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**Differentiating Pre-Capillary and Post-Capillary Pulmonary
Hypertension by Doppler Echocardiography in a Large Real-
world Database**

Pyi Naing

Thesis submitted as fulfilment of the requirements for the degree of

Master of Philosophy

School of Medicine

The University of Notre Dame Australia

2019

Abstract

Background: Pulmonary hypertension (PH) is common, dangerous and has multiple causes. Vasodilator therapy has significantly improved the prognosis of patients with pulmonary arterial hypertension (PAH), but the diagnosis can be challenging, requiring right heart catheterisation (RHC). Differentiating pre-capillary PH (prePH) and post-capillary PH (postPH) and measuring pulmonary vascular resistance (PVR) are key steps for diagnosing PAH. A novel echocardiographic parameter, the pulmonary to left atrial ratio (ePLAR), which is derived from the tricuspid regurgitation velocity (TRV) divided by the ratio between the early diastolic filling velocity and the early mitral annulus velocity (E/e'), i.e., $ePLAR = TRV/E/e'$, has been described as a surrogate for RHC. This retrospective cohort study tests the ability of ePLAR to differentiate prePH and postPH, in a large real world database.

Methods: The data from all RHC performed within a 5-year period (January 2010 to February 2015) were extracted from the hospital database. The closest corresponding echocardiograms (echos) were searched in the national echo database Australia (NEDA) using the identifiers from RHC data. The performance of ePLAR in differentiating two PH physiologies was compared against the gold standard RHC using various statistical methods.

Results: 887 pairs of echos and RHCs were merged and analysed in our study. The median time difference between RHC and echocardiography was 7 (IQR 1-62) days. The ePLAR was calculable in 184 cases (21%). Median (IQR) ePLAR values were significantly different between prePH and postPH groups: 0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s ($P=0.003$), despite both groups having similar mean pulmonary artery pressures. The optimal ePLAR cut-off of 0.28m/s had a positive predictive value of 94% for postPH, with sensitivity of 83% and specificity of 67%.

Conclusions: ePLAR helps to discriminate postPH from prePH and may be useful in evaluating these patients.

List of Publications/Presentations

Publications

- 1) Naing P, Kuppusamy H, Scalia G, Hillis GS, Playford D. Non-Invasive Assessment of Pulmonary Vascular Resistance in Pulmonary Hypertension: Current Knowledge and Future Direction. *Heart Lung Circ.* 2017;26(4):323-30
- 2) Naing P, Playford D, Scalia G, Hillis GS, Strange G. Differentiating Pre-Capillary and Post-Capillary Pulmonary Hypertension by Doppler Echocardiography in a Large Real-world Database. (Original Research Article). Under review.

Presentations

- 1) Naing P, Scalia G, Hillis GS, Playford D. Performance of a novel echocardiographic marker against right heart catheterisation in identifying pulmonary hypertension due to left heart disease. mini oral presentation at the Cardiac Society of Australia and New Zealand ASM 2017.
- 2) Chung K, Strange G, Codde J, Naing P, Bulsara M, Celermajer D, Scalia G, Playford D. NEDA PH-LHD predictive model: Validation of diastolic markers of pulmonary hypertension with Right Heart Catheterisation. Oral presentation at the Cardiac Society of Australia and New Zealand ASM 2017.
- 3) Naing P, Scalia G, Hillis GS, Strange G, Codde J, Playford D. Differentiating Pre-Capillary and Post-Capillary Pulmonary Hypertension by Doppler Echocardiography in a Large Real-World Database. Poster presentation at American Society of Echocardiography (ASE) ASM 2018, 22-26 June 2018 Nashville, TN, USA

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Dr Pyi Naing

24.11.2017

Declaration and Disclosure of Contributions by Co-authors

I declare that

- This thesis is my own work and contains no material which has been accepted for the award of any other degree or diploma in any university or institution.
- The contribution by co-authors have been indicated and acknowledged.
- The permission has been granted by all the contributing co-authors of publications included in this thesis.

Author contributions

Paper 1: Non-invasive Assessment of Pulmonary Vascular Resistance in Pulmonary Hypertension: Current Knowledge and Future Direction

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Yours sincerely,

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List of Abbreviations

PVR	Pulmonary Vascular Resistance
WU	Wood Units
TPG	Transpulmonary Gradient
DPG	Diastolic Pulmonary Gradient
CO	Cardiac Output
RHC	Right Heart Catheterisation
Echo	Echocardiography
mPAP	Mean pulmonary artery pressure
PCWP	Pulmonary Capillary Wedge Pressure
ePLAR	echocardiographic Pulmonary to Left Atrial Ratio
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
TRV	Tricuspid Regurgitation Velocity
PASP	Pulmonary Artery Systolic Pressure
RVSP	Right Ventricular Systolic Pressure
PH or PHT	Pulmonary Hypertension
PAH	Pulmonary Arterial Hypertension
PH-LHD	Pulmonary Hypertension due to Left Heart Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
prePH	Pre-capillary Pulmonary Hypertension
postPH	Post-capillary Pulmonary Hypertension
TVI _{RVOT}	Time velocity integral of blood flow through right ventricular outflow tract
NEDA	National Echo Database Australia

Chapter 1. Introduction

1.1. Background

Pulmonary Hypertension (PH) is a condition where there is an abnormally high blood pressure in the pulmonary arterial system. PH can be caused by multiple pathologies ranging from genetics, left heart diseases, lung diseases, toxins, infections to thromboembolic diseases (1). The prognosis and treatment vary greatly depending on the underlying aetiology. Regardless of the underlying pathology, PH can lead to debilitating symptoms and untimely death if left untreated. The true prevalence of PH is poorly understood: however, emerging evidence suggested that it was under-reported previously (2, 3).

Although RHC is the current gold standard for confirming the diagnosis, echocardiography (echo) usually provides first objective evidence of PH. Differentiating pre- and post-capillary PH and measurement of pulmonary vascular resistance (PVR) are the key steps in evaluation of PH patients and currently the RHC is necessary. The advanced therapy or pulmonary vasodilator therapy is costly and only beneficial for patients with PH who have increased PVR. To prescribe PBS (Pharmaceutical Benefit Scheme) subsidised advanced PH therapy in Australia, it is necessary to prove low left atrial pressure represented by pulmonary capillary wedge pressure (PCWP) and elevated PVR by RHC. Unless a patient is being assessed for the heart transplant, group 2 PH patients will not benefit from routine RHC which has rare but potential serious risks. It is also now well known that PH due to left heart disease (PH-LHD) or Group 2 PH is the commonest form of PH(4, 5). With the increasing prevalence of all forms of PH, a reliable non-invasive surrogate to RHC is urgently needed to better evaluate the patients. This will lead to overall improvement in outcomes of PH patients by earlier detection of PH, avoidance of unnecessary procedures and more appropriate use of resources.

In this study, we investigated the performance the echocardiographic pulmonary to left atrial ratio (ePLAR) in differentiating the two major physiologies of PH as a surrogate to invasive haemodynamic parameters obtained with RHC. The chapter 2 of this thesis details the literature review on pathophysiology of different type of PH and various non-

invasive surrogate of PVR. The chapter 3 describes the original research work done at Royal Perth Hospital to investigate the ePLAR in differentiating pre-vs post-capillary PH.

1.2. Study Objectives

Primary Objective

In the setting of pulmonary hypertension, to measure the accuracy of ePLAR (Echocardiographic Pulmonary Artery to Left Atrial Ratio) to differentiate the two major PH physiologies, i.e., pre-and post-capillary PH.

Secondary Objectives

1. To identify other potential echocardiographic markers useful for identifying abnormal pulmonary vascular resistance (PVR) and transpulmonary gradients (TPG) in pulmonary hypertension.
2. To better understand the haemodynamic changes in patients with pulmonary hypertension caused by different pathologies.
3. To identify echocardiographic markers of increased left heart pressure in PH to facilitate diagnosis of PH-LHD

1.3. Hypotheses

Primary Hypothesis:

In the setting of pulmonary hypertension, ePLAR measurement is an accurate method of differentiating pre-and post-capillary PH

Secondary Hypothesis:

ePLAR is superior to previously published methods of estimating PVR.

Chapter 2. Literature Review (Paper 1)

Non-invasive Assessment of Pulmonary Vascular Resistance in Pulmonary Hypertension: Current Knowledge and Future Direction

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Abstract

Pulmonary Hypertension (PHT) is relatively common, dangerous and under-recognised. PHT is not a diagnosis in itself; it is caused by a number of differing diseases each with different treatments and prognoses. Therefore, timely and accurate recognition of the underlying cause for PHT is essential for appropriate management. This is especially true for patients with Pulmonary Arterial Hypertension (PAH) in the current era of disease-specific drug therapy.

Measurement of Pulmonary Vascular Resistance (PVR) helps separate pre-capillary from post-capillary PHT, and is measured with right heart catheterisation (RHC). Echocardiography has been used to derive a number of non-invasive surrogates for PVR, with varying accuracy. Ultimately, the goal of non-invasive assessment of PVR is to separate PHT due to left heart disease from PHT due to increased PVR, to help streamline investigation and subsequent treatment.

In this review, we summarise the physiology and pathophysiology of pulmonary blood flow, the various causes of pulmonary hypertension, and non-invasive surrogates for PVR.

Keywords: Pulmonary Hypertension (PHT); Doppler Echocardiography; Pulmonary Arterial Hypertension; Pulmonary Vascular Resistance (PVR); Heart Failure with Preserved Ejection Fraction (HFpEF)

Introduction

Pulmonary Hypertension (PHT), defined by a mean pulmonary artery pressure at or above 25mmHg, can be broadly differentiated physiologically into pulmonary arterial hypertension (PAH) due to increased Pulmonary Vascular Resistance (PVR), PHT due to increased pulmonary venous pressure but with a normal PVR (usually due to left heart disease), or a combination of both abnormalities. This differentiation is a crucial step in the investigation of patients with PHT, since the treatment of PHT due to left heart disease is fundamentally different from PHT due to abnormally increased pulmonary vascular resistance. Simply identifying the presence of PHT is necessary but not sufficient to manage such patients, and measurement of PVR is a key step. However, assessment of PVR usually requires right heart catheterisation (RHC), which is invasive, has potential complications, and therefore not universally performed in the investigation of PHT.

Pulmonary hypertension is relatively common and associated with a high risk of death(1), yet often goes unrecognised for extended periods. Regardless of aetiology, the common consequence of all forms of untreated PHT is symptomatic breathlessness, progressive right ventricular failure and ultimately death. With the development of effective advanced therapy for PAH, there is a need for simple non-invasive tools that can estimate PVR and help identify patients who would benefit from more comprehensive investigation, including right heart catheterisation. In this review, we will review and summarise the biochemical compounds and mechanical variables that

affect blood flow through the pulmonary vasculature. We will also summarise techniques that have been used to non-invasively estimate PVR.

Physiology of pulmonary blood flow and pulmonary vascular resistance (PVR)

Normal pulmonary circulation is low-pressure, low-resistance and highly dynamic, which allows major increases in pulmonary blood flow in response to exercise with only small increases in pressure. Pulmonary arterial blood flow regulation is maintained by pulmonary vascular resistance and recruitment of additional pulmonary capillaries, without the option of diversion through different vascular beds. This differs markedly from the systemic circulation, in which exercise results in hyperaemia in skeletal muscles, flow-mediated dilatation of conduit arteries, and dynamic changes in peripheral vascular resistance for each relevant vascular bed.

The degree of pulmonary arterial tone, via smooth muscle contraction, is governed by a series of vasoactive compounds released by the pulmonary vascular endothelium. Patients with PAH have increased level of compounds that are responsible for vasoconstriction, thrombosis and smooth muscle cell hyperplasia (2-4). Each of the compounds exerts different effects on vascular smooth muscle, endothelial cell, surrounding blood cell responses. These responses are summarised in Table 1.

Table 1: Vasoactive compounds affecting pulmonary vascular resistance and drugs for PHT targeting those compounds

Compounds	Effects	Therapeutic agents modulating these compounds
Thromboxane A ₂ (TxA ₂)	Vasoconstrictor, stimulator of platelet aggregation and proliferation	None
Prostacyclin	Vasodilator, inhibitor of platelet aggregation and has antiproliferative property (counteracts thromboxane A ₂)	Epoprostenol, Iloprost
Endothelin-1 (ET-1)	Potent vasoconstrictor and stimulator of pulmonary artery smooth muscle cells proliferation	Endothelin receptor antagonists (e.g. bosentan, macitentan)
Nitric Oxide (NO)	Vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation, counteracts endothelin-1's actions	Inhaled NO Phosphodiesterase inhibitors (e.g. Sildenafil) reduced the inactivation of cyclic guanosine monophosphate through which NO mediates its effects
Serotonin	Vasoconstrictor	No therapeutic agent available currently

Pulmonary blood flow is further regulated via capillary recruitment. In states of resting cardiac output, a number of capillary beds are in a collapsed state having neither blood perfusion nor ventilation. As the CO increases, there is an increase in the capillary blood volume resulting in recruitment of these distensible capillary beds without an increase in PVR.

Despite the responsive nature of this system, many additional factors affect pressure through the pulmonary vasculature. The Hagen-Poiseuille equation below describes the relationship between pressure, flow, viscosity and radius in a hollow, straight, non-distensible tube (5).

$$\Delta P = \frac{8\mu LQ}{\pi r^4}$$

ΔP = pressure change
 L = length of pipe
 μ = dynamic viscosity
 Q = volumetric flow rate
 r = radius

The change in pressure across the pulmonary artery is inversely proportional to the fourth power of the radius. If the radius of the pulmonary artery decreases (e.g. due to smooth muscle hypertrophy, hypoxic vasoconstriction or pulmonary thromboembolic disease), there is an accompanying disproportionate increase in the pressure across the pulmonary artery, and a higher up-stream pressure will be required in order to maintain normal down-stream pressures.

There are additional effects on pulmonary pressures from blood viscosity (e.g. hyperviscosity syndromes increase pulmonary pressures whereas anaemia decreases pulmonary pressures or increased blood flow rates (high cardiac output or valvular disease)).

Finally, the dynamics of blood flow in the left heart affect pulmonary blood flow. In a normal heart, left ventricular relaxation during diastole is an active (ATP dependent) process, causing a rapid fall in ventricular pressure and a “suction” effect on left atrial blood. This results in relative emptying of pulmonary vein blood into the left atrium, and a fall in pulmonary capillary pressure. Further, during ventricular systole, the downward motion of the mitral valve toward the ventricular apex elongates the left atrium creating a systolic “suction” effect on pulmonary vein blood. Simultaneous right ventricular systolic contraction ensures a constant supply of blood into this low pressure circuit with rapid pulmonary capillary transit. These events cause efficient systolic and diastolic pulmonary capillary blood transit. Conditions that decrease left ventricular and left atrial compliance such as chronic atrial fibrillation, the stiff left atrial syndrome(6, 7), left ventricular hypertrophy and restrictive cardiomyopathy(8), disrupt the finely balanced transit through the pulmonary circulation and increase pulmonary capillary pressures.

Measurement of pulmonary vascular resistance (PVR)

In humans in vivo, pulmonary haemodynamics are most accurately measured invasively using right heart catheterisation (RHC). The mean pulmonary artery pressure (mPAP) can be measured by averaging the pressure inside the pulmonary artery throughout the cardiac cycle. To measure the pulmonary capillary wedge pressure (PCWP), the catheter is advanced into a branch pulmonary artery, and a small balloon attached near the tip of the catheter is inflated until the pulmonary artery is occluded. The mean pressure measured at the tip of the catheter is taken to be the back-pressure from the left heart, and approximates the left atrial pressure in the absence of pulmonary vein stenosis. A

mean PCWP <15mmHg is generally accepted to indicate normal left atrial mean pressure, and is required to diagnose PAH, excluding PHT due to left heart disease(9).

The PVR is the resistance generated by the pulmonary vasculature against which the blood must travel from right to left side of the heart and is influenced by the transpulmonary gradient and the cardiac output:

$$PVR = TPG/CO$$

$$TPG = mPAP-PCWP$$

TPG – Transpulmonary gradient

mPAP – mean Pulmonary Artery Pressure in mmHg

PCWP – Pulmonary Capillary Wedge Pressure in mmHg

CO – Cardiac Output in L/min

In general, the higher the TPG and/or the lower the CO, the higher the PVR. PVR is preferred to TPG, since it takes blood flow into account (10). The equivalent measure in the systemic circulation, the systemic vascular resistance (SVR), is generated by a number of different systemic arterial vascular beds and is approximately 10 fold higher than the PVR. A normal PVR is 1-3mmHg.min/L, and decreases further with exercise and increased CO. For convenience, the mmHg.min/L units are often dropped and presented as Wood Units (WU), in honour of Earl Wood, an early pioneer in the field.

Despite its importance in PHT diagnosis and management, RHC has a number of drawbacks. It is invasive with potential serious risks such as ventricular arrhythmias, thromboembolism, myocardial or valvular injury, pulmonary infarction and rupture of a pulmonary artery. RHC requires significant skills and standardisation of the procedure, and is not universally available. Although RHC accurately measures the PCWP, it may

not reflect the true left ventricular filling pressure (11, 12), particularly if mitral stenosis (13), pulmonary vein stenosis or a noncompliant left atrium (6) is present.

Clinical Classification and Epidemiology of Pulmonary Hypertension

PHT is defined as an increased resting mPAP at or above 25mmHg, measured with RHC (9). PHT is not a disease in itself, but simply a marker of a pathophysiological abnormality that requires explanation. A clinical classification of PHT has been provided by the World Health Organisation (WHO) with several more recent updates (14). The Latest Classification (NICE 2013) classified PHT into 5 groups, summarised in Table 2.

Table 2: NICE classification of pulmonary hypertension, with abridged examples for each group.

Pulmonary Hypertension Group	Examples
Group 1 Pulmonary Arterial Hypertension	Idiopathic PAH PAH associated with other diseases: Scleroderma Congenital heart disease
Group 2 PHT due to Left Heart Disease	Myocardial disorders: Valvular heart disease Congenital LV inflow or outflow obstruction
Group 3 PHT due to Lung Disease	COPD and Interstitial lung disease Sleep disorders Chronic hypoxia
Group 4 Chronic Pulmonary Thromboembolic Disease (CTEPH)	Multiple chronic pulmonary emboli
Group 5 PHT with multifactorial cause	Haematologic disorders Chronic renal failure

The data from recent studies suggest the true prevalence of PHT in general population is higher than previously reported (15-17). We have previously reported a minimum 'indicative' prevalence for all forms of PHT at 326 cases/100 000 inhabitants of Armadale and its surrounding area in Western Australia. Left heart disease-associated PHT was the commonest cause (250 cases/100 000) and had the worst prognosis. Patient with PAH who were treated with disease specific therapy had the best prognosis (18). Moreover, there is significant delay between symptom onset and the time of diagnosis leading to poor prognoses for patients (19, 20).

Previously, patients with group 1 PHT (PAH) had worse survival than other groups. The era of advanced therapy has improved the overall prognosis of PAH patients (21) with some trials suggesting one-year survival rates of 84 percent (22). Advanced therapy includes specific pulmonary vasodilator drugs, such as Prostacyclin, endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 (PDE-5) inhibitors. These decrease the rate of progression and complications as well as improve symptoms associated with PAH, with the greatest benefits derived from early commencement of therapy.

A Proposed Pathophysiological Classification of PHT based on PVR

The latest clinical classification for pulmonary hypertension only partially reflects the underlying pathophysiology of each disease. For this reason, there is overlap in treatment between groups. An alternative method of classification is to describe the pathophysiology underpinning the PHT. Using this method, the causes of PHT can be subdivided into two major groups: pre-capillary or post-capillary based on whether the pulmonary vascular resistance is normal or increased. Pre-capillary PHT is defined by a high transpulmonary gradient of at least 12mmHg, a high pulmonary vascular resistance

of >3 WU and pulmonary capillary wedge pressures of <15 mmHg (normal left heart filling pressure). These “high PVR” pulmonary hypertension patients may respond to pulmonary vasodilator therapy, and would include individuals with Group 1 or Group 3 PHT. Some patients from groups 4 or 5 may also be included, depending on their PVR. Post-capillary pulmonary hypertension, or “normal PVR” pulmonary hypertension, is characterised by an increased PCWP of >15 mmHg but normal or low PVR(9, 10). These patients are predominantly Group 2 (left heart disease).

Some patients have a mixed picture, with PCWP due to elevated LV filling pressures, but with coexisting increased PVR. These individuals have a disproportionate rise in their pulmonary artery pressure beyond that expected from the degree of left heart disease alone. Such patients may respond only partially to diuretic therapy and treatment of their left heart disease, however the use of pulmonary vasodilator therapy in this situation is controversial(23-26).

The range of abnormalities are summarised in Figure 1 below.

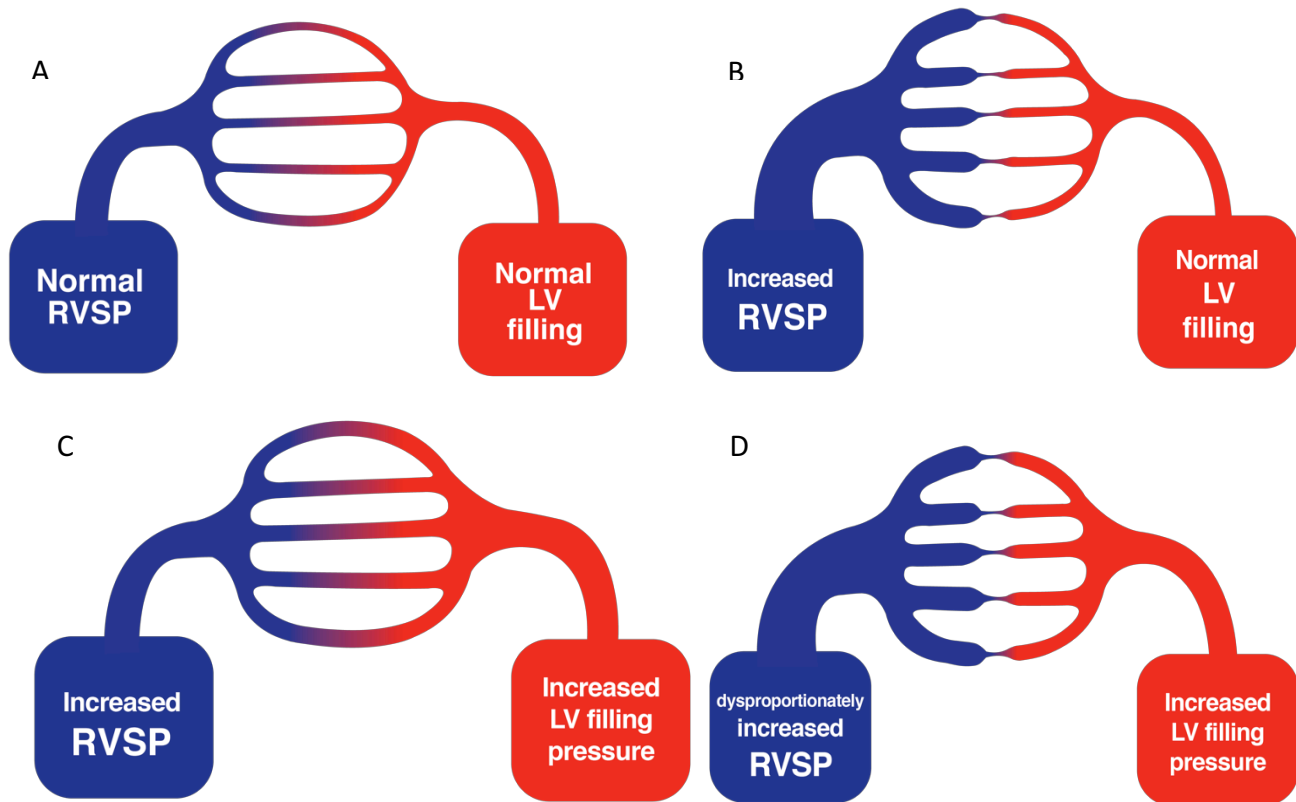


Figure 1: The range of abnormalities in PHT. Panel A shows a normal scenario with normal PVR and normal LV filling pressures. Panel B shows normal LV filling pressures but increased PVR resulting in PAH. Panel C demonstrates increased LV filling pressures with normal PVR, resulting in pulmonary hypertension due to left heart disease. Panel D shows a mixed picture, with increased LV filling pressure but a disproportionate increase in pulmonary artery pressure caused by increased PVR. PVR = Pulmonary Vascular Resistance; RVSP= right ventricular systolic pressure; LV= left ventricle.

Identifying increased PVR and/or abnormal left heart filling pressure helps guide therapy, particularly in the era of advanced therapies which target the pulmonary vasculature (27-32). Heart Failure with Preserved Ejection Fraction (HFpEF) causing PHT due to increased filling pressures should not be misclassified as PAH (33), particularly since some pulmonary vasodilator therapy in this group of patients may be harmful.

Echocardiography in Pulmonary Hypertension

Echocardiography (echo) is the most commonly used noninvasive tool for identifying PHT, and is particularly useful when screening for PHT (34). Using the velocity of tricuspid regurgitation (TRV), pulmonary artery systolic pressure (PASP) can be estimated (35-37) (Figure 2). There is a strong association between the pulmonary artery pressure (PAP) measured by right heart catheterization and that obtained by echo (18, 38).

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

Figure 2. From Apical 4 chamber view, the Tricuspid Regurgitation Velocity (TRV) is measured by using continuous wave Doppler. The pulmonary artery systolic pressure (PASP) is estimated using the modified Bernoulli equation ($\Delta P=4V^2$). P=change in pressure, V=velocity of flow(36).

Pulmonary Vascular Resistance estimation with echocardiography

A number of echocardiographic markers have been proposed for the noninvasive estimation of PVR(39-42). However, many of these markers cannot reliably separate

PHT due to left heart disease from PHT due to increased PVR. Currently, there is no single reliable method of estimating PVR non-invasively that has been tested and proven in a large-scale study.

As early as 1975, researchers have described methods to estimate PVR non-invasively. In a study by Hirschfeld et al. (39), 64 patients with congenital heart disease underwent RHCs and echo examinations. 57 patients had both examinations on the same day and 4 patients had them within one month; however, 3 patients' echoes were done 3-5 years after RHC. The ratio of right ventricular ejection time (RVET) to right ventricular pre-ejection period (RPEP) was found to correlate well with invasive measurements of pulmonary artery diastolic pressure (PADP), PVR and mPAP. The correlation coefficient of the proposed index with PVR was 0.69. The study was limited to patients with congenital heart diseases and extrapolation to PHT patients due to other etiologies may not be appropriate. Dabestani et al. examined the pulmonary artery flow velocities by Pulsed Doppler echocardiography in 39 patients and found a negative linear correlation between Pulmonary Artery acceleration time and total pulmonary resistance(43).

Scapellato, and colleagues simultaneously performed Doppler echocardiographic and RHC measurements in 63 patients with sinus rhythm and severe heart failure(40). Doppler measurements from pulmonary flow and TRV curve were correlated with invasive PVR. Among the investigated variables, the acceleration time of pulmonary systolic flow was found to have best correlation with the invasive PVR ($r=-0.68$). The correlation coefficient improved to 0.96 by using the equation:

$$PVR = -0.156 + 1.154 * [(PEP / AcT) / TT]$$

PEP = Pre-ejection period

AcT=Pulmonary acceleration time

TT= total systolic time

The principal advantages of this study were simultaneous measurement of both echo and RHC, and the relative simplicity and accuracy of their equation up to 9 WU. However, the study was small and excluded patients with atrial fibrillation and those without heart failure.

The formula described by Abbas et al. in 2003 is commonly used in echo laboratories as a noninvasive PVR assessment. They performed simultaneous echo and RHC in 44 patients (41). They found a close association ($r=0.93$, CI 0.87-0.96) between the invasively measured PVR and the ratio of the TRV to the velocity time integral of the flow through the right ventricular outflow tract (TVI_{RVOT}). Their equation approximated to the following:

$$PVR_{ECHO} = 0.16 + 10 \times TRV/TVI_{RVOT}$$

This method is easy to calculate from standard echo measurements, but the study was relatively small, did not include patients with PVR over 6WU, and did not account for left atrial pressure, an essential component of the invasively measured PVR. In subsequent analyses, the original Abbas equation was shown to underestimate invasive PVR assessment in those with PVR over 6WU(44), which could be partly corrected by incorporating assessment of LV filling pressures into the equation (using E:E' ratios). The E:E' ratio is calculated as the ratio of the early diastolic flow through the mitral valve (measured using pulsed wave Doppler echo) to the early diastolic descent velocity of the medial mitral annulus (measured using pulsed wave tissue Doppler velocities).

The E:E' ratio is commonly used as a surrogate for left ventricular filling pressure (45-47) and predicts mortality in left heart disease(48-50). Using data from five separate studies, Abbas et al. demonstrated a more robust association between PVR and TRV^2/TVI_{RVOT} (42), including patients with a PVR > 6WU. The ratio has been further validated by a similar study in post-cardiac surgery patients in an intensive care setting (51).

A further study by Haddad et al. in 2009 demonstrated that invasively measured PVR correlated well with the index of PASP to the heart rate (HR) times the TVI_{RVOT} [$PASP/(HR \times TVI_{RVOT})$] in 51 patients with established PAH (52). This method is also simple to use and the measurements required for the equation are routinely performed in most echocardiography laboratories. Small number of participants again limited this study. Additional sources of error include the need to estimate the right atrial pressure in their equation.

Table 3: Summary of echocardiographic methods for estimating PVR

Investigators and References	Surrogate Indexes/Formulae	Number of patients	Correlation coefficient (r) of surrogate index with PVR
Hirschfeld et al. (39)	RVET/ RPEP (RVET= right ventricular ejection time, RPEP =right pre-ejection period.)	64	0.69

Scapellato et al. (40)	$PVR=0.156+1.154*[(PEP/AcT) /TT]$ (PEP=Pre-ejection period, AcT=Acceleration time, TT=total systolic time of pulmonary flow.)	63	0.96
Abbas et al. (original) (41)	TRV/TVI_{RVOT} (VTR= Tricuspid Regurgitation Velocity, TVI_{RVOT} =Time Velocity Integral of the flow through the right ventricular outflow tract)	44	0.929 (95% confidence interval 0.87 to 0.96)
Abbas et al. (Analysis of raw data from 5 validation studies) (42)	TRV/TVI_{RVOT} (original) TRV^2/TVI_{RVOT} (modified)	150 patients on final analysis	0.76 0.79
Haddad et al. (50)	$PASP/(HR \times TVI_{RVOT})$	51	0.860 (95% confidence interval, 0.759-0.920)

Recently, a new echocardiographic method for estimating transpulmonary gradients has been proposed by Scalia et al (53). The ePLAR, or echocardiographic pulmonary to left atrial ratio is the ratio of peak tricuspid regurgitation velocity (a marker of pulmonary

artery systolic pressure) and E:E' ratio (a marker of left ventricular filling pressure).

$$ePLAR = \frac{TRV}{E:E'}$$

ePLAR = Echocardiographic Pulmonary to Left Atrial Ratio

TRV = Tricuspid Regurgitation Velocity

E: E' = the ratio of transmitral E-wave to septal mitral annular Doppler Tissue Imaging

E'-wave

The marker is simple, non-invasive, and uses measurements performed as part of a standard echocardiogram. For 16,356 “normal” echocardiograms without PHT, the mean ePLAR was 0.30 +/- 0.09m/s. For 133 patients with PHT, the ePLAR helped separate those with elevated PVR from those with PHT due to left heart disease: In 35 patients with pre-capillary PHT confirmed using RHC (with elevated PVR, mean 6.5+/-3.6WU), the mean ePLAR was 0.44 +/- 0.22 m/s. The ePLAR was significantly lower (0.18 +/- 0.18m/s) in those with PHT due entirely to left heart disease (81 patients, mean PVR 3.1+/-2.7WU). The major limitation of the study is non-simultaneous performance of echocardiograms and RHC. Although helpful to identify patients with elevated transpulmonary gradients, ePLAR does not take cardiac output into account.

Conclusions

PHT is common and associated with significant mortality. A rigorous approach to its diagnosis is required by every echo laboratory, starting with estimation of pulmonary artery pressure. PHT is not a diagnosis in itself, and identification of the underlying cause will determine approaches to treatment. Estimation of PVR is an important aspect of the diagnostic workup and a number of non-invasive methods for PVR measurement

have been proposed. Like their invasive counterparts, most non-invasive methods rely on a combination of pulmonary artery pressure and flow assessment; however, most studies describing these methods suffer from small sample study size, limited reliability across a broad range of patients, and do not take left atrial pressure into account. New methods such as ePLAR show promise, but require further study in large cohorts with differing forms of pulmonary hypertension.

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The literature review in the above paper highlights that there is a need for a non-invasive marker that can reliably differentiate two important PH physiologies, namely pre-capillary PH and post-capillary PH. Studies to date have been limited by small sample sizes with largest study being a meta-analysis with total of 150 patients. Instead of developing a surrogate echocardiographic marker of specific invasive measurement such as PVR, I believe developing a method of differentiating the two PH physiologies will be more useful in clinical practice. The new method should be a screening tool that can reliably identify patients who require further invasive assessment. Therefore, it should be tested in a real-world setting with large number of participants.

Chapter 3. Original Research Article (Paper 2)

Differentiating Pre-Capillary and Post-Capillary Pulmonary Hypertension by Doppler Echocardiography in a Large Real-world Database

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1. Introduction

Pulmonary hypertension (PH) is defined by mean pulmonary artery pressure (mPAP) \geq 25mmHg at rest (1, 6). It is a potentially fatal, debilitating pathology with poorly understood epidemiology (2, 7-9). The clinical classification of PH consists of 5 different groups (10) according to the underlying pathophysiology (10, 11). Management and prognoses of PH patients vary greatly depending on the underlying aetiology. The majority of PH is secondary to left heart diseases (2, 12, 13) and these patients need to be differentiated from patients with pulmonary arterial hypertension, who will benefit from modern vasodilator therapy. Right heart catheterization (RHC) can provide useful haemodynamic parameters to differentiate the underlying pathologies. However, RHC is not readily available, is operator dependent, and can be associated with potentially serious risks.

Because of the complexity in diagnosis and the low level of awareness, PAH patients are often misdiagnosed or the diagnosis is significantly delayed, leading to a worse prognosis (14, 15). The symptoms of early PAH may be subtle and non-specific. The first objective evidence of PH is usually provided by Doppler echocardiography. Pulmonary artery systolic pressure (PASP) can be estimated by applying modified Bernoulli equation to the maximal tricuspid regurgitation velocity (TRV) and adding the assumed right atrial pressure (16). A PASP of over 40mmHg is commonly used as the echocardiographic cut-off to define PH but this is non-specific and does not localise the site or mechanism of the problem. Although the former can usually be defined by RHC,

it is not feasible or appropriate for all patients with elevated estimated PASP by echo to undergo invasive investigation.

Haemodynamically, PH can be classified into pre-capillary PH (prePH) and post-capillary PH (postPH) based on the pulmonary capillary wedge pressure (PCWP) obtained by RHC (1, 6). Patients with prePH have pulmonary vascular disease manifesting as a normal PCWP (≤ 15 mmHg) and a high pulmonary vascular resistance (PVR) (> 3 Wood units, WU) (6). PostPH is characterised by a high PCWP (> 15 mmHg), usually caused by increased left heart filling pressure (e.g. systolic or diastolic heart failure). Within the PostPH group, some patients develop pulmonary vascular disease, resulting in a high PVR, causing an out-of-proportion rise in the PAP (PVR > 3 WU). Therefore, a complex picture may emerge requiring measurement of the PAP, PVR and PCWP (1, 6).

The original formula for PVR_{echo} ($TRV/TVI_{RVOT} \times 10$) was described by Abbas et al. in a study involving 44 patients (17) who had simultaneous echos and RHC. The original formula provided correlation coefficient (r) of 0.929 in the original study. However, the formula was revised to $TRV^2/TVI_{RVOT} \times 5$ in 2013 after the meta-analysis on the data of 150 patients from five validation studies. The revised formula had better correlation than the original formula ($r=0.79$ vs 0.76) to invasively measured PVR, when applied to the meta-analysis data of 150 patients (18).

The ePLAR was recently proposed as a surrogate echo marker of TPG and as a non-invasive marker of PVR in patients with PH (19). The ePLAR is a simple ratio of the

maximal velocity of tricuspid regurgitation (TRV) and the ratio of early mitral filling velocity and the mitral annular velocity (E/e'), thus the $ePLAR = TRV / (E/e')$. TRV is routinely used to estimate pulmonary artery systolic pressure (PASP) (16) and mitral E/e' is a validated marker of left atrial pressure (20-22).

2. Study Objectives

We aimed to investigate the ability of the $ePLAR$ (19), to differentiate between prePH and postPH, in a real-world database containing RHCs and echos. We also aimed to test the performance of $ePLAR$ against the previously published PVR_{echo} by Abbas et al. (17, 18, 23).

3. Methods

A retrospective cohort study was conducted at the Royal Perth Hospital, a referral centre for PH patients. Human Research Ethics Committee approvals from both the University of Notre Dame and Royal Perth Hospital were obtained. The data from all RHCs performed for various indications, between January 2010 and February 2015 was automatically extracted from the hospital database (AXIOM Sensis XP information system, version VC11D). The echos of patients in the RHC database were then extracted from the National Echo Database Australia (NEDA). The closest corresponding echo and RHC was extracted and the two databases were merged. Data analysis was performed using IBM SPSS Statistics software version 24.

The cases with calculable ePLAR were categorised into normal pulmonary pressure and PH groups using the mean pulmonary artery pressure (mPAP) values (mPAP \geq 25mmHg to define PH) from the RHC data. The PH group was further classified into prePH and postPH according to the pulmonary capillary wedge pressure (PCWP>15 to define postPH). The postPH group was further classified into in-proportion (isolated postPH) and out-of-proportion (combined pre-and postPH) using the diastolic pulmonary gradient (DPG) since pulmonary vascular resistance (PVR) was only available in a small number of cases. DPG is calculated as the difference between the diastolic pulmonary artery pressure and PCWP. DPG is less sensitive to changes in cardiac output and left atrial pressure. It has become the preferred measurement over the TPG and recommended in recent guidelines to detect the pulmonary vascular remodelling in PH-LHD(1). However, the studies that investigate the prognostic value of DPG have been showing mixed results (24-26). The TRV was recorded using continuous wave Doppler while E wave was recorded using pulsed wave Doppler. The septal e' wave by tissue Doppler was used to calculate ePLAR for consistency.

3.1. National Echo Database Australia (NEDA)

National echo database Australia (NEDA) is a large, longitudinal, non-interventional study collecting comprehensive echo measurements and text interpretation information from multiple participating echocardiography laboratories around Australia, both prospectively and retrospectively (27). NEDA is headed by 2 principal investigators and a steering committee of eminent cardiologists and researchers. It is a real-world database study aiming to take advantage of big data collection as well as increasing sophistication

of modern echocardiography practice. The linkage of NEDA with health outcome data such as national death index will provide unique ability to analyse the population data and investigate valuable echocardiographic markers that predict the risks associated with multiple cardiovascular pathologies such as pulmonary hypertension, valvular heart disease and heart failure. Currently, NEDA study has been approved in 20 large Australian Hospitals and the database is growing. It has collected the echo data from 435,122 individuals to date (28).

The vendor-neutral data extraction tool was developed by the team of NEDA engineers which can be applied to the imported data from individual echo laboratories. The imported data is then transformed into standardized database using the NEDA data dictionary, given the differing variable names with each echocardiography vendor. The NEDA data transfer and transformation process are illustrated in figure 1 and 2 in the appendix session (page 56).

4. Statistical Analysis

Continuous variables were skewed and are reported as median and interquartile range (IQR), with statistical significance assessed by Mann Whitney U test. The categorical variables are reported as number and percentages. Chi-square tests were used to compare categorical variables.

The accuracy of echocardiography to detect PH by RHC criteria ($mPAP \geq 25$ mmHg) was calculated using cross tabulation and ROC curve analyses. The sensitivity, specificity

and predictive values of various ePLAR cut-offs to detect postPH were calculated by cross tabulation and ROC curve analyses. Correlations of ePLAR to RHC variables (DPG, TPG and PVR) were also calculated using Pearson's correlation coefficient. Binominal logistic regression was used to examine the performance of ePLAR to predict postPH, in comparison with other echo variables and markers (left ventricular ejection fraction, Mitral E velocity and age). ROC curve analysis was used to compare the accuracy of ePLAR and PVRecho. The correlation between components of TPG (mPAP and PCWP) and ePLAR (TRV and E/e') were also examined by linear regression.

5. Results

During the study period, 997 RHCs were recorded on a total of 836 patients. Using identifiers from the RHC database, 887 echos on a total of 732 patients were found within the NEDA. The databases were merged into a single database for further analyses. The median time difference between the two procedures was 7 (interquartile range 1-62) days.

5.1. Agreement between Echo and RHC to diagnose PH

Pulmonary artery systolic pressure (PASP) was recorded in 73% (n=649) of echos. Fifty four percent (n=476) had pulmonary hypertension by echocardiographic criteria (PASP \geq 40mmHg). Sixty eight percent of RHC (n=601) had mPAP \geq 25mmHg. The sensitivity and specificity of echocardiography to detect pulmonary hypertension using

RHC as gold standard was 82% and 49% ($r=0.63$, $p<0.001$) using the cut-offs of $PASP\geq 40\text{mmHg}$ for echo and $mPAP\geq 25\text{mmHg}$ for RHC to define PH.

5.2. ePLAR cohort

The ePLAR could be calculated in 21% ($n=184$) of patients, of which 32% ($n=59$) did not have PH ($mPAP<25\text{mmHg}$). The median ePLAR (IQR) of these cases without PH was 0.16 (0.11-27) m/s. The breakdown on the ePLAR cohort is illustrated in figure 1. One hundred and twenty-five cases with PH ($mPAP\geq 25\text{mmHg}$) and measurable ePLAR were divided into pre-capillary ($PCWP<15\text{mmHg}$, $n=18$) and post-capillary ($PCWP\geq 15\text{mmHg}$, $n=105$) physiologies. Two RHCs had no recorded PCWP. Despite similar mPAP, prePH patients had a median ePLAR (IQR) of 0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s ($P=0.003$) for postPH patients. The comparison of demographic, RHC and echo variables between the two groups is summarized in Table 1. Similar comparison was also made for isolated postPH and combined pre-and post-capillary PH patients (table 2). The ePLAR cut-offs value of $<0.25\text{m/s}$ and $<0.28\text{m/s}$ had positive predictive values (PPV) of 93% and 94% respectively for postPH (figure 2), with reasonable sensitivity and specificity (78% and 67% for $<0.25\text{m/s}$ and 83% and 67% for $<0.28\text{m/s}$) (Appendix 3).

The correlations between the ePLAR and DPG, TPG and PVR were also examined. PVR was only calculable in 47 out of 184 cases in the ePLAR cohort due to cardiac output (CO) being infrequently measured in our database. In this subgroup, Pearson's correlation coefficients (r) of ePLAR to DPG, TPG and PVR were 0.19 ($p=0.097$), 0.02

($p=0.44$) and -0.05 ($p=0.37$) respectively (Appendix 3). Pearson's correlation coefficient (r) between TRV and mPAP was modest at 0.58 (p value = <0.001) while r between the PCWP and E/e' was weak at 0.25 ($p = < 0.001$). Binominal logistic regression was performed to test the impact of the ePLAR, left ventricular EF, mitral E velocity and age on the likelihood of individuals having postPH. Increasing ePLAR value, EF and age were associated with reduction in likelihood of postPH while increasing mitral E velocity was associated with higher likelihood of postPH. ePLAR performed better than any other covariates (regression coefficient= -6.46 , $p=0.017$) (Appendix 3).

5.3. ePLAR against PVR_{echo} in differentiating prePH and post PH

To compare ePLAR against other non-invasive echo markers used to separate postPH from prePH, we applied two commonly used formulae to our data. PVR was calculable using Abbas' formulae (17, 18) in 24% ($n=209$) of the combined echo and RHC cohort. Of these individuals 146 had a RHC that was consistent with PH ($mPAP \geq 25$ mmHg). The mean PVR_{echo} value for 33 cases with prePH was similar to that of 113 cases with postPH: 3.7 ± 2 WU vs 3.9 ± 2 WU ($p=0.67$). ROC curves confirm that ePLAR (both cut-off values of 0.25 and 0.28) is a better discriminator of postPH than the Abbas PVR_{echo} formulae (using a cut-off <3 to define postPH), figure 3.

6. Discussion

The current study confirms that the ePLAR is a useful non-invasive method to help differentiate prePH from postPH. Patients with postPH who have lower TPG and DPG

were found to have low ePLAR values, indicating the usefulness of ePLAR in highlighting patients with PH-LHD (Group 2 PH). Certainly, in the current study the clear majority of patients with PH had evidence of an isolated post-capillary mechanism and in these patients, RHCs might have been avoided if there was a well validated non-invasive surrogate to RHC – such as ePLAR. On the other hand, PH patients with higher ePLAR have prePH physiology (higher TPG and DPG) and they may require further testing including RHC to further clarify the underlying pathologies.

The main strength of ePLAR is its simplicity. Its calculation only requires two Doppler variables (TRV and E/e') which are easily measurable. It should not take extra time or effort for one to measure ePLAR while performing a routine echocardiography. Instead of using pulmonary artery systolic pressure estimation which requires the estimation of right atrial pressure which can be a further source of error, the formula uses TRV on its own. The correlation between E/e' ratio and left atrial pressure has also been well validated in previous studies, even in the presence of atrial fibrillation(22, 29, 30). In theory, the ratio between the pulmonary pressure represented by TRV to left atrial pressure represented by E/e' should correlate well with transpulmonary gradient (TPG) which is calculated as the mean pulmonary artery pressure minus the pulmonary capillary wedge pressure (PCWP) representing the left atrial pressure. Although the calculation of ePLAR does not include a measurement that represents blood flow or cardiac output, it performed better than the commonly used PVR_{echo} formulae in differentiating two major PH physiologies.

6.1. Prior Studies

Previous investigators had examined a variety of non-invasive surrogate markers of PVR (17, 18, 23) to differentiate the underlying aetiologies of PH. Some of these markers have been validated in subsequent studies and proved to be useful; however, most of these studies had small sample sizes. A combined clinical and echo risk scoring system was also proposed to identify PH-LHD and reduce the number of unnecessary RHCs (31). In its foundation study involving 133 PH patients who had RHC, ePLAR was found to have good accuracy in differentiating prePH and postPH (19).

6.2. Strengths and limitations

The data for this study were extracted automatically from large databases, minimising the risk of any human error. In addition, our study has the advantage of testing the usefulness of the ePLAR in a 'real-world' dataset. Our study is also larger than previous studies despite the low percentage of patients with calculable ePLAR. It does, however, also have some limitations. The most important of these is that the RHC and echo data were not acquired simultaneously. This may explain the modest correlation between the two modalities in terms of defining PH, though previous data have shown similar associations even during simultaneous measurements (32). Although ePLAR has provided a good discriminatory power between two PH physiologies, its accuracy needs further improvement. In the current study, the optimal ePLAR cut-off of <0.28 gives sensitivity of 83% which means there are still considerable chance of having false negative test results. To be clinically useful as a non-invasive tool, ePLAR should have very high sensitivity and low false negative rate, given the dire consequence of missing

PAH patients which has proven specific therapy.

Another inherent weakness of the ePLAR, as well as the PVR_{echo} formulae, is that both require measurement of TRV which cannot be accurately estimated in some patients. The TRV was not available in 45% of echos in our study in keeping with previous data suggesting that approximately 1 in 3 echos do not have evaluable TR velocities (2). Although we lacked clinical data in our study, the primary purpose was to compare invasive and non-invasive methods of estimating pulmonary vascular resistance rather than diagnosing the final cause of pulmonary hypertension. Moreover, cardiac output was infrequently measured during RHC and subsequently PVR_{RHC} was not calculable in most of the patients in the database. Only 4 % (n=35) of cases have both measurable PVR_{echo} and PVR_{RHC} . Furthermore, some components of ePLAR and PVR_{echo} were either not routinely measured or recorded in our database; contrary to our expectation.

Despite these limitations, ePLAR appears to be a useful non-invasive tool to help differentiate prePH from postPH. A prospective study, involving simultaneous measurements of echo and RHC parameters, in a group of patients with different haemodynamic classes of PH, is needed to further investigate the performance of ePLAR. This will also increase the percentages of studied subject with calculable ePLAR.

7. Conclusions

We have investigated the performance and feasibility of ePLAR in a large single centre, real world database containing RHC and echo data. Although ePLAR was only

calculable in 21% of the cohort, it provided good discriminatory power between pre-and postPH, and was superior in this respect to previous echocardiographic formulae. Further work is required to validate the discriminatory potential of the ePLAR prospectively and to clarify its ability to identify those individuals who will benefit from RHC and potentially from disease specific therapy.

Figure 1. ePLAR flow chart

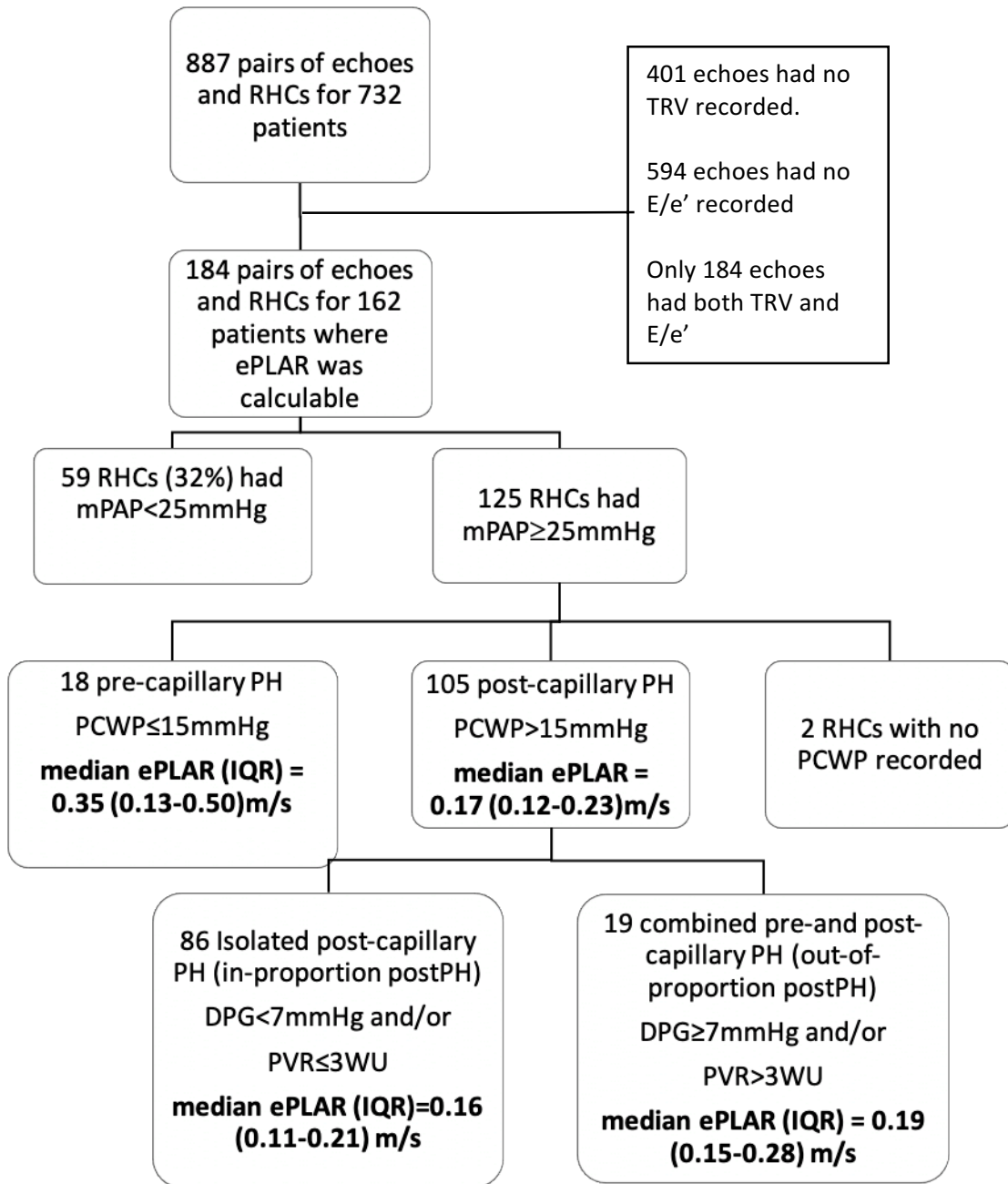


Table 1. Comparison of demographic, RHC and echo variables between the pre- and post-capillary pulmonary hypertension patients in whom ePLAR can be calculated.

Variable	Pre-capillary PH		Post-capillary PH		P value
	N	Median (IQR)	N	Median (IQR)	
Age (years)	18	70 (54-86)	105	71 (51-84)	0.983
Female (percentage)	18	61%	105	44%	0.17 [#]
BMI (kg/m ²)	16	23 (21-27)	67	26 (24-31)	0.014
Mean pulmonary artery pressure (mmHg)	18	35 (28-48)	105	36 (30-43)	0.912
Pulmonary capillary wedge pressure (mmHg)	18	13 (9-14)	105	22 (18-29)	0.000
Diastolic Pulmonary Gradient (mmHg)	18	10 (4-17)	105	1 (-3-4)	0.000
Transpulmonary gradient (mmHg)	18	21 (16-37)	105	11 (8-17)	0.000
Cardiac output (L/min)	4	4.6 (4.3-5.4)	24	4.0 (3.1-4.9)	0.211
Pulmonary vascular resistant (WU)	4	6.4 (4.8-7.1)	24	8.6 (6.6-10.5)	0.057
Ejection Fraction (%)	18	68 (61-73)	100	51 (34-64)	0.000
Mitral E:A	16	0.9 (0.7-1.2)	79	1.7 (0.8-2.9)	0.011
LA volume (indexed) (cm ³)	3	29 (27-.)	31	57 (43-71)	0.008
Tricuspid Regurgitation Velocity (m/s)	18	3.5 (2.9-4.2)	105	3.2 (2.8-3.5)	0.035
Mitral E/e'	18	10 (9-22)	105	19 (14-27)	0.004
ePLAR (m/s)	18	0.35 (0.13-0.50)	105	0.17 (0.12-0.23)	0.003
Abbas' original PVR _{echo} (WU)	14	2.6 (1.9-3.8)	52	3.2 (2.5-4.9) (n=52)	0.147
Abbas' sharpened PVR _{echo} (WU)	14	5.4 (2.9-7.7)	52	4.9 (3.5-8.8) (n=52)	0.556

[#] p value obtained by Pearson chi-square test

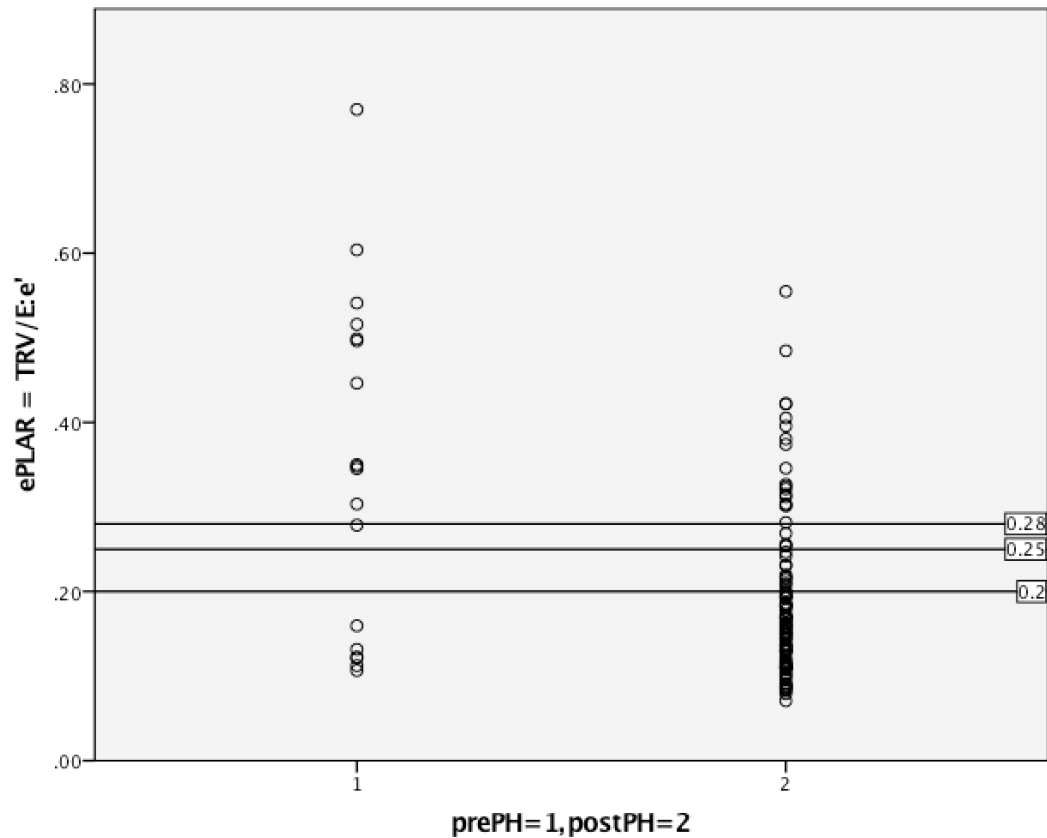
IQR= interquartile range, ePLAR= echocardiographic pulmonary to left atrial ratio, N= number of patients

Table 2. Comparison of demographic, RHC and echo variables between the isolated post capillary and combined pre-and post-capillary pulmonary hypertension patients in whom ePLAR can be calculated.

Variable	Isolated postPH		Combined pre-and postPH		P value
	N	Median (IQR)	N	Median (IQR)	
Age (years)	86	72 (51-84)	19	64 (51-83)	0.641
BMI (kg/m ²)	56	26 (23-31)	11	30 (26-31)	0.134
Mean pulmonary artery pressure (mmHg)	86	33 (29-41)	19	42 (37-49)	0.000
Pulmonary capillary wedge pressure (mmHg)	86	24 (19-29)	19	18 (17-22)	0.001
Diastolic Pulmonary Gradient (mmHg)	86	0 (-4-3)	19	10 (9-16)	0.000
Transpulmonary gradient (mmHg)	86	10 (7-13)	19	22 (17-31)	0.000
Cardiac output (L/min)	21	4.0 (3.1-5)	3	4.5 (3.1-.)	0.793
Pulmonary vascular resistant (WU)	21	8.3 (6.3-10.2)	3	10.2 (7.1-.)	0.359
Ejection Fraction (%)	81	50 (30-63)	19	58 (36-69)	0.098
Mitral E:A	61	1.7 (0.9-3)	18	1.1 (0.7-2.6)	0.183
LA volume (indexed) (cm ³)	27	57 (45-71)	4	44 (32-66)	0.239
Tricuspid Regurgitation Velocity (m/s)	86	3.1 (2.7-3.4)	19	3.8 (3.1-4.1)	0.009
Mitral E/e'	86	19 (15-28)	19	19 (13-22)	0.312
ePLAR (m/s)	86	0.16 (0.11-0.21)	19	0.19 (0.15-0.28)	0.042
Abbas' original PVR _{echo} (WU)	41	3.0 (2.4-5.2)	11	3.9 (3.1-4.6)	0.226
Abbas' sharpened PVR _{echo} (WU)	41	4.3 (3.4-8.7)	11	7.1 (4.1-9.1)	0.165

IQR= interquartile range, ePLAR= echocardiographic pulmonary to left atrial ratio, N= number of patients

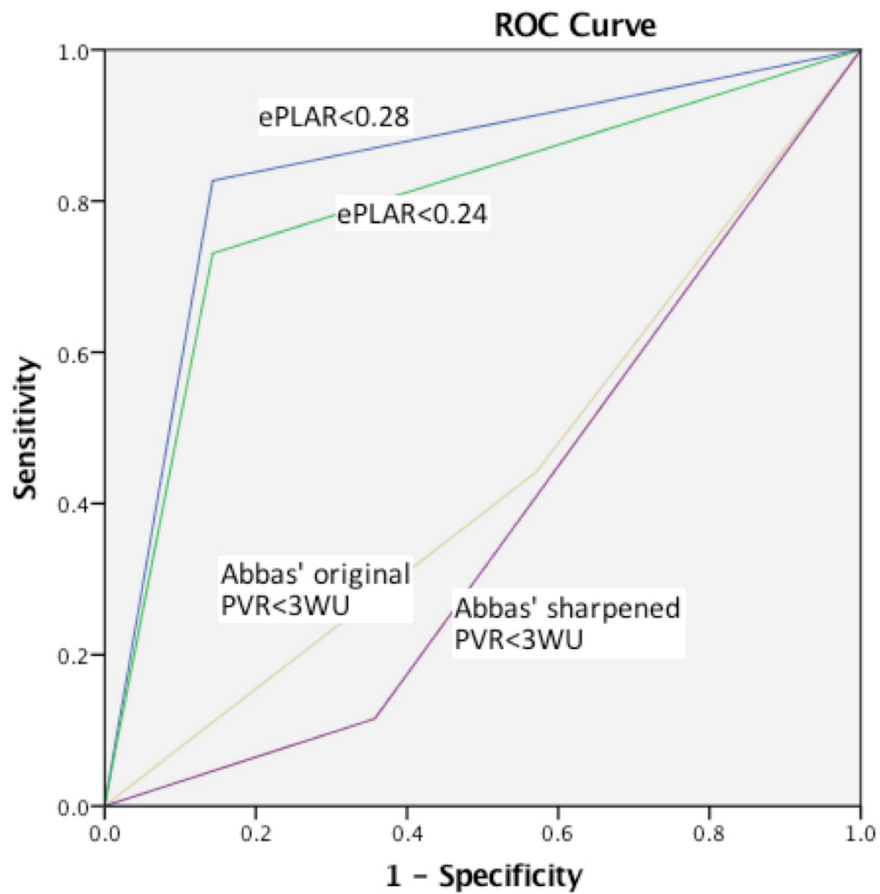
Figure 2. Scatter plot showing distribution of ePLAR values in two major physiology groups: pre-capillary PH and post-capillary PH, with the table showing sensitivity, specificity and predictive values of each ePLAR cut-off to predict postPH



ePLAR value	Sensitivity	Specificity	PPV	NPV
0.20	67%	67%	92%	25%
0.25	78%	67%	93%	34%
0.28	83%	67%	94%	40%
0.30	84%	61%	93%	40%

PPV= positive predictive value, NPV=negative predictive value

Figure 3. ROC analysis on 2 different ePLAR cut-offs compared with PVRecho formulae by Abbas et al. to detect post capillary PH



Area Under the Curve

Test Result Variable(s)	Area
ePLAR < 0.28	.842
ePLAR < 0.24	.794
Abbas' original < 3WU	.435
Abbas' sharpened < 3WU	.379

Chapter 4. Summary, Key Findings, Recommendations and Future Directions

4.1. Summary

This thesis is written to contribute to the body of knowledge in managing patients with PH which is a serious and common health problem (2). In the chapter 2, the pathophysiology of PH, its classification and underlying aetiologies were described in detail. Among the 5 PH groups as per the 2013 Nice Classification(10), group 1 or pulmonary arterial hypertension (PAH) has the specific advanced therapy targeting at pulmonary vasculature. The prognosis of PAH patients has much improved because of this advanced therapy. However, there is no evidence that the advanced therapy is beneficial for PH patients due to other causes such as left heart (group 2) and lung diseases (group 3) (1). Multiple studies have suggested that PH-LHD (pulmonary hypertension due to left heart disease) is the most common cause (2, 13). Systolic or diastolic left ventricular failure and left sided valvular diseases can lead to PH-LHD. Owing to the aging population and higher prevalence of risk factors such as diabetes and hypertension in the general population, the prevalence of HFpEF has increased dramatically. PH due to HFpEF is a particularly challenging diagnosis as the left ventricular diastolic dysfunction may not be easily recognised. It is estimated that around 50% of HFpEF patients will develop PH (33). In a cross-sectional survey of 2042 randomly selected residents older than 45 years in Minnesota between 1997 to 2000, 20.8%, 6.6% and 0.7% of population had mild, moderate and severe diastolic dysfunction (34). Even in the absence of clinical syndrome of congestive heart failure, the moderate and severe diastolic dysfunction were associated with significant increase in all-cause mortality in this study.

The physiology of pulmonary circulation and the concept of PVR were also explained in chapter 2. The PVR is an important parameter which can determine the underlying pathophysiology of PH and RHC is the gold standard method to measure it. It is calculated as transpulmonary gradient (TPG) divided by the cardiac output (CO). TPG is the pressure difference between the mean pulmonary arterial pressure and left atrial pressure represented by PCWP (pulmonary capillary wedge pressure). The importance

of differentiating prePH (pre-capillary PH) vs postPH (post-capillary PH) by measuring PCWP and PVR using right heart catheterisation (RHC) was discussed. The risks and limitations of RHC (right heart catheterisation) were also discussed. I also described how important it is for PH patients to get correct diagnosis early in their disease process for better outcomes. The prePH patients have higher TPG and PVR ($PVR > 3WU$) while postPH patients have elevated left heart pressure (PCWP) and low TPG and PVR. The PAH (pulmonary arterial hypertension) is a relatively rare form of PH where the specific advanced therapy is indicated. The advanced therapy includes vasodilators targeting the pulmonary vasculature such as endothelin receptor antagonists (e.g. macitentan, bosentan and ambrisentan) and phosphodiesterase type 5 inhibitors (e.g. sildenafil and tadalafil). The diagnosis of PAH requires the presence of prePH which is defined as $PCWP \leq 15\text{mmHg}$ and $PVR > 3WU$ in the absence of other causes of prePH (e.g. PH due to lung diseases, CTEPH (chronic thromboembolic PH) or other rare diseases (35). The postPH is mainly secondary to left heart diseases such as systolic and diastolic left ventricular failure and left sided valvular heart diseases (aortic and mitral). The management of postPH should be focused on correcting the underlying left heart diseases and advanced therapy or PAH approved therapy is not indicated.

It is not only impossible to do RHC in all PH patients but also such an approach is not necessary. A reliable echocardiographic marker which can differentiate different physiologies of PH is needed to improve PH evaluation. This will reduce the number of unnecessary RHC and will improve the utilisation of available resources by better selection of patients who require invasive tests. Researchers worldwide have been investigating for an ideal non-invasive way of estimating PVR with varying success as we described in the chapter 2. The original PVR_{echo} formula was described by Abbas et al in 2003 and it has been modified and improved by multiple researchers(36). The ePLAR (echocardiographic pulmonary to left atrial ratio) was introduced as a non-invasive surrogate of TPG (transpulmonary gradient) and its ability to differentiate between prePH and postPH was demonstrated in its pilot study involving 133 patients with PH(19). There were also studies investigating combined clinical and non-invasive investigations to identify left heart diseases among patients suspicious for PAH(31).

4.2. Key findings

Chapter 3 describes the current research in detail. This is a large real-world, single centre retrospective study involving 887 pairs of echos and RHCs. The data were automatically extracted from 2 data-bases (echo and RHC) minimising the humans error of manual data collection. The main finding was that the ePLAR provided good discriminatory power between prePH and postPH when compared with the current gold standard, RHC. There was a statistically significant difference in median ePLAR (IQR) values between prePH and postPH patients (0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s (P=0.003). It also performed better than previously published PVR_{echo} formulae(17, 18) in predicting the increased left atrial pressure (PCWP). The binomial logistic regression showed that ePLAR performed better than ejection fraction, age and mitral E velocity in predicting patients with postPH. The diastolic pulmonary gradient (DPG) has emerged as preferred marker to differentiate isolated post-capillary PH and combined pre-and post-capillary PH (1, 24). Therefore, DPG was used in our study to differentiate between the two groups in our study. The study also confirmed that the isolated post-capillary PH is the dominant physiology among patients who presented for RHC. In general, these patients will not benefit from the vasodilator therapy and RHC may not be necessary unless the patients were being worked up for heart transplant.

4.3. Recommendations and Future Directions

I do not believe that ePLAR or any other non-invasive surrogates of PVR will replace the role of RHC completely. RHC will still be the gold standard to confirm the diagnosis and to exclude significant elevation of left heart pressure (PCWP>15mmHg) in patients with PAH. However, in majority of PH patients, ePLAR may be a useful adjunct tool to other echo parameters in selecting appropriate patients who require invasive tests to further clarify the diagnosis. Development and validation of such a marker will be very useful in PH management and will lead to better resource management and early diagnosis for many patients.

Being a retrospective study, the study had inherent weaknesses such as incomplete data set and limited clinical information. These weaknesses limited our ability to investigate the accuracy of ePLAR to estimate the invasive PVR. Non-simultaneous performance of the RHC and echo for studied patients is also another limitation as the pressure measurements by both tests are dependent upon multiple factors such as fluid volume status and heart rate which are very dynamic in nature. A prospective study involving simultaneous echo and RHC in PH patients with different underlying aetiologies would be an ideal future study. A similar large retrospective study which includes comprehensive clinical information will also be a very useful study. There is also a possibility of further improving the ePLAR formula by including a surrogate for the cardiac output such as TVI_{RVOT} (time velocity integral of blood flow through the right ventricular outflow tract) and testing it in the current data set or in a future prospective study.

Appendices

1. Conference Presentations

i. Performance of a novel echocardiographic marker against right heart catheterization in identifying pulmonary hypertension due to left heart disease (mini-oral presentation at CSANZ 2017)

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Hypothesis/Aims

- Right heart catheterization (RHC) is the current gold standard for evaluation of patients with pulmonary hypertension (PH); however, it is invasive, not suitable for all patients, and has associated risk.
- We aimed to investigate the feasibility and performance of echocardiographic Pulmonary to Left Atrial Ratio (ePLAR) to differentiate between the two major physiologies (pre-capillary PH and post-capillary PH) in a large real-world database containing RHCs and echocardiograms.
- $ePLAR = TRV/E/e'$
 - ePLAR = Echocardiographic Pulmonary to Left Atrial Ratio
 - TRV = Tricuspid Regurgitation Velocity (m/s)
 - E/e' = Ratio of early mitral inflow velocity to early basal septal relaxation velocity using tissue Doppler

Methods

- A retrospective cohort study was conducted at the Royal Perth Hospital, a tertiary referral centre for PH patients.
- RHC data from hospital database and echo data from National Echo Database Australia (NEDA) were collected and merged.

Results

Variables	Pre-capillary PH (n=18)	Post-capillary PH (n=105)	p values
Mean age (SD)	67 (20) years	67 (20) years	0.99*
Females (%)	61%	44%	0.17 [#]
mPAP, mean (SD)	37 (10) mmHg	37 (9) mmHg	0.94*
PCWP, mean (SD)	12 (3) mmHg	24 (7) mmHg	<0.001*
DPG, mean (SD)	11 (8) mmHg	1 (7) mmHg	<0.001*
Ejection Fraction, mean (SD)	64 (14) % (n=18)	48 (20) % (n=100)	<0.001*
TRV, mean (SD)	3.6 (0.7) m/s	3.2 (0.6) m/s	0.01*

Mitral E/e', mean (SD)	14 (7)	20 (9)	0.004*
ePLAR, mean (SD)	0.35 (0.2) m/s	0.19 (0.1) m/s	0.004*
Abbas PVR_{echo} (original), mean (SD)	3.24 (2.2) WU (n=14)	3.92 (2) WU (n=52)	0.29*
Abbas PVR_{echo} (sharpened), mean (SD)	6.66 (5.9) WU (n=14)	6.49 (3.89) WU (n=52)	0.9*

Summary & Conclusions

- ePLAR provides good discriminatory power between pre-and post-capillary PH (0.35±0.2m/s vs 0.19±0.1m/s, P=0.004).
- ePLAR performs superiorly to non-invasive PVR assessment in predicting elevated wedge pressures.
- ePLAR cut-off of <0.28m/s provided the excellent positive predictive value of 94% for post capillary PH while maintaining good sensitivity of 83% and specificity of 67%. It also provided the best AUC on the ROC curve analysis.

ii. NEDA PH-LHD predictive model: Validation of diastolic markers of pulmonary hypertension with Right Heart Catheterisation (Oral Presentation at CSANZ 2017)



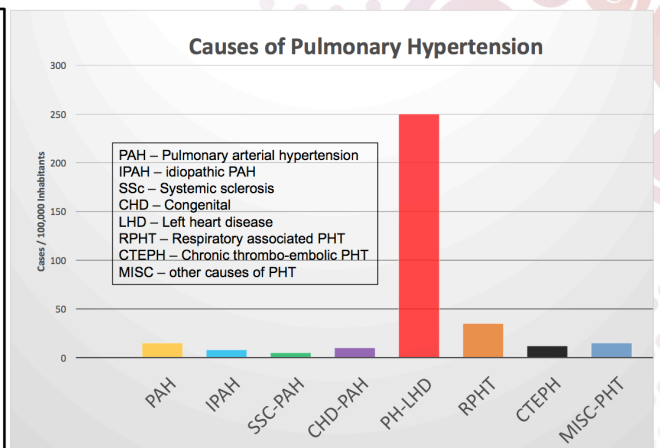
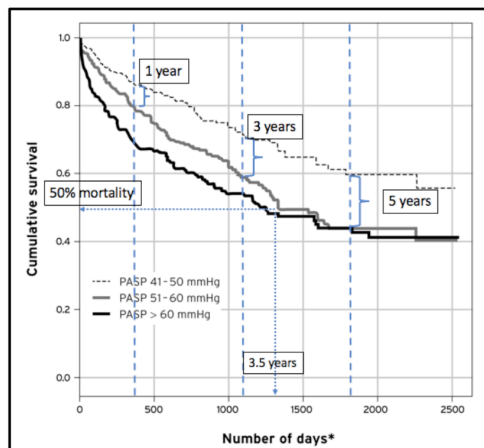
NEDA PH-LHD predictive model: Validation of diastolic markers of pulmonary hypertension with Right Heart Catheterisation

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Most PH is due to left heart disease

More severe disease leads to worse prognosis



1) Strange et. al 2012

Objectives

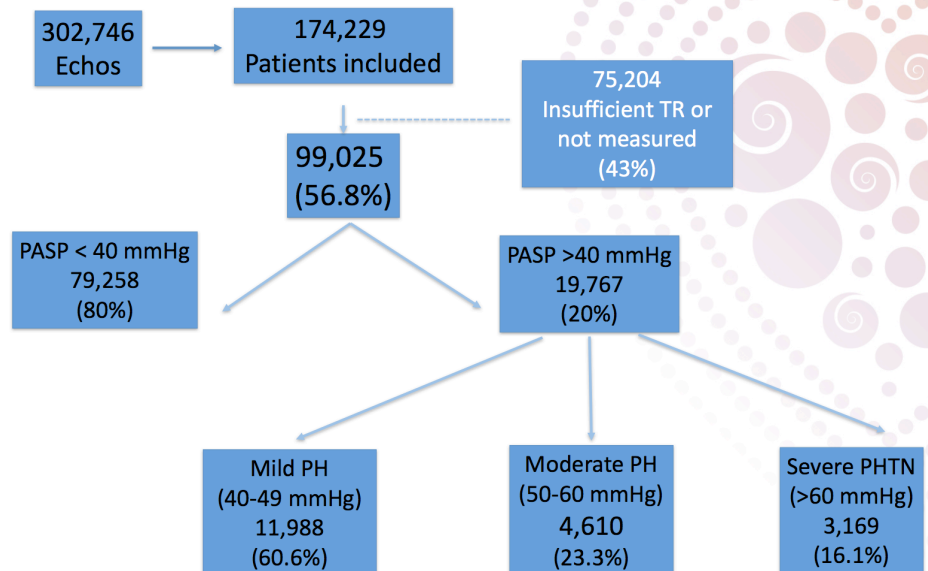
- To create a predictive model using diastolic echo markers to diagnose PH, even in the absence of a measurable TR velocity.
- To validate the predictive value of our PH-LDH model in patients undergoing RHC.

Methods



- 305 variables and 2.4 million data points
- Enrollment eligibility
 - 307,843 echo studies from the NEDA cohort
- Exclusion criteria:
 - <18 year at time of echo, invalid DOB or invalid date of echo, congenital heart disease (5,097 echos)
- RHC cohort of 887 patients with a recent echo from Royal Perth Hospital, WA (Naing et al., 2017)

NEDA population: PH is present in >20% of patients

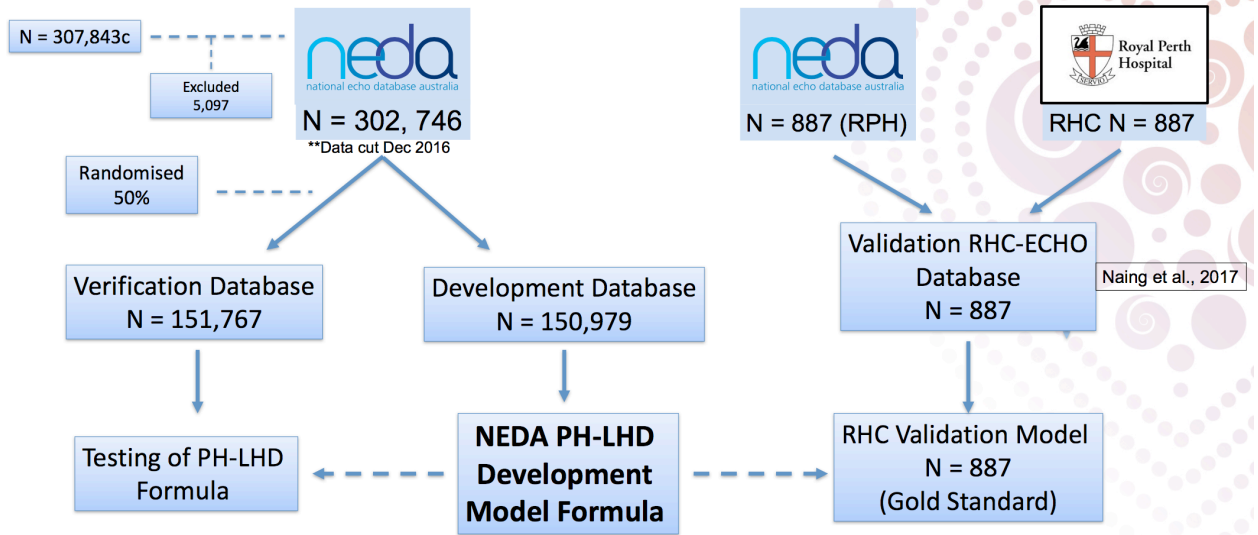


NEDA cohort: Predictors of PH from LHD

N=99,025	PASP <40mmHg (mean +/- SD)	PASP > 40mmHg (mean +/- SD)	P-value
Age (years)	62 (17)	76 (12)	< 0.00000001
PASP (mmHg)	29 (6)	51 (11)	< 0.00000001
E' septal velocity (cm/s)	8.2 (3.0)	6.7 (2.6)	< 0.00000001
E:E' ratio	10.7 (5.0)	16.7 (8.3)	< 0.00000001
E:A ratio	1.2 (0.6)	1.3 (0.8)	< 0.00000001
Left atrial volume indexed to BSA (mL/m ²)	33 (13)	46 (20)	< 0.00000001
Ejection fraction (%)	63 (8)	59 (14)	< 0.00000001

Largest effect size = Left Atrial Volume Index ($\omega^2 = 0.32$) ** large effect size >0.14

Workflow Diagram - NEDA PH-LDH model



Baseline Echo Characteristics – NEDA and RHC cohorts

Characteristics	Development Database N = 150,979 Mean (SD)	Verification Database N = 151,767 Mean (SD)	Validation RHC Database N = 887 Mean (SD)
Age (years)	63 (16)	63 (16)	68 (19)
PASP (mmHg)	34 (12)	34 (11)	47 (20)
E' septal velocity	7.9 (2.9)	7.8 (2.9)	5.5 (2.2)
E:E' ratio	11.6 (6.0)	11.6 (6.0)	19 (9.1)
E:A ratio	1.1 (0.6)	1.1 (0.6)	1.4 (0.9)
Left atrial volume index (mL/m ²)	35 (16)	34 (16)	50 (22)
Ejection fraction (%)	62 (10)	62 (10)	52 (20)

P = NS

NEDA cohort - Development Model Logistic Regression

N = 5,181	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' Velocity	.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		

NEDA cohort – PH-LHD prediction equation

Predictive NEDA PH-LHD Constant (Con) = $-6.649 + (0.035 \times \text{Age}) + (0.072 \times \text{E}') + (0.077 \times \text{E/E}') + (0.509 \times \text{E/A}) + (0.03 \times \text{LAVI})$

Probability of PH-LHD = $\text{EXP}(\text{Con}) / [1 + \text{EXP}(\text{Con})]$

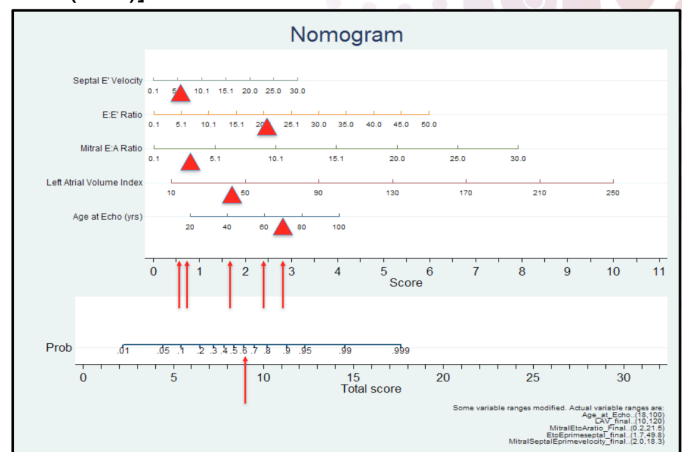
Clinical Scenario

Age = 70 yo
 E' = 5
 E/E' = 20
 E/A = 2.5
 LAVI = 40

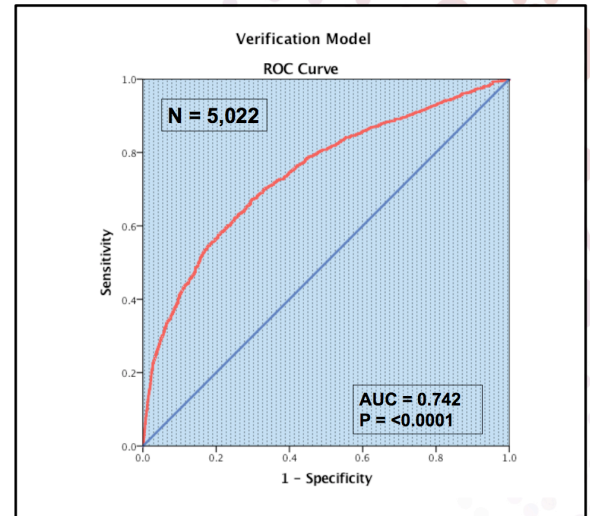
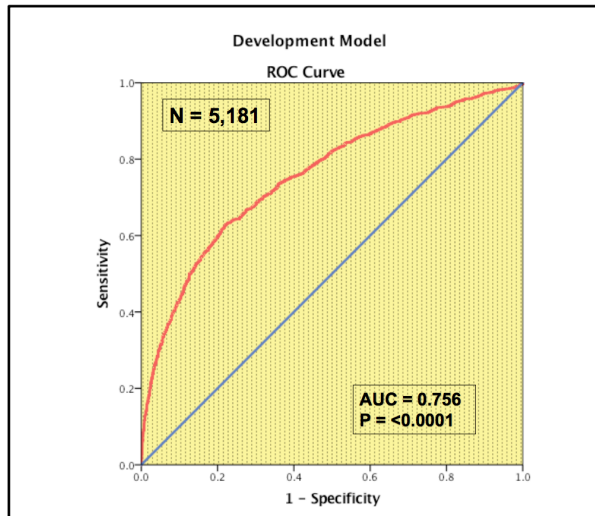
Score = 9

Probability of PH = 60%

TR is not required for PH-LHD prediction

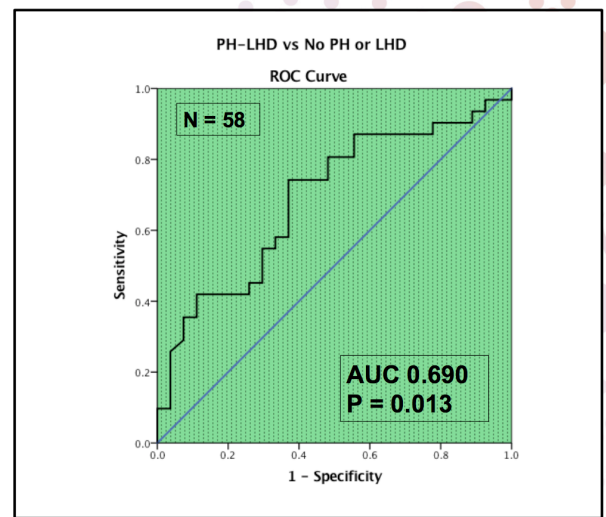
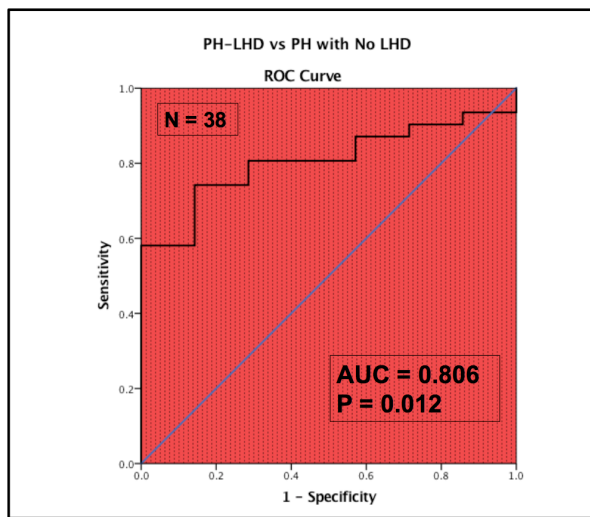


NEDA PH-LHD formula is well validated



	PH-LHD (N = 518) mPAP ≥25mmHg PCWP ≥15mmHg Mean +/- (SD)	PH with no LHD (N = 76) mPAP ≥25mmHg PCWP <15mmHg Mean +/- (SD)	P Value	No PH or LHD (N = 368) mPAP <25mmHg PCWP <15mmHg Mean +/- (SD)	P Value
Age (years)	69 (19)	65 (20)	0.10	67 (19)	0.331
mPAP (mmHg)	37.8 (10)	38.4 (12)	0.61	23.6 (11)	<0.0001
PCWP (mmHg)	24.8 (7)	10.8 (3)	<0.0001	12.2 (5)	<0.0001
PVR (WU)	3.25 (2)	3.81 (2)	0.321	2.03 (1.5)	<0.0001
TPG (mmHg)	13 (8)	28 (13)	<0.0001	10.8 (11)	0.002
DPG (mmHg)	1.1 (7.6)	13.4 (9.5)	<0.0001	2.86 (8)	0.001
ePASP (mmHg)	55 (17)	70 (22)	<0.0001	50 (20)	<0.002
E/A ratio	1.7 (1.1)	1.1 (0.6)	0.001	1.1 (0.6)	<0.0001
E' velocity (cm/s)	5.3 (2.4)	6 (1.8)	0.164	5.7 (2)	0.240
E/e' ratio	21 (10)	14 (7)	0.001	17 (8)	<0.0001
Left atrial volume index (mL/m ²)	54 (21)	49 (28)	0.339	43 (22)	0.004

NEDA PH-LHD formula can predict PH-LHD with 80% accuracy



Discussion

- Patients with LHD are a heterogeneous group
- Our model does not establish causality
- Patients with left heart disease have a worse prognosis if they develop pulmonary hypertension
- Up to 40% of patients may have undiagnosed pulmonary hypertension
- Atrial fibrillation

Conclusion

- Using Age, E', E/e' ratio, E/A ratio and LAVI we have developed the NEDA PH-LHD formula that is 80% accurate when compared to RHC (Gold Standard)
- This tool is simple to use and can be applied to any echo exam in patients who are suspected of having PH-LHD but do not have measureable TR
- This should prompt further investigation, early diagnosis and initiation of disease specific treatment

The above abstract presented at the CSANZ ASM 2017 used our data to validate the NEDA PH-LHD prediction formula. Our data formed important part of the development of this formula as right heart catheterisation remains the gold standard in PH evaluation. This abstract fulfilled the secondary objective of the thesis: identification of echo markers of increased left heart pressure in the setting of PH, i.e., PH-LHD.

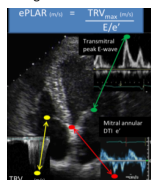
iii. Poster Presentation at ASE 2018, June 2018 in Nashville, USA

 Differentiating Pre-Capillary and Post-Capillary Pulmonary Hypertension by Doppler Echocardiography in a Large Real-world Database 

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 neoda national echo database australia

Background: Pulmonary hypertension (PH) is common, dangerous and has multiple causes. Vasodilator therapy has significantly improved the prognosis of patients with pulmonary arterial hypertension (PAH), but the diagnosis can be challenging, requiring right heart catheterisation (RHC). Differentiating pre-capillary PH (prePH) and post-capillary PH (postPH) and measuring pulmonary vascular resistance (PVR) are key steps for diagnosing PAH. A novel echocardiographic parameter, the pulmonary to left atrial ratio (ePLAR), which is derived from the tricuspid regurgitation velocity (TRV) divided by the ratio between the early diastolic filling velocity and the early mitral annulus velocity (E/e'), i.e., $ePLAR = TRV/E/e'$, has been described as a surrogate for RHC. This retrospective cohort study tests the ability of ePLAR to differentiate prePH and postPH, in a large real world database.

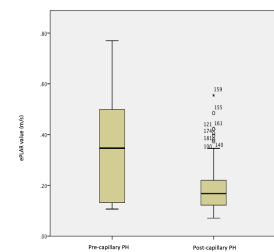


The figure depicting how ePLAR is calculated using the Doppler echocardiography

Results: 887 pairs of echos and RHCs were merged and analysed in our study. The median time difference between RHC and echocardiography was 7 (IQR 1-62) days. The ePLAR was calculable in 184 cases (21%). Median (IQR) ePLAR values were significantly different between prePH and postPH groups: 0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s (P=0.003), despite both groups having similar mean pulmonary artery pressures. The optimal ePLAR cut-off of 0.28m/s had a positive predictive value of 94% for postPH, with sensitivity of 83% and specificity of 67%.

Variables	Pre-capillary PH		Post-capillary PH		P value
	N	Median (IQR)	N	Median (IQR)	
Age (years)	18	70 (54-86)	105	71 (51-84)	0.983
Female (percentage)	18	61%	105	44%	0.17
mPAP (mmHg)	18	35 (28-48)	105	36 (30-43)	0.912
PCWP (mmHg)	18	13 (9-14)	105	22 (18-29)	0.000
DPG (mmHg)	18	10 (4-17)	105	1 (-3-4)	0.000
TPG (mmHg)	18	21 (16-37)	105	11 (8-17)	0.000
Cardiac output (L/min)	4	4.6 (4.3-5.4)	24	4.0 (3.1-4.9)	0.211
PVR (WU)	4	6.4 (4.8-7.1)	24	8.6 (6.6-10.5)	0.057
Ejection Fraction (%)	18	68 (61-73)	100	51 (34-64)	0.000
LAVI (cm ³)	3	29 (27-N/A)	31	57 (43-71)	0.008
TRV _{mitr} (m/s)	18	3.5 (2.9-4.2)	105	3.2 (2.8-3.5)	0.035
Mitral E/e'	18	10 (9-22)	105	19 (14-27)	0.004
ePLAR (m/s)	18	0.35 (0.13-0.50)	105	0.17 (0.12-0.23)	0.003

The table comparing demographic, RHC and echo variables between the pre-and post-capillary pulmonary hypertension patients in whom ePLAR can be calculated. mPAP= mean pulmonary artery pressure; PCWP= pulmonary capillary wedge pressure; PVR= Pulmonary Vascular Resistance; DPG= diastolic pulmonary gradient; TPG= transpulmonary gradient, LAVI= left atrial volume indexed



Graphical comparison of distribution of median ePLAR values, IQR, highest and lowest values and outliers between the two PH groups

Conclusions: ePLAR helps to discriminate postPH from prePH and may be useful in evaluating these patients.

Reference: Scalia GM, Scalia IG, Kierle R, Beaumont R, Cross DB, Feenstra J, et al. ePLAR The echocardiographic Pulmonary to Left Atrial Ratio: A novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension. Int J Cardiol 2016;212:379-86

2. NEDA Data Transfer and Transformation Process

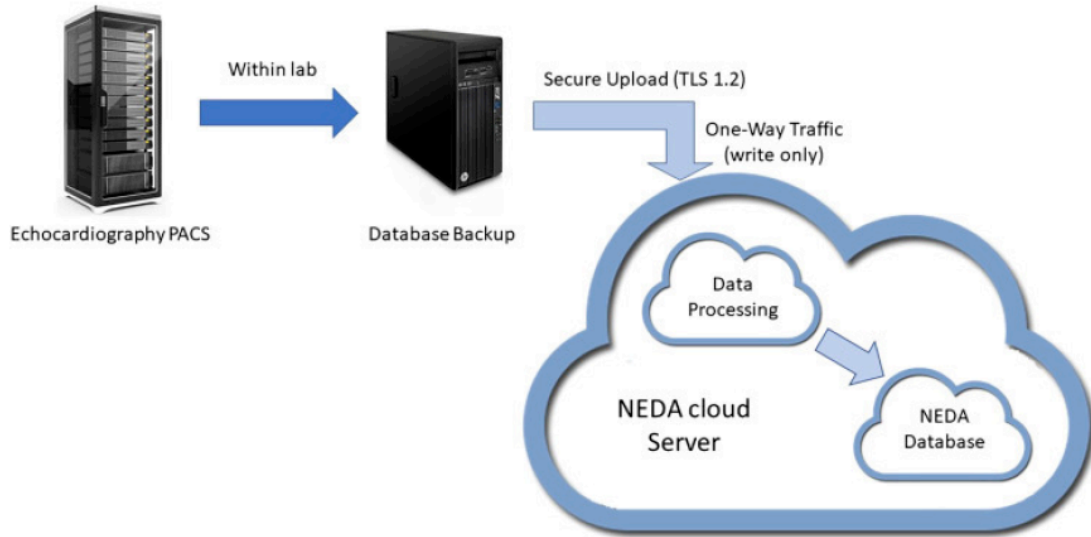


Figure 1
Data Transfer from lab into NEDA.

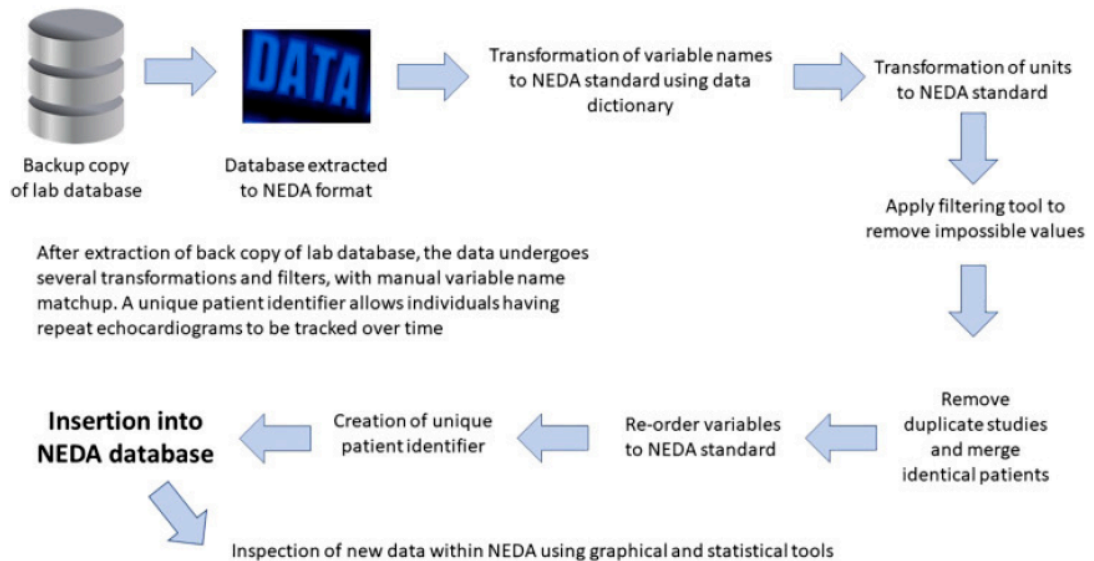


Figure 2
Data Transformation process into NEDA.

3. Statistical Calculations

2x2 tables showing specificity, sensitivity and predictive values of different ePLAR cut-offs to predict postPH

	prePH	postPH
ePLAR>0.25	12	23
ePLAR<0.25	6	82

Sensitivity = $82 / (82+23) = 78\%$

Specificity = $12 / (12+6) = 67\%$

Positive Predictive Value = $82 / (82+6) = 93\%$

Negative Predictive Value = $12 / (12+23) = 40\%$

	prePH	postPH
ePLAR>0.28	12	18
ePLAR<0.28	6	87

Sensitivity = $87 / (87+18) = 83\%$

Specificity = $12 / (12+6) = 67\%$

Positive Predictive Value = $87 / (87+6) = 94\%$

Negative Predictive Value = $12 / (12+18) = 34\%$

	prePH	postPH
high ePLAR	TN	FN
low ePLAR	FP	TP

sensitivity $TP / (TP+FN)$

specificity $TN / (TN+FP)$

PPV $TP / (TP+FP)$

NPV $TN / (TN+FN)$

Pearson Correlation of ePLAR to DPG, TPG and PVR

Correlations

		ePLAR = (TRV/E:E)/100	Diastolic Pulmonary Gradient	Transpulmonary Gradient	PVR
Pearson Correlation	ePLAR = (TRV/E:E)/100	1.000	.192	.022	-.049
	Diastolic Pulmonary Gradient	.192	1.000	.698	.161
	Transpulmonary Gradient	.022	.698	1.000	.520
	PVR	-.049	.161	.520	1.000
Sig. (1-tailed)	ePLAR = (TRV/E:E)/100	.	.097	.441	.372
	Diastolic Pulmonary Gradient	.097	.	.000	.140
	Transpulmonary Gradient	.441	.000	.	.000
	PVR	.372	.140	.000	.
N	ePLAR = (TRV/E:E)/100	47	47	47	47
	Diastolic Pulmonary Gradient	47	47	47	47
	Transpulmonary Gradient	47	47	47	47
	PVR	47	47	47	47

Binominal Logistic Regression of ePLAR and other variables that predict postPH

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Step 1a								
ePLAR = (TRV/E:E)/100	-6.409	2.694	5.661	1	.017	.002	.000	.323
PatientAge	-.011	.017	.411	1	.521	.989	.957	1.022
Ejection Fraction	-.040	.022	3.224	1	.073	.961	.921	1.004
Mitral E Point Velocity	.007	.012	.351	1	.553	1.007	.984	1.031
Constant	5.728	2.131	7.227	1	.007	307.481		

a. Variable(s) entered on step 1: ePLAR = (TRV/E:E)/100, PatientAge, Ejection Fraction, Mitral E Point Velocity.

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