the National Echo Database of Australia (NEDA), we aimed to clearly describe the prevalence of PHT, of varying severities, and then, assess the independent prognostic value of pulmonary pressure in patients with ≥moderate AS.

Methods

NEDA Database and Study Design

The NEDA is a multi-centre registry; previously described, in detail[12, 99, 100]. NEDA contains basic demographic and detailed echocardiographic data of adults from >25 centres across Australia. The database is linked with the comprehensive National Death Index (NDI). The study period included >1million echo reports from >600 000 individuals, studied between January 2000 and June 2019. Vital status was determined as of 21st May 2019 (median follow-up 6.2years, IQR 3.8-9.8years); patients alive at this date were censored alive. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and human ethics approval was obtained, protocol SLHD X15-0387 and 2019/ETH069899, with retrospective waiver of consent authorised.

Study cohort

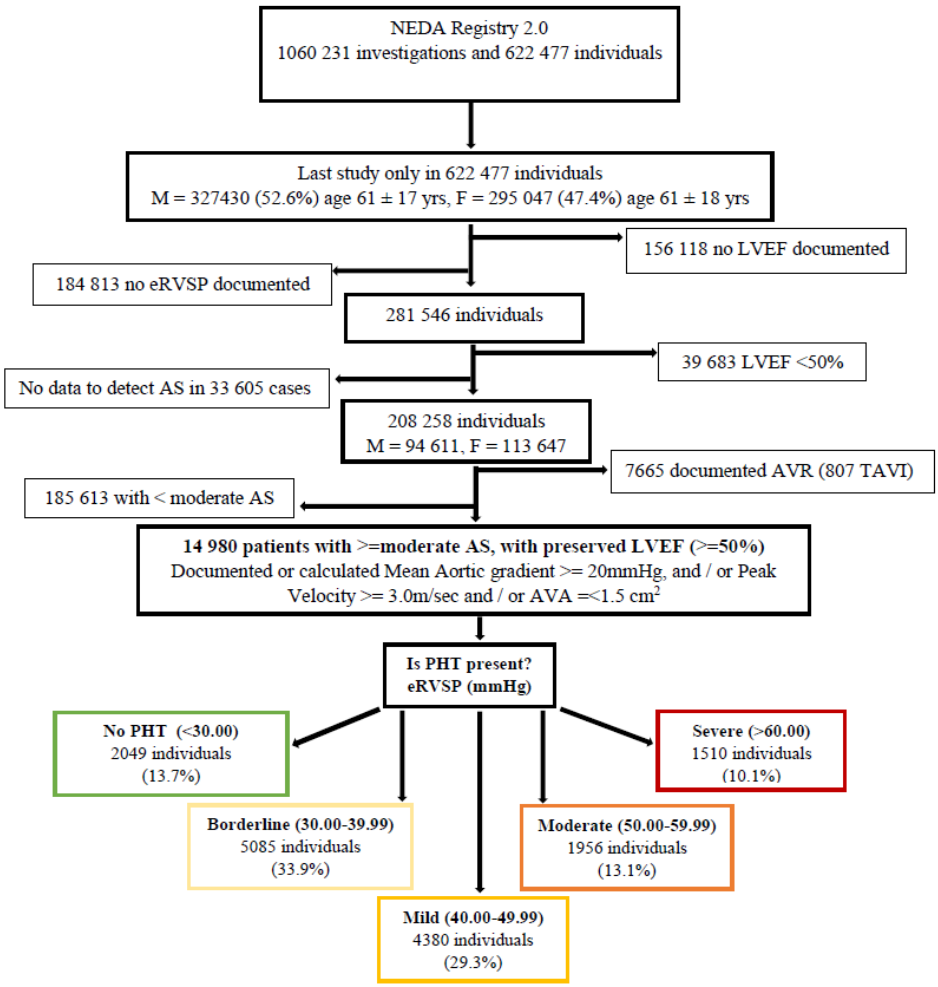
Figure 3.1 shows our study flow diagram; baseline for our study was the date of each person's last echo in the database. Survival data at study census were used to identify patients with significant AS and thence to characterise the prevalence and prognostic impact of PHT. Included subjects were 1) adults ≥ 18 years of age, 2) with at least one echocardiogram recorded (where patients had multiple studies, only the last study was analysed), 3) with a recorded LVEF, eRSVP and sufficient data to determine AS severity (aortic valve (AV) mean gradient and / AV peak velocity and / or aortic valve area (AVA) via velocity time integral (VTI)). Moderate or severe AS was defined using current diagnostic guidelines[102] with AV mean gradient ≥ 20mmHg and/or AV peak velocity ≥ 3.0m/sec and/or AVA (by VTI) ≤1.5cm^2. Patients with AV replacements were excluded from these analyses, as were patients with LVEF < 50%. eRVSP was derived using the Bernoulli equation (4x[TRV]^2 + assumed RA pressure of 5mmHg)[72]. As noted in previous NEDA literature[12] a consistent RA pressure of 5mmHg removes variation between laboratories by approximating the average value recorded overall. RV size and function were described qualitatively using text extraction from echo reports[12].

Study methods

Once the cohort of patients with moderate or greater AS was identified, subjects were categorised by their eRVSP, according to clinical guidelines, to document the distribution of PHT severity[21]. A "borderline PHT" group which has previously been determined as potentially significant in both NEDA papers and in other recent publications was also included[12, 13, 104]. Prospectively defined categories of PHT were: 1) normal (eRVSP <30mmHg), 2) borderline (30.00-39.99mmHg), 3) mildly elevated (40.00-49.99mmHg), 4) moderately elevated (50.00-59.99mmHg) and, 5) severely elevated (eRVSP ≥60mmHg)[12].

All-cause mortality was determined, during a median follow up of 2.6 years (IQR1.0-4.6years). We explored the relationship between eRVSP level and survival, looking at both the 5 clinically defined groups (as above) and the eRVSP deciles.

Figure 3.1. Study Flow Chart



This flowchart shows the points of analysis performed in this study. NEDA = National Echo Database Australia; left ventricular ejection fraction (LVEF); eRVSP = estimated right ventricular systolic pressure; AS = aortic stenosis; AVR = aortic valve replacement; TAVI = transcatheter aortic valve implantation; PHT = pulmonary hypertension.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis using ANOVA was used to test whether the trend of the mean across the categorical groups of eRVSP levels was linear. For binary variables, the chi-squared test was used to determine if there was a trend in the change in proportions across the groups.

Actuarial 1- and 5- year survival rates for all-cause mortality were calculated from the 14 173 (94.6%) and 9838 (65.7%) subjects with complete follow up for those time points[12]. Multiple logistic regression models (entry at univariate p-value <0.05) were used to derive adjusted odds ratios (OR) for mortality models at these fixed time points. Cox regression hazard models were used to derive adjusted

hazard ratios (HR) for mortality outcomes during follow up (entry model at a univariate p-value <0.05). Adjusted analyses included age and sex, as well as mean aortic valve gradient. Mortality was also assessed when the cohort was divided into 2 groups, based on AS severity (moderate AS- 10 085 patients, severe AS- 4895 patients).

Sensitivity analyses were performed excluding patients with concurrent moderate or greater concurrent mitral regurgitation and/or moderate or greater aortic regurgitation. Patients with moderate or severe AS were also assessed separately to determine if there were differences between these two groups. Severe AS, was defined as AV mean gradient ≥40mmHg, and/or AV peak velocity ≥4.0m/sec, and/or AVA (by VTI) ≤1.0cm^2 [102].

We then examined the pattern of mortality according to the decile distribution of eRVSP[12]: 1st decile- 5.00-28.00mmHg, 2nd- 28.01-32.00mmHg, 3rd- 32.01-35.00mmHg, 4th- 35.01-38.00mmHg, 5th- 38.01-40.69mmHg, 6th- 40.70-43.64mmHg, 7th- 43.65-46.48mmHg, 8th- 46.49-50.96mmHg, 9th- 50.97-60.00mmHg and 10th- >60.00mmHg.

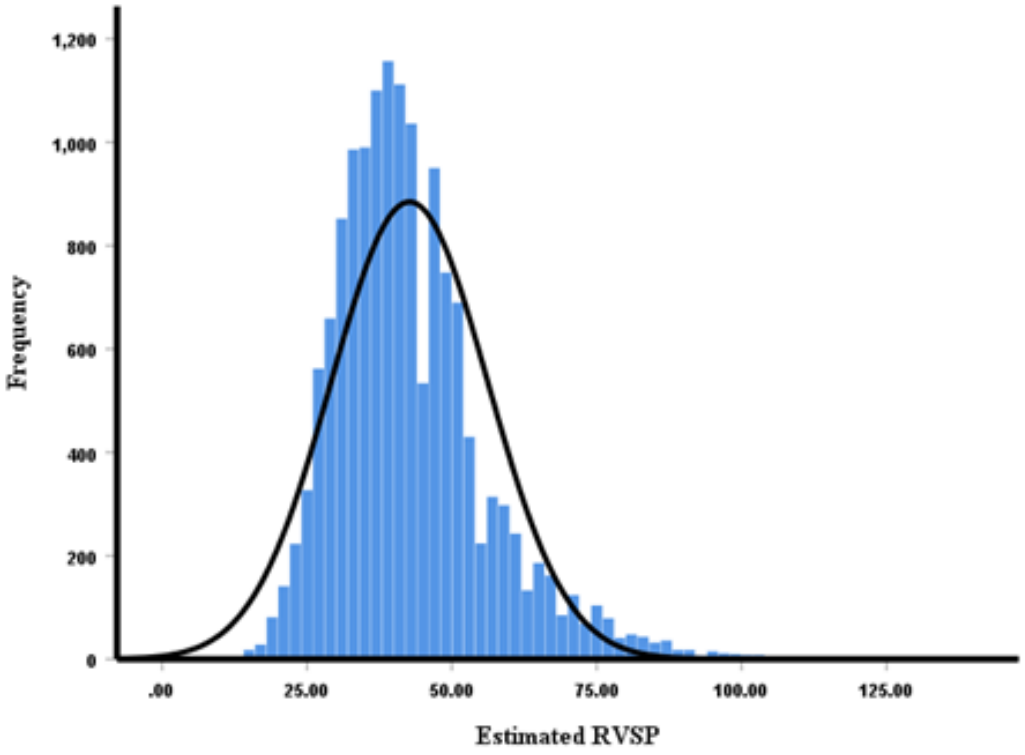
All analyses were performed with SPSS software version 25.0 (IBM Corp, Armonk, New York), and statistical significance was accepted at a 2-tailed p-value of <0.05.

Results

Prevalence of PHT and Distribution of eRVSP

A total of 14980 patients with moderate or greater AS were identified (Figure 1), with 57.4% being female. **Figure 3.2** shows the frequency distribution of eRSVP levels (median 40.69mmHg, IQR 33.23-48.44mmHg). The number of patients in each sub-group were: No PHT (eRVSP <30mmHg)- 2049 individuals (13.7%), borderline PHT (eRVSP 30.00-39.99mmHg)- 5085 individuals (33.9%), mild (eRVSP 40.00-49.99)- 4380 (29.3%), moderate (eRVSP 50.00-59.99)-1956 (13.1%) and severe (eRVSP>60mmHg)- 1510 (10.1%).

Figure 3.2. Frequency Distribution of Estimated Right Ventricular Systolic Pressure within the Cohort



These data show the statistical distribution of estimated right ventricular systolic pressure (eRVSP) levels.

Subject profiles

Table 3.1 summarises the demographic and echocardiographic characteristics of the study cohort divided into sub-groups based on estimated RVSP levels. Age was greater in those with higher eRVSP levels, from a mean of 70±17years in patients with no PHT to 81±10 years in patients with severe PHT ($p<0.0001$ for all).

A typical pattern of phenotypic response was evident along with worsening PHT. E:e' increased progressively with worsening PHT (13.18±5.67 vs. 21.2±9.5, no PHT vs severe PHT respectively, $p<0.0001$ for all). There was also a progressive increase in right atrial area and indexed left atrial volume, along with increasing frequency of aortic and mitral regurgitation with worsening PHT. The proportion of patients with RV dilation and impaired RV function increased from 3.9% to 36.8% and 1.0% to 7.8 %, respectively in those with no PHT compared with those with severe PHT. Atrial fibrillation was more common with worsening PHT (12.7% vs. 42.1%, no PHT vs severe PHT, $p <0.0001$ for all).

Table 3.1. Baseline Characteristics of Study Cohort (n = 14980)

	eRSVP 0.00-29.99 n = 2049	**eRSVP 30.00-39.99 n = 5085**	**eRVSP 40.00-49.99 n = 4380**	**eRVSP 50.00-59.99 n = 1956**	**eRVSP >60.00 n = 1510**	**P value**
Demographics						
Age, years	70 ± 17	76 ± 14	79 ± 11	81±10	81±11	<0.0001
Female (%)	1243 (60.7)	2854 (56.1)	2380 (54.3)	1136 (58.1)	992 (65.7)	<0.0001
Anthropometrics						
BMI	26.77 ± 5.55	26.9 ± 5.67	27.76 ±6.08	27.55±6.52	26.57±6.18	0.02
BSA	1.81 ±0.25	1.81 ±0.24	1.84 ± 0.25	1.82±0.26	1.78±0.25	0.27
Rhythm						
Atrial fibrillation / arrhythmia	260 (12.7)	979 (19.3)	1115 (25.5)	701 (35.8)	635 (42.1)	<0.0001
LV dimensions and function						
LVEF %	64.28 ±7.44	65.59 ±8.50	68.44±10.25	67.26±10.16	65.53±9.5	<0.0001
E:e' ratio	13.18 ± 5.67	14.19 ± 6.52	15.01±5.97	16.84±7.15	21.2±9.5	<0.0001
LVEDD	4.31 ± 0.63	4.45 ± 0.65	4.66 ± 0.72	4.65 ± 0.77	4.45 ± 0.75	<0.0001
LVESD	2.74 ± 0.53	2.76 ± 0.60	2.73 ± 0.66	2.78 ± 0.70	2.76 ± 0.67	<0.0001
Atrial dimensions						
LA volume index, mL/m^2	34.36±14.92	46.73 ± 27.52	76.05±40.32	81.78±45.62	82.98±49.16	<0.0001
RA area, cm^2	16.91±7.24	21.59±7.37	27.93±7.53	29.67±8.92	29.78±9.7	<0.0001
Right heart dimensions and function						
eRSVP, mmHg	25.61±3.41	35.12±2.89	44.39±2.75	53.91±2.93	71.8±11.19	<0.0001
TR peak velocity, m/s	2.2 ± 0.2	2.5 ± 0.2	2.9 ± 0.1	3.3±0.2	3.9±0.3	<0.0001
RV basal diameter	3.44±0.54	3.25±0.44	3.27±0.34	3.4±0.4	3.6±0.5	<0.0001
Dilated RV	80 (3.9)	303 (4.3)	952 (21.7)	549 (28.1)	556 (36.8)	<0.0001

Impaired RV function	20 (1.0)	47 (0.7)	68 (1.5)	71 (3.6)	118 (7.8)	<0.0001
Aortic valve dimensions and function						
Peak aortic velocity, m/s	2.8±1.0	3.1±0.9	3.2±0.9	3.3±0.9	3.6±0.8	<0.0001
Mean aortic gradient, mmHg	20.00±14.8	23.28±15.09	26.8±16.0	27.6±17.1	31.5±16.5	<0.0001
AV area (VTI), cm^2	1.2±0.4	1.2±0.3	1.1±0.3	1.1 ±0.3	0.9±0.4	<0.0001
Concomitant valvular pathology						
≥ moderate mitral regurgitation	126 (6.1)	404 (5.7)	594 (30.4)	444 (22.7)	377 (24.9)	<0.0001
≥ moderate aortic regurgitation	162 (7.9)	423 (5.9)	461 (10.6)	226 (11.5)	193 (12.8)	<0.0001

Values are n (%) unless otherwise indicated. eRVSP = estimated right ventricular systolic pressure (mmHg); BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; TR = tricuspid regurgitant; RV = right ventricle; AV = aortic valve; VTI = velocity time integral.

Survival data

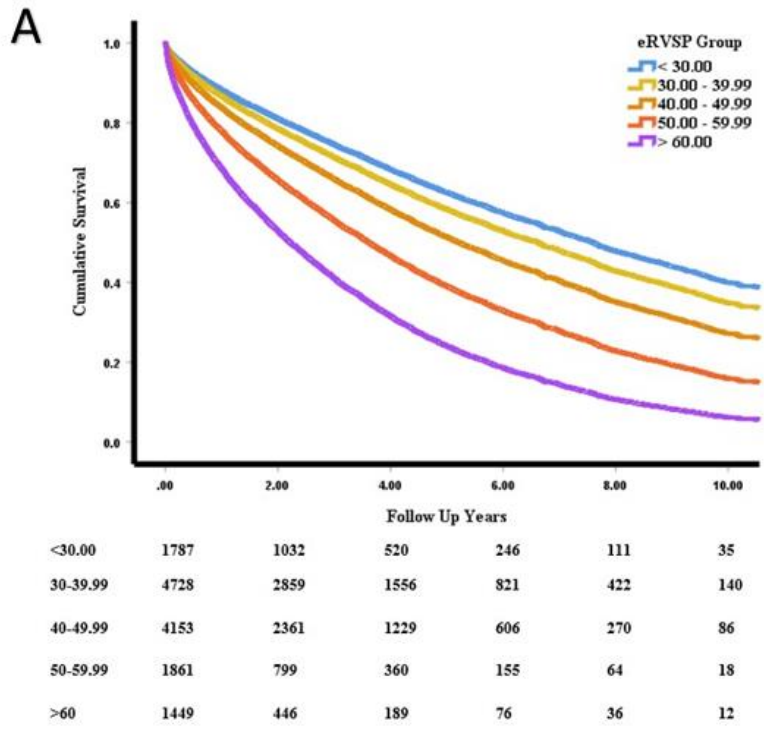
All-cause long-term survival **(Table 3.2, Figure 3.3A)** and actuarial mortality at 1 and 5 years **(Figure 3.4)** (all adjusted for age, sex and mean AV gradient) are shown for those with eRVSPs <30.00mmHg and the 4 categories of progressively higher eRSVP. Median follow-up was 2.6 years (interquartile range 1.0-4.6 years). The risk of mortality progressively increased as eRVSP level increased, as evidenced in adjusted long-term mortality results which showed a 1.14-fold increase in risk in those with borderline PHT and a 2.94-fold increase in those with severe PHT compared to those with normal eRVSP ($p<0.0001$ for all) (**Table 3.2, Figure 3.3a**). These trends were less pronounced when assessing cardiovascular mortality, although those with moderate and severe PHT still had significantly higher risk of dying (**Table 3.2**). Trends were less clear for milder elevations of eRVSP with smaller numbers and possible inaccurate coding for causes of death documented on death certificates, as possible contributing factors.

Table 3.2. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels (n = 14980)

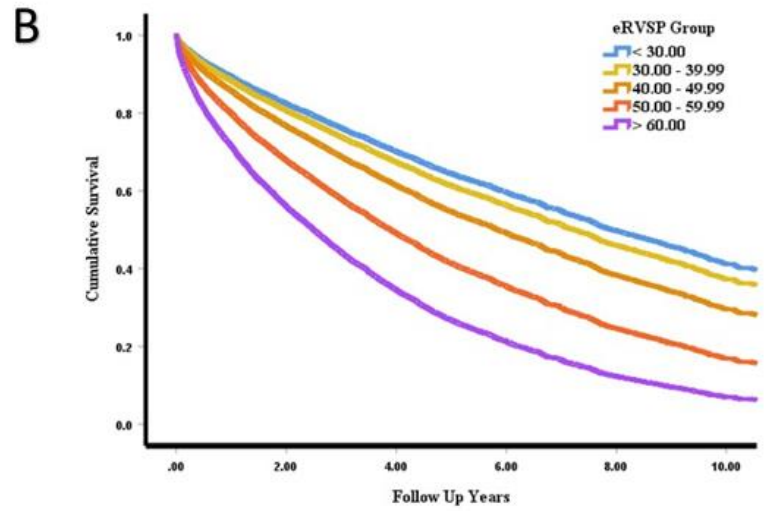
	Normal eRVSP (<30mmHg) n = 2049	**Borderline PHT (eRVSP 30.00-39.99) N = 5085**	**Mild PHT (eRVSP 40.00-49.99) N = 4380**	**Moderate PHT (eRSVP 50.00 -59.99) N = 1956**	**Severe PHT (eRVSP >60) N = 1510**
All-Cause Mortality N (%) HR (95% CI)	544 (26.5) Reference	2101 (41.3) HR 1.14 (1.03-1.25)	2371 (54.1) HR 1.38 (1.26 – 1.52)	1282 (65.5) HR 1.96 (1.77 – 2.18)	1148 (76.0) HR 2.94 (2.65 – 3.27)
Cardiovascular mortality	186 (9.1) Reference	757 (14.8) HR 0.83 (0.71-0.99)	915 (20.8) HR 0.93 (0.79- 1.09)	538 (27.5) HR 1.31 (1.11 - 1.55)	542 (40.7) HR 2.00 (1.69 – 2.37)

Cox Regression Analyses for total cohort adjusted for age, sex and mean aortic valve gradient. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 3.3. Adjusted Risk for All-Cause Mortality



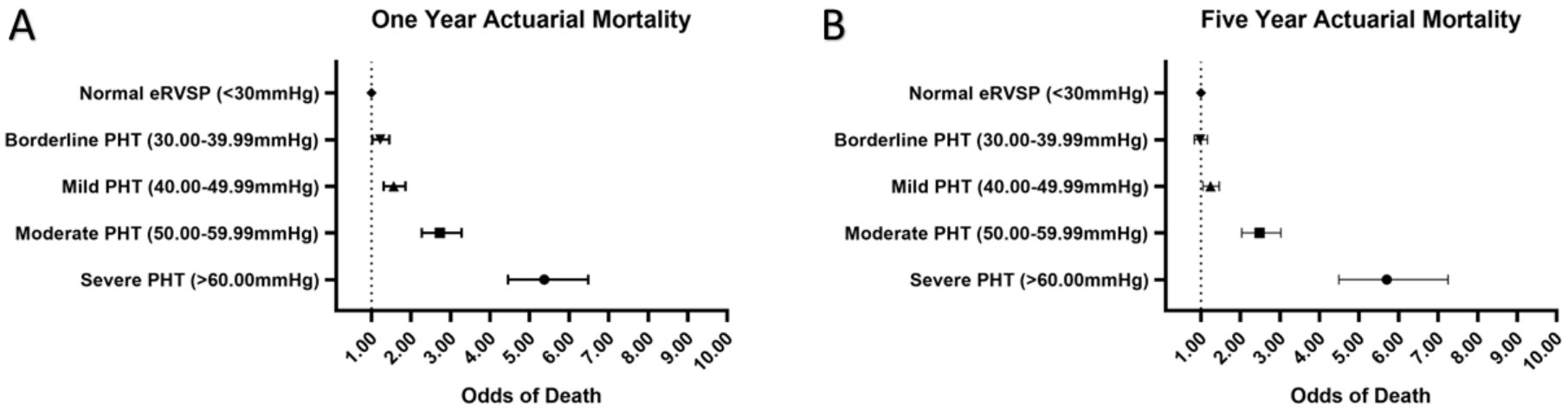
<30.00	1787	1032	520	246	111	35
30-39.99	4728	2859	1556	821	422	140
40-49.99	4153	2361	1229	606	270	86
50-59.99	1861	799	360	155	64	18
>60	1449	446	189	76	36	12



<30.00	1553	901	457	213	96	32
30-39.99	4026	2484	1369	727	373	123
40-49.99	3286	1924	1001	491	212	66
50-59.99	1298	574	259	117	48	13
>60	995	318	137	53	26	9

Adjusted risk for all-cause mortality using Cox proportional hazards showing as eRVSP level increases based on clinical severity, risk of mortality increases in, A) the total cohort (adjusted for age HR1.06, 95%CI 1.05-1.06, sex HR 0.85, 95% CI 0.81-0.89, and, mean aortic valve gradient HR 1.01 95%CI 1.004-1.007), and, B) the cohort excluding patients with ≥ moderate mitral regurgitation and/or ≥ moderate aortic regurgitation (adjusted for age HR1.06, 95%CI 1.05-1.06, sex HR0.83, 95% CI 0.79-0.88, and, mean aortic valve gradient HR1.01, 95%CI 1.003-1.007).

Figure 3.4. One and Five Year Actuarial Mortality for the Total Cohort



Actuarial all-cause mortality using logistic regression, adjusted for age, sex, and mean aortic valve gradient, for the total cohort showing increased odds of death as pulmonary pressures increase. PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

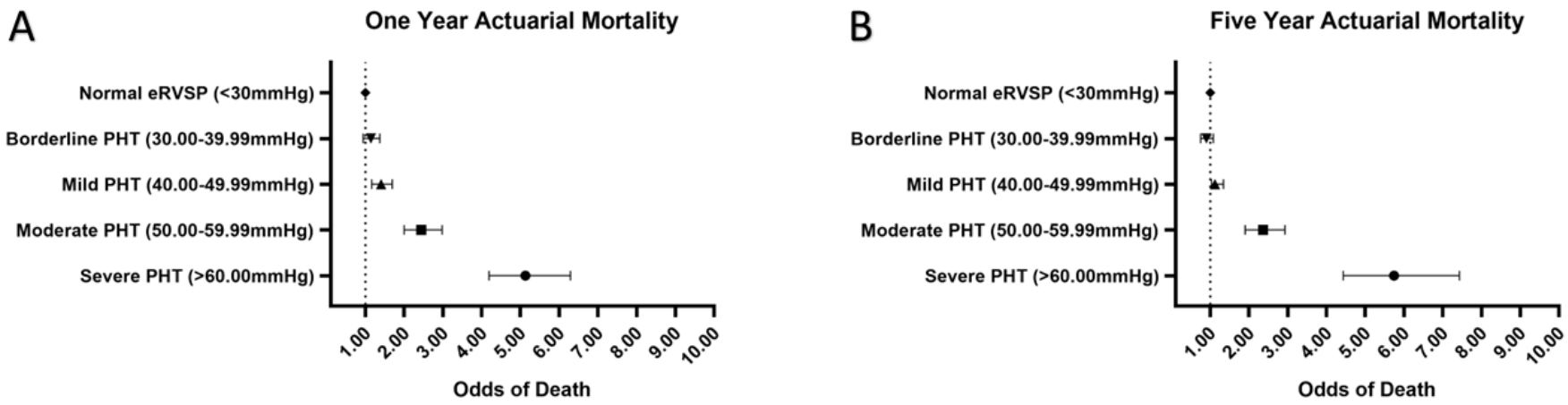
When we excluded patients where the severity was solely based on an AVA<1.5cm^2 mortality trends of the total cohort were maintained (**Table 3.3, Figure 3.5**). These trends were maintained in sensitivity analyses performed excluding patients with ≥moderate MR and/ or ≥moderate AR, though significance was not reached at milder elevations of pulmonary pressures in 1-or 5-year actuarial mortality **(Table 3.4, Figure3.3b, Figure 3.6**). These inconsistencies may be due to lower numbers and a loss of study power as well as potential confounding from unknown cardiovascular comorbidities. In all models, increasing age and male sex were also associated with increased mortality (p<0.0001, for all).

Table 3.3. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels excluding patients with just AVA<1.5cm^2 (n = 12770).

	Normal eRVSP (<30mmHg) n = 1478	**Borderline PHT (eRVSP 30.00-39.99) N = 4214**	**Mild PHT (eRVSP 40.00-49.99) N = 3964**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 1781**	**Severe PHT (eRVSP >60) N = 1333**
All-Cause Mortality N (%) HR (95% CI)	467 (31.6) Reference	1898 (45.0) HR 1.09 (1.02 - 1.20)	2200 (55.5) HR 1.28 (1.16-1.42)	1168 (65.6) HR 1.81 (1.62–2.01)	1054 (79.1) HR 2.81 (2.52–3.14)
Cardiovascular mortality	168 (11.4) Reference	728 (17.3) HR 0.83 (0.70-0.98)	888 (22.4) HR 0.94 (0.80-1.11)	493 (27.7) HR 1.30 (1.09-1.55)	535 (40.1) HR 2.21 (1.86–2.64)

Cox Regression Analyses for total cohort (n = 12770) adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 3.5. One and Five Year Actuarial Mortality excluding patients solely included based on AVA <1.5cm^2



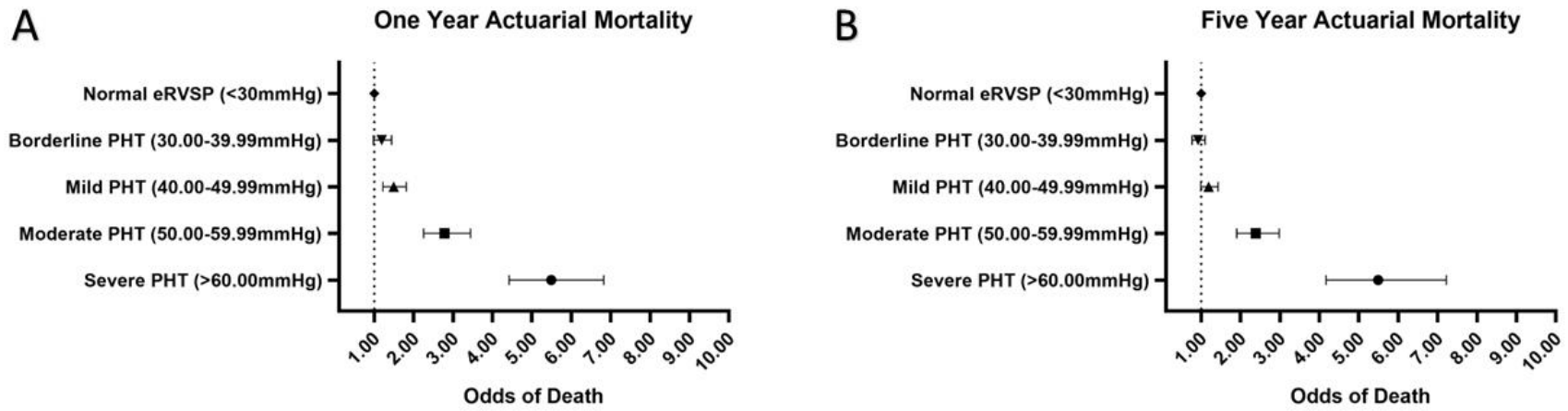
Actuarial all-cause mortality using logistic regression, adjusted for age and sex, excluding patients solely based on AVA <1.5cm^2 showing increased odds of death as pulmonary pressures increase. PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Table 3.4. Sensitivity analysis - Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels (excluding patients with significant aortic and/or mitral regurgitation, n = 12 005)

	Normal eRVSP (<30mmHg) n = 1793	**Borderline PHT (eRVSP 30.00-39.99) N = 4337**	**Mild PHT (eRVSP 40.00-49.99) N = 3464**	**Moderate PHT (eRSVP 50.00 -59.99) N = 1367**	**Severe PHT (eRVSP >60) N = 1044**
All-Cause Mortality N (%) HR (95% CI)	446 (24.9) Reference	1710 (39.4) HR 1.10 (1.002-1.21)	1809 (52.2) HR 1.33 (1.20-1.48)	875 (64.0) HR 1.98 (1.76–2.22)	760 (72.8) HR 2.92 (2.59–3.2)
Cardiovascular mortality	153 (8.5) Reference	592 (13.6) HR 0.77 (0.64-0.92)	682 (19.7) HR 0.88 (0.74-1.05)	338 (24.7) HR 1.20 (0.99-1.45)	338 (32.4) HR 1.96 (1.61–2.38)

Cox Regression Analyses for excluding patients with ≥moderate aortic regurgitation and/or ≥moderate mitral regurgitation adjusted for age, sex and mean aortic valve gradient. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 3.6. One and Five Year Actuarial Mortality, excluding patients with ≥ moderate mitral regurgitation and/or ≥ moderate aortic regurgitation



Actuarial all-cause mortality using logistic regression, adjusted for age, sex and mean aortic valve gradient, for patients without ≥ moderate mitral regurgitation and/or ≥ moderate aortic regurgitation showing increased odds of death as pulmonary pressures increase. PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

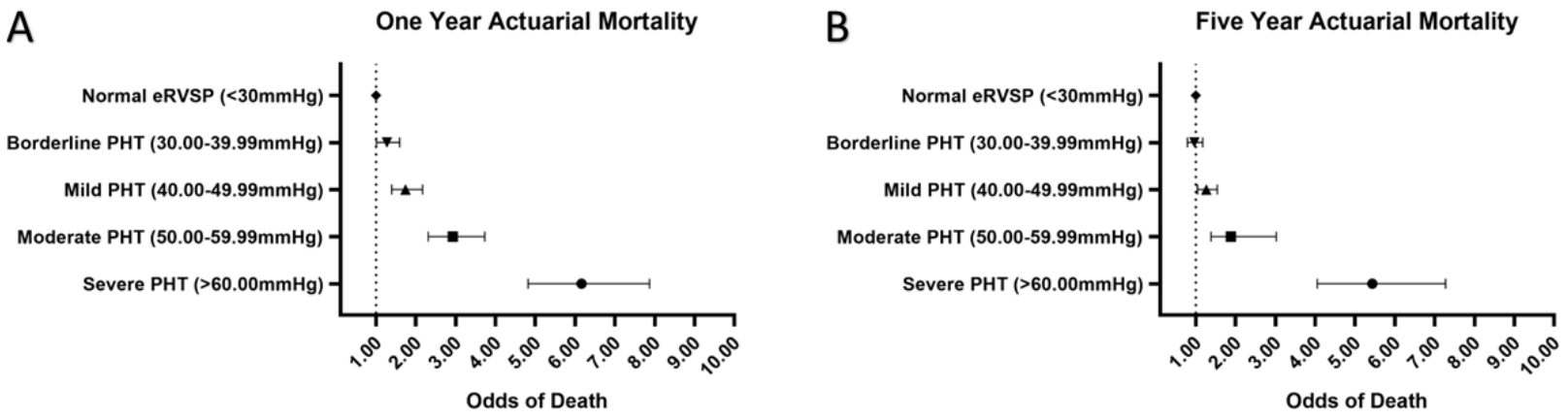
Mortality was also assessed when the cohort was divided into 2 groups, based on AS severity (moderate AS- 10 085 patients, severe AS- 4895 patients). In the moderate AS cohort, which had comparatively larger numbers, results mirrored those of the total cohort, with adjusted long-term mortality increasing progressively as eRVSP increased (HR1.13, 95%CI 1.01-1.27 for borderline PHT vs. HR3.28, 95%CI 2.87-3.73 for severe PHT) **(Table 3.5, Figure 3.7)**. Patients with severe AS had similar trends, although statistical significance was not reached at milder elevations of eRVSP, most likely a consequence of the smaller subject numbers **(Table 3.6, Figure 3.8)**.

Table 3.5. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with moderate aortic stenosis (n = 10 085)

	Normal eRVSP (<30mmHg) n = 1526	**Borderline PHT (eRVSP 30.00-39.99) N = 3540**	**Mild PHT (eRVSP 40.00-49.99) N = 2962**	**Moderate PHT (eRSVP 50.00 - 59.99) N = 1195**	**Severe PHT (eRVSP >60) N = 862**
All-Cause Mortality N (%) HR (95% CI)	363 (23.8) Reference	1311 (37.0) HR 1.13 (1.01-1.27)	1484 (50.1) HR 1.45 (1.29-1.63)	741 (62.0) HR 2.00 (1.76–2.27)	625 (72.5) HR 3.28 (2.87-3.73)
Cardiovascular mortality	110 (7.2) Reference	439 (12.4) HR 0.82 (0.66-1.01)	508 (17.2) HR 0.91 (0.74-1.12)	282 (23.6) HR 1.29 (1.03-1.61)	263 (30.5) HR 2.01 (1.61–2.52)

Cox Regression Analyses for moderate aortic stenosis adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 3.7. One and Five Year Actuarial Mortality for Moderate Aortic Stenosis Cohort



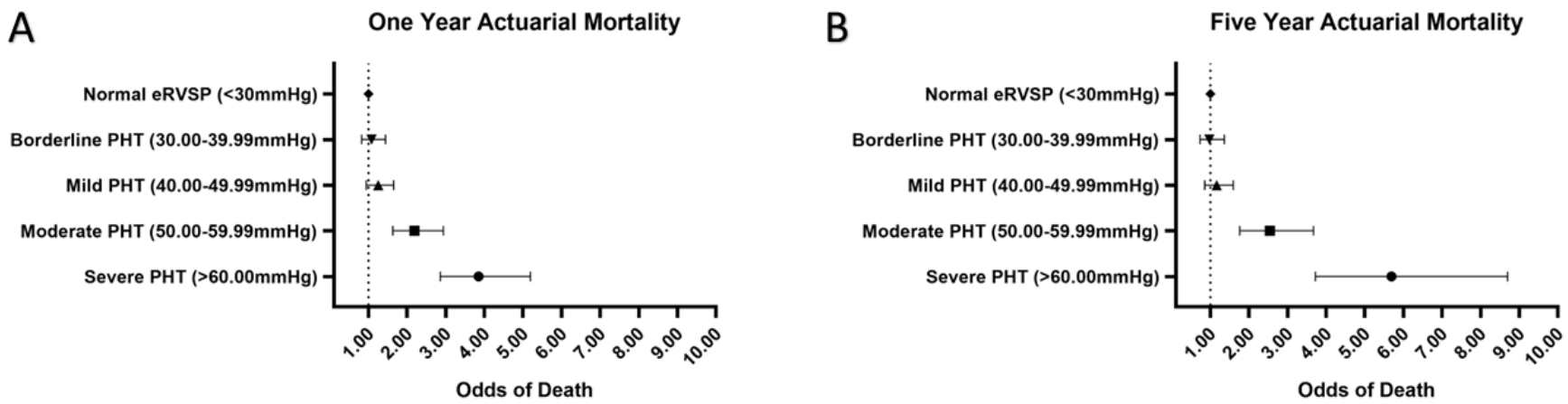
Actuarial all-cause mortality using logistic regression, adjusted for age and sex, for patients with moderate aortic stenosis showing increased odds of death as pulmonary pressures increase. PHT = pulmonary hypertension. eRVSP = estimated right ventricular systolic pressure.

Table 3.6. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with severe aortic stenosis (n = 4895)

	Normal eRVSP (<30mmHg) n = 523	**Borderline PHT (eRVSP 30.00-39.99) N = 1545**	**Mild PHT (eRVSP 40.00-49.99) N = 1418**	**Moderate PHT (eRSVP 50.00 -59.99) N = 761**	**Severe PHT (eRVSP >60) N = 648**
All-Cause Mortality N (%) HR (95% CI)	181 (34.6) Reference	790 (51.1) HR 1.15 (0.98 -1.35)	887 (62.6) HR 1.32 (1.13-1.55)	541 (71.1) HR 1.88 (1.59–2.23)	523 (80.7) HR 2.51 (2.12–2.98)
Cardiovascular mortality	76 (14.5) Reference	318 (20.6) HR 0.87 (0.67-1.11)	407 (28.7) HR 0.98 (0.76-1.25)	256 (33.6) HR 1.37 (1.06-1.77)	279 (43.0) HR 2.02 (1.56–2.61)

Cox Regression Analyses for severe aortic stenosis adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; PHT = pulmonary hypertension.

Figure 3.8. One and Five Year Actuarial Mortality for Severe Aortic Stenosis Cohort



Actuarial all-cause mortality using logistic regression, adjusted for age and sex, for patients with severe aortic stenosis showing increased odds of death as pulmonary pressures increase. PHT = pulmonary hypertension. eRVSP = right ventricular systolic pressure.

Threshold for mortality

The regression model for the decile distribution of eRVSP, adjusted for age, sex and mean AV gradient, confirmed a threshold of increased risk from eRVSP 35.01-38.00mmHg relative to the lowest decile (<28.00mmHg) (p=0.009). No significantly increased risk in the 2nd (eRSVP 28.01 – 32.00) or 3rd (eRVSP 32.01 – 35.00) deciles was observed. Increased risk was noted from the 4th decile (eRVSP 35.01–38.00; HR1.19, 95%CI 1.04-1.35) and became progressively higher through to the 10th decile (eRVSP 60.01 – 136.97; HR2.86, 95%CI 2.54-3.21) (**Table 3.7**). Hence, the adjusted risk for mortality is markedly higher in those with borderline-mild PHT and above regardless of age, sex or mean AV gradient.

Table 3.7. Survival Profile and Adjusted Risk for Mortality According to decile distribution of Estimated Right Ventricular Systolic Pressure Levels (n = 14980)

eRSVP decile distribution (mmHg)	**All Fatal Events (n= 14980) HR (95% CI), p value**
0.00 – 28.00	Reference
28.01 – 32.00	1.03 (0.90-1.18)
32.01 – 35.00	1.00 (0.88-1.14)
35.01 – 38.00	1.19 (1.04-1.35)
38.01 – 40.69	1.20 (1.06-1.36)
40.70 – 43.64	1.28 (1.14-1.45)
43.65 – 46.48	1.37 (1.21-1.55)
46.49 – 50.96	1.53 (1.34-1.73)
50.97 – 60.00	2.07 (1.84-2.33)
60.01 – 136.97	2.86 (2.54-3.21)

Analyses adjusted for age, sex and mean aortic valve gradient. eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; CI = confidence interval.

Discussion

In this "real-world" cohort study, including over 14 000 adults with ≥ moderate AS and normal LVEF, we have documented the prevalence of mild, moderate and severe PHT in these subjects and demonstrated the independent prognostic importance of PHT in the context of AS. The use of 'big data' from the NEDA, which includes over 1 million ultrasounds from over 600 000 unique adults, has yielded a more comprehensive, contemporary description of the prevalence and phenotype of patients with ≥ moderate AS, compared with smaller previous studies[35, 112-114], the largest of which included 2435[117] such patients. We confirmed the adverse prognostic impact PHT in AS and have now documented that the threshold for excess mortality lies at a relatively modest elevation of eRVSP.

PHT most likely develops in those with AS via the following mechanism: As the severity of AS worsens, LV pressure overload increases, leading to compensatory concentric hypertrophy (and progressive myocardial fibrosis), subsequent LV diastolic dysfunction and eventually elevated LV end diastolic pressure, increased LA pressure[116] and post-capillary PHT.

Prevalence and Phenotype of PHT with AS

We confirm a high prevalence of PHT in patients with AS, especially as age increases, but rates have varied considerably in previously published studies, dependent on their selection criteria[112-114, 116]. In prior echo studies, PHT was noted in 15-30% of patients with symptomatic AS (>19% mild, >10% - 45% moderate, 15% to 30% severe)[49, 112-114, 116]. Our study from community and hospital-based echo labs around Australia showed that >50% of studied patients with significant AS and normal LVEF had at least some degree of PHT, as defined by clinical guidelines (mild PHT- 29.3%, moderate- 13.1%, severe- 10.1%). Significantly, the sub-group with the highest proportion of patients was those with "borderline PHT", with eRVSP 30-39mmHg (33.9%).

Previous studies report the most frequent features of PHT in patients with AS are reduced LVEF, concomitant MR and, as confirmed in our study, more severe AS[117, 118]. Our cohort confirms the impact of PHT in patients with significant AS with normal ejection fraction[119]. The resultant echocardiographic phenotype is that of progressively increased E:e'' ratio and indexed LA volume, and progressively higher proportions of RV dilation and dysfunction. Better identification of this phenotype provides clinicians with clear parameters to monitor and allows for further understanding of the remodelling associated with worsening PHT. This has been recently described by us and others, in a cardiac damage score, which has now been validated in both high-gradient, low-flow low-gradient, symptomatic and asymptomatic severe AS patients[110, 111, 120, 121].

Outcomes of PHT in AS patients

This large study has confirmed the serious impact of worsening PHT in patients with significant AS, even in the absence of LV systolic dysfunction, with 52.4% of patients with eRVSP>40.00mmHg having a 1.4- to 2.9-fold adjusted increased risk of long-term all-cause mortality, dependent on PHT severity, compared with those without PHT. Similar to our previous studies[12, 122] we find that there is even an increased risk associated with borderline PHT (eRVSP 30.00-39.99), compared to normal estimated eRVSP. This observation was evident even at 12 months, with 1-year actuarial mortality increased 1.29-fold, and long-term all-cause mortality increased 1.14-fold, in borderline PHT subjects. Furthermore, the high numbers provided by the NEDA allowed us to identify a clear threshold for excess mortality risk at eRVSP>35.00mmHg. These results were independent of age, sex and mean AV gradient and our sensitivity analysis showed that they did not appear to be confounded by the presence of concomitant left-sided valvular pathology. Furthermore, the severity of AS did not impact on result suggesting that PHT independently predicts mortality in the setting of moderate and severe AS.

Clinical Implications

The presence of PHT is only acknowledged as an indication for 'early' intervention in asymptomatic patients with severe AS when pulmonary pressures exceed 60mmHg[74]. PHT increases mortality in patients who undergo aortic valve intervention,[35, 116, 118, 123, 124] with only modest reductions in eRVSP following intervention[21, 35, 102]. Our recent publication[100] showed that patients with moderate AS had a similarly high risk of mortality as those with severe AS, raising the question on the optimal timing of intervention. In the absence of clinical trials showing the effect of earlier valve intervention in AS, it is unclear whether earlier AVR would improve the outcome of these individuals, or whether the cardiac structural changes will reverse after valve intervention.

Limitations

NEDA provides detailed echocardiographic data and linkage to mortality; NEDA is, however, a retrospective de-identified electronic record interface which means that we were unable to directly review echocardiographic images with regards to pressure estimates or other parameters. Furthermore, NEDA does not (yet) provide granular clinical data such as symptoms, co-morbidities or pharmacological treatments. This is important in this study as we don't have information regarding key cardiovascular co-morbidities such as hypertension or coronary artery disease which may contribute to the mortality trends noted. Most patients included the database have undergone an echocardiogram for investigation of confirmed or suspected cardiac disease and should not be taken to reflect the population prevalence. A small proportion of patients in this study were included based on the AVA alone. We believe that a significant portion of these patients are likely to have normal-flow, low-gradient AS or paradoxical-flow, low gradient AS. We acknowledge that this cannot be confirmed in the present study.

Importantly, a sub-group analysis excluding these "AVA only" AS patients showed that mortality trends mirrored that of the total cohort, suggesting their inclusion did not introduce significant bias.

These studies were primarily derived from specialist centres or clinics across Australia, so some caution should be applied when applying these findings to other populations. However, Australia is a multi-ethnic population with universal health coverage, aspects captured within the NEDA database. Our data is lacking in quantitative RV measurements, so we are unable to fully assess the impact of PHT on the right heart, nor can we determine impact of RV abnormalities on mortality, in this cohort. This is an important question when assessing PHT and outcomes and thus is a limitation of this current study. Future studies should address the role of RV size and function in the relationship between AS and PHT. The prevalence and survival associated with PHT after AV replacement is not addressed in this Chapter. Future studies are needed to establish these findings in this distinct cohort with potential collaboration between the NEDA, the Australia and New Zealand Society of Cardiothoracic Surgeons and the Australian Transcatheter Valve Therapies Registry likely to provide clinically meaningful information both within Australia and worldwide.

As noted in our previous studies[12], the data concerning PHT in NEDA is based on echocardiography-based measures, rather than haemodynamic assessment at right heart catheterisation. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107], supporting the broad validity of our approach. Furthermore, echocardiography remains the commonest screening tool to detect PHT and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow up. We acknowledge that diagnosis of PHT should generally be confirmed on right heart catheterisation, after initial screening is suggestive of PHT. We also note that the absence of a tricuspid regurgitation jet does not exclude PHT and there may be a number of patients with AS and PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR. Thus, although our data indicate a threshold for mortality somewhere in the "borderline / mild" PHT range, we must acknowledge some uncertainties about where this prognostic threshold actually lies. Uncertainties in this regard relate to (i)exclusion of those with no TR, (ii)inclusion of those where TR may have been incorrectly sampled (iii)the use of an assumed RA pressure for sound methodological reasons.

Conclusion

Both AS and PHT confer an increased risk of mortality as they progress. This very large cohort study confirms that ≥ moderate AS patients have higher mortality as PHT becomes more severe. The threshold for mortality lies within the range of borderline to mild PHT.

Chapter 4 – Prevalence of Pulmonary Hypertension in Mitral Regurgitation and its Influence on Outcome

This chapter is based on the publication: Ratwatte S, Strange G, Playford D, Stewart S, Celermajer DS et al. Prevalence of pulmonary hypertension in mitral regurgitation and its influence on outcomes. OpenHeart. 2023.10(1):e002268. doi: 10.1136/openhrt-2023-002268.

Abstract

Objective: Pulmonary hypertension (PHT) commonly co-exists with significant MR, but its prevalence and prognostic importance have not been well characterised. In a large cohort of adults with ≥moderate MR, we aimed to describe the prevalence and severity of PHT and assess its influence on outcomes.

Methods: In this retrospective study, we analysed the National Echocardiography Database of Australia (data from 2000-2019). Adults with an estimated right ventricular systolic pressure (eRVSP), left ventricular ejection fraction (LVEF) >50% and with moderate or greater MR were included (n= 9683). These subjects were then categorised according to their eRVSP. The relationship between PHT severity and mortality outcomes were evaluated (median follow-up of 3.2 years, interquartile range 1.3-6.2years).

Results: Subjects were aged 76±12years and 62.6% (6038) were female. Overall, 959 (9.9%) had no PHT; and 2952 (30.5%), 3167 (32.7%), 1588(16.4%) and 1017 (10.5%) patients had borderline, mild, moderate and severe PHT respectively. A "typical left heart disease" phenotype was identified with worsening PHT, showing rising E:e', right and left atrial sizes increasing progressively, from no PHT to severe PHT ($p<0.0001$, for all). With increasing PHT severity, 1- and 5-year actuarial mortality increased from 8.5% and 33.0%, to 39.7% and 79.8% respectively ($p<0.0001$). Similarly, adjusted survival analysis showed the risk of long-term mortality progressively increased with higher eRVSP levels (adjusted hazard ratio 1.20-2.86, borderline to severe PHT, $p<0.0001$ for all). A mortality inflection was apparent at an eRVSP level >34.00mmHg (HR1.27, CI1.00-1.36).

Conclusions: In this large study we report on the importance of PHT in patients with MR. Mortality increases as PHT becomes more severe from an eRVSP of 34mmHg onwards.

Introduction

Mitral regurgitation is an increasingly prevalent valvular problem in developed countries[125], and is the second-most common valve lesion requiring operative management in Europe[126] and the USA[127], after AS. Symptoms and outcomes generally correlate with both the severity of the regurgitation and the myocardial response to volume overload[128]. The identification of prognostic factors is important to risk stratify patients and to potentially guide treatment decisions. Whilst it is recognised that PHT is a potential complication of MR, this is actually not well documented. There are varying reports, in relatively small cohorts on the prevalence[50, 129] and echocardiographic phenotype[53, 130] of these patients and, thus, an incomplete understanding of the prognostic impact of PHT in significant MR [125].

Group 2 PHT, or PHT due to LHD is the most common type of PHT[2, 37]. PHT is thought to be a predictive feature of deterioration in these patients and likely arises from elevated LA pressure causing back pressure into the pulmonary vasculature[2, 17]. In MR specifically, PHT is thought to be due to the direct effect of systolic backflow into the LA and may develop before patients experience symptoms or LV systolic dysfunction[2, 50, 51].

Echocardiography remains the commonest screening tool for PHT and is widely used in clinical practice. Utilising the power of 'big' data from the National Echo Database of Australia (NEDA), a registry with contemporary community and hospital based echo data on over 600 000 unique adult subjects from over 25 centres across Australia, we aimed to describe the prevalence of PHT in adults with ≥ moderate MR, and to assess the influence of PHT severity on outcomes.

Methods

NEDA Database and Study Design

The NEDA is a multi-centre registry; the purpose and methodology of which has been previously described[12, 99, 100]. NEDA contains basic demographic and detailed echocardiographic data of adults from >25 centres across Australia. The database is linked with the National Death Index (NDI), provided by the Australian Institute for Health and Welfare; the NDI provides mortality data on each individual. The study period included >1million echo reports from >600 000 individuals, studied between January 2000 and June 2019. Vital status was determined as of 21st May 2019 (median follow-up 6.2years, IQR 3.8-9.8years); patients alive at this date were censored alive. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and human ethics approval was obtained from the Sydney Local Health District Human Research Ethics Committee, protocol X15-0387 and 2019/ETH069899. A retrospective waiver of consent was authorised as part of this ethics protocol.

Study cohort

Figure 4.1 shows our study flow diagram, this is consistent with our previous work on PHT in left-sided valvular pathology outlined in Chapter's 2 and 3. NEDA data at the time of study census were used to identify a cohort of patients with significant MR in order to characterise their relationship to PHT: 1) adults ≥ 18 years of age, 2) with at least one echocardiogram recorded on the system (where patients had multiple studies only the last study was included in analysis), 3) with a recorded LVEF, eRVSP and 4) with moderate or greater MR. Text extraction was used to identify patients with moderate and severe MR as well as RV size and function[12]. Whilst quantitative measures of MR were interrogated sufficient data was not available in the majority of patients, a reflection of real-world practice within Australia. All participating laboratories utilize an integrative and semiquantitative approach for grading MR severity as recommended by the American Society of echocardiography (ASE)[101]. Patients with mitral valve replacements (MVR) were excluded from primary analysis as were patients with evidence of significant mitral stenosis (conservatively defined as mitral valve gradient >5mmHg), LVEF < 60% and patients with < moderate MR. eRVSP was conservatively derived using the Bernoulli equation (4x[(TRV]^2 + assumed RA pressure of 5mmHg)[72].

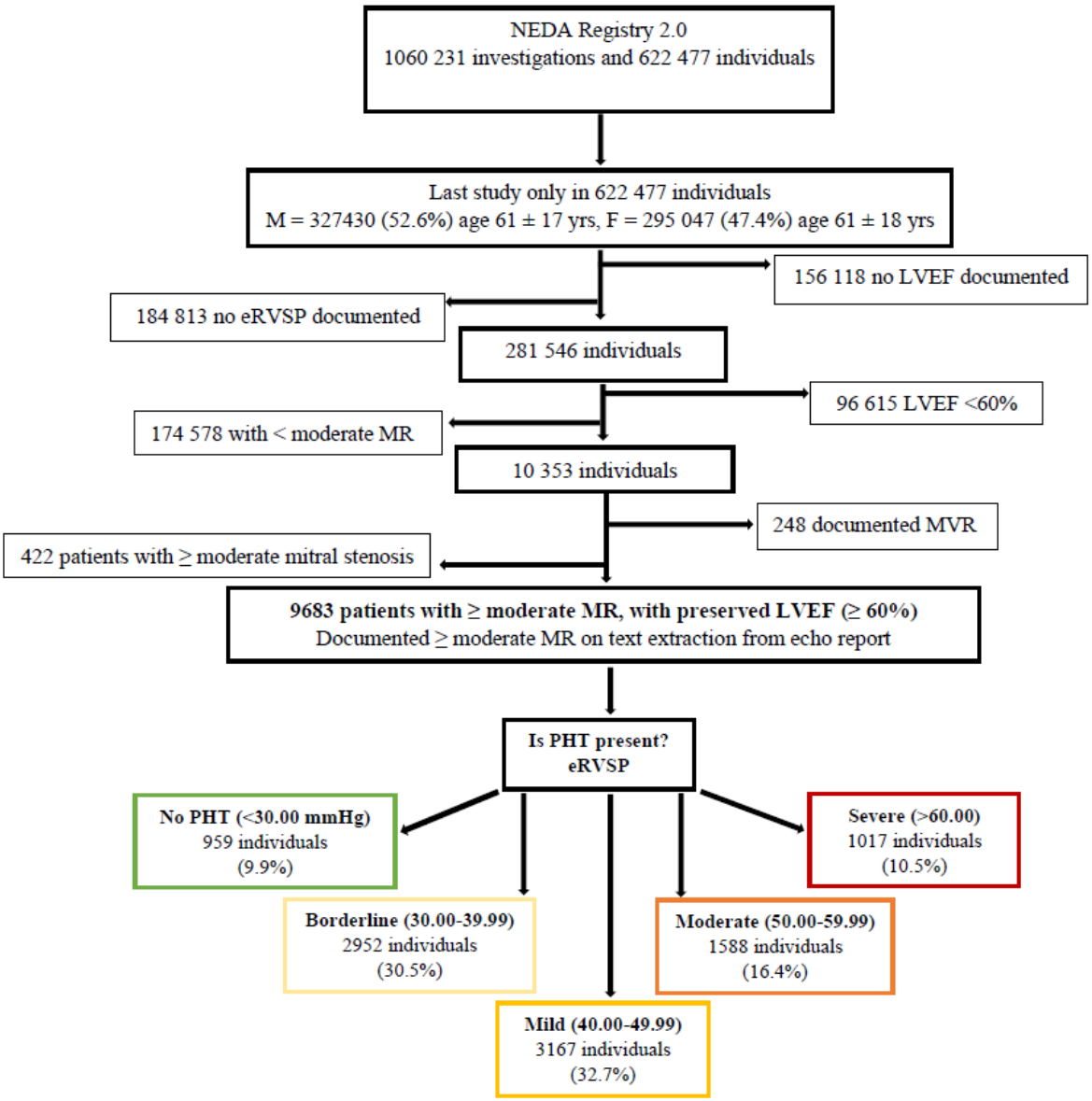
Study methods

Similar to the methodology outlined in Chapters 2 and 3, once the cohort of patients with moderate or greater MR was established, subjects were categorised according to their eRVSP, according to clinical guidelines[21, 37] to document the distribution of eRVSP and thence PHT severities. A "borderline PHT" group which has previously been determined as potentially significant in both NEDA papers and other recent prospective publications[12, 13, 104] was included. Defined categories were: 1) normal (eRVSP <30mmHg), 2) borderline (30.00-39.99mmHg), 3) mildly elevated (40.00-49.99mmHg), 4) moderately elevated (50.00-59.99mmHg) and, 5) severely elevated (eRVSP ≥60mmHg)[12, 21].

We then analysed the eRVSP data according to decile distribution[12]: 1st decile- 5.00-30.00mmHg, 2nd- 30.01-34.00mmHg, 3rd- 34.01-37.04mmHg, 4th- 37.05-39.16mmHg, 5th- 39.17-43.00mmHg, 6th- 43.01-46.00mmHg, 7th- 46.01-48.44mmHg, 8th- 48.45-53.00mmHg, 9th- 53.01-61.00mmHg and 10th- >61.00mmHg.

All-cause mortality was determined during a median follow up of 3.2years (IQR1.3-6.2years). We explored the relationship between eRVSP level and survival, looking at both clinically defined groups (as above) and the eRVSP deciles .

Figure 4.1. Study Flow Chart



This flowchart shows the points of analysis performed in this study. NEDA = National Echo Database Australia; left ventricular ejection fraction (LVEF); eRVSP = estimated right ventricular systolic pressure; MR = mitral regurgitation; MVR = mitral valve replacement; PHT = pulmonary hypertension.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis using ANOVA was used to test whether the trend of the mean across the categorical groups of eRVSP levels was linear. For binary variables, the chi-squared test was used to determine if there was a trend in the change in proportions across the groups.

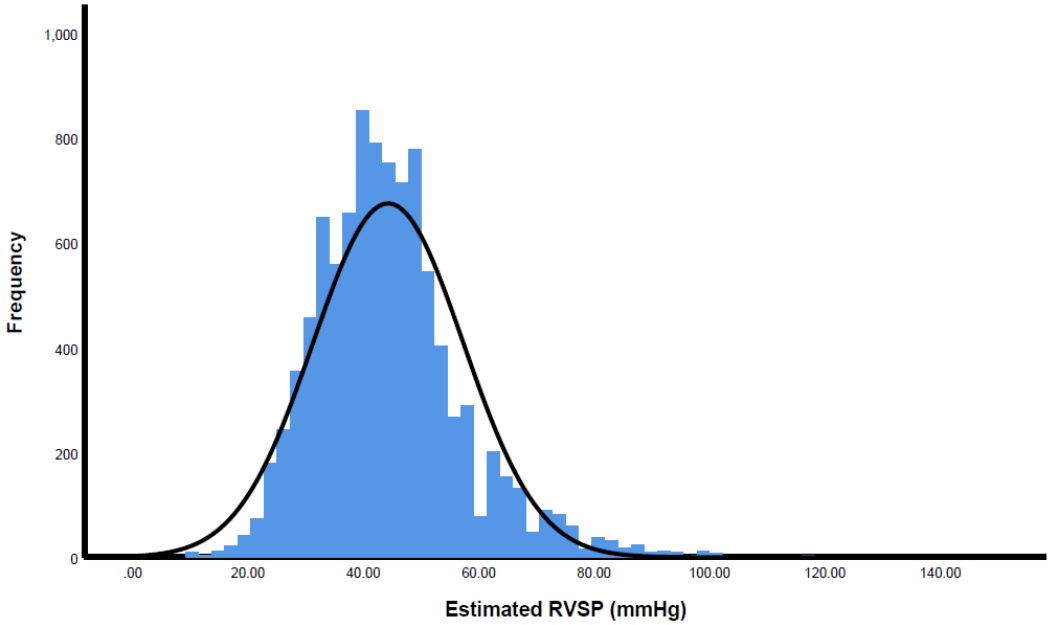
Actuarial 1- and 5- year survival rates for all-cause mortality were calculated from the 9439 (97.9%) and 6780 (70.3%) subjects with complete follow up for those time points. Multiple logistic regression models (entry at univariate p-value <0.05) were used to derive adjusted odds ratios (OR) for mortality models at fixed time points. Cox regression hazard models were used to derive adjusted hazard ratios (HR) for mortality outcomes during follow up (entry model at a uni-variate p-value <0.05). Adjusted analyses included age and sex. A sensitivity analysis was performed excluding patients with significant concurrent severe AS and moderate or greater AR. Patients with moderate and severe MR were also assessed separately to determine if there were differences between these two groups. Severe MR, was defined as 'severe mitral regurgitation' on text extraction. All analyses were performed with SPSS software version 25.0 (IBM Corp, Armonk, New York), and statistical significance was accepted at a 2-tailed p-value of <0.05.

Results

Prevalence of PHT and Distribution of eRVSP

A total of 9638 patients with moderate or greater MR, normal left ventricular systolic function and eRVSP data were identified; the majority (62.6%) being female. **Figure 4.2** shows the frequency distribution of eRSVP levels (median 43.00mmHg, IQR 35.46-50.96mmHg). The number of patients in each sub-group were: No PHT (eRVSP <30mmHg)- 959 individuals (9.9%), borderline PHT (eRVSP 30.00-39.99mmHg)- 2952individuals (30.5%), mild (eRVSP 40.00-49.99)- 3167 (32.7%), moderate (eRVSP 50.00-59.99)- 1588 (16.4%) and severe (eRVSP>60mmHg)- 1017 (10.5%).

Figure 4.2. Frequency Distribution of Estimated Right Ventricular Systolic Pressure within the Cohort



These data show the statistical distribution of estimated right ventricular systolic pressure (RVSP) levels.

Cohort Profile

Table 4.1 summarises the demographic and echocardiographic characteristics of the study cohort divided into sub-groups based on measured eRVSP levels. Age was greater in those with higher eRVSP levels, from a mean of 69 ± 17years in patients with no PHT to 81±10 years in patients with moderate PHT, before a plateau was noted in those with severe PHT (80±11 years) ($p<0.0001$ for all). The proportion of patients with atrial fibrillation or an atrial arrhythmia was greater in those with higher eRVSP levels (24.0% vs. 54.8%, no PHT vs severe PHT respectively).

A typical pattern of worsening "left heart disease" phenotypic response with worsening PHT was evident. E:e' increased progressively with increased severity of PHT (12.90 ± 5.63 vs. 17.16±7.01, no PHT vs severe PHT respectively, $p<0.0001$ for all). An increase in right atrial area and indexed left atrial volume was also noted (18.18±7.25 cm^2 vs. 33.71±9.35cm^2 and, 43.84±24.21 vs. 108.95±55.95mL/m^2, no PHT vs. severe PHT, respectively, $p< 0.0001$ for all) though indexed left atrial volume plateaued in those with severe PHT. Qualitative observations showed an increased proportion of patients with increased RV dilation and functional impairments as eRVSP level increased.

Table 4.1. Baseline Characteristics of Study Cohort (n = 9683)

	eRSVP 0.00-29.99 n = 959	**eRVSP 30.00-39.99 n = 2952**	**eRVSP 40-49.99 n = 3167**	**eRVSP 50-59.99 n = 1588**	**eRVSP >60.00 n = 1017**	**P value**
Demographics						
Age, years	69 ± 17	74 ± 13	78 ± 11	81 ± 10	80±11	< 0.0001
Female (%)	611 (63.7)	1773 (60.1)	1992 (62.9)	1011 (63.7)	651 (64.0)	<0.0001
Anthropometrics						
BMI	25.92±5.15	26.02 ± 5.40	26.52±5.76	26.56±6.03	26.05±5.73	0.48
BSA	1.80±0.24	1.80 ± 0.24	1.80±0.25	1.80±0.24	1.76±0.24	<0.0001
Rhythm						
Atrial fibrillation / arrhythmia	230 (24.0)	947 (32.1)	1268 (40.0)	770 (48.5)	557 (54.8)	<0.0001
LV dimensions and function						
LVEF %	66.14±5.41	68.13±6.89	70.53±7.90	70.40±7.89	70.02±7.90	<0.0001
Stroke Volume Index (ml/m^2)	44.06±11.97	44.98±14.37	44.96±14.79	43.49±14.09	42.15±14.99	0.06
E:e' ratio	12.90±5.63	13.07±5.68	14.14±5.27	15.35±5.51	17.16±7.01	<0.0001
LVEDD	4.50±0.67	4.71±0.69	4.87±0.73	4.92±0.77	4.85±0.82	<0.0001
LVESD	2.87±0.53	2.87 ±0.57	2.84±0.64	2.87±0.65	2.83±0.69	0.009
Atrial dimensions						
LA volume index, mL/m^2	43.84±24.23	67.90±41.04	95.53±47.82	108.92±54.28	108.95±55.95	<0.0001
RA area, cm^2	18.18±7.25	24.21±8.76	29.03±8.50	32.12±9.01	33.71±9.35	<0.0001
Right heart dimensions and function						
eRSVP, mmHg	25.66±3.63	35.43±2.94	44.69±2.76	53.97±2.93	71.10±10.84	<0.0001
TR peak velocity, m/s	2.19±0.23	2.56±0.17	2.94±0.14	3.30±0.14	3.86±0.33	<0.0001
RV basal diameter	3.53±0.75	3.30±0.47	3.36±0.37	3.44±0.40	3.56±0.47	<0.0001
Dilated RV	95 (9.9)	509 (17.2)	1051 (33.2)	673 (42.4)	521 (51.2)	<0.0001
Impaired RV function	14 (1.5)	28 (0.9)	59 (1.9)	54 (3.4)	82 (8.1)	<0.0001

Mitral valve dimensions and function						
MV mean gradient, mmHg	2.32±1.18	2.63±1.20	3.01±1.16	3.31±1.18	3.09±1.22	<0.0001
Concomitant valvular pathology						
≥ moderate aortic regurgitation	85 (8.9)	246 (8.3)	369 (11.7)	229 (14.4)	156 (15.3)	<0.0001
Severe AS < 1cm^2	26 (2.7)	89 (3.0)	121 (3.8)	82 (5.2)	77 (7.8)	<0.0001

Values are n (%) unless otherwise indicated. eRVSP = estimated right ventricular systolic pressure (mmHg); BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; TR = tricuspid regurgitant; RV = right ventricle; AV = aortic valve; VTI = velocity time integral.

The differences between male and female patients are shown in **Table 4.2.** Female patients were older than their male counterparts (77±13 years vs. 75±12 years) but did not show clinically meaningful differences in eRVSP level. Females had higher E:e' but lower right atrial area and indexed LA volume compared to males.

Table 4.2. Baseline Characteristics of Study Cohort stratified by sex

	Male n = 3645	**Female N = 6038**	**P value**
Demographics			
Age, years	75 ± 12	77 ± 13	<0.0001
Anthropometrics			
BMI	26.51±5.03	26.12 ± 5.99	<0.0001
BSA	1.95±0.21	1.70 ± 0.21	<0.0001
Rhythm			
Atrial fibrillation / atrial arrhythmia	1506 (41.3)	2266 (37.5)	0.001
LV dimensions and function			
LVEF %	68.60±7.40	69.71±7.58	<0.0001
E:e' ratio	13.56±5.14	14.65±6.13	<0.0001
LVEDD	5.14±0.74	4.58±0.66	<0.0001
LVESD	3.10±0.65	2.71 ±0.55	<0.0001

Atrial dimensions			
LA volume index, mL/m^2	95.34±54.04	85.98±48.34	<0.0001
RA area, cm^2	31.72±9.64	25.63±8.81	<0.0001
Right heart dimensions and function			
eRSVP, mmHg	44.05±12.78	44.40±13.15	0.003
TR peak velocity, m/s	2.90±0.49	2.92±0.49	<0.0001
RV basal diameter	3.53±0.42	3.28±0.39	<0.0001
Dilated RV	1515 (41.6)	1334 (22.1)	<0.0001
Impaired RV function	109 (3.0)	128 (2.1)	<0.0001
Mitral valve dimensions and function			
MV mean gradient, mmHg	2.63 ± 1.24	2.93 ± 1.21	<0.0001
Concomitant valvular pathology			
≥ moderate aortic regurgitation	389 (10.7)	696 (11.5)	<0.0001
Severe AS < 1cm^2	107 (2.9)	288 (4.8)	0.05

Values are n (%) unless otherwise indicated. eRVSP = estimated right ventricular systolic pressure (mmHg); BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; TR = tricuspid regurgitant; RV = right ventricle; AV = aortic valve; VTI = velocity time integral.

Survival data

The survival profile of the cohort based on the severity of PHT as determined on echocardiography is summarized in **Table 4.3**. All-cause mortality at 1 and 5 years (actuarial mortality) and long-term survival (all adjusted for age and gender) were reported between those with eRVSPs <30.00mmHg and the 4 categories of progressively elevated eRSVP. As predicted, the risk for mortality markedly increased with higher eRVSP levels. This was shown by the range in 1- and 5-year actuarial mortality from a low of 8.5% and 33.0%, to a high of 39.7% and 79.8%, in those with normal to severely elevated eRVSPs. This trend was mirrored in adjusted long-term mortality results which showed a 1.20-fold increase in risk in those with borderline PHT compared to a 2.86-fold increase in those with severe PHT (p<0.0001 for all) (**Figure 4.3a**). Cardiovascular mortality trends showed an increase in risk in those with moderate and severe PHT (**Table 4.3**). Trends were less clear in with smaller numbers and possible inaccurate coding for causes of death documented on death certificates, as possible contributing factors.

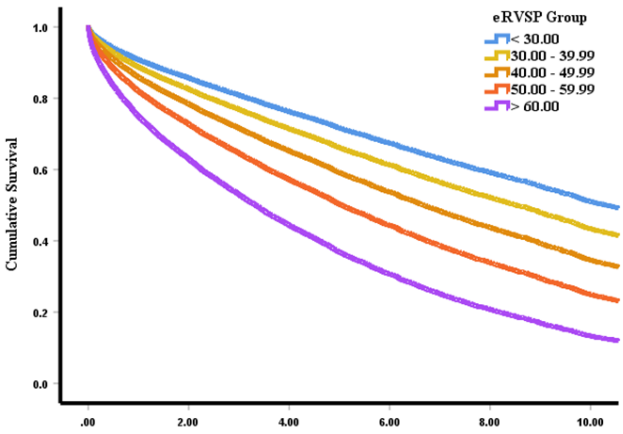
Table 4.3. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels

	1-Year Actuarial Mortality (n= 9439)	5-Year Actuarial Mortality (n= 6780)	All Fatal Events (n= 9638)	Cardiovascular mortality (n= 9638)
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 9638	1573 (16.7)	3603 (53.1)	4614 (47.9)	1777 (18.4)
Normal eRVSP (<30mmHg) n = 959	79/950 (8.5) Reference	192/581 (33.0) Reference	247 (25.8) Reference	83 (8.7) Reference
Borderline PHT (eRVSP 30.00-39.99) N = 2952	304/2869 (12.0) OR 1.14 (1.02-1.47)	791/1970 (40.2) OR 1.18 (1.01-1.45)	1098 (37.2) HR 1.20 (1.04-1.38)	383 (13.0) HR 0.77 (0.61-0.97)
Mild PHT (eRVSP 40.00-49.99) N = 3167	468/3088 (17.0) OR 1.52 (1.18-1.96) P=0.001	1179/2280 (51.7) OR 1.58 (1.34-1.86)	1612 (50.9) HR 1.54 (1.34-1.76)	607 (19.2) HR 0.81 (0.64 -1.01)
Moderate PHT (eRSVP 50.00 -59.99) N = 1588	342/1533 (25.8) OR 2.22 (1.71-2.90)	787/1129 (69.7) OR 2.93 (2.32-3.70)	922 (58.1) HR 2.00 (1.73-2.30)	383 (24.1) HR 1.19 (0.94-1.51)
Severe PHT (eRVSP >60) N = 1017	380/999 (39.7) OR 4.64 (3.55-6.08)	654/820 (79.8) OR 5.18 (3.98-6.73)	1068 (72.3) HR 2.86 (2.48-3.31)	321 (31.6) HR 1.62 (1.27-2.06)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

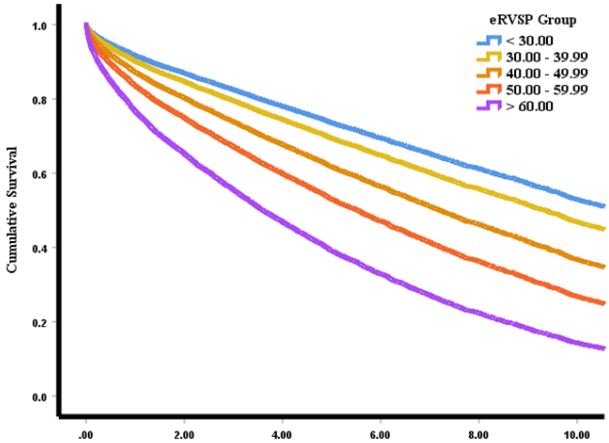
Figure 4.3. Adjusted Risk for All-Cause Mortality

A



<30.00	900	634	416	245	124	32
30-39.99	2787	1929	1301	861	532	210
40-49.99	3002	1935	1244	807	503	216
50-59.99	1491	767	420	223	114	36
>60	974	393	199	98	50	18

B



<30.00	806	574	382	226	115	30
30-39.99	2494	1771	1207	809	503	201
40-49.99	2566	1690	1101	723	458	201
50-59.99	1216	647	372	197	101	32
>60	769	324	166	78	39	13

Adjusted risk for all-cause mortality using Cox proportional hazards showing as eRVSP level increases based on clinical severity, risk of mortality increases in, a) the total cohort and, b) the cohort excluding patients with severe aortic stenosis and/or ≥ moderate aortic regurgitation.

A sensitivity analysis was performed excluding patients with ≥moderate AR or severe AS. The trends were maintained in 1- and 5-year actuarial analysis, though only achieved statistical significance from mild PHT onwards. Adjusted long-term mortality continued to progressively increase as eRVSP level increased (**Table 4.4, Figure 4.3b**). Indexed LA volume was also included as a variable in the survival models, with mortality trends mirroring the above results (**Table 4.5**). In all models increasing age and male sex were also associated with increasing mortality (p<0.0001, for all).

Table 4.4. Sensitivity analysis - Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels (excluding patients with ≥ moderate aortic regurgitation and severe aortic stenosis, n= 8293)

	1-Year Actuarial Mortality (n= 8094)	**5-Year Actuarial Mortality (n= 5793)**	**All Fatal Events (n= 8293)**	**Cardiovascular mortality (n= 8293)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 8293	1235 (15.3)	2917 (50.4)	3812 (46.0)	1419 (17.1)
Normal eRVSP (<30mmHg) n = 857	68/852 (8.0) Reference	164/523 (31.4) Reference	209 (24.4) Reference	70 (8.2) Reference
Borderline PHT (eRSVP 30.00-39.99) N = 2634	234/2566 (9.1) OR 1.09 (0.75-1.32)	648/1749 (37.0) OR 1.10 (0.88-1.38)	933 (35.4) HR 1.15 (1.03-1.34)	315 (12.0) HR 0.70 (0.54-0.91)
Mild PHT (eRVSP 40.00-49.99) N = 2704	376/2640 (14.2) OR 1.45 (1.10-1.92)	974/1949 (50.0) OR 1.58 (1.26-1.97)	1355 (50.1) HR 1.54 (1.33-1.78)	506 (18.7) HR 0.76 (0.59-0.98)
Moderate PHT (eRSVP 50.00 - 59.99) N = 1294	268/1245 (21.5) OR 2.19 (1.64-2.93)	623/925 (67.4) OR 2.77 (2.16-3.56)	741 (57.3) HR 1.99 (1.71-2.32)	297 (23.0) HR 1.12 (0.86-1.45)
Severe PHT (eRVSP >60) N = 804	289/791 (36.5) OR 4.51 (3.36-6.06)	508/647 (78.5) OR 5.18 (3.90-6.88)	574 (71.4) HR 2.96 (2.52-3.47)	231 (28.7) HR 1.50 (1.14-1.96)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Table 4.5. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels

	1-Year Actuarial Mortality (n= 9439)	5-Year Actuarial Mortality (n= 6780)	All Fatal Events (n= 9638)	Cardiovascular mortality (n= 9638)
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 9638	1573 (16.7)	3603 (53.1)	4614 (47.9)	1777 (18.4)
Normal eRVSP (<30mmHg) n = 959	79/950 (8.5) Reference	192/581 (33.0) Reference	247 (25.8) Reference	83 (8.7) Reference
Borderline PHT (eRVSP 30.00-39.99) N = 2952	304/2869 (12.0) OR 1.14 (0.87-1.48)	791/1970 (40.2) OR 1.18 (0.95-1.46)	1098 (37.2) HR 1.20 (1.05-1.38)	383 (13.0) HR 0.77 (0.61-0.98)
Mild PHT (eRVSP 40.00-49.99) N = 3167	468/3088 (17.0) OR 1.52 (1.18-1.97)	1179/2280 (51.7) OR 1.60 (1.29-1.97)	1612 (50.9) HR 1.54 (1.35-1.76)	607 (19.2) HR 0.81 (0.65 -1.02)
Moderate PHT (eRSVP 50.00 -59.99) N = 1588	342/1533 (25.8) OR 2.19 (1.67-2.86)	787/1129 (69.7) OR 2.90 (2.29-3.66)	922 (58.1) HR 1.99 (1.73-2.30)	383 (24.1) HR 1.20 (0.95-1.52)
Severe PHT (eRVSP >60) N = 1017	380/999 (39.7) OR 4.36 (3.32-5.72)	654/820 (79.8) OR 4.91 (3.77-6.40)	1068 (72.3) HR 2.75 (2.38-3.19)	321 (31.6) HR 1.62 (1.27-2.06)

Analyses adjusted for age, sex and indexed left atrial volume. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Mortality was assessed when the cohort was divided into 2 cohorts based on severity (moderate MR- 8214 patients, severe MR- 1469 patients). In the moderate MR cohort, which had larger numbers, mortality outcomes mirrored that of the total cohort (**Table 4.6**). Mortality outcomes had a similar trend in those with severe MR, although statistical significance was not reached at milder elevations of eRVSP level, most likely a consequence of the smaller subject numbers (**Table 4.7**).

Table 4.6. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with moderate mitral regurgitation (n=8214)

	1-Year Actuarial Mortality (n= 7999)	**5-Year Actuarial Mortality (n= 5669)**	**All Fatal Events (n= 8214)**	**Cardiovascular mortality (n= 8214)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 8214	1484 (14.8)	2863 (50.5)	3761 (45.8)	1379 (16.8)
Normal eRVSP (<30mmHg) n = 847	58/839 (6.9) Reference	160/519 (30.8) Reference	211 (24.9) Reference	72 (8.5) Reference
Borderline PHT (eRVSP 30.00-39.99) N = 2589	245/2513 (9.7) OR 1.27 (0.94-1.71)	666/1713 (38.9) OR 1.22 (1.03-1.54)	944 (36.5) HR 1.23 (1.06-1.43)	315 (12.2) HR 0.71 (0.55-0.92)
Mild PHT (eRVSP 40.00-49.99) N = 2747	372/2677 (13.9) OR 1.69 (1.28-2.26)	976/1957 (49.9) OR 1.62 (1.30-2.03)	1364 (49.7) HR 1.55 (1.34-1.79)	501 (18.2) HR 0.78 (0.60-0.99)
Moderate PHT (eRSVP 50.00 - 59.99) N = 1299	252/1251 (20.1) OR 2.39 (1.76-3.25)	606/900 (67.3) OR 2.87 (2.23-3.69)	723 (55.7) HR 1.98 (1.69-2.31)	284 (21.9) HR 1.10 (0.85-1.42)
Severe PHT (eRVSP >60) N = 732	257/719 (35.7) OR 5.21 (3.80-7.13)	455/580 (78.4) OR 5.27 (3.94-7.07)	519 (70.9) HR 2.97 (2.53-3.49)	207 (28.3) HR 1.50 (1.14-1.96)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Table 4.7. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels in patients with severe MR (n = 8293)

	1-Year Actuarial Mortality (n= 8094)	5-Year Actuarial Mortality (n= 5793)	All Fatal Events (n= 8293)	Cardiovascular mortality (n= 8293)
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 8293	1235 (15.3)	2917 (50.4)	3812 (46.0)	1419 (17.1)
Normal eRVSP (<30mmHg) n = 857	68/852 (8.0) Reference	164/523 (31.4) Reference	209 (24.4) Reference	70 (8.2) Reference
Borderline PHT (eRSVP 30.00-39.99) N = 2634	234/2566 (9.1) OR 1.09 (0.75-1.32)	648/1749 (37.0) OR 1.10 (0.88-1.38)	933 (35.4) HR 1.15 (1.03-1.34)	315 (12.0) HR 0.70 (0.54-0.91)
Mild PHT (eRVSP 40.00-49.99) N = 2704	376/2640 (14.2) OR 1.45 (1.10-1.92)	974/1949 (50.0) OR 1.58 (1.26-1.97)	1355 (50.1) HR 1.54 (1.33-1.78)	506 (18.7) HR 0.76 (0.59-0.98)
Moderate PHT (eRSVP 50.00 - 59.99) N = 1294	268/1245 (21.5) OR 2.19 (1.64-2.93)	623/925 (67.4) OR 2.77 (2.16-3.56)	741 (57.3) HR 1.99 (1.71-2.32)	297 (23.0) HR 1.12 (0.86-1.45)
Severe PHT (eRVSP >60) N = 804	289/791 (36.5) OR 4.51 (3.36-6.06)	508/647 (78.5) OR 5.18 (3.90-6.88)	574 (71.4) HR 2.96 (2.52-3.47)	231 (28.7) HR 1.50 (1.14-1.96)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Mortality outcomes amongst females (n=6038) matched those in the total cohort (HR1.32, 95%CI 1.10-1.58 for borderline PHT vs. HR2.92, 95%CI 2.42-3.53 for severe PHT) (**Table 4.8**). The male cohort (n=3645) had similar trends, though significance was only reached when pulmonary pressures were mildly elevated (**Table 4.9**).

Table 4.8. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels for females (n = 6038)

	1-Year Actuarial Mortality (n= 5887)	**5-Year Actuarial Mortality (n= 4186)**	**All Fatal Events (n= 6038)**	**Cardiovascular mortality (n= 6038)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 9638	928 (15.8)	2158 (51.6)	2822 (46.7)	1153 (19.1)
Normal eRVSP (<30mmHg) n = 611	46/606 (7.6) Reference	113/365 (31.0) Reference	144 (23.6) Reference	60 (9.8) Reference
Borderline PHT (eRVSP 30.00-39.99) N = 1773	167/1720 (9.7) OR 1.12 (0.79-1.58)	469/1169 (40.1) OR 1.26 (0.96-1.67)	653 (36.8) HR 1.32 (1.10-1.58)	248 (14.0) HR 0.67 (0.51-0.89)
Mild PHT (eRVSP 40.00-49.99) N = 1992	278/1950 (14.3) OR 1.51 (1.09-2.11)	698/1439 (48.5) OR 1.46 (1.12-1.91)	996 (50.0) HR 1.53 (1.29-1.83)	391 (19.6) HR 0.64 (0.49-0.84)
Moderate PHT (eRSVP 50.00 -59.99) N = 1011	205/973 (21.1) OR 2.24 (1.59-3.16)	476/695 (68.5) OR 2.91 (2.20-3.98)	567 (56.1) HR 2.03 (1.69-2.44)	246 (24.3) HR 0.94 (0.71-1.25)
Severe PHT (eRVSP >60) N = 651	232/638 (36.4) OR 4.65 (3.28-5.59)	402/518 (77.6) OR 4.77 (3.43-6.62)	462 (71.0) HR 2.92 (2.42-3.53)	208 (32.0) HR 1.23 (0.92-1.64)

Analyses adjusted for age. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Table 4.9. Survival Profile and Adjusted Risk for Mortality According to Estimated Right Ventricular Systolic Pressure Levels for males (n = 3645)

	1-Year Actuarial Mortality (n= 3552)	5-Year Actuarial Mortality (n= 2594)	All Fatal Events (n= 3645)	Cardiovascular mortality (n= 3645)
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 9638	645 (18.5)	1445 (55.7)	1792 (49.2)	624 (17.1)
Normal eRVSP (<30mmHg) n = 348	33/344 (9.6) Reference	79/216 (36.6) Reference	144 (23.6) Reference	60 (9.8) Reference
Borderline PHT (eRVSP 30.00-39.99) N = 1179	137/1149 (11.9) OR 1.16 (0.77-1.74)	322/801 (40.2) OR 1.06 (0.76-1.49)	653 (36.8) HR 1.06 (0.85-1.31)	248 (14.0) HR 1.00 (0.64-1.55)
Mild PHT (eRVSP 40.00-49.99) N = 1175	190/1138 (16.7) OR 1.52 (1.02-2.27)	481/841 (57.2) OR 1.82 (1.31-2.55)	996 (50.0) HR 1.54 (1.25-1.90)	391 (19.6) HR 1.23 (0.80-1.90)
Moderate PHT (eRSVP 50.00 -59.99) N = 577	137/560 (24.5) OR 2.20 (1.45-3.33)	311/434 (71.7) OR 2.87 (1.97-4.17)	567 (56.1) HR 1.95 (1.56-2.43)	246 (24.3) HR 1.90 (1.22-2.96)
Severe PHT (eRVSP >60) N = 366	1488/361 (41.0) OR 4.63 (3.03-7.07)	252/302 (83.4) OR 6.06 (3.90-9.41)	462 (71.0) HR 2.79 (2.21-3.50)	208 (32.0) HR 2.72 (1.74-4.28)

Analyses adjusted for age. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension.

Threshold for mortality

A Cox regression model was constructed using the decile distribution of eRVSP and adjusted for age and sex. This confirmed that the adverse effects of PHT were noted from the 3rd decile (eRVSP 34.01-37.04mmHg) relative to the lowest decile <30.00mmHg (HR1.16, CI1.00-1.36, p=0.05). Risk increased progressively from those with borderline PHT in the 3rd decile through to the 10th decile (eRVSP 60.01 – 143.63; HR2.89, CI2.51-3.32, p <0.0001) (**Table 4.10**). Hence, the adjusted risk for mortality is markedly higher in those with borderline PHT and above regardless of age, gender or cause of death.

Table 4.10. Adjusted Risk for Mortality according to decile distribution of Estimated Right Ventricular Systolic Pressure Levels

eRSVP decile distribution (mmHg)	All Fatal Events (n= 9638) HR (95% CI), p value
0.00-30.00	Reference
30.01-34.00	1.14 (0.97 – 1.34), p = 0.11
34.01-37.04	1.16 (1.00 – 1.36), p = 0.05
37.05-39.16	1.27 (1.08 – 1.48), p= 0.003
39.17-43.00	1.48 (1.29 – 1.72), p <0.0001
43.01-46.00	1.50 (1.30 – 1.72), p <0.0001
46.01-48.44	1.59 (1.36 – 1.85), p <0.0001
48.45-53.00	1.98 (1.71 – 2.29), p <0.0001
53.01-61.00	2.04 (1.76 – 2.35), p <0.0001
61.01-143.63	2.89 (2.51 – 3.32), p <0.0001

Analyses adjusted for age and sex. eRVSP = estimated right ventricular systolic pressure; HR = hazard ratio; CI = confidence interval.

Discussion

This large, "real-world" cohort study, including over 9500 patients examines the relationship between MR and PHT, in patients with preserved ejection fraction. The use of 'big data' through the NEDA, which includes over 1 million echoes in over 600 000 individuals, allowed for a more detailed, contemporary description of the prevalence and phenotype of these patients. We confirmed the negative short- and long-term prognostic impact PHT has in MR and have documented that the threshold for excess mortality lies within the range of 'borderline PHT'.

PHT is likely to occur in patients with significant MR via the following mechanism; in the initial phase the direct effect of systolic backflow into the LA and subsequent volume overload leads to compensatory LA and LV dilation[51]. Overtime, there is decompensation leading to both LV systolic and diastolic dysfunction and reduced LA compliance. This causes elevated LA pressure and increases pulmonary capillary wedge pressure (PCWP)[125] causing post-capillary PHT. This may develop before patients experience symptoms or LV dysfunction.[2, 50]

Prevalence and Phenotype of PHT with MR

The prevalence of PHT complicating significant MR remains unclear with the rate thought to be tied to the grade of MR[51]. Prevalence increases with the presence of symptoms and LV systolic dysfunction, with rates as high as 64%[52] reported in those with NYHA function class III and IV, symptoms compared to < 20% in asymptomatic patients with severe MR and preserved EF[129]. Significant PHT (eRVSP >50mmHg) was reported in 23% in a contemporary cohort of patients with severe degenerative MR[53]. In our large, contemporary cohort of hospital and community based echo patients, we confirm the high prevalence of PHT in patients with significant MR and preserved LVEF; 59.6% of patients had some degree of PHT as defined by clinical guidelines (mild- 32.7%, moderate- 16.4%, severe- 10.5%). Patients with "borderline PHT" (eRVSP 30-39mmHg) represented 30.5% of the cohort.

Prior studies have shown that increased age[53], female sex[131], increase E:e'[130], and larger LA size[53, 130, 131] are all independent predictors of raised pulmonary pressures in patients with significant MR. We confirmed this echocardiographic phenotype in our cohort and report progressively higher proportions of RV dilation and dysfunction as PHT worsens. Whilst there is a close relationship between PHT and both mitral stenosis[1] and LV systolic dysfunction[51], the prospective exclusion of these patients from our cohort allows a greater understanding of the impact of PHT *per se* in patients with MR with preserved ejection fraction. A comprehensive understanding of this echocardiographic phenotype is important as it provides clinicians with an easily accessible, non-invasive method to monitor specific parameters associated with worsening PHT and thus prognosticate these patients more accurately.

Outcomes of PHT in MR patients

The presence of PHT negatively impacts on outcome with previous studies reporting increased post-operative heart failure[52], worse LV systolic dysfunction[132, 133] and poorer survival[53, 54] in patients with pre-operative PHT compared with those without. Our much larger study confirms the serious impact of PHT on patients with significant MR, even in the absence of LV systolic dysfunction, with the 59.6% of patients with eRVSP>40.00mmHg having a 1.20-2.86-fold adjusted increased risk of long-term all-cause mortality (dependent on PHT severity) compared with those with no PHT. Similar to our previous studies[12, 122] we find that even "borderline" PHT (eRVSP30.00-

39.99mmHg) confers an increased risk of all-cause mortality compared to those with normal eRVSP. This was evident in the short term, with 1-year actuarial mortality increasing 1.14 fold, and, in the long-term, with all-cause mortality risk increasing 1.20 fold. Furthermore, the large numbers provided by the NEDA allowed us to identify an inflection point for excess mortality risk, at eRVSP>34.00mmHg. These results were independent of age and gender and did not appear to be confounded by the presence of concomitant valvular pathology including ≥moderate AR or severe AS.

Clinical Implications

Current clinical guidelines include the presence of significant PHT (eRSVP>50mmHg, confirmed on right heart catheterisation) as an indication for operative management in asymptomatic patients with severe MR[74]. Prior studies have shown that "early" MV repair in asymptomatic patients with severe MR and normal LVEF leads to improvements in long-term mortality and HF hospitalisation[134]. Furthermore, whilst there is a decrease in pulmonary pressures post intervention, a significant degree of PHT remains despite amelioration of the valvular pathology[52, 54]. Whilst we do not report on treatment effect, we demonstrate that even minor elevations in pulmonary pressures are associated with negative prognostic implications. With no specific medical therapy approved for PHT in the setting of MR, further studies will be needed to determine whether early mitral valve intervention might improve outcomes in those MR patients with early stages of PHT or perhaps even before it develops[125].

Limitations

NEDA provides detailed echocardiographic data and linkage to mortality, NEDA does not (yet) provide granular clinical data such as symptoms, co-morbidities or pharmacological treatments. Most patients included the database have undergone an echocardiogram for investigation of confirmed or suspected cardiac disease and should not be taken to reflect the population prevalence.

As noted in our previous studies[12], the data concerning PHT in NEDA is based on echocardiography-based measures, rather than haemodynamic assessment at right heart catheterisation. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107, 108], supporting the broad validity of our approach. Furthermore, echocardiography remains the commonest screening tool to detect PHT and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow up. We acknowledge that the definitive diagnosis of PHT, and its underlying etiology (pre- vs post-capillary vs combined) should generally be confirmed on right heart catheterisation, after initial screening is suggestive of PHT. We also note that the absence of a tricuspid regurgitation jet does not preclude the presence of PHT and there may be a number of patients with MR and PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR. Hence both the

prevalence and prognostic impacts reported in this cohort should be interpreted as the minimum indicative values, from an epidemiological standpoint.

These studies were primarily derived from specialist centres or clinics across Australia, so some caution should be applied when applying these findings to other populations. However, Australia is a diverse and multi-ethnic population with universal health coverage, aspects captured within the NEDA database. Finally, our data is lacking in quantitative measures of MR or RV dysfunction, a reflection of real-world echocardiographic practices in Australia. We were also unable to ascertain the underlying etiology of the MR so could not definitively differentiate between the primary versus secondary MR. However, patients with reduced LVEF were prospectively excluded, thus, our cohort likely represents a combination of patients with primary MR and atrial functional MR.

Conclusion

This is the largest series of adults to characterise the close, but incompletely understood, relationship between significant MR and complicating PHT. In patients with ≥ moderate MR and preserved LV systolic function, mortality increases progressively as PHT becomes more severe from an eRSVP 34mmHg onwards.

Chapter 5 – Association of Pulmonary Artery Pressures with Mortality in Adults with Reduced Left Ventricular Ejection Fraction

This chapter is based on the publication: Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Association of Pulmonary Artery Pressures with Mortality in Adults with Reduced Left Ventricular Ejection Fraction. JACC Heart Fail. 2024 May;12(5):936-945. doi: 10.1016/j.jchf.2024.01.016.

Abstract

Objective: The independent effect of pulmonary hypertension (PHT) severity on mortality in those with reduced left ventricular ejection fraction (LVEF) is not well known. We aimed to examine the prognostic impact of increasingly elevated pulmonary pressures, in a large clinical cohort of adults with reduced LVEF.

Methods: We analysed data from the National Echocardiography Database of Australia, a large clinical registry linking routine echocardiographic investigations to mortality. In 23675 adults with a recorded tricuspid regurgitation peak velocity (TRV) and reduced LVEF (<50%), we evaluated the relationship between conventional thresholds of increasing risk of PHT and mortality during median follow-up of 2.9 (IQR 1.0-5.4) years.

Results: Mean age was 70±15years and 7498 (31.7%) individuals were female. Overall, 8801 (37.2%) had normal (TRV<2.5m/s), 7061 (29.8%) had borderline (2.5-2.8m/s), 5676 (24.0%) intermediate (2.9-3.4m/s), and 2137 (9.0%) individuals had high-risk PHT (>3.4m/s). With increasing risk of PHT, 1- and 5-year actuarial mortality increased from 13.3% and 43.8%, to 41.5% and 81.4% respectively (p<0.0001) from normal to severely elevated TRV. The adjusted hazard risk of mortality increased by 1.31-fold (95% confidence interval 1.23-1.38), 1.82-fold (95%CI 1.72-1.93) and 2.38-fold (95%CI 2.21-2.56) in those with borderline, intermediate and high-risk of PHT respectively, compared to normal TRV. Further analyses suggested a distinctive threshold with a TRV reached >2.41m/s (adjusted HR 1.18, 95%CI 1.04-1.33).

Conclusion: We demonstrate the prevalence and negative prognostic impact of increasingly elevated TRV levels in individuals with reduced LVEF, with a threshold for mortality lying within the range of 'borderline risk' PHT.

Introduction

Reduced left ventricular ejection fraction (LVEF) is defined as <50%, in recent guidelines[135, 136]. The presence of reduced LVEF, with or without a clinical syndrome of heart failure, has been linked to poorer outcomes[137, 138]. As such, reliable risk stratification is important[137]. PHT with reduced LVEF is an important cause of PHT due to LHD, classified as Group 2 PHT. This is the most common type of PHT, representing 65-80% of reported PHT cases[2, 17, 37]. PHT in subjects with reduced LVEF is thought to be secondary to a combination of cellular and phenotypic changes in the LV that lead to increased LV filling pressure, raised LA pressure and, like with other types of PHT-LHD, a backwards transmission of this increased pressure to the pulmonary vasculature[17, 60].

Whilst the definitive diagnosis of PHT is made on right heart catheterisation, use of the TRV on transthoracic echocardiography remains the pragmatic investigation of choice, recommended in current guidelines, to determine the risk of underlying PHT[1]. A TRV of >2.8m/s is considered 'intermediate risk' of PHT and is the current guideline-recommended threshold for considering further confirmatory investigations. Despite this, there is growing evidence that mortality risk increases even in those with 'borderline' elevations in TRV[12, 13, 104, 122]. These data suggest the potential value of more proactive investigation and management of individuals with mildly elevated TRV levels.

Despite being the most common cause of PHT, patients with LHD and PHT remain incompletely characterised[2]. Chapter's 2, 3 and 4 show that in subjects with left-sided valvular pathology (such as aortic stenosis or regurgitation), the risk of mortality increases from in patients with even mild levels of echo derived PHT. The relationship between reduced LVEF and PHT risk has not been well established in large clinical cohorts, nor has the relationship been examined in those with a mildly impaired LVEF. The influence of PHT in low LVEF patients has been examined before, but only in relatively small community-based cohorts (the largest of which reported on only 1079 subjects)[23, 139] or in certain select patient groups, such as those with advanced heart failure[60, 140].

Thus, utilising the data from the large National Echo Database of Australia (NEDA) we aimed to (i) document the "point" prevalence and severity of PHT, as assessed at each patient's last echo in the NEDA database, and, (ii) to establish whether there is a graded association between increasing TRV levels and mortality outcomes, in those with reduced LVEF. Beyond examining this association according to conventional categories of elevated TRV/PHT risk, we also examined the risk of mortality on a more granular basis (that is, according to the decile distribution of individual units of TRV) to more definitively elucidate whether a threshold for excess mortality could be identified.

Methods

NEDA database and study design

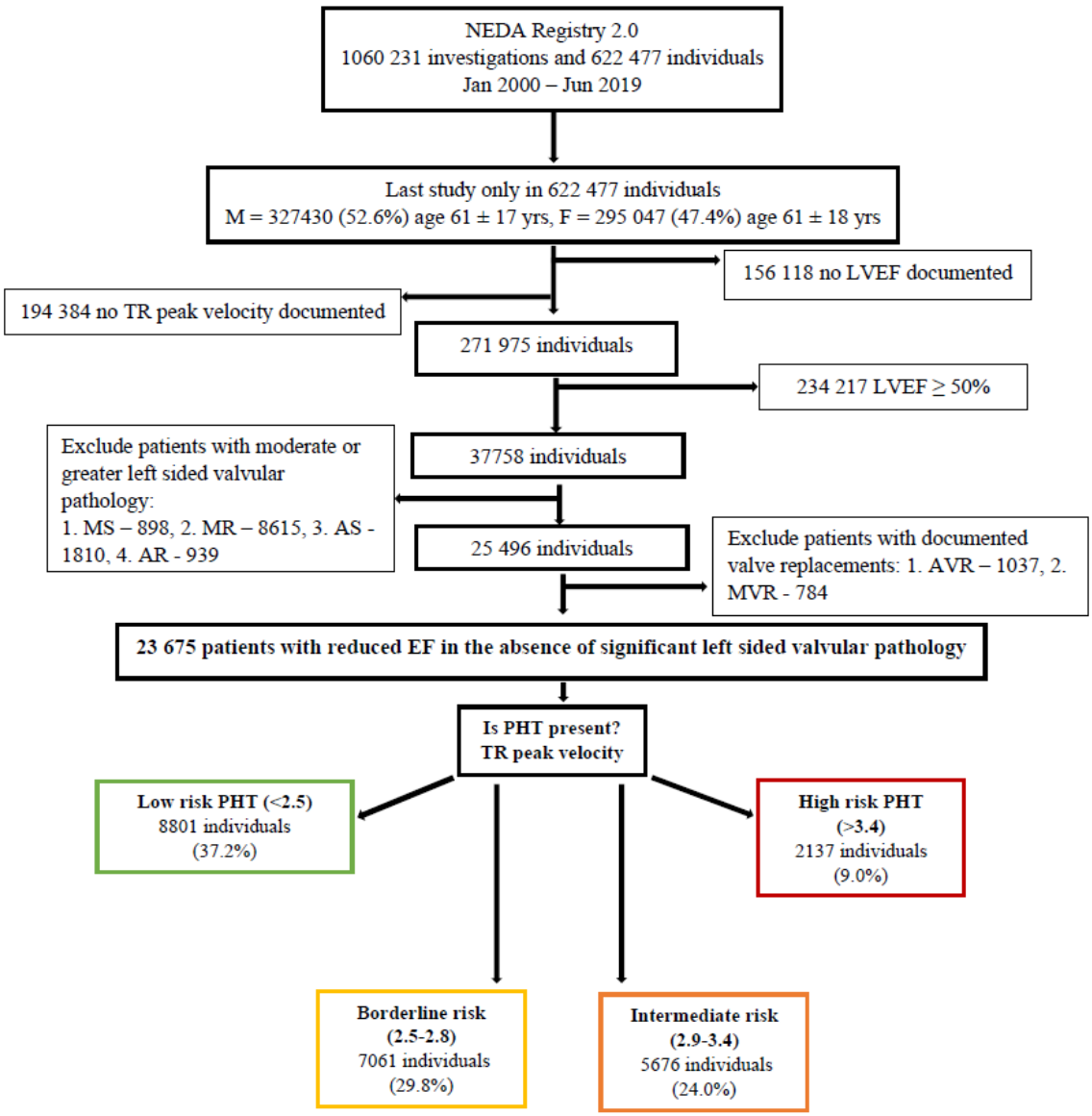
The NEDA is multi-centre echocardiography registry which provides basic demographic and detailed echocardiographic data from >25 centres across Australia. The methodology has been described previously[12, 99]. The database is linked to the NDI, to obtain mortality data for each individual. Cause of death (including cardiovascular (CV) mortality) was determined from death certificates which use standardised coding across Australia. At the time of analysis, the registry contained >1million echo reports from >600 000 subjects from January 2000 to June 2019. Vital status was determined as of 21st May 2019, subjects alive at this date were censored as alive. Median follow up was 6.2 years, interquartile range (IQR) 3.8-9.8years. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and 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 authorized.

Study Population

Previous NEDA publications have established the prognostic importance of reduced LVEF[137, 138]. Also using echo data, other recent publications have demonstrated that even mild forms of PHT are prognostically important, in terms of mortality[12, 122]. Thus, data at study census was used to identify subjects with reduced LVEF and thence to characterize the prevalence and prognostic impact of PHT risk (as determined by TRV). **Figure 5.1** shows our study flow diagram; to be included in the analysis, subjects were: 1) adults ≥ 18 years of age, 2) with at least one echocardiogram recorded (where subjects had multiple studies only the last study was analysed), 3) with a recorded LVEF and TRV. LVEF values had to be quantified (ranges and text descriptors not accepted), and consistent with guidelines[137],a hierarchical preference for Simpson's Biplane-Derived LVEF over 2D Teicholz and other quantification methods were applied[137]. Subjects with LVEF >50% were excluded to allow focus on the influence of raised pulmonary pressures *per se*, on outcomes in a cohort of adults with reduced LVEF. Subjects with documented mitral and aortic valve replacements were excluded, as were subjects with moderate or greater left-sided valvular pathology (mitral stenosis (MS), MR, AS and AR)). The effects of PHT in these subjects with significant left sided valve disease and preserved ejection fraction, in NEDA, have recently been reported in Chapters 2-4 of this thesis.

As per recent guidelines, TRV was the key echocardiographic parameter used to determine the echocardiographically assessed probability of PHT[1]. RV size and function were described qualitatively, using text extraction from echo reports.

Figure 5.1. Study Flow Chart



This Figure shows the Analysis flowchart, performed in this study.

NEDA = National Echo Database Australia; left ventricular ejection fraction (LVEF); TRV = tricuspid regurgitant volume; AS = aortic stenosis; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation; AVR = aortic valve replacement; MVR = mitral valve replacement; PHT = pulmonary hypertension.

PHT categorisation and mortality assessment

Once a cohort of subjects with reduced LVEF was established, subjects were categorised according to their TRV, according to the recent 2022 clinical guidelines on PHT[1]. We documented the distribution of TRV and thence the risk of PHT, using the TRV as a surrogate to estimate pulmonary artery pressures. A 'borderline risk' was derived as this group has been shown to be significant by both our group (in the previous chapters) and others[12, 13, 104]. Defined categories were: 1) low risk PHT (<2.5m/s), 2) borderline risk PHT (2.5–2.8 m/s), 3) intermediate risk PHT (2.9-3.4m/s) and high risk PHT (>3.4m/s).

All-cause mortality was determined over a median follow up of 2.9 years (IQR 1.0-5.4 years). We explored all-cause mortality occurring at fixed time-points of 1 and 5 years. Consistent with earlier NEDA publications, both all-case and CV mortality were assessed in a time-to-event survival analysis according to the four clinically defined TRV groups (as above)[12, 100]. We then divided the cohort into TRV deciles to perform a more granular analyses of the association of TRV and all-cause mortality (as we have previously done in other informative analyses from NEDA[12, 100].

The NEDA group has previously established sex-based differences in prevalence and prognosis with regards to LVEF[137]; thus, we performed a pre-specified analysis based on sex, to determine whether sex-based differences in prevalence in PHT risk and mortality outcomes were present.

Finally, given the prognostic importance of LV dysfunction[137, 138], we then performed a sensitivity analysis and separated the cohort based on the severity of their left ventricular systolic dysfunction, according to recent guidelines[135, 136] (mildly reduced EF or more than mildly reduced EF), to determine if there were differences between these two groups. Mildly reduced LVEF (n = 12 495) was defined as LVEF 40.00-49.99%. Reduced LVEF (n = 11 180) was defined as LVEF <40%[135, 136].

Statistical Analyses

All categorical data are expressed as frequency and percentages, unless otherwise stated, and continuous variables are expressed as mean ± standard deviation (SD). Chi-squared 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 ANOVA analysis was used to test whether the trend of the mean across the categorical groups of TRV levels was linear.

Actuarial 1-year and 5-year survival rates for all-cause mortality were calculated for all-cause mortality from the 22,686 (95.8%) and 16,277 (68.4%) subjects with complete follow up for those time points. Multiple logistic regression was performed using entry models with variables determined by an 'a

priori' approach which also met a pre-specified entry point (univariate p value <0.05) to derive adjusted ORs for mortality at these fixed time points. Cox regression models were used to derive adjusted hazard ratios (HR) for mortality outcomes during follow up, which was considered time from last echo to census date or death (entry model, using univariate p-value <0.05). Proportional hazards were confirmed by visual inspection of the log-to-log survival curves. Adjusted analyses for both logistic and cox regression models included age, sex, LVEF, left ventricular end diastolic diameter (LVEDD), and, left atrial volume indexed (LAVi). These variables were specified a priori, based on previous publications and variables which are known to be clinically likely to influence survival in patients with reduced LVEF[103, 141]. To assess the relative contribution of age at echo on outcomes between different TRV-groups, the interaction between age and TRV-groups was tested on Cox-regression models for all-cause mortality; if this interaction was significant, this interaction term was included in the model.

Similar to our earlier analyses in prior chapters we then examined the pattern of mortality according to the decile distribution of TRV[12, 100] in order to perform a more granular analysis to identify a threshold for mortality. The decile distribution was: 1st decile- 0.00-2.10m/s, 2nd- 2.11-2.28m/s, 3rd- 2.29-2.40m/s, 4th- 2.41-2.51m/s, 5th- 2.52-2.64m/s, 6th- 2.65-2.78m/s, 7th- 2.79-2.91m/s, 8th- 2.92-3.10m/s, 9th- 3.11-3.39m/s and 10th- >3.40m/s.

Our sex-based analyses were performed for the clinically defined groups of TRV specified above, and the quintile distribution for each cohort. The quintile distribution for the male cohort (n = 16 177) was: 1st- 0.00-2.28m/s, 2nd- 2.29-2.51m/s, 3rd- 2.52-2.78m/s, 4th- 2.79-3.10m/s, 5th- 3.11-6.00m/s. The quintile distribution for the female cohort (n = 7498) was: 1st- 0.00-2.29m/s, 2nd- 2.30-2.52m/s, 3rd- 2.53-2.78m/s, 4th- 2.79-3.10m/s and 5th- 3.11-5.71m/s.

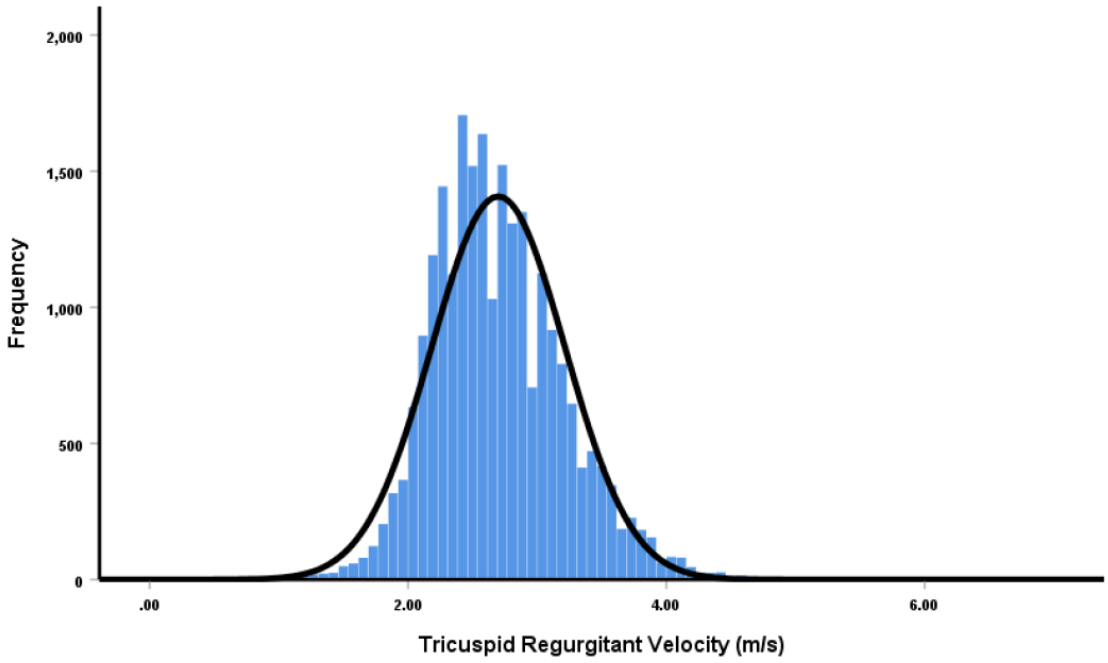
All analyses were performed with SPSS software v25.0 (IBM Corp), and statistical significance was inferred at a two-tailed p-value of <0.05.

Results

Prevalence of PHT and Distribution of TRV

A total of 23,675 subjects with reduced LVEF and TRV data, without significant left-sided valvular pathology were identified (**Figure 5.1**), with 7498/23,675 (31.7%) being female. **Figure 5.2** shows the frequency distribution of TRV levels (median 2.70m/s, IQR 2.34-3.00m/s). The number of subjects in each sub-group were: low risk PHT (TRV<2.5m/s)- 8801 individuals (37.2%), borderline risk (2.5-2.8m/s)- 7061 individuals (29.8%), intermediate risk (2.9-3.4m/s)- 5676 individuals (24.0%), high risk (>3.4m/s)- 2137 individuals (9.0%).

Figure 5.2. Frequency Distribution of Tricuspid Regurgitant Velocity within the Cohort



These data show the statistical distribution of tricuspid regurgitant velocity (TRV) levels.

Subject profiles and Prevalence of PHT

Table 5.1 summarises the demographic and echocardiographic characteristics of the cohort divided into subgroups based on TRV levels. Age was greater in those with higher TRV, from a mean of 65±16 years in those with low risk PHT, to a plateau of 74±14 years in the intermediate and high-risk groups.

A typical echocardiographic, phenotypic response to increasing PHT risk was noted. LVEF was lower in those with higher TRV, from a mean of 39.4% ± 8.9% in those with low risk PHT, to a mean of 34.6% ± 10.2% in those with high risk PHT. E:e', Mitral E velocity and Mitral E/A ratio all increased progressively with higher TRV ($p<0.0001$, for all). There was a progressive increase in indexed LA volume and right atrial (RA) area from low risk PHT to intermediate risk PHT (39.8±17.1mL/m2 to 62.6±35.3mL/m2 and, 19.7±7.1cm2 to 27.4±8.9cm2, respectively, $p<0.0001$ for all), with a plateau noted in those with high risk PHT (60.1±31.5mL/m2, and 26.9±8.7cm2 respectively). The proportion of subjects with RV impairment and dilation also increased from 6% (532/8801) and 11.2% (2161/8801) respectively in those with low risk PHT, to, 17.3% (369/2137) and 32.1% (686/2137) in those with high risk PHT ($p<0.0001$, for all).

Table 5.1. Baseline Characteristics of Study Cohort (n = 23 675)

	Low risk PHT Peak TR velocity <2.5 m/s n = 8801	**Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 7061**	**Intermediate risk PHT Peak TR velocity 2.9 – 3.4 m/s n = 5676**	**High risk PHT Peak TR velocity >3.4m/s n = 2137**	**P value**
Demographics					
Age, years	65±16	71±14	74±13	74±14	<0.0001
Female (%)	2758 (31.3)	2257 (32.0)	1837 (32.4)	646 (30.2)	0.80
Anthropometrics					
BMI	27.55±5.94	27.83±6.34	27.41 ± 6.34	26.86±6.32	<0.0001
BSA	1.95 ± 0.26	1.93 ± 0.27	1.91 ±0.28	1.88 ±0.27	<0.0001
LV dimensions and functions					
LVEF %	39.36 ± 8.93	37.58 ± 9.64	35.85 ± 9.91	34.60±10.15	<0.0001
E/E' ratio	11.60 ± 5.39	14.12 ± 6.40	16.70 ± 7.30	20.10 ± 9.42	<0.0001
LVEDD	5.17 ±0.84	5.33 ±0.91	5.43 ± 0.92	5.42 ± 0.94	<0.0001
LVESD	4.05 ± 0.87	4.23 ± 0.97	4.36 ± 0.98	4.39 ± 1.01	<0.0001
Stroke volume Index (ml/m^2)	35.02 ± 10.84	34.59 ± 11.23	32.65 ± 11.24	31.78 ± 10.92	<0.0001
Mitral E velocity	70.11 ± 23.40	80.32 ± 26.26	91.43 ± 27.19	98.05 ± 29.04	<0.0001
Mitral A velocity	70.22 ± 24.00	73.02 ± 27.41	69.93 ± 30.82	64.23±30.08	<0.0001
Mitral E/A ratio	1.06 ± 0.71	1.24 ± 1.09	1.61 ± 1.35	1.83 ± 1.13	<0.0001
Atrial dimensions					
LA volume index, mL/m^2	39.75 ± 17.08	51.97 ± 27.15	62.58 ±35.31	60.14±31.45	<0.0001
RA area, cm^2	19.70 ± 7.12	24.15 ± 8.02	27.42 ±8.89	26.85±8.71	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	28.77±4.81	38.22±3.99	48.75± 5.04	66.57±10.24	<0.0001
TR peak velocity, m/s	2.20±0.24	2.67±0.11	3.11 ±0.15	3.73±0.30	<0.0001
Impaired RV function*	532 (6.0)	531 (7.5)	759 (13.4)	369 (17.3)	<0.0001

Dilated RV*	2161 (11.2)	1177 (16.7)	1509 (26.6)	686 (32.1)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

The differences between males and females are shown in **Table 5.2**. There were no clinically meaningful differences in age, TRV, or LVEF between sexes. Females had higher E:e' but lower right atrial area and indexed LA volume, compared to males. Males had a higher proportion of RV impairment (10.1% vs, 7.1%) and RV dilation (20.8% vs, 13.2%) compared with females.

Table 5.2. Baseline Characteristics stratified by sex.

	Male **n = 16,177**	**Female** **N = 7498**	**P value**
Demographics			
Age, years	70 ± 15	70 ± 16	0.03
Female (%)	0	7498	
Anthropometrics			
BMI	27.59±5.72	27.42 ± 7.15	0.10
BSA	2.00±0.24	1.76 ± 0.25	<0.0001
LV dimensions and functions			
LVEF %	37.15±9.75	38.44±9.33	<0.0001
E/E' ratio	13.82±6.87	15.16±7.42	<0.0001
LVEDD	5.48±0.87	4.92±0.84	<0.0001
LVESD	4.38±0.94	3.85±0.87	<0.0001
Stroke volume Index (ml/m^2)	34.60±11.21	33.28±10.75	<0.0001
Mitral E velocity	78.71±26.75	83.67±28.54	<0.0001
Mitral A velocity	66.93±25.94	77.72±28.06	<0.0001
Mitral E/A ratio	1.34±1.06	1.20±1.04	<0.0001
Atrial dimensions			
LA volume index, mL/m^2	52.69±30.01	48.92±26.00	<0.0001
RA area, cm^2	24.84±8.72	20.52±7.45	<0.0001

Right heart dimensions and function			
eRSVP, mmHg	39.81±12.63	39.76±12.54	0.75
TR peak velocity, m/s	2.69±0.52	2.69±0.51	0.98
Impaired RV function	1637 (10.1)	554 (7.3)	0.001
Dilated RV	3369 (20.8)	987 (13.2)	<0.0001

Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle.

Survival Data

Total population

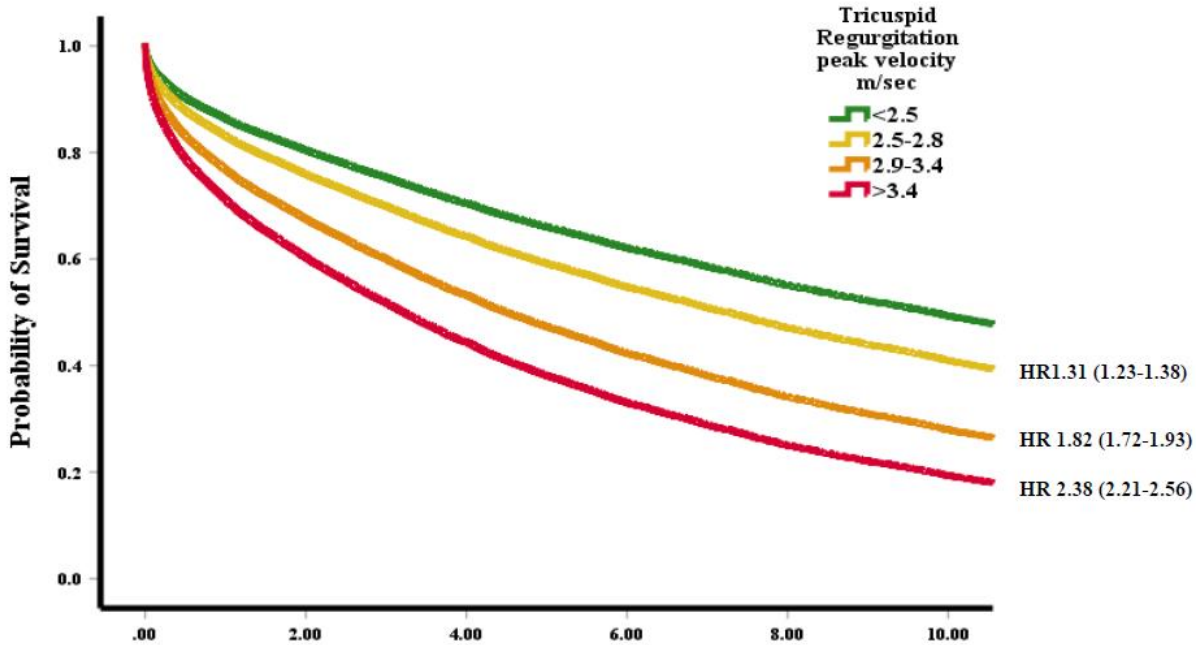
The survival profile of the cohort based on the severity of PHT risk as determined by TRV on echocardiography is summarised in **Table 5.3**. All-cause mortality at 1 and 5 years (actuarial mortality) and long-term survival (adjusted for age, sex, LVEF, LVEDD, and LAVi) were reported between those with TRV <2.5m/s and the 3 categories of progressively elevated TRV. As predicted, the risk for mortality markedly increased with higher TRV levels. This was shown by the range in 1- and 5-year actuarial mortality from a low of 13.3% and 43.3%, to a high of 41.5% and 81.4%, in those with normal to severely elevated TRV. This trend was mirrored in adjusted long-term mortality results which showed a 1.31-fold increase in risk in those with borderline risk of PHT compared to a 2.38-fold increase in those with high risk of PHT ($p<0.0001$ for all) (**Figure 5.3**). Addition of an interaction term showed that there was no significant effect modification by sex ($p=0.08$). Adjusted CV mortality also showed similar progressive, increased risk as TRV increased, with a 1.18-fold increased risk in borderline, compared to a 2.06-fold increased risk in those with high-risk PHT (**Table 5.3**).

Table 5.3. Survival Profile and Adjusted Risk for Mortality According to peak Tricuspid Regurgitant Velocity Levels (n = 23,765)

	1-Year Mortality (n= 22,686) 95.8%	**5-Year Mortality (n= 16,197) 68.4%**	**All Fatal Events (n= 23 675)**	**Cardiovascular mortality (n= 23 675)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 23 675	5103 (22.5)	9641 (59.5)	11079 (46.8)	4659 (19.7)
Low risk PHT Peak TR velocity <2.5 m/s n = 8801	1116/8362 (13.3) Reference	2310/5277 (43.8) Reference	2759 (31.3) Reference	1049 (11.9) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 7601	1387/6769 (20.5) OR 1.38 (1.25-1.52)	2751/4849 (56.7) OR 1.38 (1.25-1.52)	3262 (46.2) HR1.31 (1.23-1.38)	1358 (17.9) HR 1.06 (0.97-1.16)
Intermediate risk PHT Peak TR velocity 2.9 – 3.4 m/s n = 5676	1737/5474 (31.7) OR 2.39 (2.15-2.66)	3146/4310 (73.0) OR 2.23 (2.01-2.46)	3522 (62.1) HR 1.82 (1.72-1.93)	1529 (26.9) HR 1.21 (1.11-1.33)
High risk PHT Peak TR velocity >3.4m/s n = 2137	863/2081 (41.5) OR 4.03 (3.43-4.74)	1434/1761 (81.4) OR 3.27 (2.88-3.71)	1536 (71.9) HR 2.38 (2.21-2.56)	723 (33.8) HR 1.52 (1.37 -1.70)

Cox Regression Analyses for total cohort adjusted for age, sex, LVEF, LVEDD, LAVi. Values are n (%) or n/M (%), unless otherwise indicated. TR = tricuspid regurgitant; HR = hazard ratio; OR = odds ration; CI = confidence interval; PHT = pulmonary hypertension.

Figure 5.3. Adjusted Risk for All-Cause Mortality

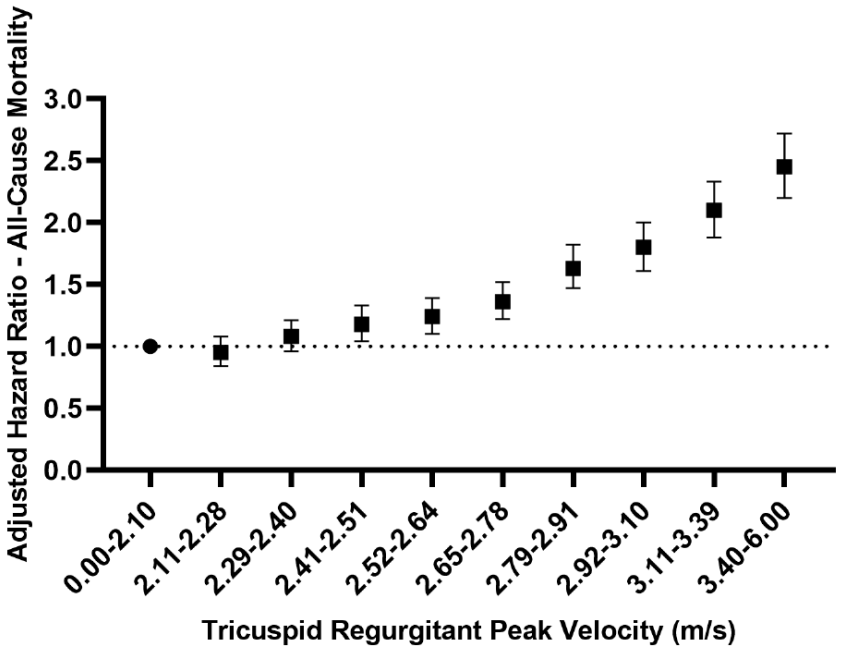


<2.5	6859	4079	2429	1336	689	245
2.5-2.8	5873	3129	1787	1012	541	202
2.9	4704	2084	1105	583	298	106
>3.4	1799	604	296	147	75	31

Adjusted risk for all-cause mortality using Cox proportional hazards, shown by TRV level increases. Adjusted for: female versus male HR0.84 (CI 0.80 – 0.88), age per year HR1.05 (CI 1.04 -1.06), LVEF % HR0.97 (0.96-0.98), LAVi ml/m^2 HR0.89 (0.85-0.92), LVDD, cm HR 0.96 (0.93-0.98).

The regression model for the decile distribution of TRV, adjusted for age, sex, LVEF, LVEDD and LAVi, showed a threshold of increased risk from the 4th decile- (TRV 2.41-2.51m/s; aHR1.18, 95%CI 1.04-1.33) and became progressively higher through to the 10th decile (TRV 3.40-6.00m/s; aHR2.45, 95%CI 2.20-2.72) (**Figure 5.4**). Hence, the adjusted risk for mortality is markedly higher in those with borderline risk PHT and above, independent of age, sex, LVEF or markers of diastolic dysfunction.

Figure 5.4. Threshold for Mortality according to decile distribution of Tricuspid Regurgitant Velocity



The decile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.41-2.51m/s.

Sex based analysis

There were statistically significantly more males than females (n=16,177, vs n=7498), with survival data shown in **Tables 5.4 and 5.5** respectively. Short term mortality, assessed via 1-year actuarial mortality, mirrored that of the total cohort from a low of 13.8% and 12.4% in those with low risk PHT, to a high of 42.0% and 40.3%, in those with high risk PHT in the male vs. female cohort respectively. Likewise, long-term, all-cause mortality showed a progressive risk in mortality as TRV increased (aHR1.28, 95%CI 1.20-1.37 vs aHR2.34, 95%CI 2.14-2.55, and, aHR1.36, 95%CI 1.22-1.51 vs aHR2.49, 95CI 2.18-2.84, low risk vs high risk PHT in male and female cohorts respectively). CV mortality in the male cohort showed significantly increased risk noted in those with intermediate and high risk PHT (**Table 5.4**). There was significantly increased risk of CV mortality in high risk PHT subjects in the female cohort with smaller numbers and possible inaccurate coding for causes of death documented on death certificates, as possible contributing factors (**Table 5.5**).

Table 5.4. Survival Profile and Adjusted Risk for Mortality According to peak Tricuspid Regurgitant Volume Levels in the male cohort (n = 16177)

	1-Year Mortality (n= 15,525) 96.0%	**5-Year Mortality (n= 11,193) 69.2%**	**All Fatal Events (n= 16,177)**	**CV Mortality (n= 16,177)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 16 177	3555 (22.9)	6732 (60.1)	7698 (47.6)	3229 (20.0)
Low risk PHT Peak TR velocity ≤ 2.8 m/s n = 6043	792/5750 (13.8) Reference	1639/3694 (44.4) Reference	1953 (32.3) Reference	732 (12.1) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 4804	954/4616 (20.7) OR 1.33 (1.18-1.50)	1903/3332 (57.1) OR 1.37 (1.22-1.54)	2262 (47.1) HR 1.28 (1.20-1.37)	945 (19.7) HR 1.09 (0.98-1.22)
Intermediate risk PHT Peak TR velocity 2.8 – 3.4 m/s n = 3839	1198/3704 (32.3) OR 2.16 (1.92-2.43)	2170/2929 (74.1) OR 2.47 (2.17-2.81)	2403 (62.6) HR 1.79 (1.67-1.92)	1040 (27.1) HR 1.27 (1.14-1.42)
High risk PHT Peak TR velocity >3.4m/s n = 1491	611/1455 (42.0) OR 3.14 (2.70-3.66)	1020/1238 (82.4) OR 4.23 (3.47-5.15)	1080 (72.4) HR 2.34 (2.14-2.55)	512 (34.3) HR 1.63 (1.43-1.86)

Cox Regression Analyses for total cohort adjusted for age, LVEF, LVEDD, LAVi. Values are n (%) or n/M (%), unless otherwise indicated. CV = cardiovascular; TR = tricuspid regurgitant; HR = hazard ratio; OR = odds ration; CI = confidence interval; PHT = pulmonary hypertension.

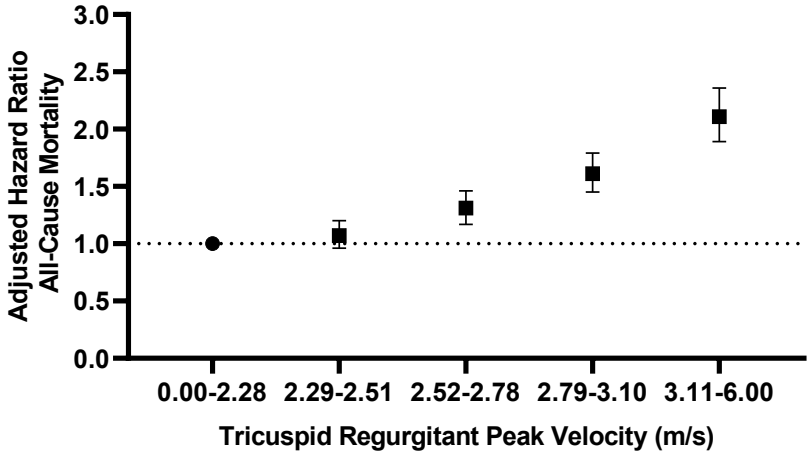
Table 5.5. Survival Profile and Adjusted Risk for Mortality According to peak Tricuspid Regurgitant Volume Levels in the female cohort (n = 7498)

	1-Year Mortality (n= 7161) 95.5%	**5-Year Mortality (n= 5004) 66.8%**	**All Fatal Events (n= 7498)**	**CV Mortality (n= 7498)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 7498	1548 (21.6)	2909 (58.1)	7698 (47.6)	1430 (19.1)
Low risk PHT Peak TR velocity ≤ 2.8 m/s n = 2758	324/2612 (12.4) Reference	671/1583 (42.4) Reference	806 (29.2) Reference	317 (11.5) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 2257	433/2153 (20.1) OR 1.50 (1.23-1.80)	848/1517 (55.9) OR 1.38 (1.16-1.64)	1000 (44.3) HR 1.36 (1.22-1.51)	413 (18.3) HR 0.98 (0.83-1.16)
Intermediate risk PHT Peak TR velocity 2.8 – 3.4 m/s n = 1837	539/1770 (30.5) OR 2.40 (2.00-2.88)	976/1381 (70.7) OR 2.24 (1.86-2.70)	1119 (60.9) HR 1.88 (1.70-2.09)	489 (26.6) HR 1.10 (0.93-1.29)
High risk PHT Peak TR velocity >3.4m/s n = 646	252/626 (40.3) OR 3.61 (2.86-4.55)	414/523 (79.2) OR 3.67 (2.78-4.86)	456 (70.6) HR 2.49 (2.18-2.84)	211 (32.7) HR 1.31 (1.08-1.60)

Cox Regression Analyses for total cohort adjusted for age, LVEF, LVEDD, LAVi. Values are n (%) or n/M (%), unless otherwise indicated. CV = cardiovascular; TR = tricuspid regurgitant; HR = hazard ratio; OR = odds ration; CI = confidence interval; PHT = pulmonary hypertension.

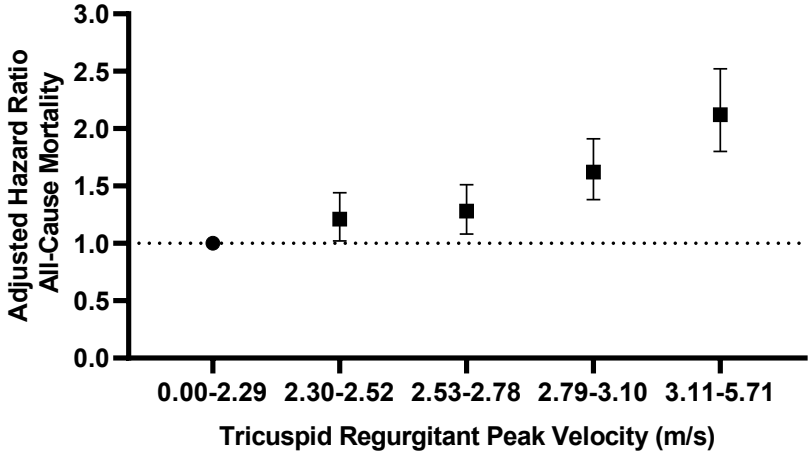
Cox regression models using the quintile distribution of TRV for each cohort was used to determine the thresholds for mortality. In the male cohort a signal towards increased risk was seen from the 2nd quintile, with a clear threshold seen from the 3rd quintile onwards (TPV 2.52-2.78m/s, aHR1.31, 95%CI 1.19-1.44) (**Figure 5.5**). A similar trend was seen in the female cohort with the signal seen from the 2nd quintile, and threshold noted from the 3rd quintile onwards (TRV 2.53-2.78m/s, aHR1.41, 95%CI1.21-1.63) (**Figure 5.6**).

Figure 5.5. Threshold for Mortality according to quintile distribution of Tricuspid Regurgitant Velocity in the Male Cohort



The decile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.52-2.78m/s.

Figure 5.6. Threshold for Mortality according to quintile distribution of Tricuspid Regurgitant Velocity in the Female Cohort



The decile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.53-2.78m/s.

Analysis by Severity of LVEF

Mortality was also assessed via a sensitivity analysis with the cohort divided into two groups based on the severity of LV systolic dysfunction (Mildly reduced LVEF: 12,495, **Table 5.6**; impaired LVEF: 11,180, **Table 5.7**). In both groups the 1 and 5-year actuarial mortality trends was similar to the total population, with the odds of death increasing progressively from those with borderline to high risk PHT. Likewise adjusted long-term mortality increasing progressively as TRV increased in both cohorts (HR1.38, 95%CI 1.27-1.50 for borderline risk PHT vs. aHR2.82, 95%CI 2.52-3.15 for high risk PHT, mildly reduced LVEF cohort; and, HR1.23, 95%CI 1.14-1.33 for borderline PHT, vs. HR2.07, 95%CI 1.88-2.28, reduced LVEF cohort) (**Tables 5.6 and 5.7**).

Table 5.6. Survival Profile and Adjusted Risk for Mortality According to peak Tricuspid Regurgitant Volume Levels in the cohort with mildly reduced LVEF (n = 12,495)

	1-Year Mortality (n= 11925) 95.4%	**5-Year Mortality (n= 8024) 64.2%**	**All Fatal Events (n= 12,495)**	**CV Mortality (n= 12,495)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 12,495	1941 (16.3)	4161 (51.9)	4892 (39.2)	1751 (14.0)
Low risk PHT Peak TR velocity ≤ 2.8 m/s n = 5372	451/5088 (8.9) Reference	1105/3050 (36.2) Reference	1348 (25.1) Reference	419 (7.8) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 3709	546/3547 (15.4) OR 1.67 (1.43-1.95)	1210/2413 (50.1) OR 1.44 (1.26-1.65)	1479 (39.9) HR 1.38 (1.27-1.50)	536 (14.5) HR 1.18 (1.02-1.36)
Intermediate risk PHT Peak TR velocity 2.8 – 3.4 m/s n = 2581	642/2481 (25.9) OR 2.85 (2.44-3.34)	1311/1888 (69.4) OR 2.76 (2.38-3.22)	1493 (57.8) HR 2.00 (1.84-2.18)	554 (21.5) HR 1.38 (1.19-1.59)
High risk PHT Peak TR velocity >3.4m/s n = 833	302/809 (37.3) OR 4.88 (3.99-5.96)	535/673 (79.5) OR 4.74 (3.73-6.02)	573 (68.8) HR 2.82 (2.52-3.15)	242 (29.1) HR 2.06 (1.72-2.46)

Cox Regression Analyses for total cohort adjusted for age, sex, LVEF, LVEDD, LAVi. Values are n (%) or n/M (%), unless otherwise indicated. CV = cardiovascular; TR = tricuspid regurgitant; HR = hazard ratio; OR = odds ration; CI = confidence interval; PHT = pulmonary hypertension.

Table 5.7. Survival Profile and Adjusted Risk for Mortality According to peak Tricuspid Regurgitant Volume Levels in the cohort with reduced LVEF (LVEF<40%), (n = 11,180)

	1-Year Mortality (n= 10761) 96.3%	**5-Year Mortality (n= 8173) 73.1%**	**All Fatal Events (n= 11,180)**	**CV Mortality (n= 11,180)**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All individuals n= 11,180	3162 (29.4)	5480 (67.1)	6186 (55.3)	2903 (26.0)
Low risk PHT Peak TR velocity ≤ 2.8 m/s n = 3429	665/3274 (20.3) Reference	1205/2227 (54.1) Reference	1411 (41.1) Reference	630 (18.4) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 3352	841/3222 (26.1) OR 1.17 (1.03-1.34)	1541/2436 (63.3) OR 1.29 (1.12-1.49)	1783 (53.2) HR 1.23 (1.14-1.33)	822 (24.5) HR 0.98 (0.87-1.10)
Intermediate risk PHT Peak TR velocity 2.8 – 3.4 m/s n = 3095	1095/2993 (36.6) OR 1.82 (1.60-2.08)	1835/2422 (75.8) OR 2.03 (1.74-2.36)	2029 (65.6) HR 1.64 (1.51-1.77)	975 (31.5) HR 1.11 (0.99-1.25)
High risk PHT Peak TR velocity >3.4m/s n = 1304	561/1272 (44.1) OR 2.45 (2.08-2.90)	899/1088 (82.6) OR 3.42 (2.75-4.26)	963 (73.8) HR 2.07 (1.88-2.28)	481 (36.9) HR 1.29 (1.12-1.47)

Cox Regression Analyses for total cohort adjusted for age, sex, LVEF, LVEDD, LAVi. Values are n (%) or n/M (%), unless otherwise indicated. TR = tricuspid regurgitant; HR = hazard ratio; OR = odds ration; CI = confidence interval; PHT = pulmonary hypertension.

Discussion

In this contemporary, 'real world' study, including over 23,000 adults with reduced LVEF without significant left-sided valvular pathology, we have confirmed that subjects with even borderline PHT risk (based on TRV values on echocardiography) have an increased risk of mortality. Where prior studies have focused on highly selected sub-groups or smaller cohorts of subjects with reduced LVEF (largest prior study had n = 1049[23]), our data drawn from over 1 million echoes from over 600,000 adults afforded us the ability provide a more comprehensive description of the whole spectrum of this population. Specifically, we have shown that there is a graded, independent, negative prognostic relationship between elevated TRV and mortality which is consistent between both sexes and exists regardless of the degree of severity of LVEF reduction.

PHT in subjects with reduced LVEF is a sub-type of PHT-LHD and is postulated to develop via the following mechanisms: triggers such as ischemic heart disease and dilated cardiomyopathy lead to cellular changes such as myocyte elongation, as well as changes to the LV chamber phenotype through dilation, hypertrophy and/or loss of LV compliance[17, 60]. These changes lead to rises in LV diastolic pressures, which in turn leads to rises in LA pressure and a backward transmission of these increased pressures into the pulmonary vasculature, causing post-capillary PHT[2, 17].

Prevalence of PHT with reduced LVEF

There have been varying reports of the prevalence of PHT in subjects with reduced LVEF, with a lack of standardised definitions contributing to this and making it difficult to make direct comparisons to our study[23]. In highly selected populations assessed via RHC, the prevalence of PHT has been reported as 40-75%[17, 140]. [26]. In smaller community-based echo studies (n=1049) the prevalence of PHT has been reported between 46-83%[23] [142]. Our study from both community and hospital-based echo laboratories showed that >30% of subjects had intermediate or high risk PHT and were therefore likely to have some degree of PHT according to clinical guidelines[1] (TRV >2.8m/s, equivalent to eRVSP >40mmHg or mPAP 25mmHg; intermediate risk- 24%, high risk- 9%). A significant proportion of our subjects were in the 'borderline' PHT risk group (29.8%).

The resultant echocardiographic phenotype includes findings suggestive of important "back pressure" through the left heart, (with consequent increased LAVi and E:e') and a higher proportion with RV dilation and dysfunction, as PHT worsens within this population. Similar findings have been reported elsewhere[23, 140]. LVEF was lower in those with higher estimated TRV, which has not been a consistent finding in previous studies[23, 140].

Outcomes of subjects with reduced LVEF based on PHT risk

This large study confirms a graded, inverse correlation between worsening PHT risk and survival. Subjects with TRV ≥2.5m/s (borderline and above) had a 1.31-2.38-fold adjusted hazard ratio of long-term all-cause mortality, dependent on the severity of PHT risk, compared with those with low-risk of PHT (**Figure 5.3**). Similar trends were seen in CV mortality trends in the total cohort. The large numbers provided to us by the NEDA allowed us to identify a threshold for excess mortality risk in the borderline risk range. This is consistent with previous NEDA publications, and others, confirming that even mild elevations in TRV are associated with risk[14, 16, 17, 19]. Significantly, these earlier studies excluded subjects with LHD. Our recent work in PHT in left-sided valvular pathology confirmed this finding within particular sub-groups of subjects with PHT-LHD. This paper confirms the independent, negative prognostic impact of mild elevations of TRV in another important and prevalent sub-group of LHD. The effect of PHT risk on outcomes was similar in subjects with reduced and mildly reduced EF, and in male and female subjects when analyzed separately. We prospectively excluded subjects with any moderate or greater left-sided valve pathology, to focus our attention on the influence of PHT risk *per se* on the outcomes in subjects with 'isolated' reduced LVEF.

Clinical Implications

Whilst we do not report on treatment effect, this large study extends our understanding of the echocardiographic phenotype and survival profile of subjects with PHT and reduced LVEF. Echocardiography remains the first line screening tool to determine subjects at increased risk[1]. Whilst current guidelines suggest that the threshold for further investigation lies in those with intermediate risk or higher[1], this study suggests that the current thresholds for PHT risk do not fully capture the clinical risk related to those with mild elevations of TRV. The presence of raised pulmonary pressures is often a marker of more severe disease in patients with reduced LVEF, and thus these patients need to be monitored closely.

Study Strengths

This study confirms the negative prognostic impact of raised pulmonary artery pressures in patients with reduced LVEF, with a major strength being the use of much larger numbers than previous studies describe (previous largest cohort size, n = 1049[23]). Furthermore, the prospective exclusion of significant left-sided valve lesions created a relatively 'pure cohort' of reduced LVEF patients, which allowed focus on the influence of raised pulmonary pressures *per se* on outcomes in such subjects. In Australia, universal health care coverage allows relatively free access to ultrasound in patients of need, and the low emigration rates from Australia with a comprehensive NDI adds to the generalisability and reliability of our results. Finally, the description of a threshold for increased mortality in patients with 'borderline-risk' of PHT is novel in this large and important subset patients with LHD.

Study Limitations

NEDA provides detailed echocardiographic data and linkage to mortality; it does not yet however, provide granular clinical data such as symptoms, co-morbidities or pharmacologic treatments, all of which may impact on each individual's health outcomes and thereby cause residual confounding in our models. As such, the underlying aetiology of the reduced LVEF was unable to be determined, nor can the impact of background medical therapy. We were also unable to determine the duration or chronicity of reduced LVEF in the cohort prior to their inclusion into the study (last echo), which may result in immortal time bias. These studies were primarily derived from community or hospital-based centres across Australia. Most subjects included in the NEDA have had an echo for investigation of suspected or known cardiovascular disease and thus, should not be taken to reflect the population prevalence.

Consistent with our previous studies[12], data concerning PHT in NEDA is based on echocardiography-based measures, rather than the gold standard hemodynamic assessment at right heart catheterization. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107], supporting the broad validity of our approach. Furthermore, echocardiography remains the commonest screening tool to determine PHT risk and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow up. We also note that the absence of a tricuspid regurgitation jet does not exclude PHT risk and there may be subjects with reduced LVEF at risk of PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR. Finally, our data is lacking in quantitative RV measurements, with only a small minority of patients having recorded RV functional parameters such as TAPSE or fractional area change, and the quality of more qualitative assessments could not be verified; thus, we are unable to fully assess the impact of raised pulmonary pressures on the right heart, nor can we determine impact of RV abnormalities on mortality, in this cohort.

Conclusion

Both reduced LVEF and PHT confer an increased risk of mortality. In this large study, we demonstrate that in subjects with reduced LVEF, the mortality risk becomes progressively higher as TRV levels increase. A threshold for higher mortality in subjects with reduced LVEF lies within the range of 'borderline risk' PHT.

Chapter 6 – Prevalence and Prognostic Significance of Pulmonary Hypertension in Adults with Left Ventricular Diastolic Dysfunction

This chapter is based on the publication: Ratwatte S, Playford D, Strange G, et al. Prevalence and prognostic significance of pulmonary hypertension in adults with left ventricular diastolic dysfunction. Open Heart 2024;11:e003049. doi:10.1136/ openhrt-2024-003049

Abstract

Aims: Pulmonary Hypertension (PHT) appears to be very common in Heart Failure with Preserved Ejection Fraction but details on its prevalence, severity and prognostic implications have not been well defined. We therefore aimed to document PHT and its impact on mortality among adults with left ventricular (LV) diastolic dysfunction (LVDD).

Methods: We analyzed the profile and outcomes of 16,058 adults with LVDD (and with preserved LV ejection fraction, >50%) from the National Echocardiography Database of Australia. Subjects were classified according to their peak tricuspid regurgitation velocity (TRV), reflecting PHT risk, and we then evaluated the relationship between conventional thresholds of increasing risk of PHT and subsequent mortality, during median follow-up of 3.1 (IQR1.6-5.2) years.

Results: Mean age was 73±12years and 9216 (57.4%) were female. Overall, 2611 (16.3%) had normal TRV levels (<2.5m/s) indicative of no PHT, compared to 3471 (21.6%), 8450 (52.6%) and 1526 (9.5%) with TRV levels indicative of borderline (2.5-2.8m/s), intermediate (2.9-3.4m/s) and high-risk for PHT (>3.4m/s). The 1- and 5-year actuarial mortality (1701/1546 and 4232/8445 deaths respectively) increased from 6.5% and 34.0%, to 27.7% and 78.5% respectively (p<0.0001) from normal to severely elevated TRV. Adjusted risk (hazard ratio) of mortality increased 1.28-fold (95%CI 1.15-1.41), 1.51-fold (95%CI 1.38-1.65) and 3.47-fold (95%CI 3.13-3.85) in those with borderline, intermediate and high-risk of PHT versus normal TRV. This observation persisted when excluding atrial fibrillation cases, and when male and female cohorts were assessed separately. Mortality rates increased perceptibly at the 2nd decile distribution of TRV (2.37-2.55m/s) with a marked increase in mortality from the 5th decile (2.91-3.00m/s) upwards.

Conclusion: We demonstrate the negative prognostic impact of elevated TRV levels in many adults with isolated LVDD. A threshold of increased mortality was observed at TRV levels equivalent to 'borderline risk' of PHT.

Introduction

Left ventricular diastolic dysfunction (LVDD) in adults with preserved left ventricular ejection fraction (pEF) is a common condition, predominantly affecting aging populations [143, 144]. It is associated with poor outcomes, with >50% mortality within 5 years[103, 144]. PHT is prevalent in this population, however reported rates have varied greatly from 36-83%[22, 24, 63]. PHT in people with LVDD with pEF is postulated to develop as a direct consequence of impaired LV relaxation and thence raised LA pressure[2, 44, 60].

Recent guidelines have recommended the use of the TRV on echocardiography to determine the risk of PHT[13]. Whilst a TRV of >2.8m/s is the current recommended threshold for further confirmatory investigations[1], there is growing literature to suggest that mortality increases from 'borderline' elevations in pulmonary pressure[12, 13, 104, 122] with this finding confirmed in other types of PHT due to LHD in earlier chapters of this thesis (Chapters 2-5). The negative prognostic influence of PHT in patients with LVDD and pEF has only been described in smaller cohorts (the largest of which reported on only 618 subjects)[22, 139, 145]. Thus, the relationship between PHT risk and LVDD in those with pEF has not been well characterized in a large, contemporary clinical cohort.

Utilizing data from the large National Echo Database of Australia (NEDA) we aimed (1) to document the point prevalence and severity of PHT and (2) to study the association between increasing TRV levels and mortality outcomes, in those with LVDD. Similar to previous NEDA work and the work outlined in earlier chapters, we also examined the risk of mortality according to the decile distribution of individual units of TRV, to more definitively elucidate whether a threshold for excess mortality could be identified[12].

Methods

Study Design and Data

This is a retrospective, clinical cohort study derived from the NEDA. NEDA is a multi-centre echocardiography registry which provides basic demographic and detailed echocardiographic data from >25 centres across Australia[12, 99]. The database is linked to NDI, to obtain mortality data for each individual. Cause of death was determined from death certificates which use standardized coding across Australia. At the time of analysis, the registry contained >1million echo reports from >600 000 subjects from January 2000 to June 2019. Vital status was determined as of 21st May 2019, subjects alive at this date were censored as alive. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and 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.

All echocardiographic measurements and basic demographic profiling were transferred into a central database via an automated data extraction process. All data was cleaned to generate uniform echo profile data with duplicate, inconsistent or impossible measurements removed.

Study Cohort

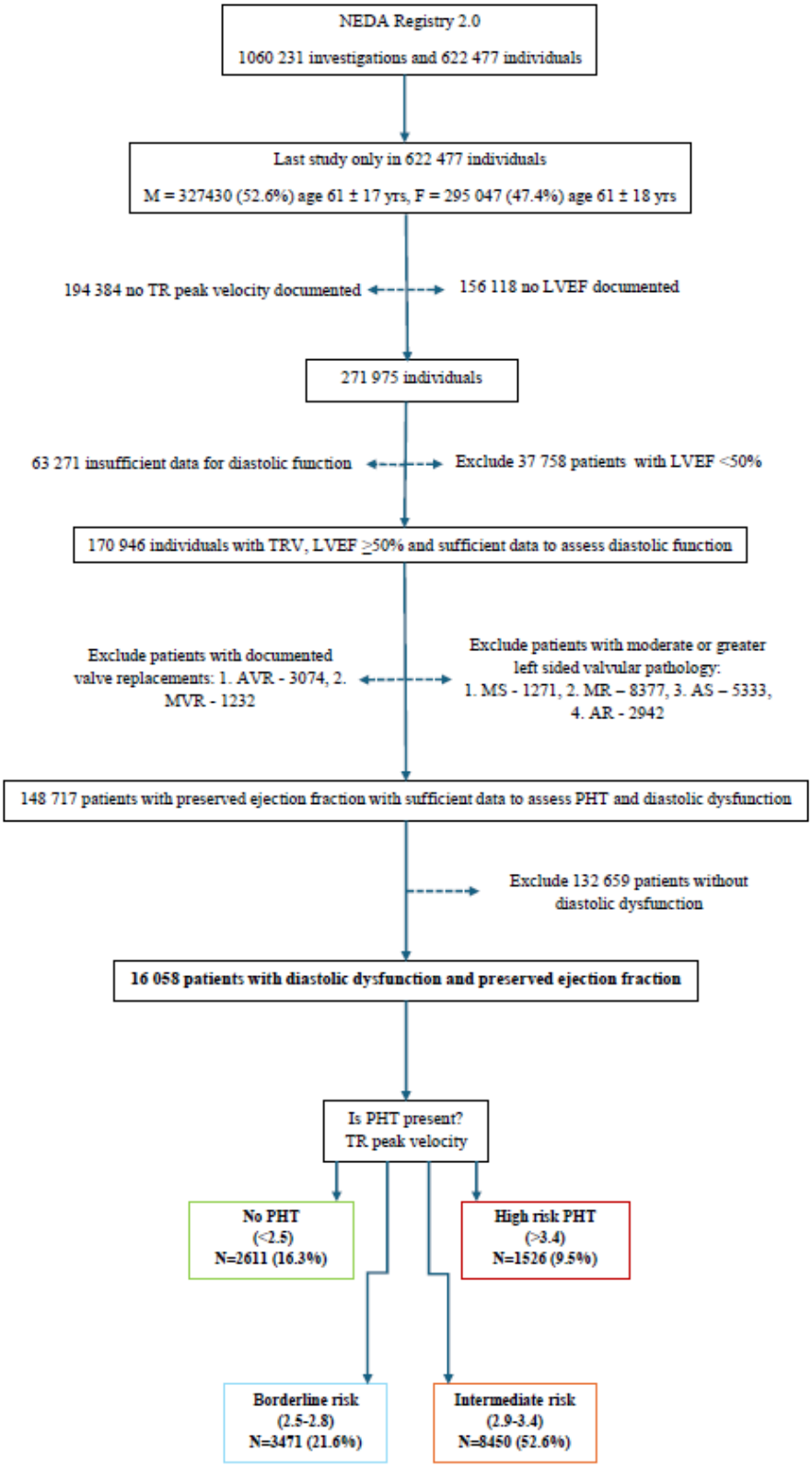
LVDD was determined via the ASE//EACVI guidelines[75, 103]. LVDD was defined as those meeting 3 or more (>50%) of the following parameters being positive: 1) E/e'>14, 2) septal e' velocity <7cm/s or lateral e' velocity < 10cm/s, 3) TRV >2.8m/s and 4) LAVi >34mL/m^2. LVEF values had to be quantified, and consistent with guidelines, a hierarchical preference for Simpson's Biplane-Derived LVEF over 2D Teicholz and other quantification methods were applied[137]. LVDD subjects were then categorised according to their TRV, according to the recent 2022 clinical guidelines on PHT[1]. A 'borderline risk' was derived as this group has been shown to be significant by prior literature and the work outlined in prior chapters[12, 13, 104]. As previously described in Chapter 5 defined categories were: 1) low risk PHT (<2.5m/s), 2) borderline risk PHT (2.5–2.8 m/s), 3) intermediate risk PHT (2.9-3.4m/s) and high risk PHT (>3.4m/s). LVDD subjects were also categorized into 'grades' of LVDD according to ASE/EACVI guidelines[75].

Figure 6.1 shows our study flow diagram; to be included in the analysis, subjects were: 1) adults ≥ 18 years of age, 2) with at least one echocardiogram recorded (where subjects had multiple studies only the last study was analysed), 3) with a recorded LVEF, TRV and sufficient data to determine diastolic function, and 4) with diastolic dysfunction. Subjects with LVEF <50% and documented mitral and aortic valve replacements were excluded, as were subjects with moderate or greater left-sided valvular pathology. RV size was described qualitatively, using text extraction from echo reports. AF and atrial arrhythmia was determined by methods previously described[103].

Mortality assessment

We documented the distribution of TRV and thence the risk of PHT, using the TRV as a surrogate to estimate pulmonary artery pressures based on the categories defined above. All-cause mortality was determined over a median follow up of 3.1 years (IQR 1.6-5.2 years). We explored all-cause mortality occurring at fixed time-points of 1 and 5 years and then in a time-to-event survival analysis according to the four clinically defined TRV groups[12]. Consistent with prior NEDA publications and the methodology in Chapter's 2-5, we then divided the cohort into TRV deciles to perform a more granular analyses of the association of TRV and all-cause mortality[12]. Our group has previously established sex-based differences LVDD[103]; thus, we performed a pre-specified analysis to determine whether sex-based differences in prevalence in PHT risk and mortality outcomes were present.

Figure 6.1. Study Flow Chart



This figure shows the analysis flowchart, performed in this study.

NEDA = National Echo Database Australia; left ventricular ejection fraction (LVEF); TRV = tricuspid regurgitant volume; AS = aortic stenosis; AR = aortic regurgitation; MS = mitral stenosis; MR = mitral regurgitation; AVR = aortic valve replacement; MVR = mitral valve replacement; PHT = pulmonary hypertension.

Statistical Analyses

All categorical data are expressed as frequency and percentages, unless otherwise stated, and continuous variables are expressed as mean ± standard deviation (SD). Chi-squared 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 ANOVA analysis was used to test the trend of the mean across the categorical groups of TRV levels. Actuarial 1-year and 5-year survival rates for all-cause mortality were calculated for all-cause mortality from the 15, 486 (96.4%) and 8445 (52.6%) subjects with complete follow up for those time points. Multiple logistic regression was performed using entry models with variables determined by an 'a priori' approach which also met a pre-specified entry point (univariate p value <0.05) to derive adjusted ORs for mortality at these fixed time points. Adjusted analyses included age, sex, LVEF and AF/atrial arrhythmia. Cox regression models were used to derive adjusted hazard ratios (HR) for mortality outcomes during follow up (time from last echo to census date or death, entry model, using univariate p-value <0.05). Proportional hazards were confirmed by visual inspection of the log-to-log survival curves. Adjusted analyses for base models included age and sex. Additional analyses included LAVi and the presence of AF/atrial arrhythmia which were specified a priori, based on previous publications[103]. We then examined the pattern of mortality according to the decile distribution of TRV to identify a threshold for mortality, with sex-based analyses based on quintile distributions. The decile distribution was: 1st decile- 0.00-2.36m/s, 2nd- 2.37-2.55m/s, 3rd- 2.56-2.70m/s, 4th- 2.71-2.87m/s, 5th- 2.88-2.90m/s, 6th- 2.91-3.00m/s, 7th- 3.01-3.10m/s, 8th- 3.11-3.20m/s, 9th- 3.21-3.40m/s and 10th- >3.40m/s. The quintile distribution for the male cohort (n = 6842) was: 1st- 0.00-2.60m/s, 2nd- 2.61-2.90m/s, 3rd- 2.91-3.00m/s, 4th- 3.01-3.20m/s, 5th- 3.21-5.70m/s. The quintile distribution for the female cohort (n = 9216) was: 1st- 0.00-2.52m/s, 2nd- 2.53-2.84m/s, 3rd- 2.85-3.00m/s, 4th- 3.01-3.20m/s and 5th- 3.21-5.91m/s. All analyses were performed with SPSS software v25.0 (IBM Corp), and statistical significance was inferred at a two-tailed p-value of <0.05.

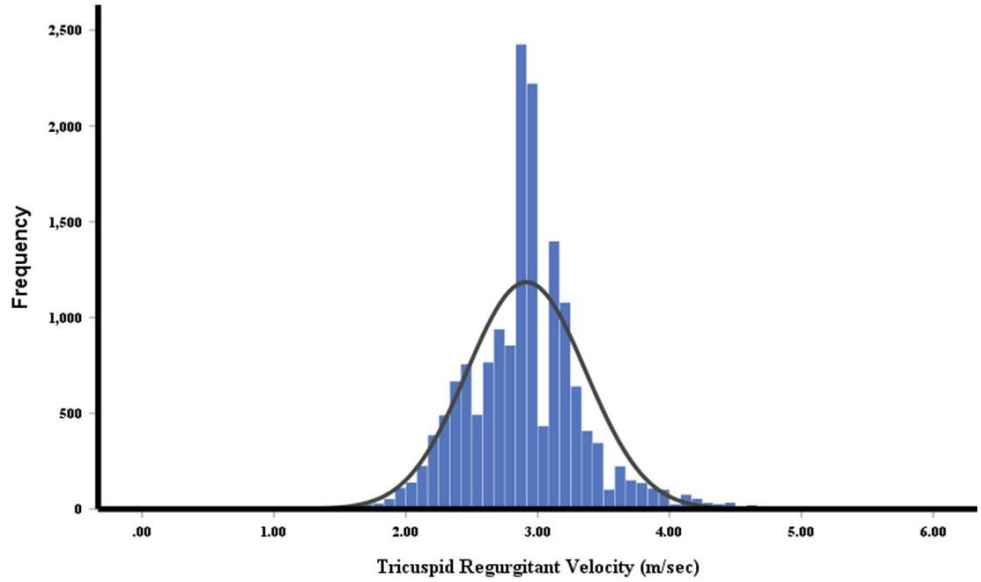
Results

Study Cohort and Prevalence of PHT

A total of 16,058 subjects with pEF, TRV data and LVDD were identified (**Figure 6.1**), with 9216/16,058 (57.4%) being female. **Figure 6.2** shows the frequency distribution of TRV levels (median 2.90m/s, IQR 2.64-3.10m/s). The number of subjects in each sub-group were low risk PHT (TRV<2.5m/s)- 2611 (16.3%) individuals, borderline risk (2.5-2.8m/s)- 3471 (21.6%) individuals, intermediate risk (2.9-3.4m/s)- 8450 (52.6%) individuals, high risk (>3.4m/s)- 1526 (9.5%) individuals.

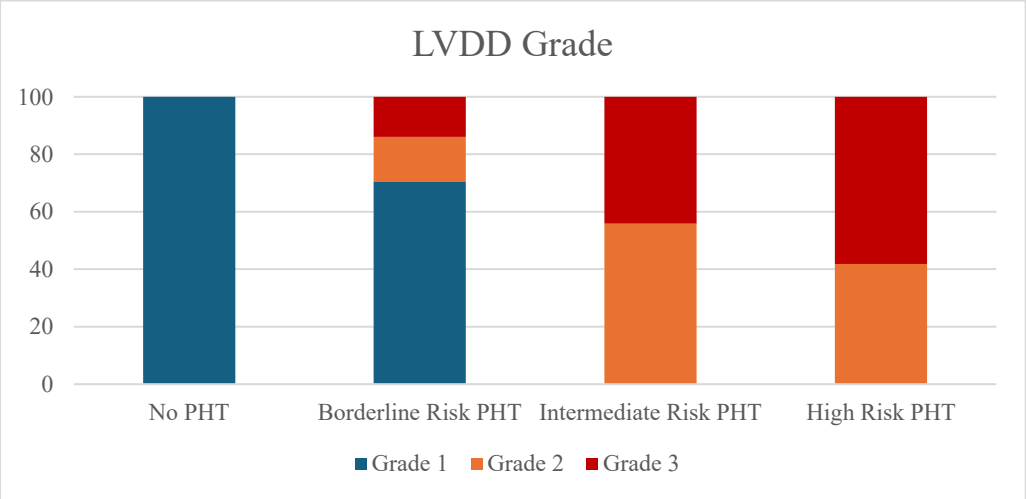
When the degree of diastolic dysfunction of the cohort was graded the proportion of patients with more severe diastolic dysfunction increased as PHT-risk increased (**Figure 6.3**). There was a progressive increase in BMI from a mean of 27.78±5.76 kg/m^2, in those with low-risk PHT, to 29.67±7.16kg/m^2 in the intermediate-risk group, before plateauing in the high-risk groups ($p<0.0001$ for all). The proportion of subjects with AF was greater in those with higher TRV, from 13% (347/2611) in those with low risk PHT, to 20.8% (317/1526) in those in high-risk groups.

Figure 6.2. Frequency Distribution of Tricuspid Regurgitant Velocity within the Cohort



These data show the statistical distribution of tricuspid regurgitant velocity (TRV) levels.

Figure 6.3. Grade of Diastolic Dysfunction based on Severity of Raised Tricuspid Regurgitant Velocity



These data showed that the proportion of patients with more severe diastolic dysfunction increased as PHT-risk increased.

Cohort Characteristics with Increasing TRV

A typical echocardiographic, phenotypic response to increasing levels of TRV and thus the presence of PHT is evident, as summarized in **Table 6.1**. There was a progressive increase in indexed LA volume from low risk PHT to intermediate risk PHT (43.46±11.61mL/m2 to 76.19±33.24mL/m2, p<0.0001), with a plateau noted in those with high-risk PHT (70.85±38.70mL/m2). The Right Atrial (RA) area increased progressively from low-risk PHT to high-risk PHT (17.47±5.64 to 29.09±8.45 cm^2). The proportion of subjects with right ventricular dilation also increased from 5.1% (133/2611) in those with low-risk PHT, to, 49.7% (759/1526) in those with high-risk PHT (p<0.0001).

Table 6.1. Baseline Characteristics of patients with diastolic dysfunction, n=16058

	No PHT TRV <2.5m/s N = 2611	**Borderline risk PHT TRV 2.5 – 2.8 m/s N = 3471**	**Intermediate risk PHT TRV 2.9-3.4 m/s N = 8450**	**High risk PHT TRV >3.4m/s N = 1526**	**P Value**
Demographics					
Age, years	71±13	75±11	73±12	75±13	<0.0001
Female (%)	1605 (61.5)	2089 (60.2)	4624 (54.7)	898 (58.8)	<0.0001
Anthropometrics					
BMI	27.78±5.76	28.21±6.30	29.67±7.16	27.81±7.09	<0.0001
BSA	1.84±0.25	1.86±0.26	1.91±0.27	1.83±0.28	<0.0001
Rhythm					
Atrial fibrillation / atrial arrhythmia	347 (13.3)	528 (15.2)	1311 (15.5)	317 (20.8)	0.001
LV dimensions and functions					
LVEF %	64.39±7.74	66.15±8.82	71.00±10.34	67.74±10.14	<0.0001
E/E' ratio	17.77±3.80	17.64±4.27	14.45±4.26	16.41±6.67	<0.0001
LVEDD	4.42±0.64	4.58±0.70	4.91±0.72	4.59±0.75	<0.0001
LVESD	2.81±0.58	2.83±0.64	2.76±0.70	2.74±0.70	0.001
Stroke volume Index (ml/m^2)	43.36±11.19	45.42±11.67	44.67±13.68	40.29±12.48	<0.0001
Mitral E velocity	82.95±20.55	86.75±22.51	83.58±26.49	90.77±33.23	<0.0001

Mitral A velocity	89.58±25.79	92.88±28.08	94.40±30.26	86.28±30.09	<0.0001
Mitral E/A ratio	0.98±0.45	1.01±0.56	0.98±0.69	1.16±0.80	<0.0001
Lateral e' velocity	6.83±2.32	7.07±2.35	7.91±2.51	8.35±2.77	<0.0001
Septal e' velocity	5.03±1.12	5.21±1.13	5.85±1.14	5.66±1.56	<0.0001
Atrial dimensions					
LA volume index, mL/m^2	43.46±11.61	56.35±26.14	76.19±33.24	70.85±38.70	<0.0001
RA area, cm^2	17.47±5.64	23.21±7.44	28.15±6.57	29.09±8.45	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	28.97±4.55	37.46±3.74	47.00±4.33	68.68±13.45	<0.0001
TR peak velocity, m/s	2.26±0.20	2.67±0.11	3.05±0.15	3.81±0.38	<0.0001
Dilated RV*	133 (5.1)	528 (15.2)	2987 (35.3)	759 (49.7)	<0.0001
Impaired RV function	15 (0.6)	25 (0.7)	101 (1.2)	127 (8.3)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

The demographics and echo characteristics of the cohort split divided by sex are shown in **Tables 6.2 and 6.3**. There were no clinically meaningful differences in age, TRV, LVEF, RV dilation or LAVi between sexes. The proportion of males with AF increased progressively from low-risk PHT to high-risk PHT. In the female cohort a marked increase in the proportion of AF was only noted in those with high-risk PHT.

Table 6.2. Baseline Characteristics of patients with diastolic dysfunction, male n=6842

	No PHT TRV <2.5m/s N = 1006	**Borderline risk PHT TRV 2.5 – 2.8 m/s N = 1386**	**Intermediate risk PHT TRV 2.9-3.4 m/s N = 3826**	**High risk PHT TRV >3.4m/s N = 628**	**P Value**
Demographics					
Age, years	70±12	72±11	72±12	74±12	<0.0001
Female (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Anthropometrics					
BMI	27.80±4.85	28.44±5.21	29.56±6.34	27.77±6.38	<0.0001
BSA	1.98±0.22	2.01±0.22	2.05±0.24	1.97±0.27	<0.0001
Rhythm					
Atrial fibrillation / atrial arrhythmia	160 (15.9)	243 (17.5)	690 (18.0)	144 (22.9)	0.001
LV dimensions and functions					
LVEF %	62.94±7.78	64.80±8.84	69.97±10.39	66.19±10.27	<0.0001
E/E' ratio	17.34±3.53	17.00±4.00	13.98±3.86	15.11±5.88	<0.0001
LVEDD	4.72±0.59	4.92±0.66	5.21±0.68	4.85±0.76	<0.0001
LVESD	3.05±0.58	3.11±0.65	3.00±0.71	2.98±0.74	0.001
Stroke volume Index (ml/m^2)	44.19±10.94	46.58±12.17	44.94±15.16	40.56±11.52	<0.0001
Mitral E velocity	80.97±21.36	85.15±22.39	81.46±26.17	85.25±32.51	<0.0001
Mitral A velocity	82.57±25.29	86.98±28.14	90.47±30.54	80.78±29.21	<0.0001
Mitral E/A ratio	1.05±0.49	1.08±0.62	1.01±0.73	1.18±0.88	<0.0001
Lateral e' velocity	7.02±2.34	7.49±2.45	8.15±2.44	8.77±2.94	<0.0001
Septal e' velocity	5.18±1.09	5.32±1.15	5.92±1.46	5.75±1.57	<0.0001

Atrial dimensions					
LA volume index, mL/m^2	43.80±12.14	61.31±29.05	82.06±34.64	76.94±42.41	<0.0001
RA area, cm^2	19.55±5.52	25.89±7.44	30.35±6.49	31.28±8.70	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	29.18±4.36	37.68±3.54	46.99±4.24	68.27±12.49	<0.0001
TR peak velocity, m/s	2.26±0.20	2.67±0.11	3.05±0.14	3.81±0.36	<0.0001
Dilated RV*	65 (6.5)	285 (20.6)	2012 (52.6)	366 (58.3)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

Table 6.3. Baseline Characteristics of patients with diastolic dysfunction, female n=9216

	No PHT TRV <2.5m/s N = 1605	**Borderline risk PHT TRV 2.5 – 2.8 m/s N = 2089**	**Intermediate risk PHT TRV 2.9-3.4 m/s N = 4624**	**High risk PHT TRV >3.4m/s N = 898**	**P Value**
Demographics					
Age, years	72±13	76±11	74±12	75±13	<0.0001
Female (%)	1605 (100)	2089 (100)	4624 (100)	898 (100)	
Anthropometrics					
BMI	27.77±6.19	28.06±6.91	29.76±7.80	27.83±7.55	<0.0001
BSA	1.76±0.22	1.76±0.23	1.80±0.24	1.74±0.25	<0.0001
Rhythm					
Atrial fibrillation / atrial arrhythmia	187 (11.7)	285 (13.6)	621 (13.4)	173 (19.3)	0.001
LV dimensions and functions					
LVEF %	65.30±7.57	67.05±8.69	71.86±10.22	68.83±9.91	<0.0001

E/E' ratio	17.99±3.92	18.05±4.39	14.85±4.83	17.31±7.04	<0.0001
LVEDD	4.23±0.59	4.35±0.62	4.66±0.65	4.41±0.69	<0.0001
LVESD	2.66±0.54	2.63±0.56	2.55±0.62	2.58±0.63	0.001
Stroke volume Index (ml/m^2)	42.90±11.31	44.76±11.32	44.50±12.68	40.11±13.12	<0.0001
Mitral E velocity	84.19±19.94	87.81±22.53	85.33±26.62	94.68±33.20	<0.0001
Mitral A velocity	93.80±25.17	96.59±27.41	97.52±29.67	89.96±30.13	<0.0001
Mitral E/A ratio	0.95±0.43	0.97±0.51	0.96±0.65	1.15±0.74	<0.0001
Lateral e' velocity	6.72±2.30	6.83±2.26	7.78±2.54	8.12±2.65	<0.0001
Septal e' velocity	4.94±1.12	5.13±1.11	5.80±1.42	5.60±1.55	<0.0001
Atrial dimensions					
LA volume index, mL/m^2	43.17±11.13	52.53±22.95	71.02±31.05	66.47±35.19	<0.0001
RA area, cm^2	15.91±5.21	20.55±6.43	25.96±5.89	27.10±7.70	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	28.84±4.67	37.31±3.87	47.00±4.40	68.96±14.08	<0.0001
TR peak velocity, m/s	2.26±0.20	2.67±0.10	3.05±0.15	3.82±0.40	<0.0001
Dilated RV*	48 (3.0)	120 (5.7)	975 (21.8)	393 (43.8)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

Tables 6.4 and 6.5 summarize the baseline characteristics delineated by age. The younger cohort was a much smaller proportion of the total (<65 years, n=3307; and ≥65years, n=12, 751) and had a higher proportion of males, with a lower proportion of AF.

Table 6.4. Baseline Characteristics of patients with diastolic dysfunction, age <65 years old, n=3307

	No PHT TRV <2.5m/s N = 674	**Borderline risk PHT TRV 2.5 – 2.8 m/s N = 599**	**Intermediate risk PHT TRV 2.9-3.4 m/s N = 1783**	**High risk PHT TRV >3.4m/s N = 251**	**P Value**
Demographics					
Age, years	55±9	56±8	56±8	53±10	<0.0001
Female (%)	395 (58.6)	300 (50.1)	844 (47.3)	138 (55.0)	<0.0001
Anthropometrics					
BMI	29.56±6.57	30.78±7.38	32.56±8.29	29.19±8.99	<0.0001
BSA	1.92±0.27	2.00±0.26	2.05±0.28	1.93±0.36	<0.0001
Rhythm					
Atrial fibrillation / atrial arrhythmia	56 (8.3)	42 (7.0)	154 (8.6)	24 (9.6)	0.001
LV dimensions and functions					
LVEF %	63.98±7.50	66.41±9.34	72.50±10.07	67.18±10.15	<0.0001
E/E' ratio	17.15±3.38	17.00±3.60	13.98±3.61	14.59±5.80	<0.0001
LVEDD	4.64±0.61	4.85±0.67	5.16±0.67	4.65±0.75	<0.0001
LVESD	2.99±0.57	3.00±0.67	2.87±0.70	2.82±0.69	0.001
Stroke volume Index (ml/m^2)	42.65±10.45	44.85±12.32	42.63±14.62	37.76±10.45	<0.0001
Mitral E velocity	86.83±21.11	90.10±21.59	83.90±26.65	81.86±32.28	<0.0001
Mitral A velocity	79.27±23.82	85.03±27.80	90.13±30.24	78.50±25.19	<0.0001
Mitral E/A ratio	1.18±0.49	1.20±0.66	1.10±0.81	1.12±0.64	<0.0001
Lateral e' velocity	7.78±2.51	7.64±2.90	9.13±2.94	9.64±2.77	<0.0001
Septal e' velocity	5.44±1.02	5.58±1.10	6.07±1.52	5.68±1.51	<0.0001
Atrial dimensions					

LA volume index, mL/m^2	44.63±14.55	61.28±25.66	78.91±27.07	66.48±39.06	<0.0001
RA area, cm^2	18.07±5.33	24.47±6.96	27.97±5.90	28.42±8.96	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	28.57±4.78	37.43±3.69	46.67±4.19	72.99±17.45	<0.0001
TR peak velocity, m/s	2.24±0.21	2.66±0.11	3.04±0.14	3.94±0.49	<0.0001
Dilated RV*	32 (4.7)	111 (18.5)	846 (47.4)	171 (68.1)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

Table 6.5. Baseline Characteristics of patients with diastolic dysfunction, age ≥65 years old, n=12751

	No PHT TRV <2.5m/s N = 1937	**Borderline risk PHT TRV 2.5 – 2.8 m/s N = 2872**	**Intermediate risk PHT TRV 2.9-3.4 m/s N = 6667**	**High risk PHT TRV >3.4m/s N = 1275**	**P Value**
Demographics					
Age, years	77±7	78±7	78±8	79±8	<0.0001
Female (%)	1210 (62.5)	1789 (62.3)	3780 (56.7)	760 (59.6)	<0.0001
Anthropometrics					
BMI	27.14±5.29	27.62±5.87	28.84±6.58	27.53±6.61	<0.0001
BSA	1.81±0.23	1.82±0.24	1.87±0.25	1.81±0.26	<0.0001
Rhythm					
Atrial fibrillation / atrial arrhythmia	291 (15.0)	486 (16.9)	1157 (17.4)	293 (23.0)	0.001
LV dimensions and functions					
LVEF %	64.54±7.81	66.10±8.71	70.60±10.38	67.86±10.14	<0.0001
E/E' ratio	17.98±3.92	17.79±4.40	14.58±4.42	16.78±6.78	<0.0001
LVEDD	4.35±0.63	4.52±0.69	4.84±0.72	4.58±0.75	<0.0001

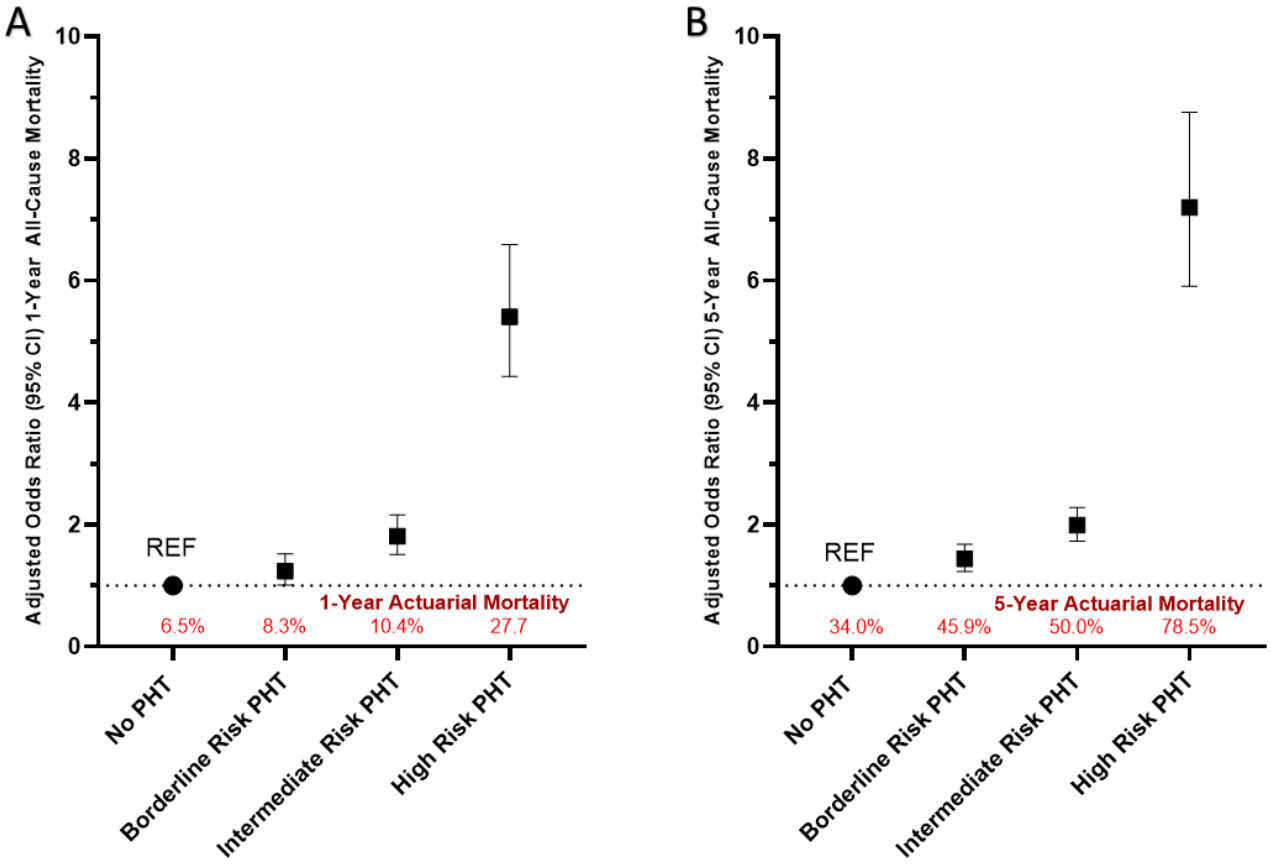
LVESD	2.75±0.58	3.00±0.67	2.73±0.70	2.73±0.71	0.001
Stroke volume Index (ml/m^2)	43.61±11.44	45.53±11.55	41.09±12.97	41.09±12.97	<0.0001
Mitral E velocity	81.59±20.19	86.05±22.64	92.56±33.15	92.56±33.15	<0.0001
Mitral A velocity	93.27±25.48	94.60±27.86	87.96±30.80	87.96±30.80	<0.0001
Mitral E/A ratio	0.92±0.42	0.97±0.52	1.17±0.83	1.17±0.83	<0.0001
Lateral e' velocity	6.43±2.11	6.93±2.18	7.90±2.63	7.90±2.63	<0.0001
Septal e' velocity	4.89±1.12	5.13±1.12	5.66±1.57	5.66±1.57	<0.0001
Atrial dimensions					
LA volume index, mL/m^2	43.12±10.58	55.32±26.12	71.39±38.64	71.39±38.64	<0.0001
RA area, cm^2	17.26±5.74	22.82±7.55	29.24±8.33	29.24±8.33	<0.0001
Right heart dimensions and function					
eRSVP, mmHg	29.11±4.46	37.47±3.76	67.83±12.34	67.83±12.34	<0.0001
TR peak velocity, m/s	2.27±0.19	2.67±0.11	3.79±0.35	3.79±0.35	<0.0001
Dilated RV*	81 (4.2)	294 (10.2)	2141 (32.1)	588 (46.1)	<0.0001

*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

Mortality with Increasing TRV

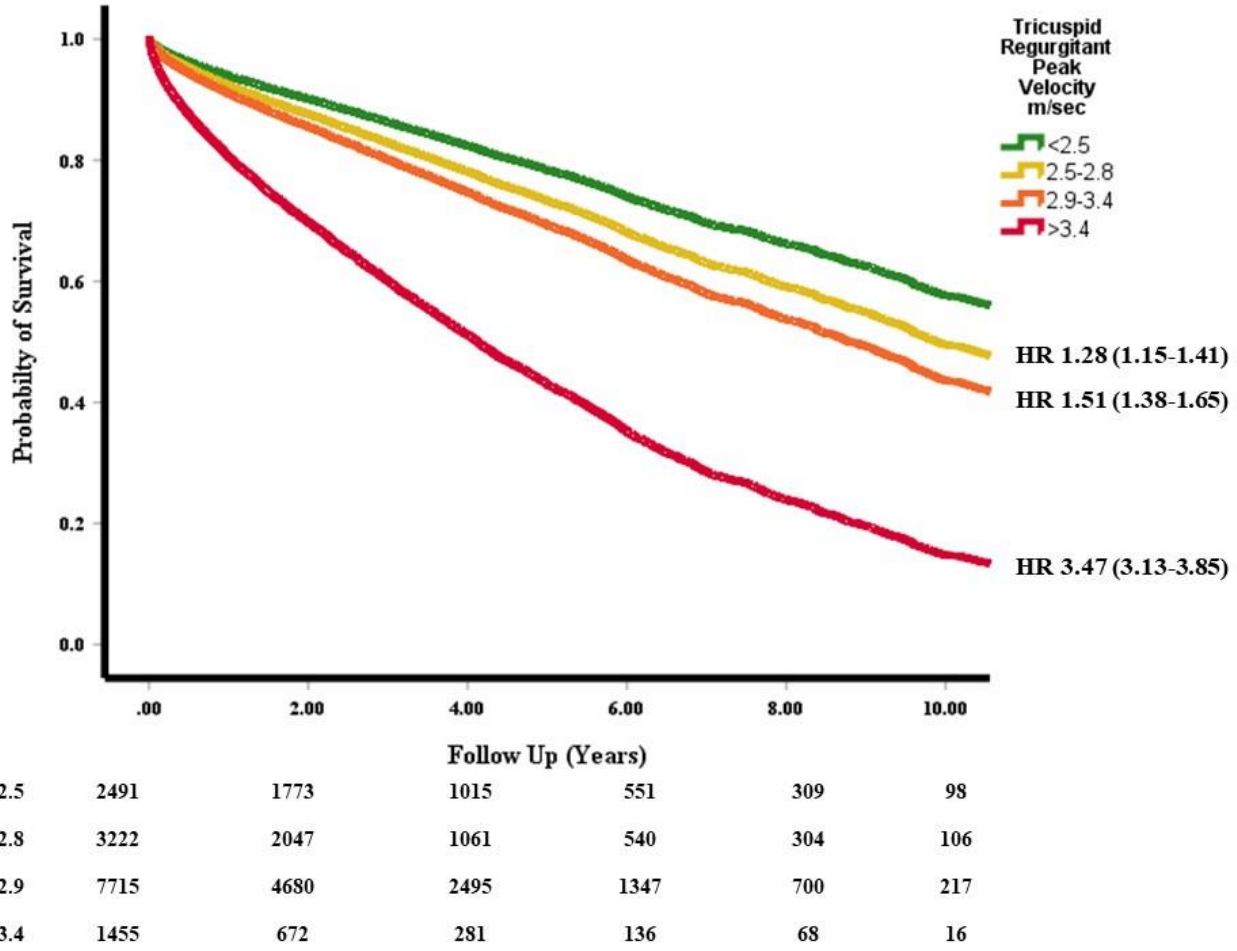
Among the 16,058 subjects with LVDD and pEF 5217 (32.5%) died from any cause during a median follow up of 3.1 years (IQR 1.6-5.2 years). **Figures 6.2A and 6.2B** show actuarial 1-year and 5-year all-cause mortality respectively, adjusted for age, sex, LVEF and presence of AF/atrial arrhythmia. Both increased progressively based on the severity of PHT-risk from a low of 6.5% and 34.0%, to a high of 27.7% and 78.5%, in those with normal to severely elevated TRV. Increased LVEF was protective (aOR0.98, 95%CI 0.97-0.98 for both 1- and 5-year mortality), and the presence of AF/atrial arrhythmia increased the odds of mortality (aOR 1.21, 95%CI1.06-1.37, and, aOR 1.39, 95%CI 1.22-1.58, for 1-year and 5-year mortality respectively).

Figure 6.2. One- and Five-Year Actuarial Mortality for subjects with Diastolic Dysfunction and preserved left ventricular ejection fraction



A) denotes 1-year survival rates, and, B) denotes the 5-year survival rates, for all-cause mortality for subjects with complete follow up at each time point. Adjusted analyses included age, sex, LVEF and AF/atrial arrhythmia. A) Age OR1.03 (95% CI 1.02-1.03), sex OR0.73 (95% CI 0.66-0.81), LVEF OR0.98 (95% CI0.97-0.98), AF / atrial arrhythmia OR1.21 (95% CI 1.06-1.37). B) Age OR1.06 (95% CI 1.05-1.06), sex OR0.73 (95% CI 0.66-0.80), LVEF OR0.98 (95% CI 0.97-0.98), AF / atrial arrhythmia OR1.39 (95% CI 1.22-1.58).

Figure 6.3. Adjusted Risk for All-Cause Mortality



<2.5	2491	1773	1015	551	309	98
2.5-2.8	3222	2047	1061	540	304	106
2.9	7715	4680	2495	1347	700	217
>3.4	1455	672	281	136	68	16

Adjusted risk for all-cause mortality using Cox proportional hazards, shown by TRV level increases. Adjusted for: female versus male HR 0.73 (CI 0.69-0.77), age per year HR 1.05 (CI 1.04-1.06).

Adjusted survival analysis (corrected for age and sex) for long-term, all-cause mortality showed markedly increased death rates with higher TRV levels. There was a 1.28-fold increase in mortality risk in those with borderline risk of PHT compared to a 3.47-fold increase in those with high risk of PHT ($p<0.0001$ for all) (**Figure 6.3**). These trends were confirmed on sensitivity analyses excluding patients with AF/atrial arrhythmia and those with a paced rhythm at time of echo, respectively (**Tables 6.6 and 6.7**).

Table 6.6. Sensitivity analysis – Cox regression mortality analysis excluding patients with atrial fibrillation or atrial tachycardia, n=13 555.

	All Fatal Events (n= 13 555)
	HR (95% CI)
All individuals n= 13 555	4254 (31.4)
Low risk PHT Peak TR velocity <2.5 m/s n = 2264	499 (22.0) Reference
Borderline risk PHT Peak TR velocity 2.5 – 2.8 m/s n = 2943	837 (28.4) HR 1.31 (1.17-1.46)
Intermediate risk PHT Peak TR velocity 2.9 – 3.4 m/s n = 7139	2209 (30.9) HR 1.52 (1.38-1.68)
High risk PHT Peak TR velocity >3.4m/s n = 1209	709 (58.6) HR 3.72 (3.32-4.18)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; PHT = pulmonary hypertension; TR = tricuspid regurgitant.

Table 6.7. Sensitivity analysis – Cox regression mortality analysis excluding patients with paced rhythm at time of echo, n=15 549.

	All Fatal Events (n= 15 649)
	HR (95% CI)
All individuals **n= 15 649**	5055 (32.3)
Low risk PHT **Peak TR velocity <2.5 m/s** **n = 2564**	592 (23.1) Reference
Borderline risk PHT **Peak TR velocity 2.5 – 2.8 m/s** **n = 3382**	990 (29.3) HR 1.28 (1.16-1.42)
Intermediate risk PHT **Peak TR velocity 2.9 – 3.4 m/s** **n = 8229**	2604 (31.6) HR 1.50 (1.37-1.64)
High risk PHT **Peak TR velocity >3.4m/s** **n = 1474**	869 (59.0) HR 3.47 (3.13-3.86)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; PHT = pulmonary hypertension; TR = tricuspid regurgitant.

A further adjusted model was performed to account for the presence of AF and the degree of diastolic dysfunction with the inclusion of LAVi. This again confirmed a progressively increased risk of mortality from those with borderline-risk PHT onwards (**Table 6.8**). When diastolic grade was adjusted for in the regression model, the negative prognostic impact of progressively rising TRV was confirmed but became significant from intermediate risk PHT onwards (**Table 6.9**).

Table 6.8. Cox regression mortality analysis adjusting for age, sex, LAVi and presence of AF.

	All Fatal Events
	HR (95% CI)
Low risk PHT **TRV<2.5 m/s**	Reference
Borderline risk PHT **TRV 2.5 – 2.8 m/s**	HR 1.21 (1.00-1.48) P = 0.05
Intermediate risk PHT **TRV 2.9 – 3.4 m/s**	HR 1.52 (1.27-1.82)
High risk PHT **TRV >3.4m/s**	HR 3.35 (2.76-4.08)

Analyses adjusted for age, sex, LAVi and AF/atrial arrhythmia. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; PHT = pulmonary hypertension; TR = tricuspid regurgitant; LAVi = left atrial volume index; AF = atrial fibrillation. Age (per year) HR1.06 (CI 1.05-1.07), Gender – female versus male HR 0.69 (CI 0.64-0.75), AF/ atrial arrhythmia HR1.10 (CI 0.99-1.21), LAVi HR1.00 (0.99-1.001)

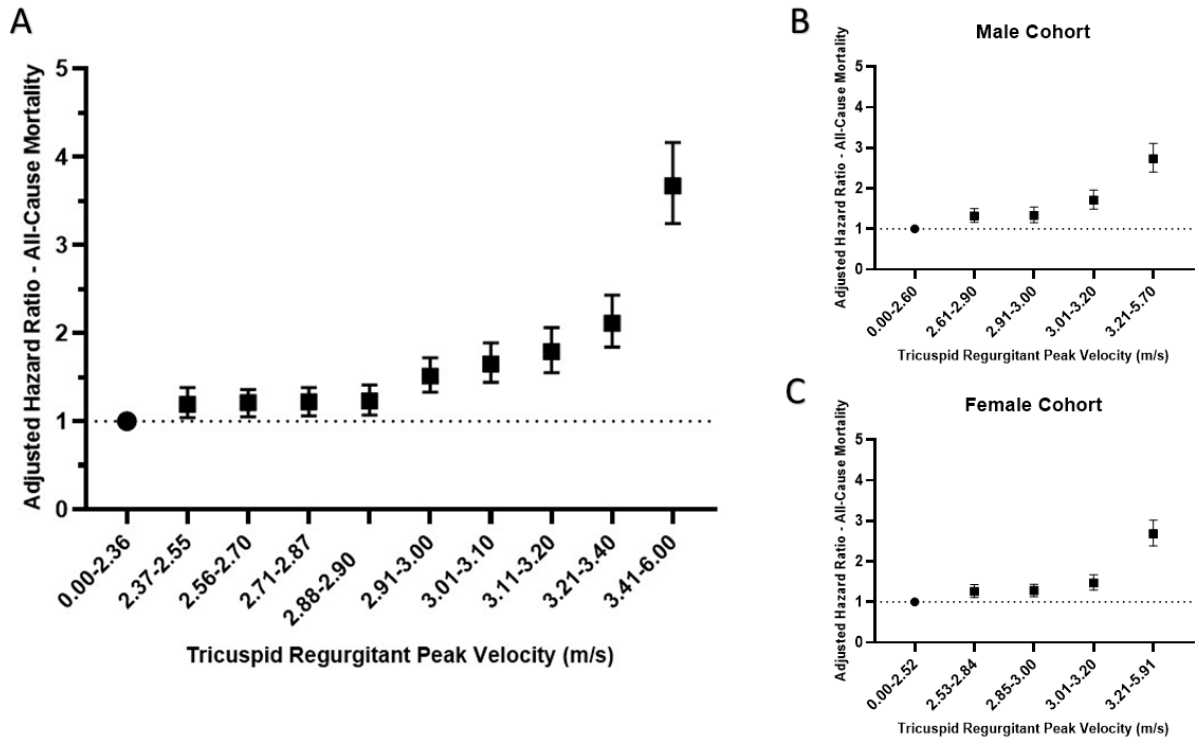
Table 6.9. Cox regression mortality analysis adjusting for age, sex, grade of diastolic dysfunction and presence of AF.

	All Fatal Events
	HR (95% CI)
Low risk PHT **TRV<2.5 m/s**	Reference
Borderline risk PHT **TRV 2.5 – 2.8 m/s**	HR 1.05 (0.88-1.26) P = 0.58
Intermediate risk PHT **TRV 2.9 – 3.4 m/s**	HR 1.10 (1.02-1.19)
High risk PHT **TRV >3.4m/s**	HR 2.15 (1.66-2.77)

Analyses adjusted for age, sex, diastolic grade and AF/atrial arrhythmia. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; PHT = pulmonary hypertension; TR = tricuspid regurgitant; AF = atrial fibrillation. Age (per year) HR1.05 (CI 1.04-1.05), Gender – female versus male HR 0.71 (CI 0.67-0.76), AF/ atrial arrhythmia HR1.06 (CI 0.97-1.15), diastolic grade (versus grade 1) LVDD grade 2, HR1.32 (CI1.07-1.64), LVDD grade 3 HR1.59 (CI1.29-1.97).

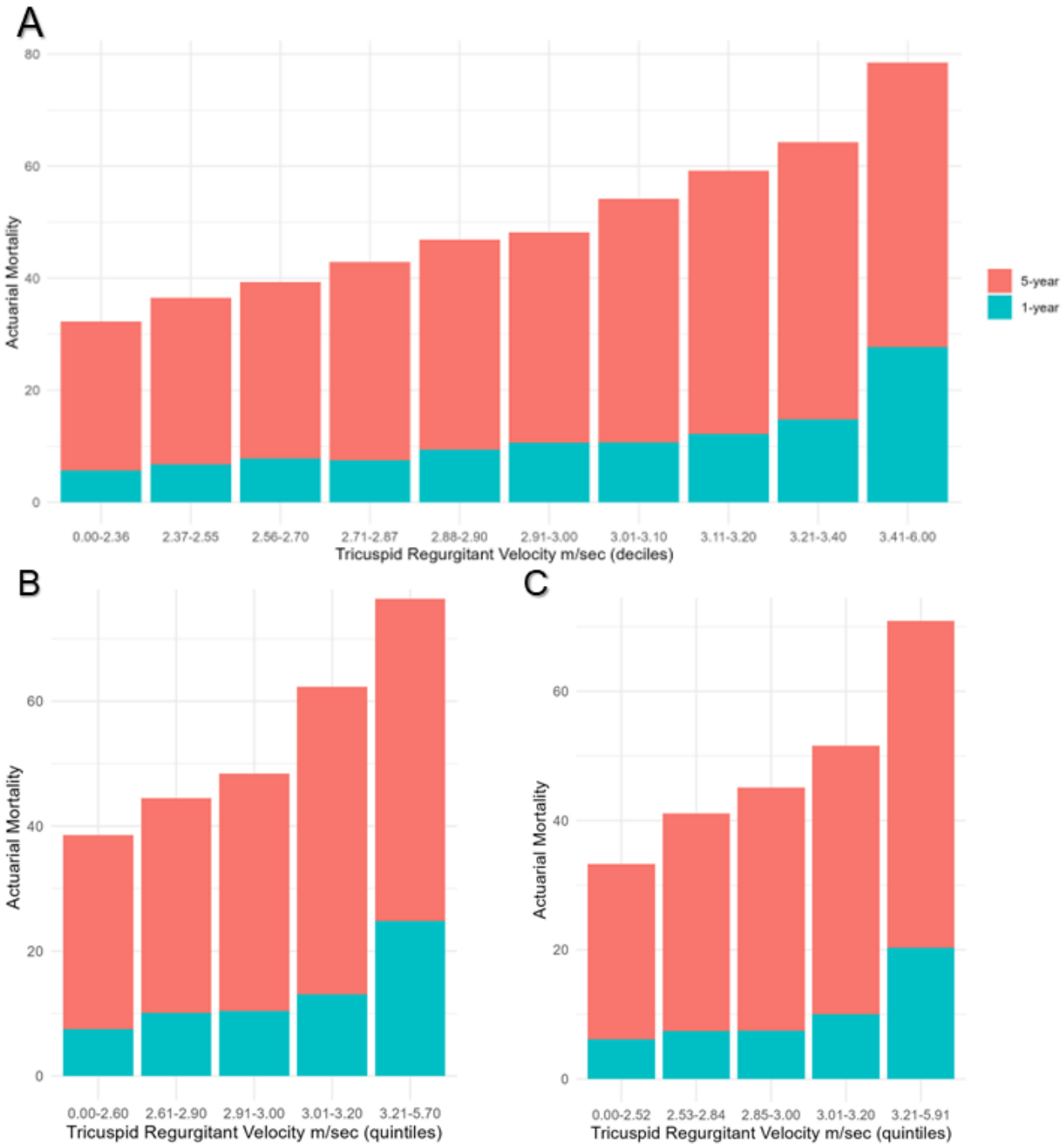
The regression model for the decile distribution of TRV, adjusted for age and sex showed a similar increased risk of mortality from the 2nd to 4th deciles (aHR range 1.19-1.23) with a distinct step up seen from the 5th decile onwards (aHR 1.51, 95%CI 1.33-1.72) (**Figure 6.4A**). **Figure 6.5A** shows the cumulative 1 and 5-year mortality of the total cohort split by decile distribution of TRV.

Figure 6.4. Threshold for Mortality according to Tricuspid Regurgitant Velocity



A) Total population: the decile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.37-2.55m/s. B) Male cohort: the quintile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.61-2.90m/s. C) Female cohort: the quintile distribution of tricuspid regurgitant peak velocity shows a threshold for mortality lies between 2.53-2.84m/s.

Figure 6.5. Cumulative 1- and 5-Year Survival



Figures show a progressive increase in cumulative 1- and 5-mortality as TRV increases in A) the TRV decile distribution of the total cohort, and, the TRV quintile distribution in the B) male cohort and C) female cohort.

There were more females than males within the cohort (n= 9216, vs n=6841), with survival data shown in **Tables 6.10 and 6.11** respectively. Short term mortality, assessed via 1-year actuarial mortality, increased progressively with worsening PHT-risk. Likewise, long-term, all-cause mortality showed a progressive risk in mortality as TRV increased (**Tables 6.10 and 6.11**). In both the male and female cohorts there was increased risk from the 2nd quintile (borderline-risk) with a marked step-up in mortality risk from the 4th quintile (intermediate-risk) onwards (**Figure 6.4B and 6.4C**). **Figure 6.5B and 6.5C** show the progressive cumulative 1 and 5-year mortality for each sex split by quintiles.

Table 6.10. Mortality data for male cohort, n = 6842

	1-Year Mortality (n= 6583) 96.2%	**5-Year Mortality (n= 3647) 53.3%**	**All Fatal Events N=6842**
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**
All individuals n= 6842	832 (12.7)	1936 (53.1)	2342 (34.2)
Low risk PHT TRV<2.5 m/s N = 1006	71/952 (7.5) Reference	195/518 (37.6) Reference	241 (24.0) Reference
Borderline risk PHT TRV 2.5 – 2.8 m/s N = 1386	127/1319 (9.6) OR 1.25 (0.93-1.70)	321/683 (47.0) OR 1.32 (1.03-1.68)	402 (29.1) HR 1.23 (1.04-1.44)
Intermediate risk PHT TRV 2.9 – 3.4 m/s N = 3826	439/3678 (11.9) OR 1.62 (1.25-2.11)	1058/2008 (52.7) OR 1.75 (1.42-2.15)	1312 (34.3) HR 1.55 (1.35-1.78)
High risk PHT TRV >3.4m/s N = 628	195/614 (31.8) OR 5.23 (3.88-7.05)	362/483 (82.6) OR 7.36 (5.34 -10.12)	387 (61.6) HR 3.55 (3.02-4.17)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension; TRV = tricuspid regurgitant velocity.

Table 6.11. Mortality data for female cohort, n=9216.

	1-Year Mortality (n= 8923) 96.9%	5-Year Mortality (n= 4798) 52.1%	All Fatal Events N=9216
	OR (95% CI)	**OR (95% CI)**	**HR (95% CI)**
All individuals n= 9216	869 (9.7)	2296 (47.9)	2875 (31.2)
Low risk PHT TRV<2.5 m/s N = 1605	93/1566 (5.9) Reference	265/836 (31.7) Reference	360 (22.4) Reference
Borderline risk PHT TRV 2.5 – 2.8 m/s N = 2089	149/2015 (7.4) OR 1.14 (0.87-1.49)	475/1053 (45.1) OR 1.48 (1.21-1.80)	615 (29.4) HR 1.32 (1.16-1.50)
Intermediate risk PHT TRV 2.9 – 3.4 m/s N = 4624	408/4460 (9.1) OR 1.51 (1.12-1.91)	1092/2295 (47.6) OR 1.75 (1.47-2.08)	1382 (29.9) HR 1.48 (1.32-1.66)
High risk PHT TRV >3.4m/s N = 898	219/882 (24.8) OR 4.84 (3.73-6.29)	464/614 (75.6) OR 6.38 (4.98 -8.15)	518 (57.7) HR 3.42 (2.99-3.92)

Analyses adjusted for age and sex. Values are n (%) or n/M (%), unless otherwise indicated. CI = confidence interval; HR = hazard ratio; OR = odds ratio; PHT = pulmonary hypertension; TRV = tricuspid regurgitant velocity.

Discussion

Findings from this contemporary, 'real world' clinical cohort study, including over 16 000 men and women with evidence of LV diastolic but not LV systolic dysfunction confirms both the echocardiographic phenotype, and increased risk of mortality seen with progressively elevated pulmonary pressures. Specifically, we have shown that there is a graded, independent, negative prognostic relationship between elevated TRV and mortality in LVDD adults, which begins from 'borderline-risk' PHT onwards and is consistent between both sexes.

PHT in subjects with LVDD and pEF is a sub-type of Group 2 PHT and is postulated to develop via the following mechanisms: triggers such as aging and obesity, as seen in our cohort, as well as co-morbidities such as hypertension and diabetes, lead to cellular changes such as myocyte thickening and fibrosis, as well as changes to the LV geometry causing concentric hypertrophy[2, 44, 60]. These changes lead to increased LV diastolic stiffness and impaired relaxation, which in turn drives increased LA fibrosis and stiffness. Ultimately, this causes "backward" transmission of elevated LA pressure into the pulmonary vasculature, causing post-capillary PHT[2, 44, 60].

Prevalence of PHT with LVDD and pEF

PHT is common in patients with LVDD and pEF, however, the prevalence reported in the literature is highly variable reflecting a lack of standardisation in definitions. Baseline echo findings from the TOPCAT study showed doppler evidence of PHT in 36% of subjects, whilst a landmark population based study reported echo evidence of PHT in 83%[22, 63]. Two catheter-based studies reported a prevalence of 53% and 77% respectively[24, 145]. Our large study, from both community and hospital-based echo laboratories, showed that >60% of the cohort had intermediate or high-risk PHT and were therefore likely to have PHT according to clinical guidelines[1].

Outcomes of subjects with LVDD and pEF

This large study confirms a graded, inverse relationship between worsening PHT risk and survival. Consistent with the growing literature from our group (as outlined in the previous chapters) and others, we identified that even those with borderline-risk PHT are associated with risk[12, 13, 104]. Subjects with TRV ≥2.5m/s (borderline and above) had a 1.28-3.47-fold adjusted hazard ratio of long-term all-cause mortality, dependent on the severity of PHT risk. These trends persisted when AF and level of diastolic dysfunction was adjusted for, and, was consistent between both sexes. The granularity afforded to us by the NEDA allowed us to identify a 'threshold' for excess mortality within the borderline-risk range through our decile analysis. This is consistent with two, smaller, prior studies (largest n=244), which highlighted cut-off's of 35mmHg, and, 39mmHg respectively as being able to discern subjects with worse prognosis[22, 139]. Whilst these prior studies suggest a linear relationship between raised pulmonary pressures and mortality risk[22], we showed mortality rates were similar from the 2nd to the 4th decile distribution of TRV (aHR range from 1.21 to 1.23), before a marked increase in mortality from the 5th decile (2.91-3.00m/s) onwards (aHR 1.51). A higher LVEF was shown to have a modest protective effect in our study, this may be associated with the improved cardiac output seen. However, given the variable prognostic impact of higher LVEF reported in LVDD populations and the unique impact of PHT in this cohort further studies are needed to determine the cause here. This study confirms the independent, negative prognostic impact of mild elevations of TRV in another important sub-set of LHD.

Clinical Implications

Whilst we do not report on treatment effect, our study had much larger numbers (previous largest, n=244) and, prospectively excluded other LHD, to focus our attention on the influence of PHT-risk *per se* in 'isolated' LVDD, allowing us to highlight important clinical implications. Firstly, we show that TRV on echocardiography can effectively determine risk of mortality. Given the high epidemiologic impact of both LVDD and PHT this important as echocardiography is a pragmatic, widely available

and cost-effective screening tool[1]. Secondly, this study suggests that the current guideline thresholds for PHT risk do not fully capture the clinical risk related to those with mild elevations of TRV[1]. The presence of increased PHT-risk is often a marker of a more advanced corollary of disease in patients with LVDD and pEF, and thus these patients require closer monitoring[44]. The universal health care coverage within Australia allows relative ease of access to echo services. This, together with a comprehensive National Death Index, makes these results both reliable and generalizable.

Study Limitations

NEDA provides detailed echocardiographic data and linkage to mortality; it does not yet however, provide granular clinical data such as symptoms, important co-morbidities such as hypertension, diabetes or coronary disease, or pharmacologic treatments. These can all impact each individual's health outcomes and thereby cause residual confounding in our models. In addition, individuals within this study may have had heart failure with preserved ejection fraction (HFpEF) or heart failure with recovered ejection fraction, however, without clinical data on symptoms or medications we were unable to confirm this clinical diagnosis. Most subjects included in the NEDA have had an echo for investigation of suspected or known cardiovascular disease and thus, should not be taken to reflect the population prevalence.

Consistent with our previous studies[12], data concerning PHT in NEDA is based on echocardiography-based measures, rather than the gold standard hemodynamic assessment at right heart catheterization. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107], supporting the broad validity of our approach. Furthermore, echocardiography remains the commonest screening tool to determine PHT risk and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow up. We acknowledge that TRV is one of the diagnostic criteria for LVDD and is also the variable used for PHT assessment which may introduce an element of bias into this study. However, the independent prognostic risk of raised TRV in this cohort was demonstrated in multiple sub-group and sensitivity analyses in this cohort, suggesting that this bias is unlikely to be significant. We also note that the absence of a tricuspid regurgitation 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 is lacking in quantitative RV measurements, with only a small minority of patients having recorded RV functional parameters, and the quality of more qualitative assessments could not be verified. Thus, we are unable to fully assess the impact of raised pulmonary pressures on the right heart, nor can we determine impact of RV abnormalities on mortality. Finally, we do not explore the 'drivers' of raised pulmonary pressures within this cohort, but plan to address this in future studies.

Conclusion

Both diastolic dysfunction and PHT confer an increased risk of mortality. In this large study, we demonstrate the prevalence and progressive, negative prognostic impact of increasingly elevated TRV levels in individuals with LV diastolic dysfunction. There was a threshold for mortality lying within the range of ‘borderline risk’ PHT.

Chapter 7 – Characteristics of Pulmonary Hypertension in Adults with Left Ventricular Diastolic Dysfunction

This chapter is based on the publication:

Ratwatte S, Stewart S, Strange G, Playford D, Celermajer DS. Characteristics of pulmonary hypertension in adults with left ventricular diastolic dysfunction. Open Heart 2025;12(1): e003174. https://doi.org/10.1136/openhrt-2025-003174.

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 LV ejection fraction (>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±12years 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>2.9m/sec). There was a progressive increase in indexed LA volume with rising TRV levels. AF and right ventricle (RV) dilation were strongly associated with the presence of PH (adjusted odds ratio, aOR 1.27; 95% confidence interval, CI, 1.12-1.43) and aOR 4.99 (95%CI 4.44-5.62) 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 0.32m/sec, RV dilation by 1.82m/sec, female sex by 0.32m/sec and age (per decade) by 0.3m/sec.

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

Introduction

Pulmonary hypertension is commonly found in adults with LVDD and pEF and its presence is known to have a negative prognostic impact on clinical outcomes[22, 143, 144]. Prior studies, including our work in *Chapter 6*, do not discern which adults with LVDD and pEF will develop PHT, only that it is a common occurrence.

Many adults with LVDD with pEF develop raised pulmonary pressures as a direct consequence of impaired LV relaxation and thence raised LA pressure[2, 44, 60]. PHT in this setting has adverse consequences[22, 139]. Cardiovascular risk factors such as AF and obesity are postulated to be important in the pathophysiology of this complication[44, 60, 146]. The characteristics of PHT in LHD may be complex. In studies focused on other left heart diseases such as mitral or aortic valve disease, the degree of PHT is independent of the severity of the valvular disease[44]. This has also been demonstrated in *Chapters 2-4*. The characteristics of PHT in adults with LVDD have not been well characterised in a large, contemporary clinical cohort.

Utilising data from the large National Echo Database of Australia (NEDA) we performed further analyses on the cohort of adults with LVDD and pEF as previously defined in *Chapter 6*, 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 multi-centre database that captured basic demographic and detailed echocardiographic data from all participating centres Australia-wide[12, 99]. 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 (NDI), to obtain mortality data for each individual. At the time of analysis, NEDA contained >1million echo reports from >600 000 subjects, from January 2000 to June 2019. Median follow up was 6.2 years, IQR 3.8-9.8years. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and 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.

Study Cohort

As per recent guidelines, PHT was defined as a TRV >2.9 m/sec[1]. LVDD was determined via the ASE//EACVI guidelines[75, 103]. LVDD was defined as those meeting 3 or more (>50%) of the following parameters being positive: 1) E/e'>14, 2) septal e' velocity <7cm/s or lateral e' velocity < 10cm/s, 3) TRV >2.8m/s and 4) LAVi >34mL/m^2. LVEF values had to be quantified, and consistent with guidelines[137]. AF and atrial arrhythmia was determined by text extraction or mitral inflow pattern, as previously described[103]. RV size was described qualitatively, using text extraction from echo reports.

This Study Flow diagram (and thus the cohort analysed) is the same as that documented in Chapter 6 (**Figure 6.1**). To summarise, to be included in the analysis, subjects were >18yrs, 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 ± standard deviation (SD). Chi-squared 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 ANOVA analysis 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- 0.00-2.36m/s, 2nd- 2.37-2.55m/s, 3rd- 2.56-2.70m/s, 4th- 2.71-2.87m/s, 5th- 2.88-2.90m/s, 6th- 2.91-3.00m/s, 7th- 3.01-3.10m/s, 8th- 3.11-3.20m/s, 9th- 3.21-3.40m/s and 10th- >3.40m/s. The decile distribution for the AF cohort (n = 2503) was 1st decile- 0.00-2.40m/s, 2nd- 2.41-2.60m/s, 3rd- 2.61-2.80m/s, 4th- 2.81-2.90m/s, 5th- 2.91-2.97m/s, 6th- 2.98-3.00m/s, 7th- 3.01-3.10m/s, 8th- 3.11-3.24m/s, 9th- 3.25-3.50m/s and 10th- >3.50m/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 was 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 PH in patients with LVDD. Further sensitivity analyses was performed on the cohort with LAVi documented (n=9872). All analyses were performed with SPSS software v25.0 (IBM Corp), 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%) female. When rhythm was assessed at time of echocardiogram, 2503 (15.6%) were in AF and 13 555 (84.4%) were in sinus rhythm. Mean BMI was 28.9kg/m^2. **Table 7.1** 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 to the subjects without PHT.

Table 7.1. Baseline Characteristics of patients with left ventricular diastolic dysfunction stratified by presence of pulmonary hypertension

	LVDD without PHT TRV <2.9m/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			
eRSVP, mmHg	33.82±5.88	50.31±10.22	<0.0001
TR peak velocity, m/s	2.50±0.25	3.17±0.34	<0.0001
Dilated RV*	482 (7.9)	3638 (36.5)	<0.0001

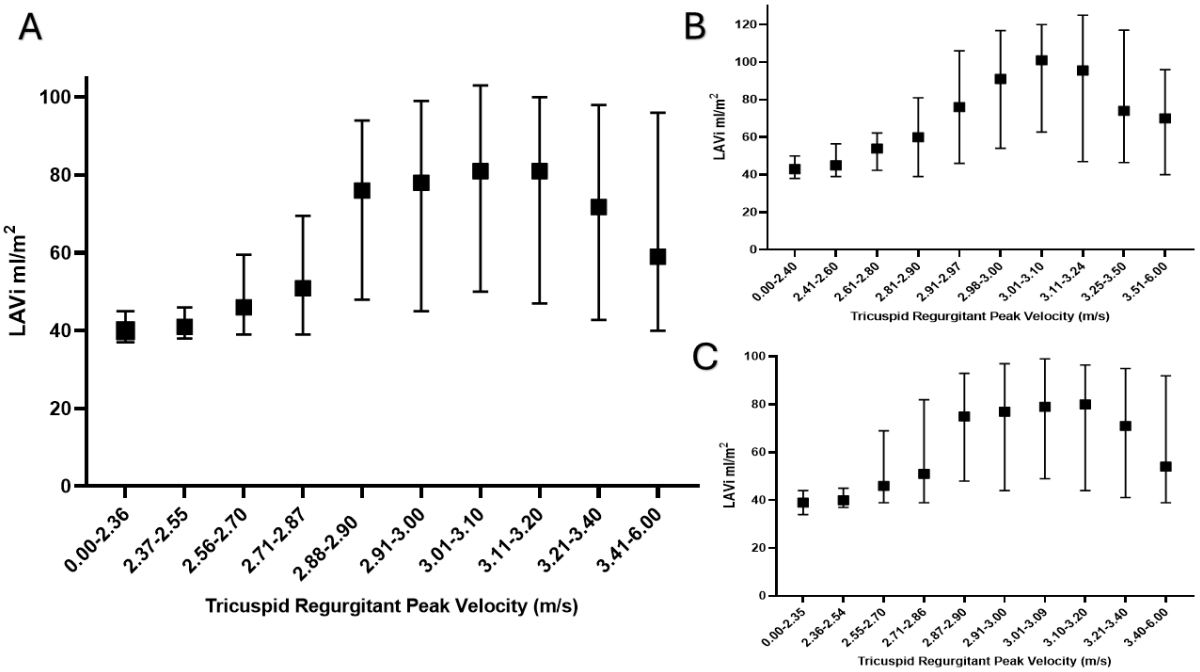
*Values are n (%) unless otherwise indicated. TR = tricuspid regurgitant; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LA = left atrial; RA = right atrial; eRVSP = estimated right ventricular systolic pressure RV = right ventricle. *Qualitative assessments based on text extraction from echo reports.*

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 7.2A** shows the association between LAVI and TRV in the total, AF and sinus rhythm cohort 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 (**Figure 7.2B**) compared with sinus rhythm (**Figure 7.2C**) cohorts, though the overall trends mirrored those of the total cohort. **Figure 7.3A** 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 7.4A**. These trends were present in both the AF and sinus rhythm cohorts (**Figures 7.3B/C and 7.4B/C** respectively), though the AF cohort had a higher median age at each decile compared to those in sinus rhythm.

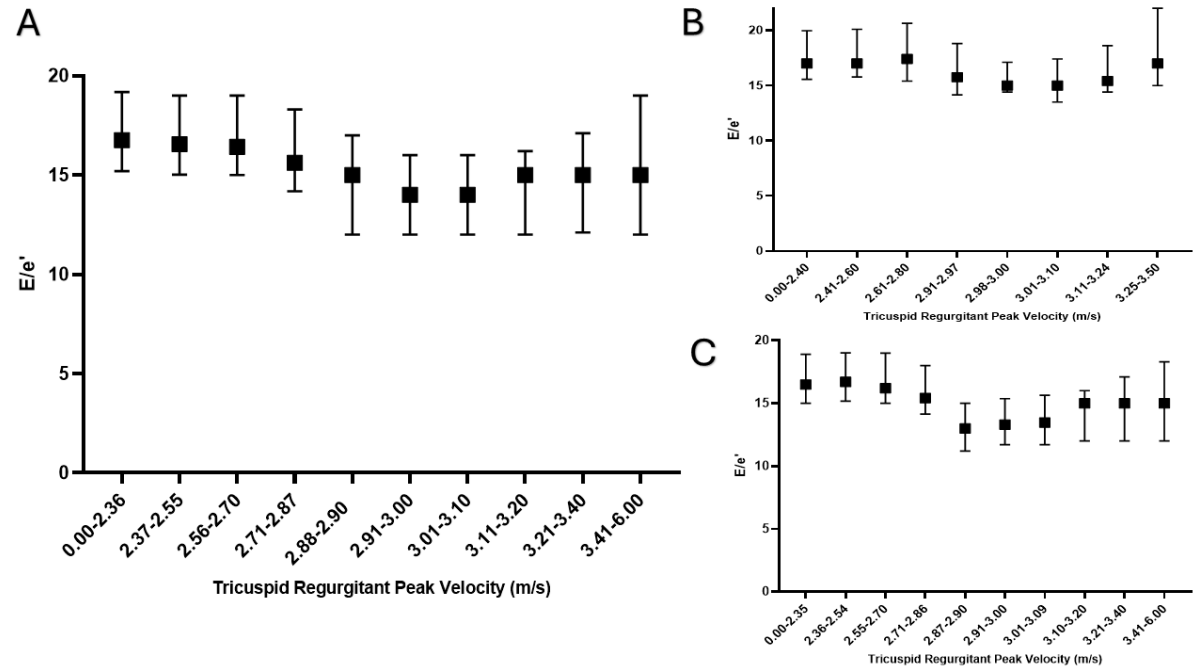
Figure 7.5 shows the distribution of LAVI against E/e'. The Spearman correlation co-efficient was -0.180 (p=<0.0001).

Figure 7.2. Univariate correlation between LAVi and TRV



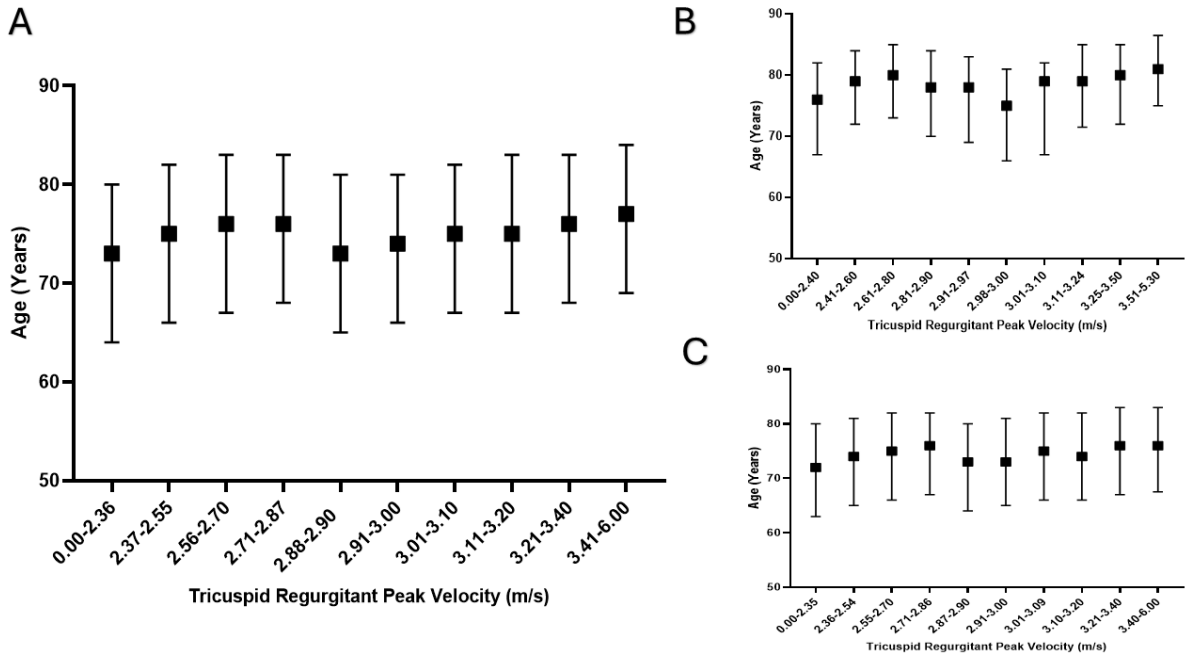
Correlation between LAVi and TRV deciles showing a progressive increase in LAVi as TRV decile increases before a plateau is noted in A) total cohort, B) AF cohort and, C) sinus rhythm cohort.

Figure 7.3. Univariate correlation between E/e' and TRV



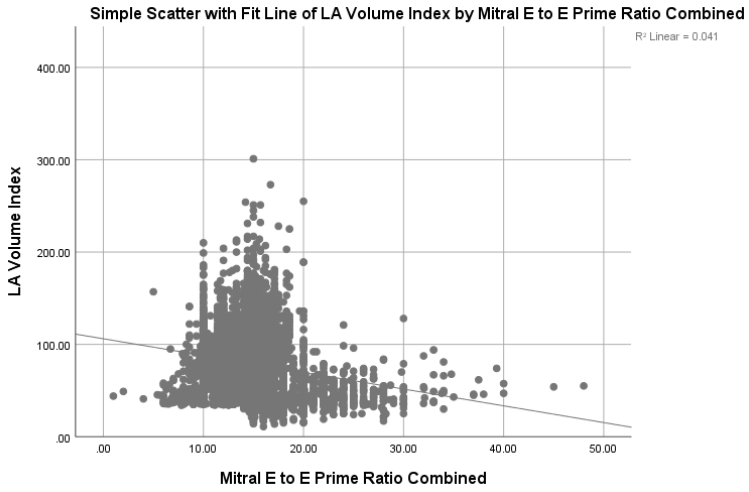
No clear correlation noted between E/e' and TRV deciles noted in A) total cohort, B) AF cohort and, C) sinus rhythm cohort.

Figure 7.4. Univariate correlation between age and TRV



No clear correlation noted between age and TRV deciles noted in A) total cohort, B) AF cohort and, C) sinus rhythm cohort.

Figure 7.5. Correlation between LAVi and E/e'



Spearman correlation co-efficient was -0.180 suggesting a weak negative correlation between the two parameters.

Factors associated with the presence of PHT in LVDD

Among the 16,058 subjects with LVDD and pEF, 9976 (62.1%) had PHT. **Table 7.2** 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 odds ratio (aOR) 1.27, 95% confidence interval (CI) 1.12-1.43, and aOR 4.99 (95%CI 4.44-5.62) respectively), whilst increased age, LVEF and BMI were 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 **Table 7.3**. **Table 7.4** 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 (aOR1.01, 95%CI 1.01-1.02) and female sex was a predictive variable.

Table 7.2. Parameters associated with Pulmonary Hypertension

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

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Table 7.3. Sensitivity analysis - Parameters associated with Pulmonary Hypertension, cohort with LAVi reported (n=9872)

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	1.0001 (0.998-1.004)	1.28 (1.12-1.49), p=0.001
Gender	0.93 (0.85-1.02)	1.02 (0.98-1.03), p=0.06
AF	1.10 (1.03-1.16)	1.13 (1.05-1.23), p<0.0001
E/e'	0.81 (0.80-0.83)	0.84 (0.83-0.86), p<0.0001
LVEF	1.06 (1.05-1.06)	1.02 (1.02-1.03), p<0.0001
BMI	1.04 (1.03-1.05)	1.01 (1.00-1.02), p=0.01
RV dilation	6.12 (5.35-7.00)	2.99 (2.45-3.48), p<0.0001

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Table 7.4. Predictors of Pulmonary Hypertension (LAVi included)

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	1.0001 (0.998-1.004)	1.02 (1.01-1.02), p<0.0001
Gender	0.80 (0.75-1.002)	1.30 (1.12-1.51), p<0.0001
LAVi	1.16 (1.06-1.27)	1.01 (1.00-1.01), p<0.0001
E/e'	0.87 (0.86-0.88)	0.85 (0.83-0.86), p<0.0001
LVEF	1.06 (1.05-1.06)	1.02 (1.01-1.03), p<0.0001
BMI	1.03 (1.02-1.04)	1.01 (0.99-1.02), p=0.07
RV dilation	6.67 (6.03-7.38)	2.44 (2.01-2.96), p<0.0001

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Tables 7.5 and 7.6 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 PHT presence in the sinus rhythm but not the AF cohort.

Table 7.5. Predictors of Pulmonary Hypertension, AF cohort = 2503

	Univariate OR (95% CI)	**Multivariate OR (95% CI)**
Age	1.01 (0.998-1.01)	1.03 (1.01-1.05), p=0.001
Gender	0.81 (0.69-0.96)	1.19 (0.81-1.75), p=0.38
LAVi	1.03 (1.02-1.03)	1.01 (1.01-1.02), p=0.001
E/e'	0.93 (0.91-0.95)	0.93 (0.89-0.97), p<0.0001
LVEF	1.05 (1.04-1.06)	1.03 (1.01-1.04), p=0.009
BMI	1.05 (1.03-1.07)	1.05 (1.01-1.08), p=0.004
RV dilation	5.83 (4.65-7.29)	2.52 (1.52-4.17), p<0.0001

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Table 7.6. Predictors of Pulmonary Hypertension, sinus rhythm cohort = 13 555

	Univariate OR (95% CI)	**Multivariate OR (95% CI)**
Age	1.00 (0.99-1.003)	1.01 (1.01-1.02), p<0.0001
Gender	0.81 (0.75-1.002)	1.32 (1.12-1.56), p=0.001
LAVi	1.03 (1.02-1.03)	1.01 (1.00-1.01), p=0.008
E/e'	0.85 (0.84-0.86)	0.83 (0.81-0.85), p<0.0001
LVEF	1.06 (1.05-1.06)	1.02 (1.01-1.03), p<0.0001
BMI	1.03 (1.02-1.04)	1.01 (0.99-1.02), p=0.43
RV dilation	6.89 (6.14-7.72)	2.41 (1.96-2.97), p<0.0001

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

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 7.7**). All were strongly and independently associated with the severity of PH 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 0.32m/sec, the presence of RV dilation increased it by 1.82m/sec and female sex increased it by 0.32m/sec. For every 10 years increase in age there was a 0.3m/sec increase in TRV , whilst for every 10% increase in LVEF there was a 0.3m/sec increase in TRV. In contrast, lower E/e' reduced the TRV. Similar trends were seen when the base model included LAVi instead of AF (**Table 7.8**) and in the sensitivity analysis of the cohort with complete LAVi data (**Table 7.9**).

Table 7.7. Predictors of the Severity of Pulmonary Hypertension

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

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Table 7.8. Sensitivity Analysis - Predictors of the Severity of Pulmonary Hypertension with LAVI as predictor

	B	Standard Error	T statistic	CI	P value
Age	0.02	0.002	8.53	(0.01-0.02)	<0.0001
Gender	0.32	0.06	5.77	(0.21-0.43)	<0.0001
LAVi	0.01	0.001	4.86	(0.003-0.006)	<0.0001
E/e'	-0.02	0.007	-3.13	(-0.04- -0.01)	0.002
LVEF	0.006	0.003	2.11	(0.00-0.01)	0.04
BMI	-0.007	0.004	-1.90	(-0.02-0.001)	0.06
RV dilation	1.23	0.06	14.98	(1.10-1.33)	0.001

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

Table 7.9. Sensitivity Analysis - Predictors of the Severity of Pulmonary Hypertension, cohort with LAVi reported; n = 9872

	B	Standard Error	T statistic	CI	P value
Age	0.02	0.002	8.43	(0.01-0.02)	<0.0001
Gender	0.32	0.06	5.67	(0.21-0.43)	<0.0001
AF	0.22	0.07	3.03	(0.08-0.36)	0.002
E/e'	-0.03	0.007	-3.94	(-0.04- -0.01)	<0.0001
LVEF	0.009	0.003	3.52	(0.004-0.01)	<0.0001
BMI	-0.007	0.004	-1.69	(-0.01-0.001)	0.09
RV dilation	1.07	0.06	18.11	(1.10-1.33)	0.001

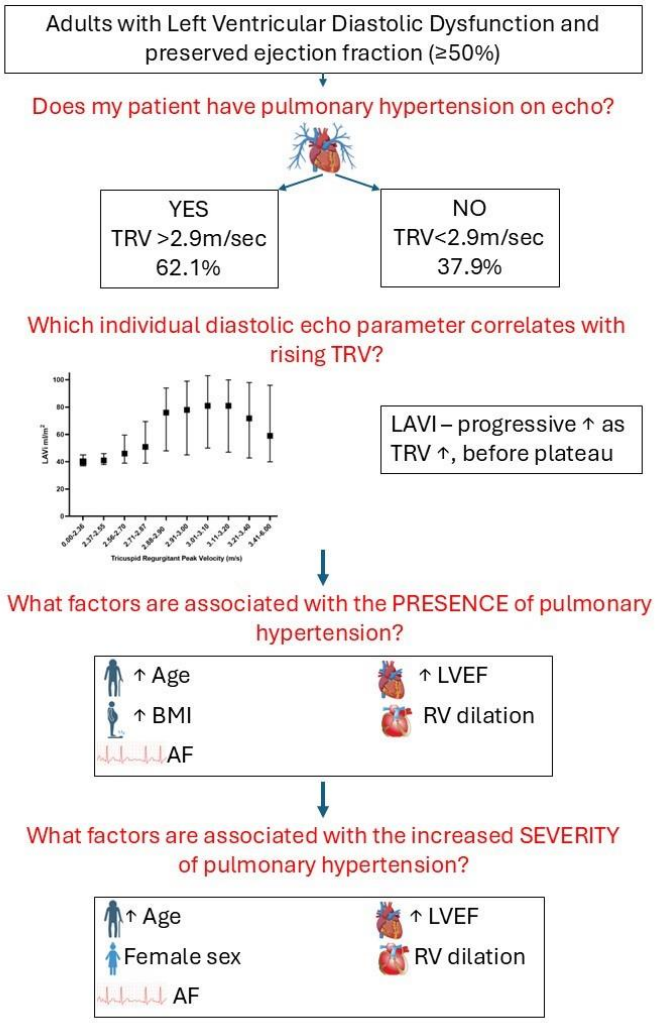
AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; RV = right ventricle.

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 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, whilst BMI was associated with the presence but not the severity of PHT (**Figure 7.6**).

Prior, smaller population-based trials have reported conflicting data regarding the demographic, clinical and echo characteristics of patients with LVDD, with and without PHT[22, 24]. The largest previous cohort (n=455) identified advanced age (>80 years), obesity and atrial arrhythmias as being strong, independent predictors of PHT[44]. Two even smaller studies confirmed advanced age as a predictor of PHT but differed on the key echo parameters associated with PHT[22, 147]. Lam et al identified increased LA size as a predictor, whilst Thennapan identified right atrial and ventricular enlargement[22, 147]. Whilst early studies documented a positive correlation between the magnitude of pulmonary pressure elevation and the degree of diastolic dysfunction as assessed on echo[148], more recent studies have suggested that this correlation is weak, possibly suggesting an additional pre-capillary component driving the raised pulmonary pressures[22, 24].

Figure 7.6. Factors associated with the Presence and Severity of Pulmonary Hypertension in Adults with Left Ventricular Diastolic Dysfunction



The factors associated with the presence and severity of pulmonary hypertension in adults with left ventricular diastolic dysfunction.

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[44, 60]. 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[44, 141, 146]. Similar to other studies, we showed that increasing LAVi and AF were both key predictors of PHT within this cohort[22, 24], although they are closely associated with each other[103, 149].

Age has been shown to have an important influence on both the worsening of diastolic dysfunction and the development of PHT[108, 150]; 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 PH, however, it did not predict the severity of PHT within our cohort[24]. Interestingly, animal and human studies have shown that myocardial fat deposition seen in obesity is a predictor of LVDD[151, 152]. 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 versus group 2 only) may explain varying results[153]. 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[44].

Our findings regarding RV dilatation 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 pathophysiologic 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 PH 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 co-morbidities such as hypertension, diabetes, obstructive sleep apnea or coronary disease, or pharmacologic 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 preserved ejection fraction. 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[12], data concerning PHT in NEDA is based on echocardiography-based measures, rather than the gold standard hemodynamic assessment at right heart catheterization. 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 post-capillary PHT from those with mixed pre- and post- capillary PHT. However, prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure[72, 107], 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 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 is 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.

Conclusion

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

Chapter 8 – Impact of Transcatheter Aortic Valve Implantations on Right Ventricular Function

This chapter is based on the publication: Ratwatte S, Coelho B, Ng MK, Celermajer DS. Impact of Transcatheter Aortic Valve Implantation on Right Ventricular Function. Heart Lung Circ. 2025 May;34(5):456-466. doi: 10.1016/j.hlc.2024.11.017.

Abstract

Background: The prevalence and predictors of right ventricular (RV) dysfunction before and after TAVI are not known. We aimed to document this and sought to identify specific RV echo thresholds, below which RV improvement was unlikely to occur.

Methods: Consecutive patients who underwent TAVI between 2017-2021 at Macquarie University Hospital (MUH) were included if 2 or more RV functional parameters were available on baseline echo; tricuspid annular plane systolic excursion (TAPSE), tissue Doppler (S') and/or RV fractional area change (FAC). Prevalence and predictors of baseline RV dysfunction were documented. Patients with a repeat echo performed at MUH at 1-3-months post-TAVI were included in further analyses to assess serial changes in RV function.

Results:
343 patients had an eligible baseline echo and 97 of these patients (28.2%) had RV dysfunction, pre-TAVI. These patients had significantly higher rates of atrial fibrillation (AF), ischaemic heart disease (IHD) and chronic lung disease (CLD), than those without ($p<0.05$ for all). Of 239 patients with 1-3-month follow-up echo data, 66 of these had had baseline RV dysfunction; of these, 20 (30.3%) patients showed improvement and 46 (69.7%) patients showed persistent RV dysfunction. Thresholds with a greater than 90% predictive value for persistent RV dysfunction were identified for each baseline RV functional parameter: TAPSE <1.4 cm, S'<6, FAC<25%.

Conclusions: Baseline RV dysfunction was present in over a quarter of pre-TAVI patients and persisted at short-term follow-up in over two-thirds of such patients. There were clear thresholds to identify patients where RV recovery was unlikely, at short-term follow-up after TAVI.

Introduction

Aortic stenosis is the commonest valve pathology in developed countries, with transcatheter aortic valve implantation (TAVI) being one of the mainstays of treatment, alongside surgical aortic valve replacement[109]. These interventions have clearly been shown to lead to reverse LV remodelling following the correction of AS and this has a positive impact on outcomes[154-156]. Recently, there has been a greater focus on the right heart in these patients. For example, in *Chapter 3*, we documented the negative prognostic impact of even mildly raised pulmonary pressures in patients with significant AS. Furthermore, raised pulmonary pressures and right ventricular (RV) systolic dysfunction have now been included in well-validated "cardiac damage scores", for risk stratification of patients with severe AS, as markers of advanced disease and poor prognosis[110, 111].

The prevalence, and importantly, the predictors of RV dysfunction in severe AS have not been comprehensively documented previously, nor have the potential changes in RV function following TAVI. Prior studies have primarily focused on the prognostic role of baseline RV dysfunction, used qualitative or only semi-quantitative assessments and have had relatively small sample sizes[157-160]. Hence, there is limited data providing quantitative assessments of RV function at follow-up after TAVI.

We therefore aimed to report the prevalence and predictors of baseline RV dysfunction in a cohort of patients with severe AS prior to undergoing TAVI. We then assessed changes in RV function following successful TAVI and sought to identify specific echo-based thresholds where RV improvement was unlikely to occur.

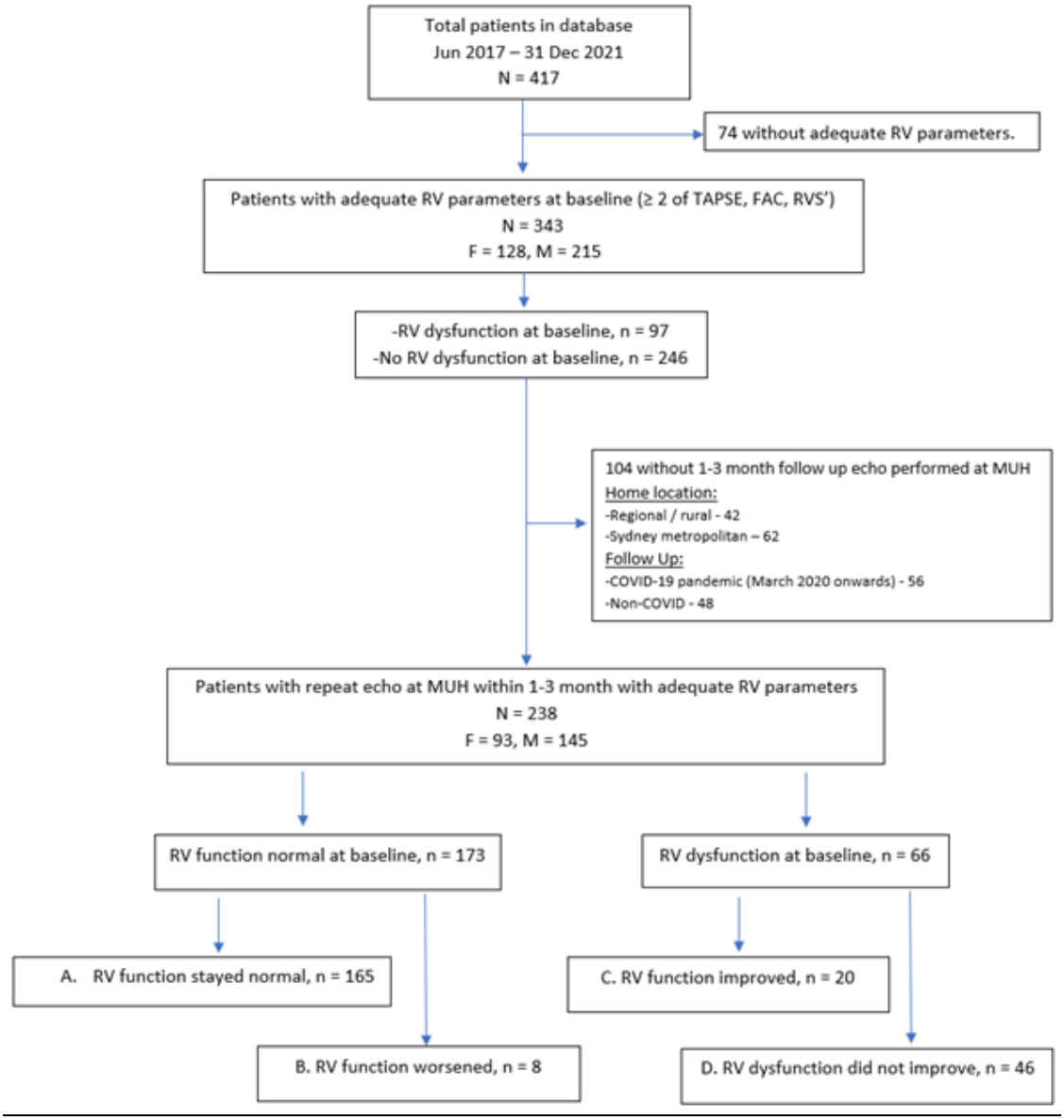
Methods

Study Population

The population included consecutive patients with severe aortic stenosis (confirmed by echo and discussed at a structural heart multi-disciplinary meeting) treated with TAVI at Macquarie University Hospital (MUH), (Sydney Australia) from June 2017 to December 2021. **Figure 8.1** shows our study flow diagram. To be included in the analysis, subjects had to have a baseline echocardiogram with adequate RV parameters to determine RV function at baseline (defined as ≥2 parameters). Parameters used to assess RV function included tricuspid annular plane systolic excursion (TAPSE), systolic movement of the RV lateral wall by tissue Doppler (S') and fractional area change (FAC). As per guideline recommendations, a transthoracic echo was performed at 1-3 months post TAVI procedure. Patients with a repeat echo performed at MUH at 1-3 months post TAVI with (i) a successful TAVI result, defined as per the Valve Academic Research Consortium-3 (VARC-3) guidelines[161] which includes freedom from death, successful access, delivery of device and correct positioning of a single prosthetic heart valve into the proper anatomical location as markers of technical success, and, (ii)

adequate RV functional parameters (defined as ≥2 parameters) were included in further analyses to assess serial changes in RV function post TAVI.

Figure 8.1. Study Flow Diagram



This flowchart shows the points of analysis performed in this study. RV = Right Ventricle, TAPSE = Tricuspid Annular Plane Systolic Excursion, RVS'= right ventricle systolic prime, FAC = fractional area change, MUH = Macquarie University Hospital

Pre-specified demographic, clinical, procedural data were prospectively collected for all patient's pre-procedure, during admission and during follow-up. Co-morbidities such as chronic lung disease (CLD) (as defined by the clinical team and correlated with pre-assessment spirometry), CKD (defined as stage 3, GFR≤60mL/min or worse) and AF (either paroxysmal or permanent) were documented if deemed significant by MDT as assessed on pre-procedure pathology, ECGs and lung function tests. Data was input into the MUH TAVI database. This data was retrospectively analysed in this study. Human ethics approval was obtained from both the Ethics Committee at Macquarie University Hospital, Sydney, Australia (protocol MQHREC #12086) and the Sydney Local Health District Ethics Committee, Australia (protocol SLHDHREC #X21-0406 & 2021/ETH11826). A retrospective waiver of consent was authorised as part of this ethics protocol.

Echocardiographic Assessment

Transthoracic echocardiograms were performed by experienced echocardiographers in accordance with ASE guidelines[102] for each patient at baseline (prior to TAVI procedure) and, where available, at 1-3 months follow-up (post TAVI procedure). Interpretation and analysis at the time was performed by cardiologists with expertise in structural heart disease. Post-TAVI echoes were performed at the MUH echo lab by the same group of experienced sonographers.

A comprehensive analysis of each patient's RV size and function was performed with each echo re-reviewed to assess RV function. Abnormal thresholds for these parameters were as per ASE guidelines[162]: TAPSE <1.7cm, S' < 9.5cm/s and FAC <0.35. RV dysfunction was defined as >50% of the available RV function parameters being abnormal. RV function was normal if <50% of parameters were abnormal. If 50% of these parameters were abnormal a hierarchal approach was taken with TAPSE <1.7cm being the primary parameter, then S' <9.5, then FAC<0.35[157, 162]. RV size was determined by measurements of RV basal and mid segment diameters made on focused RV apical views. Right ventricle-to-pulmonary artery (RV-PA) coupling was also assessed using the ratio of TAPSE / PASP with ≤0.55mm/mmHg considered significant uncoupling[163, 164].

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis was used to determine whether the trend of the mean across the categorical groups of RV dysfunction was linear. For binary variables, the chi-squared test was used to determine if there was a trend in the change in proportions across the groups stratified by RV function.

Inter-observer variability for classification of RV function category by each parameter was assessed by repeat analysis of 30 randomly selected cases of the total cohort using Cohen's Kappa method.

Logistic regression models were used to derive the adjusted odds ratios (OR) to determine predictors of RV dysfunction at baseline. Entry into multi-variable model included variables which were clinically likely to impact outcome and had a univariate p-value <0.05. Changes in echo characteristics between baseline and follow-up within respective groups were assessed using the paired T-Test.

In patients with RV dysfunction at baseline who had follow-up imaging performed at 1-3 months post TAVI, a threshold where RV dysfunction was unlikely to recover was determined for each individual RV functional parameter. This threshold was defined as the value for each parameter where >90% patients do not recover (<10% chance of recovery).

A further sub-group analysis was performed in patients with persistent RV dysfunction at follow-up to assess for deterioration versus improvement for each RV functional parameter in this cohort using a paired sample t-test.

All analyses were performed with SPSS software version 22.0 (IBM Corp, Armonk, New York), and statistical significance was accepted at a 2-tailed p-value of <0.05.

Results

Prevalence of RV dysfunction

Among the 417 patients with severe AS who underwent TAVI during the study period, 343 had a baseline echo with sufficient quality to perform an RV functional assessment (**Figure 8.1**). **Table 8.1** shows the demographics, co-morbidities and severity of AS between the patients the 343 patients included and 74 patients who did not have sufficient data for an RV assessment; there were no significant differences between these groups. Of the 343 patients, 97 (28.2%) had RV dysfunction at baseline. TAPSE was available for 336 (98.0%), S' for 331 (96.5%) and FAC for 302 (88.0%). RV-PA coupling was able to be calculated for 159 (46.4%). Inter-observer variability was 0.94 for TAPSE, 0.90 for S' and 0.81 for FAC.

Table 8.1. Baseline demographics, co-morbidities and severity of aortic stenosis in study cohort compared to excluded patients

	Study Cohort (Adequate baseline echo to assess RV function) n = 343	**Excluded patients (Baseline echo cannot adequately assess RV function) n = 74**	**P value**
Demographics			
Age	82 ± 8	81 ± 7	0.38
Sex (Female)	128 (37.3)	28 (38.0)	0.91
Anthropometrics			
BSA	2.30 ± 4.25	2.10 ± 0.24	0.16
BMI	27.9 ± 5.5	28.6 ± 6.5	0.39
Rhythm			
Atrial fibrillation	119 (34.7)	20 (27.0)	0.07
Co-morbidities			
Hypertension	288 (84.2)	58 (78.4)	0.57
Ischemic Heart Disease			
-Prior IHD	-157 (45.8)	-30 (40.5)	0.51
-Prior acute MI	-43 (12.6)	-12 (16.2)	0.48
-Prior PCI	-101 (29.5)	-16 (21.6)	0.17
-Prior CABG	-58 (16.9)	-12 (16.2)	0.96
Prior balloon aortic valvuloplasty	15 (4.4)	3 (4.1)	0.56
Diabetes mellitus	112 (32.7)	18 (24.3)	0.23
Prior CVA	22 (6.4)	7 (9.5)	0.11
Chronic kidney disease	121 (35.4)	24 (32.4)	0.30
Dialysis	2 (0.6)	1 (1.4)	0.46
Chronic lung disease	111 (35.7)	23 (31.1)	0.90
Baseline Echo Parameters			
LVEF	53 ± 10	55 ± 13	0.18
AV peak velocity	4.03 ± 0.69	4.06 ± 0.65	0.75
AV mean gradient	41 ± 14	42 ± 15	0.53
AVA cm	0.80 ± 0.32	0.82 ± 0.24	0.72

Values are n (%) unless otherwise indicated. IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; NHYA = New York Heart Association; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; AV = aortic valve; AVA = aortic valve area.

239 patients with successful TAVI had echocardiography at 1-3 month follow-up available for RV functional assessment (Figure 1). **Table 8.2** shows the demographics, comorbidities and echo characteristics of the 239 patients with adequate follow-up imaging compared the 104 patients without; there were few significant differences between these groups. Of the 239 patients, 173 had normal RV function at baseline. At 1–3-month follow-up post TAVI, 165 (95.4%) of these patients had persistently normal RV function, whilst 8 (4.6%) had worsened with new RV dysfunction. RV dysfunction was present at baseline in 66 patients, with 20 (30.3%) patients showing improvement and 46 (69.3%) patients showing persistent RV dysfunction at 1-3 months follow-up post TAVI.

Table 8.2. Baseline demographics, co-morbidities and echo characteristics of patients with follow-up imaging available versus those without

	Patients with baseline and follow up echo at MUH n = 239	**Patients with baseline echo but no follow up echo at MUH n = 104**	**P value**
Demographics			
Age	82 ± 7	83 ± 9	0.11
Sex (Female)	93 (38.9)	34 (32.7)	0.30
Anthropometrics			
BSA	2.32 ± 0.36	2.26 ± 0.38	0.90
BMI	28.1 ± 5.7	27.7 ± 5.2	0.61
Rhythm			
Atrial fibrillation	78 (32.8)	42 (40.4)	0.24
Co-morbidities			
Hypertension	202 (84.9)	86 (82.7)	0.62
Ischemic Heart Disease			
-Prior IHD	-110 (46.2)	-48 (46.2)	0.96
-Prior acute MI	-26 (10.9)	-17 (16.3)	0.17
-Prior PCI	-69 (29.0)	-32 (30.8)	0.76
-Prior CABG	-44 (18.5)	-14 (13.5)	0.23
Prior balloon aortic valvuloplasty	10 (4.2)	5 (4.8)	0.82
Diabetes mellitus	79 (33.2)	33 (31.7)	0.73
Prior CVA	16 (6.8)	6 (5.8)	0.71
Chronic kidney disease	81 (34.0)	40 (38.5)	0.55
Dialysis	0 (0.0)	2 (1.9)	0.03

Chronic lung disease	84 (35.9)	27 (26.0)	0.88
Baseline Echo Parameters			
LVEF	53 ± 10	53 ± 10	0.54
LVEDD	4.54 ± 0.72	4.61 ± 0.72	0.49
LVESD	3.13 ± 0.83	3.12 ± 0.87	0.90
E/E'	19.2 ± 7.7	20.6 ± 9.1	0.19
RA size cm^2	21 ± 7	22 ± 7	0.55
LAVi	53 ± 16	55 ± 21	0.36
TAPSE	2.06 ± 0.48	2.05 ± 0.50	0.94
FAC	37 ± 10	34 ± 9	0.03
RVS'	10.4 ± 2.6	10.5 ± 2.7	0.64
RV basal diameter	4.09 ± 0.69	4.10 ± 0.66	0.93
RV mid diameter	2.8 ± 0.5	2.8 ± 0.6	0.91
PASP	37.80 ± 14.02	36.89 ± 13.04	0.66
AV peak velocity	4.02 ± 0.66	4.06 ± 0.77	0.59
AV mean gradient	41 ± 13	42 ± 16	0.50
AVA cm	0.79 ± 0.28	0.81 ± 0.40	0.55
Tricuspid Regurgitation			0.50
-Mild	102 (42.7)	52 (50.0)	
-Moderate	27 (11.3)	12 (11.5)	
-Severe	8 (3.3)	1 (1.0)	
Mitral Regurgitation			0.62
-Mild	137 (57.3)	54 (51.9)	
-Moderate	26 (10.9)	15 (14.4)	
-Severe	2 (0.8)	2 (1.9)	
Aortic Regurgitation			0.05
-Mild	82 (34.3)	39 (37.5)	
-Moderate	25 (10.5)	20 (19.2)	
-Severe	5 (2.1)	0 (0.0)	
IVC Diameter	2.08 ±1.02	2.29 ± 1.10	0.41

Values are n (%) unless otherwise indicated. IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; NHYA = New York Heart Association; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LAVi = left atrial volume index; RA = right atrial; TAPSE = tricuspid annular plane systolic excursion, FAC = fractional area change, RVS' = right ventricle systolic prime, RV = right ventricle; PASP = pulmonary artery systolic pressure (mmHg); AV = aortic valve; AVA = aortic valve area; IVC = inferior vena cava.

Baseline Clinical and Echo Characteristics

Table 8.3 summarizes the baseline demographic, clinical and echo characteristics, stratified by the presence of RV dysfunction at baseline. There were no significant differences in age, sex, anthropometrics or procedural characteristics between the groups. Patients with baseline RV dysfunction had significantly higher rates of atrial fibrillation, prior ischemic heart disease, pacemakers and chronic lung disease, compared with those with normal RV function at baseline ($p<0.05$ for all). Patients with normal baseline RV function had significant higher mean and peak AV gradients compared to those with RV dysfunction at baseline ($p<0.05$ for all). However, AVA was significantly lower in the group with RV dysfunction at baseline ($p=0.04$).

LVEF was lower in patients with baseline RV dysfunction compared with those with normal baseline RV function (47% ± 11% versus 55% ± 9% respectively, $p<0.0001$). Markers of LV or RV diastolic dysfunction were higher in those with baseline RV dysfunction, with higher mitral E/e' ratio, right atrial (RA) size and left atrial volume index (LAVi) ($p=0.04$ and <0.0001 respectively) compared to those with normal baseline RV function. RV basal diameter was also greater in those with baseline RV dysfunction, 4.31cm ± 0.81cm, compared with those with normal RV baseline function, 4.01cm± 0.61cm ($p<0.0001$). Higher proportions of significant mitral regurgitation (MR) and TR were recorded in patients with baseline RV dysfunction ($p<0.0001$ for all). There was significant RV-PA uncoupling noted in the baseline RV dysfunction group compared to those with normal baseline RV function (0.45±0.19 versus 0.77±0.24mm/mmHg, $p<0.0001$).

Table 8.3. Baseline characteristics – stratified by presence of RV dysfunction at baseline

	Normal RV Function (baseline) n = 246	**RV Dysfunction (baseline) n = 97**	**P value**
Demographics			
Age	82 ± 8	83 ± 7	0.34
Sex (Female)	94 (38.1)	34 (35.1)	0.59
Anthropometrics			
BSA	2.48 ± 0.22	1.82 ±0.22	0.20
BMI	28.2 ± 5.8	27.2 ±4.7	0.13
Rhythm			
Atrial fibrillation	61 (24.8)	58 (59.8)	<0.0001
Left bundle branch block	15 (6.1)	10 (10.3)	0.18
Right bundle branch block	15 (6.1)	13 (13.4)	0.03
Co-morbidities			

Hypertension	211 (85.8)	77 (79.4)	0.21
Ischemic Heart Disease			
-Prior IHD	-101 (41.1)	-56 (57.7)	0.005
-Prior acute MI	-25 (10.2)	-18 (18.6)	0.03
-Prior PCI	-69 (28.0)	-32 (33)	0.34
-Prior CABG	-28 (11.4)	-30 (31)	<0.0001
Prior balloon aortic valvuloplasty	11 (4.5)	4 (4)	0.89
Diabetes mellitus	82 (33.3)	30 (31)	0.67
Prior CVA	19 (7.7)	3 (3.1)	0.11
Chronic kidney disease	82 (33.3)	39 (40.2)	0.24
Dialysis	1 (0.4)	1 (1)	0.49
Chronic lung disease	70 (28.4)	41 (42.3)	0.03
Pacemaker	13 (5.3)	16 (16.5)	0.001
Functional Status			
NYHA Class			0.02
I	4 (1.6)	3 (3.1)	
II	134 (54.5)	41 (42.3)	
III	106 (43.1)	47 (48.5)	
IV	2 (0.8)	6 (6.2)	
Procedural Characteristics			
Indication			0.78
-Predominant Aortic stenosis	238 (96.7)	93 (95.9)	
-Predominant Aortic regurgitation	2 (0.8)	0 (0)	
-Mixed Aortic stenosis / regurgitation	6 (2.4)	4 (4.1)	
Vascular access			0.51
-Femoral	237 (96.3)	93 (95.9)	
-Axillary / subclavian	8 (3.3)	3 (3.1)	
-Transapical	1 (0.4)	1 (1.0)	
STS Score	3.65 ± 2.06	4.78 ± 2.15	<0.0001
Baseline Echo Parameters			
LVEF	55 ± 9	47 ± 11	<0.0001
LVEDD	4.50 ± 0.67	4.69 ± 0.84	0.03
LVESD	3.01 ± 0.73	3.41 ± 1.03	<0.0001
E/E’	19.1 ± 7.4	21.2 ± 9.8	0.04
RA size cm^2	20 ± 6	26 ± 9	<0.0001
LAVi	51 ± 14	63 ± 22	<0.0001

TAPSE	2.27 ± 0.37	1.52 ± 0.31	<0.0001
FAC	39 ± 9	29 ± 9	<0.0001
RVS'	11.5 ± 2.1	7.7 ± 1.7	<0.0001
RV basal diameter	4.01± 0.61	4.31 ± 0.81	<0.0001
RV mid diameter	2.7 ± 0.5	2.9 ± 0.6	0.003
PASP	36.74 ± 14.71	41.44 ± 14.88	0.02
RV-PA coupling	0.77 ± 0.24	0.45 ± 0.19	<0.0001
AV peak velocity	4.11 ± 0.67	3.81 ± 0.71	0.002
AV mean gradient	43 ± 17	37 ± 15	0.001
AVA cm	0.82 ± 0.32	0.74 ± 0.29	0.04
Tricuspid Regurgitation			<0.0001
-Mild	112 (45.5)	42 (43.3)	
-Moderate	17 (6.9)	22 (22.7)	
-Severe	2 (0.81)	7 (7.2)	
Mitral Regurgitation			<0.0001
-Mild	125 (50.8)	67 (69.1)	
-Moderate	23 (9.3)	18 (18.6)	
-Severe	3 (1.2)	1 (1.0)	
Aortic Regurgitation			0.90
-Mild	124 (50.4)	48 (49.5)	
-Moderate	88 (35.8)	33 (34.0)	
-Severe	31 (12.6)	14 (14)	
IVC Diameter	2.0±1.66	2.52 ± 1.62	0.07

Values are n (%) unless otherwise indicated. IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; NHYA = New York Heart Association; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LAVi = left atrial volume index; RA = right atrial; TAPSE = tricuspid annular plane systolic excursion, FAC = fractional area change, RVS' = right ventricle systolic prime, RV = right ventricle; PASP = pulmonary artery systolic pressure (mmHg); AV = aortic valve; AVA = aortic valve area; IVC = inferior vena cava.

Predictors of Baseline RV Dysfunction

The multivariate predictors of RV dysfunction at baseline, prior to TAVI, are reported in **Table 8.4.** Whilst prior ischaemic heart disease, CLD, significant TR and MR, RV basal diameter, PASP, pacemaker presence and LAVi were associated with baseline RV dysfunction on univariate analysis, only AF and LVEF were predictive on multivariate analysis.

Table 8.4. Predictors of Baseline RV Dysfunction – multivariable analysis using logistic regression

Variable	Odds of Baseline RV Dysfunction	Significance
Atrial Fibrillation	OR2.93, 95% CI 1.25 – 6.86	P = 0.01
Prior IHD	OR 1.16, CI 0.50 – 2.72	P = 0.73
Chronic Lung Disease	OR 2.16, CI 0.93 – 5.06	P = 0.08
LVEF (for every 1% increase)	OR0.94, CI 0.94 – 0.97	P = 0.001
LAVi	OR 1.02, CI 0.99-1.04	P = 0.13
RV basal diameter	OR 1.32, CI 0.69-2.51	P = 0.40
PASP (for every mmHg)	OR 1.01, CI 0.97 – 1.04	P = 0.82
Tricuspid Regurgitation		P = 0.10
-Mild	OR 0.49, CI 0.15 – 1.56	
-Moderate	OR 1.40, CI 0.33 – 5.96	
-Severe	OR 3.39, CI 0.27-42.20	
Mitral Regurgitation		P = 0.10
-Mild	OR 2.77, CI 0.76-10.03	
-Moderate	OR 2.69, CI 0.59-12.20	
Mean AV gradient	OR 1.001, CI 0.97-1.03	P = 0.97
Pacemaker	OR 1.87, CI 0.49-7.14	P = 0.36

IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; LAVi = left atrial volume index; RV = right ventricle; PASP = pulmonary artery systolic pressure; AV = aortic valve; AVA = aortic valve area.

Follow-Up Echo Results

Table 8.5 shows the baseline demographic, clinical and echo characteristics of the 66 patients with baseline RV dysfunction and complete follow-up imaging, stratified by whether the RV dysfunction persisted (n=46) or improved (n=20). Patients whose RV function had normalized at follow-up had a significantly higher proportion of diabetes (45% vs. 21.7%, p=0.05) and chronic lung disease (68.4% versus 39.1%, p = 0.03), compared with those with persistent RV dysfunction.

Table 8.5 also shows the rhythm post-TAVI and the echo parameters at 1-3 months follow-up. There were no significant differences in the presence of conduction disease or cardiac device post-procedure between those with normalized versus persistent RV dysfunction. Whilst there were no significant

differences in post-procedure LVEF between the groups, some markers of diastolic dysfunction including E/e' ratio were significantly lower in patients with normalised RV function (p=0.04). These patients also had a significantly lower proportion of significant MR, and a smaller IVC diameter compared with those with persistent RV dysfunction (p<0.05 for all). Importantly, there were no significant differences in post-procedure transvalvular gradients, valve size, nor presence of aortic valvular or paravalvular regurgitation between the groups (**Table 8.5**). There were also no significant differences between the two groups RV size post-TAVI.

Table 8.5. Baseline and 1- 3-month Follow-up Clinical and Echo Characteristics in patients with baseline RV dysfunction stratified by presence of RV dysfunction at follow-up, n = 66

	RV dysfunction at baseline and follow-up (no improvement) n = 46	**RV Dysfunction at baseline but not follow-up n = 20**	**P value**
Demographics			
Age	82 ± 7	84 ± 6	0.23
Sex (Female)	17 (37)	7 (35.0)	0.79
Anthropometrics			
BMI	27.2 ± 4.4	26.3 ± 5.0	0.20
BSA	1.80 ± 0.22	1.78 ± 0.23	0.65
Rhythm			
Atrial fibrillation	26 (56.5)	11 (55.0)	0.91
Left bundle branch block	5 (10.9)	2 (10.0)	0.92
Right bundle branch block	6 (13.0)	3 (15.0)	0.83
Co-morbidities			
Hypertension	36 (78.3)	17 (85.0)	0.53
Ischemic Heart Disease -Prior IHD -Prior acute MI -Prior PCI -Prior CABG	 27 (58.7) 8 (17.4) 14 (30.4) 16 (34.8)	 10 (50.0) 2 (10.0) 6 (30.0) 6 (30.0)	 0.51 0.44 0.97 0.71
Prior BAV	2 (4.3)	1 (5.0)	0.91
Diabetes mellitus	10 (21.7)	9 (45.0)	0.05
Prior CVA	3 (6.5)	0 (0)	0.24
Chronic kidney disease	19 (41.3)	4 (20.0)	0.09

Dialysis	0 (0)	0 (0)	-
Chronic Lung Disease	18 (39.1)	13 (68.4)	0.03
Pacemaker	6 (13.0)	4 (20.0)	0.47
Baseline Echo Characteristics			
LVEF	47 ± 13	48 ± 10	0.91
LVEDD	4.73 ± 0.88	4.55 ± 0.74	0.43
LVESD	3.52 ± 1.08	3.22 ± 0.87	0.28
E/E'	21.2 ± 9.4	16.5 ± 6.7	0.06
RA size cm^2	26.0 ± 8.0	22 ± 9	0.16
LAVi	61 ± 16	59 ± 21	0.66
PASP	45.23 ± 16.02	36.50 ± 8.75	0.04
TAPSE	1.47 ± 0.34	1.68 ± 0.31	0.02
FAC	27 ± 9	31 ± 8	0.09
RVS'	7.4 ± 1.9	8.3 ± 1.5	0.06
RV basal diameter	4.4 ± 0.88	4.1 ± 0.64	0.19
RV mid diameter	3.1 ± 0.6	2.7 ± 0.60	0.15
RV-PA coupling	0.42±0.18	0.53±0.19	0.08
AV peak velocity	3.84 ± 0.65	3.84 ± 0.67	0.99
AV mean gradient	37.0 ± 12	36 ± 14	0.94
AVA cm	0.75 ± 0.34	0.70 ± 0.25	0.57
Tricuspid Regurgitation			0.10
-Mild			
-Moderate	23 (50.0)	7 (35.0)	
-Severe	8 (17.4)	6 (30.0)	
	6 (13.0)	0 (0)	
Mitral Regurgitation			0.14
-Mild	32 (69.6)	15 (75.0)	
-Moderate	7 (15.2)	3 (15.0)	
-Severe	1 (2.2)	0 (0)	
Aortic Regurgitation			0.92
-Mild	15 (32.6)	4 (20.0)	
-Moderate	8 (17.4)	1 (5.0)	
-Severe	2 (4.3)	0 (0)	
IVC Diameter	2.90±0.65	1.89 ± 0.63	0.37
Echo and rhythm characteristics at 1-3 month follow-up			
Rhythm post procedure			

Left bundle branch block	3 (15.0)	11 (23.9)	0.42
Right bundle branch block	2 (10.0)	3 (6.5)	0.62
Complete heart block	1 (2.2)	1 (5.0)	0.54
Pacemaker (including new insertion post-procedure)	8 (17.4)	7 (35)	0.12
Follow-up Echo Parameters			
LVEF	50 ± 11	52 ± 8	0.41
Change in LVEF	+2.80 ± 9.60	+4.60 ± 6.60	0.45
LVEDD	4.70 ± 0.7	4.7 ± 0.80	0.84
Change in LVEDD	-0.01 ± 0.56	+0.13 ± 0.63	0.38
LVESD	3.4 ± 0.8	3.2 ± 0.7	0.40
Change in LVESD	-0.12 ± 0.71	-0.07 ± 0.67	0.33
E/E’	20.4 ± 9.3	15.5 ± 5.9	0.04
Change in E/e’	-0.98 ± 4.42	-1.33 ± 4.99	0.80
RA size cm^2	25.5 ± 11.7	24.2 ± 7.8	0.69
Change in RA size	-0.69 ± 7.86	+0.73 ± 5.57	0.51
LAVi	62 ± 20	60 ± 19	0.80
Change in LAVi	+0.97 ± 13.77	+1.06 ± 12.39	0.61
PASP	38.88 ± 14.20	34.69 ± 7.94	0.32
Change in PASP	-8.03 ± 13.70	-1.33 ± 7.85	0.12
TAPSE	1.48 ± 0.30	1.99 ± 0.39	<0.0001
FAC	33 ± 8	38 ± 6	0.03
RVS’	7.4 ± 1.7	10.0 ± 2.0	<0.0001
RV basal diameter	4.3 ± 0.8	4.1 ± 0.7	0.58
RV mid diameter	2.99 ± 0.69	2.85 ± 0.54	0.44
RV-PA coupling	0.42±0.17	0.58±0.16	0.006
AV peak velocity	1.87 ± 0.54	1.95 ± 0.38	0.55
AV mean gradient	8.6 ± 4.9	9.3 ± 2.7	0.57
AVA cm	2.13 ± 0.57	1.95 ± 0.73	0.34
Tricuspid Regurgitation			0.77
-Mild			
-Moderate	18 (39.1)	7 (35.0)	
-Severe	11 (23.9)	7 (35.0)	
	1 (2.2)	1 (5.0)	
Mitral Regurgitation			0.04
-Mild	26 (56.5)	18 (90.0)	

-Moderate	4 (8.7)	0 (0)	
-Severe	1 (2.2)	1 (5.0)	
Aortic Regurgitation			0.88
-Mild	12 (26.1)	5 (25.0)	
-Moderate	0 (0)	0 (0)	
-Severe	0 (0)	0 (0)	
IVC Diameter	2.11 ± 0.62	1.95 ± 0.39	0.04

Values are n (%) unless otherwise indicated. IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; NHYA = New York Heart Association; BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LAVi = left atrial volume index; RA = right atrial; TAPSE = tricuspid annular plane systolic excursion, FAC = fractional area change, RVS' = right ventricle systolic prime, RV = right ventricle; PASP = pulmonary artery systolic pressure (mmHg); AV = aortic valve; AVA = aortic valve area; IVC = inferior vena cava.

Thresholds for Persistent RV Dysfunction

In patients with baseline RV dysfunction and follow-up imaging (n=66), thresholds were identified for each RV functional parameter to determine the point where the chance of RV recovery was <10%. If the TAPSE <1.4 cm at baseline, there was a 95% predictive value that the RV dysfunction would persist, with only 5% of patients having recovery of RV function. If the S' <6 at baseline, there was a 100% predictive value for persistent RV dysfunction, whilst if the FAC <25% at baseline, there was a 94% predictive value, with only 6.0% experiencing RV recovery (**Table 8.6**).

Table 8.6. Thresholds where RV Function is Unlikely to Improve

	Persistent RV Dysfunction 1–3 month follow-up n=46	**Normalised RV Function** 1–3 month follow-up n=20
A		
Baseline TAPSE<1.4	**19**	**1**
Baseline TAPSE≥1.4	**27**	**19**
B		
Baseline FAC<25%	**16**	**1**
Baseline FAC≥25%	**30**	**19**
C		
Baseline S'<6	**5**	**0**
Baseline S'≥6	**41**	**20**

RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; FAC = fractional area change; S' = systolic movement of the RV lateral wall by tissue Doppler.

New RV Dysfunction

Of the 173 patients with normal RV function at baseline, 8 developed new RV dysfunction at 1-3 month follow-up. These patients had significant higher LAVi at follow-up compared to those with persistently normal RV function (p=0.02) but there were no other significant differences between follow-up echo parameters between the two groups (**Table 8.7**).

Table 8.7. Echo and rhythm characteristics at 1-3 month follow up

	Normal RV function at baseline and follow up (no change) N = 165	**Normal RV function at baseline with RV dysfunction at follow up (worsened) N = 8**	P value
Rhythm post procedure			
Left bundle branch block	35 (21.3)	2 (25.0)	0.81
Right bundle branch block	7 (4.2)	0 (0.0)	0.55
Complete heart block	11 (6.7)	1 (12.5)	0.51
Pacemaker (including new insertion post-procedure)	13 (7.9)	1 (12.5)	0.64
LVEF	56 ± 7	57 ± 9	0.78
Change in LVEF	-1.36 ± 6.88	-1.13 ± 12.06	0.93
LVEDD	4.60 ± 0.7	4.3 ± 0.70	0.30
Change in LVEDD	-0.08 ± 0.54	+0.19 ± 0.71	0.18
LVESD	2.9 ± 0.7	2.8 ± 0.6	0.66
Change in LVESD	+0.07 ± 0.62	+0.16 ± 0.61	0.68
E/E'	18.4 ± 8.1	17.8 ± 7.2	0.91
Change in E/e'	+0.24 ± 5.58	3.94 ± 6.00	0.07
RA size cm^2	20.6 ± 6.3	21.9 ± 3.8	0.60
Change in RA size	-0.65 ± 4.48	+0.14 ± 5.79	0.65
LAVi	49 ± 13	63 ± 10	0.02
Change in LAVi	+1.34 ± 12.52	-10.00 ± 12.10	0.03
PASP	32.12 ± 9.46	30.57 ± 13.13	0.68
Change in PASP	4.17 ± 13.54	13.00 ± 22.70	0.18
TAPSE	2.24 ± 0.40	1.56 ± 0.23	<0.0001
FAC	40 ± 7	36 ± 10	0.17
RVS'	11.7 ± 2.2	8.4 ± 1.0	<0.0001
RV basal diameter	4.0 ± 0.6	4.2 ± 0.5	0.37

RV mid diameter	2.71 ± 0.50	3.01 ± 0.56	0.12
RV-PA coupling	0.74±0.26	0.61±0.26	0.19
AV peak velocity	2.11 ± 0.45	1.95 ± 0.43	0.35
AV mean gradient	10.2 ± 4.2	9.0 ± 1.8	0.40
AVA cm	2.03 ± 1.28	1.64 ± 0.43	0.46
Tricuspid Regurgitation			0.93
-Mild	74 (45.1)	4 (50.0)	
-Moderate	7 (4.3)	0 (0.0)	
-Severe	1 (0.6)	0 (0.0)	
Mitral Regurgitation			0.14
-Mild	92 (56.1)	2 (25.0)	
-Moderate	7 (4.3)	0 (0)	
-Severe	0 (0.0)	0 (0.0)	
Aortic Regurgitation			0.46
-Mild	39 (23.8)	1 (12.5)	
-Moderate	0 (0)	0 (0)	
-Severe	0 (0)	0 (0)	
IVC Diameter	1.74 ± 0.42	1.71 ± 0.26	0.90

Values are n (%) unless otherwise indicated. LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic pressure; LAVi = left atrial volume index; RA = right atrial; TAPSE = tricuspid annular plane systolic excursion, FAC = fractional area change, RVS' = right ventricle systolic prime, RV = right ventricle; PASP = pulmonary artery systolic pressure (mmHg); AV = aortic valve; AVA = aortic valve area; IVC = inferior vena cava.

Discussion

The present study provides quantitative phenotyping of RV size and function in patients with severe AS prior to intervention and at short-term follow-up 1-3 months following TAVI. Our major findings were that baseline RV dysfunction was identified in 28.8% of the cohort but did not normalize at short-term follow-up in greater than two-thirds of these patients. We also identified clear thresholds for each RV functional parameter where recovery was unlikely.

The aetiology of RV systolic dysfunction in patients with significant AS is thought to be multifactorial. Pressure overload from elevated LA pressure can cause post-capillary PHT which increases RV afterload and can lead to RV systolic dysfunction[2, 51]. Volume overload from concomitant TR or fluid retention can also contribute to RV dysfunction[165, 166]. Ventricular interdependence from septal dysfunction is also thought to play a role, particularly as the RV becomes increasingly reliant on oblique fibres within the interventricular septum, as PA pressures increase with chronic AS[167-169].

This may explain why in our study PA pressures did not significantly correlate with RV dysfunction at baseline.

RV dysfunction has previously been documented in close to a quarter of patients with severe AS, with two large prior studies each documenting a prevalence of 24%[157, 167] and a recent meta-analysis reporting an average prevalence of 30% across studies[170]. We report a prevalence of 28.8% of baseline RV dysfunction within our study, which is in line with previous reports.

A higher proportion of patients with baseline RV dysfunction had AF compared to those with normal RV function, and AF was found to be a predictor of RV dysfunction on multivariable analysis. This may be explained by the impaired conduction and contractility of the LA found in patients with AF[171], which can lead to a more significant backward transmission of elevated LA pressure into the pulmonary vasculature[172], causing volume loading of the right heart and eventually RV dysfunction. Likewise, LVEF was lower in those with RV dysfunction and a predictor on multivariable analysis. Prior studies have shown TAPSE, as a surrogate marker for RV dysfunction, correlates strongly with LVEF[167]. This suggests that RV systolic impairment in patients with severe AS may be due to ventricular interdependence as well as post-capillary PHT[167, 168].

The early hemodynamic effects of LV unloading after correction of aortic stenosis is clearly seen through positive re-modelling of the LV[154-156]. An invasive hemodynamic study demonstrated an acute improvement in both LV and RV systolic function, including reductions in pulmonary vascular resistance, and enhancements in RV-PA coupling following TAVI[163]. It was proposed that acute improvements in LV ejection following TAVI may explain this finding given the significance of ventricular interdependence, particularly in the context of raised PA pressures[163].

On echo however, the impact of relief of aortic valve obstruction on RV modelling remains less clear. It has recently been shown that there is an immediate reduction in RV-PA uncoupling post-TAVI[168]. This is thought to be a marker of subtle RV dysfunction and was largely driven by a reduction in PASP[168], which multiple earlier studies have shown to be only modest reductions[35]. A recent subgroup analysis from the PARTNER III trial showed that baseline RV-RA uncoupling was associated with poor clinical outcomes at 2-years, despite slight improvements post TAVI[164]. Whilst RV-PA coupling is a useful parameter to assess RV function in this cohort, as it combines information regarding both RV longitudinal systolic function and pulmonary pressures, both our “real-world” cohort and the recent PARTNER III sub-group analysis had significant numbers of patients with missing PASP data[164].

Prior echo studies have failed to show significant improvements in RV function immediately post-TAVI[157, 168]. In fact, in a small cohort including 20 TAVI patients, Keyl et al showed that longitudinal displacement, transverse shortening of the RV, RVEF and RV stroke volume, as assessed by 3D echo, remained constant at 1-week post-TAVI[173]. Similarly, smaller, semi-quantitative studies have shown no significant improvement in TAPSE at 1-3 month follow-up or at 6-12 month follow-up[158-160, 174]. In contrast to these studies, Schwartz et al, reported improvements in RV dysfunction in the majority of patients unless they had severe TR at baseline[165].

In our study, only 30% of patients with RV dysfunction at baseline had normalised their RV function at 1-3 month follow-up. These patients had significantly lower E/e' ratios and lower proportions of significant MR than the patients whose RV dysfunction did not improve. Procedural characteristics and related results such as transvalvular gradient, post-procedure rhythm and presence of a pacemaker did not significantly differ between patients with persistent RV dysfunction compared with improved RV function. This is similar to a recent publication looking the PARTNER IIa cohort where 74% of patients had persistent RV dysfunction at 30 days following TAVI[175] and confirms that the lack improvement in RV dysfunction seen immediately post-TAVI extends to the 1-3 month follow-up period. This suggests that the presence of RV dysfunction in these patients is not solely linked to the presence of severe aortic valve obstruction but is likely multifactorial, with chronic processes such as longstanding PHT likely contributing[176].

Clear thresholds were able to be identified for each RV functional parameter where recovery was unlikely. There was a <10% chance of recovery if TAPSE was <1.4cm, S'<6 or FAC<25% at baseline. Identifying these thresholds has significant clinical implications as it can help treating clinicians predict poor RV recovery which may in turn help to manage and prognosticate patients. Further studies are needed to determine whether change versus lack of improvement in RV function at both short and long-term follow-up is linked to clinical outcomes.

Study Limitations

Our study has several limitations. The study was conducted at a single, high-volume centre which may limit the generalizability of results. This also limited the population size which meant our study was relatively underpowered when looking differences and predictors of improvement following TAVI in the patients with baseline RV dysfunction. Given the fact that this was a derivation cohort the findings should be validated in a larger, prospective cohort. This analysis does however provide a consistent and easily reproducible approach to RV functional assessments on baseline and serial echoes. There were no significant differences in the co-morbidity profiles between the patients who had sufficient RV parameters assessed on baseline echo and those who did not, nor were there significant differences

between the cohort with repeat imaging and those without. Nonetheless, selection bias may have been introduced as sicker or more complex patients may have undergone broader echo examinations. Patients with RV dysfunction at baseline were more co-morbid, whilst many co-morbidities were not predictive on multivariable analysis this indicates that these patients were higher risk and potentially introduces bias. In this study, detailed measures such as RV strain analysis and 3D volumetric assessment of the RV were not routinely performed. The number of patients with RV dysfunction and echo follow up data was insufficient to allow meaningful logistic regression or ROC analyses; this would be important in future studies. Our study provides information on short term RV echo follow-up data, however, as this study was from a tertiary referral centre, longer term echo follow-up was performed by each individual patient's regular cardiologist. Thus, they were not standardised with RV focused views, nor were we able to review them. We did not assess mortality outcomes and so are unable to assess the impact that change in RV function might have had on survival. Further larger, prospective studies with longitudinal follow-up would be useful to further clarify changes in RV function post TAVI and the impact of this on clinical outcomes.

Conclusions

Our study of RV systolic function pre- and post- TAVI shows the significant prevalence of baseline RV dysfunction and highlights that RV function does not normalize at short-term follow-up in most patients. We reported thresholds for each RV functional parameter which may help to identify when RV recovery is unlikely.

Chapter 9 – The Importance of Assessing and Correcting Hydration Status prior to Right Heart Catheterisation – A Pilot Study

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Abstract

Background: Fasting and diuretic use can decrease pulmonary arterial wedge pressure (PAWP) on right heart catheterisation (RHC) and these can impact the accurate diagnosis of post-capillary pulmonary hypertension (PHT). We evaluated whether fluid status could be accurately assessed and corrected using a non-invasive method.

Methods: Consecutive eligible adults undergoing RHC for suspected post-capillary PHT underwent a "standard-of-care" fluid assessment before a non-invasive measurement of cardiac index (CI) was performed. A passive leg raise (PLR) was then performed and a change in CI of >10% was defined as 'fluid deplete'; these patients received 5mL/kg fluid bolus before measurements were repeated. RHC was then performed; if mPAP ≥20mmHg and PAWP <15mmHg, further provocation testing was undertaken; a PLR and then a 500mL fluid bolus was administered; haemodynamic measurements were recorded after these.

Results:

Fourteen patients were included, aged 75±10 years. Five (36%) were fluid deplete; and were significantly younger (68±14, vs 79±14years, p=0.04) with a longer duration of fasting (15.3±2.4 vs 8.7±4.8 hours, p=0.01) compared to replete patients. The mean IV rehydration given was 310 ± 67mL. Six patients had provocation testing; all 5 assessable patients had the same post-provocation classification following PLR and fluid bolus.

Conclusions: A novel and simple non-invasive technique allows assessment of "fluid replete" status prior to RHC and can be used to standardise fluid status. Our data also show that PLR may be an equivalent provocation test, compared to a "one dose fits all" fluid challenge.

Introduction

Group 2 pulmonary hypertension, also known as post-capillary PHT, is the most common type of PHT, representing 65-80% in published series[2, 17, 37]. It is thought to be caused by elevated LA pressure leading to 'back pressure' into the pulmonary vasculature[2, 17]. RHC is the 'gold standard' for diagnosing and differentiating between pre- and post- capillary PHT, with a PAWP >15mmHg is reflective of elevated LA pressure[76]. There is increasing acknowledgement, however, that traditional hemodynamic measurements may be insufficient to identify early stages of LHD[2, 4, 76]. Patients are very often fasting pre-procedure or already on diuretic therapy; these can both reduce intravascular volume and thence give an inaccurate picture of PAWP. This in turn may lead to incorrect diagnosis[2, 3, 67, 177].

Provocation techniques, including 'acute' fluid challenges (often a fixed "dose" of 500mL), have been proposed to better characterise patients with occult PHT-LHD[2, 67, 78]. However, there is no standardised approach and current methods do not account for important individual factors such as weight, duration of fasting, or, importantly, volume status. With no treatment specific medications available for the Group 2 PHT cohort, and evidence to suggest that treatment with PHT-specific therapy may cause harm[89, 90], accurate diagnosis is imperative and this in turn is highly dependent on the pre-procedure fluid status of each patient.

Thus, our primary aims were 1) to determine whether a patient's volume status and fluid responsiveness could be accurately assessed and (if necessary) corrected prior to RHC, and, 2) to then compare a novel provocation technique (passive leg raising) with a standard 500mL fluid bolus to assess the effects on PAWP and PVR. The secondary aim was to determine whether novel measures of fluid assessment correlate with standard assessments of fluid status.

Methods

Study population

In a prospective cohort study, consecutive adults undergoing RHC for suspected post-capillary PHT at Royal Prince Alfred Hospital between September 2022 and July 2023 were recruited. Human ethics approval was gained, protocol SLHD X22-0141 & 2022/ETH00870. Patients were defined as having suspected post-capillary PHT if they had ≥ 2 co-morbidities suggestive of LHD as defined by the AMBITION trial (hypertension, BMI ≥30, diabetes mellitus, history of significant coronary artery disease)[178]. Exclusion criteria included severe lower limb limitations precluding a passive leg raise (PLR) and scleroderma with significant peripheral skin thickening. Our planned sample size was 30 patients, however, the ClearSight device that had been provided (without charge) by Edwards

Lifesciences was removed from our hospital prior to our recruitment period ending and no funds were available to lease or purchase that equipment.

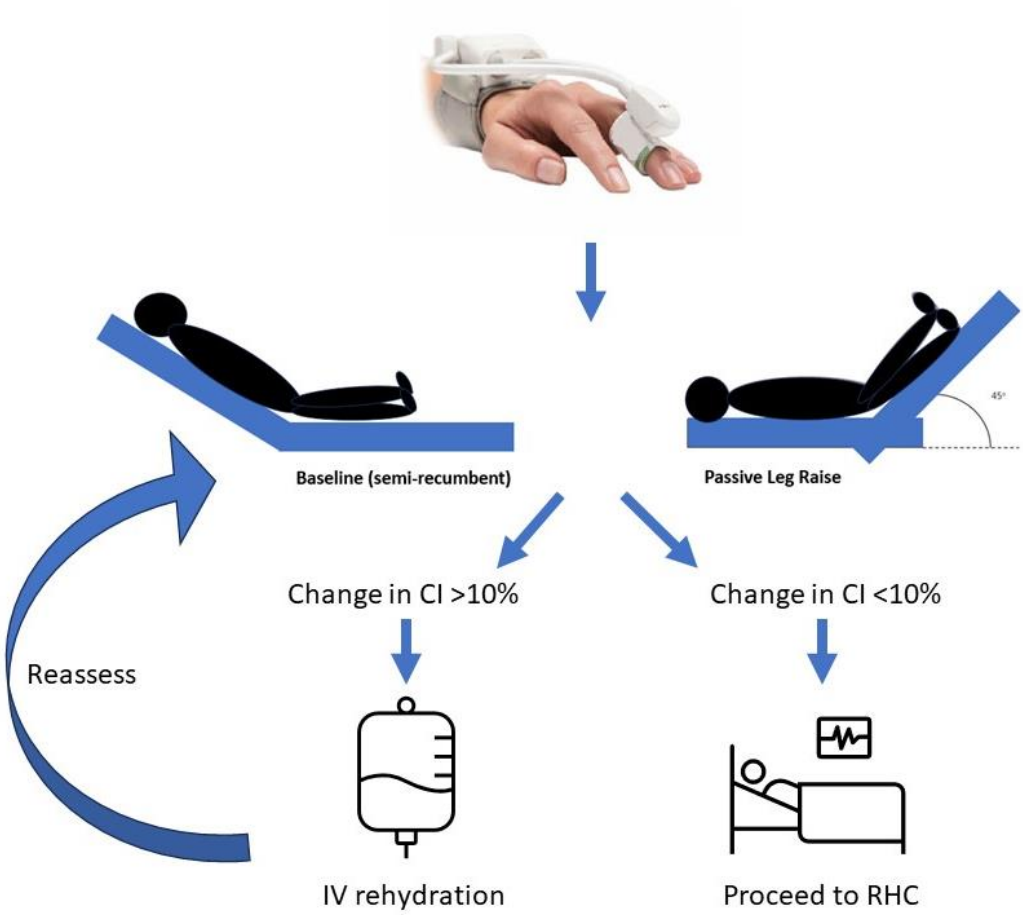
Fluid Assessment

Patients initially underwent "standard-of-care" fluid assessment which included documenting the total duration of fasting, as well as a physical examination including assessment of jugular venous pressure (JVP), chest auscultation, presence of peripheral oedema, capillary refill and skin turgor.

Cardiac index (CI), cardiac output (CO) and stroke volume index (SVI) were then measured non-invasively using an inflatable finger cuff from the ClearSight device (Edwards LifeSciences). This technology, commonly used in critical care settings, is based on the PhysioCal (physiologic calibration) method which uses the pulsatile unloading of the finger arterial walls. This involves a photoelectric plethysmograph within the finger cuff which uses pressure to maintain constant blood flow in the finger. The ClearSight system translates the finger arterial waveform to the brachial waveform to determine blood pressure (BP) using a validated algorithm. SV is calculated dividing the area under the systolic portion of the BP curve by aortic impedance which is influenced by individual patient factors including age, gender, height and weight. CO is generated beat-by-beat through multiplying SV by heart rate[179, 180]. The ClearSight technology has been validated to provide consistent, continuous measurements of CI and track changes under dynamic conditions[181].

Baseline measurements were performed with patients in a semi-recumbent position. Thence, a passive leg raise (PLR) was performed to simulate a fluid bolus (approximately 300mL)[182], but titrated to patient height and weight. Measurements were repeated 60 seconds after PLR, with a change in CI of >10% defined as 'fluid deplete'[181, 183]. Fluid deplete patients received 5mL/kg (ideal body weight) fluid bolus before non-invasive measurements were reassessed at baseline and post-PLR (**Figure 9.1**). If the change in CI was then <10% patients were considered replete and proceeded to RHC.

Figure 9.1. Non-invasive method of assessing and correcting fluid status prior to right heart catherisation.



Shows assessment of fluid status using non-invasive finger cuff to assess cardiac output, cardiac index and stroke volume at baseline and after passive leg raise.

Right Heart Catheterisation

RHC was performed as per standard practice according to local protocol. Internal jugular access was gained under direct ultrasound visualisation. Standard measurements including mPAP, PAWP, PVR and cardiac output (CO) were recorded at baseline. If mPAP ≥20mmHg and PAWP <15mmHg further provocation testing was performed to compare our study-specific test to standard-of-care testing. First a PLR was performed using a 45d wedge block under the patient's legs, with mPAP, PAWP, PVR and CO re-measured after 60 seconds. Then, patients received a standard 500mL fluid bolus with hemodynamic measurements recorded immediately after. Patients were classified as having 'baseline', 'post-PLR' / 'post-fluid' post-capillary PHT if they met the hemodynamic profile: mPAP≥20mmHg,

PAWP≥15mmHg and PVR<2WU. They were considered to have isolated post-capillary PHT (Ipc-PH) if the diastolic pulmonary vascular gradient (DPG) <7mmHg and or PVR <2WU, or combined post- and pre-capillary PHT (Cpc-PH) if DPG >7mmHg and PVR >3WU[18, 184]. Given the variation in hemodynamic definition for occult post-capillary PHT we performed a further assessment on patients who met the hemodynamic profile: mPAP≥20mmHg, PAWP≥18mmHg and PVR<2WU[185].

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis was used to determine whether the trend of the mean across the categorical groups of fluid status was linear. For binary variables, the chi-squared test was used to determine if there was a trend in the change in proportions across the groups stratified by baseline fluid status.

Logistic regression models were used to derive the adjusted odds ratios (OR) to determine predictors of fluid depletion at baseline. Entry into the multi-variable model included variables which were clinically likely to impact outcome and had a univariate p-value <0.05.

All analyses were performed with SPSS software version 22.0 (IBM Corp, Armonk, New York), and statistical significance was accepted at a 2-tailed p-value of <0.05.

Results

Baseline Characteristics

Table 9.1 shows the baseline demographics and co-morbidities of the cohort. 14 patients were included in the study; 8 (57%) were female and mean age was 75 ± 10 years. Co-morbidities included 12 (85.7%) with hypertension, 10 (71.4%) with ischemic heart disease, 4 (28.6%) with diabetes mellitus and 7 (50%) with a BMI ≥30 (mean 32.5 ± 6.9). The majority of patients (57.1%) were prescribed diuretics prior to the procedure.

Fluid Status

Five (36%) patients had a >10% increase in CI after PLR and were thus determined to be fluid deplete. Fluid deplete patients were significantly younger (68±14, vs 79±14years, p=0.04) with a longer duration of fasting (15.3±2.4 vs 8.7±4.8 hours, p=0.01) compared to replete patients. There were no other significant differences in baseline characteristics or co-morbidities between the groups (**Table 9.1**).

All 5 of the fluid deplete patients had been classified as euvolemic on initial standard-of-care fluid assessments performed by treating clinicians. Of the patients who were fluid replete 1 was classified as

underfilled, 5 as euvolemic and 3 as fluid overloaded on initial standard-of care fluid assessment (**Table 9.1 and 9.2**).

The 5 fluid deplete patients received IV rehydration; the mean amount of fluid given was 310 ± 67mL (**Table 9.2**). Repeat assessment of fluid status following rehydration showed all patients had <10% change in CI after PLR. Neither age (p=0.33) nor duration of fasting (p=0.16) were predictors of fluid deplete status on multi-variable analysis.

Right Heart Catheterisation

Table 9.2 documents the baseline haemodynamics and diagnoses of the 14 included patients. 50% of the patients had a raised PAWP on baseline measurements; with 7 being diagnosed with CpcPH. Of the remaining patients, 5 had pre-capillary PHT, 1 had raised pulmonary pressures and 1 did not have evidence of PHT.

Table 9.3 shows the pulmonary haemodynamics following provocation testing. There were 6 patients who met the hemodynamic criteria of mPAP ≥20mmHg and PAWP <15mmHg and proceeded to provocation testing. Of these, one was excluded due to a technical fault in the Swan Ganz catheter. 4 patients had an increase in PAWP to ≥15mmHg following the PLR; 3 were reclassified as combined CpcPH and 1 to IpcPH. When a standard 500mL fluid bolus was given to these patient's similar rises in PAWP and PVR were seen. All 4 patients had the same post-provocation re-classification as when PLR was used. In 1 patient the PAWP did not increase to ≥15mmHg after either the PLR or fluid bolus. When the hemodynamic profile for PAWP ≥18mmHg was used, 2 patients were re-classified using the PLR and also the standard fluid bolus.

Table 1. Baseline Characteristics at initial assessment

	Fluid Replete N = 9	**Fluid Deplete N = 5**	**P value**
Demographics			
Age	79 ± 4	68 ± 4	0.04
Sex	4 (44.4)	2 (40)	0.90
Anthropometrics			
Height (cm)	166 ± 6	167 ± 11	0.77
Weight (kg)	86.0 ± 20.3	98.9 ± 27.2	0.33
AMBITION risk factors			
Hypertension	8 (88.9)	4 (80)	0.65
Ischemic heart disease	3 (33.3)	1 (20)	0.60
Diabetes mellitus	3 (33.3)	1 (20)	0.58
BMI ≥ 30	4 (44.4)	3 (60)	0.58
Other comorbidities			
BMI	31.2 ± 6.8	34.9 ± 7.1	0.35
Chronic lung disease	2 (22.2)	3 (60)	0.28
Heart failure reduced ejection fraction	2 (22.2)	1 (20)	0.92
Diastolic dysfunction	6 (66.6)	3 (60)	0.80
Significant left sided valvular pathology	2 (22.2)	0 (0)	0.31
Chronic kidney disease	3 (33.3)	0 (0)	0.15
Immune disorders	2 (22.2)	0 (0)	0.26
Atrial fibrillation	6 (66.6)	3 (60)	0.80
Fluid Status			
Diuretic use	6 (66.7)	2 (40)	0.93
Duration of fasting (hours)	8.7 ± 4.8	15.3 ± 2.4	0.01
Standard of Care Fluid Assessment			0.21
Underfilled	1 (11.1)	0 (0)	
Euvolemic	5 (55.6)	5 (100)	
Overloaded	3 (33.3)	0 (0)	

BMI = Body mass index.

Table 9.2. Baseline fluid assessment and hemodynamics

	Standard of care fluid assessment	Fluid deplete on novel assessment	Pre-Hydration (mL)	mPAP (mmHg)	DPG (mmHg)	PAWP (mmHg)	PVR (WU)	Diagnosis
1	Euvolemic	-	0	37	3	20	3.4	Combined pre- and post- capillary PHT
2	Euvolemic	Yes	220	38	0	20	4.9	Combined pre- and post- capillary PHT
3	Underfilled	-	0	30	7	7	4.2	Pre-capillary PHT
4	Euvolemic	-	0	40	6	23	4.0	Combined pre- and post- capillary PHT
5	Euvolemic	Yes	375	39	5	19	3.4	Combined pre- and post- capillary PHT
6	Overloaded	-	0	48	9	23	4.0	Combined pre- and post- capillary PHT
7	Overloaded	-	0	48	21	13	14.0	Pre-capillary PHT
8	Euvolemic	-	0	55	22	11	7.5	Pre-capillary PHT
9	Euvolemic	-	0	31	4	16	3.2	Combined pre- and post- capillary PHT
10	Euvolemic	Yes	350	19	3	9	2.5	No PHT
11	Euvolemic	Yes	350	38	12	10	5.0	Pre-capillary PHT
12	Euvolemic	-	0	20	1	12	1.8	Raised pulmonary pressures
13	Overloaded	-	0	54	10	25	7.8	Combined pre- and post- capillary PHT
14	Euvolemic	Yes	260	47	11	14	5.8	Pre-capillary PHT

mPAP = mean pulmonary artery pressure; DPG = diastolic pulmonary gradient; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WU = Wood Units; PHT = pulmonary hypertension.

Table 9.3. Provocation Tests – PLR vs Fluid Challenge

	Baseline				Post PLR					Post Fluid				
	mPAP (mmHg)	**PAWP (mmHg)**	**PVR (WU)**	**Diagnosis**	**mPAP (mmHg)**	**DPG (mmHg)**	**PAWP (mmHg)**	**PVR (WU)**	**Diagnosis**	**mPAP (mmHg)**	**DPG (mmHg)**	**PAWP (mmHg)**	**PVR (WU)**	**Diagnosis**
3	30	7	4.2	Pre-capillary PHT	32	7	7	4.8	Pre-capillary PHT	40	7	14	5.5	Pre-capillary PHT
7	48	13	14.0	Pre-capillary PHT	48	10	24	12	Combined pre- and post-capillary PHT	48	9	27	12.0	Combined pre- and post-capillary PHT
8	55	11	7.5	Pre-capillary PHT	58	14	15	7.2	Combined pre- and post-capillary PHT	58	14	15	7.4	Combined pre- and post-capillary PHT
11	38	10	5.0	Pre-capillary PHT					Excluded, technical issues with swan Ganz					Excluded, technical issues with swan Ganz
12	20	12	1.8	Borderline	23	1	16	1.6	Post capillary PHT	25	2	15	1.9	Post capillary PHT
14	47	15	5.8	Pre-capillary PHT	51	9	18	6.1	Combined pre- and post-capillary PHT	52	8	21	6.0	Combined pre- and post-capillary PHT

mPAP = mean pulmonary artery pressure; DPG = diastolic pulmonary gradient; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WU = Wood Units; PHT = pulmonary hypertension.

Discussion

In this pilot study, we have shown a novel way to assess fluid status which yielded different results to a standard-of-care fluid assessment and was thus additive to overall patient care. Over one-third of (this small sample) of patients were actually fluid deplete, immediately prior to RHC, which may well have led to mis-diagnosis of PHT type. We also found that using a PLR as a provocation test in this cohort was equivalent to a standard-of-care fluid bolus in re-classifying patients with 'occult' post-capillary PHT.

RHC remains the investigation used to definitively diagnose PHT and differentiate between pre- and post-capillary sub-types[2]. This distinction is important as it determines patient eligibility and suitability for PHT-specific treatment. PAH-specific therapy such as endothelin receptor antagonists or prostaglandins have not only been shown to be ineffective in patients with PHT-LHD, and could even worsen outcomes in this this clinical situation[76, 90]. This was highlighted in the recent AMBITION study where patients with LHD risk factors were shown to have increased rates of clinical failure, decreased tolerability and an diminished treatment response[178]. A prior study has shown that up to one third of patients referred to a PHT centre were initially misdiagnosed, leading to inappropriate treatment[186]. PAWP is dependent on individual patients fluid status and may be impacted by diuretic use or fasting pre-procedure[3]. Static observations (HR, BP), or even baseline measures of SV, CO and CI have been previously documented as insufficient to predict fluid responsiveness[181]. Dynamic fluid assessments in critical care settings have been shown to reliably identify fluid responsive patients[181, 187, 188].

Provocation testing during RHC can be useful in eliciting dynamic responses in PAWP, and if positive, suggests the presence of LHD[67]. Prior studies show approximately 22% of patients are reclassified after such challenges[67]. This technique is largely considered safe, but concerns remain about the rapid infusion of fluids into patients with a propensity for fluid overload[76, 185]. Furthermore, a uniform 500mL bolus is not titrated to individual factors such as weight or fluid status. A PLR as a novel provocation test has the benefit of transiently increasing cardiac preload, without administering fluid, and is titrated to individual patient factors[76, 187-189]. It has the added benefits of being feasible, easily reproducible, and, both time and cost-effective[188]. It is also accurate in patients with co-morbidities such as cardiac arrhythmia or low tidal volume ventilation (which can be common in this cohort)[182, 190].

Unsurprisingly, duration of fasting was a significant (univariate) predictor of being fluid deplete, prior to RHC. Interestingly, fluid deplete patients were significantly younger than fluid replete patients. This differs from previous studies in critical care settings, particularly with regards to sepsis, which showed

elderly patients tended to be more fluid responsive[181]. This may be because older patients were more co-morbid and were more likely to be fluid overloaded prior to the procedure. Neither of these factors were shown to be significant predictors of fluid responsiveness on multi-variable analysis highlighting the complexity of identifying such patients on a standard-of-care fluid assessment alone.

All patients who were identified as fluid deplete using PLR assessment were documented as euvolemic on a standard-of-care fluid assessment. This suggests that fluid responsiveness may be sub-clinical and may not be identified on clinical examination. Thus, this novel measure of fluid responsiveness was additive to the patient's overall assessment.

In our study, 4 patients had their PAWP rise to ≥15mmHg on both the PLR and fluid challenge provocation test, suggesting in our small cohort they were equivalent manoeuvres. There is no consensus on what the PAWP threshold for an abnormal response following a fluid challenge is, with some studies using a threshold of greater than ≥15mmHg and others using ≥18mmHg[67, 76, 78, 185, 191]. If the higher threshold was used in our cohort only 2 patients would have been re-classified. It is important however to note that regardless of the threshold used, the dynamic change in PAWP was similar between the 2 techniques.

Study Limitations

This was a preliminary "pilot" study run through a single centre, with a small cohort, so further validation studies are needed to assess whether these results are generalisable. Only non-invasive methods (as opposed to invasive RHC measurements) were used to determine the need for pre-hydration as this study was performed at a busy quaternary centre with high volume turnover in the cardiac catheterisation lab. Age and sex influence the rise in PAWP following rapid fluid administration and this may be the same following PLR. Further studies are needed to identify the rise in PAWP following PLR in both healthy individuals and those with PHT. Given the small cohort, multivariable models may not be effective in identifying predictors of fluid responsiveness.

Conclusions

This pilot study suggests that this novel, non-invasive technique is a simple and convenient method to allow standardization of fluid status prior to RHC. It also suggests that a passive leg raise may be an equivalent provocation test to a "one dose fits all" challenge with a fluid bolus. Larger validation studies are needed to confirm that these techniques maximize the accuracy of this important test.

Chapter 10 – Concluding Remarks and Future Directions

PHT due to LHD is serious, prevalent and incompletely understood. The field suffers from poor understanding of phenotyping and difficulty in diagnosis due to a lack of standardisation. Treatment options are limited and patients have the potential for adverse outcomes if mis-diagnosed. Thus, this thesis aimed to make important contributions to the current understanding of the demographic, imaging and haemodynamic characteristics of these patients, as well as to strategies to standardise diagnosis.

Defining Phenotypes in Pulmonary Hypertension and Left Heart Disease

The NEDA database provided a unique opportunity to study the echocardiographic profiles and outcomes of large cohorts of patients with PHT and left-sided heart disease. *Chapters 2-4* described PHT with specifically left sided valvular diseases. *Chapter 2* reported on the largest contemporary cohort to date of adults with moderate or greater AR, *Chapter 3* on moderate or greater AS and *Chapter 4* on moderate or greater MR, all with preserved ejection fraction[192-194]. These studies clarified the prevalence of PHT in those with left sided valvular pathology in the modern era, with some degree of PHT documented in 44.4%, 52.5% and 59.6% of each cohort respectively. This highlights how common these patients are in everyday clinical practice. Furthermore, these studies were also the first document the significant proportion of patients with borderline PHT in each cohort (>30%).

Analysis of this big data allowed a comprehensive echocardiographic phenotype of adults with PHT due to left-sided heart disease to be described. As pulmonary pressures increased there was a progressive increase in E/e' and RA size. There was also a progressive increase in LAVi though in the AR and MR cohorts a plateau was noted in the group with severe elevations in pulmonary pressures.

A graded association between raised pulmonary pressures and mortality was documented across the spectrum of left sided valve disease examined. Importantly, even small elevations in pulmonary pressures represent increased mortality risk. Mortality thresholds were found in the 'borderline' elevation range for both the AS and MR cohorts, and the mild range for the AR cohort. Many previous studies were community-based cohorts limited by small cohort size. These studies, therefore, showed that PHT is common in those with significant left-sided valvular pathology, provided clinicians with an echo phenotype to screen and monitor patients with and demonstrated that even mild elevations in pulmonary pressures pertain a significant mortality risk in these cohorts.

The next group of NEDA studies focused on patients with 'isolated' reduced LVEF and LVDD with pEF respectively, where the tricuspid regurgitant peak velocity was used to determine PHT-risk according to recent guidelines. *Chapter 5* demonstrated the independent effect of PHT severity on mortality in adults with reduced LVEF[195]. Again, the resultant echocardiographic phenotype in the presence of progressively increased pulmonary pressures was increased LAVI, E/e' and higher

proportions of RV dilation and dysfunction. In another important sub-group of LHD we were able to demonstrate that the risk of mortality increased progressively as TRV increased. Granular analysis of the mortality data showed these trends were maintained on sensitivity analysis when the cohort was stratified by degree of LV impairment (mildly reduced LVEF versus reduced LVEF), as well as by sex. Of interest, CV mortality increased progressively in the male cohort but in the female cohort only became significant in the high-risk group.

Independently, LVDD and PHT are increasingly common but there are mixed contemporary data on the prevalence and prognostic impact of PHT complicating LVDD in adults with pEF. In *Chapter 6*, using a large clinical cohort with LVDD and pEF we demonstrated not only that PHT was prevalent, but that the proportion of adults with more severe diastolic dysfunction increased as PHT-risk increased[196]. In addition to an echocardiographic phenotype, we were able to demonstrate important clinical characteristics associated with raised pulmonary pressures such as increases in BMI and higher proportions of AF. Again, we showed that there was a progressive increase in mortality risk as pulmonary pressures increased. These trends persisted after adjusting for presence of AF and level of diastolic dysfunction and were consistent between sexes. These two studies highlight that PHT is a common complication in these cohorts with significant negative implications on mortality, thus, suggesting that careful monitoring of such patients is needed.

After determining that PHT is commonly found in patients with LVDD and pEF, and demonstrating that its presence has a negative prognostic impact on outcomes, we sought discern the characteristics of adults who developed PHT in this cohort. In *Chapter 7*, we demonstrated that LAVi is the diastolic parameter with the strongest univariate association with increasing TRV[197]. This likely reflects increased LA filling pressure caused by increased LV diastolic stiffness and impaired relaxation seen in LVDD. Increased age, LVEF, BMI and AF were all significantly associated with the development of PHT in adults with LVDD and pEF. Whilst increased age, female sex and AF were independently associated with increasing severity of PHT. With growing burden of such patients seen in modern clinical practice this study is particularly important as it provides clinicians with a framework for risk stratification and monitoring. These factors may also be targeted in the future to potentially prevent the development of PHT in this cohort.

The Impact of ‘isolated’ Left Heart Disease on the Right Heart

Patients with severe AS develop important changes to their right ventricle. In *Chapter 8* we document that 28.2% of patients with severe AS had RV dysfunction prior to undergoing TAVI[198]. The early haemodynamic effects of unloading the LV after relief of aortic valve obstruction through TAVI has been demonstrated by early LV remodelling. In this study however, we demonstrate that at short term

follow-up, the correction of AS does not lead to normalisation of RV function in greater than two-thirds of these patients. Further studies are needed to determine if improvements in RV function are noted in the long term and whether baseline or persistent RV dysfunction is linked to outcomes. Importantly, we identified clear thresholds on baseline echo for each RV functional parameter where there was a <10% chance of recovery - TAPSE <1.4cm, S'<6 or FAC <25%. This framework can help clinicians to further monitor, manage and prognosticate these patients.

Future Directions

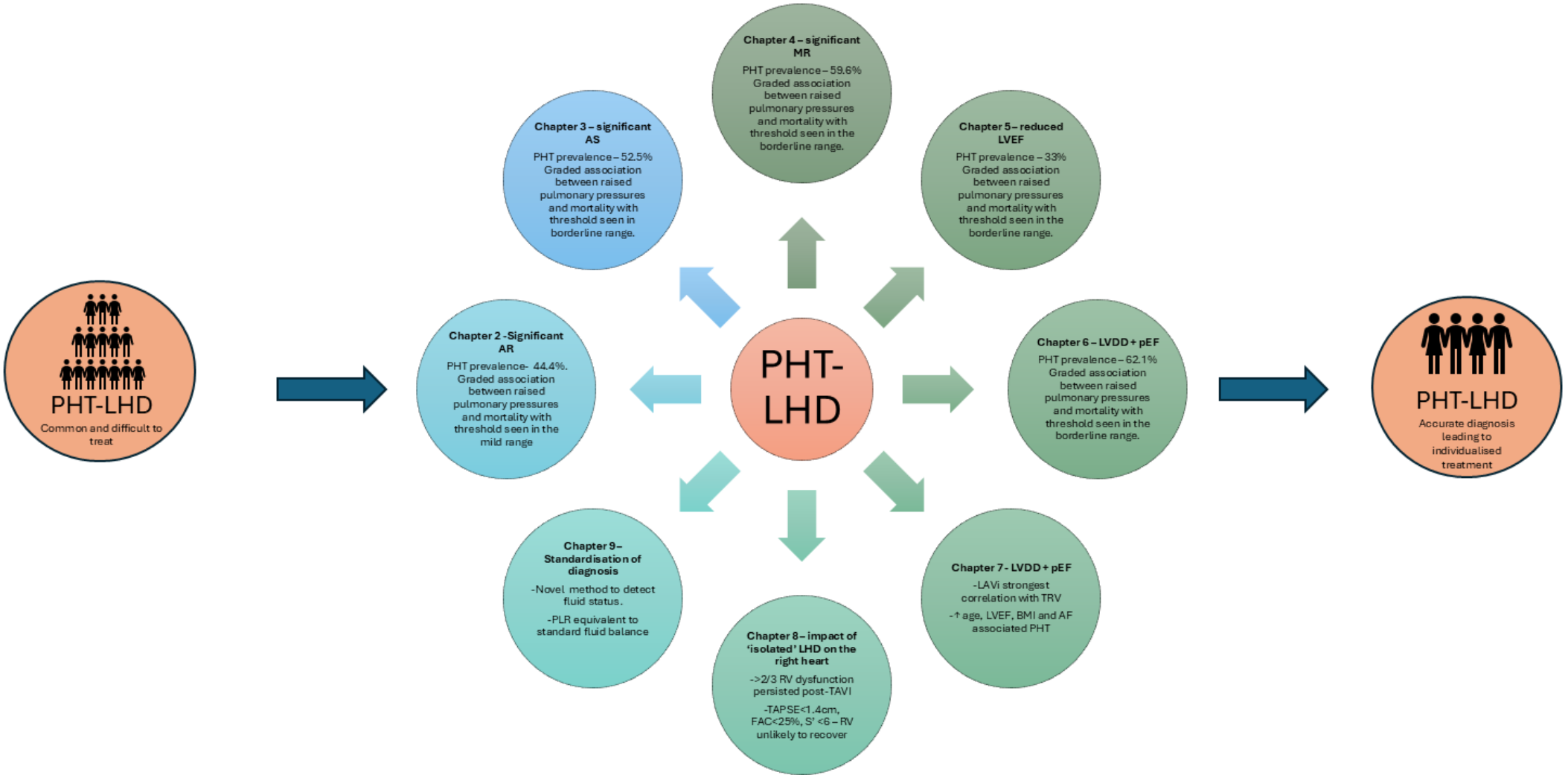
Accurate diagnosis of patients with PHT-LHD is imperative to determining appropriate treatment pathways. The prospective pilot study, documented in *Chapter 9*, identified a non-invasive technique to determine fluid status prior to RHC[199]. The non-invasive finger probe in this study is commonly used in critical care settings and was able to detect patients who were fluid deplete, which was particularly important as these patients were not identified on routine clinical assessment. Thus, this novel technique was additive to the patient's overall assessment and allowed correction of fluid status prior to haemodynamic assessment. Standard RHC may not be able to determine occult PHT-LHD, thus provocation tests are important to consider. Promisingly, this pilot study suggests that the use of passive leg raise may be an equivalent provocation test to a "one dose fits all" challenge with a fluid bolus. This test is simple, cost efficient, reproducible and is standardised to a patient's individual factors without the risk of precipitating pulmonary oedema, thus mitigating the issues faced with standard-of-care fluid boluses. This study is limited by its small cohort but lays the groundwork for larger validation studies to confirm that these techniques maximise the accuracy of this important test.

The work presented within this thesis therefore describes the facets of the heterogenous group of conditions encompassed by PHT-LHD (**Figure 10.1**). It provides granular insights into the impact PHT has on mortality across the spectrum of LHD. Despite increased recognition of how prevalent these conditions are, methods to effectively treat these patients remains incompletely understood. Current management approaches focus on the treatment of the underlying LHD and diuresis. However, with growing understanding that a significant proportion of these patients have combined pre- and post-capillary PHT it may be possible to identify a sub-group who may respond to long-term PAH therapy. The studies in this thesis contribute to the effort to accurately diagnose patients with PHT-LHD and thus, provide the platform for hypothesis generation in the future. For example, identification of intermediate and high-risk PHT patients using echo phenotyping may provide clinicians with a framework to identify appropriate patients to refer for in-depth haemodynamic phenotyping. Future studies may also consider trialling PAH therapy such as PDE5 inhibitors in patients with combined pre- and post-capillary PHT with clinical outcomes assessed at short, medium and long-term follow-up.

Conclusions

Collectively, the chapters within this thesis provide detailed information on the prevalence and negative prognostic impact of PHT in different types of LHD. The findings further document in-depth echocardiographic phenotyping for patients across the spectrum of LHD which can inform the development of future monitoring and risk stratification tools. Importantly, in this thesis a standardised diagnostic approach for accurate diagnosis is presented with the aim to be able risk stratify patients who need catheterisation, provide accurate diagnosis and ultimately, through the work of future studies, provide individualised and effective care to PHT-LHD patients.

Figure 10.1. A summary of the work in this thesis, and future directions



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