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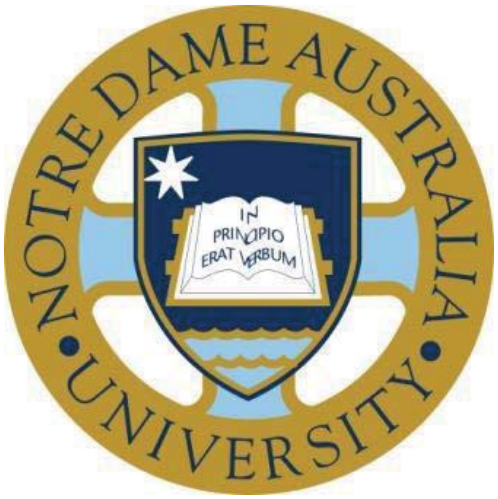
THE UNIVERSITY OF NOTRE DAME AUSTRALIA

Diagnosing Pulmonary Hypertension due to Left Heart Disease using Diastolic Echo markers: The National Echo Database of Australia (NEDA) PH-LHD Predictive Formula

Author: Dr Kevin Chung - MBBS (Hons), BNsg, Grad Cert HPE, Grad Cert Emer Nsg

A thesis submitted in fulfilment of the requirements for the degree of

Master of Philosophy



School of Medicine

The University of Notre Dame, Fremantle

2018

Supervisors:

Prof David Playford

Prof Geoff Strange

Prof Jim Codde

Prof David Celermajer

A/Prof Gregory M Scalia

Declaration of Authorship

This thesis is the candidate's own work and contains no material which has been accepted for the award of any degree or diploma in any other institution.

To the best of the candidate's knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Printed Name: Dr Kevin Chung
Date: 21/07/2018

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I would like to thank the following people for helping me and supporting me over the course of the last two and a half years.

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To Professor Geoff Strange.

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List of Publications in the course of Master of Philosophy

Journal articles:

- **Chung K**, Strange G, Codde J, Celermajer D, Scalia GM, Playford D. Left Heart Disease and Pulmonary Hypertension: Are We Seeing the Full Picture? *Heart, Lung and Circulation*. 2018;27(3):301-9.

Published conference proceedings:

- **Chung, K**, Naing, P, Strange G, Celermajer, D, Codde, J, Scalia, G, & Playford, D Assessing the Cause of Pulmonary Hypertension on Echo in the Absence of Tricuspid Regurgitation – a National Echo Database of Australia (NEDA) Study. European Society of Cardiology Scientific Meeting, Munich – Germany (August 2018)
- **Chung, K**, Naing, P, Strange G, Celermajer, D, Codde, J, Scalia, G, & Playford, D Assessing the Cause of Pulmonary Hypertension on Echo in the Absence of Tricuspid Regurgitation – a National Echo Database of Australia (NEDA) Study. *Journal of The American Society of Echocardiography*. 2018 (In Print).
- **K. Chung**, D. Playford, J. Codde, D. Celermajer, G. Scalia and G. Strange. Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA). *Pulmonary Circulation*. 2018;8(2):1.
- **K. Chung,** D. Playford, J. Codde, P. Naing, D. Celermajer, G. Scalia and G. Strange. NEDA PH-LHD predictive model: validation of diastolic markers of pulmonary hypertension with right heart catheterization. *Pulmonary Circulation*. 2018;8(2):5.
- **Chung, K.**, Naing, P., Playford, D., Celermajer, D., Codde, J., Scalia, G., & Strange, G. (2017). NEDA PH-LHD Predictive Model: Validation of Diastolic Markers of Pulmonary Hypertension with Right Heart Catheterisation. *Heart, Lung and Circulation*, *26*, S60.
- **K. Chung**, D. Playford, D. Celermajer, J. Codde, G. Scalia, Strange G. Pulmonary hypertension due to diastolic dysfunction: a predictive model using the national echo database of Australia (NEDA). *European Heart Journal.* 2017; Volume 38(Volume 38, Issue suppl_1):P2590.
- **K. Chung**, D. Playford, J. Codde, D. Celermajer, G. Scalia and G. Strange. Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA). *Heart, Lung and Circulation*, *26*, S60.

- **Chung K**, Strange G, Scalia G, Codde J, Celermajer D, Marwick T, et al. The National Echo Database Australia (NEDA) and Pulmonary Hypertension (PHT). *Pulmonary Circulation* 2017; 0(0) 1–7 DOI: 10.1177/2045893217692589
- **Chung K**, Strange G, Scalia G, Codde J, Celermajer D, Marwick T, et al. The National Echo Database Australia (NEDA) and Pulmonary Hypertension (PHT). *Heart, Lung and Circulation*. 2016. 25:S122.

Awards in the course of Master of Philosophy

- GlaxoSmithKline Travel Grant – Best Oral Abstract Presentation. The Pulmonary Hypertension Society of Australia and New Zealand Annual Scientific Meeting 2017

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Abbreviations

Term	Abbreviation
Analysis of Variance	ANOVA
Area under the curve	AUC
Aortic regurgitation	AR
Aortic stenosis	AS
Aortic valve replacement	AVR
Calcium	Ca^{2+}
Cardiac output	CO
Constant	Con
Development database	DD
Diastolic deceleration time	DDT
Diastolic dysfunction	DD
Diastolic pressure gradient	DPG
Echocardiogram	Echo
Echo Pulmonary to Left Atrial Ratio	ePLAR
Ejection fraction	EF
Endothelin	ET
Extracellular matrix	ECM
Heart failure with preserved ejection fraction	HFpEF
Heart failure with reduced ejection fraction	HFrEF
Left atrium	LA
Left atrial pressure	LAP
Left atrial volume indexed to body surface area	LAVI
Left ventricle	LV
Left ventricular hypertrophy	LVH
Left ventricular end diastolic pressure	LVEDP
Mean pulmonary artery pressure	mPAP
Metalloproteinase	MMP
Millimetres of mercury	mmHg

Mitral regurgitation	MR
Mitral stenosis	MS
National Echo Database of Australia	NEDA
National Ethics Application Form	NEAF
New York Heart Association	NYHA
Nitric oxide	NO
Protein kinase A	PKA
Pulmonary arterial hypertension	PAH
Pulmonary artery pressure	PAP
Pulmonary artery systolic pressure	PASP
Pulmonary capillary wedge pressure	PCWP
Pulmonary hypertension	PH
Pulmonary hypertension due to left heart disease	PH-LHD
Pulmonary Hypertension Society of Australia and New Zealand	PHSANZ
Pulmonary vascular resistance	PVR
Receiver operator curve	ROC
Right atrial pressure	RAP
Right atrium	RA
Right heart catheterisation	RHC
Right ventricle	RV
Smooth muscle cell	SMC
Systolic dysfunction	SD
Tissue necrosis factor	TNF
Tricuspid regurgitation	TR
Transpulmonary gradient	TPG
Tricuspid regurgitation velocity	TRV
Verification database	VD
Wood units	WU

Abstract

Aims: Pulmonary hypertension (PH) is commonly due to left heart disease caused by ischaemic heart disease, hypertension and valvular heart disease. It is under diagnosed and associated with a high mortality. PH diagnosed using echo requires a measurable tricuspid regurgitation velocity (TRV) to estimate the pulmonary artery systolic pressure (PH = PASP >40mmHg). However, up to 40% of studies have insufficient TRV to calculate a PASP. This can lead to significant delays in the diagnosis of pulmonary hypertension, increased morbidity and delays in the initiation of treatment.

This thesis seeks to determine the prevalence of PH and the diastolic echo markers related to the development of PH in left heart disease (PH-LHD) and create a predictive model using diastolic echo markers to diagnose PH in the absence of a TRV.

Methods: This study is a retrospective observational cohort study with data derived from the National Echo Database of Australia (NEDA). Using PH as the dependent variable and markers of diastolic function as the independent variables we performed univariate and multivariate analysis on the entire cohort to identify predictive diastolic markers that correlates with PH.

To create a predictive formula to diagnose PH-LHD, the entire cohort was randomised 1:1 into a development (DD) and validation database (VD). Using logistic regression analysis on diastolic markers and the presence of PH in the DD, we derived a constant (con) that could be used to predict the probability of PH. Using probability analysis, the Receiver Operating Characteristic (ROC) curve was generated using a 0.5 cut off to evaluate the accuracy of the model. The accuracy of the model was then tested using the VD.

Results: Of the 174,229 patients in the NEDA, 75,204 (43%) had insufficient TRV to calculate a PASP. Of the 99,025 patients with a PASP, 19,767 (20%) had PH. Patients with PH were older (76 vs 62 yr) ($p = <0.0001$) with evidence of diastolic dysfunction, impaired relaxation (E'= 8.2 vs 6.7 cm/s) ($p = <0.0001$) and increased left filling pressures with higher LAVI (46 vs 33 mL/m^2) ($p = <0.0001$) and E/E' (16.7 vs 10.7) ($p = <0.0001$).

The DD (150,979 echos) had 5,181 valid studies to create the NEDA PH-LHD Constant (Con) = -6.649 + (0.035 x Age) + (0.072 x E') + (0.077 x E/E') + (0.509 x E/A) + (0.03 x LAVI) to predict the probability of PH. The DD model AUC ROC is 75% accurate in

diagnosing PH-LHD. Applying our formula to the VD (151,767 echos), the AUC of the ROC curve is 0.742.

Conclusion

Using the NEDA, 20% of patients were diagnosed with PH. Using Age, E', E/E' ratio, E/A ratio and LAVI, the NEDA PH-LHD formula can diagnose PH-LHD in 75% of cases in the absence of TRV.

Statement of Contribution

Contributor	Statement of contribution
Dr Kevin Chung	Primary lead in study design, cleaning of raw data, data analysis, statistical analysis, the creation of the PH-LHD predictive formula, writing the manuscripts for all publications. Lead author in all publications listed and performed presentations at The Cardiac Society of Australia and New Zealand Annual Scientific Meeting (2016 - Adelaide, 2017 - Perth), The Pulmonary Hypertension Society of Australia and New Zealand Annual Scientific Meeting (2016, 2017 Sydney) and The European Society of Cardiology Annual Scientific Meeting (2017 – Barcelona, 2018 - Munich)
Signature:	
Date: 21/07/2018	
Prof David Playford	Primary supervisor for research undertaken by Dr Chung. Review of study design, data analysis, statistical analysis, multiple iterations of PH-LHD predictive formulae, manuscript and conference presentations. Principle investigator in The National Echo Database of Australia (NEDA) study.
Prof Geoff Strange	Co-supervisor for research undertaken by Dr Chung. Review of study design, data analysis, statistical analysis, multiple iterations of PH-LHD predictive formulae, manuscript and conference presentations. Principle investigator in NEDA study.
Prof Jim Codde	Co-supervisor for the research undertaken by Dr Chung. Review of study design, creation of syntax formula for data analysis, review of manuscripts for publication

Prof David Celermajer	Co-supervisor for the research undertaken by Dr Chung. Review of manuscripts for publication and review of oral presentation for conference presentations.
Prof Greg Scalia	Co-supervisor for the research undertaken by Dr Chung. Review of manuscripts for publication and review of oral presentation for conference presentations.
Prof Max Bulsara	Review of multiple re-iterations of NEDA PH-LHD predictive formulae and computation of nomogram.

Chapter 1

1.1 Introduction

Pulmonary hypertension is a major cause of mortality and morbidity with an estimated prevalence of 326 per 100,000 in the Western Australian community (1). The major cause of pulmonary hypertension is left heart disease with the prevalence of 250 in 100,000 in the Western Australian community (1). Left heart disease, such as ischaemic heart disease, is the number one cause of death, worldwide (2). Left heart disease causes pulmonary hypertension due to an increase in left atrial pressure that leads to increased pulmonary venous and arterial pressure. This causes breathlessness and significantly impacts on quality of life, leading to premature death.

Estimated pulmonary artery systolic pressure (ePASP) is a well validated echocardiographic (echo) measure of pulmonary artery pressure. In a population based study an elevated cutoff of 40mmHg is strongly correlated with pulmonary hypertension, assuming a right atrial pressure of 10mmHg (3). A ePASP of >40mmHg is associated with poor outcomes with median time to death of 4.1 yrs (95% CI 3.9 to 4.3) based on the first recorded echo measure of ePASP in a large Western Australian echo cohort (1). Steiner and colleagues (2015) also demonstrated that a higher ePASP (>60mmHg) is a poor prognostic marker. In their cohort of 152 patients followed up over a 5 year period, 69% of patients with a ePASP of >60mmHg died with a median time to death of 129 days (4). Prolonged exposure to increased pulmonary artery pressure from left heart disease leads to irreversible damage to the pulmonary vasculature, right ventricular failure and death.

There are many causes of left heart disease including ischaemic heart disease, valvular disease and infiltrative disease. The pathophysiological process of these diseases can lead to diastolic dysfunction, systolic dysfunction or a combination of both. In this study, we will be focusing on diastolic dysfunction however, taking into account the effects of systolic echocardiographic parameters on left atrial pressure and pulmonary artery pressure. Diastolic dysfunction, irrespective of the underlying cause, increases the risk of death (5). Importantly, worsening diastolic function is correlated to worse outcomes, in particular in patients with grade two or three diastolic dysfunction on echo analysis (6). Work by Thenappan and colleagues found that age, hypertension and presence of coronary artery disease were important patient characteristics in predicting the presence of diastolic dysfunction (7).

Using the modified Bernoulli formula (discussed later) to calculate a PASP requires sufficient

tricuspid regurgitant velocity (TRV). However, up to 40% of patients have insufficient TRV to estimate ePASP and therefore, cannot be assessed for pulmonary hypertension with echo alone.

The relationship between pulmonary hypertension and diastolic heart dysfunction is well documented (8). E/e', deceleration time, E/A ratio, e' and left atrial volume have been validated as markers of diastolic dysfunction (9). However, the determinants of diastolic dysfunction measured via echo to predict the likelihood of elevated pulmonary artery pressure and the role of these measure as a predictor of developing pulmonary hypertension needs further investigation. The end result of left heart disease, irrespective of the underlying cause, is diastolic dysfunction (discussed in detail later). Therefore, there is significant value in using abnormal diastolic function measured using echo markers to investigate its relationship with developing PH.

Large epidemiological data of echo markers have not been established. Co-investigators (DP, GS) have created the National Echo Database of Australia that has enrolled over 300,000 echo studies from multiple echo laboratories into a cloud-based master database. The proprietary software, developed by Acidion Group, adds all retrospective echo data from that site to the NEDA database. Echo data is matched with the NEDA standard by a series of matchup tools that involve site of echo being performed, variable names, variable units and grouping of similar measurement variables. There is a total of 305 echo variables that can be reproducibly matched to any echo study, irrespective of vendor specific echo software. NEDA has over 2.4 million data points configured over 305 echo variable categories.

In summary, left heart disease is the number one cause of mortality worldwide. Pulmonary hypertension is a marker of worsening left heart disease and is an independent predictor of mortality. Echo measures of diastolic function allows clinical assessment of left heart disease irrespective of the underlying pathophysiology. Echo assessment of pulmonary hypertension requires sufficient tricuspid regurgitation (absent in up to 40% of patients) and this represents the Achilles heel in clinical assessment when diastolic function is measurable.

This research will provide the evidence, from a large population of echo studies, that PH due to left heart disease remains under diagnosed. It will establish the value in using diastolic markers of left heart disease in identifying PH and identifying patients who are at risk of

death due to worsening PH and diastolic dysfunction, even in the absence of tricuspid regurgitation.

1.2 Research Hypothesis

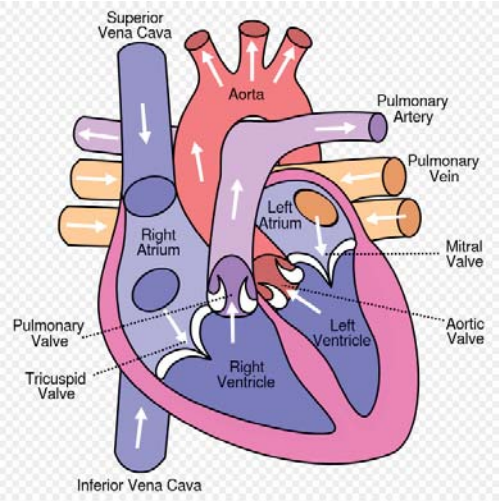
Hypothesis:

1) The prevalence of pulmonary hypertension diagnosed in patients undergoing community and hospital-based echo examinations is higher than previously documented.
2) In a large cohort of community and hospital-based echo data there is a significant difference between the diastolic echo markers of patients with pulmonary hypertension versus those without.
3) In the absence of sufficient tricuspid regurgitant velocity, diastolic echo markers can be used to predict the diagnosis of pulmonary hypertension due to left heart disease.

1.3 Background

Deoxygenated blood flows from the superior and inferior vena cava (see figure 1) into the right atrium, through the tricuspid valve and into the right ventricle. From the right ventricle blood flows through pulmonary arteries into the lung circulation, where it is oxygenated. Oxygenated blood then flows into the left atrium via the pulmonary veins and through the mitral valve into the left ventricle. Finally, blood is ejected from the left ventricle through the aortic valve into the aorta and into the systemic circulation.

Figure 1 - Blood flow through the heart



(10)

The cardiac cycle can be divided into two parts; cardiac systole and diastole. Physiological systole occurs when the tricuspid and mitral valves shut and right and left ventricles contract in order to eject blood into the pulmonary and systemic circulation, respectively. Physiological diastole starts once the pressure in the ventricles decreases to the point that the tricuspid and mitral valves open and blood flows down a pressure gradient from the atria into the ventricles.

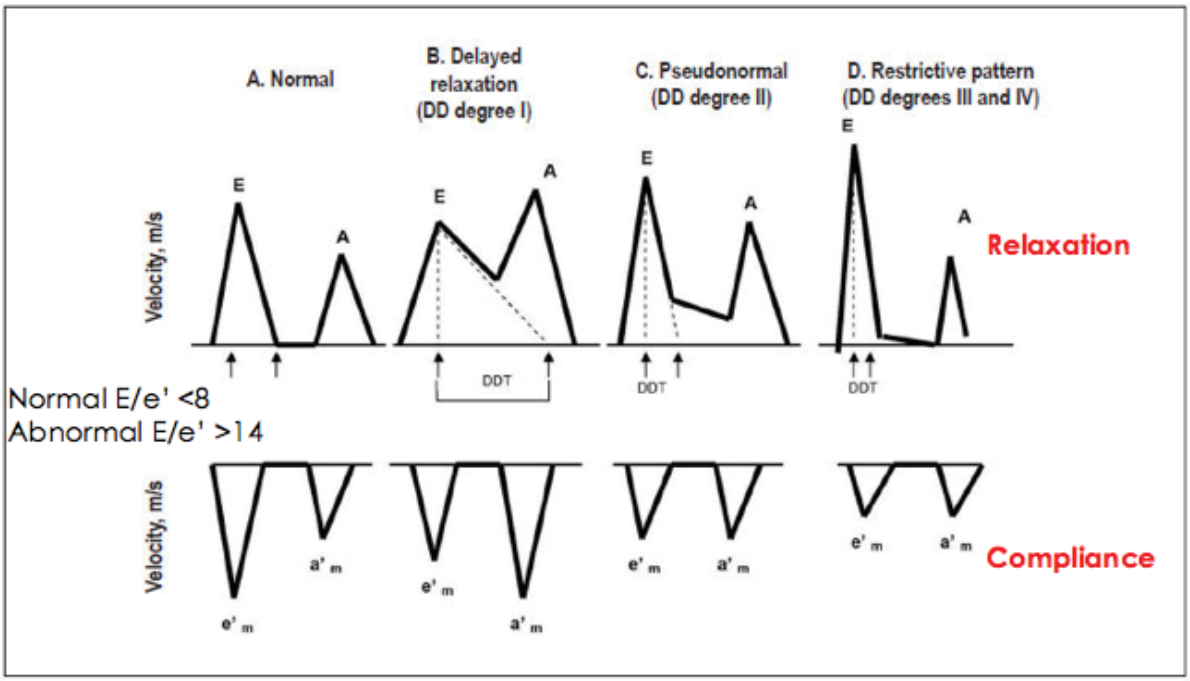
Echocardiography (echo) is the standard test used to assess systolic and diastolic function. The author will focus on diastolic function in this review. Diastolic function can be assessed using tissue Doppler, continuous wave Doppler and pulsed wave Doppler imaging via echo. As oxygenated blood flows from the lungs into the left atrium it crosses the mitral valve into the left ventricle (see figure 1). Normal physiological flow from the left atrium to the left ventricle occurs down a pressure gradient that is dependent on the ability of the left ventricle accepting blood from the left atrium. This process involves active relaxation of the left ventricle and sufficient compliance. Basic assessment of diastolic left ventricular relaxation

involves assessing early and late diastolic filling of the left ventricle. The nomenclature used in echo is E (early) and A (late) diastolic filling. As the mitral valve opens and blood flows down a pressure gradient, early filling velocity (E wave) is high. The A wave represents the end of diastole when the left atrium contracts and ejects up to 20% of the diastolic volume. Figure 2 is a representation of diastolic measure of E/A ratios. Normal E/A ratio is between 0.5-1.5 (11). As diastolic function becomes impaired patients start to develop delayed relaxation causing a decrease in early diastolic filling leading to a smaller E than A (<0.8) and prolonged deceleration time. The physiological cause of this is impaired relaxation; the left ventricle is less able to expand to accept the blood therefore, the E wave velocity slows down and filling time increases representing a smaller E wave and prolonged deceleration time (DDT in Figure 2). Once diastolic dysfunction progresses the E/A ratio reverses again due to further decrease in the left ventricle compliance and stiffness leading to an E wave that is significantly larger than the A wave (ratio >2:1). This occurs as the left atrial pressure increases and blood flows from a relative higher pressure in the left atria to lower pressure in the left ventricle.

The next aspect of measuring diastolic function is assessment of the compliance of the left ventricle. Referring to bottom graphs of figure 2 depicting measurements of tissue Doppler imaging. As the left ventricle fills it lengthens in a longitudinal motion from base to apex (11). This movement of the myocardium can be measured from the mitral valve annulus. This provides early (E') and late (A') measures of diastolic tissue Doppler, reflecting this longitudinal motion. When compared to the velocity of blood across the mitral valve the pattern is initially the same with E to A reversal however, as the diastolic dysfunction (DD) worsens patients develop a stiff ventricle. This leads to very little myocardial movement hence a small E' and A'.

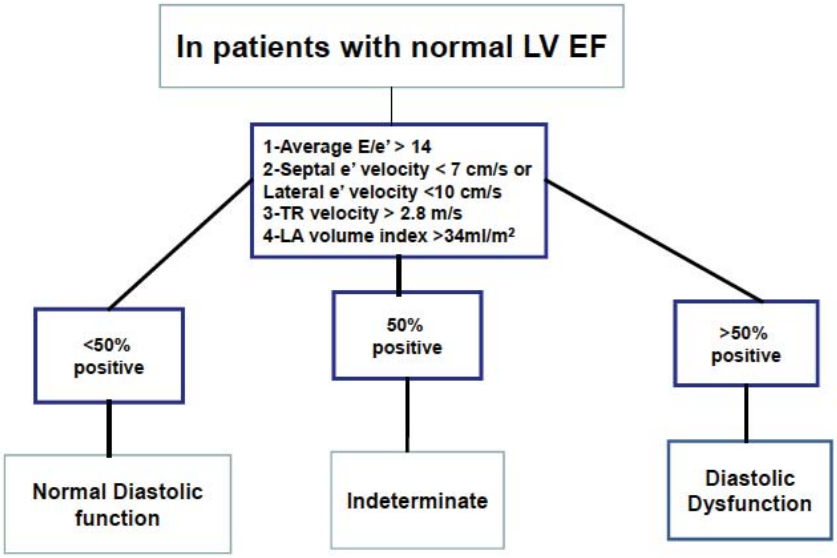
These two concepts of diastolic function on echo measurements can be combined to calculate the E/E' ratio which has been well validates as a measure of diastolic function (11). A E/E' of <8 is normal and an E/E' >14 is considered diastolic dysfunction. Whilst an E/E' between 8-14 requires further investigation of diastolic echo markers to determine whether the patient has diastolic dysfunction (11). Figure 2a depicts a diagnostic flow chart to determine the presence of diastolic dysfunction.

Figure 2 – Diastolic Mitral inflow and Tissue Doppler



(12)

Figure 2a



(13)

In terms of the pathophysiology of left heart disease, the causes can be broadly divided into systolic failure, diastolic failure or valvular heart disease. All patients with systolic dysfunction will have a degree of diastolic dysfunction. Regardless of the cause of the left heart disease, diastolic dysfunction is the final common pathway. In other words, the disease processes of left heart disease always lead to impaired left ventricular relaxation

and/or compliance and an increase in left atrial pressure. Therefore, this research will be looking at diastolic echo markers specifically as it is the final common pathway of left heart disease.

Pulmonary hypertension is a disease causing high blood pressure in the lung circulation leading to increased pressure on the right side of the heart. The symptoms that patients present with is shortness of breath and fatigue (14). There are five main groups outlining the causes of pulmonary hypertension: pulmonary artery hypertension, left heart disease, chronic hypoxic lung disease, chronic thromboembolic disease and miscellaneous causes including acute pulmonary hypertension and myeloproliferative diseases. The most common type of pulmonary hypertension is due to left heart disease, with incidence of 68% in the Western Australian community and 69% in the United States (1, 15).

Left heart disease causing pulmonary hypertension can be divided into three categories: left heart systolic dysfunction, left heart diastolic dysfunction and left heart valvular disease. Left heart systolic dysfunction is the inability of the heart to pump blood during the systolic or contractile phase of the cardiac cycle. The major causes of systolic dysfunction are ischaemic heart disease and dilated cardiomyopathy. It is important to note that all patients with systolic dysfunction will have a degree of diastolic dysfunction. However, diastolic dysfunction can occur in isolation. As previously described diastolic dysfunction is caused by failure of the left ventricle to relax in order to fill appropriately. The major causes of diastolic dysfunction include; hypertension, coronary artery disease, diabetic cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and constrictive pericarditis (11). Finally, the third category is left heart valvular disease caused by valvular disease such as: aortic regurgitation, aortic stenosis, mitral stenosis and mitral regurgitation.

The pathophysiological process that left heart disease causes pulmonary hypertension is due to an increase in left ventricular pressure leading to an increase in the left end diastolic pressure. This will cause back pressure into the left atrium and pulmonary veins. This increase in the pressure on the pulmonary veins leads to increased pressure on the alveolar capillary walls in the lungs. This causes capillaries to leak causing acute alveolar oedema. Initially this is processes is reversible however, prolonged pressure leads to remodeling of the lungs and deposition of collagen type 4 – an irreversible consequence. There is also irreversible damage to the walls of the pulmonary veins and arteries causing them to thicken and muscularise and form distal pulmonary arteries. This leads to an increase in the pulmonary vascular resistance (PVR).

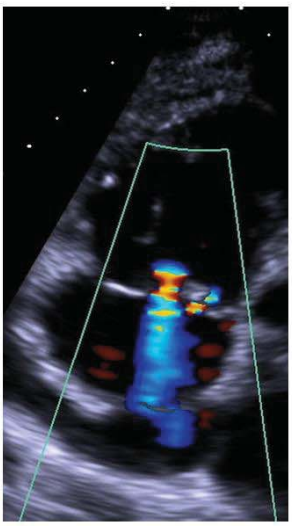
The gold standard for measurements of haemodynamics and pressure is a right heart catheterisation (16). The procedure involves the cannulation of a large peripheral vein such as the internal jugular, subclavian or femoral vein and pulmonary catheter is inserted into the heart to assess the pressures of the right heart and pulmonary arteries. Two measurements that can determine the presence of diastolic dysfunction and pulmonary hypertension is the pulmonary artery pressure and the pulmonary capillary wedge pressure. The pulmonary capillary wedge pressure is a direct reflection of the left atrial pressure. As previously discussed, the end result in diastolic dysfunction is an increase in left atrial pressure and this can be measured by the pulmonary capillary wedge pressure. The measure of the pulmonary artery pressure will determine if pulmonary hypertension is present. Therefore, if pulmonary capillary wedge pressure is raised in proportion to the pulmonary artery pressure, one can diagnose pulmonary hypertension due to left heart disease. Unfortunately, right heart catheterisation is an invasive test with a small risk of complication therefore, it is not a screening tool for assessing patients who present with breathlessness.

Echocardiogram (echo) has been established as a validated tool in estimating pulmonary artery pressures. Using echo, one can estimate the pulmonary artery pressure using the tricuspid velocity and Bernoulli's equation. The tricuspid valve lies between the right atrium and right ventricle (see figure 1). As previously mentioned, the end result of pulmonary hypertension is an increase in right ventricle and right heart pressure. During ventricular systole, the tricuspid valve closes and the right ventricle contracts causing blood to be ejected through the pulmonary arteries into the lung circulation. In approximately 70% of patients, the tricuspid valve does not close completely causing a leak or regurgitation during ventricular systole. Using echo Doppler measurements, the operator can determine the peak tricuspid regurgitation velocity. The Bernoulli principle is based on the principle of the conservation of energy and states that velocity increases simultaneously as pressure decreases. Therefore, the estimated peak pulmonary artery pressure can be calculated using an estimate of the right atrial pressure. An estimated pulmonary artery systolic pressure (PASP) above 40 mmHg is suggestive of pulmonary hypertension (17).

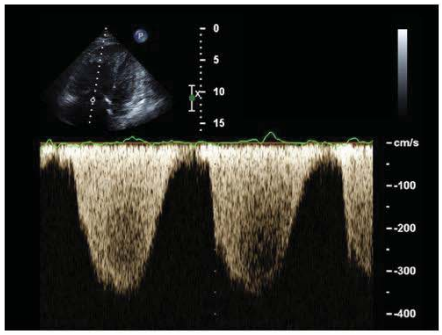
In order to obtain an accurate PASP the continuous wave (CW) doppler measurement must be placed in parallel to the intercept angle of the tricuspid regurgitant jet (11) (see Image 1). Significant attempts to obtain multiple views to achieve good aligment of the CW doppler and highest velocity will ensure that the PASP is not underestimated (18). This should include parasternal RV inflow, basal short axis, apical long axis, and subcostal views. Another method to estimate the PASP is to use the pulmonary regurgitant profile. Using the initial pulmonary regurgitant velocity one can calculate the estimated PASP using the same

modified Bernoulli's equation (18). Pulmonary acceleration time is a measure of systolic flow across the pulmonary valve using pulsed wave doppler. The principle is based on the fact that an increase in pulmonary vascular resistance (> 3 WU) and increased pulmonary pressure will cause a sharp earlier peak in velocity followed by a prolonged filling time illustrated by a mid-systolic notch in the doppler profile. A pulmonary acceleration time less than 90ms indicates the presence of elevated PVR and PH (18)

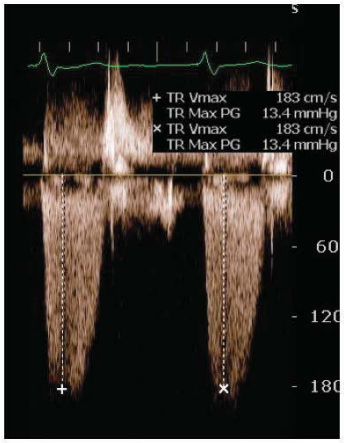
Image 1



Colour jet line-up for TR velocity



TR velocity measurement



TR profile nonimaging transducer

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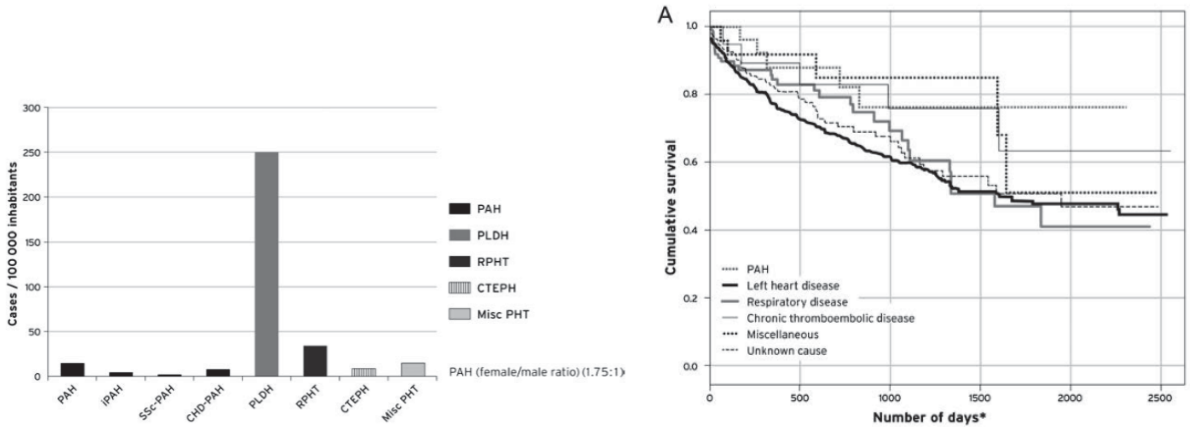
(18)

To put this into perspective, there were over 1 million echos performed in Australia in the last financial year (19). There is no echo database in Australia or the world that has looked at echo markers from a population based network. Therefore, co-investigators (DP, GS)have created the National Echocardiographic Database of Australia (NEDA). The primary objective of the NEDA is to link together the majority of digital echo laboratories in Australia and extract detailed cardiac measurement data into a central database. This database will be linked with national death database to obtain mortality risk statistics for each cardiac abnormality studied. This study is a sub-study of the NEDA study looking specifically at the effects of left heart disease and diastolic dysfunction on pulmonary hypertension.

The effects of pulmonary hypertension on mortality is significant. In a large Western Australian cohort of patients who received an echo and had an elevated PASP >40mmHg, the median time to death was 4.1 years (1). Even more alarming is the time from symptom onset to diagnosis. Work by Strange et. al., found that the mean time from symptom onset

to diagnosis was 47 ± 34 months (14). Patients also had a convoluted path from the onset of symptoms to a formal diagnosis with patients reporting 5.3 ± 3.8 GP visits and 3.0 ± 2.1 specialist reviews before being seen at a pulmonary hypertension center. This illustrates that the recognition of the pulmonary hypertension in the community is poor and is likely to be under reported. More so the survival of pulmonary hypertension due to left heart disease is the most common and has the worse prognosis (refer to Figure 3).

Figure 3



PLDH = Pulmonary hypertension due to left heart disease

(1)

The poor prognosis of pulmonary hypertension can be further examined if we compare the severity of pulmonary hypertension based on echo measurements of PASP. Referring to Figure 4 adapted from work performed by Strange et. al. (2012) there was a significant association with mortality and PASP. Patients with moderate pulmonary hypertension (PASP 51-60mmHg) had a 1.89 times greater risk of death than a patient with mild pulmonary hypertension (PASP 40-50mmHg). Further, the risk of death of patients who had severe pulmonary hypertension (PASP >60) was 3.29 fold that of a patient with moderate pulmonary hypertension (1).

Figure 4

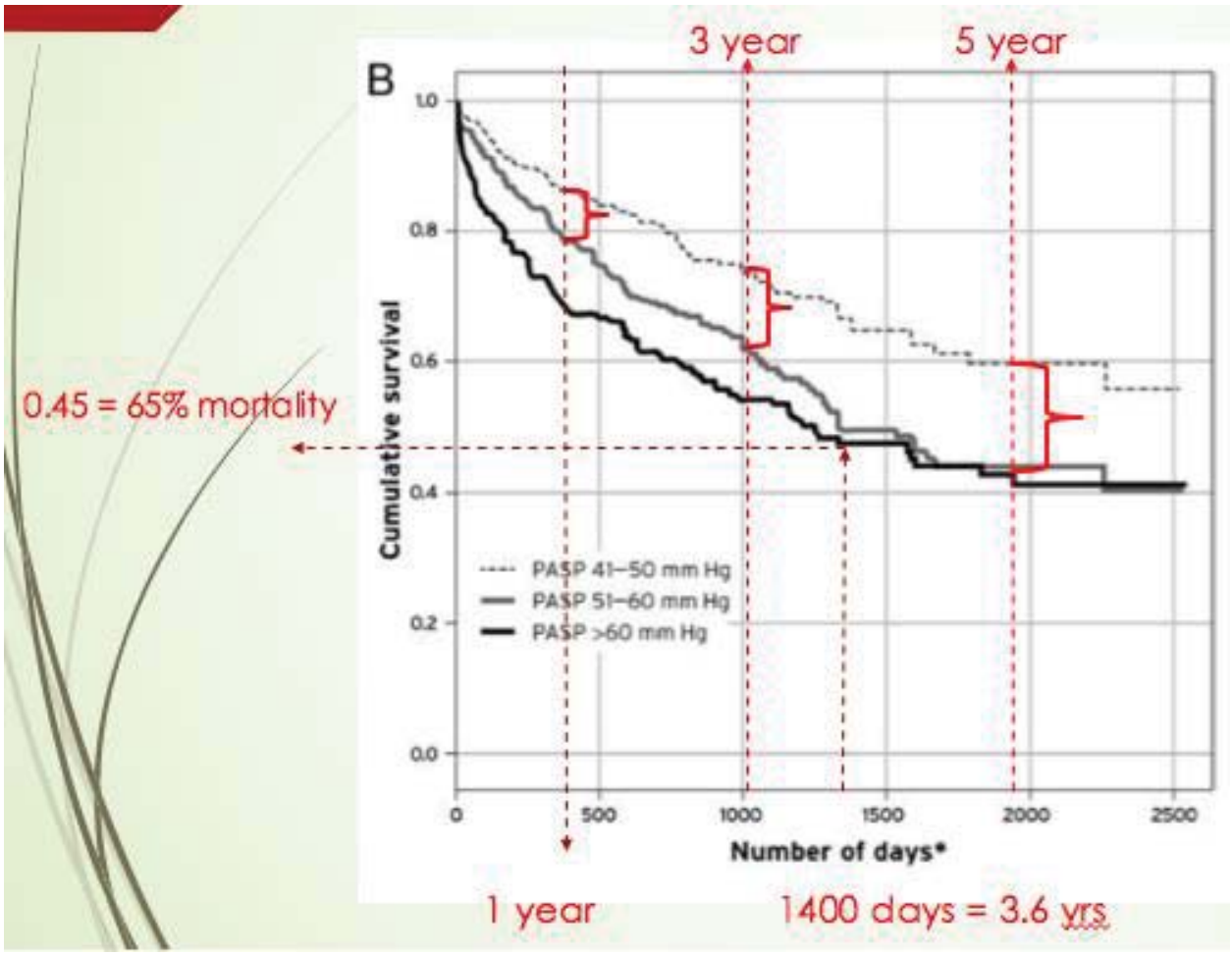
Variable	OR	p Value	95% CI
Age	1.03	<0.001	1.02 to 1.05
PAP: 40-50 ref	-	-	-
51–60	1.89	<0.001	1.34 to 2.67
>60	3.29	<0.001	2.27 to 4.78

(1)

If we compare the Kaplan Meier survival curves of patients with mild, moderate and severe pulmonary hypertension (Figure 5), adapted from Strange et. al. (2012), one can identify some significant issues. Drawing your attention to the trends in cumulative mortality we can see that patients with moderate and severe pulmonary hypertension intersect at about 3.6 years and run relatively parallel to each other. On the other hand, if we compare these to the curve of patients in dotted line (mild pulmonary hypertension) readers can see that the

gap in cumulative survival starts to widen over time, highlighting the trend at one, three years and five years respectively.

Figure 5



Adapted from (1)

This begs the question of whether there are any echo markers to identify patients with mild or “high normal” pulmonary artery pressures that can predict the risk of developing moderate or severe pulmonary hypertension.

Hence, the hypothesis being tested by this thesis is whether the development of pulmonary hypertension due to left heart disease can be predicted in patients with diastolic dysfunction through echo measurement of diastolic function, even in the absence of tricuspid regurgitation.

Chapter 2 - Literature Review[1]

2.1 Introduction

Pulmonary hypertension (PH) is common, under diagnosed and associated with a high mortality. Even when PH is suspected, there are significant delays in final diagnosis (14, 20), resulting in more severe disease when the diagnosis is eventually made. PH, regardless of cause, is an independent risk factor for death and disability (1, 21). Appropriate treatment, started early in the disease, may improve survival and quality of life. Echocardiography (echo) is the most commonly used initial investigation for PH. This review focuses on PH due to left heart disease (PH-LHD), and discusses current echo techniques, including methods to simplify the diagnosis and measures of pulmonary vascular resistance (PVR). Although many different left heart diseases (LHD) have been described, from the perspective of pulmonary hypertension all LHD exert their influence on the pulmonary circulation via increased pulmonary venous pressure. These effects may differ (e.g. mitral regurgitation vs left ventricular diastolic dysfunction) but in general, PH-LHD may be grouped together to separate them from pulmonary vascular causes. This review does not focus on individual treatment of specific LHDs.

PH is defined as a mean pulmonary artery pressure (mPAP) ≥25mmHg, measured by right heart catheterisation (16). Based on the NICE classification, there are five main forms of PH. The commonest of these is PH-LHD(22, 23). Haemodynamically, PH can be divided into pre-capillary, due to increased PVR, or post-capillary due to increase left heart filling pressure (16). Post-capillary PH is further stratified into isolated post-capillary PH (Normal PVR) or combined post and pre-capillary PH (Increased PVR (Table 1).

[1] This chapter has been published: Chung K, Strange G, Codde J, Celermajer D, Scalia GM, Playford D. Left Heart Disease and Pulmonary Hypertension: Are We Seeing the Full Picture? *Heart, Lung and Circulation*. 2018;27(3):301-9. DOI:10.1016/j.hlc.2017.09.015

Table 1

Haemodynamic definitions of PH (adapted from Galie et al., 2016) (16)

Definition	**Characteristics**	**NICE Clinical groups**
PH	mPAP ≥25mmHg	All
Pre-capillary PH	mPAP ≥25mmHg PCWP <15mmHg	1. PAH 3. PH due to chronic lung disease 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanism
Post-capillary PH	mPAP ≥25mmHg PCWP >15mmHg	2. PH-LHD 5. PH with unclear and/or multifactorial mechanism
a) Isolated Post-capillary PH	DPG <7 mmHg and/or PVR ≤3 WU	
b) Combined post and pre-capillary PH	DPG ≥7 mmHg and/or PVR >3 WU	

DPG: diastolic pressure gradient (diastolic PAP – mean PCWP); PVR: pulmonary vascular resistance; WU: Wood units

2.2 Pulmonary Hypertension from Left Heart Disease

2.2.1 Epidemiology

2.2.1.1 Australia

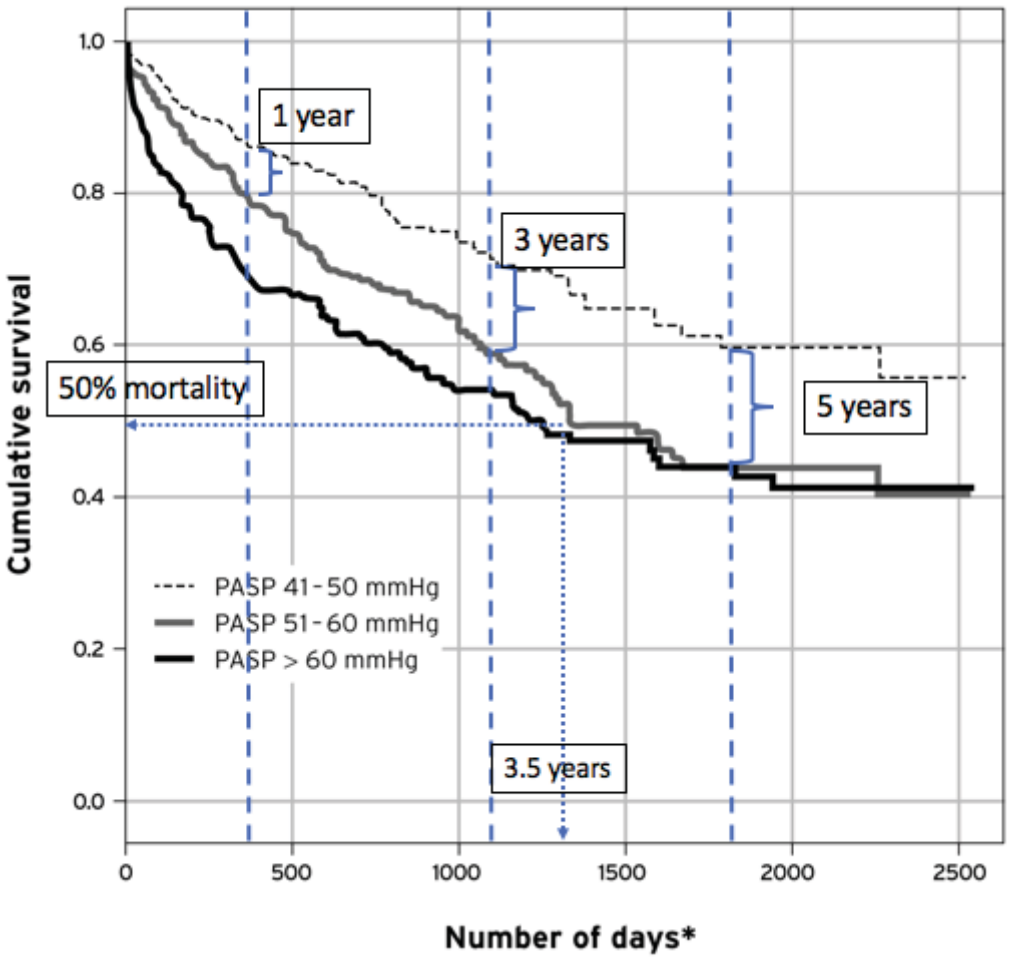
While up to four out of five people with diagnosed PH have PH-LHD (24), the true prevalence of PH-LHD in Australia remains unknown but in the current milieu of an aging population and the increasing prevalence of systemic hypertension, diabetes, sleep apnoea and metabolic syndrome, significant work is required to establish the current burden of this disease. In the absence of community based studies, measures about the prevalence and disease burden of PH have come from other clinical registers and targeted studies.

To date, the Armadale Echo Study is the largest study in Australia to investigate PH prevalence and mortality. Results from this study confirmed that PH-LHD was the commonest form of PH (70%), and that patients with this diagnosis had the worst prognosis of all forms of PH, with a median time from echo detection to death of only 4.1 years (1).

Compounding the gravity of this situation, a related study reported significant delays from symptom onset to final diagnosis (average time: 47 months) with patients reporting an average of five GP visits and three specialist reviews before being seen at a PH Centre (14). The large database of PH managed by the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ), comprising over 2500 patients, includes almost exclusively patients with groups 1, 3, 4 and 5 PH, with only a small proportion with LHD (25).

Severity of PH is associated with increased mortality (see Figure 1). Compared to patients with mild PH, those with moderate or severe PH are respectively at 1.89 times and 3.29 times greater risk of death (1). This highlights the need for early diagnosis and treatment, particularly in those with mild PH, including finding markers of disease progression to more severe PH.

Figure 1



Kaplan-Meier Survival of all-cause pulmonary hypertension: Mild (PASP 41-50mmHg), Moderate (PASP 51-60mmHg), Severe (PASP >60mmHg). Adapted from Strange et al. (2012).

2.2.1.2 Worldwide epidemiology of PH-LHD

International prevalence of PH-LHD is lacking due to poor reporting of the disease and a lack of registry data available on the demographics and clinical course.(16). Prevalence data derived from tertiary referral centres mostly have PAH as the reason for referral, whereas population prevalence studies appear most suited to identifying the true prevalence of PH-LHD. Therefore, the current literature on pulmonary hypertension is disproportionately focused on data available from PAH registries whilst lacking in group two (PH-LHD) and group three (PH due to lung disease), who make up most of the PH population.

In the United States, population based data from the Olmsted County study found that the prevalence of PH was 6.6%. Eighty three percent of patients with heart failure with preserved ejection fraction (HFpEF) had PH and the predictors for developing PH were increasing age and systemic hypertension (26).

In the United Kingdom (UK) the reported prevalence of PH is 97 cases per million with women 1.8 times more likely to have the disease (16). This is likely to be an underestimate of the true population prevalence, particularly PH-LHD. The ASPIRE registry from the Royal Hallamshire Hospital is the largest UK based PH registry. The prevalence of PH-LHD was 11.7% with a three-year survival of 73%(27). Patients with PH-LHD are older, more likely female and have better survival than patient with PAH. Survival in patients with valvular heart disease was worse than those with systolic dysfunction (SD) or diastolic dysfunction (DD), despite 36% having had valvular replacement surgery (27). These data suggest that patients with PH in the setting of valvular disease are a high risk group, with higher PVR than those with systolic or DD (5.07 ± 3.76 vs 3.54 ± 1.94 vs 3.05 ± 2.26 WU, respectively) (27).

A large single centre study in Vienna recruited 2,351 patients who underwent right heart catheterisation for investigation of raised PASP on echo. They reported that 1,259 (53%) had PH, and in keeping with the Australian Armadale Echo study, found that 86% of these patients had PH-LHD (28). In contrast, the Swiss PH Registry (n = 996), with a strong focus on PAH, reports only 3.6% of patient with PH-LHD, although like the PHSANZ database, this study probably underestimated the true number of patients with LHD due to referral bias (29). Similarly, the PulmoCor registry (Netherlands) which contains over 1,500 patients results from six tertiary PH centres, reports only 20% of patients with PH-LDH (30).

The true prevalence of PH-LHD is under-estimated but it is the most common type of PH. The delays in diagnosis and initiation of treatments will lead to higher morbidity and poor survival. This is the most important step to establish the magnitude of the disease burden, its clinical progression and treatment options.

2.2.2 Evaluation of PH-LHD and Pathophysiology

Early diagnosis of PH-LHD will help risk stratify patient for disease progression and may enable clinicians to target at-risk patients for more intensive investigation and treatment. Echo markers for PH-LHD may be clinically very useful.

Estimated pulmonary artery systolic pressure (ePASP) is a well validated echo measure of pulmonary artery pressure (PAP)(31-33). A cutoff of 40mmHg is strongly correlated with PH (3), with higher pressures associated with a worse prognosis (1), reaching a median time to death of 129 days after developing severe PH (ePASP >60mmHg)(4). The pathophysiology of LHD that may lead to developing PH include: left ventricular (LV) systolic and DD, mitral and aortic valvular disease and congenital/acquired inflow/outflow tract obstruction or pulmonary vein stenosis (16).

Heart failure with an impaired ejection fraction (EF) is associated with a poor prognosis, and significant morbidity(34), with 75% of patients diagnosed with PH(24). In patients who present to hospital with acute decompensated HFrEF, the mortality at 6 months in patients with no PH was 8.6% vs 21.8% with isolated post capillary PH vs 48.3% in patients with mixed pre/post-capillary PH ($p = <0.0001$) (35). Lam et al. (2009), further evaluated patients with HFpEF and found that those with elevated PASP >35mmHg did worse and that the age-adjusted hazard ratio was 1.28 for every increase in PASP by 10 mmHg (26).

LHD leads to an increase in left atrial pressure (LAP) and backpressure into the pulmonary veins. Increased pulmonary venous pressure causes pressure on the alveolar capillary walls and alveolar capillary stress failure due to barotrauma (36). This damages the endothelial function leading to a decrease in lung diffusion capacity, fluid reabsorption and capillary leakage (37). Clinically, this causes pulmonary oedema and patients present with shortness of breath.

Alveolar capillary stress leads to activation of the chemical mediators; endothelin I (a potent vasoconstrictor), angiotensin II and inhibition of nitric oxide (NO) (38). This is combined with release of metalloproteinases, degradation of matrix proteoglycans and release of

inflammatory mediators such as tumour necrosis factor-∝ (36, 37). This leads to impaired smooth muscle function and accumulation of collagen type 4 within the intima and media of vessels. The lung myofibroblasts then proliferate leading to muscularisation of the arterioles, neointimal formation of distal pulmonary arteries and irreversible increase in PVR (36, 39). The end result is restrictive lung syndrome and impaired gas exchange (39).

Causes of LHD can be divided into SD, DD and valvular disease. These diseases differ significantly but the final common pathway is an increase in LV and atrial pressure and the reactive increase in PAP.

2.2.3 Systolic Dysfunction (SD) and PH

SD leads to a reduction of the LV EF. The LV chamber becomes spherical in shape and dilates with an increase in mass and loss of contractile Starling's function (40). SD develops due to thinning and disorganised ECM collagen architecture leading to fibrosis (40). The myocytes remodel with a disproportionate increase in the length to width ratio (41). Sarcomeric dysfunction occurs due to proteolytic activity resulting in troponin I degradation and impaired myocyte function (42). Damaged troponin I also causes impaired phosphorylation by protein kinase A (PKA) as a result of impaired β-adreneric signalling leading to impaired cardiac relaxation (42). This complex interplay leads to altered calcium homeostasis within the myocytes and impaired contraction and SD. Trauma caused by myocardial infarction, myocarditis, volume overload, genetic mutations or drug toxicity leads to a cascade of neuroendocrine (angiotensin II, catecholamines, endothelin, TNF-∝, insulin-growth factor) release, activation of growth factors and cytokine release. The heart continues to hypertrophy and dilate leading to an increase in end systolic volume, left ventricular end diastolic pressure (LVEDP) and a reduction in stroke volume and cardiac output (41).

2.2.4 Diastolic dysfunction (DD) and PH

DD results in prolonged LV isovolumetric relaxation, slow LV filling time and increased stiffness. The development of LV stiffness occurs in the ECM and the cardiomyocytes (43). In DD the ECM stiffens due to an excess of collagen type 1 deposition. For example, in hypertensive patients there is a reduction in collagen type 1 degradation due to a down regulation of matrix metalloproteinases (MMP) (43). Cardiomyocytes stiffen due to the titin protein isoforms N2B (stiffer spring):N2BA (more compliant spring) ratio that increases in diastolic failure and conversely is decreased in SD (44). This leads to increase in LV filling

time and reduced compliance. Evidence of tissue Doppler measurements has established that patients with SD have a degree of DD.

2.2.5 Valvular Heart Disease and PH

Between 15-60% of patients with left sided valvular disease have PH (45). Aortic stenosis (AS) and aortic regurgitation (AR) cause an indirect increase in LA pressure secondary to pressure overload and volume overload, respectively (45). Mitral stenosis (MS) has a direct effect of pressure overload on the LA whilst mitral regurgitation (MR) has a direct impact on LA pressure due to volume overload (45).

2.2.5.1 Aortic Stenosis

15-30% of patients with symptomatic AS have PH due to impaired LV function, concomitant MR, increased LVEDP and LA dilatation (45). Aortic valvular replacement (AVR) is indicated if patients develop symptoms of impaired LV function however, evidence suggests that the development of PH should be a strong indication to consider early surgical intervention. Melby et al. (2011), found that patients who had PH had a higher incidence of perioperative mortality (9% vs 5%, p=0.02), increased length of stay (8 vs 7 days, p=0.001) and prolonged ventilation (26% vs 7%, p= <0.001) (46). Patients with severe PH had a significantly lower survival rate than a patient with mild PH (45% vs 78%, P= <0.001) (46).

2.2.5.2 Mitral Stenosis

More than 40% of patients with MS develop PH (46). Current American and European cardiac society guidelines (Class IIa) recommend percutaneous mitral valvuloplasty in patients who are asymptomatic with moderate-severe MS and moderate PH. The aim is to intervene prior to the development of moderate-severe PH, that has a trend towards increased mortality (46).

2.2.5.3 Aortic Regurgitation

The prevalence of PH in patients with AR is 27-37% (45). Work performed by Hirshfled et al. (1974), found a significant relationship between PH, LVEDP and left ventricular hypertrophy (LVH) vs survival in patients undergoing surgical AVR (47). Patients with PAP <25mmHg had a 6-year survival rate of 80% versus 20% if patients had PAP of >40mmHg (47). Patients with a LVEDP of 4-10mmHg had a 6-year survival of approximately 70% vs 30% if their LVEDP was 21-60mmHg (47). However, in patients with modest LVEDP (11-20mmHg) prognosis was poor only if they had developed PH. In contrast, patients with LVEDP >20mmHg had a poor prognosis independent of PH, suggesting that DD is an independent

predictor of morality. But PAP was rarely elevated in patients with normal LVEDP (47). This begs the question of whether these data on haemodynamics involved in aortic valvular disease and PH can be applied to evaluating DD in PH. Can non-invasive echo markers of LHD that correlate with elevated PAP be used to predict developing PH. This will be discussed in further detail in the next section.

2.2.5.4 Mitral Regurgitation

Primary MR

In primary MR the prevalence of PH is 20-30% in patients with symptoms and <20% in asymptomatic patients (45). In patients with NYHA class 3-4 symptoms and severe MR, 64% had moderate PH (PAP >50mmHg) (48). Five-year survival of patients undergoing MV replacement is worse in patients with PH vs those without (63 ± 5% vs 86 ± 2% p= <0.0001) (49). Early surgery (< 3 months) in patients with severe MR and PH (regardless of LV function) improved prognosis and prevented cardiovascular mortality (49). Current European and American guidelines give a Class IIa indication for surgery in patients with severe MR, normal LV function and elevated PAP at rest (50).

Secondary MR

In patients with secondary MR and LV dysfunction the prevalence of PH is 40% (49, 50). Miller et al. 2014), examined 1384 patients with functional MR with impaired LV function (mean EF = 30%) and found that PH was associated with a higher all-cause mortality (51). Magne et al. (2015), found that, regardless of LV function, a rise of 21 mmHg in PASP on exercise was strongly associated with future cardiac events (45). This highlights the dynamic nature of functional MR and the poor compliance of the LA under a pressure loaded LV leading to an acute rise in pulmonary pressures. Exercise testing patients with mild or moderate MR is required to risk stratify them for early intervention.

2.2.6 Neurohormonal effects of LHD on pathophysiology of PH

The pathophysiology in which LHD results in PH involves two pathways; the passive increase in LAP on the pulmonary circulation (isolated post capillary PH) and the increased pulmonary vascular tone due to vascular remodelling (combined pre/post-capillary PH). The latter involves an imbalance in the secretion of NO and endothelin-1 (ET-1). NO causes dilatation of smooth muscles in response to stimulation by bradykinin, acetylcholine and catecholamines (52). This process is impaired in LHD along with reduced sensitivity to other vasodilators such as brain natriuretic peptide (53). ET-1 promotes the proliferation of

smooth muscle and collagen production leading to vascular remodelling (52). ET-1 acts on two receptors; ET_A located in vascular smooth muscle cells (SMC) and cardiac myocytes and ET_B, also located in SMC but also in endothelial cells. Binding of ET-1 to ET_A leads to phosphorylation of myosin light chains and sustained vasoconstriction. Conversely, the ET-1 to ET_B complex releases NO, anti-apoptotic effects and the clearance of ET-1. However, the expression ratio of ET_A:ET_B is 9:1 in the pulmonary arteries (54).

Histologically, pulmonary artery and vein remodelling in PH-LDH leads to intimal fibrosis and medial hypertrophy (55). This process is fixed and irreversible and is a poor prognostic factor in patients undergoing cardiac transplant.

In PH-LHD, mast cell release causes upregulation of serotonin, histamine and IL-6 (potent vasoconstrictors) further worsening the proliferation of SMCs (52). There is an increase in Starling's forces due to a rise in hydrostatic pressures on the endothelial wall. Given that oncotic pressures remain the same there is a reduction in capillary permeability due to reduced function of mechanosensitive Ca^{2+} ion dependent channels leading to endothelial injury (52).

2.2.7 PH-LHD and RV dysfunction

The increase in load and pressure on the right heart due to PH leads to dilatation of the right ventricle (RV). The RV remodels from a crescent shaped ventricle to a spherical shape leading to functional tricuspid regurgitation (TR) and increase RA pressure. Prognosis is reduced if patients develop RV dysfunction due to PH-LHD however, there is not a predictable relationship between the degree of PH and the development of right heart failure (24). There is a correlation between RV dysfunction due to PH-LHD and an increase in PVR(24). Patients with HFrEF and an RV ejection fraction of <35% have a mean survival of 1.5 yrs (56). Risk factors include male sex, atrial fibrillation and coronary artery disease (57).

2.3 Diagnosis of PH-LHD using imaging

The gold standard for the diagnosis of PH using measurements of haemodynamics is a right heart catheterisation (RHC)(16, 23). RHC is an invasive test with a small risk of complication such as rupture of the pulmonary artery, thromboembolism, and arrhythmias. Therefore, although RHC is necessary for a definitive diagnosis of PH, most patients who present with breathlessness will receive an echo as an initial test.

2.3.1 Echocardiographic measure of PASP

Doppler measurement of ePASP is a validated and reproducible method of calculating the PAP when correlated with simultaneous measurements taken during RHC (33, 58). Evaluation of ePASP is performed using the modified Bernoulli equation ($\Delta P=4V^2$) and estimate of right atrial pressure (RAP):

$ePASP = RAP + 4(TRV)^2$

RAP - Right atrial pressure
TRV - Tricuspid regurgitant velocity
This method does have some caveats which need to be considered in specific patient populations. Peak TRV measured using continuous wave Doppler velocity is most accurate in patients with moderate or less tricuspid regurgitation, and at times may overestimate the true systolic pulmonary artery pressure measured by RHC (17, 59). In patients with severe TR with equalisation of right atrial and ventricular pressure, the pressure difference between RV and RA is small, and the peak TR velocity will therefore not reflect the true right ventricular systolic pressure. In this situation applying the modified Bernoulli equation result in underestimation of the true systolic PAP (59). In addition, patients with atrial arrhythmias and altered flow characteristics across the tricuspid annulus will require the averaging of multiple beats to most accurately apply the modified Bernoulli equation (33).

2.3.2 Echocardiographic evaluation of diastolic dysfunction

Diastolic measures of LV relaxation can be divided into the early (E wave) and late (A wave) filling and is represented as the E/A ratio. Impaired relaxation is represented by an E/A ratio <0.8 and prolonged deceleration time (DDT). As LV compliance reduces and becomes stiffer there is increased filling pressures and patients develop a restrictive filling pattern (E/A ratio >2) (11).

Myocardial velocity using early (E') and late (A') tissue Doppler velocity is measured as the LV moves in a longitudinal motion from base to apex and is less dependent on preload. The transmitral blood flow velocity to tissue Doppler velocity (E/E') has been well validated as a measure of diastolic function (11).

Summarised in Figure 2A is the evaluation of diastolic function in patients with normal EF. Using markers of diastolic function, left atrial volume as a marker of increased filling pressure and peak TR velocity as a maker of right ventricular systolic pressure one can establish if patients have DD (13).

Patients with impaired LV systolic function will have a degree of impaired diastolic function. Figure 2B illustrates how these patients will have a degree of impaired relaxation (E/A ≤0.8), pseudo-normal (E/A >0.8- <2.0) filling characteristics or a restrictive (E/A ≥2.0) filling pattern. This criteria is then used to grade DD (13).

Figure 2A

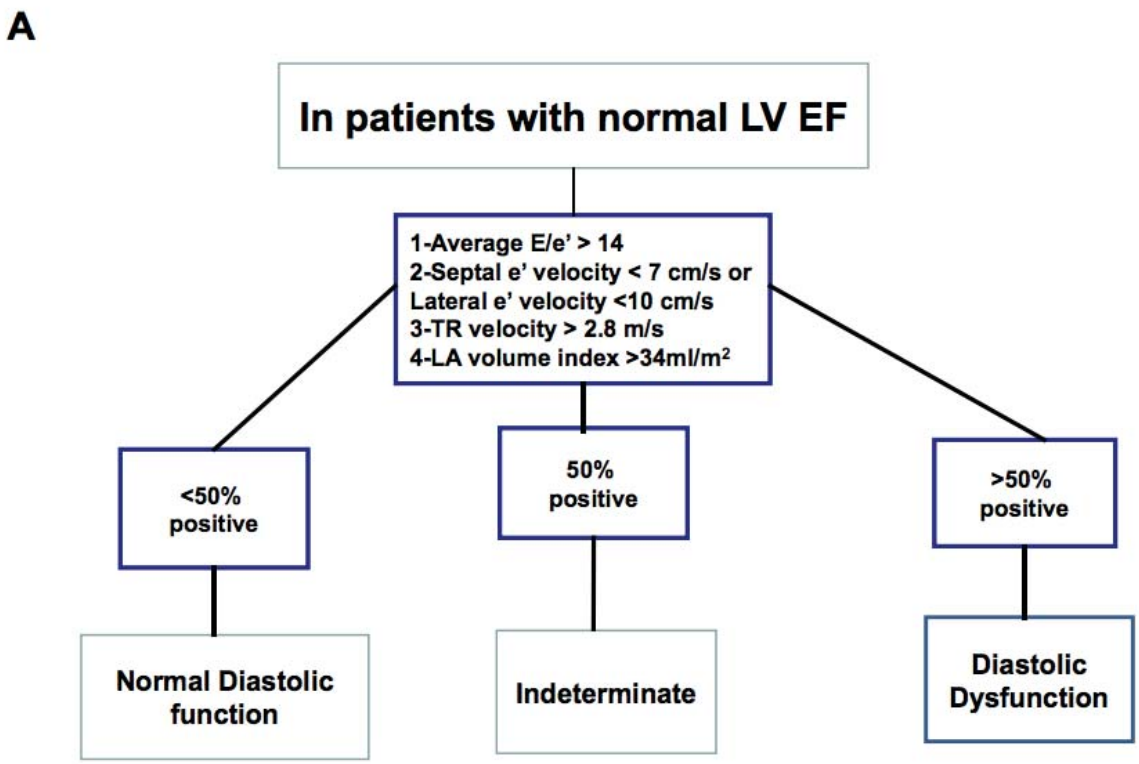
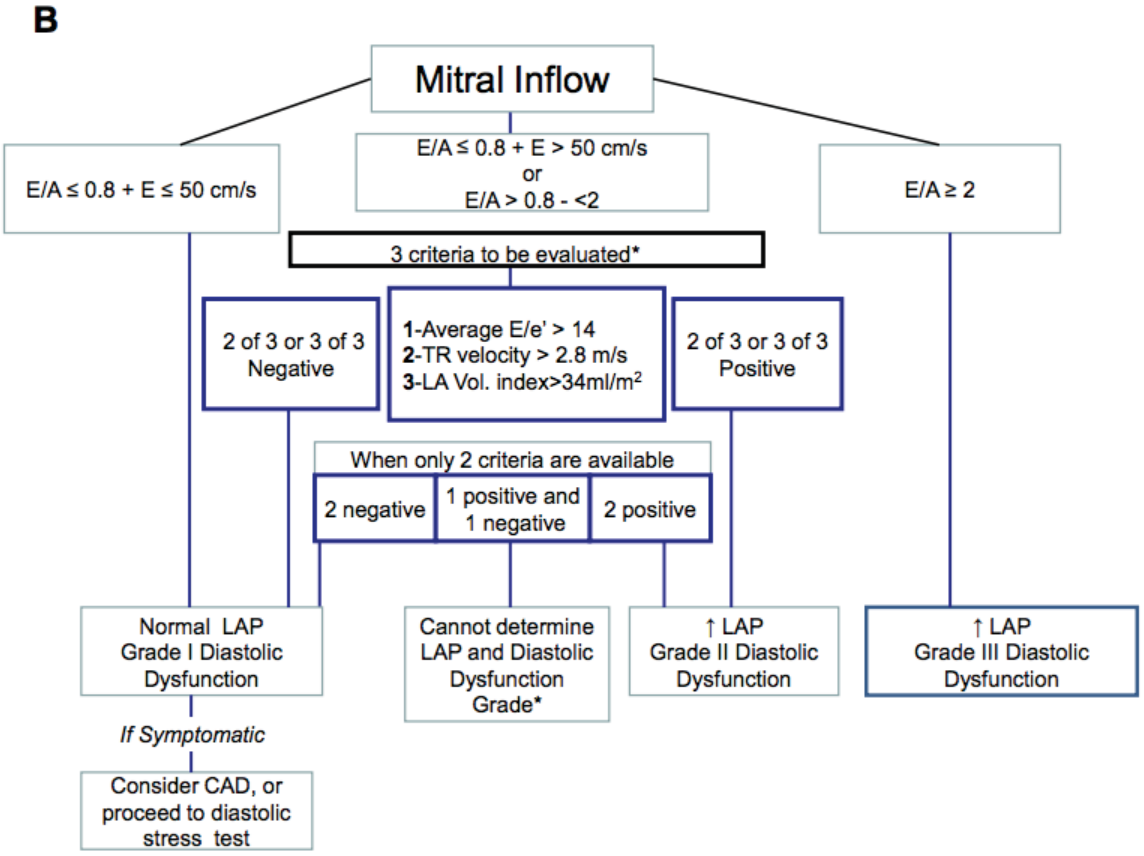

A
In patients with normal LV EF
1-Average E/e' > 14
2-Septal e' velocity < 7 cm/s or
Lateral e' velocity <10 cm/s
3-TR velocity > 2.8 m/s
4-LA volume index >34ml/m²
<50% positive
50% positive
>50% positive
Normal Diastolic function
Indeterminate
Diastolic Dysfunction

Figure 2B



Diastolic function assessment of patients with normal EF (A) and Reduced EF (B) (13).

2.3.3 Evaluation of PVR via RHC

In order to evaluate patients with PH-LDH, evaluation of PVR must be undertaken to establish those patients with isolated post capillary PH vs those with an elevated PVR (60). Determinants of PVR are transpulmonary gradient (TPG) and cardiac output:

PVR = TPG/CO

TPG = mPAP-PCWP

TPG – Transpulmonary gradient

CO – Cardiac output

mPAP – mean Pulmonary Artery Pressure in mmHg

PCWP – Pulmonary Capillary Wedge Pressure in mmHg

Patients with PH-LHD have a raised mPAP with a proportionate increase in LV filling pressure (PCWP) and normal PVR. However, a small group have a mixed picture due to an increase in the TPG and PVR leading to a disproportionate increase in PAP. In this group of patients, further investigations should be performed to evaluate PAH, chronic lung disease or thromboembolic disease.

2.3.4 Echocardiographic evaluation of PVR

Accessibility to RHC can be limited and echo is often the initial test that diagnoses patients with PH. Therefore, it would be advantageous if echo markers could evaluate PVR, determine pre vs post-capillary PH and provide information to guide management.

A recent review article by Naing et al. (2016), evaluated the surrogate echo markers of PVR (60). The challenge is to establish echo markers that take into consideration the PAP and LAP and therefore, a surrogate to transpulmonary gradient measured in RHC.

Early work by Hirschfeld et al. (1975) and Scapellato et al. (2001) looked specifically at patients with congenital heart disease and patients with severe LV dysfunction (mean EF 17%), respectively(61, 62) These studies used markers of RV function and pulmonary artery flow characteristics to predict PVR. However, these studies were small, did not incorporate markers of LAP and patients with HFpEF.

Abbas et al. (2013), have developed a formula ($5.19 \times TRV^2/TVI_{RVOT} - 0.4$) as a surrogate for PVR (63). They postulate that the TRV is a surrogate for transpulmonary gradient and the right ventricular outflow tract (TVI_{RVOT}) is a surrogate for transpulmonary flow. The predictive value was an area under the receiver operator curve (AUC) of 0.93 (63). The caveats were that the formula did not incorporate a surrogate for PCWP however, they did perform Bland Altman analysis and found a correlation in patient with PCWP >15mmHg and a higher PVR (PVR>6WU). This suggests there is has poor specificity in patients with post capillary PH.

Similarly, Haddad et al. (2009), examined patients with PAH with relatively high PVR (mean 11.0 WU) and low LAP (mean PCWP 9) using the formula $PASP/(HR \times TVI_{RVOT})$(64). They found a good correlation (r = 0.86) in patients with PAH and PVR >11 WU. However, the omission of patients with LHD make its use limited in patient with post capillary PH.

Scalia et al. (2016), have developed the echocardiographic Pulmonary to Left Atrial Ratio (ePLAR) (65).

$$ePLAR_{(m/s)} = \frac{TRV_{max\ (m/s)}}{\text{mitral E/e'}}$$

(65)

This formula incorporates the $TRV_{(max)}$ in establishing the ePASP and E/e' as a surrogate for LAP. Therefore, the ePLAR will be evaluating TPG (mPAP-PCWP) whereby $TRV_{(max)}$ will be a surrogate for mPAP and E/e' a surrogate for PCWP. Investigators postulate that the higher the ePLAR the higher the component of pre-capillary PH (rising TPG) and the lower the ePLAR the higher the component of post-capillary PH (rising LAP)(65). ePLAR is simple yet effective in differentiating between pre and post-capillary when compared to RHC(65).

Significant work has been published on surrogate markers for PVR however, limited data is available to differentiate patient with pre-capillary vs post-capillary PH. The ePLAR offers some differentiating ability however, further work is required to aid diagnosis.

2.4 Discussion and Future challenges

The prevalence of PH-LHD is under reported. Current European, American and Australian registries only provide a small snapshot of the true prevalence of PH-LDH in the community (1, 66). We have previously reported the mortality and morbidity of LHD in the community and provided evidence that once patients with LDH develop PH their prognosis is significantly reduced. The severity of the LHD doesn't necessarily correlate with the severity of PH (1, 4, 45-48). However, PH is an independent risk factor for increased mortality(1).

There is a lack of research into early recognition of PH in the community. Echo measurements of PH and DD are well validated and there is a growing body of evidence to stratify patients into pre-capillary and post-capillary causes through surrogate markers of PVR. However, identifying echo markers of DD that can predict the development of PH is lacking. Identifying markers of DD to predict developing PH or predict worsening PH may enable early intervention, treatment and reduce mortality.

Thus, the aim of this thesis is to address this shortfall by using the information contained in the National Echo Database Australia (NEDA) to evaluate potential echo markers that can predict patients at risk of developing PH

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Chapter 3 - Methodology

We have established that PH-LHD is under-recognised, worldwide, due to registry data that is highly biased towards patients with PAH and due to a lack of population based data. Left heart disease is the number one cause of mortality in the world and those who develop PH, as a result, do worse. The gold standard in measuring diastolic dysfunction due to LHD is echo. Furthermore, up to 40% of patients who undergo echo assessment have insufficient TRV to diagnose PH. PH is a time critical diagnosis with a poor prognosis once patients develop moderate or severe PH. Therefore, the investigator sought to identify diastolic markers that are correlated with the development of PH and create a formula to predict PH using common echo measurements of diastolic function in the absence of TRV. In this section, the investigator will outline the methodology and design of the project, followed by the original paper in developing the NEDA PH-LHD formula.

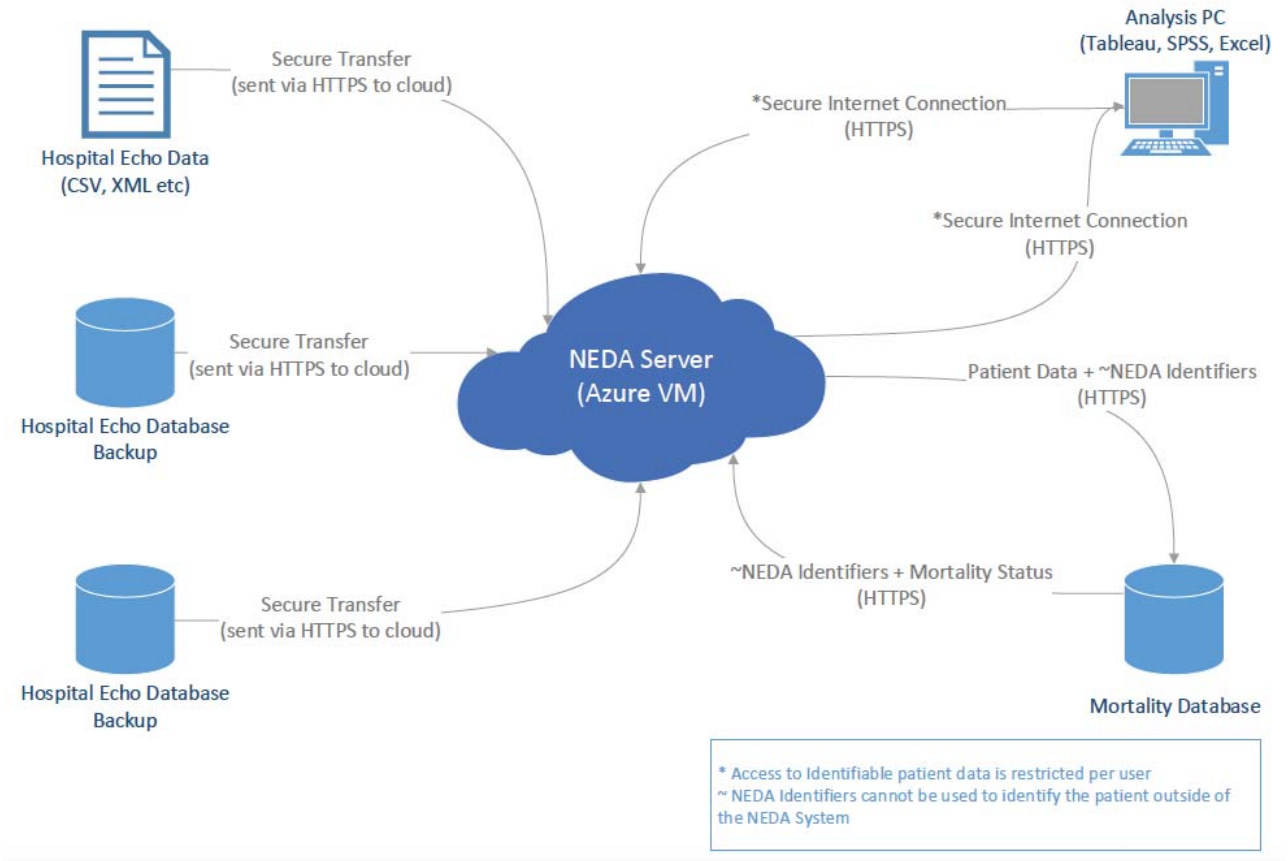
3.1 Strategy and design

This study will be a retrospective observational cohort study with data derived from the NEDA study. The NEDA collects data using a novel digital data collection tool (Figure 1). When echo laboratories are enrolled in the NEDA, it retrospectively captures past echo studies using a data collection “scraper tool” developed by the Alcidion Corporation software company and stores it on the master database.

In brief, the echo “scraper tool” filters and cleans the data of zero values and impossible values outside of data ranges. It also inserts data into formulae in order to account for commonly used echo calculations and extracts meaningful evidence from text fields in echo reports and converts them to a numerical value on the database. The echo data is stored in a cloud based on the Microsoft Azure platform and allow access only to authorised users (See Diagram A). At the time of this study, NEDA had over 300,000 echo studies. As this study forms part of the NEDA study, formulae created and data reduction methodology developed in the course of this study has been implemented into the software.

Figure 1

NEDA Schematic Workflow Diagram



3.2 Sampling

This study involved a convenience sample of echo studies from the NEDA with a data cut performed to include echos enrolled between September 1998 and December 2016. The echos enrolled into NEDA were comprised of two private echo laboratories in Queensland and Western Australia (WA). The Queensland echo data comprised of 23 sites across Queensland of patients from private hospitals (10), public hospital (1) and private cardiology practices (12). The WA echo data comprise of 1 public hospital and 1 private cardiology practice. Overall 22% of these echo data is from WA and 78% from Queensland. Three of the hospitals (Queensland 2 and WA 1) were referrals centres for PH

3.3 Sample size

This study examined 307,843 echos performed on 174,229 patients. Examination of the extracted data revealed that only 57% of echos had a tricuspid velocity value that enabled calculation of the ePASP therefore, 99,025 patients were available for analysis of PH.

3.4 Power calculation

Our power calculations are based on standard t-tests for a significant difference between those with pulmonary hypertension associated with abnormal E:E' (>14) ratios and those with normal E:E' ratios (<14). The median E:E' ratio was used to create two equal groups. Based on a 90% power to identify a 5% increase in risk of pulmonary hypertension and an alpha level of 0.05, the required number of patients is 16,814. Therefore, this study has sufficient power to identify variables of interest.

3.5 Data reduction

Outcomes of interest are pulmonary hypertension from any cause and left heart disease. The independent variables are markers of diastolic dysfunction based on echo measurements. Age, sex and systolic dysfunction were controlled for to refine the contribution of diastolic dysfunction on pulmonary hypertension (67). A correlational survey was used to study the relationship between variables of echo measurements (67).

Variables were grouped in to categorical for variables such as gender, or continuous variables for most echo measurements. In terms of the assessment of diastolic function, investigators extracted the following echo markers: Annular e' velocity, Lateral E/e', septal E/e' and average E/e' ratio, LA maximum volume index, peak TR velocity, peak E wave velocity, peak A wave velocity and mitral valve E/A ratio, pulmonary vein S and D wave velocity, AR duration and S/D ratio. The measurements for determining pulmonary pressure is ePASP from the peak TR velocity plus right atrial pressure or 10mmHg if right atrial pressure is not documented.

Some echo markers were sorted into a hierarchical system. For example, the measurement of the ejection fraction has three established methods: Final reader assessment (based on all available evidence, including visual estimation of the ejection fraction), the Teicholz method (from the parasternal long axis view) and the Simpson's biplane method (from the apical 4- and 2-chamber views). An algorithm was created using syntax to establish a hierarchical system of choosing the most accurate ejection fraction from the data published

in each echo report. The most accurate was the final reader assessment, but if this information was not provided or available within the NEDA database, the Simpson's biplane method was chosen. Finally, if neither of these two measurement methods were available, the Teicholz method was chosen.

3.6 Data Analysis

IBM SPSS Version 23 was used for data and statistical analysis. Explore functions for each of the relevant variables was investigated for outliers, impossible values and areas where large amounts of data are missing. The use of descriptive statistics was used to determine the frequencies, means, median, quartile ranges and standard deviations for each echo marker and demographic data such as age.

Normally distributed echo markers were analysed using parametric tests and non-normally distributed markers was analysed using non-parametric tests. Two-way ANOVA was used to compare variance in diastolic dysfunction and how each echo marker contributed to the development of elevated pulmonary artery pressure. Multivariate analysis was used to measure the correlation between independent variables and the risk of pulmonary hypertension.

3.7 Ethical issues: consent, access and participants' protection

This research used the NEDA database. The NEDA study has previous approval from The University of Notre Dame Human Research Ethics Committee (Ref number: 014142F) and a consent waiver has been approved.

Ethics approval for this research was gained from The University of Notre Dame, Australia Human Research Ethics Committee and assessed to meet all the requirements outlined in the National Health and Medical Research Council of Australia. Ref: 016093F

The National Ethics Application Form (NEAF) has also been approved by the Royal Prince Alfred ethics committee for all public East and South Eastern Seaboard States via the National Mutual Agreement (Ref number: Protocol X15-0387 & HREC/15/PRAH/530).

The NEDA study has been registered with the Australian New Zealand Clinical Trial Registry (Trial ID ACTRN12617001387314).

All data used for the purpose of this research was de-identified. De-identified data was stored within the NEDA servers, behind industry standard security software and hardware. The investigator had authorised access to specified de-identified data from this database which will be made available via a cloud system based on the Microsoft Azure Cloud Platform. All authorisation was password protected and all data encrypted. There was no data stored remotely to the server.

No direct contact or communication with participants occurred in the course of this research.

Chapter 4

4.1 Title Page

Diagnosing Pulmonary Hypertension due to Left Heart Disease (PH-LHD) in the absence of Tricuspid Regurgitation Velocity (TRV): A predictive model using the National Echo Database of Australia (NEDA)

Note: This paper is currently undergoing editorial review with European Heart Journal.

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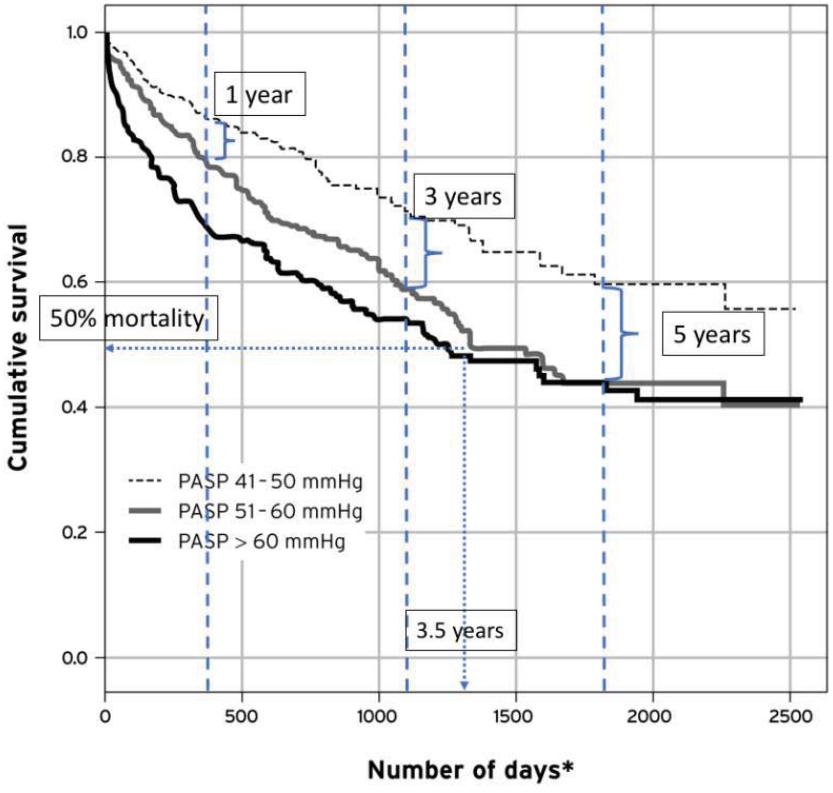
4.1 Introduction

Pulmonary Hypertension (PH) is a haemodynamic sequela that has both causal and associated relationships to more than 40 different diseases. Pulmonary hypertension associated with left heart disease (PH-LHD) makes up 70% of all cause pulmonary hypertension however, it is under diagnosed and associated with a high mortality (1). Left heart disease (LHD) is a heterogeneous group but, regardless of underlying pathology the final common pathway is an increase in left heart filling pressure, impaired relaxation and diastolic dysfunction (68). There are significant delays in the diagnosis of PH, resulting in more severe disease and increased mortality when the diagnosis is eventually made (14, 20, 21).

Patients with moderate or severe PH compared to those with mild PH, are at 1.89 and 3.29 times greater risk of death, respectively (1). Specifically, the morality trend of patients with moderate and severe PH intersect at 3.5 years which corresponds to 50% of all PH cumulative survival (See Figure 1). These data highlight the need for expedited diagnosis of PH, defining the underlying etiology and appropriate treatment.

Echocardiography (echo) remains the most commonly used tool to identify the presence of PH in the first instance. The use of the modified Bernoulli equation to estimate pulmonary artery systolic pressure (ePASP) using echo can only be calculated using the peak tricuspid regurgitation velocity (TRV) and estimated right atrial pressure (RAP) ($ePASP = 4(TRV)^2 + RAP$) (33). However, a significant proportion of patients have insufficient tricuspid regurgitation to calculate a valid ePASP. Delineating PH from Pulmonary Arterial Hypertension (PAH) is warranted as there are significant improvements in survival with modern PAH disease specific therapies. The gold standard in definitive diagnosis of PH is via the right heart catheter (RHC) (16) however, it is an invasive test, not universally available and presents with a small risk to patients.

Figure 1



Note: Figure 1 has been reproduced from Heart, Lung and Circulation (2018) 27, 301-309 published by Elsevier in March 2018 with permission from the publisher, Elservier and shows Kaplan-Meier Survival of all-cause pulmonary hypertension: Mild (PASP 41-50mmHg), Moderate (PASP 51-60mmHg), Severe (PASP >60mmHg). Adapted from Strange et al. (2012)..

One million echos are performed each year within Australia and approximately 20 million within the United States. Despite the high use of echo, there have been limited systematic population based echo studies to examine the prevalence of PH and underlying diastolic dysfunction.

Utilising the National Echo Database of Australia (NEDA), this study aimed to establish the prevalence of PH within Australia. We sort to identify echo markers that are associated with PH and create a predictive model using echo markers to diagnose PH-LHD in the absence of measurable TRV.

4.2 Methods

In this retrospective observational cohort study, we derive data on pulmonary hypertension and markers of left heart disease from the NEDA to determine correlates of LHD and PH.

NEDA is comprised of real world digital echo reports extracted from laboratories across Australia. NEDA matches and transforms data via a vendor-agnostic data extraction process for each measurement obtained during an echo study. Using our prespecified NEDA data dictionary, measurements are matched and transformed to standardised units from both shoestring output values and from free text descriptions. These data are then automatically cleaned, impossible values and data ranges set, duplicates are removed and multiple echo studies for the same patient grouped into a unique individual identifier. The NEDA is stored in an encrypted, password protected, Microsoft Azure Cloud based server.

Data was extracted from the NEDA between September 1998 to December 2016. Patients were excluded from the analysis if they were <18 years, had an invalid date of birth, an invalid date of echo or patients with congenital heart disease. The echos enrolled into NEDA were comprised of two private echo laboratories in Queensland and Western Australia (WA). The Queensland echo data comprises of 23 sites across Queensland of patients from private hospitals (10), public hospital (1) and cardiology private practices (12). The WA echo data comprise of 1 public hospital and 1 private cardiology practice. Overall 22% of these echo data is from WA and 78% from Queensland. Three of the hospitals (Queensland 2 and WA 1) were referrals centres for PH. All echos were reported by Cardiologists specialising in echocardiography and the echo quality and standardisation left to the discretion of the participating laboratories. Ethics clearance and consent waiver was obtained from the Human Research and Ethics Committee at The University of Notre Dame, Fremantle (Ref: 016193F).

Formulae were created to compute common echo data measurements, such as indexing the left atrial volume to body surface area. Measurements within NEDA using various methodology were amalgamated using a hierarchy-based syntax formula. For example, in the evaluation of the left ventricular ejection fraction (LVEF), multiple methods are used to determine the final reported EF. Therefore, we ranked them using a syntax hierarchical formula; Simpson's biplane method, Simpson's monoplane method, MMode fractional shortening method and Teichholz method from highest to lowest, respectively.

Variables were grouped into categorical or continuous variables for most echo measurements. Diastology was determined using the Annular e' velocity, Lateral E/e', septal E/e' and average E/e' ratio, LA maximum volume index, peak TR velocity, peak E wave velocity, peak A wave velocity and mitral valve E/A ratio, pulmonary vein S and D wave velocity, AR duration and S/D ratio. Pulmonary Hypertension was defined as an estimate of Pulmonary Arterial Systolic Pressure (ePASP) >40mmHg derived from the peak TRV (using the estimated RAP, if available, or assuming a RAP of 10mmHg, if unavailable) using the modified Bernoulli equation. The most recent echo was used to determine the prevalence of PH in our cohort.

Using PH as the dependent variable and markers of diastolic function as the independent variables we performed univariate and multivariate analysis to identify predictive correlates with pulmonary hypertension. Using diastolic markers such as; E, E' and E/A ratio, as predictors of PH-LHD in our multi-regression model could lead to one variable linearly predicting another. Therefore, using analysis of variance we calculated the degree of association in order to exclude multi-collinearity. The effect size of each variable was calculated using the omega square method.

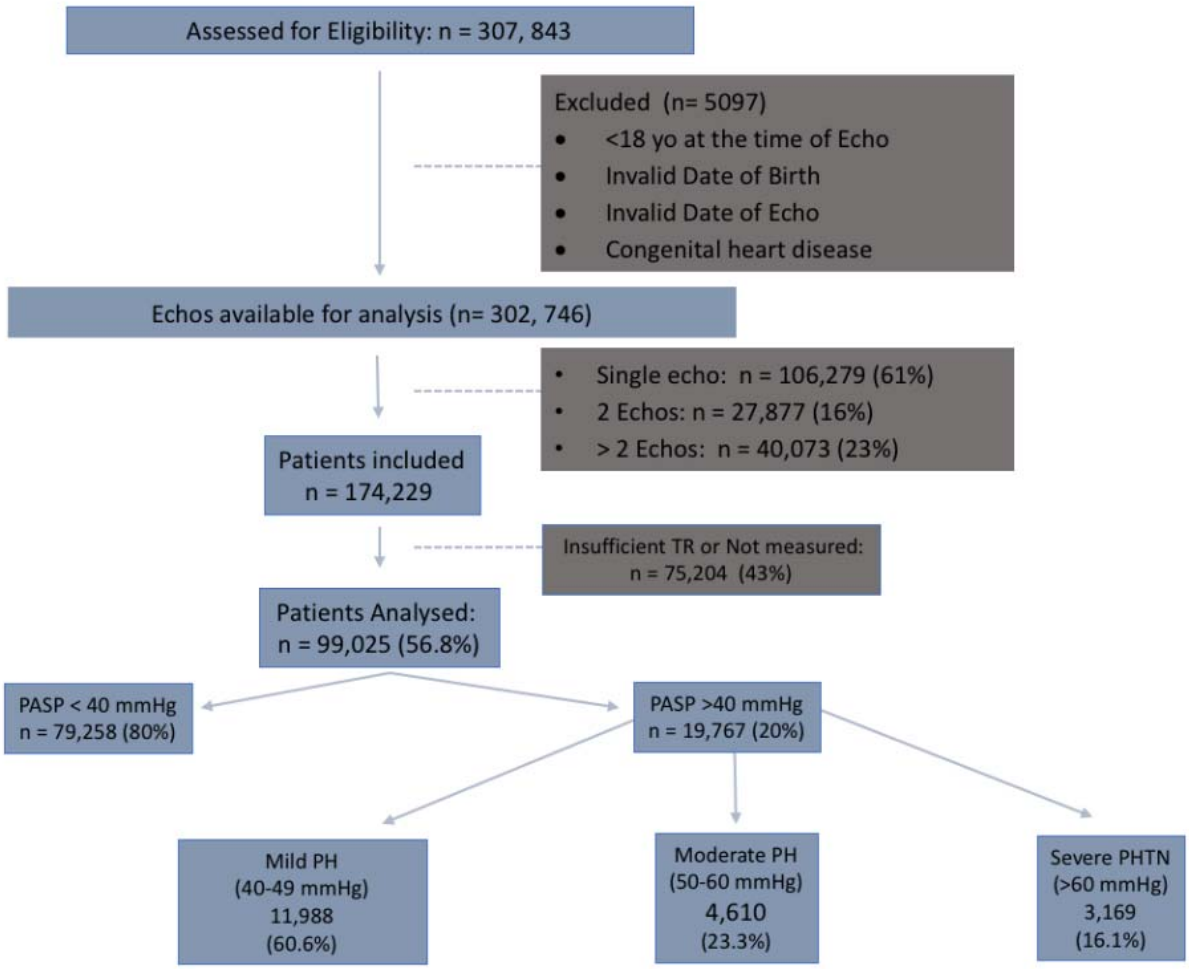
To create a predictive formula to diagnose PH-LHD we randomised the entire cohort 1:1 into a development and validation database. From the development database, logistic regression analysis was used on each diastolic marker that predicted the development of PH, constant and B coefficient, and created a NEDA PH-LHD prediction model. We created a constant (Con) for each echo, based on the dependent variables of PH (ePASP ≥40mmHg) vs no PH (ePASP <40mmHg). Using this constant we derived the probability (Prob = EXP (Con) /[1+ (EXP(Con))] that a patient with these markers of diastolic function will have PH. Using the probability analysis, we generated a Receiver Operating Characteristic (ROC) curve using a 0.5 cut off to evaluate the accuracy of our model, and coded patients with probability of >0.5 as having PH-LHD and those with probability ≤0.5 as not having PH-LHD. We then repeated our methodology on the validation database to establish the accuracy of our model in the large sample that was not used to generate the model.

Statistical analysis was performed using IBM SPSS Statistics Version 23. Normally distributed echo markers were analysed using parametric tests and non-normally distributed markers were analysed using non-parametric tests. Two-way ANOVA was used to compare variance in diastolic dysfunction and how each echo marker contributed to developing elevated pulmonary artery pressure. Multivariate analysis was employed to measure correlates between independent variables and the risk of pulmonary hypertension.

4.3 Results

307,843 echos were available from the NEDA database in December 2016. 5097 echos were excluded from the analysis population (see Figure 2). 302, 746 echos were available for analysis taken from 174,229 patients. Of these patients, 106,279 (61%) had a single echo, 27,877 (16%) had two echos and 40,073 (23%) patients had more than two echos.

Figure 2



The mean age of patients enrolled into this study was 62 ± 17 years. 75,204 (43%) patients had insufficient tricuspid regurgitation to calculate an ePASP. Of the remaining 99,025 patients with TR, 19,767 (20%) were diagnosed with PH (ePASP >40mmHg). 11,988 (61%) patients were classified as mild PH (ePASP 40-50 mmHg), 4610 (23%) had moderate PH (ePASP 50-60 mmHg) and 3169 (16%) had severe PH (ePASP >60 mmHg).

Comparing these echo data from the two NEDA laboratories, table 2 shows the differences in the reported assessment of echo markers.

Table 2

Proportion of documented echo data between WA and Queensland laboratories

N =302 746	Western Australia Echo Lab N = 67,406 (%)	Queensland Echo Lab N = 235,340 (%)
Age (years)	67406 (100%)	235,340 (100%)
PASP (mmHg)	33,879 (50.3%)	146,698 (62.3%)
E' septal velocity (m/s)	27,082 (40.2%)	166,976 (71%)
E/E' ratio	31,930 (47.4%)	168,541 (71.6%)
E:A ratio	42,541 (72%)	198,796 (84.5%)
Left atrial volume indexed to BSA (mL/m^2)	48,541 (72%)	187,560 (79.7%)
Ejection Fraction (%)	58,431 (86.7%)	172,430 (73.3%)

Within our cohort with TR available for analysis we identified age, E' (cm/s), E/E' ratio, E/A ratio and LAVI (mL/m^2) as markers of diastolic dysfunction that were associated with the development of PH (Table 1). These variables are validated markers of diastolic function and well accepted as standard measurements in echo laboratories (13). Patients with PH versus those without PH were older (mean age 76 vs 62 years) (p = <0.0001) and had impaired myocardial relaxation (E'= 8.2 vs 6.7 cm/s) (p = <0.0001). Signs of increased left heart filling pressures was also evident with larger LAVI (46 vs 33 mL/m^2) (p = <0.0001) and higher E/E' (16.7 vs 10.7) (p = <0.0001) in patients with PH compared to those without. The LV EF is lower on average in patients with PH (59% vs 63%) (p = <0.0001) vs those without.

Table 1

National Echo Database of Australia Cohort: Predictors of PH from Left Heart Disease

N=99,025	**PASP <40mmHg (mean +/- SD)**	**PASP >40 mmHg (mean +/- SD)**	**P - Value**
Age (years)	62 (17)	76 (12)	<0.0001
PASP (mmHg)	29 (6)	51 (11)	<0.0001
E' septal velocity (cm/s)	8.2 (3.0)	6.7 (2.6)	<0.0001
E/E' ratio	10.7 (5.0)	16.7 (8.3)	<0.0001
E:A ratio	1.2 (0.6)	1.3 (0.8)	<0.0001

Left atrial volume indexed to BSA (mL/m^2)	33 (13)	46 (20)	<0.0001
Ejection Fraction (%)	63 (8)	59 (14)	<0.0001

** Largest effect size using omega square formula = Left atrial volume indexed to BSA

Using the omega squared formula the investigators calculated the effect size that each diastolic marker has on the development of PH. E/A ratio (0.003) has a small effect size, E' (0.034) and age (0.106) has a moderate effect size and E/E' (0.128) and LAVI (0.321) has the largest effect size on developing PH.

Following randomisation, 150,979 echos formed the development database to create the NEDA PH-LHD formula and tested on the validation database (n = 151, 767) to establish its predictive accuracy (see figure 3). Table 2 illustrates the baseline echo characteristics of the two databases. Our development and validation databases were well randomised with similar age, PASP, E', E/E', E/A ratio, LAVI and LVEF.

Table 2
Baseline Echo Characteristics – NEDA Development and Validation Database

Characteristic	**Development Database N = 150, 979 Mean (SD)**	**Validation Database N = 151,767 Mean (SD)**
Age (years)	63 (16)	63 (16)
PASP (mmHg)	34 (12)	34 (11)
E' septal velocity	7.9 (2.9)	7.8 (2.9)
E:E' ratio	11.6 (6.0)	11.6 (6.0)
E:A ratio	1.1 (0.6)	1.1 (0.6)
Left atrial volume indexed to BSA (mL/m^2)	35 (16)	34 (16)
Ejection Fraction (%)	62 (10)	62 (10)

**P = N.S

PASP – Estimated pulmonary artery systolic pressure

BSA – Body surface area

Figure 3

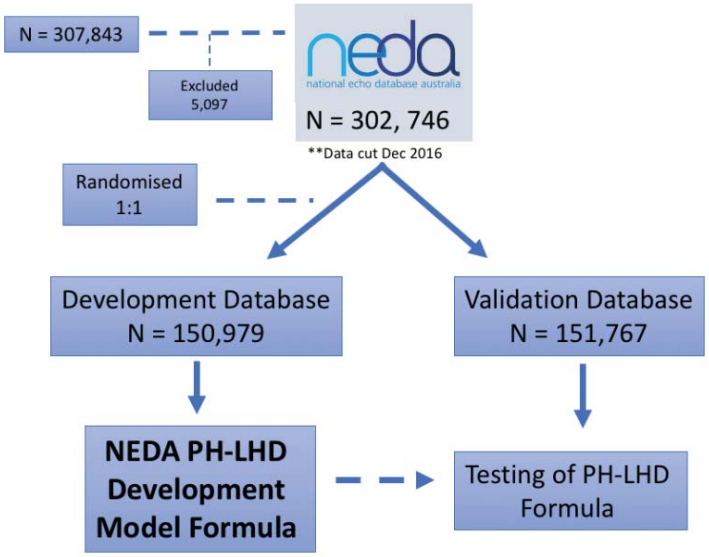


Table 3 illustrates the logistic regression analysis performed on the development model using age and the four markers of diastolic function that were the most predictive of patients developing PH-LHD. Of the 151,767 echos in our development model, 5,181 echos performed had all five variables valid to perform our model analysis. The odds ratios suggest that for every year increase in age, unit increase in E/E' and mL/m^2 increase in LAVI the risk of developing pulmonary hypertension increases by 3.5%, 8% and 3.1%, respectively. Using the regression coefficient the investigators have created the NEDA PH-LHD Constant (Con) = -6.649 + (0.035 x Age) + (0.072 x E') + (0.077 x E/E') + (0.509 x E/A) + (0.03 x LAVI). Using this constant, the investigators can predict the probability (EXP (Con) / [1 +EXP(Con)]) that a patient, using age and these four markers of diastolic function, will have pulmonary hypertension in the absence of tricuspid regurgitation. This formula is simple to install on echo software, on the echo machine and/or within echo interpretation software, to aid the clinician in interpretation of the images (Figure 4).

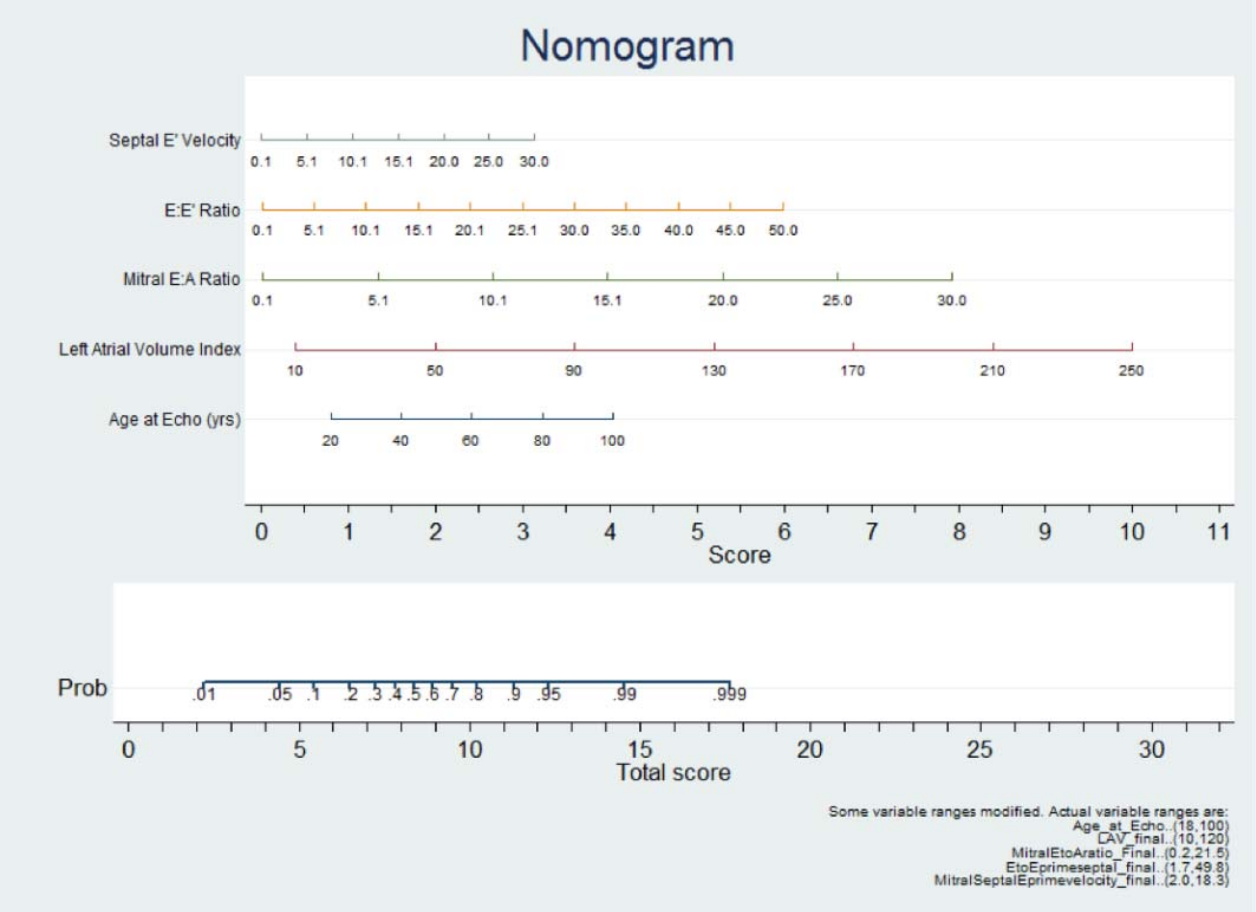
Table 3

NEDA Development Model Logistic Regression

N = 5,818	**B**	**S.E.**	**Wald**	**Sig.**	**Odds Ratio**	**95% CI for Odds Ratio Lower**	**Upper**
Age (years)	.035	.003	120.8	.000	1.035	1.029	1.042
E' septal velocity (cm/s)	.072	.025	8.602	.003	1.075	1.024	1.128

E:E' ratio	.077	.009	77.131	.000	1.080	1.061	1.098
E:A ratio	.509	.076	44.672	.000	1.664	1.433	1.932
Left atrial volume Indexed (mL/m^2)	.030	.003	92.092	.000	1.031	1.024	1.037
Constant	-6.649	.366	330.37	.000	.001		

Figure 4



Using variance inflation factor (VIF) from linear regression analysis, the investigators calculated the VIF between all of our markers of diastolic function (see Appendix 1). The highest VIF was 2.4 between septal E' velocity and E/A ratio (VIF <2.5 suggest lack of collinearity) therefore, excluding any significant multi-collinearity in our analysis.

Appendix 1

Assessment of degree of variance using Variance Inflation Factor

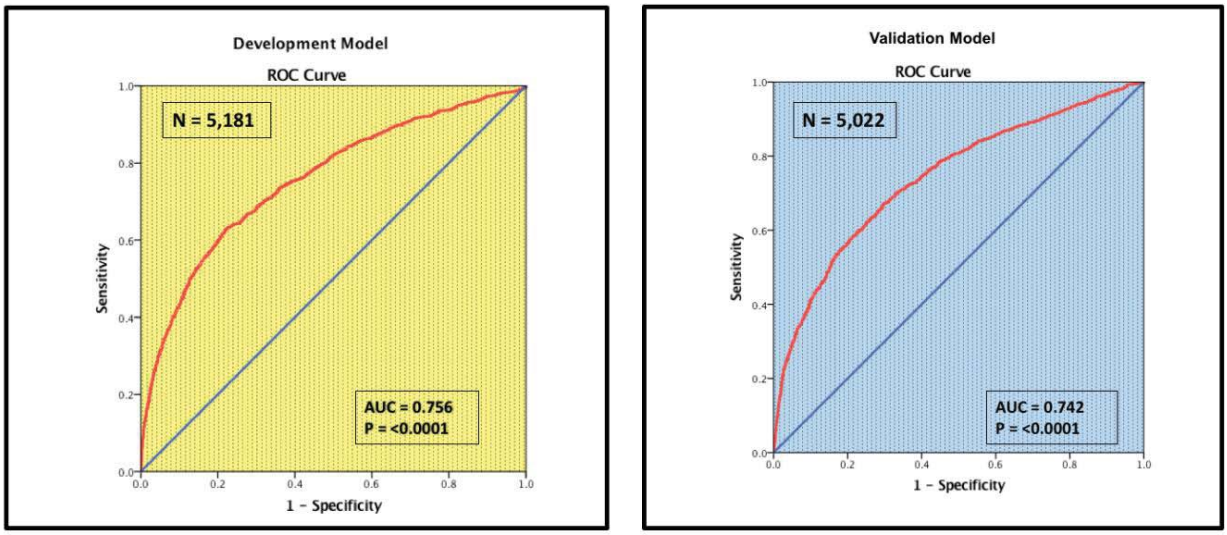
Dependent Variable	Age At Echo	E:A Ratio	E:E' Ratio	Septal E' Velocity	Indexed Left Atrial Volume
Age at Echo		1.4	2.1	2.2	1.2
E:A Ratio	1.8		1.9	2.4	1.3
E:E' Ratio	1.9	1.3		1.8	1.2
Septal E' Velocity	1.5	1.3	1.4		1.3
Indexed Left Atrial Volume	1.8	1.4	2.0	2.8	

Note: Variance inflation factor <2.5 suggest a lack of collinearity

To establish the accuracy of our development model in predicting PH-LHD the investigators used our probability scores for each echo study and created a ROC curve (cut point 0.5). Figure 5 illustrates that the area under the Receiver Operating Characteristic (ROC) curve is 0.756 (95% CI 0.729-0.762, p<0.0001). This suggests that our formula can predict PH-LDH in over 75% of cases. The investigators then tested the accuracy of our formula in our validation group, and the area under the ROC curve was 0.742 (95% CI 0.722-0.756, p<0.0001), showing similar diagnostic performance of our formula in a randomised sample of the entire cohort, not used to generate the formula. Because of the near identical ROC curves between these two unrelated groups, the formula appears to hold true across a broad spectrum of real-world patients seen in echo labs.

Figure 5

NEDA PH-LHD formula Area under the ROC curve



ROC = Receiver Operating Characteristic

4.4 Discussion

Using big echo data this study demonstrates that pulmonary hypertension is present in 20% of the population undergoing echo assessment in the Australian community. In this real-world situation, only 67% of patients could be assessed for PH because many patients lack measurable tricuspid regurgitation. The investigators identified that patients who develop PH are older and have markers of diastolic dysfunction but with relatively preserved EF. This is in keeping with epidemiological data that patients with heart failure with preserved EF (HFPEF) have a high prevalence of PH (69). More so, patient with HFPEF who develop PH have significantly increased mortality if they develop moderate or severe PH (70).

In order to address this, the investigators have described for the first time a novel method of diagnosing PH-LHD in the absence of tricuspid regurgitation using age, E', E/e'ratio, E/A ratio and LAVI. Our formula is ideally suited to be installed on echo machines and echo interpretation software to simplify the decision matrix in identifying PH-LHD, or can readily be used clinically using our nomogram (Figure 4). Our formula is 75% accurate in a large cohort of over 150,000 echos.

The limitations of our model is that it lacks specificity, as it will not account for patients with WHO group 1, 3, 4 PH. Age and echo markers of diastolic function have been used as surrogates to measure the final common pathway in LHD. The predictive power of our model, in this population based observational cohort, is dependent on the pre-test probability that PH-LHD is the most common cause of PH. Epidemiological studies suggest that up to 70% of patient with PH have PH-LHD (71). However, if patients have both pre and post-capillary PH then our model may still be useful in identifying those with PH. The application of our predictive model to patients undergoing RHC will enable us to further assess how it discriminates patients that have pre-capillary PH. In order to identify patients with pre-capillary PH in WHO group 1, 3 and 4 PH a marker of pulmonary vascular resistance (PVR) is required (16). Therefore, our model could potentially be applied to identify patients with pre-capillary PH by excluding patients with LHD or post capillary PH in conjunction with a surrogate marker for PVR such as ePLAR ($TRV_{(max)(cm/s)}$ / mitral E/E') (60, 65).

To the Authors' knowledge, NEDA is the largest population-based echo database in the world and the investigators have illustrated that the prevalence of pulmonary hypertension is much higher than previously reported (16, 26). Major international PH registries from tertiary PH centres have a referral bias toward pulmonary arterial hypertension (PAH), with disproportionately lower referrals for patients with PH-LHD (71). The majority of LHD in

today's society is caused by ischaemic heart disease (IHD), dilated cardiomyopathy, hypertensive heart disease and valvular heart disease (72-74). Therefore, population based data is best suited in truly identifying the prevalence of PH-LHD. This suggests that the prevalence of PH-LHD is under reported and is potentially a major unidentified cause or morbidity and mortality in patients with LHD.

Forty-three percent of our echo cohort had insufficient tricuspid regurgitation or a TRV not measured in order to estimate PASP. Therefore, a significant number of patients who have left heart disease are unable to be assessed for pulmonary hypertension on echo. The investigators have previously shown that there are significant delays between symptom onset and the diagnosis of PH. Furthermore, the prognosis of patients once they develop moderate and severe PH is significantly worse than patients with mild PH (1, 14). Therefore, the use of our predictive formula has the ability to identify patients early, who are at risk of developing PH or worsening PH, in the absence of TRV. This will enable clinicians to seek further assessment, prompt further testing and consider the initiation of disease specific treatment.

The NEDA has limited clinical information and therefore we cannot imply causality of underlying LHD. The investigators have described the development of diastolic dysfunction and increased left atrial pressure as the end product of LHD. However, LHD is a heterogeneous group and targeted treatment of the underlying disease process, to prevent the development of PH, may improve long term prognosis.

4.5 Conclusions

The investigators have identified that up to 43% of patients cannot be assessed for PH due to the unmeasurable TRV. From the patients who had a measureable TRV the investigators have documented that 20% of the patient in our large population-based echo cohort have PH. This is significantly more than previously documented.

Using age and the diastolic echo markers of E', E/E', E/A and LAVI the investigators have created the NEDA PH-LHD predictive formula. This formula can predict, with 75% accuracy, the diagnosis of pulmonary hypertension in the absence of tricuspid regurgitation. The formula is easy to use and can be applied to any echo software or calculated using a nomogram at the bedside.

This tool is potentially widely applicable to aid in the interpretation of echo data, to identify patients at risk of developing (or worsening of) PH. This will enable clinicians to expedite further investigations at an earlier stage in the disease trajectory, including RHC and referral to specialist centres, to facilitate more rapid initiation of disease-specific treatment.

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Chapter 5 – Thesis Discussion

This study developed a novel formula that can accurately predict pulmonary hypertension in over 75% of patients using common echo markers of diastolic function. Perhaps more importantly, it can also do this in the 40% of patients for whom tricuspid regurgitant velocity is undeterminable and thus cannot be assess for PH on echo. Development of a nomogram makes the algorithm easy to use which could also be uploaded onto echo software. This development has the potential to significantly reduce the delays in the diagnosis of PH in patients who present with breathlessness, prompt further investigations and the initiation of disease specific treatment.

While the major strength of this study is the size of the database used to develop the algorithm, the study has some limitations that could impact on its findings. These are largely related to information not collected within the NEDA database which includes the lack of demographic details, other than age and sex, and any medical history, including current medications or details of treatment. Therefore, the investigators are not able to draw conclusions on the pathophysiological processes of left heart disease and how it contributes to the development of pulmonary hypertension. However, echo markers such as the ejection fraction and severity of diastolic function provides a powerful tool in risk stratification for patients who are more likely to have pulmonary hypertension.

Another limitation is the selection bias in using big echo data to estimate the prevalence of pulmonary hypertension in the community. The mean age of patients who underwent echo examination is 63 years old therefore, a significant proportion were elderly patients. Advanced age increases the likelihood of left heart disease therefore, this study population has the potential of over-estimating the prevalence of PH (75). However, The NEDA is continuously increasing in size as more echo laboratories are enrolled into the database. The most recently published NEDA data reports a mean age of 65 years old (76). Similarly, a population based study in Olmsted County, Minnesota sought to establish the age affected increase in PASP in the general population (77). They enrolled 2042 patients at random, performed echo assessment and followed them up for a median time of nine years. Their results were similar, with 1413 (69%) of patients with a measurable PASP with a mean age of 63 years old (77). Another potential for bias is the lack of demographic data to establish the proportion of patients who underwent echo assessment in a hospital setting or an approved PH referral site versus ambulatory community clinics. However, the number of ambulatory community-based echo clinics far outweigh hospital sites for the enrolled echo laboratories.

The NEDA is limited to an Australian population and further research to other regions is required to validate the application of our formula to different ethnicities and geographic locations. Furthermore, there is an inherent lack of specificity in this formula as it will unlikely identify patient with pulmonary hypertension due to WHO group 1, 3 and 4, unless they have a degree of concurrent left heart disease (WHO group 2). In order to further clarify this argument and strengthen the predictive power of our formula we are in the process of undertaking a study to examine the accuracy of our predictive formula on patient who have undergone an echo exam and RHC (gold standard). This will allow us to test the accuracy of our model against invasive haemodynamic measurement of left atrial pressure, pulmonary artery pressure and degree of pre and post capillary pulmonary hypertension.

Looking forward, the NEDA team has now gained approval to link its echo data with the Australian Institute of Health and Welfare mortality database. This linked data will enable investigators to analyse the effects of echo markers directly with various causes of mortality. Future work analysing the effects of diastolic dysfunction with morality will significantly contribute information on how to best manage patients with PH and left heart disease.

Appendices

Appendix 1

The University of Notre Dame Notification of Ethics approval

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27 June 2016

Professor David Playford & Dr Kevin Chung
Suite 46
146 Mounts Bay Road
Perth WA 6000

Dear David and Kevin,

Reference Number: 016093F

Project Title: "Diastolic dysfunction, pulmonary hypertension and mortality: An insight into the NEDA study."

Your response to the conditions imposed by a sub-committee of the university's Human Research Ethics Committee, has been reviewed and assessed as meeting all the requirements as outlined in the *National Statement on Ethical Conduct in Human Research* (2014). I am pleased to advise that ethical clearance has been granted for this proposed study.

Other UNDA students and researchers identified as working on this project are:

Name	School/Centre	Role
Prof Geoff Strange	School of Medicine- Adjunct	Co-Supervisor to student
Prof Jim Codde	Institute for health Research	Co-Supervisor to student

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.

Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: Dr Raoul Oehmen, Acting SRC Chair, School of Medicine

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Appendix 1

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REVIEW

Left Heart Disease and Pulmonary Hypertension: Are We Seeing the Full Picture?

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Pulmonary hypertension (PH) is common, under diagnosed and associated with a high mortality. There are significant delays in the diagnosis of pulmonary hypertension leading to increased morbidity and delays in the initiation of treatment. Once PH is diagnosed, establishing the degree of pulmonary vascular resistance (PVR) enables clinicians to broadly divide the underlying pathology into pre-capillary or post-capillary causes, a crucial step in tailoring management.

Pulmonary hypertension is most commonly due to left heart disease (PH-LHD) and echocardiography (echo) is the most widely accessible investigation in its diagnosis. Regardless of the underlying pathophysiology of LHD, the sequelae lead to pressure overload on the left heart and a reactive increase in pulmonary pressures.

In this review article, we will discuss the prevalence of PH, examine the pathophysiology of PH-LHD, establish how echo can be used to identify patients with PH-LHD and discuss surrogate echo markers of PVR.

Keywords Pulmonary hypertension (PH) • Left heart disease (LHD) • Diastolic dysfunction • Echocardiography • Heart failure with preserved ejection fraction (HFpEF) • Pulmonary vascular resistance (PVR)

Introduction

Pulmonary hypertension (PH) is common, under diagnosed and associated with a high mortality. Even when PH is suspected, there are significant delays in final diagnosis [1,2], resulting in more severe disease when the diagnosis is eventually made. PH, regardless of cause, is an independent risk factor for death and disability [3,4]. Appropriate treatment, started early in the disease, may improve survival and quality of life. Echocardiography (echo) is the most commonly used initial investigation for PH. This review focusses on PH due to left heart disease (PH-LHD), and discusses current echo techniques, including methods to simplify the diagnosis and measures of pulmonary vascular resistance (PVR). Although many different left heart diseases (LHD) have been described, from the perspective of

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Table 1 **Haemodynamic definitions of PH (adapted from Galie et al., 2016) [5].**

Definition	Characteristics	NICE Clinical groups
PH	mPAP ≥25 mmHg	All
Pre-capillary PH	mPAP ≥25 mmHg	1. PAH
	PCWP <15 mmHg	3. PH due to chronic lung disease
		4. Chronic thromboembolic PH
		5. PH with unclear and/or multifactorial mechanism
Post-capillary PH	mPAP ≥25 mmHg	2. PH-LHD
	PCWP >15 mmHg	5. PH with unclear and/or multifactorial mechanism
a) Isolated post-capillary PH	DPG <7 mmHg and/orPVR ≤3 WU	
b) Combined post and pre-capillary PH	DPG ≥7 mmHg and/or PVR >3 WU	

Abbreviations: DPG: diastolic pressure gradient (diastolic PAP – mean PCWP); PVR: pulmonary vascular resistance; WU: Wood units

pulmonary hypertension, all LHD exert their influence on the pulmonary circulation via increased pulmonary venous pressure. These effects may differ (e.g. mitral regurgitation vs left ventricular diastolic dysfunction) but in general, PH-LHD may be grouped together to separate them from pulmonary vascular causes. This review does not focus on individual treatment of specific LHDs.

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg, measured by right heart catheterisation [5]. Based on the NICE classification, there are five main forms of PH. The commonest of these is PH-LHD [6,7]. Haemodynamically, PH can be divided into pre-capillary, due to increased PVR, or post-capillary due to increase left heart filling pressure [5]. Post-capillary PH is further stratified into isolated post-capillary PH (Normal PVR) or combined post and pre-capillary PH (Increased PVR (Table 1)).

Pulmonary Hypertension from Left Heart Disease

Epidemiology

Australia

While up to four out of five people with diagnosed PH have PH-LHD [8], the true prevalence of PH-LHD in Australia remains unknown but in the current milieu of an ageing population and the increasing prevalence of systemic hypertension, diabetes, sleep apnoea and metabolic syndrome, significant work is required to establish the current burden of this disease. In the absence of community based studies, measures about the prevalence and disease burden of PH have come from other clinical registries and targeted studies.

To date, the Armadale Echo Study is the largest study in Australia to investigate PH prevalence and mortality. Results from this study confirmed that PH-LHD was the commonest form of PH (70%), and that patients with this diagnosis had the worst prognosis of all forms of PH, with a median time from echo detection to death of only 4.1 years [3].

Compounding the gravity of this situation, a related study reported significant delays from symptom onset to final diagnosis (average time: 47 months) with patients reporting an average of five GP visits and three specialist reviews before being seen at a PH centre [2]. The large database of PH managed by the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ), comprising over 2500 patients, includes almost exclusively patients with groups 1, 3, 4 and 5 PH, with only a small proportion with LHD [9].

Severity of PH is associated with increased mortality (see Figure 1). Compared to patients with mild PH, those with moderate or severe PH are respectively at 1.89 times and 3.29 times greater risk of death [3]. This highlights the need for early diagnosis and treatment, particularly in those with mild PH, including finding markers of disease progression to more severe PH.

Worldwide Epidemiology of PH-LHD

International prevalence of PH-LHD is lacking due to poor reporting of the disease and a lack of registry data available on the demographics and clinical course [5]. Prevalence data derived from tertiary referral centres mostly have PAH as the reason for referral, whereas population prevalence studies appear most suited to identifying the true prevalence of PH-LHD. Therefore, the current literature on pulmonary hypertension is disproportionately focussed on data available from PAH registries whilst lacking in group two (PH-LHD) and group three (PH due to lung disease), who make up most of the PH population.

In the United States, population based data from the Olmsted County study found that the prevalence of PH was 6.6%. Eighty-three per cent of patients with heart failure with preserved ejection fraction (HFpEF) had PH and the predictors for developing PH were increasing age and systemic hypertension [10].

In the United Kingdom (UK) the reported prevalence of PH is 97 cases per million with women 1.8 times more likely to have the disease [5]. This is likely to be an underestimate of the true population prevalence, particularly PH-LHD. The Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre (ASPIRE) registry from the Royal Hallamshire Hospital is the largest UK based PH registry.

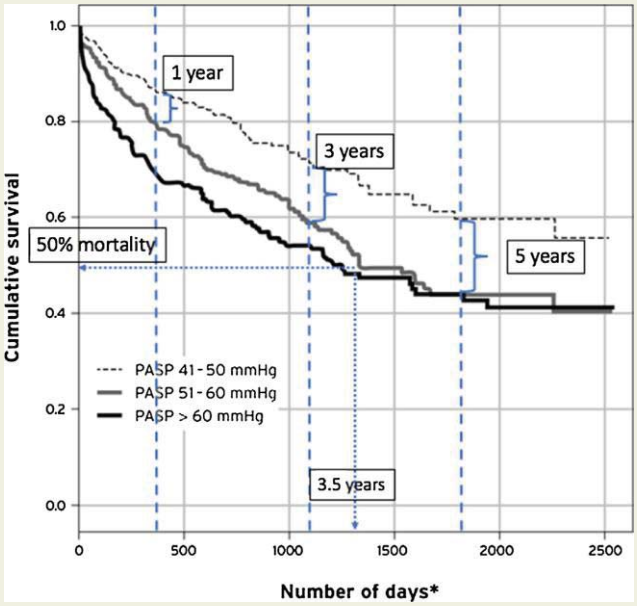

Figure 1 Kaplan-Meier Survival of all-cause pulmonary hypertension: Mild (PASP 41-50 mmHg), Moderate (PASP 51-60 mmHg), Severe (PASP >60 mmHg). Adapted from Strange et al. (2012).

The prevalence of PH-LHD was 11.7% with a 3-year survival of 73% [11]. Patients with PH-LHD are older, more likely female and have better survival than patients with PAH. Survival in patients with valvular heart disease was worse than those with systolic dysfunction (SD) or diastolic dysfunction (DD), despite 36% having had valvular replacement surgery [11]. These data suggest that patients with PH in the setting of valvular disease are a high risk group, with higher PVR than those with systolic or DD (5.07 ± 3.76 vs 3.54 ± 1.94 vs 3.05 ± 2.26 WU, respectively) [11].

A large single centre study in Vienna recruited 2351 patients who underwent right heart catheterisation for investigation of raised PASP on echo. They reported that 1259 (53%) had PH, and in keeping with the Australian Armadale Echo study, found that 86% of these patients had PH-LHD [12]. In contrast, the Swiss PH Registry (n = 996), with a strong focus on PAH, reports only 3.6% of patients with PH-LHD, although like the PHSANZ database, this study probably underestimated the true number of patients with LHD due to referral bias [13]. Similarly, the PulmoCor registry (Netherlands) which contains over 1500 patients results from six tertiary PH centres, reports only 20% of patients with PH-LDH [14].

The true prevalence of PH-LHD is under-estimated but it is the most common type of PH. The delays in diagnosis and initiation of treatments will lead to higher morbidity and poor survival. This is the most important step to establish the magnitude of the disease burden, its clinical progression and treatment options.

Evaluation of PH-LHD and Pathophysiology

Early diagnosis of PH-LHD will help risk stratify patients for disease progression and may enable clinicians to target at-risk patients for more intensive investigation and treatment. Echo markers for PH-LHD may be clinically very useful.

Estimated pulmonary artery systolic pressure (ePASP) is a well validated echo measure of pulmonary artery pressure (PAP) [15–17]. A cut-off of 40 mmHg is strongly correlated with PH [18], with higher pressures associated with a worse prognosis [3], reaching a median time to death of 129 days after developing severe PH (ePASP >60 mmHg) [19]. The pathophysiology of LHD that may lead to developing PH include: left ventricular (LV) systolic and DD, mitral and aortic valvular disease and congenital/acquired inflow/outflow tract obstruction or pulmonary vein stenosis [5].

Heart failure with an impaired ejection fraction (EF) is associated with a poor prognosis, and significant morbidity [20], with 75% of patients diagnosed with PH [8]. In patients who present to hospital with acute decompensated HFrEF, the mortality at 6 months in patients with no PH was 8.6% vs 21.8% with isolated post capillary PH vs 48.3% in patients

with mixed pre/post-capillary PH (p = <0.0001) [21]. Lam et al. (2009), further evaluated patients with HFpEF and found that those with elevated PASP >35 mmHg did worse and that the age-adjusted hazard ratio was 1.28 for every increase in PASP by 10 mmHg [10].

Left heart disease leads to an increase in left atrial pressure (LAP) and backpressure into the pulmonary veins. Increased pulmonary venous pressure causes pressure on the alveolar capillary walls and alveolar capillary stress failure due to barotrauma [22]. This damages the endothelial function leading to a decrease in lung diffusion capacity, fluid reabsorption and capillary leakage [23]. Clinically, this causes pulmonary oedema and patients present with shortness of breath.

Alveolar capillary stress leads to activation of the chemical mediators; endothelin I (a potent vasoconstrictor), angiotensin II and inhibition of nitric oxide (NO) [24]. This is combined with release of metalloproteinases, degradation of matrix proteoglycans and release of inflammatory mediators such as tumour necrosis factor-$\propto$ [22,23]. This leads to impaired smooth muscle function and accumulation of collagen type 4 within the intima and media of vessels. The lung myofibroblasts then proliferate leading to muscularisation of the arterioles, neointimal formation of distal pulmonary arteries and irreversible increase in PVR [22,25]. The end result is restrictive lung syndrome and impaired gas exchange [25].

Causes of LHD can be divided into SD, DD and valvular disease. These diseases differ significantly but the final common pathway is an increase in LV and atrial pressure and the reactive increase in PAP.

Systolic Dysfunction (SD) and PH

Systolic dysfunction leads to a reduction of the LV EF. The LV chamber becomes spherical in shape and dilates with an increase in mass and loss of contractile Starling's function [26]. SD develops due to thinning and disorganised ECM collagen architecture leading to fibrosis [26]. The myocytes remodel with a disproportionate increase in the length to width ratio [27]. Sarcomeric dysfunction occurs due to proteolytic activity resulting in troponin I degradation and impaired myocyte function [28]. Damaged troponin I also causes impaired phosphorylation by protein kinase A (PKA) as a result of impaired β-adreneric signalling leading to impaired cardiac relaxation [28]. This complex interplay leads to altered calcium homeostasis within the myocytes and impaired contraction and SD. Trauma caused by myocardial infarction, myocarditis, volume overload, genetic mutations or drug toxicity leads to a cascade of neuroendocrine (angiotensin II, catecholamines, endothelin, TNF-$\propto$, insulin-growth factor) release, activation of growth factors and cytokine release. The heart continues to hypertrophy and dilate leading to an increase in end systolic volume, left ventricular end diastolic pressure (LVEDP) and a reduction in stroke volume and cardiac output [27].

Diastolic Dysfunction (DD) and PH

Diastolic dysfunction results in prolonged LV isovolumetric relaxation, slow LV filling time and increased stiffness. The development of LV stiffness occurs in the ECM and the cardiomyocytes [29]. In DD the ECM stiffens due to an excess of collagen type 1 deposition. For example, in hypertensive patients there is a reduction in collagen type 1 degradation due to a down regulation of matrix metalloproteinases (MMP) [29]. Cardiomyocytes stiffen due to the titin protein isoforms N2B (stiffer spring):N2BA (more compliant spring) ratio that increases in diastolic failure and conversely is decreased in SD [30]. This leads to increase in LV filling time and reduced compliance. Evidence of tissue Doppler measurements has established that patients with SD have a degree of DD.

Valvular Heart Disease and PH

Between 15 and 60% of patients with left sided valvular disease have PH [31]. Aortic stenosis (AS) and aortic regurgitation (AR) cause an indirect increase in LA pressure secondary to pressure overload and volume overload, respectively [31]. Mitral stenosis (MS) has a direct effect of pressure overload on the LA whilst mitral regurgitation (MR) has a direct impact on LA pressure due to volume overload [31].

Aortic Stenosis

Fifteen to thirty per cent of patients with symptomatic AS have PH due to impaired LV function, concomitant MR, increased LVEDP and LA dilatation [31]. Aortic valvular replacement (AVR) is indicated if patients develop symptoms of impaired LV function however, evidence suggests that the development of PH should be a strong indication to consider early surgical intervention. Melby et al. (2011), found that patients who had PH had a higher incidence of perioperative mortality (9% vs 5%, p = 0.02), increased length of stay (8 vs 7 days, p = 0.001) and prolonged ventilation (26% vs 7%, p = < 0.001) [32]. Patients with severe PH had a significantly lower survival rate than a patient with mild PH (45% vs 78%, p = < 0.001) [32].

Mitral Stenosis

More than 40% of patients with MS develop PH [32]. Current American and European Cardiac Society Guidelines (Class IIa) recommend percutaneous mitral valvuloplasty in patients who are asymptomatic with moderate-severe MS and moderate PH. The aim is to intervene prior to the development of moderate-severe PH, that has a trend towards increased mortality [32].

Aortic Regurgitation

The prevalence of PH in patients with AR is 27–37% [31]. Work performed by Hirschfeld et al. (1974), found a

significant relationship between PH, LVEDP and left ventricular hypertrophy (LVH) vs survival in patients undergoing surgical AVR [33]. Patients with PAP <25 mmHg had a 6-year survival rate of 80% versus 20% if patients had PAP of >40 mmHg [33]. Patients with a LVEDP of 4–10 mmHg had a 6-year survival of approximately 70% vs 30% if their LVEDP was 21–60 mmHg [33]. However, in patients with modest LVEDP (11–20 mmHg) prognosis was poor only if they had developed PH. In contrast, patients with LVEDP >20 mmHg had a poor prognosis independent of PH, suggesting that DD is an independent predictor of morality. But PAP was rarely elevated in patients with normal LVEDP [33]. This begs the question of whether these data on haemodynamics involved in aortic valvular disease and PH can be applied to evaluating DD in PH. Can non-invasive echo markers of LHD that correlate with elevated PAP be used to predict developing PH. This will be discussed in further detail in the next section.

Mitral Regurgitation

Primary MR

In primary MR the prevalence of PH is 20–30% in patients with symptoms and <20% in asymptomatic patients [31]. In patients with NYHA class [3,4] symptoms and severe MR, 64% had moderate PH (PAP >50 mmHg) [34]. Five-year survival of patients undergoing MV replacement is worse in patients with PH vs those without (63 ± 5% vs 86 ± 2% p = < 0.0001) [35]. Early surgery (<3 months) in patients with severe MR and PH (regardless of LV function) improved prognosis and prevented cardiovascular mortality [35]. Current European and American guidelines give a Class IIa indication for surgery in patients with severe MR, normal LV function and elevated PAP at rest [36].

Secondary MR

In patients with secondary MR and LV dysfunction the prevalence of PH is 40% [35,36]. Miller et al. 2014), examined 1384 patients with functional MR with impaired LV function (mean EF = 30%) and found that PH was associated with a higher all-cause mortality [37]. Magne et al. (2015), found that, regardless of LV function, a rise of 21 mmHg in PASP on exercise was strongly associated with future cardiac events [31]. This highlights the dynamic nature of functional MR and the poor compliance of the LA under a pressure loaded LV leading to an acute rise in pulmonary pressures. Exercise testing patients with mild or moderate MR is required to risk stratify them for early intervention.

Neurohormonal Effects of LHD on Pathophysiology of PH

The pathophysiology in which LHD results in PH involves two pathways; the passive increase in LAP on the pulmonary circulation (isolated post capillary PH) and the increased pulmonary vascular tone due to vascular remodelling (combined pre/post-capillary PH). The latter involves an imbalance in the secretion of NO and endothelin-1 (ET-1). Nitric oxide causes dilatation of smooth muscles in response to stimulation by bradykinin, acetylcholine and catecholamines [38]. This process is impaired in LHD along with reduced sensitivity to other vasodilators such as brain natriuretic peptide [39]. ET-1 promotes the proliferation of smooth muscle and collagen production leading to vascular remodelling [38]. ET-1 acts on two receptors: ET_A located in vascular smooth muscle cells (SMC); and cardiac myocytes and ET_B, also located in SMC but also in endothelial cells. Binding of ET-1 to ET_A leads to phosphorylation of myosin light chains and sustained vasoconstriction. Conversely, the ET-1 to ET_B complex releases NO, anti-apoptotic effects and the clearance of ET-1. However, the expression ratio of ET_A:ET_B is 9:1 in the pulmonary arteries [40].

Histologically, pulmonary artery and vein remodelling in PH-LDH leads to intimal fibrosis and medial hypertrophy [41]. This process is fixed and irreversible and is a poor prognostic factor in patients undergoing cardiac transplant.

In PH-LHD, mast cell release causes upregulation of serotonin, histamine and IL-6 (potent vasoconstrictors) further worsening the proliferation of SMCs [38]. There is an increase in Starling's forces due to a rise in hydrostatic pressures on the endothelial wall. Given that oncotic pressures remain the same there is a reduction in capillary permeability due to reduced function of mechanosensitive Ca^{2+} ion dependent channels leading to endothelial injury [38].

PH-LHD and RV Dysfunction

The increase in load and pressure on the right heart due to PH leads to dilatation of the right ventricle (RV). The RV remodels from a crescent shaped ventricle to a spherical shape leading to functional tricuspid regurgitation (TR) and increase RA pressure. Prognosis is reduced if patients develop RV dysfunction due to PH-LHD however, there is not a predictable relationship between the degree of PH and the development of right heart failure [8]. There is a correlation between RV dysfunction due to PH-LHD and an increase in PVR [8]. Patients with HFrEF and an RV ejection fraction of <35% have a mean survival of 1.5 yrs [42]. Risk factors include male sex, atrial fibrillation and coronary artery disease [43].

Diagnosis of PH-LHD Using Imaging

The gold standard for the diagnosis of PH using measurements of haemodynamics is a right heart catheterisation (RHC) [5,7]. RHC is an invasive test with a small risk of complications such as rupture of the pulmonary artery, thromboembolism, and arrhythmias. Therefore, although RHC is necessary for a definitive diagnosis of PH, most patients who present with breathlessness will receive an echo as an initial test.

Echocardiographic Measure of PASP

Doppler measurement of ePASP is a validated and reproducible method of calculating the PAP when correlated with simultaneous measurements taken during RHC [17,44]. Evaluation of ePASP is performed using the modified Bernoulli equation ($\Delta P = 4\ V^2$) and estimate of right atrial pressure (RAP):

$$ePASP = RAP + 4(TRV)^2$$

RAP - Right atrial pressure
TRV - Tricuspid regurgitant velocity

This method does have some caveats which need to be considered in specific patient populations. Peak TRV measured using continuous wave Doppler velocity is most accurate in patients with moderate or less tricuspid regurgitation, and at times may overestimate the true systolic pulmonary artery pressure measured by RHC [45,46]. In patients with severe TR with equalisation of right atrial and ventricular pressure, the pressure difference between RV and RA is small, and the peak TR velocity will therefore not reflect the true right ventricular systolic pressure. In this situation applying the modified Bernoulli equation results in underestimation of the true systolic PAP [46]. In addition, patients with atrial arrhythmias and altered flow characteristics across the tricuspid annulus will require the averaging of multiple beats to most accurately apply the modified Bernoulli equation [17].

Echocardiographic Evaluation of Diastolic Dysfunction

Diastolic measures of LV relaxation can be divided into the early (E wave) and late (A wave) filling and is represented as the E/A ratio. Impaired relaxation is represented by an E/A ratio <0.8 and prolonged deceleration time (DDT). As LV compliance reduces and becomes stiffer there are increased filling pressures and patients develop a restrictive filling pattern (E/A ratio >2) [47].

Myocardial velocity using early (E') and late (A') tissue Doppler velocity is measured as the LV moves in a longitudinal motion from base to apex and is less dependent on preload. The transmitral blood flow velocity to tissue Doppler velocity (E/E') has been well validated as a measure of diastolic function [47].

Summarised in Figure 2A is the evaluation of diastolic function in patients with normal EF. Using markers of diastolic function, left atrial volume as a marker of increased filling pressure and peak TR velocity as a maker of right ventricular systolic pressure one can establish if patients have DD [48].

Patients with impaired LV systolic function will have a degree of impaired diastolic function. Figure 2B illustrates how these patients will have a degree of impaired relaxation (E/A ≤0.8), pseudo-normal (E/A >0.8- <2.0) filling characteristics or a restrictive (E/A ≥2.0) filling pattern. This criteria is then used to grade DD [48].

Evaluation of PVR via RHC

In order to evaluate patients with PH-LDH, evaluation of PVR must be undertaken to establish those patients with isolated post capillary PH vs those with an elevated PVR [49]. Determinants of PVR are transpulmonary gradient (TPG) and cardiac output:

$$PVR = TPG/CO$$

$$TPG = mPAP - PCWP$$

TPG – Transpulmonary gradient
CO – Cardiac output
mPAP – mean Pulmonary Artery Pressure in mmHg
PCWP – Pulmonary Capillary Wedge Pressure in mmHg

Patients with PH-LHD have a raised mPAP with a proportionate increase in LV filling pressure (PCWP) and normal PVR. However, a small group have a mixed picture due to an increase in the TPG and PVR leading to a disproportionate increase in PAP. In this group of patients, further investigations should be performed to evaluate PAH, chronic lung disease or thromboembolic disease.

Echocardiographic Evaluation of PVR

Accessibility to RHC can be limited and echo is often the initial test that diagnoses patients with PH. Therefore, it would be advantageous if echo markers could evaluate PVR, determine pre vs post-capillary PH and provide information to guide management.

A recent review article by Naing et al. (2016), evaluated the surrogate echo markers of PVR [49]. The challenge is to establish echo markers that take into consideration the PAP and LAP and therefore, a surrogate to transpulmonary gradient measured in RHC.

Early work by Hirschfeld et al. (1975) and Scapellato et al. (2001) looked specifically at patients with congenital heart disease and patients with severe LV dysfunction (mean EF 17%), respectively [50,51] These studies used markers of RV function and pulmonary artery flow characteristics to predict PVR. However, these studies were small, did not incorporate markers of LAP and patients with HFpEF.

Abbas et al. (2013), have developed a formula ($5.19 \times TRV^2/TVI_{RVOT} - 0.4$) as a surrogate for PVR [52]. They postulate that the TRV is a surrogate for transpulmonary gradient and the right ventricular outflow tract (TVI_{RVOT}) is a surrogate for transpulmonary flow. The predictive value was an area under the receiver operator curve (AUC) of 0.93 [52]. The caveats were that the formula did not incorporate a

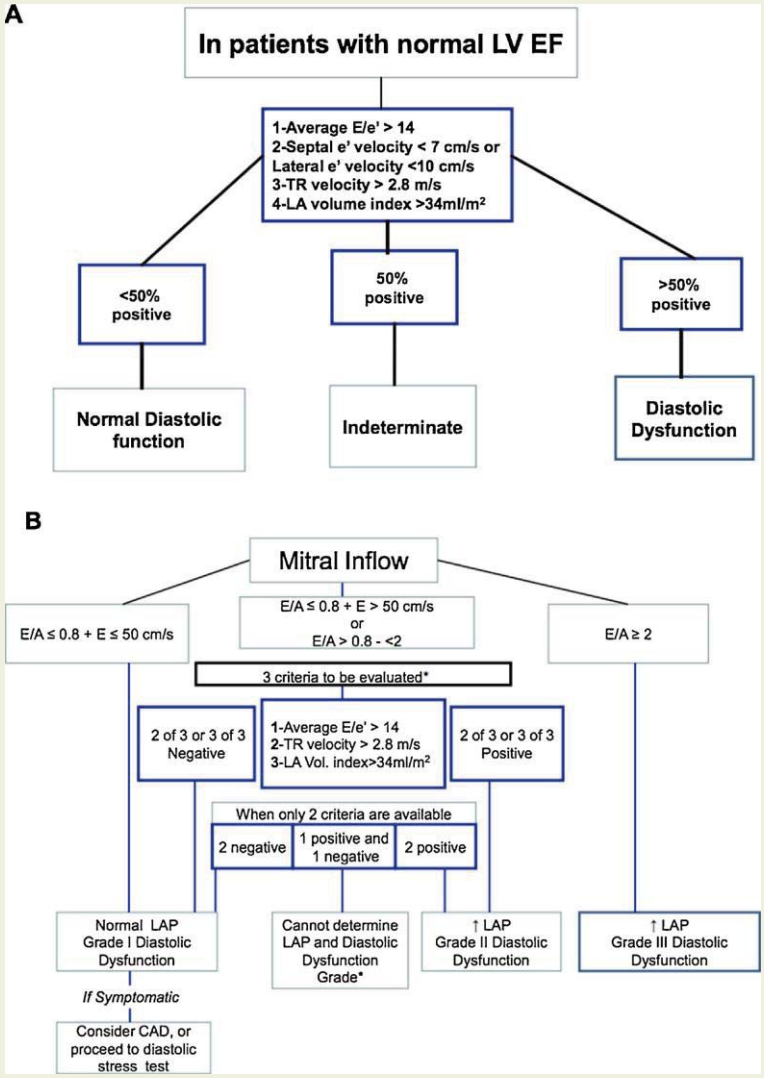

Figure 2 Diastolic function assessment of patients with normal EF (A) and Reduced EF (B) [48].
Abbreviations;: EF = ejection fraction.

surrogate for PCWP however, they did perform Bland Altman analysis and found a correlation in patients with PCWP >15 mmHg and a higher PVR (PVR > 6WU). This suggests there is was poor specificity in patients with post capillary PH.

Similarly, Haddad et al. (2009), examined patients with PAH with relatively high PVR (mean 11.0 WU) and low LAP (mean PCWP 9) using the formula PASP/(HR x TVI_{RVOT}) [53]. They found a good correlation (r = 0.86) in patients with PAH and PVR >11 WU. However, the omission of patients with LHD make its use limited in patient with post capillary PH.

Scalia et al. (2016), have developed the echocardiographic Pulmonary to Left Atrial Ratio (ePLAR) [54].

$$ePLAR_{(m/s)} = \frac{TRV_{max\,(m/s)}}{mitral\,E/e'}$$

[54]

This formula incorporates the $TRV_{(max)}$ in establishing the ePASP and E/e' as a surrogate for LAP. Therefore, the ePLAR will be evaluating TPG (mPAP-PCWP) whereby $TRV_{(max)}$ will be a surrogate for mPAP and E/e' a surrogate for PCWP. Investigators postulate that the higher the ePLAR the higher the component of pre-capillary PH (rising TPG) and the lower the ePLAR the higher the component of post-capillary PH (rising LAP) [54]. ePLAR is simple yet effective in differentiating between pre and post-capillary when compared to RHC [54].

Significant work has been published on surrogate markers for PVR however, limited data is available to differentiate patients with pre-capillary vs post-capillary PH. The ePLAR offers some differentiating ability however, further work is required to aid diagnosis.

Discussion and Future Challenges

The prevalence of PH-LHD is under reported. Current European, American and Australian registries only provide a small snapshot of the true prevalence of PH-LDH in the community [3,55]. We have previously reported the mortality and morbidity of LHD in the community and provided evidence that, once patients with LDH develop PH, their prognosis is significantly reduced. The severity of the LHD doesn't necessarily correlate with the severity of PH [3,19,31–34]. However, PH is an independent risk factor for increased mortality [3].

There is a lack of research into early recognition of PH in the community. Echo measurements of PH and DD are well validated and there is a growing body of evidence to stratify patients into pre-capillary and post-capillary causes through surrogate markers of PVR. However, identifying echo markers of DD that can predict the development of PH is lacking. Identifying markers of DD to predict developing PH or predict worsening PH may enable early intervention, treatment and reduce mortality.

Systematic analysis of large data sets, such as the National Echo Database Australia (NEDA), which is currently underway, will provide mortality-linked surrogates for PH and will help to determine the prognostic value of these markers. Analysis of large right heart catheterisation databases where the diagnosis of PH has been definitively determined, when compared with multiple echo markers and linked with mortality, will help to clarify the true place of echo markers for pulmonary vascular disease.

Research Protocol/Ethics

Ethics approval for this research was gained from The University of Notre Dame, Australia Human Research Ethics Committee and assessed to meet all the requirements outlined in the National Health and Medical Research Council of Australia. Ref: 016093F.

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Appendix 2

Abstract Presentation – "Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA)." The Pulmonary Hypertension Society of Australia and New Zealand Annual Scientific Meeting 2017

University Hospitals Leuven, Leuven, Belgium; Mater Misericordiae Hospital, Dublin, Ireland; University of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany; Imperial College London, UK; Charles University, Prague, Czech Republic; Medical University of Vienna, Allgemeines Krankenhaus, Vienna, Austria; LHSC University Hospital, London, Ontario, Canada; Ignacio Chávez National Heart Institute, Mexico City, Mexico; CARE Hospitals, Hyderabad, India; Hôpital de Bicêtre, Le Kremlin-Bicêtre, France; INCOR Heart Institute, University of Sao Paulo, Sao Paulo, Brazil; CMKP European Health Centre, F. Chopin Hospital, Otwock, Poland; Cedars-Sinai Medical Center, Los Angeles, USA; Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; University of California, San Diego Medical School, San Diego, USA; Università di Bologna, Bologna, Italy

Rationale/Background: Clinical and registry data suggest that pulmonary arterial hypertension (PAH) progression is indicative of poor prognosis.

Methods/Materials: The prognostic relevance of PAH-related morbidity was evaluated based on observations from randomized controlled trials SERAPHIN (n = 742) and GRIPHON (n = 1156). Both studies were double-blind, long-term, event-driven Phase III trials. In both, the primary endpoint was a composite of morbidity/mortality, prospectively defined and independently adjudicated. At three landmark time points—months 3, 6, and 12—the risk of all-cause death until end of study was assessed according to whether patients had experienced a primary endpoint morbidity event up to the landmark.

Results: At month 3, 720 SERAPHIN patients were at risk of death. Of those, 38 had experienced a morbidity event up to month 3. Within the median follow-up period of 27 months, patients had a more than threefold increased risk of death compared with the 682 patients who had not experienced a morbidity event up to month 3 (hazard ratio [HR] = 3.39, 95% confidence interval [CI] = 1.94–5.92). Similar observations were made in the GRIPHON population: 1127 patients were at risk of death at month 3; 62 patients had experienced a morbidity event up to month 3 and had a more than fourfold increased risk of death within the next 20 months (median follow-up) compared with the 1065 patients who had not (HR = 4.48, 95% CI = 2.98–6.73). In both studies, analyses at months 6 and 12 yielded similar findings.

Summary/Conclusions: These results confirm the prognostic relevance of PAH-related morbidity and the importance of its prevention in patients with PAH.

Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA)

K. Chung, D. Playford, J. Codde, D. Celermajer, G. Scalia and G. Strange

The University of Notre Dame Australia; Pulmonary Hypertension Society, Australia and New Zealand; Royal Prince Alfred Hospital Sydney; The University of Sydney; Heart Research Institute; The University of Notre Dame Australia; The Prince Charles Hospital and The University of Queensland

Rationale/Background: Pulmonary hypertension due to left heart disease (PH-LHD) is common, but may be difficult to diagnose by echo in the absence of sufficient tricuspid regurgitation (TR). Once PH has progressed to moderate or severe disease, prognosis is poor.

Our objective is to create a predictive model using diastolic echo markers to diagnose PH, even in the absence of a measurable TR velocity.

Methods/Materials: A total of 302,746 echos (174,229 patients) were analyzed. Univariate analysis was used to establish significant diastolic markers of PH in 99,025 patients with sufficient TR (79,268 with PH vs. 19,767 with no PH). The whole cohort (including no measurable TR velocity) was randomized to two groups: Group A (151,373 echos) to perform multivariate regression analysis on the diastolic markers and to create a predictive model; and Group B to validate the predictive model (151,373 echos).

Results: Age, E', E/e', E:A, and indexed left atrial volume (LAVI) were identified in group A as markers of PH-LHD. A constant ($-6.649 + [0.035 \times \text{age}] + [0.072 \times E'] + [0.077 \times E/e'] + [0.509 \times E/A] + [0.03 \times \text{LAVI}]$) was developed and applied in group A to predict PH-LHD, with an area under the curve (AUC) of 0.746 (95% confidence interval [CI] = 0.729–0.762). We then validated this model on group B, with an AUC of 0.757 (95% CI = 0.741–0.773). TR is not measurable in 40% of echos. We have developed a new model that can predict PH-LHD with 75% accuracy, regardless of measurable TRV, using Age, E', E/e', E:A, and LAVI. Our model may be useful in echo software to automatically calculate a probability of PH-LHD.

Summary/Conclusions: TR is not measurable in 40% of echos. We have developed a new model that can predict PH-LHD with 75% accuracy, regardless of measurable TRV, using Age, E', E/e', E:A, and LAVI. Our model may be useful in echo software to automatically calculate a probability of PH-LHD.

APPENDIX 3

Abstract Presentation – “NEDA PH-LHD Predictive Model: Validation of Diastolic Markers of Pulmonary Hypertension with Right Heart Catheterisation.” The Pulmonary Hypertension Society of Australia and New Zealand Annual Scientific Meeting 2017 (Winner of best abstract presentation)

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NEDA PH-LHD predictive model: validation of diastolic markers of pulmonary hypertension with right heart catheterization

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Rationale/Background: Our group has developed a predictive model to diagnose pulmonary hypertension due to left heart disease (PH-LHD) using markers of diastolic function. This has been validated in a cohort of 302,746 echos (174,229 patients) and the model has an accuracy of 75%. The gold standard in the diagnosis of PH-LHD is a right heart catheterization (RHC).

Our objective is to establish the predictive value of our PH-LDH model in patients undergoing RHC.

Methods/Materials: Data were extracted for patients undergoing RHC from a tertiary cardiology center in addition to their most recent echo results. Diastolic markers of age, E^{0}, E/e^{0}, E:A ratio, and indexed left atrial volume (LAVI) were used to apply our predictive model in patients with PH-LHD diagnosed on RHC (pulmonary capillary wedge pressure > 15 mmHg, mean pulmonary arterial pressure [mPAP] > 25 mmHg).

Results: A total of 887 patients with a mean (±SD) age of 68 (±18) years, 56% male, mPAP of 31 (±13) mmHg and mean pulmonary arterial systolic pressure (PASP) of 53 (±18) mmHg. The incidence of PH on RHC was 68% (mPAP > 25 mmHg) vs. 50% on echo ePASP (> 40 mmHg). We applied our formula constant (–6.649 þ [0.035 × age] þ [0.072 × E^{0}] þ [0.077 × E/e^{0}] þ [0.509 × E/A] þ [0.03 × LAVI]) to establish the predictive value of our model in RHC diagnosis of PH-LHD. The AUC was 0.793 (95% CI 0.651–0.934, P¼0.017).

Conclusion: Using our predictive model, we are able to predict, with 80% accuracy, patients with PH-LHD previously diagnosed by RHC using Echo-derived diastolic markers of LHD.

Limiting the learning curve for pulmonary endarterectomy: an Australian single-center experience

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Rationale/Background: Despite advances in medical treatment, pulmonary endarterectomy (PEA) remains the most curative option for patients with chronic thromboembolic pulmonary hypertension (CTEPH). The majority of centers initiating a PEA service report a significant surgical learning curve. This study examines the outcomes of patients undergoing PEA for CTEPH in a single institution with initial surgical mentoring and double evaluation of patient suitability with an established high-volume center.

Methods/Materials: Forty-three patients (21 women, 22 men; average age 61.1 ± 14.7 years) with surgically amenable CTEPH underwent PEA between November 2010 and July 2017. Functional (New York Heart Association [NYHA] class, 6-minute walk test [6MWT]), hemodynamic (right heart catheterization) and survival outcomes were examined after 12 months. Eleven of the 43 patients (25.6%) had a preoperative pulmonary vascular resistance (PVR) of > 1000 dynes.

Results: Significant post-PEA improvements were observed in NYHA class (pre 3.0 ± 0.5 vs. post 1.7 ± 0.6, P< 0.01), 6MWT (pre 329.7 ± 112.1 m vs. post 451.7 ± 95.6, P< 0.01), mean pulmonary artery pressure (pre 49.3 ± 12.4 mmHg vs. post 31.1 ± 10.0, P< 0.01), PVR (pre 795.6 ± 326.7 dynes vs. post 276.1 ± 115.0, P< 0.01), and cardiac output (pre 4.1 ± 1.2 L/min vs. post 5.4 ± 1.2, P< 0.01). The one-year mortality rate was 2.3%.

Summary/Conclusions: PEA remains an effective treatment for CTEPH with significant improvements demonstrated in pulmonary hemodynamics and functional outcomes. Furthermore, instituting a PEA service in conjunction with an established center can mitigate the learning curve, associated with significant mortality, and produce comparable results to those from high-volume centers.

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Appendix 4

Abstract Presentation – "NEDA PH-LHD Predictive Model: Validation of Diastolic Markers of Pulmonary Hypertension with Right Heart Catheterisation." The Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017

cardiovascular risk as sustained hypertension; increased cardiovascular morbidity/mortality and target organ damage. Ambulatory BP monitoring was the preferred diagnostic method although Home BP monitoring was a useful alternative. Anecdotal evidence supports risk factor modification(OSA), however the evidence for drug treatment of MHT is scant.

Conclusion: MHT/MUCH is widely prevalent. Patients with high normal clinic BP should be screened for MHT/MUCH. RCTs are needed to assess the efficacy of drug treatment of MHT.

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037

This abstract has been withdrawn

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038

NEDA PH-LHD Predictive Model: Validation of Diastolic Markers of Pulmonary Hypertension with Right Heart Catheterisation

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Background: Our group has developed a predictive model to diagnose pulmonary hypertension due to left heart disease (PH-LHD) using markers of diastolic function. This has been validated in a cohort of 302,746 echos (174,229 patients) and the model has an accuracy of 75%. The gold standard in the diagnosis of PH-LHD is a right heart catheterisation (RHC).

Objective: To establish the predictive value of our PH-LDH model in patients undergoing RHC.

Methods: Data was extracted for patients undergoing RHC from a tertiary cardiology centre in addition to their most recent echo results. Diastolic markers of age, E', E/e', E:A ratio and indexed left atrial volume (LAVI) were used to apply our predictive model in patients with PH-LHD diagnosed on RHC (PCWP >15 mmHg, mPAP >25 mmHg)

Results: 887 patients with a mean (± SD) age of 68 (±18), 56% male, mean pulmonary artery pressure (mPAP) of 31 (±13)mmHg and mean PASP of 53 (±18)mmHg. The incidence of pulmonary hypertension on RHC was 68% (mPAP >25 mmHg) vs 50% on echo ePASP (>40 mmHg). We applied our formula constant [-6.237 + (0.03 x Age) + (0.03 X LAVI) + (0.197 x E:A ratio) + (0.089 x E:e') + (0.078 x E')] to establish the predictive value of our model in RHC diagnosis of PH-LHD. The AUC was 0.793 (95% CI 0.651–0.934 p = 0.017).

Conclusion: Using our predictive model, we are able to predict, with 80% accuracy, patients with PH-LHD previously diagnosed by RHC using Echo derived diastolic markers of LHD.

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039

Nitroglycerin Protection of Radial Artery Function after Coronary Angiography

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Background: Transradial cardiac catheterisation is rapidly becoming preferred over the femoral approach. However, some studies have shown that it leads to persistent functional impairment of the artery. We aimed to assess changes in radial artery endothelial function after transradial catheterisation and determine whether intravenous nitroglycerin (IV GTN) infused during angiography might improve arterial dysfunction post-angiography.

Methods: Patients undergoing diagnostic coronary angiography were invited to participate. Doppler ultrasound assessment of radial artery function was performed using flow-mediated dilation (FMD) prior to angiography. FMD tests endothelial function by measuring the degree of arterial dilatation following inflation of a pneumatic cuff for 5 min. Patients were then randomised (1:1) to IV GTN (10mcg/min, commenced 10 min prior to radial access) or placebo. Radial artery FMD was reassessed 4 hrs and 1 month post-angiography.

Results: 27 patients (intervention n = 14, placebo n = 13) underwent transradial catheterisation. FMD decreased markedly from baseline to 4 hrs in both groups (intervention 12.9 to 7.5%, p = 0.025; placebo 14.7 to 8.1%, p = 0.035). At one month FMD had returned towards baseline with no significant difference in either group. The reduction in FMD was numerically less in the intervention group than the placebo group at both time periods (baseline to 4 hrs and baseline to one month), although these results did not meet statistical significance.

Conclusion: Transradial cardiac catheterisation causes transient endothelial dysfunction which is not ameliorated by GTN. This endothelial dysfunction is fully reversible at one month.

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Appendix 5

Abstract presentation “Pulmonary hypertension due to diastolic dysfunction: a predictive model using the national echo database of Australia (NEDA)” The European Society of Cardiology Annual Scientific Meeting 2017

m corresponding to a net increase of 63 m (p<0.001). The proportion of patients in WHO-FC III increased from initially 5% to 37.5% at 12 months. Furthermore, RV function showed a moderate improvement (TAPSE from 16.9±0.7 to 18.8±0.8 mm, p=0.01), and NTproBNP levels decreased after 12 months of therapy from initially 3.191±559 ng/L to 2.130±472 ng/L (-33%, p=0.004). The body weight of the patients was constant during the observation period (71.7±3 kg initially vs. 71.5±2 kg at 12 months), so that the treatment effect may not be due to an optimized volume status and reduced left ventricular filling pressure. Serious adverse events did not occur in the investigated group and the typical side effects of PDE5i (headache, flushing, nasal congestion) were observed.
Conclusion: These data indicate that precisely characterized patients with HFpEF and Cpc-PH who tolerate PDE5i can benefit from this therapy. A randomized study in this particular subpopulation is warranted.

P2588 | BEDSIDE
Pulmonary vascular gradients, right ventricular afterload and outcomes in pulmonary hypertension due to left heart disease

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Background: In pulmonary hypertension (PH) due to left heart disease (LHD), both high wedge pressure (PAWP) and the presence of a pre-capillary component (eventually described by the diastolic pressure gradient, DPG) may affect the resistance (PVR) – compliance relationship, with possible implications for (RV) afterload and prognosis.
Purpose: To characterize PH-LHD according to baseline haemodynamics and to describe their prognostic implications.
Methods: Retrospective analysis including: PH due to left heart disease (LHD), further subdivided in Isolated post-capillary PH (IpcPH: DPG<7 mmHg and PVR≤3 WU, n=37), Combined post- and pre-capillary PH (CpcPH: DPG≥7 mmHg and PVR>3 WU, n=27), and “indeterminate” (“discordant” DPG and PVR, n=29); treatment-naïve idiopathic/heritable pulmonary arterial hypertension (PAH, n=35).
Results: Despite worse pulmonary haemodynamics in PAH than in PH-LHD, survival did not differ between the two conditions. Severity of the haemodynamic profile (pulmonary pressures, pulmonary gradients and PVR) increased (p<0.001) from IpcPH, to “indeterminate”, to CpcPH in spite of similar PAWP and cardiac index between the three groups, so that CpcPH had a haemodynamic profile closer to that of PAH. Prevalence of RV failure was linearly correlated with DPG and PVR but not with pulmonary arterial compliance. CpcPH had worse prognosis (p<0.05) than IpcPH and PAH, but similar to “indeterminate” patients (Figure 1).

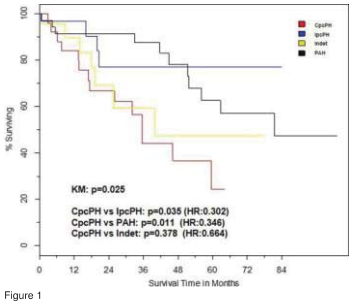

Figure 1

Conclusions: In PH-LHD, haemodynamic phenotyping according to DPG and PVR provide informative elements concerning disease severity, predisposition to RV failure and prognosis. CpcPH may present with a pulmonary haemodynamic profile closer to PAH but with even worse prognosis than PAH.
Acknowledgement/Funding: Dr Caravita is the recipient of: ERS PAH Short-Term Research Training Fellowship (STRTF 2014-5264); “Cesare Bartorelli” SIIA grant for the year 2014

P2589 | BEDSIDE
Non invasive discrimination between pre and post capillary pulmonary hypertension: comparison of three published scores

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Background: Pulmonary hypertension (PH) is frequent and usually detected by echocardiography. To avoid systematic right heart catheterization, three scores have been recently published especially for those with postcapillary phenotype and normal ejection fraction.
Purpose: The objective of this study was to test and compare three diagnostic strategies used to identify postcapillary PH due to left heart failure.
Methods: We retrospectively collected clinical and echocardiographic parameters in PH patients defined by invasive mean pulmonary arterial pressure ≥25 mmHg. Patients were dichotomized in pre- or postcapillary phenotype if wedge pressure was ≤15 or >15 mmHg, respectively. Score 1, 2 and 3 were proposed by a PH referral center, ESC/ERS guidelines, and ASE/EACVI guidelines. Those scores included age, atrial fibrillation, NYHA functional class, metabolic syndrome, structural left heart abnormalities, Doppler indices, right ventricular function, as well as pericardial effusion. They were compared to right heart catheterization.
Results: 164 patients (83 males) were included, 82 in each group. Mean age was 66±12 yo, NYHA functional class was 2.5±0.7, ejection fraction averaged 59.1±10.4%. Mean pulmonary artery and wedge pressure were 40.9±10.7 and 15.7±8.7 mmHg respectively. ROC curves analysis did not show any difference between score 1 and 2 (p=0.578) while score 3 was significant (p<0.0001). Positive predictive value for each score is depicted in various range of systolic pulmonary artery pressure (table 1). All scores are acceptable above 50 mHg and incremental power is provided by combination of scores 1 and 3.

Table 1. Predictive positive values (%)

	sPAP (mmHg)			
	<40	40–59	50– 9	>60
Score 1	100	86.7	94.4	94.7
Score 2	100	90.9	93.3	100
Score 3	75	86.7	94.1	88.9
Combined scores 1 and 3	100	100	100	100

sPAP: systolic pulmonary artery pressure.

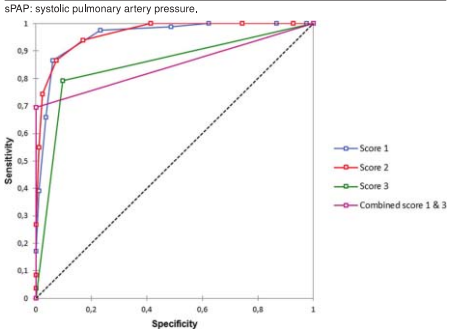

Figure 1. ROC curves

Conclusion: To avoid right heart catheterization in patients with postcapillary pulmonary hypertension, it is necessary to merge two published scores.

P2590 | BEDSIDE
Pulmonary hypertension due to diastolic dysfunction: a predictive model using the national echo database of Australia (NEDA)

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Background: Left heart disease (LHD) is the commonest cause for pulmonary hypertension (PH), and diastolic dysfunction is the dominant pathophysiology. The National Echo Database Australia (NEDA) is an Australian multicenter systematic database of patient echo parameters.
Purpose/Methods: 302,746 echos (174,229 patients >18 years) were included in this cohort. PH (ePASP >40mmHg) was estimated using TR velocity (TRV). The diastolic markers most significantly associated with PH were identified using univariate analysis. The entire cohort was then randomized to two groups: Group A (151,373 echos) to perform multivariate logistic regression analysis on the identified diastolic markers, to establish a novel predictive model; Group B to validate the predictive model on the remaining group (151,373 echos). A nomogram was formulated to predict the PH probability based on diastolic markers.
Results: 75,204 patients (43%) had insufficient TR to measure ePASP. Of the 99,025 remaining patients with TRV present, 19,767 (20%) had an ePASP >40 mmHg. 11,988 (61%), 4,610 (23%) and 3,169 (16%) had mild (40–49mmHg), moderate (50–60mmHg) and severe (>60mmHg) PH, respectively. Age, E' velocity (cm/s), E/e', E:A ratios, indexed left atrial volume (LAVI) and ejection fraction were significantly (p<0.00001) different in patients with PH vs those without (80,273 patients). Using multivariate logistic analysis, Group A (diastolic predictors for PH) produced an area under the ROC curve of 0.746. When the same logistic regression equation from Group A was applied to Group B, the area under

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Appendix 6

Abstract Presentation “Pulmonary hypertension due to left heart disease: a predictive model using the National Echo Database of Australia (NEDA).” The Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017

040

Outcomes in Aortic Dissection in Patients Presenting to Launceston General Hospital

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Background: Aortic dissection is uncommon however its presentation can mimic that of an acute coronary syndrome with significant haemodynamic compromise and death if not considered. Little is known about the patient's trajectory if they survive the initial presentation. We intend to look at outcomes of these patients at our institution.

Method: Patients admitted between 2010-2016 were evaluated. They must have had a Type A or B dissection recorded as their primary or secondary diagnosis. Data was obtained by reviewing patient medical records, GP and patient telephone calls. Baseline demographics and cause of dissection were recorded. Outcome evaluated included management plan and mortality.

Results: 30 patients had a diagnosis of aortic dissection. In 13.3%, 6.7% and 0% of cases, the cause of dissection was attributed to surgery, inflammatory and CTD respectively.

53.3% of total patients underwent surgery (68% in Type A, 12.5% in Type B) and 43.3% conservative management (27.3% in Type A, 87.5% in Type B). 2/30 (6.7%) did not survive their initial presentation. In-hospital mortality was 9.1% (Type A) and 0% (Type B). During follow-up 7/30 (23.3%) had died.

Discussion: Over half of patients presenting with aortic dissection underwent surgery. They were more likely to have Type A dissection. 1 person did not survive the initial resuscitation attempt. Although in-hospital mortality was low, almost a quarter of the patients were found to have died during follow-up.

Conclusion: Patients presenting with aortic dissection have high mortality rates even despite surviving their initial hospitalisation.

http://dx.doi.org/10.1016/j.hlc.2017.06.041

041

Pulmonary Hypertension (PH) Due to Left Heart Disease: A Predictive Model Using the National Echo Database of Australia (NEDA)

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Background: PH due to left heart disease (PH-LHD) is common, but may be difficult to diagnose by echo in the absence of sufficient tricuspid regurgitation (TR).

Objective: To create a predictive model using diastolic echo markers to diagnose PH, even in the absence of a measurable TR velocity.

Methods: 302,746 echos (174,229 patients) were analysed. Univariate analysis was used to establish significant diastolic markers of PH in 99,025 patients with sufficient TR (79,268 with PH vs 19,767 with no PH). The whole cohort (including no measurable TR velocity) was randomised to 2 groups: Group A (151,373 echos) to perform multivariate regression analysis on the diastolic markers and to create a predictive model; Group B to validate the predictive model (151,373 echos).

Results: Age, E', E/e', E:A and indexed left atrial volume (LAVI) were identified in group A as markers of PH-LHD. A constant [-6.237 + (0.03 x Age) + (0.03 X LAVI) + (0.197 x E:A ratio) + (0.089 x E:e') + (0.078 x E')] was developed and applied in group A to predict PH-LHD, with AUC of 0.746 (95% CI 0.729-0.762). We then validated this model on Group B, with AUC of 0.757 (95% CI 0.741-0.773).

Conclusion: TR is not measurable in 40% of echos. We have developed a new model that can predict PH-LHD with 75% accuracy, regardless of measurable TRV, using age, E', E/e', E:A and LAVI. Our model may be useful in echo software to automatically calculate a probability of PH-LHD.

http://dx.doi.org/10.1016/j.hlc.2017.06.042

Appendix 7

Abstract presentation “The National Echo Database Australia (NEDA) and Pulmonary Hypertension” The Pulmonary Hypertension Society of Australia and New Zealand Annual Scientific Meeting 2016

CI, 1.014–1.032; $P < 0.001$) remained significant. Percentage predicted is not superior to absolute 6MWD as a predictor of mortality in PAH.

Climbing Kilimanjaro: time-course changes in pulmonary pressures and gas-exchange during altitude exposure in 27 non-acclimatized climbers

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High altitude exposure results in hypoxic pulmonary vasoconstriction (HPV) and increased pulmonary pressure. This study examined the relationship between acute changes in resting pulmonary pressure and pulmonary gas-exchange measures during exercise in a group of non-acclimatized climbers summiting Mount Kilimanjaro. Twenty-seven climbers (age, 44 + 15 years) completed the study. Exercise testing (4-min step test with gas-exchange) and echocardiographic measurements were completed at four different altitudes: 8801 m (barometric pressure, PB = 690 mmHg); 3500 m (PB = 505 mmHg); 4600 m (PB = 428 mmHg) and on return to 880 m (8802 m). Right ventricular systolic pressure (RVSP, mmHg) progressively increased as PB fell during the ascent (8801 m: 19 + 4; 3500 m: 27 + 8; 4600 m: 33 + 8 mmHg). During exercise, the fall in PB was associated with a decrease ($P < 0.01$) in oxygen saturation (nadir SpO2(%): 8801 m: 96 + 2; 3500 m: 82 + 3; 4600 m: 73 + 4). The time-course changes in gas exchange tracked changes in RVSP during ascent with a progressive decrease ($P < 0.01$) in SpO2 and end tidal carbon dioxide production (end-exercise PETCO2, mmHg: 8801 m: 37.1 + 3.6; 3500 m: 28.5 + 2.6; 4600 m: 20.8 + 1.9) and an increase in breathing efficiency (VE/VCO2: 8801 m: 28.5 + 2.9; 3500 m: 35.8 + 4.6; 4600 m: 50.7 + 5.8). However, while SpO2 and RVSP normalized on return to lower altitude (8802 m), gas-exchange measures remained altered (PETCO2, mmHg: 31.2 + 3.0; VE/VCO2: 32.8 + 3.2, $P < 0.01$ versus 8801 m). With high altitude exposure, there is an increased ventilatory drive characterized by altered gas exchange and associated changes in SpO2 and pulmonary pressures. However, following high altitude exposure and once SpO2 and pulmonary pressures are normalized, gas-exchange measures remain altered suggesting that HPV is no longer a potential stimulus for an increased ventilatory drive.

The National Echo Database Australia (NEDA) and pulmonary hypertension

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We have previously demonstrated that pulmonary hypertension (PHT), identified using echocardiography (echo) is common and that left heart disease accounts for the majority of PHT. Echo measurements of left heart disease may be helpful in predicting the cause of PHT. The aim of this study is to examine prevalence of PHT within NEDA, and uncover left heart predictors of PHT. NEDA utilizes novel database engineering to combine individual databases into a single database. A total of 307,656 echocardiograms from two laboratories have been included in this analysis. We defined PHT as a right ventricular systolic pressure (RVSP) over 40 mmHg. In total, 180,374 echos (59%) had a measurable tricuspid regurgitation (TR) velocity profile from which an RVSP could be calculated. PHT from any cause was identified in 39,699 (22%) echos. Of those in which PHT was identified, the mean RVSP was 51 ± 11 mmHg, compared with 29.5 ± 5.8 in those without PHT ($P < 0.0001$). These patients were older than the overall average for NEDA (mean age, 74.9 ± 12.1 years versus 62.9 ± 16.6, $P < 0.0001$). The ejection fraction (EF) was similar but significantly different between those with PHT and those without (58.1 ± 13.7 versus 61.9 ± 8.7%, $P < 0.0001$). Measures of diastolic function were markedly different (E:E' ratio 17.1 ± 8.5 versus 11.3 ± 5.5, $P < 0.0001$). PHT is common, representing 22% of those with a measurable RVSP in a large echo cohort (over 300,000 echos). Overall, the EF was similar in PHT compared to those without PHT, whereas surrogate markers of filling pressure such as E:E' ratio were markedly different, underpinning the importance of measuring diastolic function in the evaluation of PHT.

Appendix 8

Abstract presentation “The National Echo Database Australia (NEDA) and Pulmonary Hypertension” The Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2016

cardiac surgery vs transplant were evaluated. She was listed for heart transplantation in June 2015.

However clinically she responded to the inpatient treatment, and her heart failure continued to improve in the ambulatory environment. She was a committed participant in Cardiac Rehabilitation exercise program. Strong determination was a psychological feature of this patient. By August she was clinically NYHA Class I, although her BNP was still elevated ~4000. CMRI was performed and no evidence of late gadollinium enhancement was observed. Her case was discussed again.

In October 2015 she underwent AVR/Bentalls procedure at St Vincents Hospital. She had an uneventful postoperative course and was discharged home 7 days post-operation.

A transthoracic echo performed 6 weeks following surgery demonstrated an excellent AVR&aortic repair, with an estimated ejection fraction of 40% and LVEDD of 48 mm. Clinically she remains well and BNP performed 3 months after surgery is normal.

This case highlight options for treatment for severe heart failure from aortic regurgitation; particularly benefit of aggressive heart failure treatment including cardiac rehabilitation programs.

http://dx.doi.org/10.1016/j.hlc.2016.06.289

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The National Echo Database Australia (NEDA) and Pulmonary Hypertension (PHT)

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Background: We have previously demonstrated that PHT identified using echocardiography (Echo) is common and that left heart disease accounts for the majority of PHT. Echo measurements of left heart disease may be helpful in predicting the cause of PHT.

Aims: To examine prevalence of PHT within NEDA, and uncover left heart Echo predictors of PHT.

Methodology: NEDA utilises novel database engineering to combine individual databases into a single database. 307,656 Echos from two laboratories have been included in this analysis. We defined PHT as a right ventricular systolic pressure (RVSP) over 40 mmHg.

Results: 180,374 Echos (59%) had a measurable tricuspid regurgitation (TR) velocity profile from which an RVSP could be calculated. PHT from any cause was identified in 39,699 (22%) Echos. Of those in which PHT was identified, the mean RVSP was 51+/-11 mmHg, compared with 29.5+/-5.8 in those without PHT (p<0.0001). These patients were older than the overall average for NEDA (mean age 74.9+/-12.1 vs 62.9+/-16.6 years, p<0.0001). The ejection fraction (EF) was similar but significantly different between those with PHT and those without (58.1+/-13.7 vs 61.9+/-8.7%, p<0.0001). Measures of diastolic function were markedly different (E:E' ratio 17.1+/-8.5 vs 11.3+/-5.5, p<0.0001).

Conclusions: Pulmonary hypertension is common, representing 22% of those with a measurable RVSP in a large echo cohort (over 300,000 Echos). Overall, the EF was similar in PHT compared to those without PHT, whereas surrogate markers of filling pressure such as E:E' ratio were markedly different, underpinning the importance of measuring diastolic function in the evaluation of PHT.

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The Perils of Pregnancy; A Review of Post-Partum Cardiomyopathy in a Tertiary Centre

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Introduction: Peri-partum cardiomyopathy (PPCM) is a distinct clinical entity of unclear aetiology with a high incidence of adverse outcomes.

Methods: We conducted a retrospective, single centre study including eight patients with newly diagnosed PPCM. Medical records were reviewed with follow-up to 2 years.

Results: 7/8 patients presented in the post partum with the median age being 33. 6/8 patients were non-caucasian.1 women had a twin pregnancy and one was complicated by pre-eclampsia and gestational diabetes. Dyspnoea was the presenting symptom with 7/8 being New York Heart Association (NYHA) Class I or II. Severe global left ventricular dysfunction (ejection fraction <20%) was seen in 5/8 women. 1/8 had an LV thombus and 2/8 had pericardial effusions. Mitral regurgitation was the predominant valvular abnormality. Median duration of hospital admission was 9 days with one patient requiring ICU admission for cardiogenic shock with no patient deaths. All patients received standard heart failure therapy. 7/8 received an angiotensin converting enzyme inhibitor (ACEI) and all received beta-blockade. 4/8 were anticoagulated;1/8 for LV thrombi; 1/8 for pulmonary embolus and 2/8 for akinetic apex and 2/8 received bromocriptine. 2/8 patients had recovered LV function at 12 months, five had persisting LV dysfunction (LV ejection fraction <40%) despite standard therapy. Four out of those five patients demonstrated late gadolinium enhancement on cardiac MRI (diffuse myocardial distribution) with 2/5 receiving a primary prevention implantable cardioverter defibrillator.

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