ADVANCED CHARACTERISATION OF PULMONARY HYPERTENSION: ASSESSMENT OF RIGHT VENTRICULAR DIASTOLIC FUNCTION AND PULMONARY ARTERY WAVE REFLECTION

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Submitted in total fulfilment of the requirements of the degree of Doctor of Medical Science

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Declaration

This is to certify that:

i. The thesis comprises only my original work towards the degree of Doctor of Medical Science except where indicated in the Preface,

ii. Due acknowledgement has been made in the text to all other material used,

iii. The thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.
Preface

The inspiration for this thesis was threefold: the observation by Dr Andrew Burns that high fidelity pressure data obtained in the right ventricle and pulmonary artery from a Radi PressureWire would allow analysis of diastolic function and pulmonary wave reflection; and recent guidelines published by the American Society of Echocardiography that proposed a grading system for the echocardiographic assessment of right ventricular diastolic function based wholly on assumptions from the left ventricle. Finally, one cannot complete training in cardiology without witnessing first-hand the devastating effects of pulmonary hypertension. In particular, the frustrations of late diagnosis and not being able to treat patients until the damage has already been done are all too commonplace.

It became clear that right ventricular diastolic function had not been studied in detail in humans, with doubt as to whether diastolic dysfunction even exists in patients with pulmonary hypertension. It occurred that similar to the situation in the left heart, right ventricular diastolic dysfunction might provide an early clue to the presence of pulmonary hypertension. The theme of invasive high fidelity pressure assessment of patients with pulmonary hypertension is continued with investigation of whether assessment of pulmonary artery wave reflection can assist in better characterising patients with disease.

The content of this thesis is the result of contributions and support from many people, who are acknowledged specifically later. The study design, data analysis and manuscript preparation are all predominantly my own work. The invasive procedures described were performed with the assistance of Dr Andrew Burns and the staff at the cardiac catheterisation laboratory at St Vincent’s Hospital Melbourne. All echocardiograms were performed by myself.
Sections of this thesis have been previously published in peer-reviewed journals or presented in abstract form at national and international cardiology conferences.

Publications:


Abstracts:


Abstract

Pulmonary hypertension is the net haemodynamic consequence of a wide variety of underlying pathologies. As disease progresses, right ventricular systolic dysfunction may develop. However, by the time this occurs, prognosis is poor. Like the situation in the left ventricle, chronically increased right ventricular afterload first leads to right ventricular hypertrophy and hypothetically, diastolic dysfunction. Although there is some evidence from animal models for this, human data is limited. Theoretically, the identification of right ventricular diastolic dysfunction may assist in the earlier diagnosis of pulmonary hypertension.

This thesis provides evidence that right ventricular diastolic dysfunction does exist in the setting of pulmonary hypertension, that it occurs earlier than systolic dysfunction, and that it can be identified by invasive pressure measurement in the right ventricular cavity. Although echocardiography provides a useful way to assess left ventricular diastolic function, data presented here will show that currently available echocardiographic measurement of right ventricular diastolic function may not be sensitive enough to detect abnormal function.

The secondary hypothesis tested is that a pressure/time analysis of pulmonary wave reflection can provide additional information in the assessment of patients with pulmonary hypertension. Data suggests that a metric of wave reflection, the pulmonary augmentation index, is closely associated with standard measures of right ventricular afterload, and therefore may not add value. However, the time to wave reflection is related to the site of obstruction in the pulmonary circulation and could theoretically assist in identifying disease aetiology.
Acknowledgments

My heartfelt thanks to all the patients who took part in the studies that form this thesis.

I would like to thank all the staff from the Cardiac Investigations Unit at St Vincent's Hospital Melbourne who assisted with every aspect of patient care during these studies, and ensured that comfort and dignity was maintained at all times.

Thank you to my supervisors, Dr Andrew Burns and A/Prof David Prior for their expert guidance, constructive criticism and encouragement.

My thanks also to Prof Andre La Gerche for his endless supply of wisdom and positive feedback. To A/Prof Andrew Maclsaac for providing the opportunity.

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<table>
<thead>
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<th>Full Form</th>
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<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BMPR2</td>
<td>Bone morphogenetic protein receptor type II</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CSANZ</td>
<td>Cardiac Society of Australia and New Zealand</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DPG</td>
<td>Diastolic pressure gradient</td>
</tr>
<tr>
<td>Ea</td>
<td>Effective arterial elastance</td>
</tr>
<tr>
<td>EDPVR</td>
<td>End diastolic pressure volume relation</td>
</tr>
<tr>
<td>Ees</td>
<td>End systolic elastance</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>FFR</td>
<td>Fractional flow reserve</td>
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<tr>
<td>HFpEF</td>
<td>Heart failure with preserved ejection fraction</td>
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<tr>
<td>HHT</td>
<td>Hereditary haemorrhagic telangiectasia</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
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<td>IVRT</td>
<td>Isovolumic relaxation time</td>
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<tr>
<td>LBNP</td>
<td>Lower body negative pressure</td>
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<tr>
<td>LFT</td>
<td>Liver function tests</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>mPAP</td>
<td>Mean pulmonary artery pressure</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal prohormone of brain natriuretic peptide</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>PADP</td>
<td>Pulmonary artery diastolic pressure</td>
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<tr>
<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>PAI</td>
<td>Pulmonary augmentation index</td>
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<tr>
<td>PAP</td>
<td>Pulmonary artery pressure</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>--------</td>
<td>------------------------------------------------</td>
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<tr>
<td>PAPP</td>
<td>Pulmonary artery pulse pressure</td>
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<td>PAWP</td>
<td>Pulmonary artery wedge pressure</td>
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<tr>
<td>PCH</td>
<td>Pulmonary capillary haemangiomatosis</td>
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<tr>
<td>Pes</td>
<td>End systolic intraventricular pressure</td>
</tr>
<tr>
<td>PH</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>PHT</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>PVOD</td>
<td>Pulmonary veno-occlusive disease</td>
</tr>
<tr>
<td>PVR</td>
<td>Pulmonary vascular resistance</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium</td>
</tr>
<tr>
<td>RHC</td>
<td>Right heart catheterisation</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>RVEDP</td>
<td>Right ventricular end diastolic pressure</td>
</tr>
<tr>
<td>RVSP</td>
<td>Right ventricular systolic pressure</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>TAPSE</td>
<td>Tricuspid annular plane systolic excursion</td>
</tr>
<tr>
<td>TEE</td>
<td>Transoesophageal echocardiogram</td>
</tr>
<tr>
<td>Tinf</td>
<td>Time to inflection point</td>
</tr>
<tr>
<td>TPG</td>
<td>Trans-pulmonary gradient</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic echocardiogram</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Ved</td>
<td>End diastolic volume</td>
</tr>
<tr>
<td>Ves</td>
<td>End systolic volume</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WU</td>
<td>Wood units</td>
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</tbody>
</table>
1 Introduction and literature review

Pulmonary hypertension is a relatively uncommon condition with a variety of aetiologies and symptoms. Symptoms such as shortness of breath often develop very gradually and lag behind pathologic changes in the pulmonary vasculature, leading to diagnostic delay (1,2). Furthermore, measurement of the pulmonary artery pressure itself is problematic and poorly reproducible, as it can vary depending on a variety of factors, as well as not representing all components of the load faced by the right ventricle (3). Therefore, there is an urgent clinical need for alternative methods to identify patients at an earlier stage of disease.

The role of the right ventricle in adapting to increased afterload is critical to the prognosis of patients with pulmonary hypertension. Over the last two decades, it has been recognised that systemic hypertension is an important cause of left ventricular diastolic dysfunction, and that this can lead to heart failure in the absence of systolic dysfunction (4,5). It is plausible that a similar phenomenon occurs in the right ventricle, leading to raised systemic venous pressures and their consequent effect on organ function (6). Therefore, accurate measurement of right ventricular diastolic function (and dysfunction) might be an attractive means to identify patients with pulmonary hypertension earlier, and before the onset of systolic dysfunction.

The flow of blood in an artery is pulsatile and characterised by reflected pressure waves from distal sites in the circulation (7). Changes in the structure and stiffness of arteries can change the site and magnitude of wave reflections, and has been studied in some detail in the systemic circulation where altered wave reflection can have adverse loading consequences on the left ventricle. Analysis of pressure waveforms in the pulmonary artery could theoretically provide additional information above and beyond that obtained from the
pulmonary artery pressure (and its inherent limitations), thereby helping to better identify patients with disease.

In the following chapter, the background and rationale for further study of right ventricular diastolic function and pulmonary wave reflection will be explored. This necessitates an overview of the current assessment of patients with pulmonary hypertension, followed by a discussion of the critical role of the right ventricle in the circulation in general, and this patient group specifically. Lessons learned from the study of diastolic function in the left ventricle, and existing invasive and echocardiographic techniques for quantification are discussed. Finally, the current state of knowledge of pulmonary artery wave reflection will be examined.

1.1 Overview of pulmonary hypertension

Pulmonary hypertension is objectively defined as an increase in the mean pulmonary arterial pressure to 25mmHg or greater at rest as assessed by right heart catheterisation (8). It is the result of a wide variety of different pathologies, and can be classified clinically into one of five groups as summarised in Table 1-1. It may also be broadly differentiated by haemodynamic assessment into either pre-capillary or post-capillary pulmonary hypertension, which is summarised in Table 1-2.
Table 1-1 Clinical classification of pulmonary hypertension
Adapted from (8)

1. **Pulmonary arterial hypertension (PAH)**
   1.1. Idiopathic
   1.2. Heritable
      1.2.1. BMPR2 mutation
      1.2.2. Other mutations
   1.3. Drugs and toxins induced
   1.4. Associated with (APAH)
      1.4.1. Connective tissue disease
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
   1.5. Persistent pulmonary hypertension of the newborn

1'. **Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**
   1'.1 Idiopathic
   1'.2 Heritable
      1'.2.1 Eukaryotic translation initiation factor 2 alpha kinase 4 mutation
      1'.2.2 Other mutations
   1'.3 Drugs, toxins and radiation induced
   1'.4 Associated with:
      1'.4.1 Connective tissue disease
      1'.4.2 HIV infection

1''. **Persistent pulmonary hypertension of the newborn**

2. **Pulmonary hypertension due to left heart disease**
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   2.5. Congenital / acquired pulmonary vein stenosis

3. **Pulmonary hypertension due to lung diseases and/or hypoxia**
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental lung diseases

4. **Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions**
   4.1. Chronic thromboembolic pulmonary hypertension
   4.2. Other pulmonary artery obstructions
      4.2.1. Angiosarcoma
      4.2.2. Other intravascular tumors
      4.2.3. Arteritis
      4.2.4. Congenital pulmonary arteries stenoses
      4.2.5. Parasites (hydatidosis)

5. **PH with unclear and/or multifactorial mechanisms**
   5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension
Table 1-2 Haemodynamic classification of pulmonary hypertension
Adapted from (8)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical Group</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary hypertension (PH)</td>
<td>Mean pulmonary artery pressure (PAP) ≥ 25mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥ 25mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery wedge pressure (PAWP) ≤ 15mmHg</td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥ 25mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt; 15mmHg</td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>DPG &lt; 7mmHg and/or PVR ≤ 3WU</td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH</td>
<td>DPG ≥ 7mmHg and/or PVR &gt; 3WU</td>
<td></td>
</tr>
</tbody>
</table>

1.1.1 Classification by pathology

The histopathology of the pulmonary artery in patients with pulmonary hypertension is variable depending on aetiology (9,10). In Group 1 patients, the pathology tends to affect the distal pulmonary arteries, where medial hypertrophy, intimal proliferation and fibrosis are seen. Group 2 pulmonary hypertension patients have left heart disease, resulting in hypertrophy and enlargement of the pulmonary veins, pulmonary capillary dilatation and interstitial oedema. The distal pulmonary arteries can show medial hypertrophy and intimal fibrosis. Group 3 pulmonary hypertension patients (those with lung disease and/or hypoxia) usually show medial hypertrophy and intimal obstructive proliferation of the distal pulmonary arteries. In patients with chronic thromboembolic disease (Group 4), organised thrombi are attached to the pulmonary arterial medial layer, replacing the normal intima. These then lead to different degrees of occlusion within the proximal pulmonary vasculature.
Patients with Group 5 pulmonary hypertension form a heterogeneous group of diseases with a wide variety of underlying pathological patterns.

These different patterns of disease may result in varied total load on the right ventricle, even at the same absolute level of pulmonary pressure, which will be elaborated below. The underlying pathology also has a marked effect on ultimate prognosis. Patients with scleroderma related pulmonary hypertension have a worse prognosis than patients with idiopathic pulmonary arterial hypertension, while patients with pulmonary hypertension related to congenital heart disease have a relatively good prognosis (11).

1.1.2 Traditional assessment

1.1.2.1 Diagnosis

A thorough clinical history and examination, followed by a multitude of different investigations are used to evaluate patients with suspected pulmonary hypertension. These investigations can include an electrocardiogram, chest x-ray, pulmonary function tests and arterial blood gases, echocardiography, nuclear ventilation/perfusion scans, high resolution computed tomography, cardiac magnetic resonance, blood tests, immunology and abdominal ultrasound scans. However, the main purpose of these investigations is to clarify the aetiology of pulmonary hypertension, while right heart catheterisation remains the gold standard test for confirming the diagnosis. A diagnostic algorithm has been proposed by the European Society of Cardiology (ESC) (8).

It is also important to note that the development of increased pulmonary artery pressure occurs relatively late in the course of pulmonary vascular disease. Under normal circumstances, the pulmonary vascular bed provides very low resistance to right ventricular outflow. By way of comparison, it is roughly 10% of the resistance delivered by the systemic vasculature. Furthermore, the pulmonary circulation can accommodate large increases in flow (for example
during maximal exercise flow can increase by 400-500\%, with only small elevations in pressure \((12,13)\). The high capacitance of the pulmonary circulation allows for compensation of early levels of obstruction, with up to 50\% obstruction possible before an increase in pulmonary pressure is seen \((14,15)\).

Additionally, and possibly raising some concern about the accuracy of the standard diagnostic approach, in a study using 24 hour ambulatory pulmonary artery pressure monitoring there was significant variation in pulmonary artery pressure with changes in activity and posture. There was also a poor relationship between the average pressure and the measured resting pressure at right heart catheterisation \((16)\). It is theoretically possible then to miscategorise a patient if the pulmonary artery pressure is measured at only one single point in time.

1.1.2.2 Evaluation of severity and prognosis

The prognosis of patients with pulmonary hypertension is highly dependent on aetiology as discussed above. Other factors important for prognosis include functional measures such as exercise capacity, World Health Organisation (WHO) functional class and biomarkers such as plasma NT-proBNP concentration \((11)\). Importantly, patients with clinical evidence of right heart failure or impaired right ventricular systolic function by echocardiography have also been demonstrated to have worse outcomes, highlighting the critical role of right ventricular adaptation in this condition. In addition, the most prognostic haemodynamic measures are those which reflect right ventricular failure, such as low cardiac index and elevated right atrial pressure rather than the degree of elevation of pulmonary artery pressure.

Forfia et al established the role for assessment of the tricuspid annular plane systolic excursion (TAPSE), a measure of RV systolic function, in this setting \((17)\). They showed that in patients with pulmonary hypertension from a variety of causes, reduced right ventricular longitudinal shortening, as measured by
TAPSE < 1.8cm was associated with worse survival. Meluzin et al have also shown the value in tissue Doppler techniques for the assessment of right ventricular systolic function for assessment of prognosis (18). In this study of patients with heart failure and pulmonary hypertension, patients with lower systolic myocardial velocities measured at the tricuspid annulus had worse survival.

Unfortunately, right ventricular systolic abnormalities tend to manifest late in the course of pulmonary hypertension, so the utility of these measures for diagnosis, rather than prognosis, is less certain. The potential role of echocardiographic assessment of right ventricular diastolic function is not well defined for diagnosis or prognosis assessment, and does not currently form part of formal guidelines for assessment of patients with pulmonary hypertension. The evidence for the utility of this form of assessment is discussed in detail later.

1.2 The right ventricle

Historically, study of right ventricular physiology has lagged behind that of the left ventricle. It has been argued that this asymmetry continues even today (3). In particular, investigation of the diastolic properties of the right ventricle, both in normal physiology and in disease conditions, has been limited. The reasons for this are multiple, and likely include the concept that the right ventricle is unnecessary for the maintenance of resting haemodynamics as well as the idea that the left ventricle does the most work in generating blood flow through the circulation (19). Patients with a Fontan circulation live without contribution of a venous ventricle to cardiac output, although they do have limited ability to increase cardiac output during exercise as a result. It is true that the relatively thinner walled right ventricle is exposed to the low-pressure pulmonary circuit and needs to generate substantially lower pressures than the left ventricle. Additionally, the complex shape of the right ventricle has hampered attempts to
obtain accurate volume measurements, both invasively and non-invasively, which in turn has rendered haemodynamic study challenging (20).

However, right ventricular performance has been shown to be critical to the prognosis of patients with congenital heart disease, pulmonary arterial hypertension, cardiomyopathy and ischaemic heart disease (17,21-25). Furthermore, recent study has shown that during strenuous exercise, right ventricular work increases proportionally more than left ventricular work, and may be an important determinant of exercise capacity (26).

1.2.1 Structure and function of the right ventricle

The right and left ventricles of the mammalian heart are anatomically related by a common septum and by circular and spiral bundles of muscle fibres which encircle both ventricles (27-30). Compared to the left ventricle, the right ventricle has greater regional variation in wall thickness and a more complex geometric shape (19). This is illustrated by the fact that when viewed from the front, the right ventricle appears roughly triangular in shape, however in cross section takes on a crescent shaped appearance (31). In about 80% of people, the blood supply to the right ventricular free wall is from the right coronary artery, and in contrast to the left ventricle, which receives its blood flow almost entirely during diastole, there is almost equal flow to the right ventricular myocardium in systole and diastole (32,33).

In terms of microscopic structure, cardiac myocytes are predominantly arranged longitudinally in the sub-endocardial layer, and circumferentially in the thinner sub-epicardial layer (34). Consequently, Rushmer et al showed that right ventricular contraction is accomplished primarily by a shortening of the chamber along its longitudinal axis, with a drawing of the tricuspid ring towards the apex, and little change in right ventricular width (30). In contrast to the left ventricle, there is minimal torsional contraction. This lends weight to the idea of the right ventricle as a “piston pump”, with base to apex piston-like motion. However, an
alternate analogy of the RV as a hydraulic ram is also compelling (35). The hydraulic ram concept is where a pressure surge is generated when a fluid in motion is forced to stop or change direction. This would help to explain the development of pulsatile flow (pulmonary artery) from a continuous flow (inferior and superior vena cava). Overall, significant question remains as to the physiological significance of the complex geometry of the right ventricle.

1.2.2 The importance of the right ventricle to the circulation

Prior to the 1940s, the prevailing belief was that peripheral venous congestion indicated disproportionate failure of the right ventricle (36,37). In 1943, Starr et al showed that both cauterization of the right ventricular free wall and ligation of coronary blood vessels supplying the right ventricular free wall resulted in only a minimal change in right ventricular and venous pressures (38). This suggested that although right heart failure could be a factor in venous congestion, it only plays a minor role, and that actively functioning right ventricular myocardium is not required for the maintenance of adequate blood flow through the low-pressure pulmonary circulation. Studies by Bakos and Kagan confirmed these findings following cautery of the right ventricular free wall, and Donald et al in patients where the right coronary artery was ligated (39-41).

Moreover, Rodbard and Wagner performed a number of experiments in canines where a number of different types of anastomoses were created between the systemic venous circulation and pulmonary artery while the right ventricle was occluded (42). In these models, the animals survived for up to one hour, further lending weight to the idea that the right ventricle played only a small role in the maintenance of normal haemodynamics, and that central venous pressure alone is adequate to drive blood through the pulmonary circulation. Another hypothesis was that at low resting pressures, contraction of the septum and contraction at the periphery of the right ventricular free wall, (which are both supplied by branches of the left coronary system in canines) may be adequate to maintain pulmonary blood flow (43).
The concept of the right ventricle existing simply as a passive conduit was questioned in the 1950s following experiments by Rose et al which demonstrated that after acute occlusion of the pulmonary artery, IVC pressures rose and the right ventricle dilated markedly (44). This suggested that the pressure fall from aorta to pulmonary artery was too great to be sustained without some contribution from the right ventricle. Re-examination of previous data from the studies of Bakos, Kagan and Donald et al also revealed the presence of a pressure pulse in the pulmonary artery following destruction of the right ventricular free wall, suggesting that some right ventricular function is retained even after these procedures, likely from the motion of the ventricular septum (44).

Landis et al recognised the importance of studying the right ventricle during exercise, when pulmonary pressure increases. In a canine model, they showed the function of the intact right ventricle in the maintenance of normal venous pressures during and following exercise (45). In a canine model analogous to pulmonary hypertension, Brooks et al demonstrated that in the presence of high levels of pulmonary arterial resistance and an occluded right coronary artery, right ventricular failure results and causes a reduction of venous return to the left ventricle (46).

Holt explained the essential function of right ventricular early systole in creating the pericardial pressure gradient, which is associated with blood flow in the superior vena cava into the right atrium (47). Brecher further observed that there is decreased venous return towards the RA when the pericardium is opened (48). As right atrial end diastolic pressure increases, the magnitude of this right atrial filling gradient created by the pericardium increases (49).
1.2.3 The right ventricle and pulmonary artery as a unit

Contemporary understanding of the right ventricle revolves around the concept of ventriculo-arterial coupling. That the right ventricle is coupled to the pulmonary circulation now seems self-evident, but was understood by the physician William Harvey almost 400 years ago (50). However, the complexity of the interaction has only recently been appreciated and studied, firstly in the systemic circulation by Salisbury et al in 1962, and applied to the right ventricle and pulmonary artery by Piene et al in 1979 (51,52).

One of the initial problems to be addressed in expressing the way in which ventricular function is linked to arterial function was that the optimal way to express the function of these structures is different. Therefore coupling would not be able to be expressed as a simple ratio (53). While there is general agreement that the best way to describe vascular load is by means of the frequency domain in the form of impedance spectra, ventricular properties are not usually described in this way (although it is theoretically possible) (54,55). Also, functions or measurements expressed in the frequency domain are not used in clinical medicine, and so are less likely to be understood by clinicians.

Therefore to simplify the relationship, experimental work has used the effective arterial elastance (Ea) to describe vascular impedance (56). Sunagawa et al proposed that the mean and end ejection arterial pressure could be approximated by the ventricular end-systolic pressure and expressed by the following equation (57):

$$Ea = \frac{Pes}{SV}$$

Where Pes is the end systolic intra-ventricular pressure and SV is the stroke volume. The end systolic elastance of the ventricle (Ees) can be estimated as the slope of the end systolic pressure volume relation, and is assumed to be
relatively linear and independent of loading conditions (53). This can be expressed as:

$$E_{es} = \frac{P_{es}}{V_{es} - V_0}$$

Where $V_{es}$ is the end systolic volume and $V_0$ the volume-axis intercept. The coupling ratio can then be expressed as:

$$Coupling \ ratio = \frac{E_{es}}{E_a}$$

A schematic representation of how these variables are obtained from a pressure/volume loop is presented in Figure 1-1. A more comprehensive overview of the use of pressure volume loops will be presented later in the chapter.
Fourie et al. investigated the ventricular-vascular interaction of the intact pig right heart under conditions of normal pulmonary artery pressures and increasing pulmonary artery pressure induced by injection of glass beads into the pulmonary artery producing microvascular obstruction (58). They found that right ventricular efficiency (defined as the ratio of stroke work to myocardial oxygen consumption) reaches a maximum when the Ea is approximately 1 mmHg/ml (corresponding to a mean pulmonary artery pressure of 15-20 mmHg). At the point of maximum efficiency, the Ees/Ea ratio was 1.7. In fact, in control conditions, Ea was found to be 0.6 mmHg/ml and Ees 1 mmHg/ml, indicating that in normal operating conditions, the ventricle works at maximum efficiency but submaximal stroke work. However, maximum stroke work occurs...
at an Ea value of 2mmHg/ml (corresponding to a mean pulmonary artery pressure of 30-40mmHg), indicating that although the right ventricle has significant reserve, as pulmonary artery pressure rises and compliance decreases, eventually stroke work will fall, heralding the start of uncoupling.

In the canine left ventricle, Sunagawa et al showed that external work is maximised when Ees/Ea is approximately one, while cardiac efficiency is maximal with values closer to two (59). Burkhoff et al showed similar findings in that Ees/Ea ratio values of two are associated with a maximal ratio between mechanical work production and myocardial oxygen consumption (60). Sagawa et al demonstrated that right ventricular function adaptation to afterload has an optimal Ees/Ea ratio of approximately 1.5 to minimise energy cost (61).

Overall, for the right ventricle there is general agreement that values of Ees/Ea greater than one occur in healthy subjects, whereas values closer to, or lower than one occur with disease (58,62-64).

Recently, Brimioulle et al developed a cardiac magnetic resonance imaging (CMR) method to estimate the end systolic pressure volume relation from a single heartbeat, without the need for measuring volume or modifying preload or afterload (65). This data can then be combined with invasively derived pressure data to estimate a coupling ratio. Furthermore, Pes can be substituted by mPAP given their close relationship, further simplifying calculations of Ees and Ea (66,67).

The coupling ratios obtained from this methodology showed reasonable agreement with those established by animal experimental work. This single-beat methodology has been criticised for not being able to detect changes in contractility following infusions of dobutamine or esmolol described by Lambermont (68), compared to multi-beat approaches using conductance catheters. The reasons for this were hypothesised to include the fact that this method assumes symmetric pressure development and pressure decay, which
may not be reflective of actual pressure/time curves. Another problem is that curve fits are extrapolated from the very short measured time periods of isovolumic contraction and relaxation in the right ventricle. However, there may have been methodological issues in this study (69). Others have also used this single-beat technique successfully to estimate coupling ratios (70-73).

It is interesting to note that theoretically Ees could be supported by increasing contractility (for example with an inotrope), particularly in the setting of acute pulmonary hypertension, thereby maintaining the Ees/Ea ratio at a higher level (58). The clinical implication of this is that in patients with acute increases in pulmonary artery pressure, such as the situation with pulmonary embolus, haemodynamic collapse may be avoided with inotropic support.

1.2.4 Right ventricular adaptation to pulmonary disease

Chronic pressure overload results in complex changes to both the structure and function of the right ventricle and has been the subject of multiple comprehensive reviews (3,74-79). Observations regarding the patterns in which the right ventricle changes have been well described, however the mechanism by which all of these changes occur is not fully understood. It is hypothesised that a complex interaction of factors such as neuro-hormonal activation, coronary perfusion, myocardial metabolism and genetic factors takes place, resulting in a spectrum of ventricular remodelling (78). This may include right ventricular hypertrophy, cell matrix remodelling, and/or changes in right ventricular contractility. Of course, the underlying aetiology, the duration since the onset and the rate of progression of pulmonary disease also impacts on the pathology observed at any given time point.

Some studies have distinguished between adaptive remodelling and maladaptive remodelling, where adaptive remodelling is characterised by more concentric ventricular wall remodelling and preservation of function, while
maladaptive remodelling is typified by more eccentric wall hypertrophy and worse function (78,80,81).

However, broadly the pattern of right ventricular adaptation to pulmonary hypertension can be characterised by an initial compensatory hypertrophy where contractility increases and overall function is maintained, followed by progressive dilatation accompanied by decreasing function and ultimately failure (3). This is illustrated by cardiac magnetic resonance imaging in Figure 1-2.
Figure 1-2 CMR appearance of right ventricular adaptation to pulmonary hypertension
Panels A and B are the end diastolic and end systolic frames respectively from a patient with normal pulmonary pressures. In contrast, panels C and D are the end diastolic and end systolic frames respectively from a patient with mild pulmonary hypertension, where right ventricular hypertrophy is seen. Panels E and F are from a patient with severe pulmonary hypertension. The right ventricle is dilated and hypertrophied, with septal flattening seen. There is minimal change in volume from diastole to systole, indicating systolic dysfunction.
The initial response of the right ventricle to increased afterload is to hypertrophy through a combination of increased protein synthesis and increasing cell size through the addition of sarcomeres (76). The Laplace relationship states that:

\[ \text{Ventricular wall stress} \propto \frac{\text{Intracavitary pressure} \cdot \text{ventricular radius}}{2 \cdot \text{ventricular wall thickness}} \]

It follows that any increase in cavity pressure will result in an increase in wall stress unless accompanied by an increase in wall thickness (77).

This phenomenon was shown in experimental work by Dias et al in goats who underwent pulmonary trunk banding for 96 hours (82). Following this, right ventricular mass was significantly increased by 74% compared to a control group, with a corresponding increase in myocyte size, and no microscopic evidence of oedema or inflammation to explain the increase in right ventricular mass.

The hypertrophic response of the right ventricle to chronic pressure overload was also illustrated by Saba et al, who used CMR to show that right ventricular mass index correlated strongly with pulmonary artery systolic pressure in patients with pulmonary hypertension (83). Although confidence intervals were wide, indicating limited precision, they were narrower than for Doppler echocardiography estimates in the same study. Right ventricular mass index is actually an attractive novel measure of chronic right ventricular pressure afterload, as it should not be affected by short-term changes in preload, posture, or activity which hamper the measurement of the pulmonary pressure itself. However, its limited precision, alluded to above and related to the complex geometry and extensive trabeculation, may restrain its use for the diagnosis of early pulmonary hypertension. There is experimental evidence that right ventricular mass index is associated with prognosis in patients with scleroderma associated pulmonary hypertension, but whether it is independently predictive is uncertain (84,85).
Eventually, the right ventricle cannot sustain adaptive hypertrophy in the face of chronic pressure overload and a transition to dilatation and failure takes place (3). The factors that lead to this shift are not fully understood, however it is recognised that chronic pulmonary artery pressure elevation by itself is insufficient to explain right heart failure (86). It may be that ischaemia plays an important role, resulting from both decreased coronary perfusion pressures in the highly pressure overloaded right ventricle and inhibition of cardiac angiogenesis (87,88). CMR studies have demonstrated reduced right coronary artery blood flow during systole in patients with pulmonary hypertension, which is associated with ischaemia as demonstrated by nuclear perfusion scans (88,89). Studies have also linked chronic sympathetic activation, oxidative and nitrostatic stress, immune activation and cardiac myocyte apoptosis to the progression to right ventricular failure (91,92).

The development of right ventricular to pulmonary coupling inefficiency may also play a role in the development of right ventricular failure. The single beat method for estimation of the end systolic pressure volume relation developed by Birimioulle et al was used by Kuehne et al in a study using CMR combined with invasive measures of pressure to construct pressure volume loops in patients with pulmonary hypertension and in control subjects (62). They showed that while myocardial contractility was increased in the pulmonary hypertension patients, coupling was inefficient compared to controls (coupling ratios of 1.1 vs 1.9, p<0.01). Pagnamenta et al also demonstrated, in a canine model of heart failure, that even with minor elevations in mean pulmonary artery pressure, there was evidence of ventriculo-arterial uncoupling (71). This may have been related to increased pulsatile load.

It is accepted in the systemic side of the circulation that left ventricular remodelling processes which may be initially compensatory may be detrimental in the long run, and that intervention in this process reduces morbidity and mortality in patients with left heart failure (93-95). This has led some to
hypothesise that adverse right ventricular remodelling might be treated with similar strategies to those used for left heart failure (96). It is also known that right ventricular failure is often reversible, for example there is usually good recovery in right ventricular function following lung transplantation or pulmonary endarterectomy for pulmonary hypertension related to chronic thromboembolic disease (97,98). Whether prolonged or severe right ventricular loading and dysfunction may reach a point where recovery is not possible due to the development of fibrosis and myocyte loss is less clear.

### 1.3 Ventricular diastole and diastolic function

#### 1.3.1 The cardiac cycle and definition of ventricular diastole

The cardiac cycle can be divided into the periods of systole (contraction) and diastole (relaxation and filling). Historically, systole has been defined as being the time between the mechanical events of mitral valve closure to aortic valve closure, with the rest of the cycle being defined as diastole (99). Diastole itself is composed of four phases: isovolumic relaxation, early diastolic filling, diastasis and atrial filling. It is now clear that the boundary between systole and diastole is indistinct, and parts of the diastolic period may be contemplated to be part of systole at a myocardial level (100). The definitions of diastole may even change in disease states; an example being the recent observation in patients with pulmonary hypertension of continued contraction of the right ventricular free wall following pulmonary valve closure (101), which would normally be termed the isovolumic relaxation period of diastole. However, the mechanical definition may still provide a useful framework for research, and will be used for the purposes of this thesis.

#### 1.3.2 Left ventricular diastolic function and dysfunction

Before attention is turned back to the right ventricle, it is important to review some concepts from study of left ventricular diastolic function.
Left ventricular diastolic dysfunction was first identified in patients with hypertension and aortic stenosis (i.e. conditions resulting in increased left ventricular afterload), and also in patients with hypertrophic cardiomyopathy (i.e. intrinsic heart muscle disease) (102-105). It was recognised that these abnormalities of diastolic function could actually result in heart failure without major abnormality of systolic function (when measured by the left ventricular ejection fraction), and this syndrome is now termed heart failure with preserved ejection fraction (or HFpEF) (106). Some studies have indicated that HFpEF accounts for approximately 50% of clinical heart failure patients, and outcomes are similar to those of heart failure with reduced ejection fraction (107). The importance of systemic hypertension in the aetiology of LV diastolic dysfunction was illustrated by Kostis et al who demonstrated a marked reduction in the incidence of heart failure following the treatment of hypertension (108). The presence of abnormal left ventricular relaxation has also been demonstrated in patients with left ventricular hypertrophy secondary to aortic valve disease (109).

The characteristic features of HFpEF are slow left ventricular relaxation, which may reduce stroke volume, particularly at high heart rates, and increased stiffness (4,110). These abnormalities can ultimately lead to increased left ventricular filling pressures, increased left atrial pressure and pulmonary capillary pressures, which in turn lead to significant clinical consequences.

The pathophysiological changes that occur in the left ventricular myocardium contributing to increased stiffness include increased collagen deposition and increased intrinsic cardiac myocyte stiffness secondary to alterations in the phosphorylation state of the giant elastic protein titin (111-114). Impaired relaxation may result from myocardial energy deficit, or reduced nitric oxide signalling of myocyte cross bridge detachment (115-117).
The gold standards for measurement of left ventricular diastolic dysfunction are tau for active relaxation in early diastole and assessment of the slope of the end diastolic pressure-volume relation for stiffness. Yet invasive measurements are rarely performed in clinical practice. While debate still takes place with respect to exact cut-off values and potential limitations, non-invasive echocardiographic measures, particularly utilising tissue Doppler, form the mainstay of guidelines for diagnosis in this setting (106,118,119).

### 1.4 Measuring right ventricular diastolic function

Given that there are several components to diastole, the problem of measuring function or dysfunction can be addressed from many angles. No single measure can provide a comprehensive assessment of diastolic function. The question of which measure is best clinically will ultimately be answered by which, if any, can differentiate normal from disease, or separate different prognostic groups.

#### 1.4.1 Invasive measurement

Broadly, the components of diastolic function able to be assessed with invasive measurements include ventricular relaxation, ventricular compliance (or stiffness), and ventricular filling pressures (specifically, the atrial or ventricular end diastolic pressure).

#### 1.4.1.1 Relaxation

The gold standard measure of ventricular relaxation is tau, or the time constant of isovolumic pressure fall. This was first proposed by Weiss et al as a relatively load independent measure (120). Prior to this, the only available measure of relaxation was dP/dt min, which is a measure of relaxation at only one time point and is load dependent (121). The calculation of tau is based on the observation that the pressure fall in the left ventricle after dP/dt min follows an exponential time course. A detailed description of the method to calculate tau is
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provided in Section 3.5.2, and Figure 3-2. Weiss et al demonstrated that \textit{tau} is independent of peak ventricular systolic pressure, end-systolic volume or fibre length, minimally dependent on heart rate, and primarily a function of systolic fibre shortening. Subsequent to the original description by Weiss, a number of other models have been described (122,123).

One of the main criticisms of the Weiss method is that it assumes a zero asymptote, which infers that ventricular relaxation is finished by the time left ventricular pressure starts to increase with filling. This may not be true in patients with severely impaired relaxation (110).

Some have argued that \textit{tau} should not be used in the right ventricle as the period of isovolumic relaxation is very short when pulmonary pressures are normal (124). In fact, in a canine model, the period of isovolumic relaxation was found to be absent. However, a recent CMR study found an average isovolumic relaxation period of 36ms in normal patients. Furthermore, Leeuwenburgh et al (125) found an average isovolumic time period of 57ms in lambs. By way of comparison, a study performed in the left ventricle assessing \textit{tau} in normal controls against those with left ventricular hypertrophy secondary to aortic valve disease, found the duration of the early relaxation phase of diastole was 53ms in normal controls (109). Therefore these time periods, while marginally shorter than found in the left ventricle, are measurable with high fidelity catheter tipped micromanometers (126). Other studies have also found reasonable time periods over which to evaluate \textit{tau} (127,128). Moreover, one could argue that even if there are some patients in whom \textit{tau} cannot be measured, that this would be a reassuring finding suggestive of normal pulmonary pressures, and that \textit{tau} could still function as a useful measure in patients with disease.

\textbf{1.4.1.2 Ventricular compliance and the pressure volume loop}

Ventricular compliance is best evaluated using pressure/volume loops. Pressure volume analysis was first proposed by Frank over a century ago, but
widespread interest in using this method in cardiovascular research only began in the late 1950s and 1960s (129-132).

Briefly, the cardiac cycle can be described as the relation between pressure and volume at any given time point. Sample pressure volume loops from the left and right ventricles are presented in Figure 1-3 below. With varying loading conditions, the position of the pressure volume loop changes, but is always contained between the end systolic pressure volume relation (ESPVR) and the end diastolic pressure volume relation (EDPVR). Suga and Sagawa demonstrated that in the left ventricle, the slope of the ESPVR (termed the end systolic elastance, Ees) was insensitive to changes in preload and afterload, but sensitive to changes in the contractile state of the left ventricle, rendering this a measure of contractility (131). With increasing contractility, the slope of the ESPVR becomes steeper. Likewise, the slope of the EDPVR is a function of ventricular compliance; with decreasing compliance, the slope becomes steeper.

In relation to the Ees, this metric of contractility is superior to haemodynamic measures of systolic function such as ejection fraction or stroke volume, as these are relatively load dependent (133).
Compared to the LV, the right ventricular pressure-volume loop is trapezoidal, or almost triangular in shape. Maughan et al demonstrated similar findings in the canine right ventricle, with a linear relationship between pressure and volume at specified time points in the cardiac cycle for differently preloaded and afterloaded beats (19). Comparable to the left ventricle, the end systolic elastance was sensitive to changes in inotropic state. However, they also showed important differences. Firstly, the shape of the pressure-volume relation is trapezoidal, or nearly triangular in the right ventricle (see Figure 1-3 above), with ejection continuing past peak pressure. This creates difficulties in defining the point of end systole given the rounded top left corner of the pressure volume relation. Secondly, the canine right ventricles had lower values for Ees than the left ventricles at the same baseline conditions.

The EDPVR reflects the net effect of all aspects of myocardial material properties, (such as fibrosis or oedema), chamber structural properties and
extracellular matrix (134). In contrast to the ESPVR, in both the left and right ventricles the EDPVR is curvilinear, rendering a simple measure of slope difficult to define. Several methods using nonlinear regression analysis have been described to fit curves to the EDPVR. The most widely used curve fit uses the equation:

\[ P = Ce^{\beta V} \]

Where \( P \) is pressure, \( V \) is volume, \( C \) is a curve fitting constant and \( \beta \) is the chamber stiffness constant. In this model, the chamber stiffness increases linearly with pressure, and the slope of that relationship is described by \( \beta \) (134). \( \beta \) is dependent on chamber size, and can therefore be indexed with the multiplication of left ventricular wall volume (\( V_w \)). This is then the chamber stiffness index \( \beta_w \), and is dependent on myocardial material properties and ventricular chamber characteristics.

The passive, intrinsic myocardial stiffness properties can also be approximated from the EDPVR. These are characterised by the relation between stress (force per unit of cross-sectional area) and strain (segment length relative to a specified standard length) (134). However, this requires the assumption of chamber geometry as either a sphere or ellipse, from which wall stress and strain at any given value of pressure and volume can be estimated. This can be integrated into a dimensionless myocardial stiffness index \( k \), which has been used in studies of left ventricular stiffness. However, the obligatory geometric assumptions render this measurement not feasible in the right ventricle.

The major difficulty in recording pressure volume loops in the right ventricle is related to problems measuring volume accurately (19). The complex shape of the right ventricle makes methods based around measurement of one or two dimensions followed by the application of assumptions inaccurate (such as bi-plane Simpson’s method for measuring left ventricular ejection fraction by echocardiography). This can lead to unpredictable under or over-estimation of
volume (135). Conductance catheters are used successfully in the left ventricle, however in the right ventricle the thin wall and complex geometry present difficulties (20). More recently, techniques such as gated cardiac CT and CMR have allowed for accurate non-invasive volume measurement, however are limited by temporal resolution. Simultaneous pressure measurement during these investigations is also logistically challenging and requires specialised equipment to avoid image artefact.

1.4.1.3 Right atrial pressure

Right atrial pressure is an important measure of diastolic function as it represents the best measure of right ventricular filling pressures. Theoretically, if there is a major abnormality of diastolic function, it will ultimately manifest in increased right atrial pressure, as the heart attempts to maintain cardiac output. Unlike the situation in the left heart, where left atrial pressure is difficult to measure (requiring trans-septal puncture and consequent risk of complication), the right atrium is directly accessible by right heart catheterisation via the venous system. Pressure can be measured either with a fluid-filled catheter (which is more prone to error) or catheter tipped micromanometer.

Why should other diastolic abnormalities be studied at all if right atrial pressure measurement provides a summary of diastolic function as a whole? It is possible that modest abnormalities of relaxation or stiffness could occur without elevation in right atrial pressure. This finding is well documented in the left ventricle, where abnormal relaxation without elevation of left atrial pressure can occur as the first evidence of diastolic dysfunction. It is plausible that identifying these sorts of abnormalities could help to detect patients with inadequately controlled hypertension for example. Therefore, every component of diastolic function has the possibility of operating as a marker of disease, even if abnormal results are not immediately significant in terms of patient symptoms.
1.4.2 Echocardiographic measurement

A number of echocardiographic measures have been employed to assess right ventricular diastolic function both directly and indirectly.

1.4.2.1 Right ventricular free wall thickness

Although this measures structure rather than function *per se*, its use can be rationalised as hypothetically correlating with the degree of right ventricular hypertrophy that has developed in response to chronically elevated right ventricular afterload. For example, right ventricular mass index measured by cardiovascular magnetic resonance correlates with pulmonary artery systolic pressure and predicts survival (84). Whether there is a direct relationship between the degree of right ventricular hypertrophy and diastolic dysfunction has not been established.

The right ventricular free wall thickness is usually measured from the right ventricular anterior wall in the subcostal view by either 2-dimensional measurement or M-mode. The normal range has been described as between 3 and 5mm, with more than 5mm indicating hypertrophy (136). The limitations of this parameter include variability in measuring angle, and variability of right ventricular trabeculation. In patients with infiltrative diseases of the myocardium, it is also likely to reflect the degree of infiltration rather than myocyte hypertrophy due to increased right ventricular afterload.

1.4.2.2 Isovolumic relaxation time

The isovolumic relaxation time (IVRT) is by definition the time between the closure of the pulmonary valve and the opening of the tricuspid valve and can be measured by tissue Doppler techniques. By nature, it is difficult to measure as it is very short in normal people, and so any technique used for its assessment needs to have high temporal resolution. The most straightforward
Echocardiographic way to measure this is with tissue Doppler interrogation of the lateral tricuspid annulus. As will be discussed later, previous work has demonstrated a linear relationship between the IVRT and pulmonary artery systolic pressure (137,138). However, a recent cardiovascular magnetic resonance study indicates that the IVRT lengthens because of prolonged post-systolic contraction rather than an actual prolonged period of relaxation, therefore it may not be a true reflection of diastolic function (101). Nonetheless, it may still be a useful metric to estimate pulmonary artery systolic pressure in the setting of a poor trans-tricuspid flow signal.

1.4.2.3 Pulsed wave Doppler assessment of trans-tricuspid flow

Trans-tricuspid valve flow can be described by an early (E) wave of passive ventricular filling (due to ventricular relaxation) and a late atrial (A) wave of active atrial contraction. This flow can be measured by ultrasound using a pulsed wave Doppler technique, and the parameters acquired include the peak E and A wave velocities, and the E wave deceleration time.
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Figure 1-4 Pulsed wave Doppler evaluation of trans-tricuspid inflow
The E wave corresponds to passive right ventricular filling and A wave with active filling from right atrial contraction.

The normal ranges are well described, and multiple studies have demonstrated changes in right ventricular filling patterns with changes in therapy (139-142). However, the question of whether these measures correlate with actual changes in myocardial stiffness and active relaxation has not been studied. Furthermore, there are a number of pitfalls in their measurement.

Firstly, there is a significant (up to 20%) respiratory variation in the peak velocities measured (143). Therefore, one time point of respiration should be used such as end-expiration, when intrathoracic pressure is equal to atmospheric pressure. Alternatively, when five beats of more are averaged, the results obtained are very similar to end-expiration (144). Secondly, increasing age is associated with a gradual decrease in peak E wave velocity and a gradual increase in peak A wave velocity (143). Third, tachycardia causes an increase in E wave peak velocity but a relatively greater increase in peak A
wave velocity, therefore an overall decrease in the E/A ratio (144). Finally, preload reduction leads to a decrease in peak E wave velocity, but a relatively smaller decrease in peak A wave velocity, causing a net decrease in the E/A ratio (145,146).

1.4.2.4 Tissue Doppler assessment of the right ventricular free wall at the tricuspid valve annulus

Tissue Doppler is an echocardiographic technique, which measures the velocity of the myocardium itself and can be performed with either pulsed Doppler or colour-coded tissue Doppler. The diastolic motion of the right ventricle is usually interrogated in the basal right ventricular free wall at the level of the tricuspid valve annulus. It can be described by the peak velocities of the E’ and A’ waves which occur during the passive and active phases of ventricular filling respectively. The use of the ratio E’/A’ has also been described, but the value of this for assessment of diastolic function has not been studied. Figure 1-5 below shows some characteristic recordings of pulsed tissue Doppler. Colour-coded tissue Doppler generally yields lower velocities because the encoded data represent mean velocities within the region sampled rather than true peak velocities (147).
E’, A’ and S’ correspond to the peak myocardial velocity of the right ventricular free wall at the tricuspid annulus during the passive and active phases of ventricular filling and ventricular systole respectively.

Comparable to the measurement of trans-tricuspid flow, there are a number of pitfalls in measurement. Firstly, as age increases, peak E’ velocity decreases and peak A’ velocity increases (148). Furthermore, the effect of loading conditions was assessed by Pela et al in a study in which placing the lower body under negative pressure (LBNP) was used to acutely reduce preload. At LBNP of -40mmHg, the peak E’ and A’ velocities decreased by roughly the same amount, and there was no change in E’/A’ ratio (146).

In the left ventricle, the observation that the trans-mitral peak E wave velocity is directly influenced by left atrial pressure and inversely related to changes in the time constant of relaxation, led to the development of the E/E’ ratio to estimate left ventricular filling pressures (149). As E’ is a marker for myocardial relaxation, the E/E’ ratio corrects for the influence of myocardial relaxation on
the E velocity, and improves its relationship to filling pressures. At a clinical level, a septal mitral E/E' greater than 15 is associated with a high probability of elevated left atrial pressure, and an E/E' less than 8 generally reflects normal left atrial pressure. At values between 8 and 15, significant uncertainty exists.

The same concept has also been applied to the right side of the heart. The normal value for the tricuspid E/E' ratio ranges between two and six. In a small study of cardiac transplant patients, an E/E' ratio greater than eight predicted a right atrial pressure of more than 10 mmHg (150). In another small study of non-cardiac surgery intensive care patients, an E/E' greater than four predicted a right atrial pressure of more than 10 mmHg (151).

Nageh et al showed that the tricuspid E/E' ratio correlated strongly with catheter measured right atrial pressure in 62 unselected patients undergoing right heart catheterisation, regardless of right ventricular systolic function (r = 0.75, p < 0.001) (152). However, it is acknowledged in this paper that the confidence intervals of this relationship are wide, thereby limiting any potential clinical utility.

1.4.2.5 Myocardial performance (Tei) index

This is a global measure of right ventricular function rather than specifically describing diastolic function (153). It can be calculated by means of a pulsed wave or continuous wave Doppler trace across the tricuspid valve and is expressed by the following equation:

\[
Tei \ index = \frac{isovolumic \ contraction \ time + isovolumic \ relaxation \ time}{ejection \ time}
\]

In patients with primary pulmonary hypertension, the Tei index was a strong independent predictor of clinical status and survival (153). However, its usefulness must be questioned given the potential pitfalls of using the
isovolumic relaxation time described above. It has also been tested only in highly selected patient groups.

1.4.2.6 Estimation of right atrial pressure

The eventual result of diastolic dysfunction and impaired right ventricular filling is an elevation of right atrial pressure. Therefore, any measure of this can be thought of as an indirect assessment of diastolic dysfunction. Of course right ventricular systolic dysfunction or elevated blood volume may also result in an elevation of right atrial pressure, so this is by no means a specific measure. Nevertheless, if measured systolic function is normal, the tricuspid E/E’ may be a useful indicator of diastolic dysfunction. The prevalence of elevated right atrial pressure in patients with pulmonary hypertension and normal right ventricular systolic function is unknown and would be an interesting area for future research. Without this information it is difficult to appreciate the clinical importance of pure diastolic dysfunction in the right ventricle.

Right atrial pressure estimation is an especially valuable metric as it is one of the haemodynamic parameters which has the strongest correlation with prognosis in pulmonary hypertension, although many patients in these studies also had systolic dysfunction (11,22,154,155).

Apart from the method already described above to estimate filling pressures based on tissue Doppler techniques (i.e. the E/E’ ratio), a multitude of methods have been described to estimate the right atrial pressure. These have used various composites of measures including right atrial size, the diameter of the inferior vena cava, and its degree of collapsibility during inspiration, and are summarised in a recent review (156). According to the most recent guidance from the American Society of Echocardiography, it is suggested to categorise right atrial pressure into low (0-5mmHg), normal (6-10mmHg), or elevated (11-20mmHg) (147).
Finally, at low or normal right atrial pressures, there is systolic predominance in hepatic vein flow (i.e. the velocity of the systolic wave is greater than the diastolic wave). At elevated right atrial pressures, the systolic predominance is lost. The hepatic vein systolic filling fraction can be described as:

\[
\frac{V_{TI}s}{V_{TI}s + V_{TI}d}
\]

Where \(V_{TI}s\) is the velocity time integral of the systolic wave, and \(V_{TI}d\) is the velocity time integral of the diastolic wave. A value of less than 55% was found to be a sensitive and specific sign of elevated right atrial pressure, greater than 8 mmHg (157).

### 1.4.2.7 Guidelines for echocardiographic assessment

Guidelines released by the American Society of Echocardiography in 2010 recommend that echocardiographic measurement of right ventricular diastolic function should be considered in patients with suspected right ventricular impairment as a marker of early or subtle right ventricular dysfunction, or in patients with known right ventricular impairment as a marker of poor prognosis (147). The preferred measures suggested are the trans-tricuspid E/A ratio, E/E' ratio and right atrial size as these have been most validated. A grading scheme was proposed as follows:

1. Trans-tricuspid E/A ratio < 0.8 suggests impaired relaxation.

2. Trans-tricuspid E/A ratio 0.8 – 2.1 with E/E' > 6 or diastolic flow predominance in the hepatic veins suggests pseudo-normal filling.

3. Trans-tricuspid E/A ratio > 2.1 with a deceleration time < 120ms suggests restrictive filling.
This grading scheme is based entirely on normal reference ranges and expert opinion. It has not been validated prospectively, with respect to either an invasively measured gold standard or against prognosis.

1.4.3 Summary

The available methods to assess right ventricular diastolic function all have pitfalls and may not truly reflect actual physiology. Ideally, a gold standard method might be to construct pressure volume loops and calculate the end diastolic pressure volume relationship. However, this is not feasible in routine clinical practice with technology currently available.

In particular, available echocardiographic techniques have been insufficiently studied, and there has been limited validation of these against invasive gold standards in adult humans. This must be kept in mind when contemplating the following discussion in the next section.

1.5 The evidence for right ventricular diastolic dysfunction in pulmonary hypertension

1.5.1 Invasive studies

The finding of a prolonged isovolumic relaxation period in patients with pulmonary hypertension was first described by Burstin in 1967 (137). In this landmark study of 120 patients (40 normals, 61 patients with pulmonary hypertension and 19 patients with heart disease and no pulmonary hypertension), a combination of phonocardiogram traces, electrocardiogram traces and jugular phlebogram were used to measure the duration between the closure of the pulmonary valve and the opening of the tricuspid valve (i.e. the isovolumic relaxation period). He was able to demonstrate a strong linear correlation between the isovolumic relaxation time and the pulmonary artery systolic pressure. Subsequently, multiple studies have confirmed the finding of
a prolonged isovolumic relaxation period using a variety of different modalities including echocardiographic and invasive techniques in patients with pulmonary hypertension (125,153,158-160).

However, two recent CMR studies of right ventricular function have shown that much of the prolongation of the period referred to as the isovolumic relaxation period is actually due to a prolonged post-systolic contraction, in patients with pulmonary hypertension (101,161). In other words, the isovolumic period is composed of a post-systolic contraction period followed by the isovolumic relaxation period. Nonetheless, in the study by Mauritz et al, there was a trend towards a longer isovolumic relaxation period following the post-systolic contraction in patients with pulmonary hypertension. Furthermore, the absence of a lengthened isovolumic relaxation period does not imply that relaxation is “normal” in these patients.

Stein et al undertook an invasive study of 34 patients (eight normals, 17 with pulmonary hypertension without right ventricular failure and nine with pulmonary hypertension and right ventricular failure) (124). Maximal negative dP/dt was shown to be load dependant, although for any given pulmonary pressure, maximal negative dP/dt was lower in patients with concomitant right ventricular failure compared to those without. Maximal right ventricular negative dP/dt strongly correlated with maximal positive dP/dt, suggesting a close coupling of contractility and relaxation.

Stein et al also attempted to calculate right ventricular tau using methods described for the left ventricle but found that in patients with normal pulmonary pressures that maximal negative dP/dt (i.e. the starting point of the time period tau is measured over) occurred late on the downstroke of ventricular pressure, and in some patients the defined interval for measurement of tau was absent. Therefore, they found that tau was not measurable in patients with normal pulmonary pressures. This is a somewhat surprising finding, given that more
recent studies have clearly shown the presence of an isovolumic period in normal humans (101,127).

Chen et al showed that in a canine model of induced pulmonary hypertension, significant right ventricular hypertrophy accompanied a roughly twofold increase in mean pulmonary artery pressure when measured 8 weeks after injection of monocrotaline pyrrole (162). Diastolic properties were measured invasively and \( \tau \) and the chamber stiffness constant were obtained. RV \( \tau \) was significantly prolonged (84 vs 35ms, \( p < 0.05 \)) and chamber stiffness constant was significantly greater (0.724 vs 0.383, \( p<0.005 \)) following monocrotaline pyrrole. Afterload was then manipulated by nitric oxide and milrinone administration. Both agents resulted in a fall in pulmonary artery systolic pressure, which was accompanied by decreases in the chamber stiffness constant and shortening of \( \tau \). This called into question the load dependence of these measures.

This question was explored in detail by Leeuwenburgh et al, who performed a comprehensive study of invasive indexes of right ventricular diastolic function in lambs using a combined pressure/conductance catheter (125). They found that in normal lambs, \( \frac{dP}{dt} \) min and \( \tau \) were lower in the RV than in the LV, whereas the chamber stiffness constant was similar. Following preload manipulation by inferior vena caval occlusion, \( \frac{dP}{dt} \) min was found to be strongly load dependent, with \( \tau \) shown to be weakly load dependent. Following progressive pulmonary artery banding to increase afterload over a period of 8 weeks, both RV \( \tau \) and \( \frac{dP}{dt} \) min were significantly increased compared with controls, and the RV EDPVR shifted up and to the left indicating greater RV stiffness. The increase in \( \frac{dP}{dt} \) min could be completely explained by load dependence, while the change in \( \tau \) could not, suggesting that \( \tau \) is a reasonable measure of early diastolic relaxation in the right ventricle.

In a mouse model of pulmonary hypertension induced by a combination of chronic hypoxia and anti-proliferation treatment by SU5416, Wang et al showed a decrease in right ventricular \( \tau \) with early pulmonary hypertension (after 14
days), which returned towards control levels after 21 days (163). However, measured $tau$ was very short in these animals.

Borgdorff et al studied the effect of different patterns of right ventricular afterload in rats, who were exposed to either pulmonary artery banding (proximal loading) or monocrotaline induced pulmonary hypertension (distal loading) (164). After four weeks, right ventricular hypertrophy was equally induced in both groups, however end-diastolic elastance and $tau$ were increased in only the pulmonary banding group but not in the distal obstruction group. These findings raise the possibility of differential effects of different types of loading conditions (e.g. more static vs more pulsatile) on the development of diastolic dysfunction. However, this may have been explained by the higher pulmonary artery pressures seen in the pulmonary artery banding group, as evidenced by higher peak systolic pressure, higher dP/dt max and dP/dt min. Thus it may be the final haemodynamic effect rather than the site of loading.

In a small invasive study of patients with pulmonary arterial hypertension related to scleroderma or idiopathic pulmonary arterial hypertension, Tedford et al found no difference between these two groups with respect to invasively measured right ventricular $tau$, while measures of contractility (Ees) and coupling (Ees/Ea) were less favourable in the scleroderma group (164). This lends weight to the argument that scleroderma patients have intrinsic myocardial involvement resulting in systolic dysfunction and rendering them less able to compensate for higher afterload. However, diastolic function seemed unaffected, which is discrepant to data from non-invasive studies (158,166,167). Measures of diastolic function were also not compared to a normal control group in this study.

More recently, Rain et al undertook the first comprehensive invasive human study of right ventricular diastolic function in patients with pulmonary arterial hypertension using a combination of right heart catheterisation and non-simultaneous CMR (168). They showed that the diastolic stiffness constant
determined by a single-beat estimation method was significantly increased in PAH patients and was closely associated with disease severity, as measured by 6 minute walk distance, right atrial pressure and NT-proBNP concentration. Tissue specimens from some of these patients who were undergoing heart-lung transplantation were compared to non-failing donor heart controls. The patient tissue specimens revealed increased right ventricular fibrosis, and increased passive tension in cardiac myocytes at different sarcomere lengths, mediated by reduced titin phosphorylation. Unfortunately, the relaxation component of right ventricular diastole was not assessed in this study.

In summary, the isovolumic relaxation time, once thought to be highly correlated to pulmonary artery pressure, has been recently shown to be related to a prolonged systolic contraction period. Similar to the situation in the left ventricle, maximal negative dP/dt has been shown to be a load dependent measure of right ventricular diastolic function. Right ventricular tau has been found to be prolonged in animal models of pulmonary hypertension, and minimally load dependent. However, a single human study found tau not measurable in normal human subjects, while another study was able to measure tau in patients with pulmonary hypertension.

1.5.2 Non-invasive studies

Gan et al studied 25 patients with pulmonary hypertension and 11 control subjects using a combination of CMR and right heart catheterisation on consecutive days (142). For 10 patients, a vasodilator challenge was given with inhaled NO and oral sildenafil, where CMR measurements were repeated 50 minutes after sildenafil administration. This study focused on time and volume measurements to assess right ventricular diastolic function, and showed a correlation between the isovolumic relaxation time and right ventricular mass index as well as pulmonary vascular resistance at rest. Their major finding was that pulmonary hypertension patients had altered right ventricular filling patterns, with reduced passive filling, increased atrial contribution to filling and a
decreased E/A ratio. Acute afterload reduction with sildenafil was associated with a reduction in IVRT, however there was no change in right ventricular filling characteristics, suggesting that altered right ventricular compliance may be a more chronic adaptation to pressure overload. Furthermore, it raises the possibility that IVRT is an afterload dependent measure of right ventricular diastolic function, which may limit its clinical usefulness.

Giunta et al undertook an echocardiographic pulsed wave Doppler study of tricuspid flow in patients with scleroderma (167). This was based on the observation that scleroderma patients often have abnormalities of left ventricular diastolic function in the absence of any obvious other pathology, which is assumed to be related to underlying myocardial fibrosis. Seventy-seven scleroderma patients were studied with 36 control subjects for comparison. No significant differences were detected between the groups with respect to peak E or A wave velocities or the E/A ratio. However, when the patients were categorised by their tricuspid E/A ratio, patients with scleroderma and an inverted ratio (i.e. an E/A < 1.0) had a significantly higher estimated pulmonary artery systolic pressure compared to controls (43.8 vs 26.0, p < 0.001). This finding suggested that some patients with scleroderma have abnormal right ventricular diastolic dysfunction, and this tended to be associated with higher pulmonary artery systolic pressures (although not necessarily in the pathologic range according to published guidelines).

These findings were further evaluated by Lindqvist et al who studied 26 patients with scleroderma and 25 age-matched controls with Doppler echocardiography including tissue Doppler (158). Patients with scleroderma had increased RV free wall thickness (5.8 vs 3.7mm, p < 0.001) and reduced E/A ratio (1.2 vs 1.7, p < 0.01) compared with controls, however there was no significant difference in the right atrial to right ventricular pressure gradient, a surrogate for pulmonary artery systolic pressure (albeit with a trend to an increased pressure fall in the scleroderma group (22.1 vs 18.9mmHg, p=0.10). There were no significant differences with respect to tissue Doppler velocities between the two groups.
Huez et al undertook a similar study in evaluating echocardiographic tissue Doppler measures of right ventricular diastolic function in a study of 25 patients with scleroderma and 13 age matched healthy controls (166). Their major findings were confirmatory in that patients with scleroderma (without pulmonary hypertension) had significantly increased RV wall thickness and reduced E and E/A ratio. In addition, they demonstrated a reduced tissue Doppler velocity during passive right ventricular filling (E') in the scleroderma group compared to controls.

Neither the Lindqvist or Huez studies specifically included patients with elevated pulmonary artery pressures, however in both papers the scleroderma patient group had, on average, a shorter pulmonary acceleration time. In the Lindqvist paper, mean pulmonary acceleration time was 141ms in the control group vs 119ms in the patient group (p < 0.05). In the Huez paper, mean pulmonary acceleration time was 141ms in the control group vs 123ms in the patient group (p = 0.02). This time period is an indirect measure of the pulmonary artery systolic pressure (169), with a shorter time associated with higher pressure. It is plausible then, that a low-grade elevation, or intermittent elevation of pulmonary artery pressure is present in some of these patients with scleroderma. This may be below the cut-off range used in guidelines for the formal diagnosis of pulmonary hypertension, but may be contributory to right ventricular diastolic abnormalities. In this context, changes in any metric of pulmonary artery systolic pressure or right ventricular diastolic function would be expected to be small in these patients, and it may be simply that these two studies were underpowered to detect a significant difference. In contrast, a study of patients with severe pulmonary hypertension and normal controls was able to show a clear difference in E/A ratio (160).

This basic concept was extended by Faludi et al in a study of 43 patients with connective tissue disease (mostly scleroderma), and 15 healthy controls who underwent echocardiography and right heart catheterisation before and during
exercise stress (170). Compared to normal controls, patients with connective tissue disease and pulmonary hypertension at rest or induced by exercise had a reduced E’. At the same time, there was no significant difference between controls and patients with connective tissue disease and no pulmonary hypertension. This is suggestive that the changes measured in right ventricular diastolic function are the result of pressure overload rather than intrinsic myocardial fibrosis related to scleroderma.

The utility of tissue Doppler to evaluate abnormal right ventricular diastolic function in patients with pulmonary hypertension was further demonstrated by Ruan et al (171). In this study of 70 patients with pulmonary arterial hypertension and 35 age-matched controls, tissue Doppler E’ at the right ventricular free wall was significantly reduced in the pulmonary hypertension group (8.5 vs 15.3cm/s, p < 0.05).

These findings were confirmed by Huez et al who studied 18 patients with severe pulmonary hypertension (12 with pulmonary arterial hypertension and 6 with chronic thromboembolic disease), and 14 healthy controls (160). In the group with a mean estimated pulmonary artery systolic pressure of greater than 71mmHg, tissue Doppler E’ was significantly lower when compared to controls (4.4 vs 10.8cm/s, p < 0.001).

Okumura et al studied how well echocardiographic measures correlate to invasive measures of right ventricular diastolic function (including tau, dP/dt min and right ventricular end diastolic pressure) in 16 children with pulmonary hypertension related to congenital heart disease (128). Significant but modest correlations were found between tau and E’, E/E’, and A wave velocity. dP/dt min correlated significantly with A’. RV myocardial performance index and RV isovolumic relaxation time did not correlate with any of the invasive reference measures. Overall, no single echocardiographic parameter correlated strongly with tau, dP/dt min or RVEDP. Furthermore, the authors admit that the reference invasive parameters obtained have not been shown to predict
outcome or guide treatment in this patient group. As this was a small study in a paediatric population it is uncertain how these results relate to adults.

The value of tissue Doppler for predicting right atrial pressure in patients with pulmonary arterial hypertension has been shown by Utsunomiya et al (172). In this study of 50 patients there was a strong linear correlation of E/E' with mean right atrial pressure ($r = 0.80, p < 0.001$).

In summary, a CMR study showed evidence of altered right ventricular filling pattern in patients with pulmonary hypertension. Patients with scleroderma appear to have reduced tricuspid E/A ratio and reduced tissue Doppler E' velocities in the right ventricular free wall. There is a strong suggestion that this reflects a response to pulmonary hypertension, however an effect from scleroderma related myocardial fibrosis cannot be completely excluded. Other studies of patients with pulmonary arterial hypertension are supportive of this suggestion. The limited data available comparing echocardiographic parameters to invasive assessment of right ventricular diastolic dysfunction suggest no significant correlation, however large robust studies have not been undertaken.

1.5.3 Right ventricular diastolic dysfunction in other conditions

1.5.3.1 Endurance exercise

Before a discussion of right ventricular diastolic dysfunction in various disease states, it is interesting to note a study of a cohort of endurance athletes compared to a control group by Pagourelias et al (173). In this study, despite the endurance athlete group having significantly greater right ventricular and right atrial cavity sizes than the control group, there were no significant differences with respect to diastolic tissue Doppler velocities or trans-tricuspid flow velocities.
1.5.3.2 Systemic hypertension

Chakko et al performed the initial echocardiographic study of right ventricular diastolic function in patients with systemic hypertension (174). Fifty patients with mild, uncomplicated essential hypertension (diastolic blood pressure 95-109mmHg) and ten normotensive controls were studied. The hypertensive group had significantly greater LV mass index and altered Doppler measures of left ventricular diastolic function. Doppler measures of tricuspid flow were also significantly different with a reduced peak E wave velocity and increased peak A wave velocity, which led to a reduced E/A ratio (1.1 vs 1.7, p < 0.001).

However, a number of technical issues were present, including the analysis of tricuspid flow velocities without consideration of respiration or heart rate. Habib et al addressed these issues in a similar study, but nevertheless confirmed the original findings of Chakko et al (175). Additionally, it was demonstrated that the alteration in right ventricular filling dynamics were independent of left ventricular mass, but closely correlated to the disturbance of left ventricular filling dynamics.

Cicala et al further confirmed and extended these findings in a tissue Doppler echocardiographic study of 30 patients with systemic hypertension (defined as clinic blood pressure greater than 140/90mmHg) and 30 normotensive patients. Hypertensive patients had reduced peak E wave velocity, reduced E/A ratio and lengthened E wave deceleration time and isovolumic relaxation time (176). Hypertensive patients also had significantly reduced tissue Doppler measured E’ and E’/A’ ratio with no difference in the systolic myocardial velocity S’.

The mechanism for these findings is not clear. It may be that some of the patients in the hypertensive groups also had left ventricular diastolic dysfunction, raised left atrial pressure and consequent pulmonary hypertension. However, it is also plausible that hypertension mediated changes in left ventricular filling dynamics and the existence of left ventricular pressure overload may have a functional interaction with the right ventricle mediated by
the septum and pericardium; in other words, ventricular interdependence may play a role here.

1.5.3.3 Valvular disease

The contribution of ventricular interaction to abnormal diastolic function was examined in a study of patients with isolated severe aortic regurgitation and normal pulmonary artery pressures by Dourvas et al (177). The aortic regurgitation patients had increased left ventricular end diastolic and systolic volumes compared with controls, and thicker septa. Tricuspid E/A ratio was significantly reduced (0.8 vs 1.2, p < 0.001) in the aortic regurgitation group, corresponding to a reduced peak E wave velocity and increased A wave peak velocity. Similar findings were found in aortic stenosis and mitral regurgitation patients by Efthimiadis et al (178) (179). This redistribution of right ventricular filling from early to late diastole is thought to be related to the dilated left ventricle and rightward septal shift during diastole, and it is interesting to note that the opposite effect of RV volume or pressure overload on left ventricular diastolic function has also been described (180).

1.5.3.4 Hypertrophic cardiomyopathy

Maeda et al studied right ventricular diastolic function invasively in patients with hypertrophic cardiomyopathy (127) using a high fidelity micromanometer for pressure recording and biplane cine ventriculograms for near simultaneous volume assessment. Their major findings were that right ventricular diastolic function was abnormal in the hypertrophic cardiomyopathy patient group compared to normal controls, and was characterised by impaired isovolumic relaxation (measured by tau), delayed early diastolic filling (measured by the peak filling rate) and decreased diastolic compliance (assessed by the diastolic pressure-volume relation), while systolic function remained normal (measured by right ventricular ejection fraction). Similar to the situation in hypertensive patients, the mechanism for these findings is not clear however a similar
concept of ventricular interdependence may be in operation. An echocardiographic study by Efthimiadis et al demonstrated similar findings in hypertrophic cardiomyopathy patients to hypertension patients, with a reduced E/A ratio, and strong correlation of right ventricular filling parameters with left sided filling parameters (181).

Although predominantly a disease of the left ventricle, right ventricular hypertrophy has also been reported in approximately 18% of hypertrophic cardiomyopathy patients and has been observed rarely to result in RV outflow tract obstruction and reduced right ventricular diastolic filling (182-184). Although pulmonary artery pressure was not measured in the Maeda study, it is interesting to note that right ventricular systolic pressure was significantly higher in the hypertrophic cardiomyopathy patient group (31mmHg vs 24mmHg, p<0.01). Although on average not in the pulmonary hypertension range, it raises the possibility that a chronic low grade increase in pulmonary pressure may independently influence right ventricular diastolic function.

1.5.3.5 Prognostic value

The prognostic value of right ventricular diastolic parameters has been assessed by a number of studies. Pagourelas et al evaluated this in hypertrophic cardiomyopathy patients (185). An increased ratio of tricuspid early diastolic filling E over the early diastolic tissue Doppler velocity E’ (i.e. the E/E’ ratio), with a cut off > 6.88, predicted a 1.3x increased risk of death from heart failure. However, this was only shown in a univariate analysis and multivariate analysis was not undertaken.

Utsunomiya et al showed that patients with pulmonary arterial hypertension who ultimately had a cardiac event had a significantly higher tricuspid E/E’ to a non-event group (171). This finding was confirmed by Balaji et al, who demonstrated that a tricuspid E/E’ ratio > 10 was predictive of a cardiac event in this patient group (186).
Shiina et al also showed significantly higher E/E’ values in patients with pulmonary hypertension from chronic thromboembolic disease who experienced a cardiac event than those who did not (187). In the setting of pulmonary hypertension associated with idiopathic pulmonary fibrosis, Pitsiou et al demonstrated the reverse, with decreased values of tricuspid E/E’ associated with reduced survival (188). The reasons for this are unclear, but suggests more work is required to define any association between tricuspid E/E’ and prognosis.

Efthimiadis et al demonstrated that patients with thalassaemia major, normal left ventricular function and restrictive right ventricular filling patterns defined by an E/A ratio > 2 had significantly reduced survival over a 15 year period (189). Finally, Tallaj et al showed that right ventricular diastolic dysfunction assessed by a ratio of right atrial pressure to stroke volume was an independent predictor of mortality following heart transplant (190). The earlier development was associated with worse prognosis.

**1.5.3.6 Summary**

Taking these studies together, it is clearly difficult to separate the roles of right ventricular afterload and ventricular interaction in the development of right ventricular diastolic dysfunction. Nevertheless, there is some (although conflicting) data supporting the possible prognostic value in assessment of these parameters in a number of disease states.

**1.6 Wave reflection analysis**

**1.6.1 Blood flow in the pulmonary artery is pulsatile**

Historically, right ventricular afterload has been thought of as static, and measured by the mean pulmonary artery pressure or pulmonary vascular resistance. Even today, these static measures underpin the current guidelines
for the diagnosis of pulmonary hypertension (8). However, these measures do not take into account the pulsatility of blood flow in the pulmonary artery. This is of great importance in the pulmonary circulation, as in normal conditions resistance and pressure are low compared with the systemic circulation. Correspondingly, the pulsatile component of load on the right ventricle is proportionately much higher than for the left ventricle. Some studies have estimated that the pulsatile component of load is between one third and one half of the total load on the right ventricle (3).

The pulsatile component of load is dependent on ejection dynamics, arterial properties (the most important being arterial stiffness), and wave reflection in the artery (7).

Broadly, right ventricular pulsatile load may be assessed quantitatively in the time domain with respect to the pressure curve in the pulmonary artery, or in the frequency domain with respect to pulmonary arterial impedance (3). In terms of qualitative assessment, Murgo and Nichols have proposed a system of categorisation of arterial pressure wave patterns, however these have been derived from the aorta, and not previously extended to the pulmonary circulation (191-193). Although providing a comprehensive assessment, wave analysis in the frequency domain is complex, and measurements are expressed as functions of frequency. It also requires simultaneous measurement of both flow and pressure in the artery using invasive methods. Therefore, it has not previously been considered attractive for routine clinical practice. Time domain analysis has consequently been the most widely used method to assess pulsatile load.

The two most frequently used time domain analyses in the pulmonary circulation are measurement of pulmonary arterial capacitance and the pulmonary augmentation index. Although some authors have used the ratio of right ventricular stroke volume to pulmonary artery pulse pressure to approximate capacitance, this method is considered crude and there has been
recommendation against using it for future research (194-196). The pulmonary augmentation index utilises the phenomenon of wave reflection to provide insight into pulsatile load.

### 1.6.2 Wave reflection

A characteristic of arteries is that the forward pressure wave within the lumen generated by the ventricle reflects backwards at a variety of points along the arterial tree (7). These reflecting points are generally thought to be at points of change in arterial impedance, and at the points of vascular branching (197,198). This phenomenon has been well studied in the systemic circulation. In normal young people, the reflected pressure wave in the aorta is visible during diastole, and is thought to be advantageous in augmenting coronary, cerebral and renal blood flow in diastole (199,200).

A change in arterial properties, such as increasing stiffness, or a change in pulse wave velocity can lead to a substantial change in the pattern of wave reflection. For example, in the systemic circulation, the increase in aortic stiffness associated with advancing age (and other pathology such as hypertension, diabetes and renal disease) causes both an increased magnitude and earlier timing of wave reflection (201-205). The wave reflection then arrives during systole instead of diastole, leading to a higher systolic blood pressure, and thereby increasing ventricular work (206). Clearly then, increased, or earlier wave reflection can be detrimental to the maintenance of normal physiology.

In fact, there is very little wave reflection in the normal pulmonary circulation (207-209), and this is further reduced during exercise (210). The low amplitude wave reflection from the normally elastic pulmonary artery peaks at or just after the dicrotic notch, and may be one of the ways in which right ventricular-pulmonary arterial coupling is optimised (208,209-213).
However, in patients with pulmonary hypertension, substantial change in the magnitude, timing and pattern of wave reflection is seen. The occurrence of altered wave reflection in patients with pulmonary arterial hypertension was first established by a study using frequency domain analysis by Laskey in 1993 (210). This study clearly showed that in these patients, the magnitude of wave reflection is greatly increased, and that the composite reflected wave occurs much earlier, in the mid-portion of right ventricular ejection. This may in turn adversely affect right ventricular-pulmonary arterial coupling, and contribute to the development of the clinical syndrome of right heart failure (214).

1.6.3 Measurement of pulmonary wave reflection: augmentation index

To characterise all aspects of wave reflection quantitatively is problematic, given the complexity of arterial pressure/time curves. The augmentation index is a straightforward measure, which is relatively easy to obtain in clinical practice, albeit with some limitations. First proposed as the “reflection wave ratio” in 1985 by Yaginuma et al, the augmentation index is a simple ratio of the change in pressure of the reflected wave to the total pulse pressure (215). This is shown diagrammatically in Figure 1-6 below. This has been extensively studied in the systemic circulation, where the aortic augmentation index has been found to correlate with aortic pulse wave velocity and aortic stiffness (7).
Figure 1-6 Pulmonary augmentation index
A pressure waveform in the proximal pulmonary artery is shown. PAPP is the pulmonary artery pulse pressure and $\Delta P$ is the change in pressure of the reflected wave, identified by an inflection point in the pressure trace. The pulmonary augmentation index (PAI) = $\Delta P / \text{PAPP}$.

Theoretically, the pulmonary augmentation index should be a composite measure of both static and pulsatile right ventricular afterload, as it is influenced by the compliance of the pulmonary arterial wall, site of any obstruction and the peak pulmonary artery systolic pressure by way of the pulse pressure.

Clearly there are important differences between aortic and pulmonary wave reflection. Compared to the aorta, the pulmonary circulation is characterised by a shorter length, reduced arterial wall thickness, absence of well-developed arterioles, as well as a lower pulse pressure (7). Furthermore, pulmonary arteries do not exhibit increasing stiffness between central and peripheral sites (216), and a significant percentage of pressure and flow pulsation (20-30%) extends through normal lungs to the left atrium (217). The overall effect of these
differences is that the pressure waveform in the main pulmonary artery is more rounded than in the aorta.

### 1.6.4 The augmentation index in pulmonary hypertension

It is clear that the pulmonary augmentation index has the potential to add information to any assessment of the pulmonary circulation. This may allow for earlier diagnosis of pulmonary hypertension, or assist with determining the cause of pulmonary hypertension.

Castelain et al studied 14 patients with severe pulmonary hypertension who were grouped by diagnosis from either chronic thromboembolic disease or pulmonary arterial hypertension (218). Although the two groups were similar with respect to mean pulmonary artery pressure and pulmonary artery pulse pressure, there were significant differences in indexes of wave reflection. This included a higher augmentation index in the chronic thrombo-embolic disease group (0.26 vs 0.09, p < 0.05), and a shorter time to the inflection point of wave reflection (90ms vs 126ms, p < 0.05). The implication of this result is that different pathological processes may result in different patterns of wave reflection. For example, in chronic thromboembolic disease, the site of obstruction to the pulmonary tree is more proximal, and there may be abnormal mechanical properties and geometry of the proximal pulmonary arteries. This could be contrasted with pulmonary arterial hypertension, where the pathology mainly affects the distal pulmonary arteries.

Nakayama et al further explored this concept in a study of 62 patients with pulmonary hypertension from either chronic thromboembolic disease or pulmonary arterial hypertension (219). This confirmed the finding that patients with chronic thromboembolic disease have a higher augmentation index (0.27 vs -0.25, p < 0.001) and an earlier time to the inflection point of wave reflection (97ms vs 210ms, p < 0.001). However this study was criticised for using fluid filled pressure manometers rather than high fidelity catheter-tipped micro-
manometers, as evidenced by the unusual finding of negative augmentation index in patients with pulmonary arterial hypertension (220). Fluid-filled catheter pressure measurement presents a number of inherent limitations, including signal distortion, pressure drift and damping, and therefore the results of this study should be interpreted with caution. Nevertheless, the two studies were broadly in agreement in terms of the potential for the augmentation index to separate two discrete pathologies causing pulmonary hypertension.

More recently, experimental work in six anaesthetised sheep demonstrated that the pulmonary augmentation index increases during passive pulmonary hypertension caused mechanical constriction of branch pulmonary arteries compared to control conditions (221). In contrast, the augmentation index increased by a lower amount compared to control during active pulmonary hypertension induced by infusion of phenylephrine. There were also significant decreases in the time to inflection point under both conditions, which paralleled the changes in the augmentation index. This further suggests, albeit in a small animal study not directly comparable to human pathological conditions, that the augmentation index may be sensitive to changes in the mechanism of pulmonary hypertension.

1.7 Summary and rationale for further study

Pulmonary hypertension is the haemodynamic consequence of a wide variety of pathologies. One of the main problems in current practice is that it is often diagnosed relatively late in the course of disease, when right ventricular systolic dysfunction has already developed. There is a critical clinical need for novel ways to assess the pulmonary circulation and its effect on right ventricular function, particularly early in the course of disease.

Although there is conflicting data, there is some evidence that right ventricular diastolic dysfunction develops in response to chronic pressure overload, and some suggestion that this may happen prior to the development of systolic
Introduction and literature review

dysfunction. However, current invasive methods to assess this are complex, time-consuming and not readily applicable in clinical practice. Equally, current non-invasive methods to assess right ventricular diastolic function are limited by the absence of validation against invasive measures. Both of these issues need to be addressed to provide a robust framework for further study of right ventricular diastolic dysfunction. Only then can its role in the diagnosis and prognosis in patients with pulmonary hypertension be elaborated.

Pulmonary wave reflection may aid in the understanding of the hydraulic load placed on the right ventricle. Specifically, it may help to explain why patients with the same measured pulmonary artery pressure but different underlying pathology have a different outcome. However, current human data is limited, and therefore the incremental benefit of this analysis compared to traditional measures of right ventricular afterload is uncertain.

Pressure analysis of both right ventricular early relaxation to calculate $\tau$ and the pulmonary augmentation index with high fidelity catheter tipped micromanometers are now feasible for routine clinical practice. Previously, specific equipment was required which was often expensive and post-processing of data as laborious. The Radi PressureWire is a catheter tipped micromanometer system designed for measurement of intracoronary pressures to calculate a fractional flow reserve (FFR) to guide coronary intervention. Following the success of the FAME studies in demonstrating the clinical utility and cost effectiveness of FFR assessment, Radi PressureWires are now ubiquitous in cardiac catheter labs in North America, Europe and Australasia (222).

$\tau$ has not been extensively studied in the right ventricle, and there is conflicting data in relation to its feasibility for measurement. At the current time there is considerable circumstantial evidence for the presence of abnormal right ventricular relaxation in human patients with pulmonary hypertension, however definitive experiments have not been performed.
Echocardiographic measurement of left ventricular diastolic function, particularly tissue Doppler assessment, has revolutionised diagnostics in the setting of heart failure with preserved ejection fraction. Given its non-invasive nature, it presents an attractive modality for assessment of right ventricular diastolic dysfunction, and there is some data to support its use for both assessment of patients with possible or definite pulmonary hypertension and for prognosis assessment. However, with the exception of prediction of right atrial pressure, correlations with invasive measures are sparse. Further work is required to assess these relationships.
Introduction and literature review
2 Objectives

The central hypothesis to be explored is that pulmonary hypertension results in abnormal right ventricular diastolic relaxation, that this could be measured in routine clinical practice by invasive high fidelity pressure micromanometer, and ultimately non-invasively by echocardiography.

The secondary hypothesis is that a pressure/time analysis of pulmonary wave reflection can provide additional information in the assessment of patients with pulmonary hypertension compared to standard measures of pulmonary haemodynamics.

Therefore, the objectives of this thesis are to examine:

1. Whether pulmonary hypertension is associated with an invasive measure of abnormal right ventricular diastolic relaxation ($\tau$).
2. The load dependence of $\tau$ in the right ventricle.
3. Whether current echocardiographic measures of right ventricular diastolic function correlate with invasive measures.
4. The relationship between the pulmonary augmentation index and traditional measures of right ventricular afterload.
5. Whether the pulmonary augmentation index can differentiate patients with respect to aetiology of pulmonary hypertension.
3 General Methods

3.1 Ethics

All research was carried out at St Vincent's Hospital Melbourne, between February 2011 and February 2013. A hospital ethics committee operating in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007) approved the studies (HREC-A 002/10). All patients gave informed consent to take part.

3.2 Patient selection

Patients who were scheduled for right heart catheterisation in the Cardiac Investigations Unit at St Vincent's Hospital Melbourne for the investigation of breathlessness and/or suspected pulmonary hypertension were invited to participate. Patients with pulmonary valve stenosis, atrial fibrillation, permanent pacemaker or congenital heart disease were excluded.

3.3 Experimental protocol

All of the patients discussed in the following chapters underwent standard right heart catheterisation in the supine position in the cardiac catheterisation laboratory at St Vincent's Hospital Melbourne. A 7Fr femoral venous sheath was inserted, and a Swan-Ganz thermo-dilution catheter was advanced to the pulmonary artery under fluoroscopic guidance. Pressure measurements were recorded during end expiratory apnoea with the catheter wedged in a pulmonary artery (pulmonary artery wedge pressure), in the proximal pulmonary artery, right ventricle and right atrium. Cardiac output was measured by the thermo-dilution technique using an average of at least three measurements. Measurements were repeated until there was less than 10% difference between them. Pulmonary vascular resistance (Wood units) was calculated as:
\[ PVR = \frac{mPAP - PAWP}{CO} \]

Where mPAP is mean pulmonary artery pressure, PAWP is the pulmonary artery wedge pressure and CO is cardiac output.

In addition to standard right heart catheterisation, there were four distinct components to this study, performed during the same catheterisation procedure:

1. Right ventricular micromanometer study to characterise right ventricular diastolic function (chapter 4).
2. Observation of the effect of adenosine on right ventricular and pulmonary haemodynamics (chapter 5).
3. Comparison of echo parameters of right ventricular function against micromanometer measurements (chapter 6).
4. Pulmonary artery micromanometer study to characterise the pulmonary augmentation index (chapter 7).

Because of technical considerations, not all subjects underwent all four components of the study. Table 3-1 details the patients studied in each component.
Table 3-1 Patients included in each study component

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3.3.1 Right ventricular micromanometer study

Following right heart catheterisation, a 7Fr Multi-Purpose guiding catheter was exchanged over a 260cm 0.025-inch wire passed through the Swan-Ganz catheter under fluoroscopic guidance. A high fidelity micromanometer mounted at the distal tip of a 0.014-inch diameter guidewire (Radi PressureWire, St Jude Medical), was calibrated by equalising the pressure waveforms with the transducer at the tip of the guiding catheter. The wire was then advanced to a stable position in the right ventricle via the Multi-Purpose guiding catheter. Continuous pressure data was obtained at 100Hz for at least five cardiac cycles. The operating characteristics of the Radi PressureWire are an operating pressure range of -30 to +300mmHg with zero drift <7mmHg per hour and pressure accuracy +/- 1mmHg plus 1% (<50mmHg), plus 3% (>50mmHg). The micromanometer was connected to a RadiAnalyzer base station (St Jude Medical) at its proximal end.

The Radi PressureWire was chosen to measure right ventricular pressure rather than other high fidelity micromanometer systems. The Radi system is now ubiquitous in cardiac catheterisation laboratories worldwide, used for the measurement of fractional flow reserve in the coronary arteries to guide percutaneous coronary intervention procedures. If proven to be a useful measurement, this would allow for straightforward replication of results and further study, as well as potential application in clinical practice. Pilot data obtained from the Radi PressureWire was adequate to perform subsequent analysis of right ventricular diastolic function (3.4 and 3.5).

3.3.2 Adenosine study

Patients undergoing adenosine infusion also had a 6Fr femoral arterial sheath placed for accurate measurement of systemic arterial pressure.
Adenosine measurements were obtained during an intravenous infusion of adenosine, which was commenced into the femoral vein at a rate of 140mcg/kg/min. All measurements were obtained when steady state vasodilation was achieved, which was defined as the onset of stable systemic arterial blood pressure following an initial fall, as measured by a pressure transducer connected to the femoral arterial sheath.

With respect to timing, adenosine was infused following the standard right heart catheterisation procedure, with the Swan-Ganz catheter still in situ. Standard right heart catheterisation measurements were repeated during adenosine as described above. Adenosine was then ceased, the Swan-Ganz catheter removed and the right ventricular manometer component of the study performed as described above. Following this, with the Radi PressureWire still in the right ventricle, adenosine was infused again. Right ventricular manometer measurements were then obtained again during adenosine infusion. The adenosine infusion was then ceased following the acquisition of these measurements.

### 3.3.3 Echocardiography study

During the right ventricular micromanometer study, and with the patient in a supine position, echocardiography was performed with a General Electric Vivid 7 or E9 ultrasound system (GE Corporation, Wauwatosa, WI, USA). Gain and compression were optimised. M-mode and Doppler measurements were recorded at sweep speeds of 50mm/s. Tricuspid inflow was recorded from an apical four-chamber view and the peak early (E) and late (A) diastolic velocities and their ratio (E/A) measured. Tissue Doppler was recorded from the apical four-chamber view with the pulse-wave Doppler sample volume placed on the tricuspid lateral annulus. Peak early (E'), late (A') diastolic and systolic (S') myocardial annular velocities were measured. The ratios between tricuspid E and early diastolic myocardial velocity (E/E') and early diastolic myocardial velocities and late diastolic velocities (E'/A') were calculated. TAPSE was
measured from an M-mode signal that intercepted the tricuspid lateral annulus in the apical four-chamber view.

Echocardiography measurements were not acquired at a fixed phase of respiration, however pulse-wave Doppler measurements were averaged over five cardiac cycles which has previously shown good agreement with end-expiratory measurements (144). Tissue Doppler measurements were averaged over three cardiac cycles.

Echocardiography measurements were obtained contemporaneously with right ventricular pressure measurements, although not using simultaneous cardiac cycles.

3.3.4 Pulmonary artery micromanometer study

The same technique and equipment was used as for the right ventricular micromanometer study, except that the Multi-Purpose guide and RadiWire were advanced to a stable position in the proximal pulmonary artery under fluoroscopic guidance. Continuous pressure data was obtained at 100Hz for at least five cardiac cycles.

3.4 Analysis of micromanometer data

Data from the Radi PressureWire was stored in the RadiAnalyzer base station during each study. At the end of each procedure, data was exported in raw form to a desktop computer running Windows XP (Microsoft), and RadiView software (St Jude Medical). From RadiView, data was exported to an ASCII file that was then imported into Microsoft Excel for processing. The ASCII file contained five channels of data, with channel three containing pressure measurements at 0.01s intervals. This was isolated into discrete cardiac cycles and then imported cycle by cycle into GraphPad Prism for further analysis.
3.5 Methodology to calculate invasive parameters of right ventricular function

3.5.1 RV $dP/dt$ min and $dP/dt$ max

The pressure vs time data imported into GraphPad Prism was used to create a second data set that contained time and the first differential of pressure and time ($dP/dt$). The maximal value of $dP/dt$ was selected as $dP/dt$ max, and the minimal value for $dP/dt$ min.

3.5.2 RV tau

RV tau was calculated using the method proposed by Weiss (120) using a zero asymptote. Some have argued that an estimate of the actual pressure asymptote should be included in the calculation of tau to provide a measure which is more independent of end diastolic pressure (122). However, others have found no significant difference in values obtained by the zero asymptote method and the true value based on a non-filling cardiac cycle (223). Furthermore, a recent landmark study of diastolic function in the left ventricle also used the zero asymptote method (110).

The pressure decay analysis used time-pressure data points from the time at $dP/dt$ min to the time point where pressure passed through RVEDP on the initial pressure decay curve. The time point of $dP/dt$ min was identified from the time vs $dP/dt$ data. RVEDP was defined as the pressure when $dP/dt$ reached a threshold of 10% of $dP/dt$ max, which identified the start of the next contraction (123). A graphical representation of this process is shown in Figure 3-2.
General Methods

Figure 3-1 Identification of the diastolic time period for calculation of \( \text{tau} \)

The time-pressure points used for calculation of \( \text{tau} \) are shown in blue. This period is delimited by \( \frac{dP}{dt} \) min and the pressure at 10% of \( \frac{dP}{dt} \) max on the downslope of the previous cardiac cycle.

To allow for a more exact identification of this pressure, a cubic spline interpolation process to create additional data points was used, with the number of additional data points created proportional to the length of the cardiac cycle.

The general form of the mono-exponential equation that describes pressure decay during this time period is:

\[
P = (P_0 - P_\infty) \exp(-t/T) + P_\infty
\]

Where \( P_0 \) is the pressure at time zero, \( P_\infty \) is the pressure at large time (i.e. the asymptote), \( t \) is time, and \( T \) is the time constant characterising the rate of pressure fall (\( \text{tau} \)) (223). Assuming that the working ventricle and the
unstressed ventricle will relax to the same condition of zero trans-mural pressure, this can be simplified as:

\[ P = P_0 \exp(-t/T) \]

This equation can be linearised as:

\[ \ln P = \ln P_0 - t/T \]

Therefore, \textit{tau} is the inverse slope of the linear \( \ln P \) vs time plot:

\[ T = -\frac{t}{\ln P - \ln P_0} \]

Figure 3-2 shows an example of calculation of \textit{tau} in GraphPad Prism.
Figure 3-2 Example of \textit{tau} calculation in GraphPad Prism
A shows the mono-exponential form of the time-pressure points in this period of diastole after dP/dt min. B shows the same points following log transformation. \textit{Tau} is then the inverse of the slope of the regression line (x1000 to convert from seconds to milliseconds). In this case \textit{Tau} = 77ms.
3.5.3 Methodology to estimate right ventricular-pulmonary arterial coupling

3.5.3.1 Estimating Pmax of an isovolumic beat

Using Fourier analysis, Sunagawa et al found that the pressure-time relationship of a left ventricular isovolumic beat is very close to a sine wave (224). Following on from this, they were able to estimate the maximal pressure (Pmax) achieved during an isovolumic beat by curve fitting points of the isovolumic portions of an actual beat to a sinusoidal function. They were able to show a good correlation between this estimated Pmax and the observed Pmax for an isovolumic beat. These findings were confirmed in the left ventricle by Takeuchi et al, and extended to the right ventricle by Brimioulle et al (65,225).

Raw pressure-time data for individual cardiac cycles was imported into Matlab (Mathworks). A custom algorithm was applied to curate data points before curve fitting. Data points before 30% dP/dt max and after 30% dP/dt min along with data points between dP/dt max and dP/dt min were excluded. The purpose of excluding these points was to ensure that only points that were part of isovolumic contraction and relaxation were included in the curve fit. Using 30% cut-off values lead to optimal curve fitting, with a balance between the need to manually curate data to exclude non-isovolumic points, while including as many data points as possible. Other investigators have used values down to 10% dP/dt max, however we found that this often included portions of end diastole (68). In the left ventricle, others have used absolute values of dP/dt, however this would have been unpredictable as there was a great deal of variation in the magnitude of dP/dt min and dP/dt max between patients (226). In the original right ventricular validation study by Brimioulle et al, the cut-offs for data point inclusion before dP/dt max and after dP/dt min were not specified (65).

A sinusoidal curve fit was applied using the following equation to estimate an isovolumic beat from the included data points:
General Methods

\[ P = a + b \sin(c \cdot t + d) \]

Where \( P \) is pressure, \( t \) is time, and \( a, b, c \) and \( d \) are curve-fitting constants. An example of a curve fit given by this method is presented in Figure 3-3.

![Figure 3-3 Example of Pmax curve fit in Matlab](Image)

Data Points in green are the original time/pressure data from an actual beat that were excluded from the curve fit. Data points in blue are included in the curve fit. The red line indicates the curve fit, with the peak pressure estimating \( P_{\text{max}} \).

\( P_{\text{max}} \) was then computed as:

\[ P_{\text{max}} = a + b \]
3.5.3.2 Estimation of ventriculo-arterial coupling

Right ventricular end systolic elastance (Ees) was estimated as:

\[ E_{es} = \frac{P_{max} - P_{es}}{\text{Stroke volume}} \]

Where \( P_{es} \) is the end systolic pressure. As mPAP is closely related to end systolic right ventricular pressure, this was substituted for \( P_{es} \) (66). Arterial elastance (Ea) was then estimated as:

\[ E_{a} = \frac{P_{es}}{\text{Stroke volume}} \]

Where mPAP was again substituted for \( P_{es} \). The coupling ratio Ees/Ea was then calculated.

This methodology allowed for estimation of coupling using only time-pressure data and knowledge of stroke volume from a single beat, thereby avoiding the need for simultaneous pressure-volume data and manipulation of preload. Some assumptions are made however. It is assumed that the duration of an isovolumic beat is the same as an ejecting beat and that the pressure-time curve is symmetric. In reality, an isovolumic beat is longer than an ejection beat, and tends to be skewed (227,228). Nonetheless, errors introduced from these assumptions may not be large, given the close agreement in Pmax values found in multiple experiments.

3.6 Methodology to calculate pulmonary augmentation index

The inflection point of wave reflection was determined as the point of first zero crossing from positive to negative of the fourth derivative of the pressure/time curve (Figure 3-4). This methodology was described by Kelly et al in 1989,
based on the finding that the shoulder of the pressure wave occurs at the same time as the peak of flow (229).

Figure 3-4 Methodology for identification of the inflection point of wave reflection.
The time of the inflection point of wave reflection is identified in panel A from panel B, as the first zero crossing from positive to negative of the fourth derivative of pressure/time.

Figure 3-5 shows the method then used to calculate the pulmonary augmentation index.
Figure 3-5 Calculation of the pulmonary augmentation index
The pulmonary augmentation index (PAI) is calculated as the ratio of the difference in pulmonary artery systolic pressure to the pressure at the inflection point of wave reflection ($\Delta P$) over the total pulmonary artery pulse pressure (PAPP). The time to the inflection point ($T_{inf}$) was defined as the time between the pulmonary artery minimum diastolic pressure and the inflection point.
4 Results 1: Invasively measured right ventricular diastolic function

4.1 Introduction

Systemic hypertension is recognised to be one of the major causes of diastolic dysfunction in the left ventricle (5). The hypertrophied myocardium becomes stiff and abnormalities in both active myocardial relaxation and passive elastance are observed, eventually leading to an increase in left ventricular filling pressures, and left atrial pressure (4,106).

Evidence for a similar phenomenon occurring in the right ventricle (RV) has been sparse. Although a thinner walled structure, which is exposed to much lower absolute afterload, the law of Laplace dictates that the RV is subjected to increased wall stress under conditions of pulmonary hypertension (PHT) (230). Compensatory right ventricular hypertrophy is often seen (3). A recent human study also demonstrated RV hypertrophy and collagen deposition, increased sarcomeric stiffness and reduced titin phosphorylation in pulmonary arterial hypertension patients compared to controls (168).

In 1967, Burstin first described the association between PHT and the post-systolic isovolumic period in the RV, suggesting the presence of diastolic dysfunction (137). Previously, this time period has been referred to as the isovolumic relaxation period, and multiple studies have confirmed that there is a linear relationship between the length of this period and the pulmonary arterial pressure (142,158,159). However, recent cardiac magnetic resonance studies have demonstrated that this may be related to continued post-systolic contraction rather than a prolonged relaxation period (101,161). Nonetheless, echocardiographic studies suggest the presence of abnormal active myocardial relaxation, with decreased diastolic tissue Doppler velocities in the RV free wall of patients with scleroderma and PHT (166,170).
We hypothesised that PHT is associated with abnormal RV active relaxation, and in light of discrepant non-invasive data, this could be better demonstrated by an invasive gold standard. We chose the time constant of ventricular pressure decay (\(\text{tau}\)) as our primary measure of active relaxation, which is well validated in the left ventricle as a relatively preload independent measure of early diastolic ventricular function (231).

### 4.2 Methods

#### 4.2.1 Study population

Patients referred to St Vincent’s Hospital Melbourne for right heart catheterisation for the investigation of breathlessness and/or suspected PHT were invited to participate. Patients with pulmonary valve stenosis, atrial fibrillation, permanent pacemaker or congenital heart disease were excluded. This study was conducted with the approval of the Human Research Ethics Committee of St Vincent’s Hospital Melbourne and all patients provided written informed consent.

#### 4.2.2 Study protocol

Studies were undertaken in the cardiac catheterisation laboratory with subjects in the supine position. All patients underwent routine right heart catheterisation using a Swan-Ganz catheter from the right femoral venous approach and haemodynamic data was obtained in a standard fashion. A high fidelity micromanometer mounted at the distal tip of a 0.014 inch diameter guidewire (Radi PressureWire, St Jude Medical), was calibrated and advanced to a stable position in the RV via a 7Fr Multi-Purpose guiding catheter. Continuous pressure data was obtained at 100Hz for at least five cardiac cycles. Measurements for RV peak systolic pressure (RVSP) and RV minimum diastolic pressure (RVDP) were obtained. The first derivative of maximal (RV dP/dt max)
and minimal (RV dP/dt min) pressure change were calculated offline using raw pressure/time data imported into GraphPad Prism 6 (GraphPad Software). RV end diastolic pressure (RVEDP) was defined as the pressure at 10% RV dP/dt max on the upstroke of the pressure curve of the subsequent cardiac cycle. RV tau was determined using the method initially described by Weiss et al (120). RV isovolumic relaxation time was defined as the time between RV dP/dt min and the pressure at RVEDP during initial pressure decay. Contractility and right ventriculo-arterial coupling was estimated using the single-beat method described by Brimioulle et al (65). Briefly, peak systolic pressure (Pmax) of an isovolumic beat was estimated by curve fitting time/pressure points obtained before dP/dt max and after dP/dt min to the expression P=a+b.sin(C.t+d). Pmax was then obtained as a+b. End systolic elastance (Ees) was then estimated as (Pmax-Pes)/stroke volume where mPAP was substituted for end systolic right ventricular pressure (Pes) (66). Arterial elastance (Ea) was estimated as mPAP /stroke volume. The coupling ratio Ees/Ea was then calculated. All measurements were averaged over three to five cardiac cycles.

Patients were divided into a PHT group and a non-pulmonary hypertension (non-PHT) group based on a derived mean pulmonary artery pressure (0.61xRVSP) of 25mmHg, consistent with current European Society of Cardiology criteria for the diagnosis of PHT (8). This was obtained from our invasive measurement of RVSP.

4.2.3 Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software). Based on previous data, we hypothesised a mean RV tau of 30ms in patients without PHT with standard deviation of 10ms (127). With an alpha error of 0.05 and a power of 80% we estimated a minimum sample size of 24 patients would be required to demonstrate a difference in tau of 10ms. Results are expressed as mean ± standard deviation. Statistical significance was set at a value of p < 0.05. Comparisons between patient groups were made with
unpaired t-tests, without correction for multiple comparisons. Correlations of RV pressure data were examined with Pearson correlations.

### 4.3 Results

Twenty-five patients were studied in total. The baseline characteristics of the two groups are presented in Table 4-1. Fourteen patients were classified as non-PHT, and 11 with PHT. There were no significant differences with respect to age, gender or body mass index. Of the patients in the PHT group, five were classified as Group 1 pulmonary hypertension (one idiopathic, four associated with scleroderma), five had Group 2 pulmonary hypertension (four with left ventricular diastolic dysfunction, one with mitral stenosis), and one had Group 3 pulmonary hypertension (interstitial lung disease). The majority of patients in the non-PHT group were in NYHA functional class II, while the PHT patients were split between functional classes II and III. No patient was receiving specific pulmonary vasodilator therapy for PHT, reflecting that most patients studied were in the early phase of diagnosis and treatment. With respect to haemodynamic data, the PHT group had a significantly higher pulmonary artery pressure and pulmonary arterial wedge pressure, and there was a trend towards higher PVR. Heart rate, cardiac output and stroke volume were similar between the two groups.
### Table 4-1 Demographics and pulmonary haemodynamic data for non-PHT and PHT patients

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<td>3 (21.4%)</td>
<td>4 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>29.1±1.5</td>
<td>28.5±2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class 1:2:3:4</td>
<td>1:12:1:0</td>
<td>0:6:5:0</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonist</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Calcium channel antagonist</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Haemodynamic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>35.4±8.8</td>
<td>60.2±22.8</td>
<td>0.001</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>14.4±5.8</td>
<td>22.4±10.1</td>
<td>0.02</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>23.9±7.5</td>
<td>38.5±14.5</td>
<td>0.003</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>12.1±5.7</td>
<td>17.5±7.5</td>
<td>0.05</td>
</tr>
<tr>
<td>PVR (Wood Units)</td>
<td>2.0±0.8</td>
<td>3.4±3.0</td>
<td>0.11</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>73±14</td>
<td>74±14</td>
<td>0.81</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.0±1.7</td>
<td>6.5±1.9</td>
<td>0.52</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>83.3±17.7</td>
<td>89.2±21.1</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. BMI = Body Mass Index, NYHA = New York Heart Association, PASP = pulmonary artery systolic pressure, PADP = pulmonary artery diastolic pressure, mPAP = mean pulmonary artery pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, HR = heart rate, CO = cardiac output, SV = stroke volume.
Results 1: Invasively measured right ventricular diastolic function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PHT</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ees (mmHg/ml)</td>
<td>0.52±0.21</td>
<td>0.73±0.37</td>
<td>0.07</td>
</tr>
<tr>
<td>Ea (mmHg/ml)</td>
<td>0.29±0.08</td>
<td>0.49±0.40</td>
<td>0.07</td>
</tr>
<tr>
<td>Ees/Ea</td>
<td>1.88±0.77</td>
<td>1.69±0.68</td>
<td>0.52</td>
</tr>
<tr>
<td>RVEDP (mmHg)</td>
<td>3.8±3.7</td>
<td>11.0±6.3</td>
<td>0.004</td>
</tr>
<tr>
<td>RV min diastolic pressure (mmHg)</td>
<td>-0.1±3.3</td>
<td>5.1±6.6</td>
<td>0.03</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>30.0±5.2</td>
<td>56.0±21.5</td>
<td>0.002</td>
</tr>
<tr>
<td>RV dP/dt max (mmHg/s)</td>
<td>436±146</td>
<td>521±209</td>
<td>0.27</td>
</tr>
<tr>
<td>RV dP/dt min (mmHg/s)</td>
<td>-304±78</td>
<td>-530±219</td>
<td>0.006</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>38±16</td>
<td>52±25</td>
<td>0.13</td>
</tr>
<tr>
<td>RV tau (ms)</td>
<td>31±13</td>
<td>53±32</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. RVEDP = right ventricular end diastolic pressure. RVSP = right ventricular peak systolic pressure, RV IVRT = right ventricular isovolumic relaxation time.

Right ventricular micromanometer data is presented in Table 4-2. There was a trend towards increased Ees (a measure of right ventricular contractility) and Ea in the PHT group, but preserved coupling ratios. The PHT group had significantly higher minimum RV diastolic pressure and end-diastolic pressure. RV tau was also significantly prolonged. RV dP/dt max was not significantly different between the groups, while the magnitude of RV dP/dt min was significantly greater in the PHT group.

To further illustrate these results, example time/pressure traces are given in Figure 4-1.
Results 1: Invasively measured right ventricular diastolic function

Figure 4-1 Example RV time/pressure traces
Representative time/pressure traces from a non-PHT patient (A) and a PHT patient (B). Pressure points in blue were used for calculation of $\tau$. The non-PHT patient has a short $\tau$ and low RVEDP while the PHT patient has a prolonged $\tau$ and high RVEDP. Coupling ratios for both patients would be considered within normal limits.

There was a strong linear correlation between RV $\tau$ and RV minimum diastolic pressure ($r=0.93$, $p<0.0001$), and between RV $\tau$ and RVEDP ($r=0.87$, $p<0.0001$), Figure 4-2. There was a strong linear correlation between RVSP and RV dP/dt max ($r=0.58$, $p=0.003$), and a strong negative linear correlation between RVSP and RV dP/dt min ($r=-0.79$, $p<0.0001$), Figure 4-3. These correlations were maintained when each patient group was analysed individually.

A

\[
\begin{align*}
\text{Ees/Ea} &= 1.21 \\
\text{dP/dt min} &= -270\text{mmHg/s} \\
\text{\tau} &= 17\text{ms} \\
\text{RVEDP} &= -2.1\text{mmHg}
\end{align*}
\]

B

\[
\begin{align*}
\text{Ees/Ea} &= 1.54 \\
\text{dP/dt min} &= -401\text{mmHg/s} \\
\text{\tau} &= 80\text{ms} \\
\text{RVEDP} &= 15.2\text{mmHg}
\end{align*}
\]
Figure 4-2 Relationships between RV tau and RV diastolic pressures
Relationship between RV tau and (A) RV minimum diastolic pressure and (B) RVEDP. PHT patients are represented by open blue circles and non-PHT patients by open red circles. Regression lines are shown for PHT patients (blue), non-PHT patients (red), and when groups are combined (black).
Results 1: Invasively measured right ventricular diastolic function

Figure 4-3 Relationships between RVSP and rate of RV pressure rise and fall
Relationship between RVSP and (A) dP/dt max and (B) RV dP/dt min. PHT patients are represented by open blue circles and non-PHT patients by open red circles. Regression lines are shown for PHT patients (blue), non-PHT patients (red), and when groups are combined (black).

4.4 Discussion

We have demonstrated that an invasive measure of early RV relaxation, tau, is abnormal in patients with PHT. This finding strongly suggests that RV diastolic dysfunction does exist in this setting, despite recent data showing that the prolonged post-systolic isovolumic period in patients with PHT is related to a continued post-systolic contraction. We contend that both of these disturbances
can exist simultaneously, and may both contribute to increased RV minimum diastolic pressure.

*Tau* has been validated in the left ventricle as a relatively load independent measure of active relaxation, as opposed to $dP/dt$ min and $dP/dt$ max, which have greater load dependence (120,232). While active relaxation has been studied in some detail in the left ventricle, data from the RV is sparse. Some questions exist in relation to the appropriateness of the use of *tau* in the RV. The time period over which *tau* is measured, the isovolumic relaxation period, begins with $dP/dt$ min. Data from a canine model has indicated that in contrast to the left ventricle, where $dP/dt$ min occurs shortly after aortic valve closure, RV $dP/dt$ min occurs substantially before the end of RV ejection, and the normal cardiac cycle does not include an isovolumic relaxation period (233). Early human data also questioned whether an isovolumic relaxation period exists in the normal RV, given that RV $dP/dt$ min can occur late on the downstroke of pressure decay (124). However, the presence of an isovolumic relaxation period in normal humans has clearly been shown in a recent study (101). Furthermore, right ventricular *tau* has been shown to be prolonged in patients with hypertrophic cardiomyopathy, and lambs exposed to chronic pressure overload (125,127). We were able to measure right ventricular *tau* in all of our patients, and the average time periods that *tau* was measured over were 38 and 52ms in the non-PHT and PHT groups respectively. Although shorter than similar time periods in the left ventricle, these are still measurable with high-fidelity micromanometers, and our values for *tau* compare favourably to other recent studies (128). Moreover, one could argue that even if there are some patients in whom *tau* cannot be measured, that this would be a reassuring finding suggestive of normal pulmonary pressures, and that *tau* could still function as a useful biomarker in this situation.

We found that prolonged right ventricular *tau* is strongly associated with a higher minimum and end diastolic RV pressure, suggesting that impaired relaxation may impact on RV filling pressures and that RV minimum diastolic
pressure was higher in patients with PHT. This phenomenon is well
documented in the left ventricle, and is responsible for considerable clinical
sequelae (110). The systemic effect of chronically elevated right atrial pressure
is also no doubt important, as shown by its impact on renal function in heart
failure and its prognostic impact in PH (6,22,234,235). Moreover, LV minimum
diastolic pressure is important in the creation of a suction gradient to augment
left ventricular filling, and is an accepted index of diastolic suction in clinical
studies (236). Negative RV minimum diastolic pressures are frequently seen in
normal humans, and a canine model suggests that the RV is capable of
generating an early diastolic suction gradient independent of changes in
intrathoracic pressure (124,237). A non-invasive study has also suggested the
presence of a diastolic filling gradient in humans (238). A major caveat to the
above is that we do not have data on diastolic stiffness or RV volume in our
patients. Further study is needed to clarify the relative impact on RV filling
pressures of changes in these factors versus active relaxation.

It is plausible that abnormal relaxation precedes the development of overt
systolic dysfunction in the RV. RV systolic dysfunction tends to be associated
with very high pulmonary artery pressures, and is known to be a marker for poor
prognosis in the disease (3). Routinely available clinical measures of RV
systolic function such as tricuspid annular plane systolic excursion (TAPSE) and
RV fractional area change may remain normal until late in disease progression.
Our data indicated a trend towards increasing contractility in the PHT group as
evidenced by Ees and dP/dtmax, with preserved overall systolic function, as
demonstrated by similar stroke volumes. Ventriculo-arterial coupling ratios were
also preserved in the PHT group. On the other hand, RV \textit{tau} is clearly impaired.
Given that the patients in the PHT group had relatively mild elevations in
pulmonary pressures, this finding suggests that measured RV systolic function
may be falsely reassuring in the early stages of disease, while relaxation is
abnormal. This deserves further study, as there is significant clinical need for
novel approaches to the initial diagnosis and novel markers of early disease
progression to help guide management of this challenging condition.
4.5 Study limitations

The relaxation phase is just one component of ventricular diastole. The other major component, filling, can best be described by a pressure/volume loop, with stiffness described by the slope of the end-diastolic pressure volume relation (67). Although this relation is curvilinear, several methods have been proposed to approximate this with as few as two data points (239). However, this is still not trivial given the challenges in obtaining accurate volume data simultaneously with pressure data, in the geometrically complex RV (19,20). In light of these issues, and the paucity of previous data, the current study has focused on the active relaxation phase of RV diastole. We believe that interrogation of individual parameters of diastole may still be useful if they are able to independently identify disease. Furthermore, our methods are easily reproducible with equipment already available in many cardiac catheter laboratories (Radi PressureWire; used for fractional flow reserve determination in coronary arteries to guide percutaneous coronary intervention).

We adopted an “all-comers” approach to patient recruitment, rather than use a defined control group of normal subjects given the invasive nature of our study. This may then have led to an underestimation of the magnitude of difference in tau, as although these patients did not meet the formal mPAP cut-off value for diagnosis of pulmonary hypertension, some of these patients had higher pulmonary artery pressures than would have been anticipated. Moreover, given the small number of patients studied, we cannot exclude the possibility that different underlying aetiologies of PHT result in different changes in RV adaptation. There is some animal evidence that the type of pulmonary hypertension and location of obstruction influences changes in RV diastolic function (164). Examination of RV diastolic function in patients with different types of pulmonary hypertension would therefore be interesting.
4.6 Conclusion

Invasive measures of early active relaxation in the RV are abnormal in patients with PHT, even while measures of contractility are static or increasing, compared to patients with normal pulmonary pressures. This suggests that RV diastolic dysfunction may precede overt systolic dysfunction in this setting. Moreover, abnormal relaxation is associated with higher RV filling pressures, which could theoretically be clinically important. This deserves further study as a potential novel marker of early disease or disease progression, and also provides a framework for future non-invasive study of RV diastolic function.
Results 1: Invasively measured right ventricular diastolic function
5 Results 2: Effect of afterload modification on right ventricular diastolic function

5.1 Introduction

The current gold standard invasive measure of ventricular relaxation is the time constant of isovolumic relaxation, $\tau$, which was first proposed by Weiss et al in 1976 (120). They established that in the left ventricle, $\tau$ was relatively load independent, both to changes in afterload and end systolic volume, and minimally dependent on heart rate. Subsequently, studies have questioned whether $\tau$ is truly load-independent. Raff and Glantz showed that $\tau$ was prolonged when preload was acutely increased in the intact dog heart (240). Gaasch et al confirmed these findings in experiments where volume loading was sufficient to produce an increase in aortic pressure (241). Karliner et al also found that primary increases in left ventricular afterload resulted in a lengthening of $\tau$ (242). However there is also much evidence that $\tau$ is not significantly altered by only modest alterations in loading conditions (243-245).

The load-dependence of $\tau$ in the right ventricle has also been called into question, however the subject has not been studied in humans (125,162).

Adenosine is a short-acting, purine nucleoside which has a variety of physiological actions, including systemic and pulmonary vasodilation (246). Its vasodilation action is mediated by the activation of the specific cell membrane receptor A2, which leads to increased intracellular cAMP (247). Given its short half-life (of 5-10 seconds), adenosine administered intravenously results in higher plasma concentrations in the pulmonary circulation. This may explain its relatively greater effect on pulmonary rather than systemic vasodilation, as evidenced by a reduction in the ratio of pulmonary vascular resistance to systemic vascular resistance (246).
Adenosine has been used routinely in the evaluation of patients with pulmonary arterial hypertension, in relation to vaso-reactivity testing (248). The rationale for this testing in these patients is to determine the degree of fixed versus reversible pulmonary arterial constriction contributing to increased pulmonary vascular resistance. If the reversible component of vasoconstriction is found to be significant, a patient may benefit from long term calcium channel blocker therapy (249). However, with the advent of more specific pulmonary vasodilator therapy for pulmonary arterial hypertension, some have questioned the relevance of vaso-reactivity testing in contemporary practice.

We sought to investigate the effects of acutely altering right ventricular afterload by adenosine infusion on invasively measured right ventricular tau. We hypothesised that, in the face of relatively modest reduction in afterload, there would be no significant change in tau.

5.2 Methods

5.2.1 Study population

The same study population described in the previous chapter was investigated, however of the 25 patients, high fidelity pressure measurements in the right ventricle during adenosine infusion were not recorded in the first seven. Therefore, this was a smaller group, comprising 18 patients. Given that there was no systematic clinical reason why the first seven patients from the original group were not studied, the missing data was considered as "missing at random", and therefore these patients were excluded from any analysis.

5.2.2 Study protocol

The patients were divided into non-PHT and PHT groups based on an mPAP cut-off value of 25mmHg, which resulted in nine patients in each group. During the right heart catheterisation procedure, and following the measurement of
resting parameters, an intravenous infusion of adenosine was commenced into the femoral vein at a rate of 140mcg/kg/min. Repeat measurements were obtained with the methodology described in 3.3.2. All measurements were averaged over three to five cardiac cycles.

5.2.3 Statistical analysis

Unpaired t-tests were used for comparison of demographic data. Paired t-tests were used for comparisons of variables before and during adenosine infusion. Two-way ANOVA testing was used for evaluation of changes between the two groups. Results are expressed as mean ± standard deviation. Statistical significance was set at a value of p<0.05.

5.3 Results

Demographics for the two groups are recorded in Table 5-1. The PHT group was marginally older, but was not significantly different with respect to gender or BMI. The non-PHT group patients tended to be in a better NYHA functional class. Of the nine patients in the PHT group, three were classified as Group 1 pulmonary hypertension (associated with scleroderma), five had Group 2 pulmonary hypertension (four with left ventricular diastolic dysfunction, one with mitral stenosis), and one had Group 3 pulmonary hypertension (interstitial lung disease). None were on specific pulmonary vasodilator therapy.
The effect of adenosine on the pulmonary pressures of both the non-PHT group and the PHT group are summarised in Table 5-2 and Table 5-3 respectively. In the non-PHT group there were small statistically significant increases in pulmonary artery diastolic pressure and pulmonary artery wedge pressure, although these would not have been clinically significant. In contrast, the PHT group patients experienced no significant change in pulmonary artery pressures with adenosine.
Results 2: Effect of afterload modification on right ventricular diastolic function

Table 5-2 Baseline vs adenosine haemodynamic data in non-PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Adenosine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)</td>
<td>33.3±8.9</td>
<td>35.1±8.4</td>
<td>0.17</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>11.3±4.1</td>
<td>13.6±3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>21.3±7.1</td>
<td>23.2±6.0</td>
<td>0.06</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>9.7±5.1</td>
<td>12.4±4.2</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 5-3 Baseline vs adenosine haemodynamic data in PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Adenosine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)</td>
<td>56.9±23.7</td>
<td>55.2±25.5</td>
<td>0.38</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>21.9±11.2</td>
<td>21.9±9.9</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>36.7±15.4</td>
<td>36.8±16.0</td>
<td>0.92</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>19.2±7.1</td>
<td>19.4±6.4</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Figure 5-1 shows the changes in right ventricular and pulmonary haemodynamics in both patient groups with adenosine. There were significant increases in heart rate, cardiac output and stroke volume, and a significant decrease in pulmonary vascular resistance. The magnitude of reduction in PVR was slightly greater in the non-PHT group (40% reduction vs 30% reduction, p=0.006).
Figure 5-1 Pulmonary and right ventricular haemodynamics at rest and with adenosine
The effect of adenosine is shown on PVR (A), stroke volume (B), heart rate (C), and cardiac output (D). Resting values are shown in blue and values recorded during adenosine in red. Values are shown as means with 95% confidence intervals.

The micromanometer data pre and during adenosine infusion is summarised for the non-PHT and PHT groups in Table 5-4 and Table 5-5 respectively. In summary, there were no significant differences with respect to right ventricular pressures, dP/dt max, dP/dt min, IVRT or tau, following adenosine infusion in either group.
Table 5-4 Baseline vs adenosine micromanometer data in non-PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Adenosine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDP (mmHg)</td>
<td>3.4±4.5</td>
<td>4.8±4.7</td>
<td>0.07</td>
</tr>
<tr>
<td>RV min diastolic pressure (mmHg)</td>
<td>-0.5±4.0</td>
<td>0.5±3.9</td>
<td>0.28</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>28.5±5.4</td>
<td>31.0±7.0</td>
<td>0.09</td>
</tr>
<tr>
<td>RV dP/dt max (mmHg/s)</td>
<td>373±101</td>
<td>376±114</td>
<td>0.84</td>
</tr>
<tr>
<td>RV dP/dt min (mmHg/s)</td>
<td>-313±91</td>
<td>-322±110</td>
<td>0.49</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>39±18</td>
<td>35±19</td>
<td>0.21</td>
</tr>
<tr>
<td>RV tau (ms)</td>
<td>29±17</td>
<td>31±15</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Table 5-5 Baseline vs adenosine micromanometer data in PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Adenosine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDP (mmHg)</td>
<td>12.3±6.0</td>
<td>10.3±6.3</td>
<td>0.08</td>
</tr>
<tr>
<td>RV min diastolic pressure (mmHg)</td>
<td>6.2±6.6</td>
<td>5.3±5.5</td>
<td>0.35</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>53.6±23.3</td>
<td>52.7±23.8</td>
<td>0.49</td>
</tr>
<tr>
<td>RV dP/dt max (mmHg/s)</td>
<td>528±207</td>
<td>521±144</td>
<td>0.86</td>
</tr>
<tr>
<td>RV dP/dt min (mmHg/s)</td>
<td>-461±173</td>
<td>-424±169</td>
<td>0.26</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>50±27</td>
<td>54±23</td>
<td>0.61</td>
</tr>
<tr>
<td>RV tau (ms)</td>
<td>58±34</td>
<td>57±26</td>
<td>0.91</td>
</tr>
</tbody>
</table>
5.4 Discussion

We have confirmed that adenosine is an effective pulmonary vasodilator in humans, with significant reductions in PVR in both patient groups studied. Our findings are in agreement with multiple previous studies, which have shown that adenosine lowers PVR and increases cardiac output, although these have mainly been performed in patients with pulmonary arterial hypertension (250-252). The effect on mPAP has been variably reported, with some studies showing a decrease, increase or no change (251-253).

The magnitude of the reduction in PVR was slightly greater in the non-PHT group of patients. This likely reflects that some of the patients in the PHT group had some degree of fixed vasoconstriction (i.e. corresponding to a non-responder to vaso-reactivity testing). Why did PVR also fall in the non-PHT group, when at rest in normal humans, pulmonary vascular tone is already low? It is important to note that the non-PHT group was defined as patients with a derived mPAP < 25mmHg, and therefore may have contained patients with borderline or early pulmonary hypertension not yet reaching the cut-off for formal diagnosis. This is highlighted by the relatively high mean baseline PVR (2 Wood Units) in this group (with 1.6 considered the upper limit of normal).

The explanation for no significant change in pulmonary artery pressures with adenosine is likely complex. While a bolus of adenosine can result in AV block and sinus node suppression, a continuous infusion is known to have a positive chronotropic effect (247,254). Cardiac output, as the product of heart rate and stroke volume, is thereby increased with increasing heart rate. Given the relation:

\[ PVR = \frac{mPAP - PAWP}{CO} \]
Assuming relatively stable left atrial pressure, any increase in cardiac output would be expected to result in a compensatory increase in mPAP (or decrease in PAWP). As adenosine also has a direct vasodilatory effect on pulmonary arterioles, thereby lowering PVR, the overall effect on mPAP is unpredictable, and will depend on the magnitude of the change in CO vs PVR. It is likely, however, that mPAP will remain relatively constant unless PVR falls relatively more than pulmonary blood flow increases. In fact, the criteria for a positive vasodilator challenge in patients with pulmonary arterial hypertension is a decrease in mPAP of at least 10mmHg to reach an absolute value of 40mmHg or less without a decrease in cardiac output (248).

In the patients studied, the reduction in PVR was offset by increased pulmonary blood flow as evidenced by increased cardiac output, but no significant change in pulmonary artery pressures. This calls into question the usefulness of adenosine as an appropriate afterload modulator, as the magnitude of afterload reduction achieved here was small. There was no change in either dP/dt min or dP/dt max with adenosine, which further reinforces the assessment that any change in afterload was small, as both of these measures are known to be highly load dependent (124,125).

At this modest level of afterload reduction, with no change in mean pulmonary artery pressures, no change in right ventricular \( \tau \) was evident. In contrast, Chen et al showed that in a canine model of induced pulmonary hypertension, afterload reduction with nitric oxide and milrinone administration resulted in a reduction of mean pulmonary artery pressures of approximately 10-25% and a shortening of \( \tau \) (162).

Heart rate also increased modestly with adenosine infusion, with no change in right ventricular \( \tau \). It is possible that this increase in heart rate counteracted the effect of reduced afterload, as some previous investigators have found that increased heart rate results in a shortening of \( \tau \) in the left ventricle (255,256).
5.5 Limitations

Ventricular afterload, by definition, is the force opposing ventricular fibre shortening during ejection. With many assumptions made, both PVR and PASP are proportional to right ventricular afterload, and are commonly used as indexes of afterload clinically. However, a better measure of ventricular afterload would be end systolic wall stress, which incorporates the effects of peripheral loading conditions, ventricular chamber pressure, dimension and wall thickness. Given the complexity of computing this, and the need for simultaneous volume measurements, this was beyond the scope of our study.

Furthermore, an ideal intervention to modify afterload would result in exactly the same decrease in afterload in both groups studied. In other words, the magnitude of reduction in end systolic wall stress in the right ventricle should be the same. This is clearly unattainable with any pharmacological strategy; as individual patients will respond differently to any given drug. Invasive methods for afterload modification (such as pulmonary artery banding) may allow for more predictable and consistent changes in afterload, however are still imperfect, and not ethical to perform in humans. Likewise, mechanical preload manipulation with inferior vena caval obstruction is clearly not feasible in routine human studies.

An alternative method for changing load conditions might have been to give an additional intravenous fluid bolus to increase right ventricular preload, however this was considered too time consuming to perform given the complexity of the current experiment. Similarly, the effect of a fluid bolus may not be isolated to an increase in preload.

Finally, without simultaneous volume data, we cannot be sure that preload was not also acutely altered with our intervention, however this was not thought to be likely given the known haemodynamic effects of adenosine (247).
5.6 Conclusion

Adenosine is an effective pulmonary vasodilator, but has a minimal effect in reducing right ventricular afterload. At this level of reduction, there was no change in measures of right ventricular diastolic function, including the time constant of early relaxation and end diastolic pressure. A modest increase in heart rate also had no effect on parameters of right ventricular diastolic function. A counterbalancing effect of increasing heart rate and afterload reduction on measures of diastolic function cannot be excluded.
Results 2: Effect of afterload modification on right ventricular diastolic function
6 Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

6.1 Introduction

Echocardiography, as a non-invasive modality, presents an attractive means to assess cardiac structure and function. Although a great deal of research has explored the use of echocardiographic techniques to characterise left ventricular diastolic function, data from the right ventricle is relatively sparse.

An ideal echocardiographic parameter of right ventricular diastolic function would accurately characterise ventricular relaxation, stiffness or right atrial pressure, and track changes with disease or therapy. However, even in the left ventricle, no echocardiographic parameter is known to be a pure measure of any of these properties.

Recent guidelines for the echocardiographic assessment of right ventricular function suggest assessment of diastolic function in patients suspected to have right ventricular impairment (147). Therefore, it is timely to assess some of these measures against invasive gold standard measures of diastolic function. We chose to focus on pulsed wave and tissue Doppler methods, as these directly interrogate ventricular filling and myocardium, and have been well established in the left ventricle in relation to prediction of ventricular filling pressures. We explored the relationships between these measures and both active relaxation and right ventricular end diastolic pressure measured invasively.
6.2 Methods

6.2.1 Study population

The same study population described in the previous chapter was investigated, however of the 18 patients, an echocardiogram was not performed in one patient in the PHT group, and so was excluded from analysis.

6.2.2 Study protocol

The patients were again divided into non-PHT and PHT groups based on an mPAP cut-off value of 25mmHg, which resulted in nine patients in the non-PHT group and eight patients in the PHT group.

During the same right heart catheterisation procedure as described in the previous two chapters, and with the patient in a supine position, echocardiography was performed with a General Electric Vivid 7 or E9 ultrasound system (GE Corporation, Wauwatosa, WI, USA). Echocardiography measurements were obtained using the methodology described in 3.3.3.

6.2.3 Statistical analysis

The demographic, haemodynamic and echocardiographic parameters of the two groups were compared by multiple t-tests with Holm-Sidak correction for multiple comparisons. Multiple Pearson correlations were performed to assess correlations between echocardiographic and invasive measures. Results are expressed as mean ± standard deviation. Statistical significance was set at a value of p<0.05.
6.3 Results

The demographics of the two groups are presented in Table 6-1. Once again, the PHT group was marginally older, but there were no significant differences with respect to gender and BMI. The non-PHT patients tended to be in a better NYHA functional class. Of the eight patients in the PHT group, three were classified as Group 1 pulmonary hypertension (associated with scleroderma), four had Group 2 pulmonary hypertension (three with left ventricular diastolic dysfunction, one with mitral stenosis), and one had Group 3 pulmonary hypertension (interstitial lung disease). None of the patients were receiving specific pulmonary vasodilator therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PHT</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.1±9.6</td>
<td>66.6±5.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>3 (33%)</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5±4.9</td>
<td>28.4±8.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class 1:2:3:4</td>
<td>1:8:0:0</td>
<td>0:4:4:0</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel antagonist</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The pulmonary haemodynamic data, right ventricular micromanometer data, and echocardiography data for the two groups are shown in Table 6-2. As anticipated, the PHT group had significantly higher pulmonary artery pressures than the non-PHT group, but the groups were similar with respect to PVR, heart rate, cardiac output and stroke volume. Right ventricular pressures were also significantly higher in the PHT group, along with increased dP/dt max,
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

decreased dP/dt min, and prolonged \( \tau \). Echocardiography parameters were not significantly different between the two groups.
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

Table 6-2 Invasive and echocardiography data in Non-PHT vs. PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PHT</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>33.3±8.9</td>
<td>58.4±25.0</td>
<td>0.013</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>11.3±4.2</td>
<td>22.4±11.8</td>
<td>0.018</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>21.3±7.1</td>
<td>37.4±16.4</td>
<td>0.017</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>9.7±5.1</td>
<td>17.9±8.0</td>
<td>0.022</td>
</tr>
<tr>
<td>PVR (Wood Units)</td>
<td>2.0±0.8</td>
<td>3.6±3.5</td>
<td>0.20</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>71±12</td>
<td>73±14</td>
<td>0.76</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.0±1.9</td>
<td>5.9±1.3</td>
<td>0.90</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>83.8±18.6</td>
<td>82.4±19.5</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Invasive right ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>28.5±5.4</td>
<td>56.8±23.9</td>
<td>0.03</td>
</tr>
<tr>
<td>RVDP (mmHg)</td>
<td>-0.5±4.0</td>
<td>7.3±6.4</td>
<td>0.008</td>
</tr>
<tr>
<td>RVEDP (mmHg)</td>
<td>3.4±4.5</td>
<td>13.2±5.4</td>
<td>0.0009</td>
</tr>
<tr>
<td>dP/dt min (mmHg/s)</td>
<td>-313±91</td>
<td>-488±176</td>
<td>0.019</td>
</tr>
<tr>
<td>dP/dt max (mmHg/s)</td>
<td>373±101</td>
<td>553±223</td>
<td>0.04</td>
</tr>
<tr>
<td>RV tau (ms)</td>
<td>29±17</td>
<td>61.4±34.8</td>
<td>0.025</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>39±18</td>
<td>53±25</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid E (cm/s)</td>
<td>44.0±10.1</td>
<td>48.4±10.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Tricuspid A (cm/s)</td>
<td>50.7±14.3</td>
<td>53±12.5</td>
<td>0.73</td>
</tr>
<tr>
<td>Tricuspid E/A</td>
<td>0.9±0.2</td>
<td>1.0±0.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Tricuspid annular E' (cm/s)</td>
<td>7.4±2.2</td>
<td>6.0±2.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Tricuspid annular A' (cm/s)</td>
<td>10.6±2.4</td>
<td>10.2±2.4</td>
<td>0.74</td>
</tr>
<tr>
<td>E/E'</td>
<td>6.5±2.4</td>
<td>9.8±6.2</td>
<td>0.16</td>
</tr>
<tr>
<td>E'/A'</td>
<td>0.7±0.17</td>
<td>0.6±0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Tricuspid annular S' (cm/s)</td>
<td>9.6±1.8</td>
<td>9.0±1.7</td>
<td>0.49</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>2.2±0.5</td>
<td>2.0±0.5</td>
<td>0.42</td>
</tr>
</tbody>
</table>
The correlations between the invasively measured parameters and echocardiographically measured parameters of RV diastolic function are recorded in Table 6-3. Echocardiographic measurements thought to be associated with early diastole were compared against invasive measures of early relaxation, while all available echocardiographic measurements were compared against invasively measured RVEDP.

There were no significant correlations between any of the echocardiography measures and \( \tau \). Given our original hypothesis, the important relationship of RV \( \tau \) vs \( E' \) is also shown graphically in Figure 6-1.

With respect to RV \( dP/dt \) min, both the \( E/A \) and \( E/E' \) ratios showed strong correlations in non-PHT patients, but no correlation in PHT patients. When all patients were considered, significant correlations between RV \( dP/dt \) min and \( E' \), \( E/E' \) and \( E'/A' \) were seen.
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

Table 6-3 Correlations of invasive vs. echocardiography parameters, by group and overall
Significant correlations are highlighted in bold

<table>
<thead>
<tr>
<th>Invasive parameter</th>
<th>Echo parameter</th>
<th>Non-PHT r</th>
<th>p value</th>
<th>PHT r</th>
<th>p value</th>
<th>All patients r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV tau</td>
<td>E</td>
<td>-0.15</td>
<td>0.34</td>
<td>0.21</td>
<td>0.31</td>
<td>0.19</td>
<td>0.24</td>
</tr>
<tr>
<td>E/A</td>
<td>0.09</td>
<td>0.41</td>
<td>0.05</td>
<td>0.45</td>
<td>0.14</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>E'</td>
<td>0.20</td>
<td>0.30</td>
<td>-0.30</td>
<td>0.24</td>
<td>-0.26</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>E/E'</td>
<td>-0.21</td>
<td>0.29</td>
<td>0.18</td>
<td>0.33</td>
<td>0.28</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>E'/A'</td>
<td>0.20</td>
<td>0.30</td>
<td>-0.07</td>
<td>0.43</td>
<td>-0.11</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>RV dP/dt min</td>
<td>E</td>
<td>-0.23</td>
<td>0.27</td>
<td>0.44</td>
<td>0.14</td>
<td>0.02</td>
<td>0.47</td>
</tr>
<tr>
<td>E/A</td>
<td>0.77</td>
<td><strong>0.008</strong></td>
<td>-0.14</td>
<td>0.37</td>
<td>-0.03</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>E'</td>
<td>0.44</td>
<td>0.12</td>
<td>0.51</td>
<td>0.10</td>
<td><strong>0.54</strong></td>
<td><strong>0.013</strong></td>
<td></td>
</tr>
<tr>
<td>E/E'</td>
<td>-0.65</td>
<td><strong>0.03</strong></td>
<td>-0.59</td>
<td>0.06</td>
<td><strong>-0.66</strong></td>
<td><strong>0.0018</strong></td>
<td></td>
</tr>
<tr>
<td>E'/A'</td>
<td>0.15</td>
<td>0.34</td>
<td>0.58</td>
<td>0.07</td>
<td><strong>0.50</strong></td>
<td><strong>0.021</strong></td>
<td></td>
</tr>
<tr>
<td>RVEDP</td>
<td>E</td>
<td>-0.07</td>
<td>0.43</td>
<td>0.51</td>
<td>0.10</td>
<td>0.31</td>
<td>0.11</td>
</tr>
<tr>
<td>A</td>
<td>-0.01</td>
<td>0.49</td>
<td>-0.08</td>
<td>0.42</td>
<td>0.03</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>-0.08</td>
<td>0.42</td>
<td>0.44</td>
<td>0.14</td>
<td>0.29</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>E'</td>
<td>-0.04</td>
<td>0.46</td>
<td>-0.29</td>
<td>0.24</td>
<td>-0.33</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>A'</td>
<td>-0.01</td>
<td>0.49</td>
<td>-0.29</td>
<td>0.24</td>
<td>-0.16</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>E/E'</td>
<td>0.07</td>
<td>0.43</td>
<td>0.41</td>
<td>0.15</td>
<td><strong>0.46</strong></td>
<td><strong>0.03</strong></td>
<td></td>
</tr>
<tr>
<td>E'/A'</td>
<td>0</td>
<td>0.50</td>
<td>-0.09</td>
<td>0.42</td>
<td>-0.19</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

Figure 6-1 Relationship of RV tau to tricuspid E’
Relationship between RV tau and tricuspid E’. PHT patients are represented by open blue circles and non-PHT patients by open red circles.

The relationship between E/E' and RVEDP is presented graphically in Figure 6-2:

\[ r = -0.26, p = 0.15 \]

- ○ non-PHT
- ○ PHT
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

Figure 6-2 RVEDP vs tricuspid E/E'
Relation between RVEDP and tricuspid E/E'. PHT patients are represented by open blue circles and non-PHT patients by open red circles. The regression line is shown for the combined population with 95% confidence intervals.

The outlier data point to the top of the graph was from a patient in the PHT group with mitral stenosis. On further interrogation, this patient had a low E' compared to the other patients studied, raising the possibility that this patient fundamentally represents a different population. However, following exclusion of this data point, the relationship between E/E' and RVEDP remained significant and of similar magnitude ($r=0.47$, $p=0.03$). The 95% confidence intervals are wide for this relationship, regardless of the outlier point (-0.04 < $r$ < 0.78).
Results 3: Comparison of echocardiographic parameters with invasive measurements of right ventricular diastolic function

Figure 6-3 RV dP/dt min vs tricuspid E'.

Relationship between RV dP/dt min and tricuspid E'. PHT patients are represented by open blue circles and non-PHT patients by open red circles. The regression line is shown for the combined population with 95% confidence intervals.

Figure 6-3 presents the relationship between RV dP/dt min and tricuspid E'.

6.4 Discussion

Previous work in patients with scleroderma has suggested the presence of right ventricular diastolic dysfunction, manifested by abnormal E’ and E/A ratios, in the absence of formally diagnosed pulmonary hypertension (158,166,167). Our study, which included patients with a number of different aetiologies of pulmonary hypertension, and patients with higher pulmonary pressures than those studied previously, failed to detect a difference in E’ or E/A ratio in patients with pulmonary hypertension compared to normal patients. This raises the possibility that the diastolic abnormalities seen in scleroderma patients are related to intrinsic involvement of the myocardium by disease, rather than a secondary effect from pulmonary hypertension.
A difference in E/A ratios between the two groups was not shown in this study. It is hypothesised that as right ventricular diastolic dysfunction progresses, the E/A ratio decreases, coinciding with impaired relaxation, and then progressively increases, back through a normal range (pseudo-normal) until it becomes elevated, consistent with restrictive filling (147). Therefore, if there were a wide range of E/A ratios in the pulmonary hypertension group, including low, high and pseudo-normal ratios, it would be theoretically possible that the average E/A ratio would be similar to a normal group. This is unlikely in our study, as the standard deviations of values were similar in both groups.

Our findings likely indicate that in patients with mild pulmonary hypertension, the E/A ratio is not sensitive enough to detect a difference in diastolic function. In contrast, Huez et al studied patients with severe pulmonary hypertension (with average PASP greater than 71mmHg), and were able to show a clear difference in E/A ratio compared with a normal group (160).

We also found no difference in E', E/E', or E'/A' between the two groups of patients studied, despite a clear and significant difference in RV tau. This may also indicate that these measures are not sensitive to small changes in diastolic function in mild pulmonary hypertension. However, in a study of patients with severe pulmonary hypertension (mean estimated PASP of 73mmHg), Ruan et al found a significantly reduced tissue Doppler E' compared to normal controls (171). Huez et al also found reduced E' and E'/A' ratios in a severe pulmonary hypertension population (160).

Our finding that no parameter correlated significantly with RV tau further highlights the insensitivity of echocardiographic measures to changes in right ventricular diastolic function. Specifically, there was no correlation between RV tau and either E' or E/E', suggesting that although these parameters are useful in assessing left ventricular diastolic function, they have no utility in the right ventricle. Nevertheless, E', E/E', and E'/A' correlated with the load dependent
measure RV dP/dt min. While E and E’ are known to be load dependent, E'/A' has been shown to be relatively independent of load (146). This finding is probably of minor importance, since dP/dt min is not thought to be a clinically useful variable.

Our results are in conflict with those of Okumura et al, who performed a similar study in children with pulmonary hypertension related to congenital heart disease (128). They found significant but modest correlations between tau and E', E/E' and A wave velocity, while dP/dt min only correlated significantly with A'. Some of these findings are difficult to explain, as they would suggest that echocardiographic parameters of late diastole correlate with early relaxation. It may be that there are fundamental differences between this paediatric population and adults. It is also possible that our study was underpowered to detect a significant relationship. However, if this were true and higher patient numbers were required, any correlation would be modest and extremely unlikely to be of clinical utility.

Perhaps the most important development in the non-invasive assessment of left ventricular diastolic function were methods to estimate left atrial pressure. This is critical in the left ventricle as it is a difficult quantity to measure, even invasively. In contrast, right atrial pressure can be measured more easily by invasive methods, and significant elevations in right atrial pressure can be appreciated by physical examination.

We confirmed the findings of Nageh et al and Utsunomiya et al that tricuspid E/E' correlates with right ventricular filling pressures (152,172). However, similar to those studies, the confidence intervals of this relationship are wide, suggesting limited clinical utility, when there are many methods available to estimate right atrial pressure (156). In other words, it would not be possible to define an appropriate cut-off point for E/E' to predict a "high" RVEDP.
Interestingly, the echocardiographic measures of right ventricular systolic function, TAPSE and tricuspid annular S' were not significantly different between groups while a significant difference was again seen in RV \( \text{tau} \). This lends weight to the argument that abnormal right ventricular relaxation can exist in patients with pulmonary hypertension, prior to abnormalities of right ventricular systolic function becoming evident on routinely available clinical investigations such as echocardiography.

### 6.5 Limitations

This was a relatively small study, however the simultaneous comparison of echocardiography to invasive gold standards of early relaxation is logistically difficult to accomplish for large patient numbers.

Echocardiography was challenging to perform in the cardiac catheter laboratory during an invasive study, with bright background lighting and with patients in the supine position. It is possible that this patient position could subtly change interrogation angles of the Doppler signals with respect to the tricuspid annulus compared to images acquired routinely in clinical practice. Furthermore, many of the patients had concomitant pulmonary disease that limited available imaging windows. In retrospect, it may have been fruitful to also acquire a full echocardiogram on the same day as the invasive study under optimal conditions.

### 6.6 Conclusion

The echocardiographic parameter E/E' was correlated with RVEDP, however the clinical utility of this may be limited by wide confidence intervals. Some echocardiographic measures of RV diastole, including E', E/E' and E'/A' were associated with load dependent measures of RV relaxation, however none were correlated with RV \( \text{tau} \). These findings indicate that these echocardiography
techniques are not sensitive enough to differentiate patients with abnormal early relaxation.
7 Results 4: Pulmonary wave reflection analysis

7.1 Introduction

Wave reflection is an important component of pulmonary artery pulsatile hydraulic load on the right ventricle, and may be associated with stiffness in the pulmonary artery. However, the relationships between the pulmonary augmentation index (PAI) and traditional, static measures of right ventricular afterload have not been previously evaluated. In the systemic circulation, augmentation index is correlated with systolic blood pressure (257). We speculated that there might be significant associations given that the absolute pulmonary pressure is a fundamental component in the calculation of the augmentation index.

Previous studies have suggested that the pulmonary augmentation index and time to the inflection point of wave reflection are linked to the underlying pathology of pulmonary hypertension, in patients with chronic thromboembolic disease and pulmonary arterial hypertension (218,219). We hypothesised that this may also be the case for pre vs post-capillary pulmonary hypertension.

7.2 Methods

7.2.1 Study population

Twenty-five patients undergoing right heart catheterisation for the investigation of dyspnoea and/or suspected pulmonary hypertension were studied.

7.2.2 Study protocol

The patients were again divided into non-PHT and PHT groups based on an mPAP cut-off value of 25mmHg, which resulted in seven patients in the non-PHT group and 19 patients in the PHT group. To test the hypothesis that
different aetiologies of pulmonary hypertension might have different indexes of wave reflection, the PHT group was further divided into low and high PAWP groups. This was based on the haemodynamic classification of PHT into pre-capillary PHT with PAWP ≤ 15mmHg and post-capillary PHT with PAWP > 15mmHg (see Table 1-2), and resulted in 10 patients in the high PAWP group, and nine in the low PAWP group.

Studies were undertaken in the cardiac catheterisation laboratory with subjects in the supine position. All patients underwent routine right heart catheterisation using a Swan-Ganz catheter from the right femoral venous approach and haemodynamic data was obtained in a standard fashion. A high fidelity micromanometer mounted at the distal tip of a 0.014 inch diameter guidewire (Radi PressureWire, St Jude Medical), was calibrated and advanced to a stable position in the proximal pulmonary artery via a 7Fr Multi-Purpose guiding catheter. Continuous pressure data was obtained at 100Hz for at least five cardiac cycles.

The methodology to identify the inflection of point of wave reflection and the pulmonary augmentation index is described in detail in 3.6. Briefly, the inflection point of wave reflection was determined as the point of first zero crossing from positive to negative of the fourth derivative of the pressure/time curve. PAI was calculated as the ratio of the difference in pulmonary artery systolic pressure to the pressure at the inflection point of wave reflection over the total pulmonary pulse pressure. Tinf was defined as the time between the pulmonary artery minimum diastolic pressure and the inflection point. Because of the possible interaction of heart rate and time to wave reflection, a heart rate indexed Tinf was also calculated.
7.2.3 Statistical analysis

The demographic data of the three groups was analysed by one way ANOVA. The pulmonary haemodynamic data and indexes of wave reflection were compared by multiple t-tests with Holm-Sidak correction for multiple comparisons. Multiple Pearson correlations were performed to assess correlations between wave reflection indexes and standard measures of static right ventricular afterload. Results are expressed as mean ± standard deviation. Statistical significance was set at a value of p<0.05.

7.3 Results

The augmentation index was able to be determined in 25 of the 26 patients studied. In the remaining patient, the inflection point of wave reflection could not be identified, and this patient was therefore excluded from further analysis, leaving six patients in the non-PHT group. This patient had unequivocally normal pulmonary artery pressures, and it is therefore possible that very little wave reflection was present.

The demographics of the groups studied are described in Table 7-1. There were no significant differences with respect to age, gender or BMI. As anticipated, patients with pulmonary hypertension tended to be in a poorer NYHA functional class.
Table 7-1 Demographics of the Non-PHT and PHT (low and high PAWP) groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PHT</th>
<th>PHT Low PAWP</th>
<th>PHT High PAWP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59.3±10.6</td>
<td>57.9±13.2</td>
<td>64.4±7.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Male</td>
<td>1 (17%)</td>
<td>4 (44%)</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.2±1.9</td>
<td>32.2±8.9</td>
<td>26.7±4.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class 1:2:3:4</td>
<td>0:6:0:0</td>
<td>0:4:5:0</td>
<td>0:7:3:0</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel antagonist</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

The pulmonary haemodynamics and indexes of wave reflection in the PHT and non-PHT groups are presented in Table 7-2. As expected, the PHT group was characterised by significantly higher pulmonary pressures, although pulmonary vascular resistance was not significantly greater. There was a trend to a higher heart rate in the PHT group, and cardiac output was significantly higher. There were no significant differences between the two groups with respect to augmentation index or time to inflection point, even when corrected for heart rate.
Table 7-2 Pulmonary haemodynamics and indexes of wave reflection for non-PHT and PHT patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PHT</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>29.5±6.5</td>
<td>54.7±19.9</td>
<td>0.006</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>9.8±2.8</td>
<td>21.8±8.5</td>
<td>0.002</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>18±3.8</td>
<td>35.8±12</td>
<td>0.001</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>8.3±3.7</td>
<td>16.3±7.6</td>
<td>0.021</td>
</tr>
<tr>
<td>PVR (Wood Units)</td>
<td>2.1±1.0</td>
<td>3.2±2.6</td>
<td>0.32</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>65±10</td>
<td>77±13</td>
<td>0.05</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.9±0.7</td>
<td>6.5±1.7</td>
<td>0.03</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>76.4±11.6</td>
<td>87.6±24.3</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Wave reflection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.21±0.16</td>
<td>0.30±0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Time to inflection point (ms)</td>
<td>140±50</td>
<td>120±50</td>
<td>0.4</td>
</tr>
<tr>
<td>Time to inflection point / HR</td>
<td>2.3±1.1</td>
<td>1.7±0.9</td>
<td>0.19</td>
</tr>
</tbody>
</table>

The PHT group was further separated into low and high PAWP groups, and the pulmonary haemodynamic and wave reflection data is described in Table 7-3. The groups were similar with respect to pulmonary pressures, with a trend towards a lower cardiac output in the high PAWP group. While there was no significant difference in the augmentation index between the two groups, the high PAWP group had a longer time to inflection point, which remained significant when corrected for heart rate.
Table 7-3 Pulmonary haemodynamic and indexes of wave reflection for low vs high PAWP patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low PAWP</th>
<th>High PAWP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>56.8±15.6</td>
<td>52.9±23.8</td>
<td>0.68</td>
</tr>
<tr>
<td>PADP (mmHg)</td>
<td>19.3±5.3</td>
<td>24.0±10.4</td>
<td>0.24</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>35.3±8.6</td>
<td>36.3±14.8</td>
<td>0.86</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>9.9±2.0</td>
<td>22.1±5.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR (Wood Units)</td>
<td>3.7±1.7</td>
<td>2.7±3.3</td>
<td>0.43</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>79±10</td>
<td>76±16</td>
<td>0.64</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>7.3±1.9</td>
<td>5.8±1.1</td>
<td>0.05</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>93.6±23.2</td>
<td>82.3±25.2</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Wave reflection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.36±0.20</td>
<td>0.25±0.18</td>
<td>0.22</td>
</tr>
<tr>
<td>Time to inflection point (ms)</td>
<td>100±30</td>
<td>150±50</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to inflection point / HR</td>
<td>1.3±0.5</td>
<td>2.1±1.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Representative examples from each group are shown in Figure 7-1.

**Figure 7-1 Examples of pressure waves in high and low PAWP**

A representative time/pressure trace in a patient with (A) high PAWP and (B) low PAWP. Both patients have similar pulmonary augmentation index, however the time to inflection point is shorter in the patient with low PAWP.

Relationships between traditional measures of static right ventricular afterload and the augmentation index are shown in Figure 7-2. There were significant positive correlations between mPAP, PVR and TPG with the pulmonary augmentation index. There were significant negative correlations between mPAP, PVR and TPG with the time to inflection point.
Figure 7-2 Relationships between traditional measures of right ventricular afterload and indexes of wave reflection

Boxes A-C show the relationship between the pulmonary augmentation index and (A) mPAP, (B) PVR and (C) transpulmonary gradient. Boxes D-F show the relationship between the time to inflection point and (D) mPAP, (E) PVR, and (F) transpulmonary gradient.
7.4 Discussion

There is significant variation in the pulmonary augmentation index and time to inflection point that is explained by traditional measures of right ventricular afterload. This is perhaps not surprising, given that the augmentation index has been proposed as a marker of both static and pulsatile components of right ventricular load. Furthermore, a degree of co-linearity would be expected for the augmentation index given that its formula incorporates aspects of pulmonary pressure. However, the time to inflection point would not be expected to be affected by this phenomenon, and therefore may represent an independent means of assessing the pulmonary vasculature.

Despite these relationships, it was not possible to separate a "normal" group from a group of patients with pulmonary hypertension by means of either the augmentation index or the time to wave reflection. This probably reflects that the confidence intervals for these relationships are wide, and will therefore also limit their clinical usefulness.

However, it was possible to demonstrate a difference in the time to wave reflection between patients with pre and post-capillary pulmonary hypertension. To our knowledge, this is the first time this has been demonstrated, although it parallels previous studies that indicated a difference in augmentation index and time to inflection in patients with pulmonary arterial hypertension compared to those with chronic thrombo-embolic disease (218,219). In these studies, patients with chronic thrombo-embolic disease tended to have shorter times to inflection and higher augmentation indexes than those with pulmonary arterial hypertension. The implication of these results is that different pathological process may result in different patterns of wave reflection. For example, in chronic thromboembolic disease, the site of obstruction to the pulmonary tree is more proximal, and there may be abnormal mechanical properties and geometry of the proximal pulmonary arteries. This could be contrasted with pulmonary arterial hypertension, where the pathology mainly affects the distal
pulmonary arteries. Our findings suggest that although the magnitude of wave reflection is unchanged, patients with post-capillary pulmonary hypertension have even later wave reflection compared to those with pulmonary arterial hypertension (although the timing is likely similar to those without pulmonary hypertension). This is consistent with the pathology of patients with pulmonary arterial hypertension, who have obstruction at the level of the small pulmonary arteries or arterioles (9,10). This is in contrast to patients with pulmonary hypertension due to left heart disease, where obstruction is likely to be at the level of the pulmonary capillaries and into the left side of the circulation.

There exists a group of patients with post-capillary pulmonary hypertension and so-called “out of proportion” pulmonary hypertension, characterised by an increased trans-pulmonary gradient. These patients are thought to have a superimposed component of reactive remodelling in the pulmonary arterioles, causing an elevation in the pulmonary pressure higher than would be anticipated based on the increased PAWP alone (258). Our results indicate that the time to wave reflection is moderately inversely correlated with the trans-pulmonary gradient (albeit in all patients), suggesting that the site of wave reflection may be related to the degree of secondary pulmonary arteriolar obstruction. This finding is unlikely to be clinically useful, as the trans-pulmonary gradient is already straightforward to calculate during standard right heart catheterisation.

### 7.5 Limitations

The Radi PressureWire samples pressure at 100Hz, rendering accurate identification of the inflection point of wave reflection difficult in some patients, and lead to the exclusion of one patient. A higher fidelity micromanometer may have increased confidence in the identification of the inflection point and allowed for assessment of the entire patient group. However, the benefit of using our technique is that it utilises technology readily available in most cardiac catheterisation laboratories.
Pulmonary arterial stiffness was not assessed, which would have allowed for further characterisation of the relative contributions of static and pulsatile flow to the augmentation index.

Lastly, this was a small study that highlighted the challenges of classifying this diverse patient group. The PAWP was chosen to further categorise our patients, but the underlying pathophysiologic aetiologies of pulmonary hypertension were more varied than is reflected by this parameter. Furthermore, other variables are likely important in explaining wave reflection in the pulmonary artery, such as duration of disease and treatment status, which are difficult to integrate appropriately into studies with small patient numbers.

### 7.6 Conclusion

There is considerable overlap between traditional measures of right ventricular afterload and the pulmonary augmentation index. While the magnitude of wave reflection was similar, the time to inflection point was shorter in patients with pre-capillary pulmonary hypertension than those with pulmonary hypertension due to left heart disease, and was inversely related to the trans-pulmonary gradient.
Results 4: Pulmonary wave reflection analysis
8 Conclusions

An invasive measure of early active relaxation (tau) in the right ventricle is abnormal in patients with pulmonary hypertension compared to human patients with “normal” pulmonary pressures. This builds on previous evidence that this occurs in other animals, and that right ventricular diastolic stiffness is abnormal in humans with pulmonary hypertension. There is also a parallel to be drawn to a similar phenomenon of left ventricular diastolic dysfunction developing in the setting of systemic hypertension.

Right ventricular tau was found to be abnormal in patients with pulmonary hypertension while measures of right ventricular contractility were static or increasing, suggesting that right ventricular diastolic dysfunction occurs prior to the development of overt systolic dysfunction. A significant problem in the contemporary diagnosis of pulmonary hypertension is the reliance on the pulmonary pressure itself for diagnosis. It is clear that many patients who have a mean pulmonary arterial pressure of close to the cut-off threshold of 25mmHg, have substantially greater pressure than what would be anticipated under normal conditions, and may later have a formal diagnosis of pulmonary hypertension. This suggests that the ideal use of right ventricular tau might be in conjunction with the pulmonary pressure to better characterise patients with borderline disease, and to potentially allow for earlier diagnosis and initiation of treatment. The relationship of RV tau to prognosis is also unknown. Further work is needed to clarify these issues.

Abnormal right ventricular relaxation is associated with higher RV filling pressures, which could be clinically important, as higher right atrial pressures have been associated with poorer prognosis in patients with pulmonary arterial hypertension and heart failure. When higher right atrial pressures are transmitted to the venous circulation, renal function can also be affected.
Future study could also address the question of whether different patterns of right ventricular diastolic dysfunction emerge from different underlying aetiology of pulmonary hypertension. Specifically, whether a patient with pulmonary hypertension secondary to left sided heart disease has a fundamentally different right ventricular adaptation to a patient with pulmonary arterial hypertension. There is also an outstanding question as to whether patients with scleroderma have intrinsic myocardial involvement resulting in a degree of RV diastolic dysfunction, independent of the pulmonary artery pressure. This may help to clarify why prognosis varies so widely depending on the underlying pulmonary hypertension pathology.

Right ventricular relaxation could theoretically be measured invasively in routine clinical practice with equipment readily available in many cardiac catheterisation laboratories in the developed world. However, further validation work is required in larger patient numbers to study normal ranges, confounding factors and temporal variability. Confidence intervals are relatively wide, which may limit the application of this measurement for an individual patient.

Ideally, one would measure accurate pressure-volume loops in the right ventricle to be able to better characterise the entirety of right ventricular diastolic function. The simultaneous measurement of right ventricular volume with pressure remains challenging with current technology, although a hybrid CMR and cardiac catheter laboratory setup could potentially overcome this issue in future studies.

A limited evaluation of the load dependence of right ventricular tau was undertaken, in the setting of a human study. Although adenosine has been used widely as an effective pulmonary vasodilator, it did not substantially change right ventricular afterload, and therefore could be considered as “not fit for purpose”. True assessment of load dependence will continue to be challenging in human studies, however future work might explore the possibility
of using preload modification with a fluid bolus, or afterload modification with a more selective pulmonary vasodilator such as sildenafil.

The echocardiographic measures studied were insensitive to detect abnormal right ventricular relaxation in patients with mild to moderate pulmonary hypertension. This contrasts with findings in a small number of other studies which did show differences in patients with pulmonary hypertension, albeit in patient groups with much higher pulmonary pressures. Overall, the pulsed wave and tissue Doppler echocardiographic measures of RV diastolic function studied only correlated with load dependent invasive measures, rather than the relatively load independent $\tau$.

Echocardiographic measures of right ventricular systolic function were also not significantly different in patients with pulmonary hypertension, despite a different RV $\tau$, adding further weight to the concept that diastolic dysfunction occurs before overt, clinically measurable systolic dysfunction.

The relationship between tricuspid E/E’ with right ventricular filling pressures (and thereby right atrial pressure) was confirmed, however the confidence intervals of this relationship are wide. In clinical practice, it would be more appropriate to use a different method to estimate right atrial pressure, and these are already ubiquitous.

Current guidelines from the American Society of Echocardiography suggest a possible role for measuring right ventricular diastolic function as a marker of early or subtle dysfunction in patients with suspected right ventricular dysfunction. A proposed grading system for right ventricular diastolic dysfunction has also been proposed. Caution must therefore be applied to the interpretation of these guidelines in light of the data presented in this thesis. Further work is required to explore the relationship of other novel measures of right ventricular diastolic function such as RV diastolic strain to invasive measurements.
The pulmonary augmentation index parallels changes in standard measures of right ventricular afterload, and therefore likely does not add any useful information in the assessment of patients with pulmonary hypertension. However, the time to the inflection point of wave reflection was able to differentiate patients with pre and post capillary pulmonary hypertension. This suggests that the site of wave reflection is influenced by the degree of pulmonary arteriolar obstruction. Although this is unlikely to be clinically useful, it adds to the understanding of this disease process.

Based on these findings, it would not be recommended to routinely measure a pulmonary augmentation index in clinical practice. However, better measures of the pulsatile component of right ventricular load are needed, as this may be important in determining the pattern or degree of right ventricular adaptation to pulmonary hypertension. While pulsatile load can be expressed easily in the frequency domain, further work is required to transform this into a readily measurable and relevant clinical measurement, and a novel approach will likely be needed.
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10 Appendices

10.1 Location of research

All the studies were carried out in the Cardiac Investigations Unit at St Vincent's Hospital Melbourne.

10.2 Supervision

Primary project supervisor: Dr Andrew Burns

Secondary supervisor: A/Prof David Prior

10.3 Funding

1. Research higher degree scholarship, University of Melbourne 2011

2. Unrestricted grant from Actelion Pharmaceuticals
Author/s: Murch, Stuart David

Title: Advanced characterisation of pulmonary hypertension: Assessment of right ventricular diastolic function and pulmonary artery wave reflection

Date: 2016

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