Ambulatory Pulmonary Artery Pressure Monitoring in Pulmonary Vascular Disease in Man

A thesis by

DAVID ALEXANDER RAESIDE MB ChB, MRCP

Submitted for the degree of Doctor of Medicine

to

The University of Glasgow

From

The Scottish Pulmonary Vascular Unit
Western Infirmary
Glasgow G11 6NT

September 2002

Dedication

To Jane and Tom.

Declaration

The work for this thesis was carried out during my tenure as a clinical research fellow in the Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow. All studies reported have been published or submitted for publication. A list of these papers is included as is a list of presentations and published abstracts.

All the work presented in this thesis was carried out by, me with the assistance of friends and colleagues who are formally acknowledged. I performed the statistical analyses and the writing of this thesis was entirely my own work.

Acknowledgements

The work for this thesis was carried out under the supervision of Dr Andrew Peacock. His encouragement, patience and perseverance were greatly appreciated, as was his (essential) sense of humour. Andy made the unit, above all else, a fun place to work.

None of this work would have been possible without the help and advice of Dr David Welsh, Chief Scientist in the Scottish Pulmonary Vascular Unit. Initially a research collaborator his generous encouragement and tireless willingness to assist in any way he could has been of enormous support to me.

Dr Kanti Patel, Consultant Respiratory Physician, guided me patiently through the early mysteries of cardiopulmonary exercise testing and Mrs Aileen Brown, Senior Respiratory Technician was more than generous with her time in helping me carry out the exercise tests. I am grateful to both.

The work presented in this thesis was made possible by a British Heart Foundation project grant. I am forever indebted to the volunteers and charity workers whose efforts afforded me the luxury of two years devoted to full time research.

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List of Abbreviations

CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CREST	Calcinosis, Raynauds phenomenon, oEsophageal involvement, Sclerodactyly, Telangectasia
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CVD	Collagen vascular disease
CXR	Chest radiograph
ECG	Electrocardiogram
EDRF	Endothelium derived relaxing factor
HIV	Human immunodeficiency virus
HPV	Hypoxic pulmonary vasoconstriction
INR	International normalised ratio
LAP	Left atrial pressure
LVEDP	Left ventricular end diastolic pressure
MCTD	Mixed connective tissue disease
MRI	Magnetic Resonance Imaging
NO	Nitric oxide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAOP	Pulmonary artery occlusion pressure
PAP	pulmonary artery pressure
PAP_m	Mean pulmonary artery pressure

PHT	Pulmonary hypertension
PSS	Progressive systemic sclerosis
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RAD	Right axis deviation
RVH	Right ventricular hypertrophy
SLE	Systemic lupus Erythematosis
TPR	Total pulmonary resistance

Published Papers Relating to this Thesis

Raeside DA, Peacock AJ Making measurements in the pulmonary circulation: when and how? Editorial. *Thorax* 1997; **52** (1):9-11.

Peacock AJ, Raeside DA Pulmonary Hypertension. *Presciber's Journal* 1998;**3**:158-166.

Raeside DA, Chalmers G, Clelland J, Madhok R Peacock AJ Pulmonary artery pressure variations in patients with connective tissue disease: 24 hour ambulatory pulmonary artery pressure monitoring. *Thorax* 1998;**53**(10):853-857.

Raeside DA, Smith A, Brown A, Patel KR, Madhok R, Cleland J, Peacock AJ Pulmonary artery pressure measurement during exercise testing in patients with suspected pulmonary hypertension. *Eur Resp J* 2000;**16**:282-287.

Raeside DA, Brown A, Patel KR, Welsh DJ, Peacock AJ ambulatory pulmonary artery pressure monitoring during sleep and exercise in normal individuals and patients with COPD. *Thorax* 2002;**57**:1050-1053.

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Presentations and Abstracts

Raeside DA, Chalmers GC, Peacock AJ. Pulmonary artery pressure variations in patients with connective tissue disease: 24 hour ambulatory pressure monitoring. Verbal presentation, *European Respiratory Society*, Stockholm September 1996.

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Am J Respir Crit Care Med 1997;**159**(3):A168.

Abstract

The pulmonary circulation is a relatively dynamic environment in comparison to the systemic circulation. There is no easily applied sphygmomanometer for the pulmonary circulation and conventional methods of measurement have limitations which reduce their usefulness. New treatments for pulmonary hypertension have improved considerably the prognosis for many patients and there is an emerging consensus that they are more effective if given earlier in the course of the disease. However these treatments are expensive and inconvenient to the patient and must be utilised in the context of high quality, objective assessment of the pulmonary circulation, both before and during treatment.

Ambulatory pulmonary artery pressure monitoring has been used in patients with heart disease to provide an indicator of left ventricular haemodynamics. It had not been used in patients with pulmonary vascular disease due to other causes before and has been shown to be safe and well tolerated in this group.

The hypothesis of this thesis was that ambulatory pulmonary artery pressure monitoring, by allowing assessment of the pulmonary circulation in a variety of real life situations in which patients commonly report symptoms, would permit the correlation of symptoms with haemodynamic changes in the pulmonary vasculature. These high fidelity pressure measurements in a low pressure system might permit a greater understanding of the total haemodynamic burden faced by these patients and (if abnormal pulmonary vascular responses to stress are indicative of the future development of pulmonary hypertension) may facilitate the early diagnosis of pulmonary hypertension.

In this thesis ambulatory pulmonary artery pressure monitoring has been used to assess changes in pulmonary artery pressure with posture in a group of patients with

pulmonary hypertension secondary to connective tissue disease, during exercise and sleep in a group with chronic obstructive pulmonary disease compared with normal individuals and during exercise in a group with connective tissue disease where pulmonary artery pressure was correlated with non-invasively measured variables measured during cardiopulmonary exercise testing. These non-invasively measured variables were then used to assess the response to conventional treatment in a group of patients with pulmonary hypertension secondary to connective tissue disease.

These studies have shown that pulmonary artery pressure varies considerably in these circumstances and that rises in pulmonary artery pressure are not always predicted by resting pressure and can be correlated with symptoms. This work suggests that the contribution of secondary pulmonary hypertension to morbidity and mortality in patients with lung disease is considerable and underestimated.

The technique of ambulatory high fidelity pressure measurement obtains a more complete picture of the haemodynamic variations induced by normal daily activity and under stress and contributes to our appreciation of the morbidity of pulmonary hypertension. Abnormal pulmonary vascular responses in these circumstances in individuals with normal resting pressure allows the identification of those at risk of resting pulmonary hypertension thus facilitating the early diagnosis of pulmonary vascular disease. The identification (during exercise) of non-invasive surrogates of pulmonary artery pressure is an area for future study since non-invasive, repeatable and reliable assessment of the pulmonary circulation is highly desirable.

Chapter 1

Introduction

1 General Introduction

Primary pulmonary hypertension (PPH) is a rare and devastating condition, but pulmonary hypertension (PHT) also occurs as a consequence of most heart and lung diseases where it is largely unrecognised and untreated and is therefore a major clinical challenge. The consequence of this failure to assess the pulmonary circulation is that the process may progress to the point where treatment is less likely to be beneficial. It is because the symptoms and signs of pulmonary hypertension are often rather vague and non-specific that it is important to be aware of methods of measurement in the pulmonary circulation and their sensitivity, specificity and relative merits. There is no easily applied sphygmomanometer for the pulmonary circulation, but there are a number of techniques – both invasive and non-invasive – which can help us to make the diagnosis. Implicit in the desire to make an earlier diagnosis of pulmonary hypertension is the belief that there is some point in doing so – that is, that the condition itself is of significance and that we may be able to offer some additional treatment to the patient. This thesis will describe the available methods of measurement in the pulmonary circulation and focus on the novel technique of ambulatory pulmonary artery pressure monitoring. This technique has not been used previously in patients with pulmonary hypertension secondary to lung disease. Ambulatory pulmonary artery pressure measurement allows the detection of pulmonary hypertension on exercise in patients with normal resting pressure and thus offers an opportunity to detect the development of pulmonary hypertension in its earliest stages.

1.1 Structure and Function of the Normal Pulmonary Circulation

The human pulmonary circulation has been conventionally regarded as a low - pressure conduit designed to facilitate gas exchange and subject to relatively little vaso-motor control. Despite this however, a variety of physiological and physical influences effect a balance between vasoconstriction and vasodilatation, growth promotion and growth inhibition and many of the complex relationships between these factors are not fully understood.

Thus the pulmonary circulation retains an element of "plasticity" when compared with the systemic circulation and in particular has the ability to react to changing pressures and consequently demonstrates the complex anatomy and physiology this entails. In order to assess the value of any new method of measurement of the pulmonary circulation it is important to first appreciate the normal responses of this system. The basic anatomical structure of the pulmonary circulation, aspects of pulmonary vascular function and regulatory mechanisms will be described here

1.1.1 Anatomy of the Pulmonary Circulation

In contrast to the systemic circulation where the capillary system is configured to deliver the minimum nutritional requirement, in the pulmonary circulation the goal is gas exchange. At rest the pulmonary circulation is a low-pressure system ideally suited to facilitate gas exchange with the alveolar space and to minimise demand on the right heart. The normal pulmonary artery is about 30% less thick than the healthy aorta and the small pulmonary arterioles contain very little muscle. Small pulmonary arteries are lined by an initma consisting of endothelium and basement membrane. The medial layer is made up of vascular smooth muscle and the whole is lined by both an internal and external elastic lamina (double elastic lamina). The extracellular

matrix consists of the fibroblast layers. The precursors to vascular smooth muscle cells are the intermediate cells or pericytes. Pericytes are found in the non-muscular regions of the vessel wall and intermediate cells in the partially muscularised arteries. This muscle coat thins and eventually disappears, and the thickness of the adventitial compartment decreases, before the pulmonary capillary bed (Reid *et al* 1982). Generally, vessels with an external diameter of <80μm are non-muscularised while those with a diameter between 80 and 120μm are partially muscularised. Pericytes are found in non-muscular walls and intermediate cells (between pericytes and smooth muscle cells) are found in partially muscularised arteries. (Meyrick *et al* 1978) A variety of stimuli can cause all three layers of the pulmonary artery to proliferate, the process of pulmonary vascular remodelling (Chapter 1.2).

The complex nature of the pulmonary circulation has made its quantification difficult. Consequently an ordering system was developed (Strahler *et al* 1957) describing the circulation as being akin to the tributaries of a river, in which branching vessels are numbered, 1 being assigned to smallest peripheral vessel with the value increasing backwards toward the hilum.

Pulmonary capillaries are large with frequent anastamoses, such that the alveoli are supported in a mesh of blood vessels, which have been described as **alveolar** and **extra alveolar** vessels (Howell *et al* 1961).

1.1.1.1 Extra Alveolar Vessels

Extra alveolar vessels are unique to the lung as are its conducting vessels. The arteries are of two types, axial or supernumerary (Hislop *et al* 1973). The former are so called because they run alongside the bronchi within the wedge shaped units which compose the lung. The latter (which greatly outnumber the former) leave the axial arteries at

90° and insert into the alveolar parenchyma where they branch and end by opening into the capillary networks at different locations. Thus, unlike their counterparts in the systemic circulation, the pulmonary capillaries are periodically fed and drained by arterioles and venules. These arteries, (axial or supernumerary) are never exposed directly to alveolar air but are always surrounded by a loose connective tissue sheath into which alveolar septae are inserted. Axial arteries share their connective tissue sheath with a bronchiole, whereas supernumerary arteries are in isolation. This connective tissue compartment is continuous throughout the lung parenchyma, all of its parts being in communication with each other. Consequently all these compartments, and the extra alveolar vessels they contain, are subject to the same, variable and negative air pressure.

1.1.1.2 Alveolar Vessels

The alveolar vessels constitute the pulmonary microcirculation. Unlike the situation in the systemic circulation (where the arterioles flow into capillaries which reform as venules) the pulmonary capillaries, as they enter the alveolar walls, are relatively disordered. Arterioles and venules feed and drain the capillary circulation at various points, and blood flows in different directions and into adjacent lung units. The alveolar wall is composed mainly of blood vessels separated from the air by a thin layer of cells. The alveoli can be considered to be virtually surrounded by a meshwork of blood vessels and there is controversy over exactly how blood flows in these. Weibel (1963) first described the theory of capillary blood flow while others describe the situation as blood flowing in sheets interrupted by "posts" of supporting tissue (Fung *et al* 1969). Re-oxygenated blood is then carried back to the left atrium in the

pulmonary veins. The conducting airways have an independent blood supply from the bronchial circulation. This carries a fraction of the blood volume of the pulmonary circulation and is much less important.

1.1.2 Function of the Pulmonary Circulation

This arrangement of alveolar and extra alveolar vessels is of great functional importance. The continuous, connective tissue compartment supporting the extra alveolar vessels is subject to a variable, negative pressure which increases during inspiration and is at its least on expiration. Thus the distensible, extra alveolar vessels become wider and longer on inspiration and the opposite on expiration. Alveolar vessels however are subject to the increased alveolar pressure during inspiration and may be collapsed with no flow: the exception to this are the "corner vessels" which are capillaries anatomically (situated in the alveolar microcirculation) but which behave like extra alveolar vessels in that they resist collapse on inspiration. This is because of their position in the connective tissue at the junctions of alveoli enabling them to resist collapse as alveolar pressure rises on inspiration; because of this ability to resist collapse with increased pressures, these vessels constitute an uninterrupted communication between the right and left sides of the heart, even when high pressures prevent flow in the rest of the system, and consequently are always available for gas exchange.

1.1.3 Passive Regulation of Pulmonary Haemodynamics

The vascular arrangement in the lung means that blood flow is exquisitely dependent on pressure, air, arterial or venous. The three zones of pulmonary blood flow have been described (West *et al* 1964) in which the different relationships of these pressures determine the prevailing conditions for gas exchange.

- Zone 1. Here air pressure exceeds arterial or venous pressure, and consequently blood can flow only through the corner vessels for the reasons discussed above. *In vivo* this state of affairs will not normally exist, except where air pressure is abnormally high (e.g. in ventilated patients) or blood pressure is abnormally low (e.g. following haemorrhage).
- Zone 2. Arterial pressure exceeds air pressure and venous pressure. Here the arterial pressure increases the farther down the lung while the alveolar pressure remains constant throughout and venous pressure is very low. This gives rise to increasing flows down the zone, the so called "waterfall effect". The pressure differences in this zone lead to the majority of capillaries being in a slit like state.
- Zone 3. Here arterial and venous pressures both exceed alveolar pressure. Unlike the other zones, these pressure relationships (i.e. venous pressure exceeds air pressure) mean that the capillaries bulge into the alveolar walls, which create very efficient conditions for gas exchange.

Other authors (Hughes *et al* 1975) have also described Zone 4 in which the increase in dependent blood flow is not seen and which cannot be explained in terms of arterial, venous or air pressures. Blood flow in zone 4 may be dependent on an increase in the

resistance of the extra alveolar vessels, although active control of the pulmonary circulation may be involved.

Thus gas exchange is variable throughout these zones with least favourable conditions existing in zone 1 and optimal conditions in zone 3.

1.1.4 Active Regulation of the Pulmonary Circulation

Because the pulmonary circulation is a low-pressure system it is very sensitive to mechanical influences as described above, and this can make measurements of pressure and flow very difficult. Active mechanisms of control (e.g. neuro-humoral) play a relatively small part in the regulation of the pulmonary circulation, with the notable exception of hypoxic pulmonary vasoconstriction (HPV).

1.1.4.1 Hypoxic Pulmonary Vasoconstriction

The pulmonary and systemic circulations differ fundamentally in their response to hypoxia. In the systemic circulation a drop in PO_2 leads to vasodilatation and increased local blood flow to maintain tissue oxygenation. In the pulmonary circulation HPV occurs, where a similar fall in PO_2 results in vasoconstriction to the affected lung unit, a drop in blood flow and hence the maintenance of arterial PO_2 (von-Euler and Liljestrand 1946). Since this initial observation on the arterial blood pressure in the cat, much progress has been achieved in the understanding of this phenomenon in animal models, but its exact nature in the human pulmonary circulation is still not fully understood.

HPV seems to exist in all mammalian species though varies considerably between species in its intensity. The response to hypoxia is initiated within 1-2 minutes and is

established between 3 and 5 minutes (Hughes 1975, Grover *et al* 1983, Fishman 1985).

The essential components of HPV consist of an oxygen sensor linked by a chain of events to an effector. The effector in the human pulmonary circulation is the pre-capillary smooth muscle cell; however there is still much debate over the nature and location of the oxygen sensor (Voelkel 1996).

The oxygen sensor may be a specific cell (or part of a cell) located in the airways. It seems likely that the stimulus to the oxygen sensor is delivered via the airways as isolated lung (i.e. perfused but not ventilated) demonstrates a very small HPV response when perfused with deoxygenated blood (Naieje 1996).

This physiological mechanism of hypoxic pulmonary vasoconstriction protects ventilation perfusion matching in the healthy lung and is most effective in mild ventilation perfusion mismatch. It is responsible for the pulmonary hypertension seen in the foetal circulation, in chronic hypoxic lung disease and in individuals who live continuously at high altitude. The mediator of this response remains unknown and a number of candidates have been ruled out including catecholamines, histamine, serotonin prostaglandins, Angiotensin II and leukotrienes. Recent attention has focused on L-arginine nitric oxide pathway as a possible candidate (Dinh-Xuan 1992).

1.1.4.2 Neural control of pulmonary vascular tone

The effects of neural influences on pulmonary vascular regulation are not fully understood. The pulmonary vasculature has long been known to be well supplied with sympathetic and cholinergic nerve endings. There is extensive evidence of adrenergic influence on the pulmonary vascular tone where α agonists produce vasoconstriction

and β agonists vasodilatation. The effects of sympathetic stimulation are less predictable however (Fishman 1985 and Grover *et al* 1983). Further work suggests that the sympathetic nervous system exerts a net vasodilator effect (Naieje *et al* 1989) although intense sympathetic stimulus is known to produce vasoconstriction (Fishman 1985 and Grover *et al* 1983). The parasympathetic nervous system is now thought not to influence normoxic or hypoxic pulmonary vascular tone (Lejeune *et al* 1989).

1.1.5 Humoral Control of Pulmonary Vascular Tone

A large number of mediators (Table 1.1) have been implicated in the humoral control of the pulmonary vasculature (Fishman 1985, Grover *et al* 1983 and Dinh-Xuan 1992).

With the exceptions of Prostacyclin and nitric oxide (NO) - both of which have been shown to reduce pulmonary vasculature tone in several experimental models - none of the others have been shown to have consistent effects on the pulmonary circulation.

From the foregoing it is clear that our understanding of the physiology and regulation of the pulmonary circulation is incomplete. It is on this basis that we must attempt to discuss the impact of disease on the pulmonary circulation.

Table 1.1

Vasodilators	Vasoconstrictors
Acetylcholine	Histamine
Bradykinin	Serotonin
Prostacyclin	Prostaglandin F series
Prostaglandin D_2	Angiotensin II
Prostaglandin E series	Vasopressin
Vasoactive intestinal peptide	Thromboxane A_2
Atrial naturetic peptide	Endothelin
Nitric oxide	Leukotrienes

Table 1.1 Vasoactive mediators in the pulmonary circulation

These substances are suspected mediators in the pulmonary circulation. With the exception of prostacyclin and nitric oxide (which are vasodilators) none of the others have been shown to have consistent effects.

1.2 Pulmonary Circulation in Disease

1.2.1 Pulmonary Vascular Remodelling

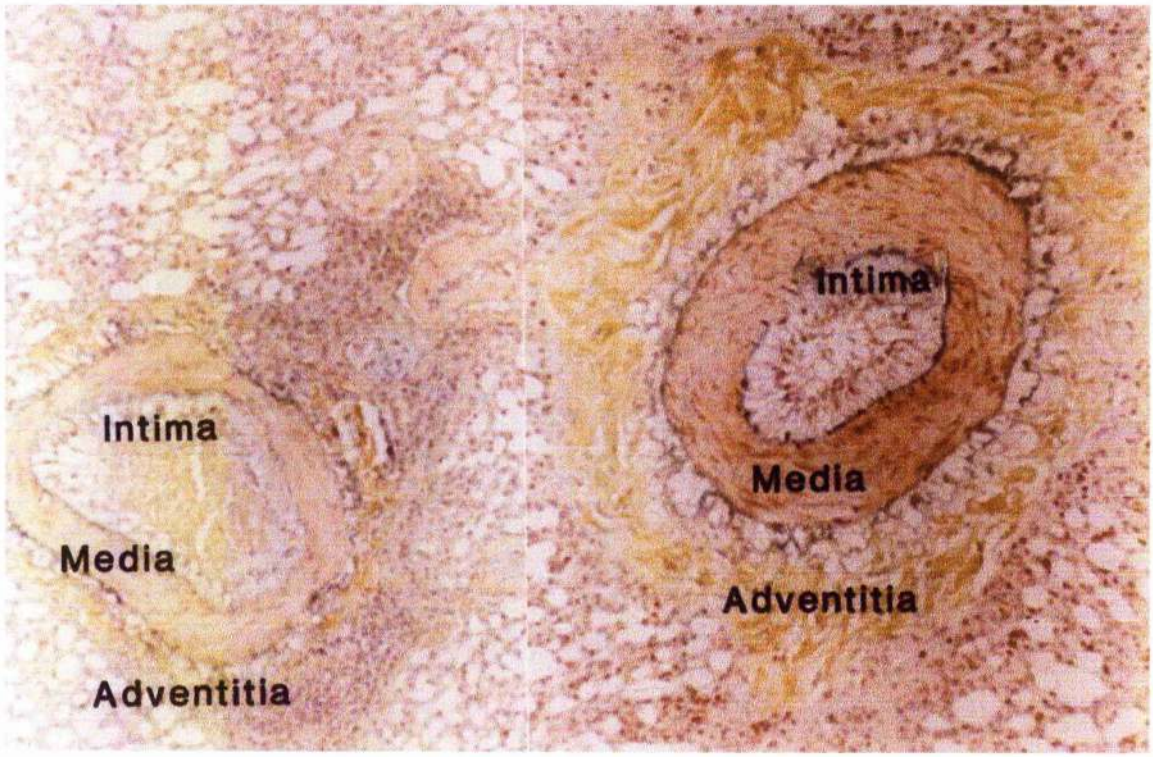
The pulmonary circulation is sensitive to changes in pressure (air, arterial or venous). In the short-term this is manifest as change in pulmonary vascular resistance while, in the longer-term, pulmonary vascular remodelling can occur. Pulmonary vascular remodelling is an important process clinically because it adversely affects the pulmonary circulation's response to therapy.

The pathological changes responsible for the clinical findings we associate with pulmonary hypertension are seen in the pre-capillary pulmonary arteries. These become muscularised and consequently there is interference with normal pressure and flow relationships in addition to functional changes in compliance and distensability (Hunter *et al* 1974, Reid *et al* 1982). In addition to increased muscle mass the pathological changes associated with pulmonary vascular remodelling may progress to include endothelial cell damage, inflammation, vessel wall destruction, intravascular thrombosis and intimal proliferation. (Wagenvoort *et al* 1979, Harris *et al* 1986) Changes also take place in the extra-cellular matrix and adventitia with synthesis and deposition of collagen and elastin and adventitial fibroblast proliferation (Welsh *et al* 1998), Figure 1.1. In the early stages these changes are reversible however in all models an irreversible element supervenes after a relatively short time.

1.2.1.1 Mechanisms of Remodelling

The mechanisms responsible for pulmonary vascular remodelling are complex and not yet fully understood, however they have been summarised as consisting of four separate events (Zhao and Winter 1996).

Figure 1.1



Normal **Pulmonary Hypertension**

Figure 1.1 Pulmonary Vascular Remodelling

The left hand panel shows a normal small pulmonary artery from a chicken. In the pulmonary hypertensive panel vascular smooth muscle has extended into normally non-muscularised arteries with an increase in the intima and media which encroaches on the lumen. The adventitia is also affected by the synthesis and deposition of collagen and elastin and adventitial fibroblast proliferation (American Review of Respiratory Disease).

1. the detection of altered physical and haemodynamic forces
2. the relay of the signals to the cells involved in the process of remodelling
3. the synthesis of the substances that may initiate and promote cell division and growth
4. alteration of the composition of both vessel wall and extracellular matrix

Clinical and experimental models have been developed to investigate a variety of candidate substances and conditions and from these much greater understanding of the processes involved in remodelling has been gained.

Although vasoconstriction and pulmonary vascular remodelling lead to pulmonary hypertension they are not essential prerequisites of it (Jones *et al* 1985).

Vascular injury (McMurtry *et al* 1988) and high blood flow (Esterly *et al* 1968) can cause pulmonary vascular remodelling; platelets may be responsible for intimal proliferation by their adhesion to injured vessel walls and the production of a platelet derived growth factor (PDGF) (Schwartz *et al* 1987); the endothelial cell may also release substances implicated in remodelling with evidence for both detrimental (Zhao *et al* 1993) and beneficial (Peacock *et al* 1992) effects through the production of endothelin and endothelium-derived relaxing factor (EDRF).

In-vitro, a variety of blocking agents have been tested which offer some protection against these insults (Sugget *et al* 1988 and McMurtry *et al* 1988) and it is possible that in the future agents which prevent or reverse pulmonary vascular remodelling will become available.

1.2.1.2 Pulmonary Vascular Resistance

Measuring the effects of pathological processes in the pulmonary circulation requires an understanding of the relative contributors to haemodynamic disturbance. In addition to those pulmonary haemodynamic variables which are directly measured, others are derived including Pulmonary Vascular Resistance (PVR) and Total Pulmonary Resistance (TPR). The equations used to calculate these are shown below.

$$PVR = \frac{PAM-PAOP}{CO} \qquad TPR = \frac{PAM}{CO}$$

PAP_m= pulmonary artery mean pressure

PAOP= pulmonary artery occlusion pressure (left atrial pressure)

CO= cardiac output

PVR can be expressed either in Woods units or in dynes/s/cm^5. The normal value of resting pulmonary vascular resistance is between 0.3 and 1.6 Woods units or 20 and 130 dynes/s/cm^5. Woods units are expressed as dynes by multiplying by 80.

Haemodynamic assessment of the pulmonary circulation still relies heavily on the calculation of pulmonary vascular resistance (PVR). Measurements of haemodynamics in systems with constant flow calculate resistance as the drop in pressure from the inflow point to an outflow point, divided by the flow. In tubes with steady flow, Poiseuille's law states that,

$R= (P_{in}-P_{out})/Q = 8 \times l \times \eta/\pi \times r^4$

Where l is the length of the tube, η is a co-efficient of viscosity, and r is the radius of the tube. When this equation is transposed to the pulmonary circulation inflow pressure becomes the pulmonary arterial pressure, outflow pressure the left atrial pressure, and flow, the cardiac output. Thus in the pulmonary circulation,

PVR= PAP-PAOP/CO.

However a number of at least partially inaccurate assumptions have to be made about the pulmonary circulation for the application of Poiseuille's law to be valid. The flow of blood through the pulmonary circulation is not steady but pulsatile. Pressure and flow measurement in the pulmonary vasculature is conventionally made with fluid filled, balloon tipped, pulmonary artery catheters which necessarily measure mean pressures over several cardiac cycles and cannot take this natural pulsatility into account. Blood is not a Newtonian fluid as foreseen by the equation but a complex substance of variable viscosity and the "tube" in which it flows is not laminar but a distensible, branching conduit (Mitzner and Chang 1989). The measurement of pressure and flow in the pulmonary circulation is relatively difficult because of its situation inside a pressure chamber (i.e. the thorax) and its sensitivity to these pressures. The resistance of the pulmonary circulation is, as mentioned above, very small thus allowing adequate perfusion of the lungs at minimum cost to the right heart. Further more it has the capacity to reduce its resistance even further by distension of functioning vessels, or by the recruitment of previously collapsed vessels.

Thus the calculation of PVR is unsatisfactory for a number of reasons but is the conventional "gold standard" measurement in the assessment of the pulmonary circulation. When left atrial pressure is not measured, TPR is sometimes substituted, expressed as TPR = PAP/CO.

It is clear from these calculated values that many variables interact to produce the clinical picture of pulmonary hypertension and that the pulmonary circulation has a large capacity to accommodate changes in pressure and flow without consequent increases in PVR.

1.2.2 Definition of Pulmonary Hypertension

The pulmonary circulation differs from the systemic circulation in its greater potential to react to changing pressures (air, arterial or venous). It is a low-pressure system and, unlike the systemic circulation it reacts to hypoxia by vasoconstriction.

A practical definition of pulmonary hypertension is a mean pulmonary artery pressure (PAP) of 20 mmHg or greater at rest and at least 30 mmHg on exercise, with a normal pulmonary artery occlusion pressure (Weitzenblum *et al* 1996). It is common practice to consider a mean PAP of 40 mmHg to be inadequate to merit specific treatment, while a mean PAP of > 40 mmHg is likely to require therapy targeted at lowering the pressure itself. These statements assume that other contributing factors (e.g. airways disease) have been addressed.

Normal values for steady flow pulmonary haemodynamic measurements are given in Table 1.2.

1.2.2.1 Physiological Effects of Raised PAP

Irrespective of the aetiology of the pulmonary hypertension the sequence of events which follow its development is similar.

The normal pulmonary circulation is uniquely adapted in a number of ways which make it capable of responding to considerable variations in pulmonary blood flow, without major rises in pulmonary artery pressure. At rest the pulmonary circulation is a high flow, low resistance system which reacts to the increased pulmonary blood flow of exercise by reducing its resistance and recruiting vessels which were not perfused at rest. The right ventricle is thin walled, with the capacity to react to large changes in venous return without any significant changes in filling pressures. Thus in

Table 1.2

Variable	*Mean*	*Normal limits*
Q, L/min	6.5	4-8.3
HR, Beat/min	69	40-100
PAP, mmHg	13	8-20
PAOP, mmHg	9	5-14
RAP, mmHg	5	2-9

Table 1.2 Normal Values for Pulmonary Haemodynamic Measurements (Naeije 1983)

The mean and normal ranges for human pulmonary haemodynamics. These values were obtained at right heart catheterisation in 32 supine, healthy volunteers.

Q: pulmonary blood flow

HR: heart rate

PAP: pulmonary artery pressure

PAOP: pulmonary artery occlusion pressure

RAP: right atrial pressure

the normal situation, the increased cardiac output of exercise can be accommodated by the pulmonary circulation without any major rise in pulmonary artery pressure, and hence no additional stress being placed on the right ventricle.

In the situation of raised pulmonary artery pressure, the right ventricle initially hypertrophies in response to the increased forward pressure and at this stage pulmonary hypertension may be present without any evidence of right heart failure, and with normal cardiac output. However with persistent pulmonary hypertension the cardiac output will initially fail to rise adequately on exercise and the patient will experience limitation of their exercise tolerance. As the right ventricle further hypertrophies its demands may exceed its myocardial blood flow leading to right ventricular ischaemia and chest pain.

Eventually the cardiac output becomes decreased at rest and right ventricular volume overload develops with the clinical signs of right ventricular failure. Advanced pulmonary hypertension (primary or secondary) is complicated by progressive right ventricular failure and sudden death. The latter may be due to a variety of causes including dysrhythmias, pulmonary emboli, pulmonary haemorrhage and right ventricular ischaemia.

1.2.2.2 Clinical Features of Pulmonary Hypertension

The presenting features of pulmonary hypertension are non-specific. Patients with PPH are usually young and appear well and therefore their complaints of dyspnoea, syncope or atypical chest pain will often be attributed to other causes.

A detailed history may reveal past ingestion of anorexic agents or recreational drug use, or of an embolic event, while physical examination will elicit the signs listed above, or may reveal an underlying cause such as connective tissue disease.

Likewise in individuals with respiratory disease, the complaint of worsening breathlessness will usually be thought to be a reflection of deterioration in the underlying condition. Pulmonary hypertension should be suspected in individuals with persistent hypoxaemia (Pao_2 <7.3kPa) who complain of decreasing exercise tolerance in the face of static spirometric values, or those who develop evidence of fluid retention.

Thromboembolic pulmonary hypertension should always be considered in a patient with a past history of deep venous thrombosis or pulmonary embolus who develops unexplained symptoms of breathlessness. This complication probably affects about 0.1% of all embolic patients and can present after months or years, though in about half of all such cases the initial event was unrecognised. (Moser *et al* 1990)

The commonest presenting feature of pulmonary hypertension is dyspnoea. This is present in 60% of patients initially and in almost all as the disease progresses. Chest pain is often present (in 47% of patients with PPH) and can be typically anginal in nature, or relatively non-specific. Other clinical features of more advanced pulmonary hypertension include dyspnoea at rest, poor peripheral perfusion, tachycardia and a low volume pulse.

On physical examination the jugular venous pressure is commonly raised and "a" and "v" waves may be seen. Peripheral oedema indicates advanced disease. The pulmonary component of the second heart sound is sometimes palpable, as is a left parasternal heave and a tapping cardiac impulse. On auscultation in addition to the

loud second sound, third or fourth heart sounds may be heard, as may a systolic murmur, which is usually due to tricuspid regurgitation.

1.2.3 Classification of Pulmonary Hypertension

Previously pulmonary hypertension was classified as primary or secondary. There were a number of problems with this approach; in particular that Primary Pulmonary Hypertension (PPII) actually encompassed a number of aetiologies with various definitions in use in different countries. PPH is rare, but pulmonary hypertension also occurs as a consequence of a wide variety of conditions, including most heart and lung diseases, where it is largely unrecognised and untreated and is therefore a major clinical challenge. The consequence of this failure to assess the pulmonary circulation is that the process may progress to the point where treatment is less likely to be beneficial.

Consequently in 1998 at an international symposium in Evian, sponsored by the World Health Organisation (WHO), a group of recognised international experts produced a consensus re-classification (Rich *et al* 1998). This new classification is intended for practical clinical use, including greater detail and providing fuller descriptions of clinical entities. Consequently it is more valuable in describing and following patients, than were previous classifications (Fishman 1998).

1.2.3.1 Primary Pulmonary Hypertension

PPH is a rare and progressive disorder, which usually affects the arterial side of the circulation. If left untreated (and where treatment is unsuccessful) right heart failure

and death are inevitable. PPH has an incidence of one to two cases per million people per year in Western populations. Because of this and due to the fact that this disease is commoner in individuals in their mid 30s (female to male ratio of 1.7:1) there is often a delay in diagnosis of many months. During this time progressive and increasingly irreversible damage is done to the pulmonary circulation.

Previously the prognosis has been uniformly bleak with median survival of less than 2 years, however significant advances in the diagnosis and treatment of PPH have been made in the last decade which constitute grounds for new optimism. Central to these was the observation that vasoconstriction is only part of the process by which pulmonary hypertension is generated and that marked histopathological changes are seen in PPH and in severe pulmonary hypertension associated with other disorders. In particular the introduction of continuous intravenous Prostacyclin has transformed the outlook for individuals with PPH.

The WHO classification suggests that the term PPH should be reserved for unexplained cases of pulmonary hypertension. There are a large number of associations with severe pulmonary hypertension (Table 1.3) and numerous risk factors associated with the development of severe pulmonary hypertension (Table 1.4). The available treatments may have greater efficacy the earlier they are used, therefore the issue of screening becomes important (Peacock 1999).

1.2.3.2 Risk Factors for Pulmonary Hypertension

A risk factor for pulmonary hypertension may be necessary to cause the condition or a facilitator in the development of the disease. Consequently there are a variety of

Table 1.3

WHO Classification of Pulmonary Hypertension (Rich S. ed.1998)

Diagnostic classification

1. **Pulmonary arterial hypertension**
   - 1.1 Primary pulmonary hypertension
     - (a) Sporadic
     - (b) Familial
   - 1.2 Related to:
     - (a) Collagen vascular disease
     - (b) Congenital systemic to pulmonary shunts
     - (c) Portal hypertension
     - (d) HIV infection
     - (e) Drugs/toxins
       - (1) Anorexigens
       - (2) Others
     - (f) Persistent pulmonary hypertension of the newborn
     - (g) Other

2. **Pulmonary venous hypertension**
   - 2.1 Left sided atrial or ventricular heart disease
   - 2.2 Left sided valvular heart disease
   - 2.3 Extrinsic compression of the pulmonary veins
     - (a) Fibrosing mediastinitis
     - (b) Adenopathy/tumours
   - 2.4 Pulmonary veno-occlusive disease
   - 2.5 Other

3. **Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia**
   - 3.1 Chronic obstructive airways disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Neonatal lung disease
   - 3.7 Alveolar-capillary hyperplasia
   - 3.8 Other

4. **Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Obstruction of distal pulmonary arteries
     - (a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
     - (b) In situ thrombosis
     - (c) Sickle cell disease

5. **Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature**
   - 5.1 Inflammatory
     - (a) Schistosomiasis
     - (b) Sarcoidosis
     - (c) Other
   - 5.2 Pulmonary capillary haemangiomatosis

(A) Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

(B) Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(C) Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(D) Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Table 1.3 WHO Classification of Pulmonary Hypertension
(Rich S. ed. 1998)

Table 1.4

A. Drugs and Toxins

1. Definite
    - Aminorex
    - Fenfluaramine
    - Toxic rapeseed oil
2. Very likely
    - Amphetamines
    - L-tryptophan
3. Possible
    - Meta-amphetamines
    - Cocaine
    - Chemotherapeutic agents
4. Unlikely
    - Antidepressants
    - Oral contraceptives
    - Oestrogen therapy
    - Cigarette smoking

B. Demographic and Medical Conditions

1. Definite
    - Sex
2. Possible
    - Pregnancy
    - Systemic hypertension
3. Unlikely
    - Obesity

C. Diseases

1. Definite
    - HIV infection
2. Very likely
    - Portal hypertension/liver disease
    - Collagen vascular diseases
    - Congenital systemic-pulmonary vascular shunts
3. Possible
    - Thyroid disorders

Table 1.4 WHO Classification of Risk Factors for Pulmonary Hypertension

strengths of association and the WHO classification recognises this (Abenheim *et al* 1998).

- **Definite-** indicates an association based on several observations and probably a major study.
- **Very likely-** indicates a similar series of observations or a consensus amongst experts.
- **Possible-** indicates a basis on the existence of case reports, registries or expert opinion.
- **Unlikely-** indicates risk factors which have aroused suspicion but for which no supporting evidence has been forthcoming.

The importance of early diagnosis and treatment in PPH is widely accepted but remains unproven. Furthermore the condition is very rare and the suggestive symptoms diffuse and vague. Hence it is important that screening programmes strike a balance between the risks of the invasive tests necessary to confirm the diagnosis, the likelihood of a good outcome from treatment, the use of scarce resources and cost.

1.2.3.3 Secondary Pulmonary Hypertension

Pulmonary hypertension can complicate a large number of conditions and may be a consequence of any cardiorespiratory disease. However a few conditions dominate clinical practice. The main causes of secondary pulmonary hypertension are:

- Chronic hypoxic lung disease including chronic airflow obstruction, fibrosing lung disease, and ventilatory failure due to primary chest wall dysfunction.
- Thromboembolic pulmonary hypertension.

- Connective tissue disease, especially CREST syndrome.

1.2.3.4 Chronic Hypoxic Lung Disease

The most commonly encountered cause of secondary pulmonary hypertension in clinical practice is chronic hypoxic lung disease. The extent of the problem is difficult to define and is further complicated by the debate about the term "cor- pulmonale" which is often used when patients with respiratory failure develop oedema. This expression implies dysfunction of the heart when, in fact, the fluid retention is probably renal in origin, though is associated with the pulmonary hypertension. For this reason many authors would prefer that the term be no longer used and that it should be replaced with "fluid retention in association with secondary pulmonary hypertension" (Weitzenblum et al 1996)

There is controversy about the contribution of secondary pulmonary hypertension to the mortality and morbidity of chronic hypoxic lung disease; however the important variations in PAP caused by exercise, sleep (due to alveolar hypoventilation) (Boysen *et al* 1979), and episodes of respiratory failure secondary to acute infection are now accepted. The latter have been shown to return to normal before becoming resistant to treatment as the disease progresses (Weitzenblum *et al* 1979). Clearly these variations in PAP are difficult to measure routinely because of the difficulty in making reliable measurements of pulmonary haemodynamics repeatedly. The signs and symptoms of pulmonary hypertension are usually overwhelmed by those of chronic obstructive pulmonary disease (COPD), but pulmonary hypertension should be suspected in patients with persistent hypoxaemia (PaO_2 <7.3 kPa) who complain of deteriorating

exercise tolerance in the face of static spirometric values, or in those who develop evidence of fluid retention. This can be a difficult clinical diagnosis and one American study noted that up to 30% of admissions to hospital with a diagnosis of congestive cardiac failure actually had fluid retention associated with pulmonary hypertension (Intersociety Commission for Heart Disease Resources 1970).

There is little doubt that secondary pulmonary hypertension is an important factor in the morbidity and mortality of chronic hypoxic lung disease and other conditions. Quantifying pulmonary haemodynamics should be an important part of assessment of these patients and can assist us in future decisions about the success or otherwise of treatment directed both at the primary respiratory disease and at the pulmonary circulation itself. Clearly, the first therapeutic objective must be the treatment of the pulmonary condition (Peacock 1990), but we should be monitoring the effects of this treatment and the use of vasodilators, if appropriate, on the pulmonary circulation (Peacock 1993).

1.2.3.5 Thromboembolic Pulmonary Hypertension

This diagnosis should always be considered in a patient with a past history of deep venous thrombosis or pulmonary embolus who subsequently develops unexplained symptoms of breathlessness. Where the patient presents soon after the event the diagnosis may seem obvious, but Moser (1996) has described the "honeymoon period" after pulmonary embolism where the patient's symptoms can improve for a period of months or years before deteriorating again, sometimes rapidly. Significantly, his group estimated that between 0.1% and 1.0% of all embolic patients

go on to develop thromboembolic pulmonary hypertension, and that in nearly half the initial event was unrecognised.

1.2.3.6 Connective Tissue Disease

Pulmonary arterial hypertension (PAH) has been described as a complication of every kind of collagen vascular disease (Hoeper 2002). PAH may occur as a result of interstitial lung disease in collagen vascular disease but can also be the sole pulmonary complication. Pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis and pulmonary vasculitis (<2% of patients with SLE) have also been reported in association with collagen vascular disease but are very rare, though serious, complications (Deveraux *et al* 1998, Gugnani *et al* 2000, Morassut *et al* 1992, Gross 1972).

There is considerable variation in the frequency of PAH in collagen vascular disease being very rare in rheumatoid arthritis yet complicating as many as 50% of cases of the Calcinosis, Raynaud's phenomenon, oesophageal involvement, sclerodactyly and telangectasia (CREST) syndrome (Yousem 1990). PAH is the most important cause of mortality and morbidity in this condition.

PAH complicates Systemic Lupus Erythematosis (SLE) in between 5 and 10% of cases (Asherson *et al* 1990, Pan *et al* 2000, Shen *et al* 1999), 10-30% of cases of progressive systemic sclerosis (PSS) (Yamane *et al* 2000, Murata *et al* 1997) and in greater than 30% of cases of mixed connective tissue disease (MCTD) (Hoffman and Greidinger 2000).

In all cases the pathology of PAH associated with collagen vascular diseases is similar to that in PPH. Thus the predominant lesions are medial and intimal thickening of the small and medium sized pulmonary arteries. Plexiform lesions (previously thought to be the hallmark of PPH) have also been described in PAH associated with collagen vascular disease (Cool *et al* 1997).

Thrombosis *in situ* is an important feature of PPH and can also occur in pulmonary hypertension associated with collagen vascular disease (Welsh *et al* 1996, Hoeper *et al* 1998). In collagen vascular disease with a pro-coagulant tendency such as SLE it is very important therefore to exclude thromboembolic disease.

Patients may present with minimal or no clinical respiratory signs other than breathlessness, but a clue is a low carbon monoxide gas transfer factor in the face of normal spirometric values. Patients at risk of developing PAH may exhibit abnormal PAP responses to exercise as a first sign as has been shown by stress exercise echocardiography (Grunig *et al* 2000) however at the present time this cannot be advocated as a routine screening tool. High-risk individuals (i.e. those with PSS, CREST and MCTD) should have annual echocardiography.

The contribution of PAH to morbidity and mortality may be subtle, overwhelmed by the symptoms of the underlying condition and its clinical significance may be negligible; alternatively pulmonary hypertension may be the obvious problem. In some cases occult pulmonary hypertension may have caused irreparable damage before manifesting itself clinically. The ambulatory pulmonary artery pressure monitoring system permits the assessment of the pulmonary circulation during exercise and allows the detection of abnormal exercise responses in individuals with

normal resting PAP. This may allow the early diagnosis of pulmonary hypertension, which is an important theme of this thesis.

1.2.4 Treatment of Pulmonary Hypertension

Pulmonary hypertension may present as an incidental finding or be obviously the predominant cause of disability. In either case the importance of an individually tailored treatment plan in every patient with pulmonary hypertension of any aetiology cannot be overemphasised. In many cases the potential side effects (or harm) from treatment may greatly outweigh any therapeutic gain which might reasonably be expected. In the context of secondary pulmonary hypertension the importance of treating the underlying condition greatly exceeds the necessity to treat the pulmonary artery pressure in the vast majority of instances. Table 1.5 lists some of the clinical mechanisms of pulmonary hypertension.

1.2.4.1 Treatment Models

Treatment philosophy can be summarised by considering a "pure" form of vascular disease (PPH) and COPD where the mechanism of injury is alveolar hypoxia.

The therapeutic goals of treatment should include improvement in symptoms and hence functional capability and prevention of progression. Ideally survival benefit would be conferred by a treatment.

These end points would be brought about by a decrease in cardiac work and an improvement in systemic oxygen transport (Weir *et al* 1992).

COPD appears akin to a "pure" example of vasoconstrictive pulmonary hypertension (provoked by hypoxia) but again the situation is more complex with long-term hypoxia producing changes in the small vessels very similar to those seen in PPH. This explains why oxygen does not entirely reverse the vasoconstriction seen in COPD.

Table 1.5

- **Passive**- increased left atrial pressure
- **Hyperkinetic**- increased pulmonary blood flow
- **Obliterative**- destruction of vessels or parenchyma
- **Vasoconstriction**- increased vascular smooth muscle tone

Table 1.5 Clinical Mechanisms of Pulmonary Hypertension (Weir *et al* 1992)

Clinical mechanisms responsible for the genesis of pulmonary hypertension. These different mechanisms may co-exist.

1.2.4.2 Treatment of Primary Pulmonary Hypertension

The majority of the advances seen in the treatment of pulmonary hypertension have been established in studies of patients with PPH. PPH is a "pure" form of pulmonary vascular disease and while it is not always the case that conclusions from the study of patients with PPH will be readily generalisable to other patient groups some of the principles of treatment have been accepted. Consequently it is important to review the treatment of PPH before considering the treatment of pulmonary vascular disease of other aetiologies.

PPH is incurable and treatment is inevitably aimed at alleviating symptoms. The current consensus is that there is a place for vasodilator drugs and anticoagulation (Rich *et al* 1998). This is based on the concept that patients with PPH have increased vascular tone in the pulmonary circulation, and chronic, low-grade stimulation of their coagulation cascade (Rubin 1993). Table 1.6 lists some of the pathophysiological mechanisms of pulmonary hypertension in PPH.

Continuous intravenous prostacyclin can also be used in patients who do not seem to benefit from oral vasodilators. This is an expensive treatment, especially as tachyphylaxis seems to occur, but may offer a bridge to transplantation in patients with severe disease.

Both oral vasodilators and prostacyclin have been shown to improve function in patients with PPH and although it is not clear how long these improvements will last one study has shown benefit sustained for 5 years (Rich *et al* 1992).

PPH is the purest model of pulmonary hypertension and consequently by far the largest literature exists in this condition. It is useful therefore to consider the mechanisms involved in genesis of pulmonary hypertension in PPH prior to discussing treatment (Weir *et al* 1992).

Table 1.6

- Increased vascular smooth muscle tone
- Abnormal cellular proliferation
- Disordered endothelial cell function
- Abnormalities of coagulation
- Neurogenic and myogenic reflexes

Table 1.6 Pathophysiological Mechanisms of Pulmonary Hypertension (Weir *et al* 1992)

Pathophysiological entities involved in pulmonary hypertension. Some of these mechanisms are simultaneously a consequence of pulmonary hypertension and promoters of its further development

The pathogenesis of PPH remains obscure however intimal and medial proliferative changes in small pulmonary vessels with intravascular thrombosis or embolisation occurs.

Additionally there is a vasoconstrictive component with increased vascular tone in most patients. The cause or effect relationship of this with the anatomical changes described is unclear. Hence there is a therapeutic rationale for the use of vasodilators in PPH.

Vasoconstriction is the accepted predominant mechanism and this is based on histopathological studies and the favourable response many patients demonstrate to vasodilators (Rich *et al* 1992).

Although vasoconstriction is the important pathophysiological mechanism it may, or may not, be the primary event. It has been suggested that in susceptible individuals a number of triggers may be responsible for initiating a process of which it is a result (Weir *et al* 1992). These factors include

- hypoxia (normobaric or hypobaric)
- autoimmune disorders
- drugs and toxins (including HIV)
- increased pulmonary blood flow, + or – increased pressure and shear stress.
- lung injury
- increased sympathetic tone and catecholamine induced injury.

In the susceptible individual these factors can damage the pulmonary vascular endothelium causing an imbalance in its production of mediators. Examples of this imbalance include an increase in the production of thromboxane v prostacyclin, which results in the promotion of a hypercoagulable state. This can initiate vasoconstriction

but will also lead to increased platelet activation. Consequently the damaged vascular endothelium is acted on by both cellular and humoral components of the blood which may result in pulmonary vascular remodelling and further vascular injury (Chapter 1.2).

Additional factors at work include the release of an unidentified chemotactic agent, from pulmonary vascular endothelial cells, which stimulates the migration of smooth muscle cells in pulmonary arterioles (Gaiad *et al* 1993, Newby and George 1993).

Thrombosis *in situ* can also occur as a result of pulmonary endothelial cell damage. The normal anticoagulant state of the pulmonary vascular bed is due to its production of prostacyclin and plasminogen activator inhibitors which is reduced in the pathological state as noted above. In PPH there are elevated levels of Fibrinopeptide A, suggesting *in situ* thrombosis. This theory is further supported by the survival benefit these patients obtain from anticoagulation (Rich *et al* 1992).

Despite the confusing array of treatments which have been used in pulmonary hypertension, in the last 10 years a consensus has begun to emerge particularly in PPH. Many treatments now have a sound scientific basis for their use (Peacock *et al* 1999). These include,

- Anticoagulants
- Oral vasodilators
- Other vasodilators
- Inotropic agents
- Prostacyclin
- Surgical methods
- Transplantation

1.2.4.3 Anticoagulants

Some of the earliest work in PPH addressed the problem of the chronic, low -grade pro-thrombotic state endured by patients with significant pulmonary hypertension (Rubin *et al* 1993).

It has been shown that anticoagulants double survival in patients who are non-responders to vasodilators from 31% to 62% at three years (Rich *et al* 1992). It is now therefore standard practice to use warfarin to achieve an internationalised normalised ratio (INR) of 2 in patients with a mean resting PAP of > 30 mmHg in the absence of a contraindication (Gaine and Rubin 1998).

1.2.4.4 Oral Vasodilators

Approximately 30% of PPH patients will respond positively to vasodilators though it is not possible to predict which. However, about 25% of patients may be adversely affected by these drugs, reinforcing the need to provide individually tailored therapy regimens for all patients with PPH.

It has now been shown that high dose oral vasodilators are beneficial in patients with a positive vasodilator response (Rich and Brundidge 1987, Rich and Kaufman 1991) and the dihydropyridine drugs are the group with which there is most experience in PPH.

Patients who demonstrate a potentially beneficial response to a trial of an acute vasodilator drug at cardiac catheterisation should be given an oral calcium channel

blocker, titrated to the highest tolerated dose up to a maximum of for example Diltiazem 720mg. per day or Nifedipine 240mg. per day.

The principle problem with the administration of these drugs at such high doses is their potential to depress the myocardium. They can be dangerous in patients who do not have an acute vasodilator response and consequently must not be used prior to a formal vasodilator study. Dose titration is best carried out in specialist units where patients must also be closely followed in case side effects develop. These include systemic hypotension, worsening of ventilation-perfusion mismatching, right ventricular dysfunction, cardiac arrhythmias and death. The most serious of these is heart failure which can progress quickly with grave consequences.

From the foregoing it is clear that the presumed mechanism of action is vasodilatation of the pulmonary vascular bed; however there are other possible mechanisms for the beneficial action of oral vasodilators in pulmonary hypertension including inhibition of growth of smooth muscle or other pulmonary vascular cells.

Combined with oral anticoagulants in suitable patients oral vasodilators can produce survival figures of the order of 90% at five years (Peacock *et al* 1999) and are beginning to constitute a challenge to transplantation as the most effective treatment for such individuals.

1.2.4.5 Other Vasodilators

A number of other vasodilators have been tried in pulmonary hypertension, mostly without success or with unacceptable side effects. These include captopril (Ikram *et al* 1982), diazoxide (Honey *et al* 1980) and hydralazine (Packer *et al* 1982).

Nitric oxide is an attractive candidate as a specific pulmonary vasodilator but delivery problems restrict its use to specialist units. Oxygen is a non-specific vasodilator of the pulmonary circulation but its role relates to the correction of hypoxic lung disease complicated by pulmonary hypertension. Presently the calcium channel blockers remain the vasodilators of choice in PPH.

1.2.4.6 Inotropic Agents

There is very little data to support the use of inotropes in PPH. Their rationale is nonetheless sound in that in the context of right ventricular failure (in severe pulmonary hypertension) where maximum vasodilatation has been obtained using substances which are themselves negative inotropes (calcium channel blockers) it would seem logical to use a drug which might improve right ventricular function. At present the use of inotropes in severe pulmonary hypertension should be restricted to specialist units.

1.2.4.7 Prostacyclin

Perhaps one of the most important advances in our understanding of pulmonary hypertension has been the observation that prostacyclin confers benefits over and above those which might be expected from a vasodilator alone and is sometimes beneficial in individuals in whom no acute vasodilator response has been demonstrated (McLaughlin *et al* 1998). This led to a sea change in the way that vasodilators were used in the treatment of severe pulmonary hypertension.

Initial observations had suggested that prostacyclin acted as a vasodilator in patients with PPH (Rubin *et al* 1982) and initially its place was felt to lie in providing a therapeutic bridge to transplantation (Higgenbottam *et al* 1984). Subsequent studies have shown additional benefit in a large group of patients with PPH receiving conventional treatment (Rubin *et al* 1990) and since then continuous intravenous prostacyclin has been shown to be superior to conventional treatment both in the short term over 12 weeks (Barst *et al* 1996) and over a longer period (McLaughlin *et al* 1998).

The observation that prostacyclin may reverse the disease process has led to a review of its place in the treatment of primary pulmonary hypertension and the realisation that it may offer an alternative to transplantation. There are problems associated with its long-term use however.

Prostacyclin has a half-life of three minutes meaning that infusion pumps must be reloaded quickly. It must be stored at between 2 and 8 °C and used within 24 hours of reconstitution. The drug, at present, must be administered by continuous intra-venous infusion by a pump via a Hickman line. This exposes an individual to the risks of indwelling central venous catheters such as infection, catheter clot, breakage and migration. Patients must be taught to make up the drug using aseptic technique. The possibility of life threatening rebound pulmonary hypertension means that a back up system must be in place.

Side effects of prostacyclin include nausea, diarrhoea, headache, flushing, sweating, postural hypotension, palpitations, skin rashes and jaw pain. Almost all patients will experience some side effect and while some relate to the drugs vasodilator action, others (such as jaw pain) are unexplained.

There is no general agreement about the correct starting dose and practices have varied. Patients described in this thesis were commenced at two nanograms per kilogram per minute and increased in similar increments until side effects limited further increases. Tachyphylaxis is a problem and necessitates continuous review of the dose with attendant increases in cost.

Cost is a major issue with the averaging between £50,000 -£60,000 per patient in the UK. This necessitates that prostacyclin must be administered under the supervision of one of the specialist pulmonary vascular units in the UK.

Prostacyclin is contraindicated in pulmonary veno-occlusive disease (Rubin *et al* 1990) and pulmonary capillary haemangiomatosis (Humbert *et al* 1998).

Clearly, while prostacyclin has vastly improved the outlook for many patients with PPH, its impact on quality of life and cost implications are considerable. An alternative would be highly desirable and these are discussed later.

1.2.4.8 Surgical Treatment

1.2.4.8.1 Atrial Septostomy

In severe pre-capillary pulmonary hypertension the creation of an atrial septal defect can effectively reduce the load faced by the right ventricle while simultaneously improving pre-load to the left heart. This will result in a reduction in the oxygen content of arterial blood however this will be offset by the anticipated increase in cardiac output and an overall increase in tissue oxygen delivery.

There are no large-scale trials of this technique in pulmonary hypertension but some units have gained considerable experience with encouraging results (Rich and Lamb 1983, Kerstein *et al* 1995, Rich *et al* 1997).

The technique of atrial septostomy is essentially palliative and should be restricted to experienced units, however it is a useful adjunct to the other available treatments.

1.2.4.8.2 Transplantation

Prior to improvements in medical therapy, transplantation was the best option for individuals with severe intractable pulmonary hypertension and considerable experience has accumulated. Transplantation offers survival benefits to patients with

favourable vasodilator responses which are slightly inferior to those obtained with modern medical therapy; one year survival of 70% and three year survival of 50-60% (Peacock 1999).

The principal problem with transplantation remains the supply of donor organs; this is complicated further by the donor lung's fragility and the matching of suitable donors to recipients. The outcome for patients with severe pulmonary hypertension seems comparable to those transplanted for other indications and no procedure confers additional benefit, though single lung transplantation seems to be associated with a slightly worse outcome in pulmonary hypertension (Peacock *et al* 1999).

With improved medical treatment it is now more difficult to decide when to refer for transplant assessment. The essential message must be that it is preferable to refer too early than too late and there is extensive guidance available in the literature (D'Alonzo *et al* 1991, Nootens *et al* 1994 and Rubin 1997).

1.2.4.8.3 Pulmonary thromboendarterectomy

This operation is specific to the clinical situation of chronic thromboembolic pulmonary hypertension (CTEPH) but merits mention, as it is potentially curative. The first operation was carried out in 1957 however the technique has evolved considerably in recent years. The most experienced units now quote operative mortality rates of 7% and demonstrate improvements in NYHA functional class and in haemodynamics (Dunning and M°Neil 1999). Patients with CTEPH who have a mean PAP in excess of 50mmHg have a five-year survival of 10%. Thus a corrective surgical procedure with a mortality rate of 7% (which compares favourably with transplantation) is an attractive therapeutic option.

1.2.4.9 Treatment of Secondary Pulmonary Hypertension

The treatment of secondary pulmonary hypertension remains a much more contentious area than in PPH and initially treatment should be directed primarily at the underlying condition (Peacock 1990). In the absence of contraindications all patients with significant pulmonary hypertension should be anticoagulated, long-term oxygen therapy (LTOT) prescribed for those who are hypoxic and venesection considered where chronic hypoxia causes polycythaemia.

1.2.4.9.1 Chronic Hypoxic Lung Disease

In contrast to the situation in PPH, in pulmonary hypertension secondary to COPD (by far the commonest cause of secondary pulmonary hypertension) any reduction seen in pulmonary artery pressure will not usually translate to an improvement in function. Pulmonary hypertension progresses slowly in COPD rising by only 3mmHg per year in one group of patients followed over 5 years (MRC Council Working Party 1981) but nonetheless has been shown to imply a poor prognosis (Weitzenblum *et al* 1996). Furthermore in certain situations transient pressure rises can be much greater, e.g. during infective exacerbations, on exercise or when asleep (due to alveolar hypoxia).

Oxygen (a selective pulmonary vasodilator) remains the mainstay of treatment and although levels of pulmonary hypertension may not be reduced, further progression is prevented (MRC Council Working Party 1981). It remains unclear whether calcium channel blockers are helpful in this situation (Peacock 1996, Sajkov *et al* 1997) and there have been no studies of prostacyclin.

Hypoxia is the most important functional factor affecting pulmonary vascular tone and in the context of COPD there are two mechanisms responsible for this. The first is the pulmonary vasoconstriction seen caused by acute hypoxia and the second the structural changes induced in the pulmonary vascular bed by chronic hypoxia.

Acute hypoxia was first noted to cause a rise in PVR in the cat by Von-Euler and Liljestrand (1946). Since then the human response to hypoxia has been described (Motley *et al* 1947, Fishman *et al* 1952) and a rise in PAP demonstrated. There is inter-individual variation in this response (Grover 1990) which has also been demonstrated in individuals with COPD (Weitzenblum *et al* 1988). COPD patients have been characterised as "responders" or "poor responders" to hypoxia (Weitzenblum *et al* 1996) though the significance of this has not been clear. Patients with COPD are subject to variations in their baseline values of oxygen saturation for a variety of reasons as described above. Ambulatory pulmonary artery pressure monitoring offers the opportunity to correlate symptoms with the fluctuations in PAP caused by these changes and may lead to an improved understanding of their importance. Chapter 4 describes the measurement of PAP during exercise and sleep in a group of patients with severe COPD compared with normal individuals and found elevations in PAP during sleep (breathing air) similar to those seen on exercise in the COPD subjects.

Further to the acute effects of hypoxia on the pulmonary circulation, chronic reductions in oxygen levels leads to remodelling of the pulmonary vascular bed. In the circumstance of mild hypoxia (as is the case for a majority of individuals with COPD) the rationale for this assumption has been based on studies of people living at high altitude. Such populations tend to have mild elevations of PAP (20-30mmHg) and have been shown to have pulmonary vascular remodelling (Harris and Heath 1986).

The situation in COPD is probably more complex with mechanical factors playing a part (Wilkinson *et al* 1988). This is supported by the observation that while the elevated PAP of high altitude dwellers is potentially reversible, this is rarely fully the case in COPD (Timms *et al* 1985).

Pulmonary hypertension in COPD is rarely severe with normal resting levels of 20 and 35 mmHg (Weitzenblum *et al* 1981) and non-invasive investigations unhelpful in this group. In particular Doppler echocardiography can be very difficult in patients with COPD and hyperinflation (Tramarin *et al* 1991). The signs of pulmonary hypertension may also be masked by the underlying lung disease and for these reasons pulmonary hypertension – or its contribution to morbidity- is probably underestimated in patients with mild to moderate COPD. ambulatory pulmonary artery pressure monitoring (in the research setting) can add useful information to the assessment of such patients by allowing accurate pressure measurement in a variety of clinical situations which can be compared with symptoms.

1.2.4.9.2 Connective Tissue Disease

The situation in pulmonary hypertension secondary to connective tissue disease is similar to that in PPH where oral vasodilators (Sanchez *et al* 1999 and Alpert *et al* 1991) and warfarin probably have a beneficial effect in "responders".

Patients should not be given oral vasodilators unless they have been shown to have a favourable acute vasodilator study (Chapter 2.4.3.1) as these drugs may have a deleterious haemodynamic effect in patients who are non-responders to acute vasodilators and the proportion of responders is smaller in patients with connective tissue disease than in PPH (Raffy *et al* 1996, Sitbon *et al* 1998).

Continuous intravenous prostacyclin has also been shown to be beneficial for some patients with connective tissue disease (Humbert *et al* 1999, McLaughlin *et al* 1999, Badesch *et al* 2000, Robbins *et al* 2000). Because of the inconvenience and complications of permanent central venous catheters alternative methods of prostacyclin delivery have been explored and a stable prostacyclin analogue (Treprostinil) has been shown to be effective given subcutaneously in large randomised studies in patients with PPH (Barst *et al* 2000, Bailey *et al* 2001). It is likely that this therapy will be considered for patients with PAH and connective tissue disease in the future.

There is some evidence that controlling the underlying disease process may improve PAH associated with other pulmonary complications (Davas *et al* 1999) however where PAH develops in isolation there is no evidence for benefit from immunosuppression. Conversely it has been observed that prostacyclin has improved some of the extra-pulmonary manifestations of collagen vascular diseases (Hoeper 2002).

Transplantation should be considered for patients with collagen vascular disease in whom the extra-pulmonary manifestations are not severe. There is considerable evidence that the survival of such patients after transplantation is comparable with other groups (Pigula *et al* 1997, Rosas *et al* 2000, Levy *et al* 1993).

With growing interest in the treatment of pulmonary hypertension in patients with collagen vascular diseases and with increasing treatment options, accurate and objective measurement of treatment responses is important. In Chapter 3 the utility of ambulatory pulmonary artery pressure monitoring was assessed in a group of patients with connective tissue disease and the effects of posture were observed; in Chapter 5 the technique was used to measure PAP responses to exercise in a similar patient

group and non-invasively measured correlates of PAP were obtained from cardiopulmonary exercise testing variables. In Chapter 6 these non-invasive correlates of PAP were used to assess response to treatment with oral vasodilators in a group of patients with connective tissue disease. If patients with connective tissue disease are to be offered prostacyclin or its analogues where oral vasodilators have not benefited them then it is essential to assess response adequately. Ambulatory pulmonary artery pressure monitoring is useful in the research setting to measure haemodynamics during treatment and has led to the identification of non-invasively obtained correlates of PAP measured on exercise.

1.2.4.9.3 Pulmonary Thromboembolic Disease

Oral vasodilators have not been studied in pulmonary thromboembolic disease (PTE). There is evidence of benefit from prostacyclin in pulmonary hypertension secondary to distal thrombosis (McLaughlin *et al* 1999).

Surgical treatment (Chapter 1.2.4.6) should be considered where proximal clot is demonstrated. Patient selection is very important but in experienced units the outcome is good with the potential to improve haemodynamics, extend survival and improve quality of life (Mayer *et al* 1996).

1.2.4.10 Future Management

1.2.4.10.1 Vasodilators

Calcium channel blockers with effects specific to the pulmonary circulation seem unlikely to be forthcoming in the near future. A more realistic hope might be the refinement of those drugs which exert fewer adverse effects on the myocardium.

Pulmonary vascular smooth muscle cells have potassium channels which are thought to be involved in sensing flow changes and interacting with the endothelium to activate pulmonary vascular remodelling (Olesen *et al* 1988). Drugs which interact with these channels exist, but have not yet been assessed in pulmonary hypertension.

Nitric oxide in the form of oral NO donors is another therapeutic aim and it is possible that such compounds will be available for inhalational use also.

1.2.4.10.2 Prostacyclin Alternatives

Iloprost is an alternative to prostacyclin with a longer half-life and similar effects when given intravenously (Higgenbottam *et al* 1998). The longer half-life offers for potential for different routes of administration and in particular there is interest in nebulised iloprost. Nebulised prostacyclin has also been assessed and found superior to inhaled nitric oxide in one study (Mikhail *et al* 1997)

An oral form of prostacyclin (Beraprost) has been developed but is not yet available for clinical use (Miyata *et al* 1996 and Saji *et al* 1996). Bosentan, an orally administered endothelin receptor antagonist has been found to improve exercise capacity in patients with pulmonary hypertension (Rubin *et al* 2002).

Currently large scale randomised trials of nebulised Iloprost are in progress and a subcutaneous prostacyclin analogue, Treprostinil has recently been shown to be an effective treatment for pulmonary arterial hypertension (Simonneau *et al* 2002).

1.2.4.10.3 Genetics of Primary Pulmonary Hypertension

Familial PPH accounts for 6% of all cases and has been shown to be an autosomal dominant inheritance with markedly reduced penetrance (Massague *et al* 2000). The gene for familial primary pulmonary hypertension was localised to chromosome 2q31-32 in 1997 (Nichols *et al* 1997) and recently the genetic mutation underlying this condition has been reported (Deng *et al* 2000, The International PPH Consortium, Lane *et al* 2000).

These discoveries have led to speculation that targeted gene therapy may become possible in primary pulmonary hypertension (Rudarakanchana *et al* 2001)

1.2.4.11 Conclusions

PPH is a rare but serious condition whose early diagnosis is desirable in order that patients can be fully assessed and offered appropriate treatment. Advances in medical therapy in the last ten years have greatly improved the prognosis and rendered transplantation a treatment of last resort.

Secondary pulmonary hypertension is an important complication of many cardiorespiratory diseases and its recognition is important. Patients whose history, signs or symptoms suggest pulmonary hypertension should be screened non-invasively (Section 1.3.1) and referred to a specialist centre for further investigations if necessary.

While there is an emerging consensus for the treatment of PPH the situation in secondary pulmonary hypertension remains much less clear-cut. Undoubtedly the underlying condition should be aggressively managed; the risk/benefit ratio of the other available treatments can then be considered in each individual case.

In the future new treatments may become available, including new delivery systems for existing treatments (such as oral or nebulised forms of prostacyclin) or new classes of drugs acting on the pulmonary circulation.

1.3 Methods of Measurement in the Pulmonary Circulation

Because the symptoms and signs of pulmonary hypertension are often rather vague and non-specific, it is important to be aware of methods of measurement in the pulmonary circulation and their sensitivity, specificity, and relative merits. There is no easily applied sphygmomanometer for the pulmonary circulation, but there are a number of techniques - both invasive and non-invasive - which can help us to make the diagnosis. Implicit in the desire to make an earlier diagnosis of pulmonary hypertension is the belief that there is some point in doing so - that is, that the condition is itself of significance and that we may be able to offer some additional treatment to the patient.

1.3.1 Non-Invasive Methods of Measurement

Traditional methods of assessment include tests which suggest the presence of pulmonary hypertension (clinical examination, electrocardiography, chest radiography, and conventional echocardiography) and those which suggest a cause (pulmonary function tests, ventilation perfusion scanning, and arterial blood gas tensions).

The clinical features of raised PAP are non-specific. Patients with isolated pulmonary vascular disease (PPH or pulmonary hypertension secondary to connective tissue disease) are often young and appear otherwise well and dyspnoea, syncope and atypical chest pain are often attributed to other causes. A detailed history is essential as it may reveal past ingestion of anorectic agents, recreational drug use or an embolic event.

The commonest presenting feature of pulmonary hypertension is dyspnoea. This is present in 60% of cases rising to 100% as the disease progresses and (in patients with respiratory disease) is often attributed to the underlying condition. pulmonary hypertension should be suspected in those with persistent hypoxaemia (PaO_2 < 7.3 kPa) or in those who develop oedema.

Thromboembolic pulmonary hypertension should be considered in patients with a past history of deep venous thrombosis or pulmonary embolism who develop unexplained breathlessness. This complication can develop many years after the initial event, affects approximately 0.1% of individuals with venous thromboembolism and in about 50% of cases the initial event was unrecognised (Moser *et al* 1990).

Chest pain (often relatively non-specific) is a feature of pulmonary hypertension and is most common in PPH affecting 47% of patients. As pulmonary hypertension from any cause advances other clinical features include dyspnoea at rest, poor peripheral perfusion, tachycardia and a low volume pulse.

Physical examination in early pulmonary hypertension can be completely normal however as the pressure increases the signs of right heart strain predominate. The jugular venous pressure is commonly raised and "a" and "v" waves may be seen. The pulmonary component of the second heart sound is sometimes palpable, as is a left parasternal heave and a tapping cardiac impulse. Third or fourth heart sounds may also be heard as might a systolic murmur due to pulmonary regurgitation. The development of peripheral oedema is a late development and usually indicates advanced disease.

The electrocardiogram (ECG) may indicate right axis deviation, right atrial hypertrophy or right ventricular hypertrophy, but will often be normal, particularly in secondary pulmonary hypertension.

The chest X-ray in established pulmonary hypertension may show prominence of the pulmonary arteries and sometimes pruning of the peripheral vessels. Radiological assessment of pulmonary artery diameter, M mode echocardiography, and electrocardiography were compared in one study (Algeo *et al* 1984) and each was found to have a high specificity for detection of pulmonary hypertension (particularly at higher levels of pulmonary hypertension) but were individually too insensitive to be useful for routine clinical screening; a normal test does not exclude pulmonary hypertension. More recent work (Bishop & Csukas 1989) has employed complex data analyses to assess the combined value of these tests, including forced expiratory volume in one second (FEV_1), arterial blood gas tensions, electrocardiography, pulmonary arterial dimension on chest radiography, M mode echocardiography, and myocardial thallium scanning, and confirmed that this approach allows the prediction of the presence of pulmonary hypertension but gives no indication of the actual value of the pulmonary artery pressure.

Ventilation / perfusion lung scanning is widely used in the evaluation of patients with pulmonary hypertension, primarily to exclude thromboembolic disease and to assess the need for pulmonary angiography. Where clinical suspicion of pulmonary embolism is high and the V/Q scan is non-diagnostic, further imaging (such as pulmonary angiography or CT angiography) is essential.

Pulmonary function tests may likewise point to an underlying cause for suspected pulmonary hypertension such as COPD. Furthermore, an isolated reduction in diffusing capacity may be a pointer to pulmonary hypertension in a breathless patient with normal spirometric values.

These have recently been augmented by techniques which tell us about the severity of pulmonary hypertension, such as Magnetic Resonance Imaging (MRI) and Doppler echocardiography which will be considered in more detail.

However, the traditional methods are still of value. From the above it is clear that the signs and symptoms of early pulmonary hypertension may be very subtle. One of the principal advantages of ambulatory pulmonary artery pressure monitoring is that it permits the assessment of the pulmonary circulation during exercise in individuals with normal resting pressures in whom the clinical suspicion of pulmonary hypertension is high.

1.3.1.1 Doppler Echocardiography

The techniques described above, most of which remain in routine clinical use, can detect pulmonary hypertension but give no assessment of its severity. Hence, they cannot be used to follow the clinical course of patients with pulmonary hypertension or assess the benefits of intervention.

In 1984, Yock and Popp described a technique which allowed estimation of pulmonary arterial pressure from the measurement of the maximum velocity of the regurgitant jet in patients with tricuspid regurgitation (TR). When TR is present the velocity of the regurgitant jet is determined solely by the pressure difference between the right ventricle (RV) and the right atrium (RA) and not by the geometry of the orifice. To make this estimate the TR jet is identified and located using pulsed or colour Doppler before continuous wave Doppler recordings are made to determine peak TR jet velocity. Providing that the angle between the ultrasound beam and the

direction of flow is less than 20 degrees, velocity of flow can be calculated accurately. This maximum velocity can then be used in a modified form of the Bernouilli Equation which states that: RV to RA pressure gradient = 4 x (maximum velocity of TR jet)^2

The calculated gradient is added to the right atrial pressure (which can be estimated clinically) to give an estimated value of right ventricular systolic pressure. Assuming there is no pulmonary stenosis, which can be excluded by echocardiography, this value will be equal to pulmonary arterial pressure (Figure 1.2). The authors have shown these values to correlate closely with those found at right heart catheterisation even when not measured simultaneously. Figure 1.3 illustrates a comparison of PAP measured non-simultaneously by Doppler echocardiography and fluid filled pulmonary artery catheter.

This technique confers a number of advantages. The values obtained are accurate over a wide range of pressures and are not affected by changes in cardiac output. Inter-observer variability is <3%, though clearly the technique is, to some extent, operator dependent (Berger *et al* 1985, Currie *et al* 1985, Chan *et al* 1987) Continuous Doppler echocardiography has attained widespread use and recent data suggest that the error limits for Doppler TR derived pressure calculations are only 5-9 mmHg (Naeije *et al* 1995). The technique is well tolerated, safe, and repeatable, but there are some disadvantages. In particular, it is difficult to recover a TR signal of sufficient quality in patients with COPD where success rates may be as low as 30% (Torbicki *et al* 1989). There is no such difficulty in examining flow characteristics in the right ventricular outflow tract. The pulsed Doppler signal is directed at the pulmonary valve and two important measurements are made - namely, acceleration time (AT) and right ventricular ejection time (ET) (Kitabatake *et al* 1983). AT is defined as the

Figure 1.2 **Doppler Echocardiography Estimation of Systolic PAP**
Calculation of PAP from the tricuspid regurgitant jet as measured by Doppler Echo

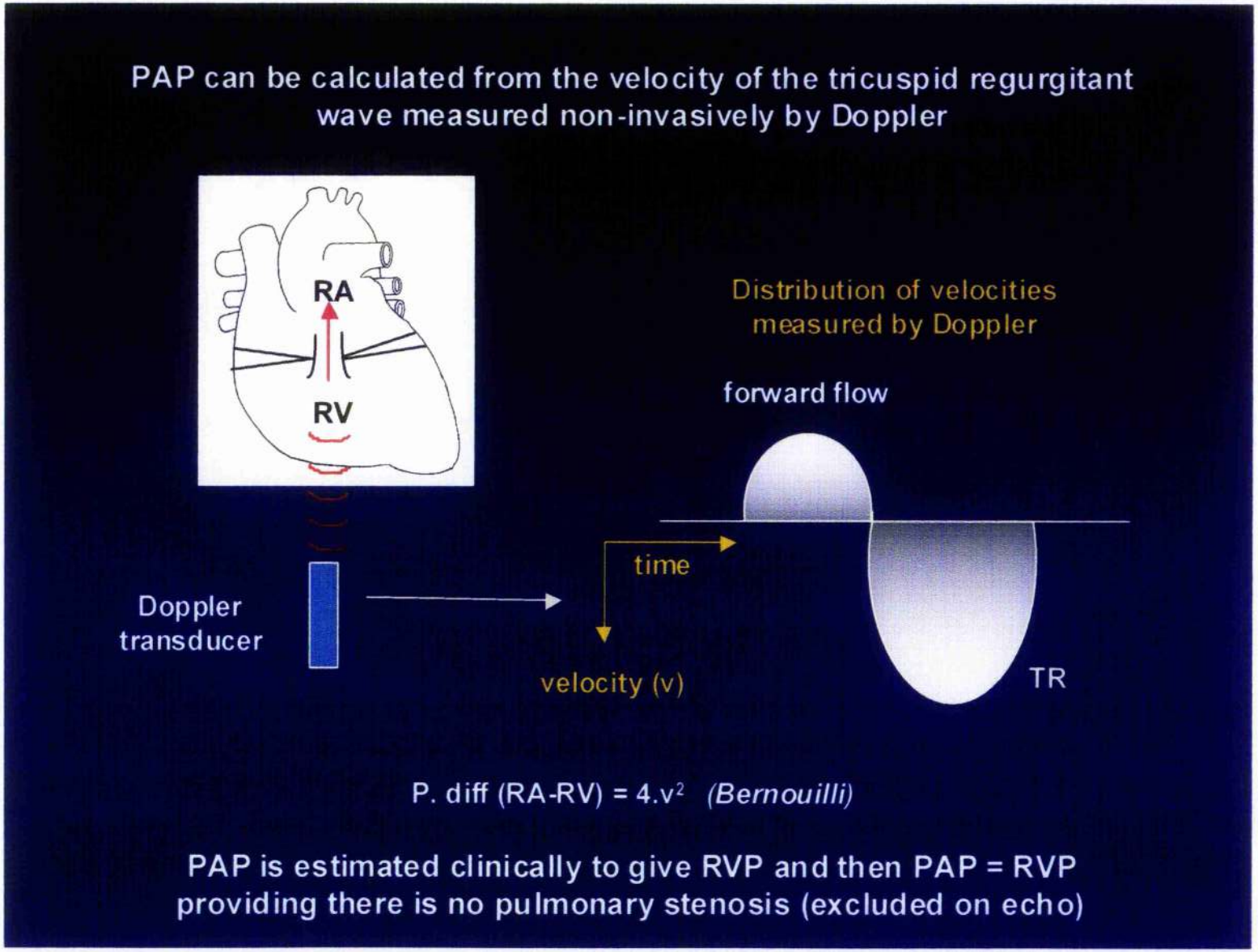
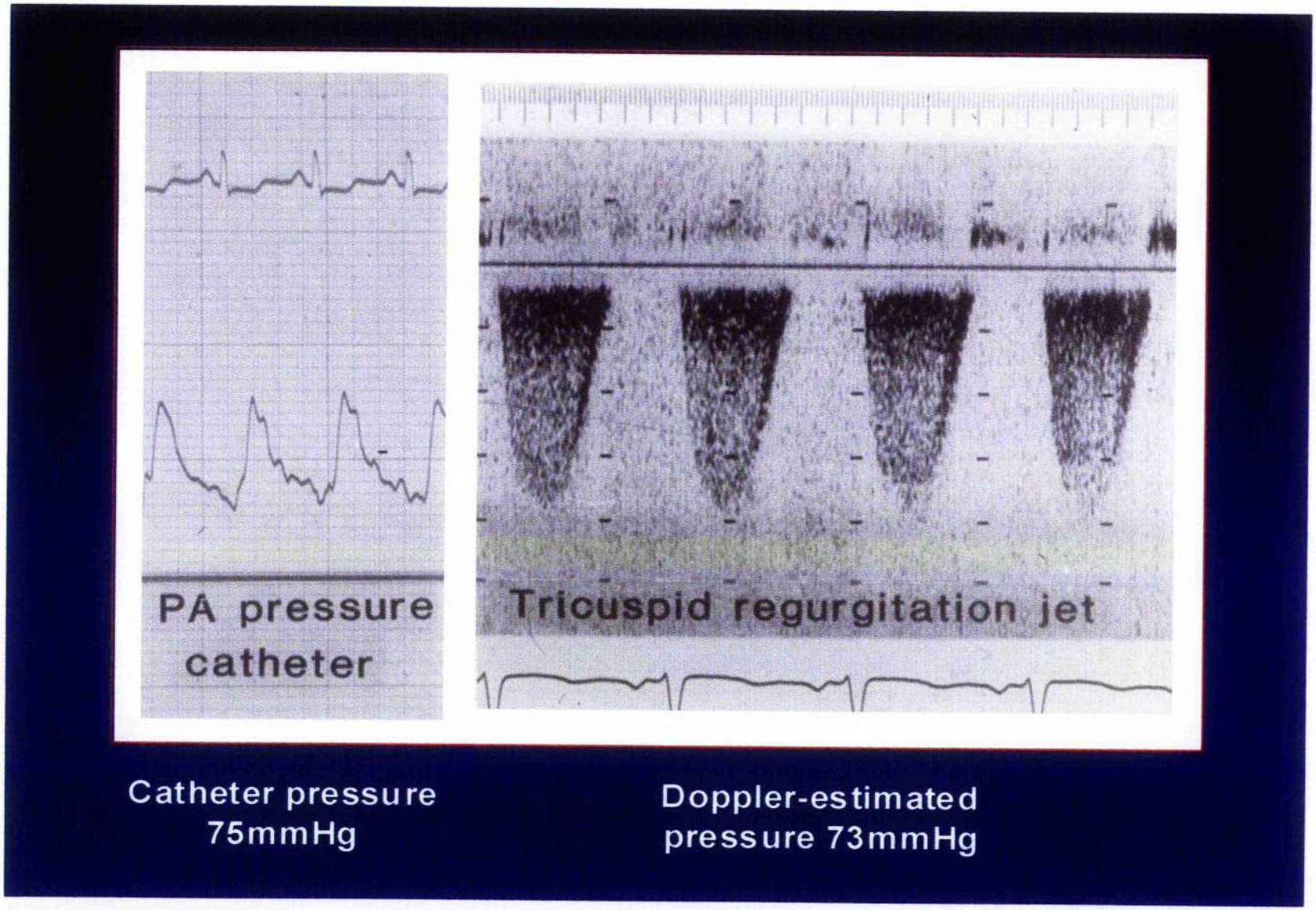


Figure 1.3 **PAP Measured by Cardiac Catheterisation and Estimated by Doppler Echocardiography**
PAP trace from a fluid filled pulmonary artery catheter compared with the estimated PAP from a Doppler echo trace of tricuspid regurgitation



time from the onset of ventricular ejection to the attainment of maximum flow velocity through the pulmonary valve, and ET is defined as the interval between the beginning and end of flow in the right ventricular outflow tract. These flows have characteristic pulsed wave Doppler velocity envelopes. Normal subjects have a smooth dome-shaped envelope while patients with pulmonary hypertension show a notched pattern caused by a shortened AT followed by a second slower rise during deceleration. AT and ET can therefore be used to demonstrate the presence of pulmonary hypertension but, unlike continuous wave Doppler assessment of TR jet velocity, the calculation of underlying values of pulmonary artery pressure is poor (Tramarin *et al* 1991). Intra and inter-observer variability is slightly worse than with continuous wave Doppler and the technique is less sensitive to factors which induce acute changes in pulmonary artery pressure (Torbicki *et al* 1990). However, compared with the success rate for continuous wave Doppler in COPD of approximately 30%, pulsed wave Doppler can detect pulmonary hypertension in over 90% of cases.

1.3.1.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can provide accurate anatomical information about the cardiac ventricles and normal ranges for ventricular volumes and masses have been established (Lorenz *et al* 1999). It has been used to estimate pulmonary artery blood flow and distensability (Paz *et al* 1993) as well as cardiac output and stroke volume (Tarvidon *et al* 1994) and has been shown to be more accurate than echo in monitoring left ventricular mass (Bellenger *et al* 2000). Recent work has attempted to correlate the Ventricular Mass Index (ratio of right ventricular mass to left ventricular mass) with mean PAP and found this to be superior to the correlation

of Doppler echocardiography with the same variable (Saba *et al* 2002). The authors suggest that this might be because MRI reflects the right ventricle's response to sustained pulmonary hypertension and is less susceptible to short-term variables - such as posture and heart rate - which affect Doppler echocardiography. MRI is not yet widely available and again provides an estimate of PAP.

1.3.2 Invasive Methods of Measurement

Conventionally, fluid filled thermodilution catheters have been taken as the gold standard against which other techniques have been compared, though this view is not accepted by some authors (Naeije *et al* 1996). Right heart catheterisation is usually carried out using a fluid filled thermodilution catheter of the Swan Ganz type (Swan *et al* 1970). The procedure can be used to answer a number of questions and is very fully described elsewhere (Groves *et al* 1996) but essentially, the catheter is inserted via a central vein and advanced until the tip is placed in the pulmonary artery. Position can be determined either from the pressure trace or by direct screening with fluoroscopy. The catheter has two fluid filled lumina from which pressure traces of right atrial and pulmonary artery pressures are recorded simultaneously by external transducers, and a thermistor for measurement of pulmonary blood flow by the thermodilution technique. Pressure measurements are conventionally made in the right atrium, right ventricle, pulmonary artery, and in the wedge position to record pulmonary artery occlusion pressure, which is an estimate of left atrial pressure. Pressure and flow measurements can be repeated following interventions such as the administration of vasodilators or oxygen, or after exercise. Thus, in addition to the direct measurement of pressures, a number of variables are derived which can be used

to calculate further information such as pulmonary vascular resistance (PVR) which is calculated by subtracting the pulmonary artery occlusion pressure (estimated left atrial pressure) from the mean pulmonary artery pressure and dividing by the cardiac output. Changes in PVR (expressed in Wood's units) give a measure of the vasoreactivity of the pulmonary circulation.

1.3.3 Risks and Complications of Invasive Assessment of the Pulmonary Circulation Using Fluid Filled Cardiac Catheters

1.3.3.2 Risks and Complications of the Procedure

Cardiac catheterisation is generally a safe and well-tolerated procedure. Complications of pulmonary artery catheters are traditionally divided into those related to catheter insertion and those related to the presence of the catheter itself (Mansfield 1999). The overall mortality is 0.4% (Shah *et al* 1984)

1.3.3.2.1 Procedure related complications

There are a number of minor complications such as bleeding at the catheter insertion site and trivial arrhythmias during the procedure. There are risks associated with the placement of the venous sheath but these can be minimised by using the appropriate approach. The subclavian approach is associated with a 1-6% risk of pneumothorax and when unintentional arterial cannulation occurs, bleeding is difficult to control (Matthey and Chatterjee 1988). For these reasons access via the internal jugular vein is preferred. The peripheral veins (antecubital or femoral) were not appropriate for the passage of the relatively stiff micromanometer tipped pulmonary artery catheter and were not used.

Arryhthmias provoked during the passage of the catheter are usually benign and sustained ventricular tachycardia is rare (3%) (Weidemann *et al* 1984).

1.3.3.2.2 Catheter Related Complications

1.3.3.2.2.1 Infection

Indwelling pulmonary artery catheters (>24 hours) are associated with varying risks of infection from 0.7% to 11.4% (ASA task force on Pulmonary artery Catheterisation 1993) and the incidence of bacterial endocarditis can be as high as 7% (Rowley *et al* 1984). Higher infection rates are associated with the right internal jugular route for venous access, catheter repositioning and prolonged catheter insertion times (>96 hours) (McGrath 1986).

1.3.3.2.2.2 Thrombosis

The incidence of mural thrombi found at post mortem in the right ventricle of patients with a pulmonary artery catheter has been estimated at 30%, however this was not associated with an increased risk of pulmonary thromboembolism (Weidemann et al 1984).

1.3.3.2.2.3 Balloon Rupture

Balloon rupture (releasing air into the circulation) complicates 3% of procedures and is not usually associated with serious consequences (Sise *et al* 1981).

1.3.3.2.2.4 Pulmonary Artery Rupture

This is an extremely rare complication of right heart catheterisation occurring during 1 in every 3000 procedures (Kearney and Shabot. 1995). Possible causes are thought to include prolonged balloon inflation or catheter manipulation. Pulmonary artery rupture is more likely in older subjects, in the presence of pulmonary hypertension and in the anticoagulated. This complication did happen during conventional right heart catheterisation while studying a subject for this thesis and the patient survived.

Other complications are particularly relevant to patients with relatively low and fixed cardiac output and these are detailed below (Groves and Badesch 1996).

- Vasovagal reactions with systemic hypotension and bradycardia
- Supraventricular tachycardia may occur as a direct consequence of catheter passage through the right heart. These can be significantly disabling to patients in whom the contribution of atrial contraction to cardiac output is important.
- Systemic hypotension as a consequence of vasodilator administration.

1.3.3.3 Advantages, Disadvantages and Limitations of Conventional Cardiac Catheterisation

Cardiac catheterisation in the catheter laboratory is conventionally regarded as the "gold standard" against which other techniques must be compared. It is a safe procedure in a controlled environment which, when performed correctly will produce high quality, reliable data which is suitable for comparison with that produced by the many centres using very similar techniques. Patients do not require prolonged hospital admissions and in some centres are managed as out patients. During the procedure the opportunity exists to collect additional data as seems appropriate e.g. angiography

(Chapter 2.4.4.1) a saturation run (Chapter 2.4.4.2) or vasodilator studies (Chapter 2.4.3) may be performed provided that consent is adequate.

The most important disadvantages of conventional cardiac catheterisation are the limitations placed on the circumstances in which data can be collected. Because of the external transducer and the need for accurate levelling with the catheter tip, measurements must be made in supine patients usually at rest. Such circumstances may bear little relation to the pulmonary haemodynamics actually experienced by patients when they complain of symptoms.

Finally there are technical problems with fluid filled, pulmonary artery catheters, which may be subject to catheter whip, catheter impact and end pressure (Ellis *et al* 1951, Grossman 1986) and have a tendency to damp the signal making them unreliable for the measurement of instantaneous pressures.

Thus conventional cardiac catheterisation with fluid filled, pulmonary artery catheters makes limited measurements in unrepresentative surroundings in an unrepresentative position and in an unrepresentative state.

Apart from the risks of cardiac catheterisation, hospital admission is usual which may be inconvenient for patients. There are also problems inherent in the technique. The fluid filled catheter acts as a damper of the signal and is incapable of measuring instantaneous pressures. Furthermore, these catheters rely on an external transducer, which is levelled with the right atrium making it impossible for the patient to change position and allowing limited manoeuvres on the catheter table. Hence the results obtained, though of value, bear little relation to the pulmonary haemodynamics actually experienced by patients.

In conclusion, there is now a formidable array of tools available for the investigation of a patient with suspected pulmonary vascular abnormalities. Though the more traditional methods have been shown to be too insensitive to be valuable in isolation, collectively they remain important screening techniques by which patients who require further investigation can be identified.

Pulmonary hypertension is an important complication of many cardiorespiratory diseases and its recognition is important. When it is suspected, usually on the basis of the patient's signs and symptoms and the traditional screening tests, referral should be made, in the first instance, for echocardiography. This should include assessment by both continuous wave and pulsed wave Doppler. When pulmonary hypertension is confirmed, or where there continues to be any doubt, the patient should be referred to a pulmonary vascular centre for further assessment.

1.4 Evolution of Systems of Measurement in the Systemic Circulation and Parallels with the Pulmonary Circulation

It has been known for some time that blood pressure measured by physicians in clinical surroundings are different from those obtained at home (Ayman and Goldshine 1940) and that placebo effects on blood pressure are only seen in the clinical setting (Goul *et al* 1981).

Thus there has been a move towards ambulatory blood pressure monitoring in the systemic circulation based on the belief that this provides more accurate information about blood pressure and consequently better prognostic information. This is important in pathology where small changes in recommended blood pressure targets for populations might translate into major epidemiological benefits. This observation seems likely to hold true for the pulmonary circulation (albeit on a much smaller scale) and indeed in a low-pressure system small reductions are even more significant. Hence there are implications for the measurement of the pulmonary circulation in the way that ambulatory blood pressure monitoring has developed.

The conclusions of a number of investigators in the late 1980's was that ambulatory blood pressure measurement offered significant advantages over conventional measurement. Studies suggested that measurements made by attending physicians (office blood pressure measurements) were not predictive of ambulatory blood pressure measurements and that the latter offered a better assessment of individual cardiovascular risk and a more accurate evaluation of therapy (Brunner *et al* 1985). Others had previously shown that ambulatory blood pressure differed from office pressures and that this correlated with a significant increase in fatal and non fatal adverse events; the benefits of ambulatory blood pressure measurement were shown to be greatest in those individuals with borderline hypertension (Perloff *et al* 1983).

The technique also allowed the distinction between pseudo and true hypertension and because ambulatory blood pressure measurements correlate even more strongly with future disease than casual pressures and because of the large number of readings obtained, clinician confidence improved (Sleight 1985).

Another important advantage of ambulatory blood pressure measurement is that it measures not only mean pressure but also blood pressure variability which is important in mortality and morbidity (Mancia *et al* 1985) and has been subsequently shown to correlate with target organ damage (Parati *et al* 1987, Palatini *et al* 1992).

In conclusion, it is now understood that office hypertension is not associated with the same degree of cardiovascular risk as sustained hypertension revealed by ambulatory monitoring. Ambulatory blood pressure measurement can be used to define those at risk either due to sub optimal blood pressure control or because of patterns of hypertension associated with a poor outcome such as nocturnal hypertension. The technique allows the more rigorous assessment of antihypertensive agents (Prasad *et al* 1996).

In the assessment of the pulmonary circulation pressure measurements are usually made in unrepresentative surroundings, position and state (Raeside and Peacock 1997). The importance of early recognition of pulmonary hypertension is widely accepted if not yet scientifically proven and the efficacy and cost benefit ratios of treatment very hard to balance. For these reasons it seems logical that investigators into the pulmonary circulation might see some parallels in the development of ambulatory measurement systems in the systemic circulation.

1.5 Measurement Of The Pulmonary Circulation Using Micro Manometer Tipped Pulmonary Artery Catheters

1.5.1 Previous Work to Develop an Integrated System for the Measurement, Recording and Analysis of PAP

In 1941 Cournand & Ranges performed the first right heart catheterisation in man using the technique to sample blood and measure cardiac output before demonstrating in 1945 that measurement of pressure was also possible.

The realisation that "pulmonary capillary blood" could be obtained by taking samples with the catheter in the wedge position (Dexter *et al* 1946, Hellems *et al* 1949) led to right heart catheterisation being used to investigate cardiovascular physiology and assess the effects of treatment (Lenegre and Maurice 1944, McMichael and Sharpey-Schafer 1944, Stead and Warren 1947). Subsequently it has been shown that pressure measured in the wedge position can be an accurate approximation of pressure in the left atrium (Werko *et al* 1953, Nathan *et al* 1983, Levy *et al* 1987).

Right heart catheterisation was shown to be a useful technique in the management of critically ill patients (Bradley 1964, Fife and Lee 1965) and in 1970 Swan and Ganz described a simple method for catheterising the pulmonary circulation without the need for fluoroscopy.

There are disadvantages inherent in fluid filled catheters however, which lead to problems of signal damping, catheter whip and inadequate frequency response (Grossman 1980). This led to interest in solid, micromanometer tipped pulmonary artery catheters which can overcome these problems and the development of systems for clinical use which allow the high fidelity recording of pulmonary artery pressure (Ellis *et al* 1951). Solid pulmonary artery catheters permit high fidelity pressure

recordings and accurate measurement of rate of pressure change (Gould *et al* 1973). Gauer and Gienapp (1950) reported the development of a miniature pressure recording device designed for insertion into the circulation and based on original work by Wetterer (1943). This device deployed the transducer at the catheter tip and allowed high fidelity tracings of the pulmonary artery pressure wave to be made. The advantages of such a system were that it allowed measurement in active subjects and eliminated the artefacts generated by the transmission of a pressure signal by a fluid filled tube such as a conventional pulmonary artery catheter. Furthermore micromanometer tipped catheters eliminate the need for levelling with an external transducer and allow subjects to be fully ambulant.

Such systems have been investigated in cardiac disease (Chapter 1.5.3). One of the principle disadvantages of such catheters is their tendency to baseline or zero drift and the catheter described in this thesis incorporates a novel method of *in vivo* calibration to counteract this phenomenon (Chapter 1.5.2).

The subsequent development of transducer tipped systems with no need for levelling with an external transducer meant that high quality pressure recordings could be made in ambulant patients. The system described above also allows the *in vivo* correction of zero drift.

The system used in this thesis was then developed by Gibbs *et al* (1992) in order to produce a complete system for the measurement, recording and analysis of ambulatory pulmonary artery pressure.

1.5.2 The PAP Recording System

1.5.2.1 The Catheter

The ambulatory pulmonary artery catheter described here is a 7F NIH, double lumen catheter (Gaeltech Ltd UK), Figure 2.1.

A pressure transducer is located at the catheter tip, which eliminates the necessity for levelling with an external transducer. Because the catheter tip incorporates its own zero reference point patients are able to be fully ambulant with no disruption to the recording. This catheter is designed for multiple use and is gas sterilised in ethylene oxide for 48 hours. The principal advantage of this system is that the catheter incorporates an *in vivo* calibration system, which allows correction for "zero drift".

1.5.2.2 The Ambulatory Recorder

The data are recorded by a portable battery powered recorder (Type MPR/2, Gaeltech Ltd, Isle of Skye, UK). The recorder dimensions are 188 by 135 by 45mm and its weight 850 g including four AA size batteries. Figure 2.2.

The recorder incorporates two buttons which have start/stop and event marker functions. The latter, pushed by the patient or investigator, marks an event and time on the trace, which can then be compared with an activity diary kept by the patient or investigator. This permits direct comparison of the pressure trace with activity. The recorder incorporates a liquid crystal display showing the amount of memory used and a clock allowing annotation of the trace in real time. The memory incorporates a 2 MB expansion card giving more than 24 hours continuous recording and is protected by an internal power source during battery changes.

The catheter is connected to the recoding box through a port at its rear and a socket on its side is used to attach a serial link to a desktop computer for storage and analysis (Mitsubishi Apricot Pentium 100). This link can also be used to interrogate the recording box and alter its parameters at any time (including during recording) and permits the pulmonary artery pressure tracing to be displayed on the computer screen in real time. Pulmonary artery pressure can be recorded in the range of –30 to 223 mmHg. The analogue pressure signal from the catheter is amplified and filtered to limit the highest frequency to 16 Hz and compressed.

1.5.2.3 Data Compression

Mean pressures are derived from the recorded pressure waveform. Point values are taken from the pressure trace every 0.03 seconds and then divided by the total time for which a mean pressure is required.

In order to allow studies to be performed without interruption the recorder compresses the data it receives. This is a particular problem in the pulmonary circulation because of the irregularity of the pressure wave. Large swings in intrathoracic pressure can occur with respiration and the system must accommodate these. This is achieved by applying an algorithm to the pressure trace which selects representative data points at a rate of 32 per second. These samples are at inflection points to reduce subsequent errors in pressure calculation (<1mmHg) and are linked by straight lines in order to minimise deviation of other points. Because of inter-individual variations in pulmonary artery pressure waveform this system has been validated against real time, non-compressed data (Gibbs *et al* 1992).

1.5.3 Technical Characteristics and Validation of this System

1.5.3.1 Zero-drift

Micro manometer tipped pulmonary artery catheters are prone to zero-drift; this refers to a change in the baseline voltage at which the catheter output has been set when the transducer was exposed to atmospheric pressure (Gibbs *et al* 1989). Provided that the sensitivity and gain stability of the recording equipment remain unchanged, zero-drift will result in a similar alteration in output voltage to the same applied pressure.

The principle of calibrating a pressure transducer by applying equal pressure above atmospheric to both of its surfaces has previously been described (Eversden 1970).

This technique was exploited in the development of the catheter described in this thesis to allow the correction of zero-drift while the catheter was in the circulation (Gaeltech UK Ltd). The transducer lies in the stainless steel tip of the catheter between the two catheter lumina (both of which are exposed to the atmosphere); on one side a $2mm^2$ window exposes it to the circulation from which it is protected by a silicone elastomere membrane. The two lumina are in communication with a luer fitting on the catheter into which 0.4 ml air is injected using a one ml syringe. This action results in a pressure of 124 mmHg being applied via the catheter lumina to both sides of the transducer causing the membrane to be temporarily lifted off its surface before springing back into place. While the membrane is lifted off the transducer surface the pressure on both of its sides is high and equal, allowing calibration to be performed.

Gibbs (1989) has shown that this reference calibration is a valid function of zero and confirmed that the zero drift observed during bench testing can be used to predict how much zero drift will occur in ambulant patients.

1.5.3.2 Validation equipment and experiments

A series of experiments were performed in the laboratory followed by clinical evaluation (Gibbs *et al* 1989).

Prior to testing the catheter tip was soaked in normal saline for at least two hours to stabilise the elastomere membrane. Measurements of zero were made with the tip exposed to atmospheric pressure and measurements of catheter voltage output made when the membrane was under inflation were referred to as reference calibrations. These measurements were all performed on at least two catheters.

Static pressure testing demonstrated an accuracy of ±0.1% of the applied pressure mass at 20°C and a temperature error of ±0.07% between 20-25°C.

Dynamic pressure testing was carried by subjecting the catheter tip to morphologically accurate pulmonary artery pressure waveforms using a blood pressure systems calibrator (Bio-Tek Instruments Inc.). The frequency response of the catheter generated waveforms was flat from 0-150Hz and the pressure range was –20-200mmHg with an accuracy of ±2% of the reading.

When performing reference calibrations the pressure applied is unimportant provided that it is greater than atmospheric and the pressure being measured. The volume of air required to achieve this varied from 0.1-0.6ml and was compared with the catheter output in milli-volts. The pressure within the catheter during reference calibrations was determined by applying a known pressure to the catheter using a dead weight pressure balance; the pressure immediately prior to a sharp rise in the catheter's output was taken to be that at which the known applied pressure and the catheter pressure were balanced.

The relationship between reference calibration and zero was determined. During bench testing, transducers are subject to very little zero-drift and therefore this had to

be induced using by subjecting the catheter to temperature variations (4-50°C). This resulted in the zero reading drifting by 7.4mmHg (10% of full scale). Measurements were made during static and dynamic testing.

Further experiments were performed to ascertain that the catheter output altered by the same amount as the zero-drift measured and to determine the influences of the pressure being measured the morphology of its waveform and heart rate on the reference calibration. Temperature changes at the catheter tip did alter the pressure volume relationship under the elastomere membrane and the effect of these was assessed over a range of temperatures (20-43°C).

Dynamic testing was achieved by subjecting the catheters to pressure changes generated by the blood pressure calibrator for five days. Zero measurements were made every 20 minutes for the first 12 hours and randomly thereafter.

No difference was found between the two catheters. The optimum volume of air for a reference calibration was found to be 0.4ml as that which was sufficient to exert the required pressure and unlikely to damage the membrane.

The relationship between the reference calibration and zero was shown to be linear with no important changes at extremes of zero-drift. The change in zero was seen to be similar to the changes seen in other pressures.

The influence of the pressure being measured on the reference calibration was greater during static than dynamic testing (1.45% of full scale v 0.7%) and the morphology of the pressure waveform affected the reference calibration by 0.0005% of full scale.

Catheter tip temperature differences altered the reference calibration by 0.004% of full scale per °C.

The zero-drift seen during dynamic testing was 5.2mmHg for catheter one and 0.37mmHg for catheter two.

1.5.3.3 Clinical evaluation

Ambulatory pulmonary artery pressure measurement was carried out in eight patients for between eight and 48 hours. Catheter drift was seen to vary in amount and direction and was a function of time with the most rapid period of drift occurring in the first four hours of recording. Again calibration lines did not alter significantly before and after periods of pressure recording.

Gibbs (1989) concluded that that zero-drift is likely to occur during ambulatory pulmonary artery pressure measurement with micromanometer tipped pulmonary artery catheters and is not predictable. The differences observed between laboratory and *in vivo* testing probably relate to the stresses the catheter endures passing through the right side of the heart and with each heartbeat. The design modifications made by Gibbs (1989) to the catheter used in this thesis allow for *in vivo* correction of zero-drift and minimise the effects of artefactual pressure changes.

1.5.3.4 Risks And Complications Of Cardiac Catheterisation Using Micro Manometer Tipped Pulmonary Artery Catheters

The procedure carries the same general risks and complications as those described for conventional cardiac catheterisation (Chapter 1.3.3). Specific risks related to the use of the micromanometer tipped pulmonary artery catheter are that it is stiffer than a fluid filled catheter which may cause difficulties in placement and increase the risk of ventricular rupture. Complications specific to the micromanometer tipped pulmonary artery catheter were not encountered in the procedures described here.

1.5.3.5 Advantages, Disadvantages And Limitations Of Micromanometer Tipped Pulmonary Artery Catheter PAP Monitoring

The principal advantage of this system is its ability to provide high quality recordings of PAP in fully ambulant patients as described in Chapter 2.3.

There is no facility to measure cardiac output or pulmonary artery occlusion pressure, which limits the haemodynamic obtained with this system. There are theoretical risks of infection, catheter migration, arrhythmia and bleeding from the insertion site associated with long term indwelling pulmonary artery catheters, but these were not observed in the studies described in this thesis.

When used with the relevant recording and information storage systems, these catheters allow the accurate recording of long term (>24 hours) pulmonary pressures (Gibbs *et al* 1992). These, when analysed in conjunction with a simple patient diary, reveal changes in pulmonary artery pressure with everyday activity such as sleeping, standing, walking, or exercising (Chalmers *et al* 1996). More formal exercise testing can also be carried out with the catheter *in situ*. However, though superior to fluid filled catheters in many respects, micromanometer tipped catheters are expensive, less flexible, and lack a flotation balloon, which can lead to difficulties in placement. Since the patient should be ambulant to gain maximum information, the femoral route is not possible and the internal jugular or subclavian route must be used.

Despite their advantages, neither type of pulmonary artery catheter takes into account all the complex forces which constitute pulmonary haemodynamics. However, when combined with Doppler echocardiography a much more complete picture is obtained.

1.5.4 Previous Work Measuring Ambulatory PAP in Heart Disease

Initial interest in ambulatory pulmonary artery pressure monitoring followed from the observation that that left ventricular end diastolic pressure (LVEDP) is related to indices of physical performance (Sarnoff and Mitchell 1962). In the absence of mitral valve disease or raised pulmonary vascular resistance pulmonary artery diastolic pressure is an accurate estimate of left ventricular end diastolic pressure in man (Hodges *et al* 1969, Russell *et al* 1969, Falicov and Resnekov 1970) and consequently a number of authors have utilised ambulatory pulmonary artery pressure measurement in the investigation of heart disease.

Jenkins *et al* (1970) studied this relationship in patients with acute and chronic cardiac disease and found that it only held true where PVR was normal. Later work utilised ambulatory pulmonary artery pressure measurement to demonstrate the relationship between ST segment changes and rises in PAP in patients with ischaemic heart disease subjected to stress (Levy *et al* 1986). The same authors also observed that a similar relationship existed between chest pain and haemodynamic changes in patients with variant angina and asymptomatic ST segment changes but not in the situation of chest pain and normal coronary angiography (Syndrome X). In this sequence of papers Levy and co-authors (1986) concluded that ambulatory pulmonary artery pressure monitoring provided a useful surrogate for changes in left ventricular haemodynamic function in patients with coronary artery disease.

Gibbs *et al* (1989) studied the assumed changes in PAP in chronic heart failure due to posture and sleep. Measuring ambulatory pulmonary artery pressure they demonstrated that these variations were not wholly explained by posture as the observed changes were gradual and absent in two subjects. Again the advantages of real time comparison between activity and PAP changes were important in the

conclusions of this study. Richards *et al* (1989) studied variations in PAP using an ambulatory pulmonary artery pressure measurement system in patients with PPH compared with a control group during activities of daily living. They observed that these changes were more variable and had greater magnitude in the PPH group.

Gibbs *et al* (1990 and 1991) again studied subjects with chronic heart failure comparing rises in PAP during activities of daily living with those seen during maximal exercise tests. They observed that neither symptoms nor PAP variations during normal activity are the same as those experienced during exercise and questioned the validity of maximal exercise tests in the assessment of patients with chronic heart failure.

Further work assessed the neuroendocrine response to cardiac catheterisation in patients with chronic heart failure. The authors found no relationship and therefore questioned the accepted practice of delaying haemodynamic measurements following cardiac catheterisation.

The use of ambulatory pulmonary artery pressure measurement in heart disease evolved from a physiological observation that it offered a useful surrogate for LVEDP to the realisation that the technique permitted real time comparisons between applied stress and haemodynamic responses.

1.5.5 The Re-Evaluation of Ambulatory PAP Monitoring in Patients with Pulmonary Hypertension Secondary to Lung Disease

This thesis examines the utility of ambulatory pulmonary artery pressure monitoring in patients with pulmonary hypertension secondary to lung disease. Such patients usually complain of symptoms when active while haemodynamic monitoring of the pulmonary circulation is conventionally carried out at rest. The benefits of ambulatory

pulmonary artery pressure monitoring described in Chapter 1.5.4 therefore seemed equally applicable to the pulmonary circulation and the measurement of PAP even more so.

- Postural changes in a model of PPH.

PPH offers the "purest" clinical presentation of pulmonary hypertension but is very rare. The pulmonary hypertension associated with connective tissue disease is very similar clinically and pathologically to PPH and connective tissue disease a much commoner condition. This therefore provides a useful model of PPH which was used in Chapter 3 to study the effects of posture on the pulmonary circulation using ambulatory pulmonary artery pressure monitoring.

- Changes in PAP with sleep in COPD.

COPD is as common as PPH is rare and is the predominant clinical situation in which most clinicians will encounter pulmonary hypertension. Important changes in PAP are known to occur due to a variety of stresses including exercise and sleep. The accurate assessment of these changes in the pulmonary circulation may have implications for treatment in COPD, particularly with reference to oxygen treatment. In Chapter 4 ambulatory pulmonary artery pressure monitoring was carried out during sleep and exercise in a group of patients with COPD and a control group and the effects of oxygen treatment in the COPD group was assessed.

- Surrogate markers for PPH.

Invasive haemodynamic monitoring is safe and well tolerated, however carries a small risk and is inconvenient and expensive. Ideally reliable surrogates of PAP will be identified to avoid the need for invasive procedures and to widen the kinds of patients studied. The ambulatory pulmonary artery pressure monitoring system

has advantages which make it particularly suitable for identifying these surrogates i.e. the capacity to make accurate measurements of PAP during exercise. In Chapter 5 a group of patients with connective tissue disease were studied (again as a model of PPH). The ambulatory pulmonary artery pressure monitoring system was used to measure changes in PAP simultaneously with variables measured during cardiopulmonary exercise testing and correlations sought.

- Treatment of pulmonary hypertension.

The physiological variability of the pulmonary circulation makes the assessment of treatment a particular challenge. In Chapter 6 the surrogates of PAP identified using the ambulatory pulmonary artery pressure monitoring system were used to assess the responses to treatment with oral vasodilators of a group of patients with connective tissue disease (again as a model of PPH).

1.6 Hypothesis and Aims of this Thesis

1.6.1 Hypothesis

The hypothesis of this thesis is that variations in pulmonary artery pressure in man during activities of daily living, sleep and exercise secondary to respiratory disease can be measured using an ambulatory pulmonary artery pressure measurement system.

Conventional methods of assessment of the pulmonary circulation have disadvantages in these settings while it is likely that the ambulatory pulmonary artery pressure monitoring system has particular strengths in allowing the measurement of pulmonary artery pressure in fully ambulant patients.

1.6.2 Aims

The primary aim of this thesis was to prove that ambulatory pulmonary artery pressure monitoring is safe and well tolerated in patients with respiratory disease.

Secondary aims were:

- To evaluate ambulatory pulmonary artery pressure monitoring in pulmonary hypertension secondary to pulmonary vascular disease. Specifically to assess changes in pulmonary haemodynamics related to posture, sleep and exercise.
- To assess the relationship of ambulatory pulmonary artery pressure monitoring to the other available methods of measurement in the pulmonary circulation.
- To determine the relationship between pulmonary artery pressure measured during exercise and other variables measured non-invasively during cardiopulmonary exercise testing.

- To assess the effect of treatment of secondary pulmonary hypertension using the ambulatory pulmonary artery pressure monitoring system.

Chapter 2

Materials and Methods

2.1 Patient Recruitment

The patients studied in the course of this thesis were recruited from the respiratory clinics of the West Glasgow Hospitals University NHS Trust, and via referral from respiratory physicians from other trusts across Scotland.

Ethical approval for all studies was obtained from the West Glasgow Hospitals University NHS Trust's West Ethics Committee. All patients gave written, informed consent prior to participation in all studies (Figure 2.1).

2.2 Routine Work Up

Routine investigations performed on every patient included routine blood tests, electrocardiogram, chest radiograph, ventilation/ perfusion lung scan, CT scan of thorax, conventional, cardiac catheterisation, and cardiopulmonary exercise testing. All these investigations were carried out using the facilities of the Western Infirmary (Glasgow).

2.2.1 Doppler Echocardiography

Echo Doppler measurements (Acuson 128 XP/10C, Acuson Ltd, Mount View, California, USA) (Fig 2.2) were made in the semi-recumbent position. The jet of tricuspid regurgitation was identified, its maximum velocity measured, and pressure gradient calculated. This gradient was added to an assumed right atrial pressure (10 mm Hg) to give an estimate of pulmonary artery systolic pressure. Echo measurements were made by the same operator in almost all cases and at least 24 hours in advance of cardiac catheterisation, so the operator was ignorant of the "true" PAP.

Figure 2.1 **Consent Form For Ambulatory Pulmonary Artery Pressure Monitoring**

GREATER GLASGOW HEALTH BOARD
THE WEST ETHICAL COMMITTEE

FORM OF CONSENT FOR PATIENTS / VOLUNTEERS IN CLINICAL RESEARCH PROJECT

RIGHT HEART CATHETERISATION WITH 24 HOUR MONITORING
Patient's Summary

We invite you to participate in a trial of measurement of the pressures in the lung circulation. We believe that you have high pressures in the heart as a consequence of problems either with your lungs or the vessels leading from your heart to the lung. Since these pressures may be the cause of your breathlessness, we would like to make measurements of these pressures both at rest and while you exercise quietly. Exercise will be gentle on a treadmill at a fixed work rate within your capacity, which will be estimated beforehand. We will stop the exercise if you become breathless. We aim to measure the difference in pressure from rest to exercise because we believe that arise in pressure with exercise may be a major cause of breathlessness experienced with exercise. The order of measurements, i.e. measurements at rest and measurements on exercise will be randomised so that some subjects will have resting measurements made before exercise and some after exercise. This will not affect the character of the study nor the length of time it takes.

To measure these pressure we will insert a thin catheter via a neck vein into your heart and attach this to a tape recorder which will allow us to continually measure the pressure and should provide useful information as to how this varies as you go about your daily activities. There are slight risks associated with the insertion of the catheter. These include; damage to the blood vessels, leakage of air into the lining of the lung and irregular heart beat. However the catheter will be placed either by or under the supervision of Dr Peacock who has experience of placing hundreds of these catheters and has had no serious problems to date.

You should not take part if you are pregnant and can refuse to participate or withdraw at any time without detriment to your current or future medical care. The results may not prove of any direct benefit to you. Your general Practitioner will be notified of your involvement.

Consent
I, ... of .....
give my consent to the research procedures described above, the nature, purpose and possible consequences of which have been described to me by .....

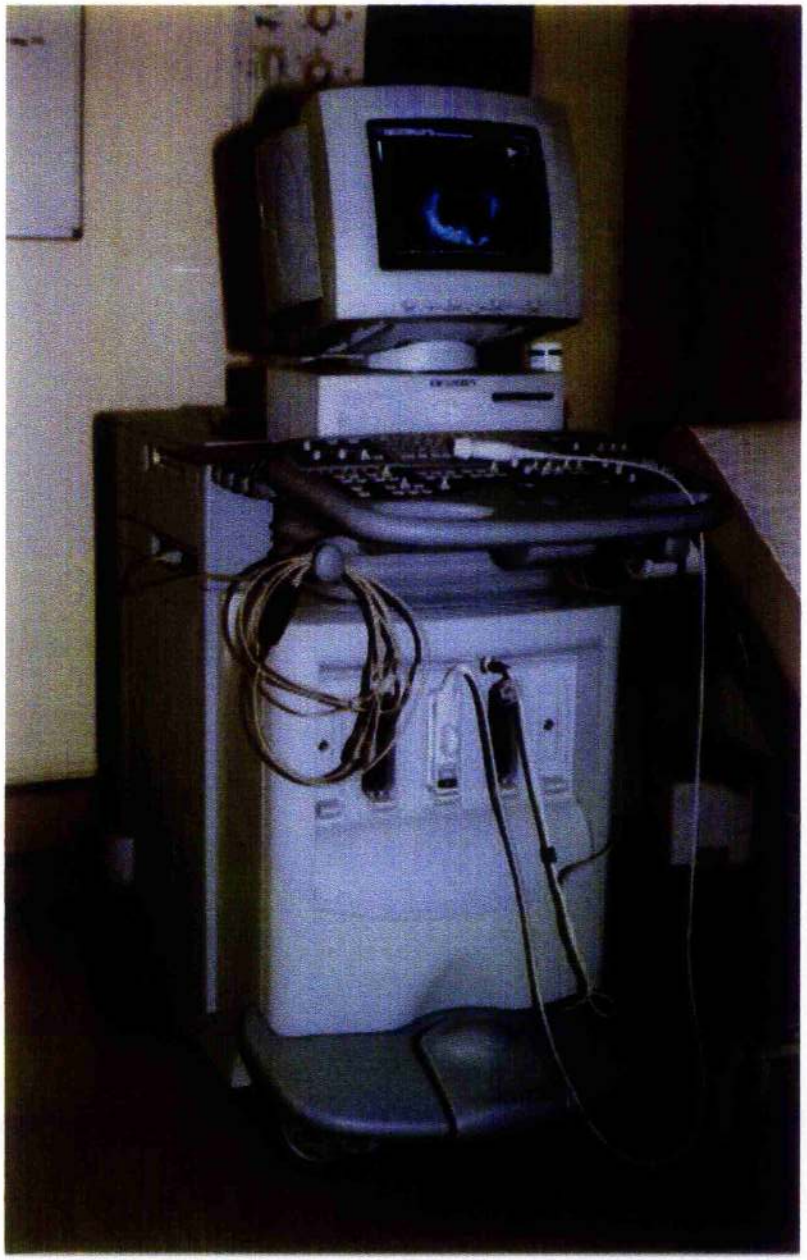
Signed ..... Date .....

Witness .....

Figure 2.2

The Acuson 128XP/10C Echocardiography Machine

All echocardiography data was obtained by a single operator using the machine shown



2.2.2 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing in this thesis was carried out using the SensorMedics V Max System (Sensormedics, Yorba Linda, California) (Fig 2.3) wearing an adult facemask (Hans Rudolph, inc.7200, Kansas City, Mo. 64114 USA). This is a breath by breath measurement system the main components of which are described below.

2.2.2.1 Components of the Sensormedics V Max System

The Mass Flow Sensor^{TM} makes volume measurements by exposing laminarised streams of gas to a pair of heated, stainless steel wires. The principal of measurement involves the assumption that the rate at which heat is lost from the wires is directly proportional to the mass of the individual gas molecules flowing across them.

Gases are measured by the Multi-gas Analyser using a Non-Dispersive Infrared (NDIR) technique which permits real time measurement of carbon dioxide (CO_2) and methane (CH_4). Specifically the system measures gas concentrations by directing the infrared beam through the relevant gas and measuring how much of it is absorbed. Particular gases are selected by adjusting the wavelength of the band.

The Paramagnetic Oxygen Analyser is a fast response oxygen analyser which works on the principal of the high paramagnetic susceptibility of oxygen. This allows sufficiently fast response times to provide real time breath by breath analyses.

The Carbon Dioxide Analyser utilises the same NIDR measurement technique as described above for the multi-gas analyser. The sample chamber size has been minimised to enhance response characteristics as with the oxygen analyser.

The One-way Breathing Valve exhibits low flow resistance and is used for mixing gases during exercise.

Figure 2.3

The Sensormedics V MAX System

All subjects were studied using the cycle ergometer and were wearing a Hans Rudolph face mask.

The mixing chamber has a capacity of 2.6 litres and is used for mixing expired gas during exercise.

2.2.3 Exercise protocols

The exercise protocol described in Chapter 3 required subjects to exercise at 30% of their VO2 max achieved in a previous maximal test; because some of these subjects found a maximal test relatively difficult it was subsequently decided to change this protocol. Furthermore whereas the comparisons of exercise data in Chapter 3 were within subjects, subsequent studies would require a repeatable and reliable exercise protocol which permitted valid comparisons between subjects. Thus with the exception of the data presented in Chapter 3 exercise data was obtained during steady state exercise testing. Exercise was performed on the electromagnetic, cycle ergometer and consisted of a steady state exercise test at a workload of 30 Watts for a maximum of 8 minutes or at a percentage of Vo_{2max} predetermined during a maximal exercise test. Constant work rate testing was chosen because it is particularly suitable for measuring cardiovascular, ventilatory and gas exchange kinetics (Nery *et al* 1982). The electromagnetically braked cycle ergometer was chosen over the treadmill because it is safer and can maintain a given work-rate despite fluctuations in the frequency of pedalling. This relatively low workload for steady state testing was chosen as manageable, and likely to be below the anaerobic threshold, for patients with expected limited exercise capacity.

2.2.4 Cardiopulmonary Exercise Testing Data

In each case breath by breath measurements of gas exchange were made. These included ventilation, tidal volume, respiratory rate, end tidal oxygen and carbon

dioxide concentrations, oxygen saturations, oxygen uptake (VO_2) and carbon dioxide production (VCO_2). From these measurements other variables were derived including oxygen pulse (oxygen uptake / heart rate), and the ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) i.e. the ratios of ventilation to oxygen uptake and carbon dioxide output respectively. During exercise the PAP was recorded continuously with the micro-manometer tipped pulmonary artery catheter. The exercise data presented in this thesis are the mean pressures recorded at the onset of the fourth minute of steady state exercise.

2.3 Treatment and Follow Up

Where indicated, subsequent treatment and follow up was performed in the out patient clinics and wards of the Western Infirmary or Gartnavel General Hospital. Patients who demonstrated a positive vasodilator response were readmitted for the initiation and dose titration of an oral vasodilator: those in whom the vasodilator study was negative were transferred to the respiratory unit for the initiation of intravenous prostacyclin.

2.4 Cardiac Catheterisation

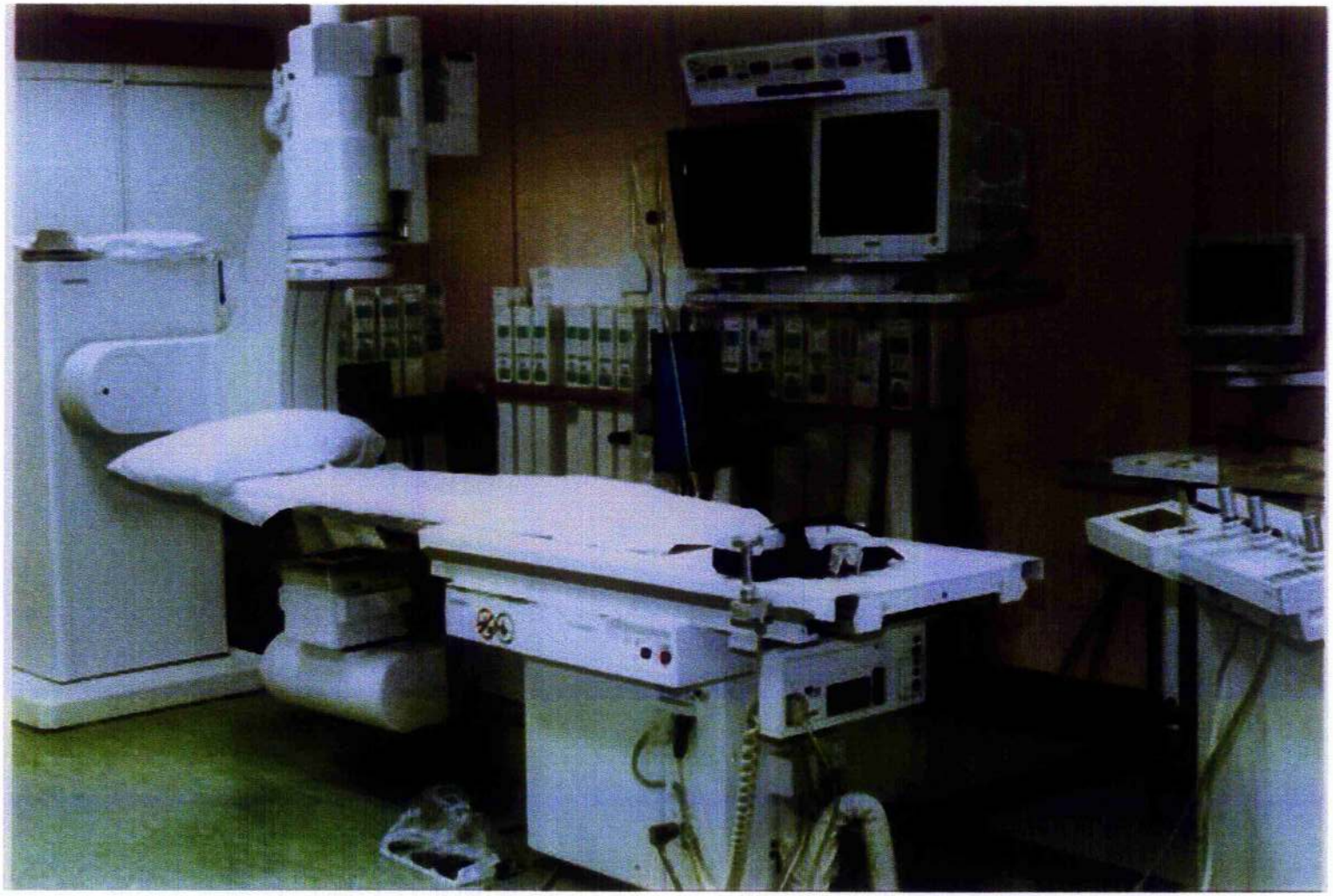
2.4.1 Technical Considerations and Equipment Tolerances

Cardiac catheterisation was carried out in the laboratory at the Western Infirmary in Glasgow (Fig 2.4). All patients were admitted for the procedure; diuretics and calcium channel blockers were stopped on the night prior to cardiac catheterisation. Sedation was not routinely given; very anxious patients were occasionally pre-medicated with a short acting benzodiazepine prior to the placement of the introducer.

An 8F introducer was placed in the right internal jugular vein, using a high anterior approach, not less than three hours prior to the procedure. Right heart catheterisation was performed using a triple channel thermodilution Swan Ganz catheter (Swan Ganz 7 F Thermodilution Catheter, Baxter Healthcare, Irvine, California, USA). The transducer was levelled with the right atrium with the patient lying supine. Pressure measurements for comparison with the other systems were made in the right atrium (RA), right ventricle (RV) pulmonary artery (PA) and in the wedge position to measure pulmonary artery occlusion pressure (PAOP). Pressure values were recorded while patients breath held at functional residual capacity (to eliminate the effects of respiration on PAP). A mean of six beats was recorded and systolic and diastolic pressures were averaged. Pressures were recorded in the right atrium, right ventricle and proximal pulmonary artery, and an estimate of pulmonary artery occlusion pressure was made with the catheter in the wedge position. Cardiac output was averaged over a minimum of three measurements using the thermodilution technique.

Figure 2.4 The Cardiac Catheterisation Laboratory

Conventional cardiac catheterisation and the insertion of the micromanometer tipped pulmonary artery catheter was performed in this laboratory.



2.4.2 Exercise

In all patients the effects of exercise on pulmonary artery pressure was assessed by asking them to perform 3 minutes of straight leg raising. The subject was asked to lift each leg alternately to a measured height of 60 seconds as many times as possible in 3 minutes. This method of exercise assessment is dependant on patient effort and much encouragement was given however it is clearly not reproducible; while the use of a metronome might improve repeatability it will still be difficult to determine retrospectively the extent to which an individual was cooperative and made good effort. Nonetheless this weakness in data collection means that direct comparisons between catheter laboratory exercise pressures and those obtained with the micromanometer tipped pulmonary artery catheter must be interpreted with caution. This demonstrates an advantage of the micromanometer tipped pulmonary artery catheter in that it allows standardised exercise protocols to be employed in ambulant patients. In the last 30 seconds of exercise measurements of pulmonary artery pressure, and cardiac output were repeated. Pulmonary artery occlusion pressure was not re-measured if the resting value had been normal. This is our standard practice, as we believe that repeat measurement after exercise slightly increases the risk to the patient.

2.4.3 Assessment of the Pulmonary Circulation

Early in the disease process pulmonary vasoconstriction is likely to be prominent and its identification and magnitude serve as a guide to subsequent vasodilator treatment. Patients may have relatively fixed & low cardiac outputs with high RAP. Hence drugs which cause systemic, but not pulmonary, vasodilatation can cause catastrophic systemic hypotension and even death (Reeves *et al* 1991).

There are alternative strategies to the assessment of the pulmonary circulation; accept the risk of systemic hypotension, using a drug with a short duration of action, such as prostacyclin given intravenously so that any systemic hypotensive effect can be reversed within seconds by stopping the drug.

Use a substance with an even shorter duration of action such that its effects cease before it reaches the systemic circulation (Morgan *et al* 1991). Acetylcholine, Adenosine and NO are such drugs. Acetylcholine has not found general use because of its potential to slow conduction through the SA node. NO requires cumbersome delivery systems which has limited its widespread use.

2.4.3.1 Acute Vasodilator Studies

Acute vasodilator drugs are used to determine reversibility in the pulmonary circulation. Most drugs in common usage result in simultaneous systemic hypotension which limits their usefulness. A vasodilator with effects limited to the pulmonary circulation would have advantages.

Adenosine is a purine nucleoside with a variety of effects including systemic vasodilation, inhibition of platelet aggregation and of lipolysis, and in vitro has a relaxant effect on human pulmonary vessels.

All patients in whom pulmonary hypertension was confirmed at cardiac catheterisation had an acute vasodilator trial using Adenosine. Adenosine at a concentration of 1mg per ml for patients < 55kg or 1.5 mg per ml for patients > 55kg, was infused via a small-bore peripheral IV line. The starting dose was 100 micrograms per kg per min rising in increments of 50 micrograms per kg per min every 2 minutes until either side effects appeared, or the maximum dose of 300 micrograms per kg per min was reached.

Adenosine has actions on both circulations however has been shown to decrease the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) indicating that adenosine has a preferential vasodilator effect on the pulmonary circulation.

The indications for a study should be reconsidered if the mean right atrial pressure is > 15mmHg as the procedure carries greater risk in this circumstance. Severe asthma or a history of reaction to contrast media was also considered a contraindication. In this thesis all acute vasodilator studies were carried out using adenosine as detailed below.

During the last 2 minutes of the infusion haemodynamic variables were re-measured i.e. either as the patient began to complain of side effects or as the maximum dose was being reached. Adenosine was mixed with N. saline to a total volume of 100mls and run through an intravenous infusion pump (Graseby UK) set to run at hourly flow rates. These volumes and flow rates allowed an adenosine study to be completed in about 10 minutes.

2.4.3.2 Oxygen Therapy

In patients with significant resting hypoxaemia 100% oxygen was administered for 10 minutes and haemodynamic variables re-measured. In individuals receiving long term oxygen therapy supplemental oxygen was administered at the usual flow rate.

2.4.4 Determining Pulmonary Vasoreactivity

In this thesis a positive vasodilator study has been defined as a fall in pulmonary vascular resistance (PVR) or total pulmonary resistance (TPR) of >30%. This value was originally described by Rubins et al (1982) who defined it arbitrarily on the basis

of a study of prostaglandin as an acute vasodilator in patients with PPH. 30% of these patients demonstrated such a reduction in PVR hence its choice as a reasonable measure of pulmonary vasoreactivity. Because of the manner in which these variables are calculated it is possible for the PVR or TPR to have fallen without any reduction in PAP. Where PAP is shown to have fallen with a concomitant rise in cardiac output this combination carries the most positive prognostic value.

2.4.4.1 Pulmonary Angiography

If the ventilation/perfusion (V/Q) scan is low probability and/or the patient had had a negative spiral CT angiogram, or if the mean right atrial pressure is >15 mmHg, we did not perform pulmonary angiography.

2.4.4.2 Saturation Run

A saturation run was only performed if a left to right shunt could not otherwise be excluded. When necessary this was performed by the withdrawal of one ml of whole blood from multiple sites including PA, high RA, mid RA, low RA, high superior vena cava (SVC), low SVC, high inferior vena cava (IVC) and low IVC.

2.5 24 Hour Ambulatory Pulmonary Artery Pressure Monitoring

The pulmonary artery pressure monitoring system described in this thesis consists of a 7 F catheter supplied by Gaeltech Ltd (Dunvegan, Isle of Skye, UK) (Fig 2.5), the ambulatory recorder (Fig 2.6) and a personal computer with the analysis software.

2.5.1 Catheterisation Procedures

The catheter is designed for multiple uses and is gas sterilised in ethylene oxide for a minimum of five days.

Central venous access was acquired on the morning of the cardiac catheterisation not less than three hours prior to the procedure. An 8F sheath was inserted in the right internal jugular vein using local anaesthetic and secured with tape.

The computer and recorder were taken to the cardiac catheterisation laboratory with the patient. The placement of the ambulatory pulmonary artery catheter immediately followed the right heart catheterisation. The ambulatory catheter was removed from its sterile packaging and coiled and placed in sterile saline. 0.4 millilitres (mls.) of air were injected into a port on the side of the catheter using an insulin syringe with the needle removed and the transducer membrane observed immersed in the sterile saline to check that there is no air leakage. The catheter then remained under the saline for a minimum of 2 minutes to allow the catheter insulation to absorb some of this fluid. The catheter was then connected to the recording box, which was switched on, and the programme started. On the monitor the set up menu was entered and the legend "calibrate pressure transducers" selected.

This offered a positive or negative pressure calibration and a negative pressure calibration was always used in the studies in this thesis. When this was selected the menu required the recorder to be stopped. At this stage non-sterile rubber tubing was

Figure 2.5

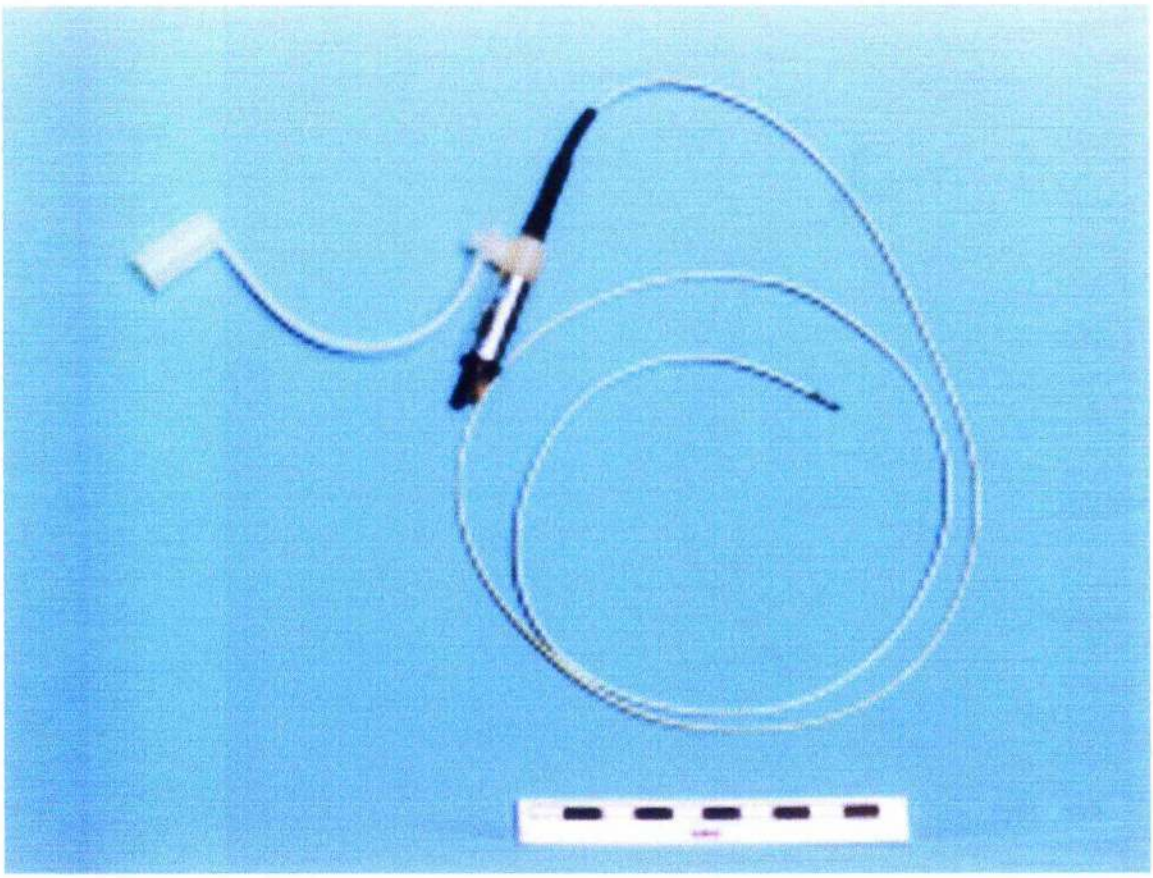


Fig 2.4 The Micromanometer Tipped Pulmonary Artery Catheter

The external luer fitting allows injection of air for calibration. The stainless steel tip houses the transducer.

Figure 2.6

Figure 2.5 The Ambulatory Recorder

The recorder weighs 650g and is carried over the patient's shoulder. The liquid

crystal display reads real time and available memory. The event button

marks the trace.

connected to the port on the catheter and, via a 3-way tap, to the port on the rear of the recording box. The 3-way tap was opened to air and return pressed on the computer keyboard. The instruction menu then specified that the system should be open to air before the pressure calibration was continued, return was pressed again and a pressure of zero was established. The programme then required the negative pressure calibration to be performed in which a 20 millilitre (ml) syringe was connected to a 3-way tap in communication with the recording box and the catheter. The syringe plunger was then withdrawn until the programme read "calibration complete". This instruction also appeared on the display of the recording box. At this stage the catheter was ready for insertion into the patient.

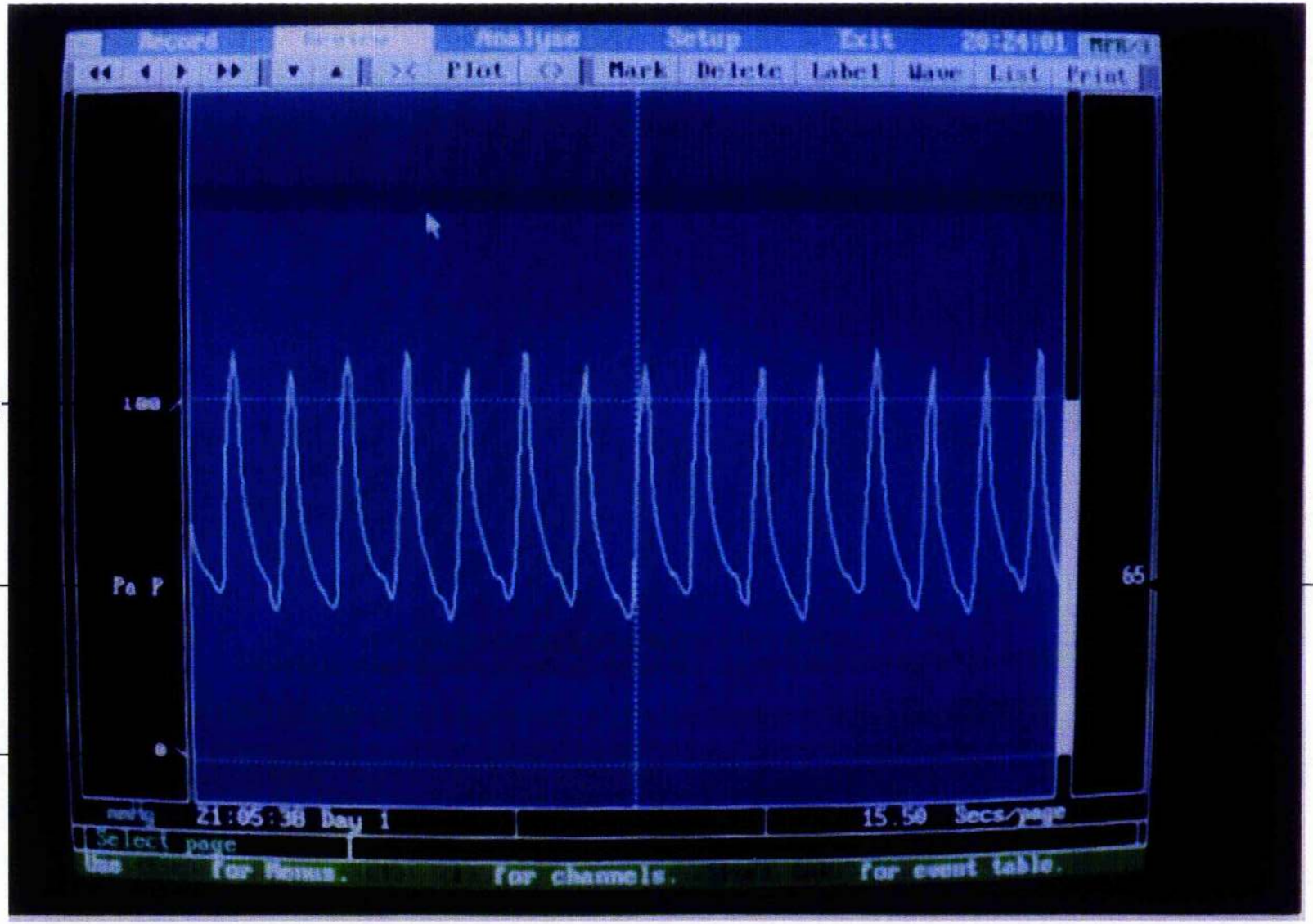
This was placed in the usual way in the proximal pulmonary artery. Care was taken not to advance the tip too far into the pulmonary circulation (i.e. no further distal than the transverse processes, preferably on the right) as wedging led to loss of trace as well as complications.

Once the catheter was satisfactorily positioned it was re-connected to the recording box and on the computer screen the "record" menu selected and "start new real time recording" option selected. This displayed a real time pressure tracing (Fig 2.7). 0.4mls of air was again injected into the port in the catheter to check that the pre-set zero was satisfactory. So long as the value lay between plus or minus 32 the error could be corrected later.

With the catheter in a satisfactory position the sheath was pulled back over the catheter to its end and left in this position. This tended to displace the catheter further forward into the pulmonary circulation, therefore a further fluoroscopy screening check was made before finally securing the catheter with a suture at the point of insertion.

Figure 2.7 **Pulmonary Artery Pressure Trace**

Recorded with the ambulatory catheter in a supine patient in the cardiac catheterisation laboratory. This trace has been opened out to 15 seconds per screen and shows pulmonary hypertension.



the patient was then returned to the general ward (Fig 2.8). At the end of the study the ambulatory recorder was stopped and the data processed as described in Chapter 2.3.4.

The ambulatory catheter was removed and hand washed in warm soapy water. The transducer membrane was re-checked by the injection of 0.4mls of air into the catheter port during repeat immersion. The catheter was then dried and re-connected to the recording box and a "new real time recording" started under the Record menu. The end of the catheter was then placed in a sealed pressure chamber (Gaeltech UK Ltd.) and plastic tubing connected to the end of this chamber and, via a 3-way tap, to a conventional sphygmomanometer. A syringe was then connected to the 3-way tap and a pressure (measured by the sphygmomanometer) applied to the pressure chamber and hence the catheter. This pressure appeared on screen as a square wave trace with a given value at the side of the screen for the pressure being measured by the catheter. Thus for an applied pressure of 50 mmHg. ideally the pressure wave on screen also recorded 50 mm but where error was observed, the recorded value was noted and the whole test trace saved to the hard disc as a real time record.

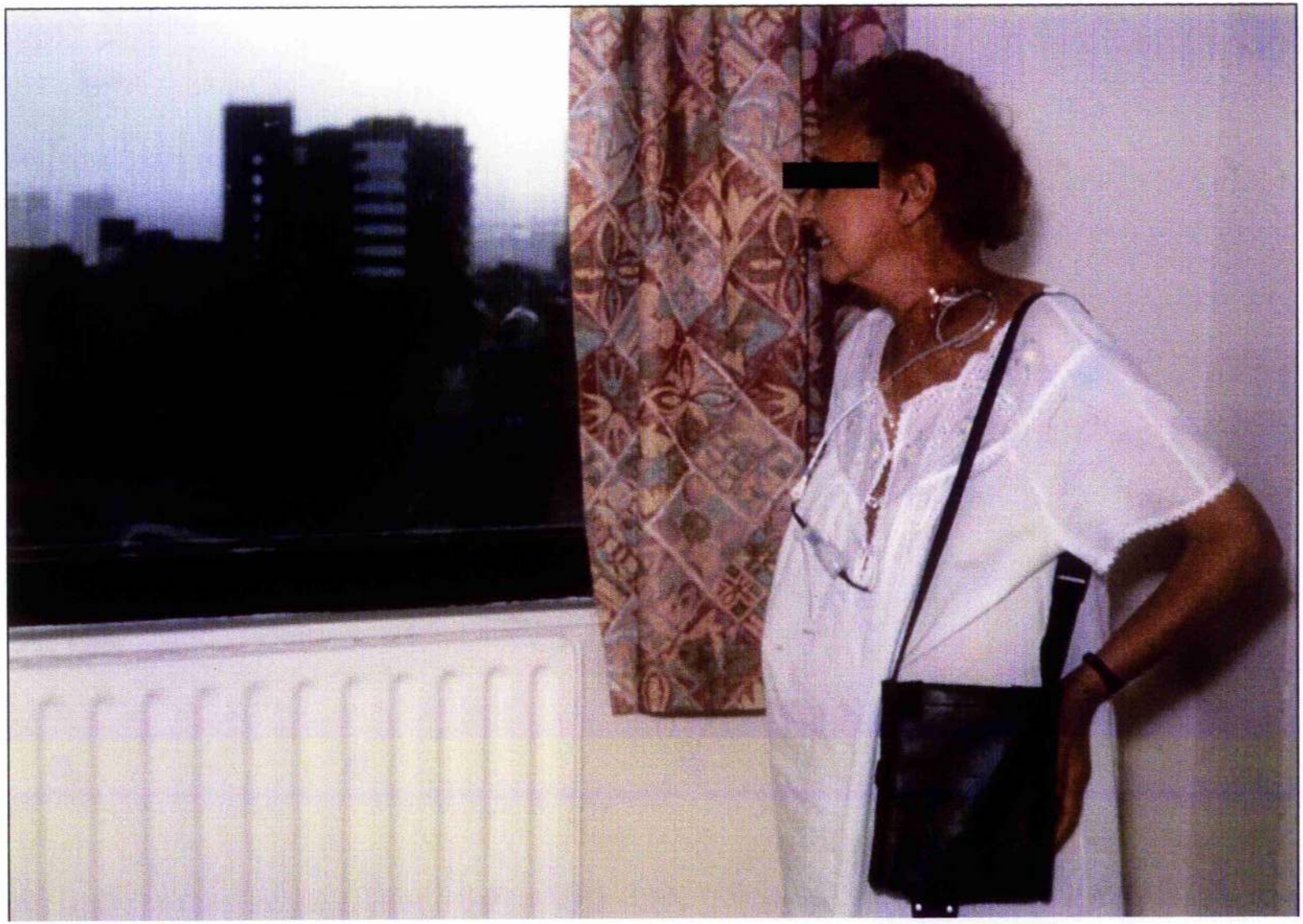
2.5.2 Data Recording, Handling and Analysis

2.5.2.1 The Programme

The ambulatory pulmonary artery pressure monitoring programme is Windows based and is accessed in DOS via the "C" prompt by typing "PAP return, AMB return".

Figure 2.8 **The Ambulatory PAP Measurement System**

A patient with micromanometer tipped catheter in the left internal jugular vein, carrying the ambulatory recorder over the left shoulder.



2.5.2.2 Making a 24 hour Pulmonary Artery Pressure Recording

On return to the ward area the "record" menu was opened and "start real time recording" selected. This displayed the pulmonary artery pressure tracing on screen and confirmed that the catheter was continuing to record satisfactorily. The recorder battery voltage was checked at this stage using the selection from the same menu and if this was adequate a new recording was started.

A two-megabyte RAM card was inserted in the slot in the base of the recording box and "start recorder" selected from the record menu. This cleared the memory card for a new recording and gave the time on the liquid crystal display at which the new recording was being started. At this point, this recording was being recorded on the memory card and on the hard disc of the computer.

At any time during recording the actual trace could be viewed on screen using the "start new real time" record option in the record display and early in the trace this was done on a number of occasions to check that zero calibrations were adequate.

2.5.2.3 Troubleshooting

When this was not the case i.e. injection of 0.4mls of air into the catheter port resulted in the trace recording a figure beyond the limits of plus or minus 32, an *in vivo* calibration was performed. To carry this out, under the "record" menu, the recorder was stopped, the balloon on the catheter inflated with 0.4 mls of air and kept inflated and the "enter terminal mode" selection made from the record menu. This took the programme back into DOS where at the C prompt the instruction PZERO in continuous upper case was entered and return pressed.

The programme then inserted a new zero into the catheter and at this stage the ambulatory PAP programme was re-entered. "Start new real time recording" was then selected from the record menu and zero rechecked viewing the screen trace. If this procedure had been successful, the zero calibration should now result in an adequate trace, which records close to the actual zero line when calibrated.

If the tracing was still not satisfactory, the above procedure was repeated (several times if necessary).

Zero calibrations were performed every half-hour at the beginning of a trace and ideally at this frequency throughout the recording, and hourly throughout the night. However, where this was difficult, a minimum of hourly zero calibrations were performed until midnight, after which, the next were done at 8 a.m. by either the nursing staff or the patient.

The liquid Crystal display on the recording box indicated the time and the percentage of memory which had been used. If the patient was tachycardic, sufficient memory may not have been available to record a full 24 hour trace in which case the recorder was stopped, the trace downloaded to the hard disc of the computer and the trace re-started for the remaining required recording.

2.5.2.4 Postural Manoeuvres and Exercise Testing

Study subjects were put through a series of postures which were done in the same order of lying awake, sitting legs down, standing and the "event" button on the recording box was pressed at the beginning and end of these manoeuvres and the patient diary marked accordingly. Where possible, particularly in the lying awake position, patients did not speak or make any unnecessary movements and were in the

same position i.e. in terms of number of pillows etc., as they would be at night when asleep. The nursing staff in the ward were asked to note times at which the patient was definitely asleep.

Exercise testing was carried out at between two and three p.m. on the second study day. At the beginning and end of each segment of exercise, the trace was annotated using the event button and frequent calibrations were performed at these points.

2.5.2.5 Completing a Trace

At the end of a 24-hour ambulatory recording, from the record menu the "stop recorder" option was selected. The two-megabyte RAM card was then removed from the recording box and inserted in a card reader device, which was connected to the computer via the printer port.

On the "record" menu the "read data from PC card slot" was then selected and the patient file was then transferred from the RAM card to the hard disc of the PC. This was then saved to the hard drive and patient details entered as appropriate. Under "comments", the catheter used for this catheterisation was always recorded as subsequent problems which might have occurred during recordings, and which were specific to individual catheters, could be identified.

To check that satisfactory data transfer had been achieved the "review menu" was opened, "list load recordings" selected, followed by, "load from disc C" when the trace should have appeared as the most recent recording. If the data had not transferred satisfactorily then the data remained on the RAM card and could be loaded again to the hard disc.

2.5.2.6 Analysing a Trace

The original pressure trace was viewed on screen by selecting the "review" option. "Review" menu - "list load recordings", "list load from Disc C" commands are sequenced, and the patient trace was selected and loaded. Changing the time scale could then open out the pressure trace. Traces could be viewed in segments of just over one second to just over 33 hours. Figures 2.9, 2.10 and 2.11 show traces of approximately one minute, 2 hours and 21 hours respectively. The trace was then corrected for any zero drift.

Using the "Select page" option at the foot of the screen, the cursor was dragged to the beginning of the trace where the time should have corresponded with that noted as the start time in the patient diary.

At this point the trace was opened out to 1.03 minutes per page and using the page scrolling facilities the first of the *in vivo* calibrations was brought onto the screen. The cursor was then placed on the middle of the zero calibration and the value to the right of the screen read the actual measurement which was made at that time (Fig 2.12). At this stage, if there was any error inherent in the catheter's calibration revealed against the true pressure applied in the pressure chamber with the sphygmomanometer, then this should now be corrected for.

The CTRL F9 keys were pressed simultaneously and a window appeared on screen, showing "Channel normalising procedure". "Enter value at cursor" appeared and zero was entered. Return is then pressed and the menu requested the "Enter the output observed output observed for a thousand unit step".

The error noted against the measured pressure of 50 was then calculated for a unit step of 1000 (e.g. a reading of 40 mm against a measured pressure of 50 would have required 800 to be entered). Return was then pressed and the "continue" option on the

Figure 2.9 **1 Minute PAP Trace**

The micromanometer PAP trace displays one minute of pressure recording

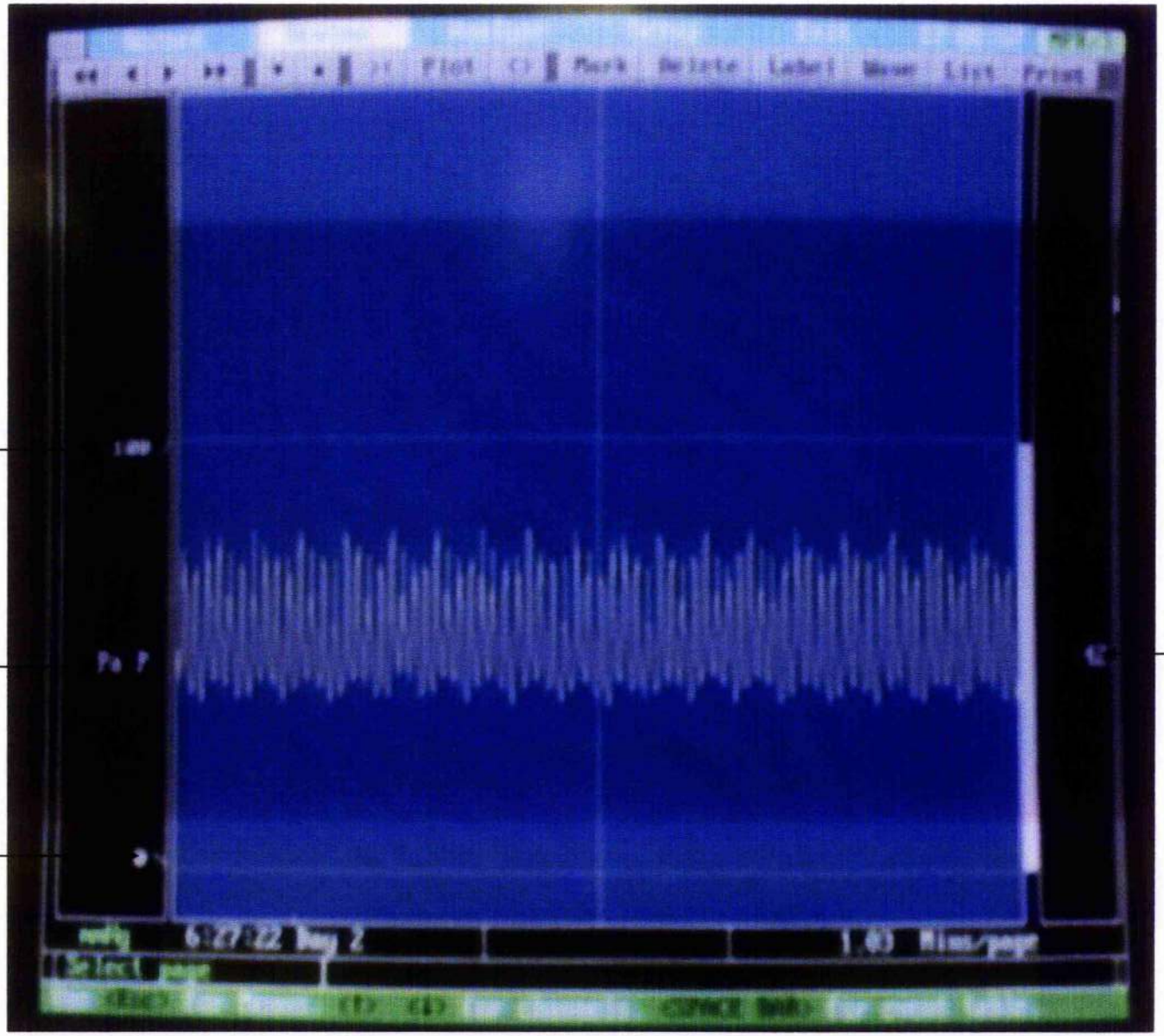


Figure 2.10 **2 Hour PAP Trace**

The micromanometer PAP trace has been opened out to display 2 hours of pressure recording

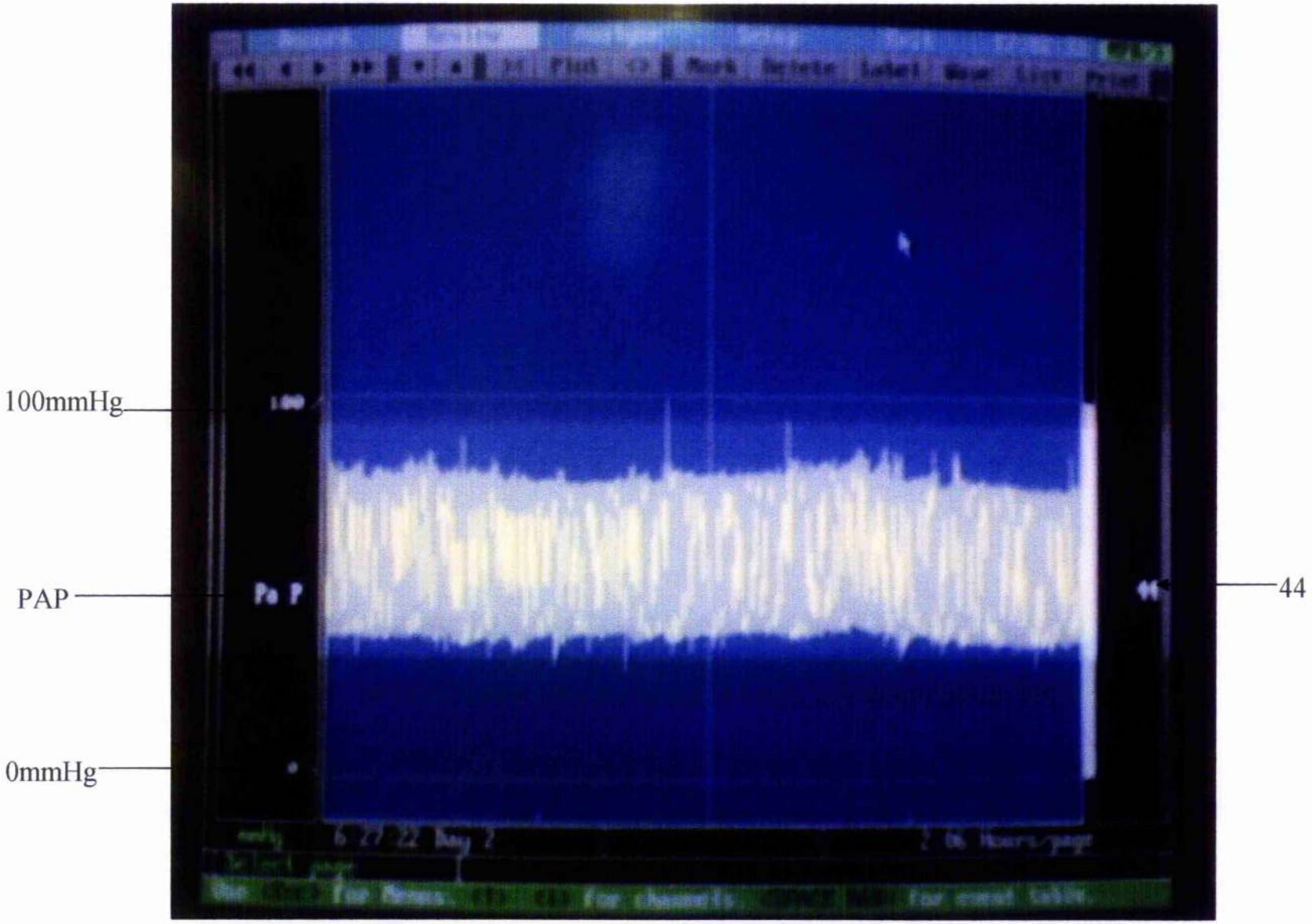


Figure 2.11 **21 Hour PAP Trace**

A micromanometer tipped catheter tracing of PAP in a patient with pulmonary hypertension. This trace constitutes an entire recording.

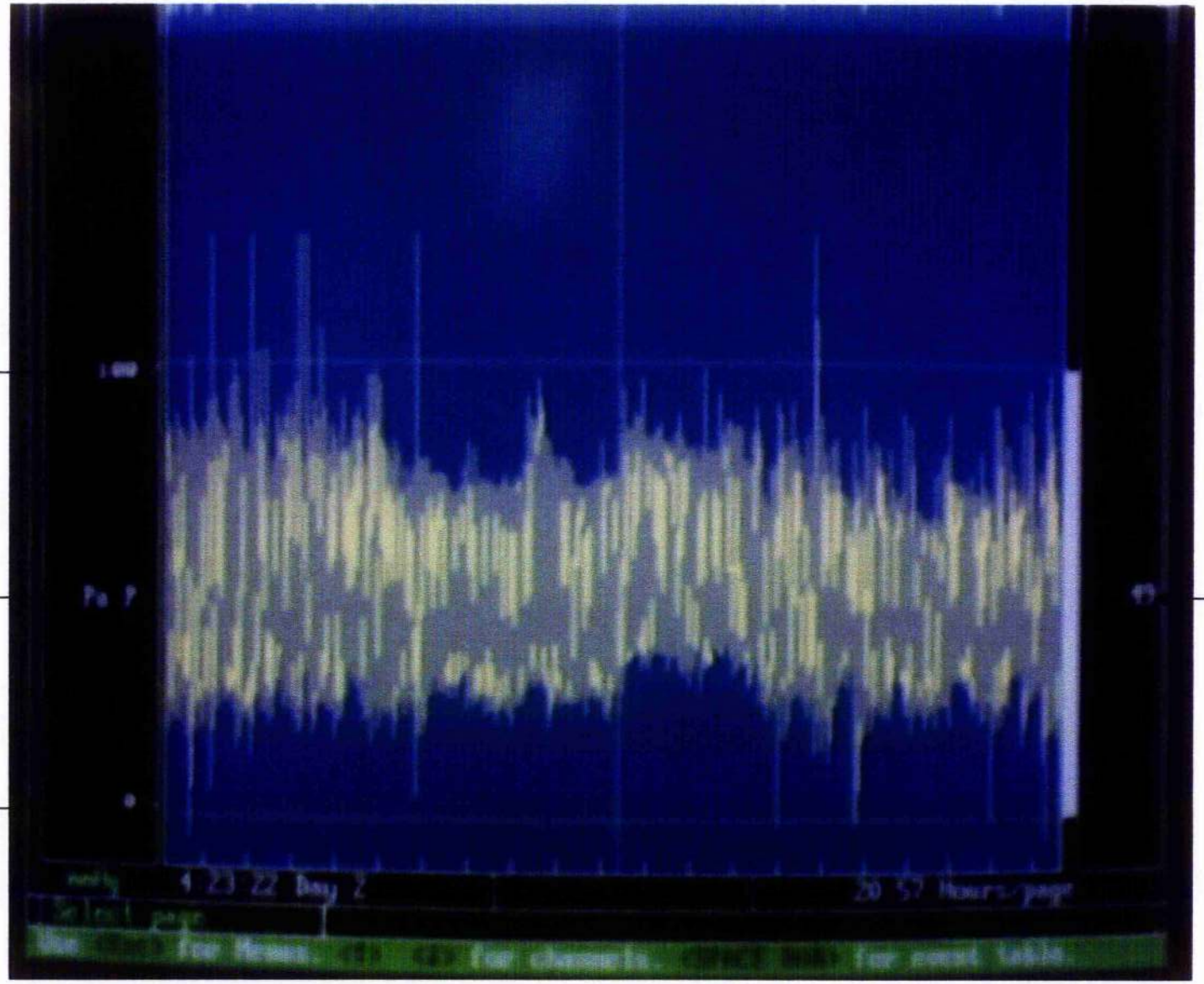
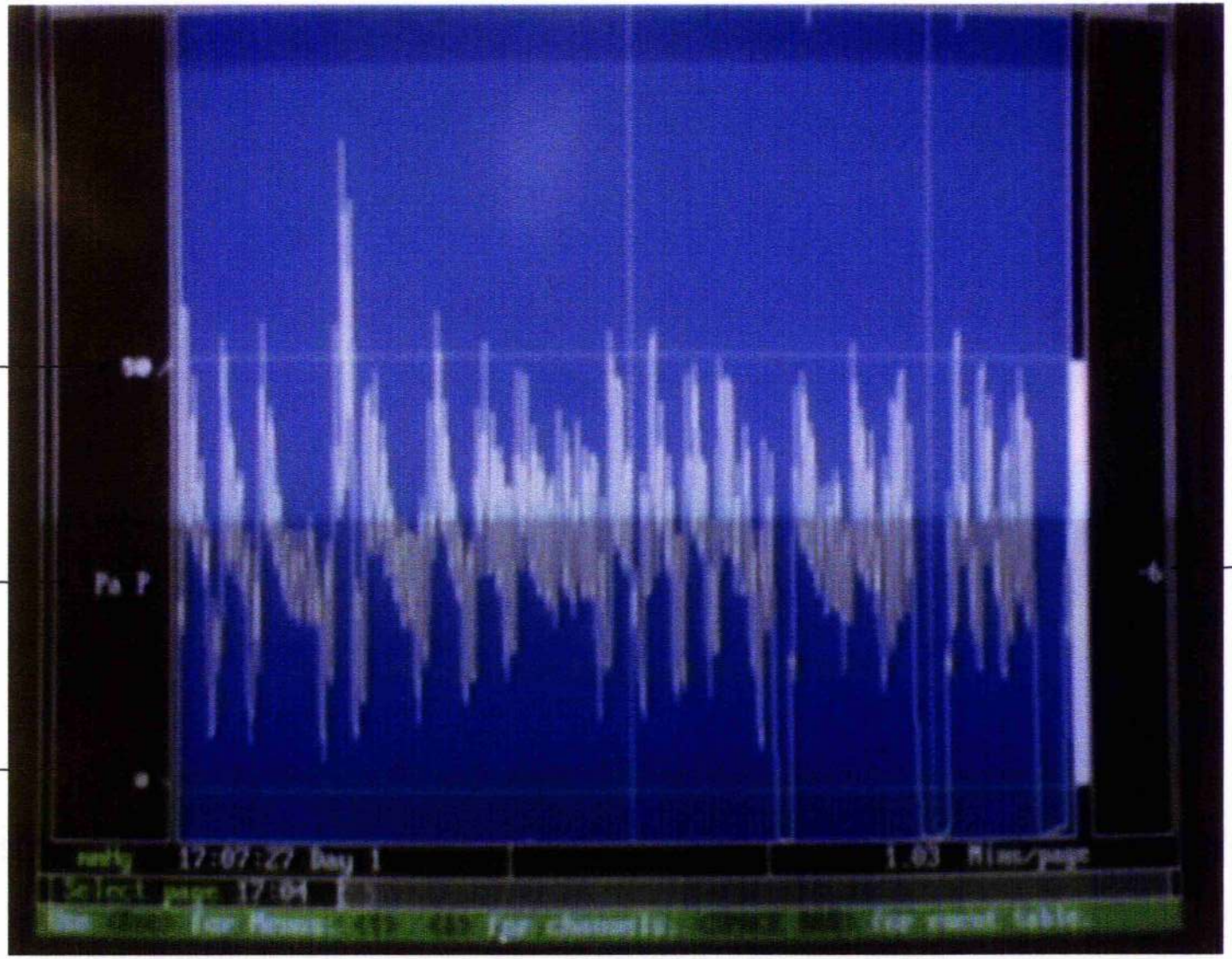


Figure 2.12

PAP Trace; *In-vivo* Calibrations

A micromanometer PAP trace showing three *in-vivo* calibrations at the beginning of the recording period. Zero-drift has occurred with a pressure reading of –6mmHg. The patient has COPD. Mild pulmonary hypertension and respiratory variation can be seen



bottom line selected and the channel was "normalised", i.e. corrected for the calculated error. The trace was then re-checked at the first and last zero points which should have been on the baseline. If this was not the case, then in addition to the correction having been inserted, the trace also required to be levelled. The cursor was once again placed on the first zero calibration, and the F9 key pressed. The box on screen indicated that the channel levelling procedure was being used and that the cursor indicated the first point to be included. Return was then pressed and the cursor moved to the next zero point, F9 pressed again and so on until the end of the trace. Once the last zero had been selected using F9, Shift F9 was pressed and the entire trace levelled. At this stage the trace had been corrected and levelled and was ready for analysis (Fig 12.13).

2.5.2.7 Data Analysis

The "analyse" option was selected and from the review menu and "make beat by beat" file selected. The programme then analysed the entire trace beat by beat removing any artefacts. At the end of this procedure a "beat file" had been created and this was stored on the hard drive (Fig 2.14). Once the beat-by-beat file had been created the next option "Start new average file" was selected and the procedure repeated. In this case the programme selected every 16 beats of information and created a new "average file" (Fig 2.15). This was again stored on the hard disc.

Further analysis was carried out using the "use average data file" option. Where more than one recording was made, the second was added to the first using the command in the review menu "Add to Average File".

Figure 2.13 **A Corrected Trace**

A micromanometer PAP trace opened out to one minute.
An *in-vivo* calibration is shown after normalising and levelling
The patient has moderate pulmonary hypertension

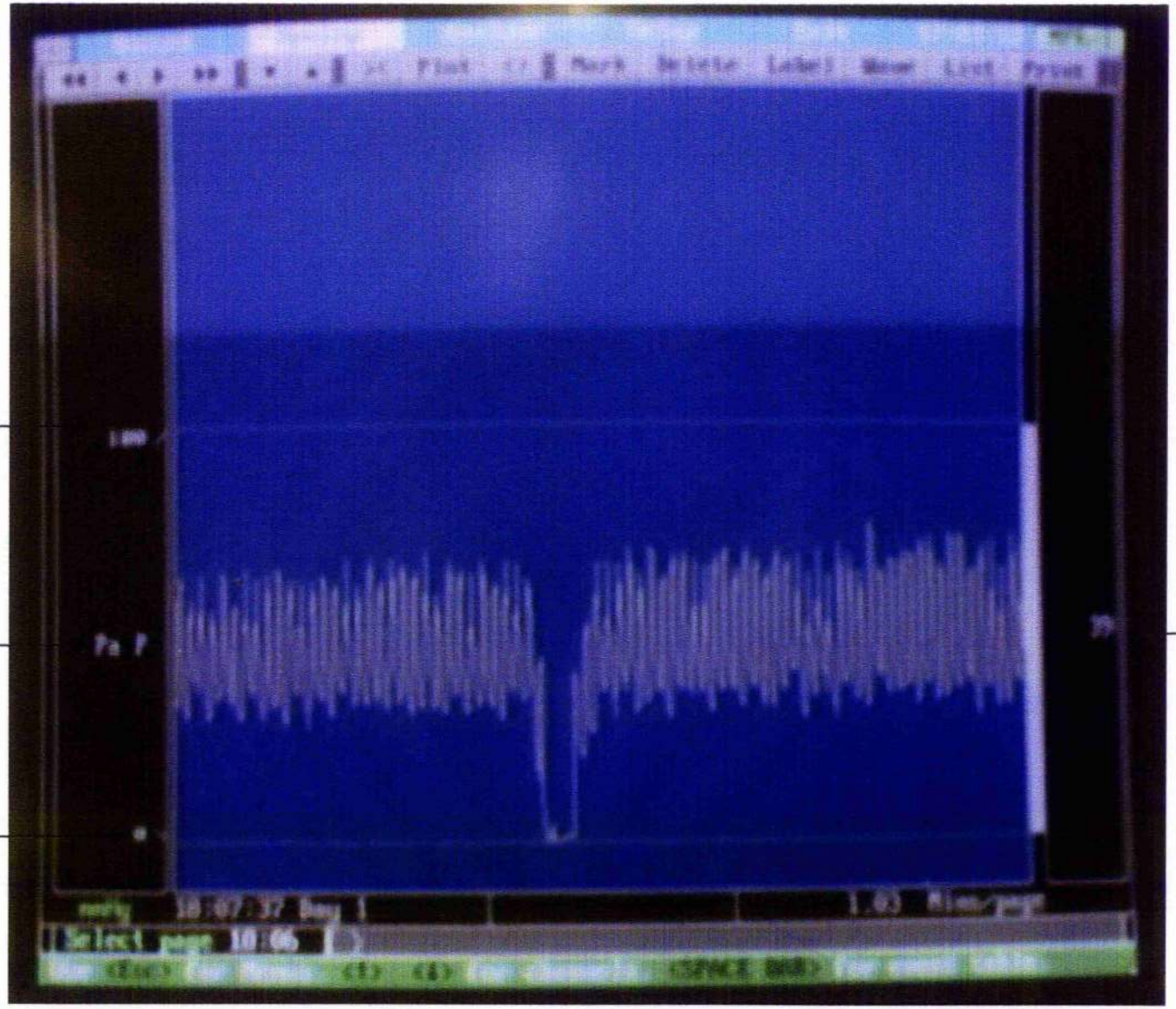


Figure 2.14 **A Beat by Beat Trace**

The micromanometer pressure trace has converted to a beat by beat file by the analysis programme. The patient has severe pulmonary hypertension such that the systolic PAP and heart rate traces are superimposed

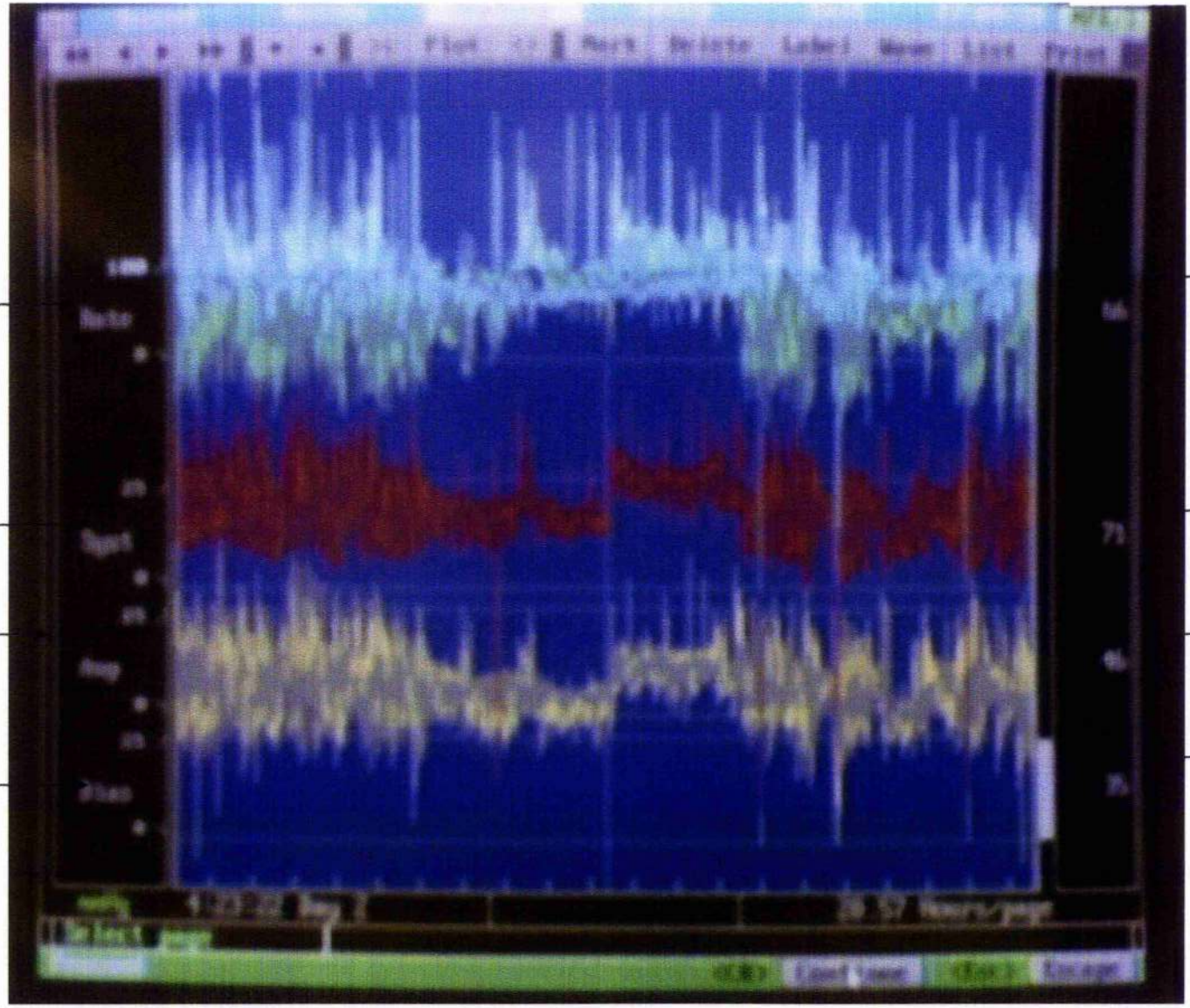
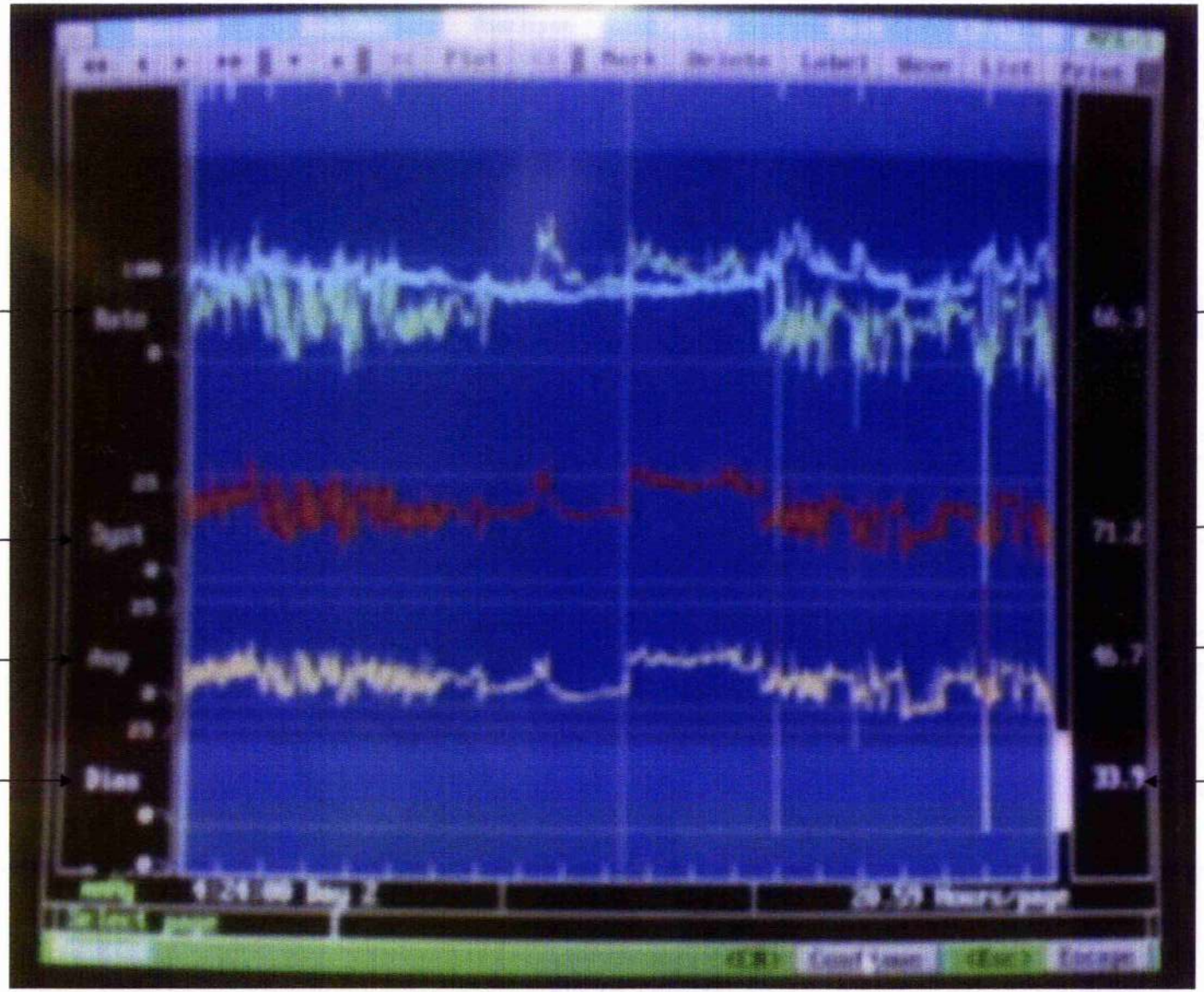


Figure 2.15 **An Average File**

The beat by beat file has been converted to an average file by the programme ready for further analysis



2.5.2.8 Creating an ASCII File

To create data files for further statistical analysis the "average data file" was converted to the ASCII format.

The "use average data" file was selected and this trace appeared on screen. The trace was opened out to 1 min. per page and using the "select page" option the cursor dragged to the beginning of the trace. Using the mouse the trace was then marked as close to the beginning as possible. Using the "select page" option the cursor was then dragged to the end of the file and the 2nd point marked at the end of the trace. Under the "analyse" option "Create ASCII file" appeared and this was selected. The programme then created an ASCII file for the entire average trace and this was stored to the hard drive. Figure 2.16 shows the selection of approximately 2 hours of a standard trace and the creation of an ASCII file from this segment.

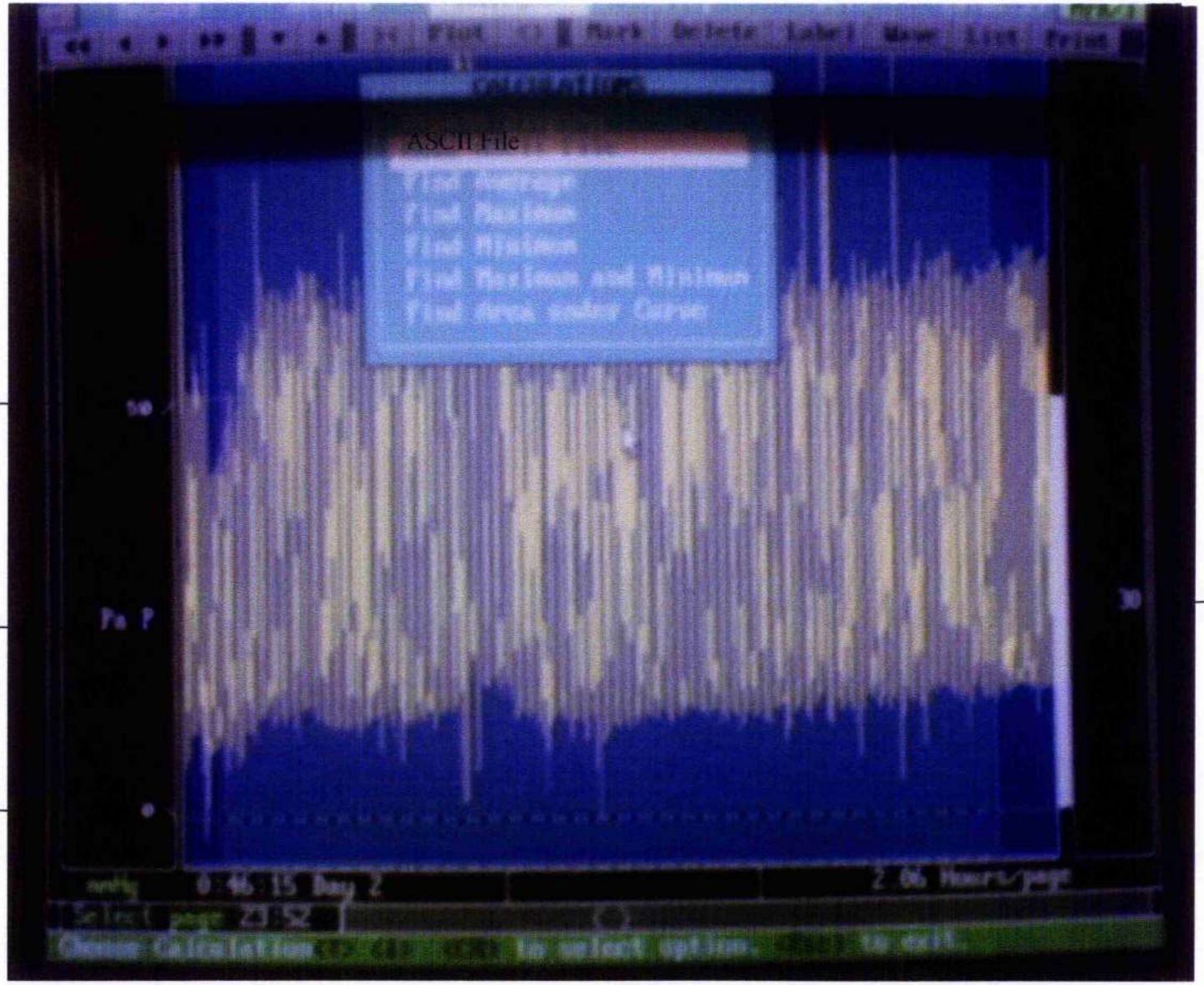
For statistical analysis the ASCII files were imported into an Excel file.

2.5.2.9 Creating an Excel ASCII File

The ambulatory PAP programme was exited and a Microsoft Excel file opened. Under the command "Open" the C drive prompt in DOS was highlighted and the PAP menu selected. A sub heading of the average file in PAP contained the ASCII files which were highlighted. At this stage the file which had just been stored was not in the form of an Excel file but a text tabbed delimited file and therefore under the "Select files" command was accessed via the "all files" option. The Microsoft wizard text import appeared and the commands followed. Once the file had been imported it was saved as a Microsoft Excel file and saved to disc.

Figure 2.16 **Creating an ASCII File**

A micromanometer PAP trace from a patient with mild pulmonary hypertension opened out to two hours. The programme is deriving an ASCII file from the shaded (selected) area



At this stage the raw data tracing was stored on the computer hard drive. The "beat by beat" file, "average file" and ASCII files were stored in the computer hard drive. The ASCII file was also stored as a Microsoft Excel file on the hard drive, and the original raw date trace was stored on floppy disc as a ZIP file as was the Excel ASCII.

2.5.2.10 Analysing ASCII Files

The data, which appeared in the ASCII file, was in four columns. The first was an indicator of time i.e. 0.664 of a day. The second column was the diastolic pulmonary artery pressure - the third column the mean pulmonary artery pressure - the 4th the systolic pulmonary artery pressure and the 5th indicates whether the event button had been pressed by marking one instead of zero.

Conversion to real time from the ASCII file was carried out as follows: the time was expressed as a total number of minutes, which was then divided by 1440 minutes (i.e. the number of minutes in a day). This gave the time as a decimal representation of a day. Therefore, e.g., 14.38 was expressed as 14 x 60 x 24 (+ 38) ÷ 1440. Thus the timings from the patient recording box could be selected very accurately on the ASCII trace. The ASCII traces were then analysed in total or in segments as required.

2.5.2.11 Common Problems Encountered With The Ambulatory Pulmonary Artery Pressure Measurement System

Few insurmountable problems were encountered using this system. A recording was lost due to transducer failure and another due to phase shift. On one occasion the catheter could not be negotiated through the right heart, probably because it was too stiff.

One catheter was found to have a ruptured transducer membrane prior to insertion and a second sterile catheter was always available for this eventuality.

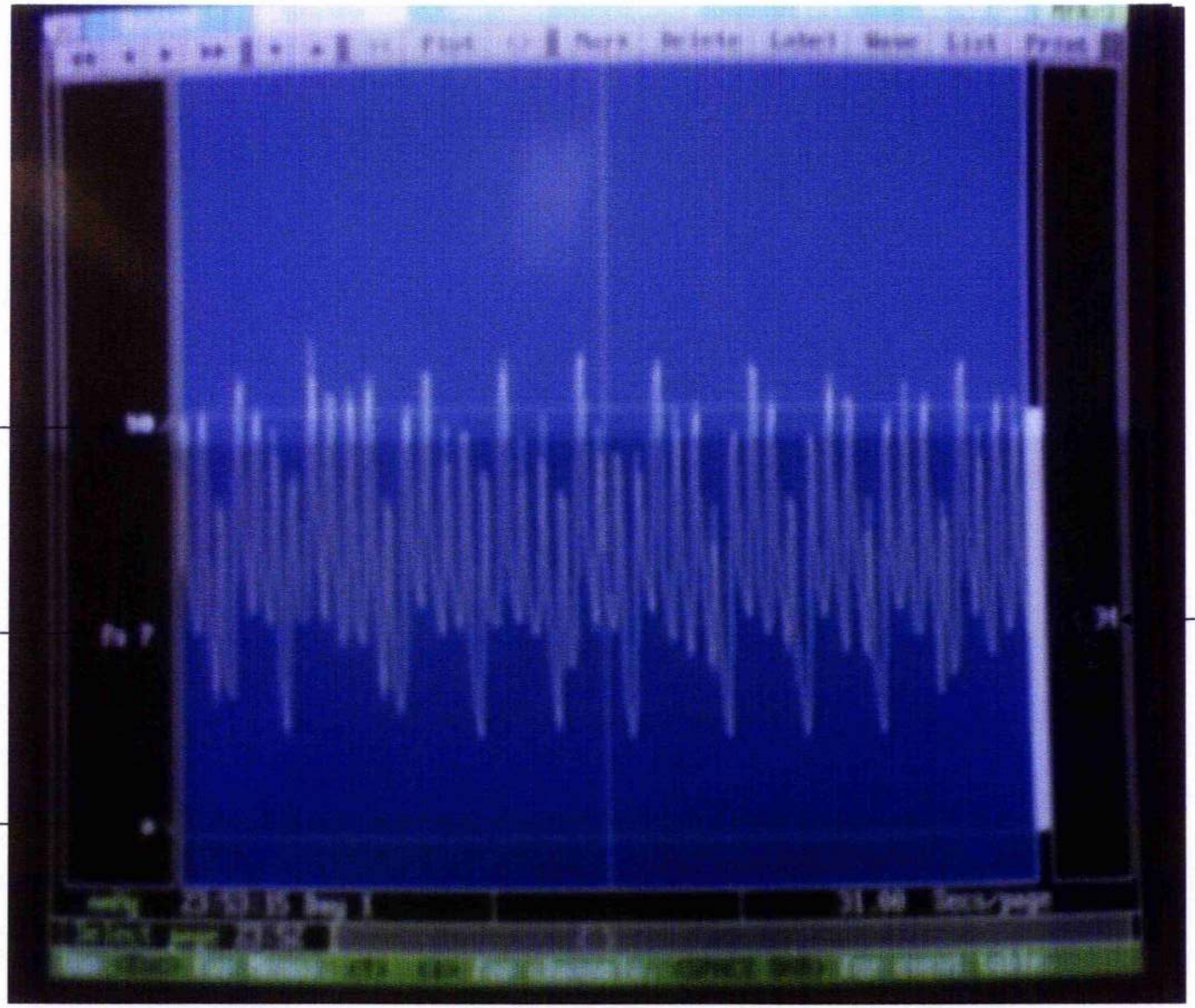
Otherwise most problems occurred during recording and were usually correctable *in-vivo* or (following completion of recording) by manipulation of the trace. Patients with COPD occasionally had pressure variation imposed on the waveform by the changes in intra-thoracic pressure with respiration caused by their lung disease (Fig 2.17). This did not interfere with the waveform analysis because of the facility to derive average traces.

Phase shift refers to delays in the output signal of the recording system relative to the input signal. Relatively small delays in output will lead to significant phase shifts and recording errors because of the relationship between phase and frequency. Thus certain frequency components of the system must not be delayed in order for the signal to be accurately represented. The Gaeltech catheter incorporates a method of measurement of the phase response and playback systems which ascertains that signal output delay is constant (Levy et al 1986). This permits high fidelity recording without significant phase shift. It is not anticipated that phase shift should be a significant problem with this recording system based on our experience.

Zero-drift (Chapter 1.5.3.1) occurs most commonly at the beginning of a trace. For this reason it is advisable to perform as many *in-vivo* calibrations as possible at the start of a period of recording, as these facilitate accurate correction of the trace at the immediate pre-analysis stage. While the majority of these calibrations are performed by the investigator while viewing the trace in real time on the computer screen, the subject also often did them. This could lead to a greater sense of involvement for some of the patients and (because of the sheer number of calibrations achieved by

Figure 2.17 **Respiratory Variation**

A micromanometer PAP trace from a patient with COPD and mild pulmonary hypertension. The trace demonstrates the changes in PAP caused by variations in intra-thoracic pressure with respiration



motivated individuals) made such traces easier to analyse. During periods of sleep the ward nursing staff could calibrate the trace without disturbing the patient.

Zero-drift was rarely significant and never sufficient to require the cessation of a record. Where the error exceeded the limit correctable by an in vivo calibration (>30mmHg) a correction could be applied by interrogating the catheter with the computer programme via the recorder. In DOS mode the command PZERO was entered followed by the required correction. This was then applied to the catheter and the trace could be reviewed on screen; if necessary this procedure could be repeated until a satisfactory trace was obtained.

The recording system had sufficient memory to complete 24 hours of recording without interruption. Where this was not possible (e.g. in patients with tachycardia) the recording box display indicated that the memory usage was approaching 100% and the recording had to be stopped. The data was then downloaded and then recording recommenced. This caused no inconvenience to the patient other than the need to increase the frequency of *in-vivo* calibrations at the start of the new recording. Exercise testing was carried out towards the end of the recording period and was relatively demanding of memory. Where any doubt existed about sufficient remaining capacity it was essential that a new recording be started to avoid data loss.

The correction of traces prior to analysis is described in Chapter 2.5.2.6. Using these procedures it was possible to achieve accurate analysis of all traces. Each catheter had an individual serial number, which was recorded with each 24 hour trace. This would have allowed the identification of any recurring faults with a particular device though no such problems were found in the work in this thesis.

In conclusion the ambulatory pulmonary artery pressure measurement system used in this thesis proved robust and reliable and did not lead to data loss. This was

particularly important when the technique required patients to be subjected to invasive procedures.

Chapter 3

Changes in Pulmonary Artery Pressure with Posture in a Group of Patients with Connective Tissue Disease

3.1 Introduction

In Chapter 1.5.4 it was shown that interest in ambulatory pulmonary artery pressure monitoring in cardiac disease developed because of a desire to relate symptoms and haemodynamic changes. Pulmonary hypertension can complicate many diseases of the heart or lungs but there has been debate about its role in the mortality and morbidity of patients with primary lung disease. We have little understanding of the epidemiology of pulmonary hypertension in these conditions because, unlike the systemic circulation, there is no easily applied sphygmomanometer for the pulmonary circulation. Consequently the development of pulmonary hypertension can be missed in the early stages and its progression can be difficult to monitor. The currently available methods of measurement in the pulmonary circulation have some disadvantages. Echocardiography may be non-invasive, accurate and repeatable, but gives only an estimate of systolic pressure at rest or on limited exercise and can be technically difficult in some patients, especially those with COPD. Cardiac catheterisation with fluid filled catheters has long been considered to be the gold standard but the position (lying supine on the catheter table) and the circumstances (at rest) during which the measurements are made may not reflect the situation in which an individual experiences symptoms.

In an attempt to overcome this difficulty, some authors have exercised patients while catheterised to reveal changes in pulmonary haemodynamics apparent only with increased cardiac output. However, even when measurements are made on exercise, the catheterisation procedure allows measurements to be made only over a short period of time and may not give information which represents accurately the pressures experienced during normal activities such as exercise and change in posture. Furthermore, cardiac catheters of the Swan Ganz type do not measure instantaneous

pressures, the signal obtained may be damped by the fluid filled lumen (Grossman 1980), and it is difficult to maintain the necessary fixed relationship between the position of the external transducer and the right atrium.

This thesis attempts to address some of these difficulties by using (for the first time in this group of patients) a micromanometer tipped pulmonary artery catheter which can continuously record PAP in various postures and during different activities without loss of accuracy, and can make recordings for 24 hours. This allows collection of data of possibly greater relevance to the circumstances in which patients are likely to experience symptoms such as on exercise.

This chapter addresses whether there are significant variations in PAP with changes in posture and exercise in patients with pulmonary hypertension. To examine this hypothesis, the variations in PAP over 24 hours were studied, both at rest and on exercise, in a group of patients with connective tissue disease.

3.2 Methods

3.2.1 Patient Group

All 6 patients described in this chapter had connective tissue disease, as defined by immunopathological patterns, with antibody profiles suggestive of the categories stated in Table 3.1. 5 had progressive systemic sclerosis (3 with CREST variant - calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangectasia-), and one had systemic lupus erythematosis. There were 2 men and 4 women of mean age 58 years (range 31-68). This study did not include a control group as the invasive nature of the investigation would have made this ethically difficult.

Written informed consent was obtained for all patients. The study was approved by the West Glasgow Hospitals University NHS Trust Ethics Committee.

3.2.2 Measurements

All patients underwent pre-catheterisation investigations as described in Chapter 2.1.2. These included a chest radiograph, electrocardiogram, pulmonary function tests, echocardiography, and a CT scan of the thorax to exclude other causes of secondary pulmonary hypertension. Parenchymal lung disease was excluded using high resolution CT scanning. Pulmonary artery systolic pressure was estimated from Doppler measurements. A symptom limited exercise test was also performed.

3.2.3 Cardiac Catheterisation

Conventional cardiac catheterisation described in this chapter was carried out as described in Chapter 2.4. Pressure measurements for comparison with the other

Table 3.1

Patient no.	*Age*	*Sex*	*Diagnosis*	*FEV_1 (% predicted)*	*K_{CO} (% predicted)*	*Vo_{2max} (% predicted)*
1	59	F	PSS	102.0	79.7	17
2	66	F	PSS	101.6	45.1	45
3	31	F	SLE	78.1	80.6	58
4	68	M	PSS	94.4	53.9	45
5	64	F	PSS	69.6	11.8	37
6	62	M	PSS	75.6	42.7	N/A
Mean (±SD)				86.9 (±14.2)	57.8 (±17.7)	50.6 (±12.3)

Table 3.1 Patient Demographics

FEV_1- Forced expiratory volume in one second

KCO- Carbon monoxide gas transfer co-efficient

Vo_{2MAX}- Maximal oxygen uptake

PSS- Progressive systemic sclerosis

SLE- Systemic Lupus Erythematosis

systems were made in the proximal pulmonary artery. Pressure values were recorded while patients breath held at functional residual capacity (to eliminate the effects of respiration on PAP). A mean of 6 beats was recorded and systolic and diastolic pressures were averaged.

3.2.4 Ambulatory PAP Monitoring

Ambulatory pulmonary artery pressure monitoring was carried out using a 7 F catheter supplied by Gaeltech Ltd (Dunvegan, Isle of Skye, UK) as described in Chapter 2.5.

The micromanometer tipped pulmonary artery catheter was left *in situ* for 24 hours. During this period the patient carried out normal daily activities in addition to a number of pre-set postural manoeuvres performed according to instructions from the investigator. These consisted of periods of 10 minutes each of lying awake, sitting, and standing in that order, performed 2-4 hours after returning from the cardiac catheterisation laboratory. During the final hour of data recording, on the second day, a second exercise test was carried out with the catheter *in situ*.

3.2.5 Echocardiography

Echocardiography data were obtained as described in Chapter 2.2.1. The same operator made echo measurements in all cases 24 hours in advance of cardiac catheterisation, so the operator was ignorant of the "true" PAP. It was not possible logistically to make simultaneous measurements with echo Doppler and the micromanometer tipped pulmonary artery catheter.

3.2.6 Cardiopulmonary Exercise Testing

Exercise testing was performed as described in Chapter 2.2.2. An exercise test was carried out before cardiac catheterisation and repeated with the micromanometer tipped pulmonary artery catheter *in situ*. Initially patients performed a maximal exercise test on the cycle ergometer. During the repeat exercise test patients were exercised under steady state conditions at 30% of the maximum oxygen uptake (VO_2max) achieved in the initial test. This workload was chosen as likely to be manageable for sustained exercise in this patient group as constant work rate testing is preferable to maximal testing for the measurement of cardiovascular, ventilatory and gas exchange kinetics (Chapter 2.2.3). This workload was not used in subsequent studies because it was felt that reproducibility and repeatability, in addition to comparisons between patients, would be improved by steady state exercise at the same defined workload for each patient (i.e. 30 watts). The exercise data presented are the mean pressures recorded at the onset of the fourth minute of steady state exercise. Figure 3.1 shows an exercise trace recorded with the micromanometer tipped pulmonary artery catheter.

3.2.7 Data Recording, Handling and Analysis

Data were recorded and processed as described in Chapter 2.5.1.

3.2.8 Patient Diary

An important component of the recording system described in the present chapter is the patient diary. This consisted of a simple paper record of time and current activity plus a note of when calibrations were made and the event button pressed. This diary

was compared with the pulmonary artery pressure trace to relate patient activity or posture with haemodynamic changes.

3.2.9 Statistics

All results reported in this chapters are presented as mean (±SD) unless otherwise stated. Differences between grouped mean pulmonary artery pressures measured in different postures were examined by analysis of variance (ANOVA) calculations, a p value of 0.05 being regarded as statistically significant.

Figure 3.1

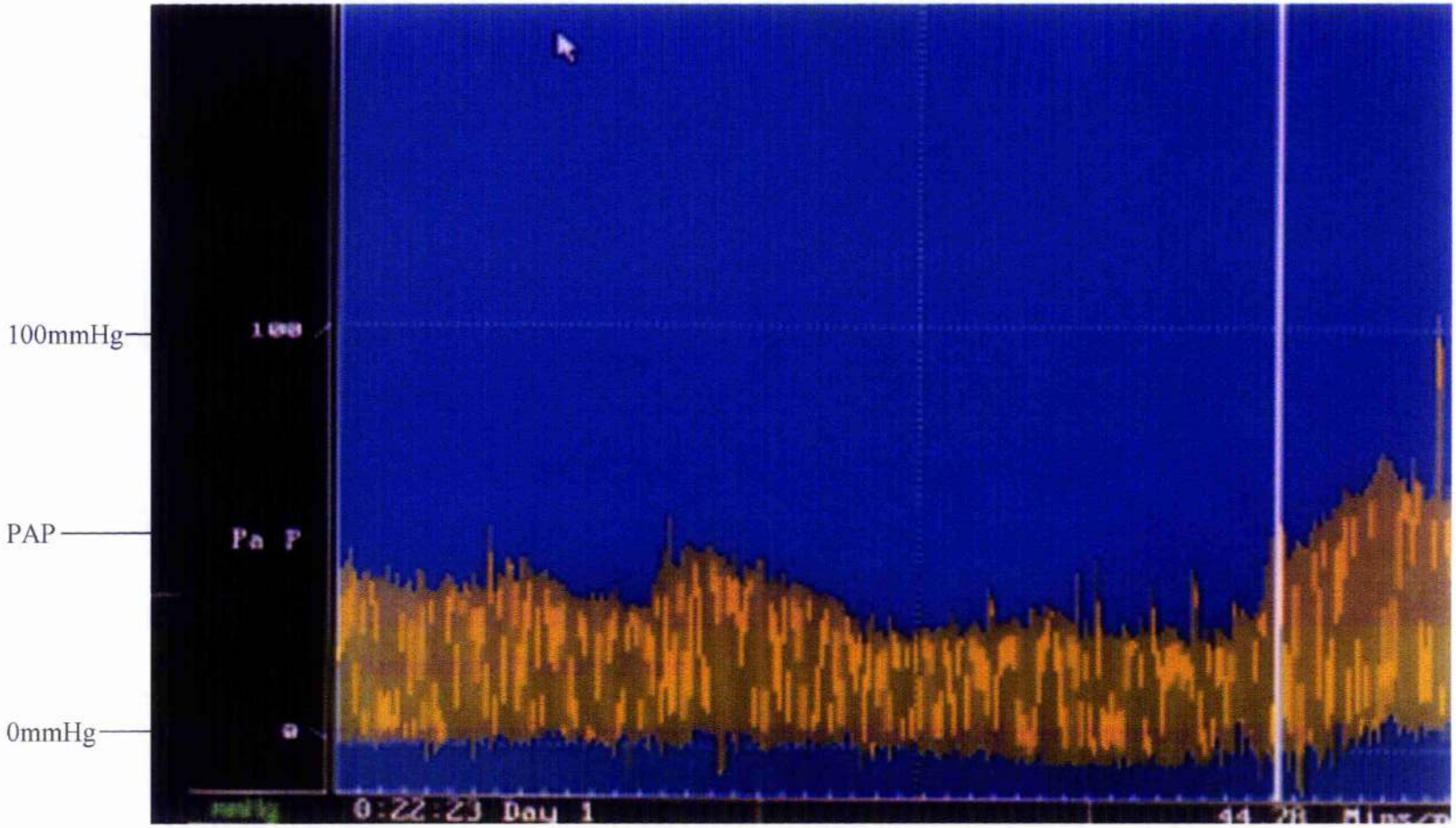


Figure 3.1 An Ambulatory Pressure Trace

This trace is from a patient with mild pulmonary hypertension and is recorded over 45 minutes. In the last 10 minutes of the recording the patient is undergoing an exercise test and there is a rise in PAP.

3.3 Results

3.3.1 Baseline Investigations

Baseline investigations are shown in Table 3.1. Pulmonary function tests revealed virtually normal spirometric values with a mean forced expiratory volume in 1 second (FEV_1) of 86.9% predicted but marked impairment in gas transfer, carbon monoxide transfer coefficient (KCO) 0.93 (0.4) mmol/min/kPa/l, 57.8% predicted (range 11.8-80.6). All of the 5 patients who were able to complete a cardiopulmonary exercise test demonstrated impaired exercise responses (mean VO_{2max} = 50.6% predicted, range 17-58).

3.3.2 Measurement of Resting PAP by Three Methods

A comparison of values obtained using three methods of measurement of PAP is shown in Table 3.2. Systolic PAP measured by echocardiography and micromanometer tipped pulmonary artery catheter is compared with systolic PAP obtained using the fluid filled catheter in Figure 3.2. There was no significant difference between the values obtained for systolic PAP using these three methods.

3.3.3 Heart Rates

Heart rates were obtained from the 24-hour recordings and are shown in Table 3.3. The expected increase with exercise and fall during sleeping was observed.

3.3.4 Ambulatory PAP Recording

Ambulatory PAP was measured over 24 hours in all subjects and the results are shown in Table 3.3 and Figure 3.3. Changes in PAP on exercise were not predicted by

Table 3.2

Patient no.	*Echo systolic PAP (mmHg)*	*Catheter laboratory systolic PAP (mmHg)*	*Ambulatory catheter systolic PAP (mmHg)*
1	40	34	37
2	70	65	59
3	68	90	101
4	88	90	117
5	100	85	98
6	70	90	99
Mean (±SD)	72.7 (20.4)	75.8 (22.6)	85.2 (30.4)

Table 3.2 Individual Values of Systolic PAP Measured by Three Techniques

Values shown are systolic PAP for each patient while lying awake measured by three techniques

- Doppler echocardiography (Echo)
- Cardiac catheterisation with fluid filled catheter (Catheter laboratory)
- Micromanometer tipped pulmonary artery catheter (Ambulatory catheter)

Figure 3.2

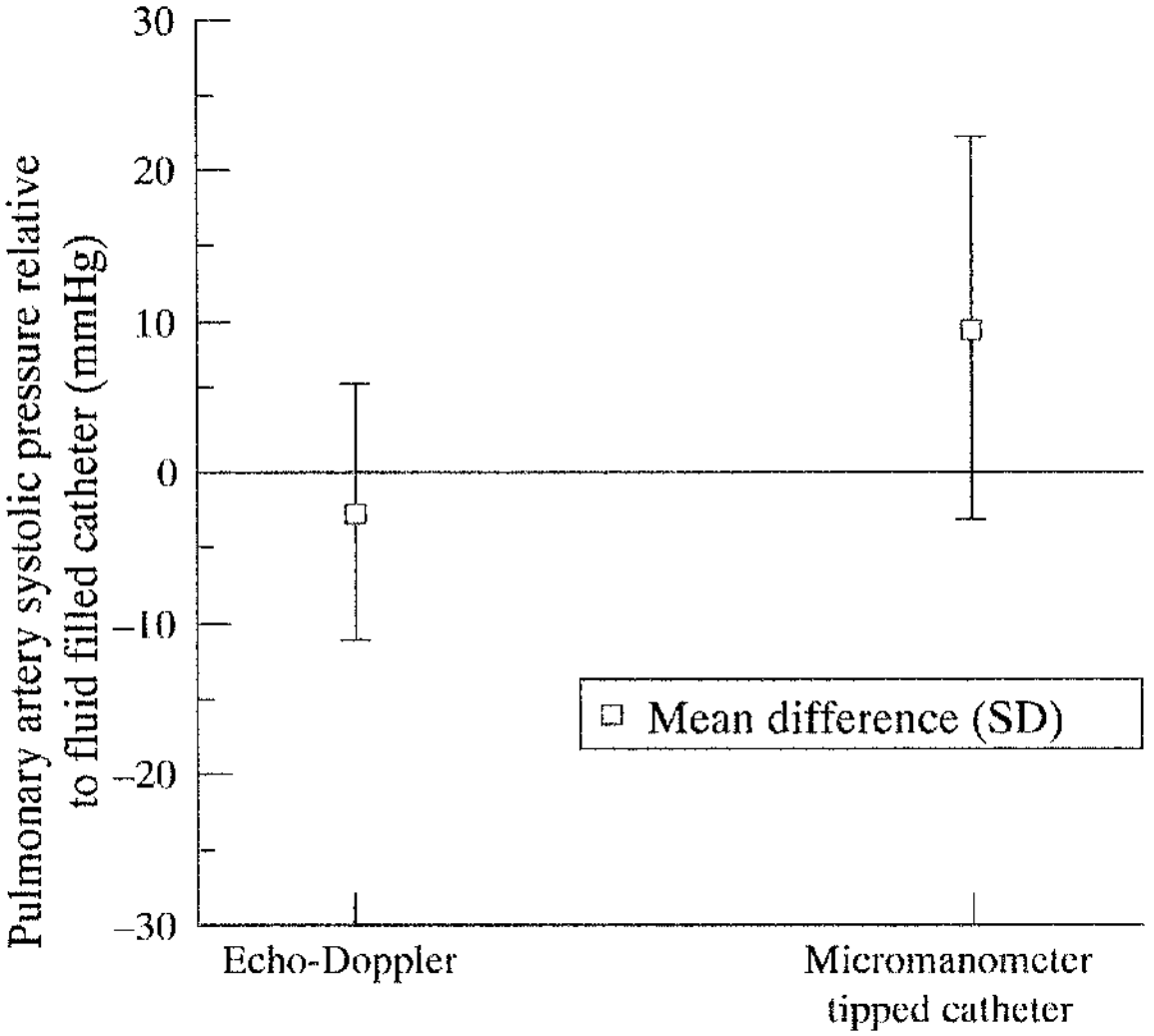


Figure 3.2 Comparison of Three Methods of Measurement

Differences in the values obtained for systolic PAP by Doppler echocardiography and micromanometer tipped pulmonary artery catheter from the values obtained by the fluid filled catheter. The differences between the three techniques are not significant.

Table 3.3

Patient no.	*24 hour average PAP*	*Lying asleep PAP*	*Lying awake PAP*	*Sitting PAP*	*Standing PAP*	*Exercise (bicycle) PAP*
1	21	20	26	19	17	28
2	32	29	36	27	28	41
3	49	56	68	59	57	69
4	69	66	75	68	64	76
5	65	64	68	65	67	73
6	55	45	68	48	68	85
PAP mean (±SE)	48.5* (±7.7)	46.7* (±7.7)	56.8 (±8.3)	47.7* (±8.3)	50.2* (±9.0)	62.0 (±9.1)
Heart rate mean (±SE)	86 (±5.8)	75 (±5.8)	92 (±3.7)	88 (±2.9)	100 (±9.0)	115** (±3.4)

Table 3.3 Mean Ambulatory PAP and Heart Rate

Mean ambulatory PAP and heart rate measured with the micro manometer tipped pulmonary artery catheter. PAP and heart rate are the means of 10 minutes measurement in each posture and during exercise.

The exercise values were obtained at the beginning of the 4th minute of a steady state exercise test at 30% measured Vo_{2max}.

*PAP significantly different from lying awake ($p<0.05$, ANOVA).

**Heart rate significantly different from lying awake ($p<0.05$, ANOVA).

Figure 3.3

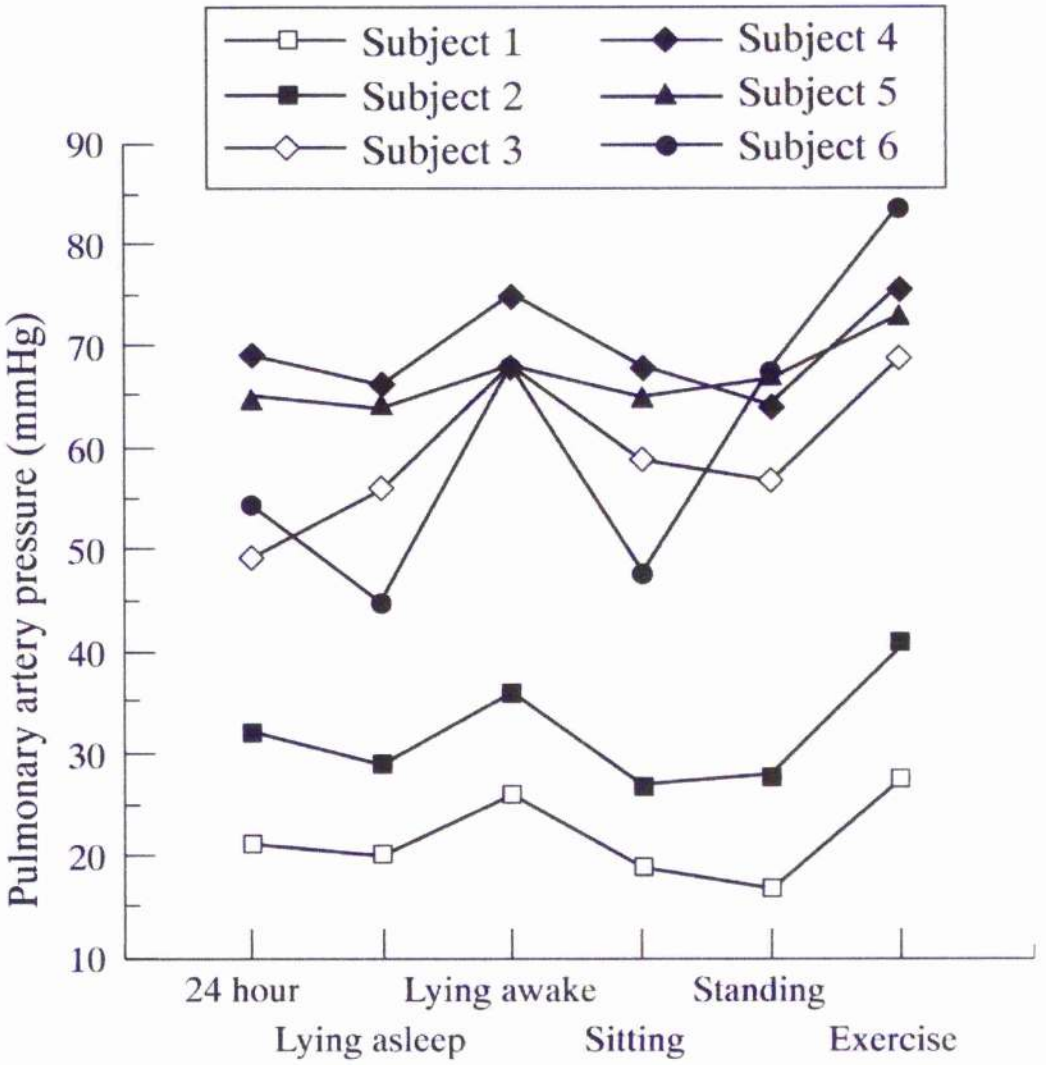


Figure 3.3 PAP by Posture for each Subject

The mean PAP recorded by the micromanometer tipped pulmonary artery catheter, for each subject, for a period of 24 hours. Pressures were recorded for each posture for a period of 10 minutes. The exercise values were obtained at the beginning of the 4th minute of steady state exercise.

resting values of PAP. A higher PAP occurred while lying awake than when sitting or standing. There were significant variations in mean PAP for the group between different postures compared with lying awake (Figure 3.4). Lying awake was chosen for this comparison because it is the position in which conventional measurements are made.

Figure 3.4

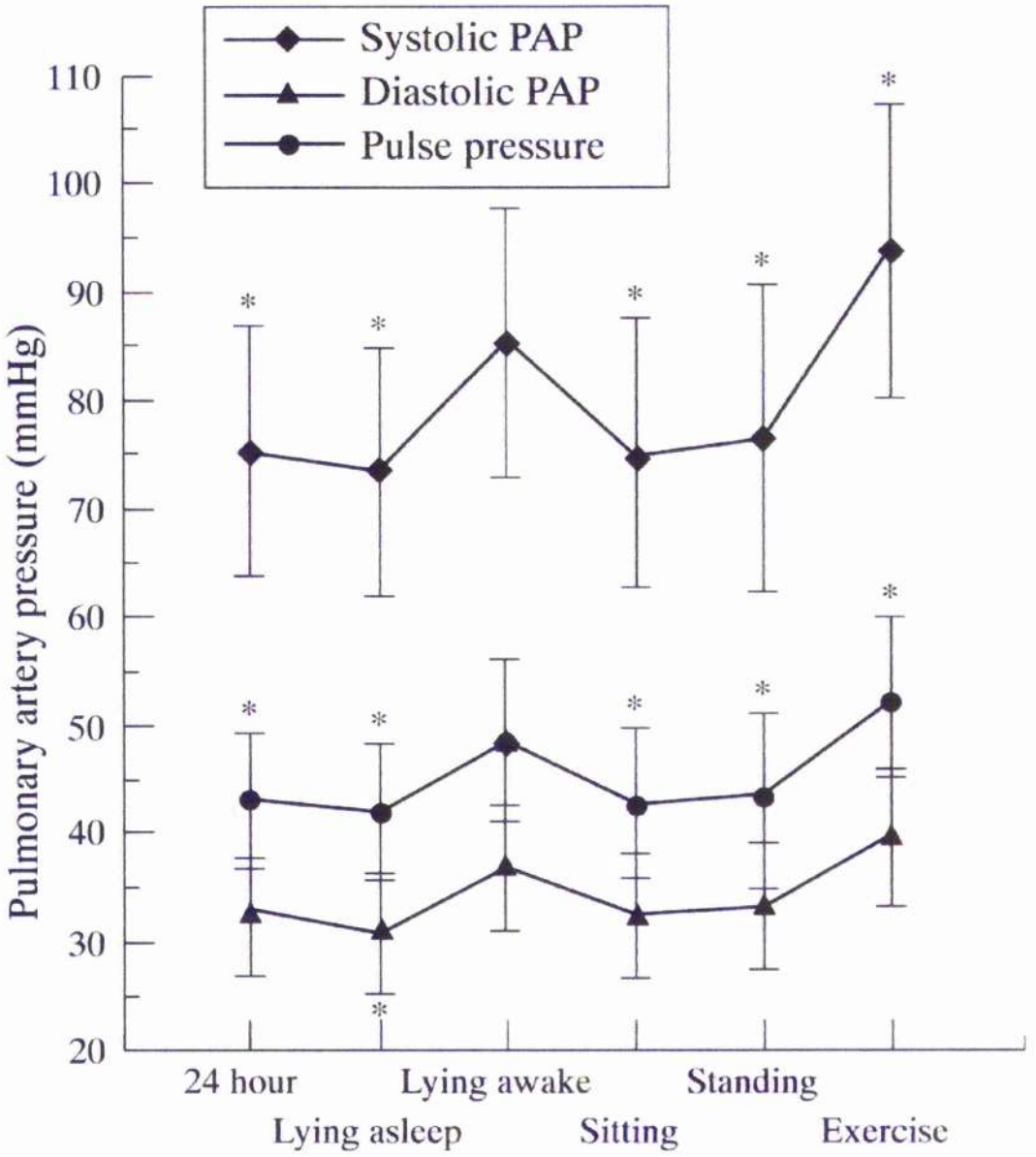


Figure 3.4 GroupMean PAP by Posture

Mean PAP recorded with the micromanometer tipped pulmonary artery catheter for the group of subjects averaged over 24 hours and for each posture over 10 minutes. The exercise values were obtained at the onset of the 4th minute of steady state exercise. The asterisks indicate that the values are significantly different from the measurement lying awake.

3.4 Discussion

This chapter has shown that ambulatory 24 hour PAP monitoring in patients with connective tissue disease is feasible in the clinical setting. The data indicate that PAP varied with different postures and activities and that mean PAP in these patients fell on sitting up or standing compared with lying awake. Only five patients were able to complete exercise tests; this small number makes it virtually impossible to draw meaningful statistical conclusions and the results must be interpreted with caution as the possibility of type II errors arises. However trends in the exercise results may be observed.

While it may not be surprising that a physiological variable such as pulmonary artery pressure changed over 24 hours, these variations have not been measured previously in such patients.

In mild pulmonary hypertension (such as in the group studied) PAP measured lying awake equalled exercise pulmonary artery pressure and exceeded the mean total pulmonary artery pressure over 24 hours. Within the limitations of the micromanometer tipped pulmonary artery catheter measurement system we were not able to explain this phenomenon. It was consistently observed in all subjects therefore seemed to be real.

"Lying awake" was chosen as the baseline measurement for comparison with the other postures because it is the position in which conventional pressure measurements are usually made. It was observed that the change in PAP seen on exercise was not predicted by the resting PAP (measured lying awake) in this group of patients with varying levels of pulmonary hypertension. The patient group in this chapter had reduced exercise tolerance compared with that predicted (Table 3.1). A number of explanations have been proposed for this.

Previous work in patients with connective tissue disease using Doppler echocardiography has shown reduced exercise capacity, thought to be due in part to a rise in pulmonary vascular resistance on exercise (Winslow *et al* 1993). Other authors have highlighted the importance of pulmonary artery haemodynamics during exercise and the consequent increase in right ventricular workload in patients with primary pulmonary hypertension (Laskey *et al* 1993). The data presented in this chapter suggest that, not only are there significant variations in pressure with exercise, even in patients with only mild resting pulmonary hypertension, but there are also pressure variations during normal daily activity. This may indicate that the stresses faced by the right ventricle over a 24 hour period may also vary considerably and that conventional methods of measurement of PAP may underestimate this variation. A number of issues arise from these observations:

(1) PAP while lying awake is higher than when measured sleeping in the same position.

(2) PAP falls on adopting a sitting or standing posture.

(3) PAP variation appears to be due to changes mainly in systolic, and hence pulse, pressure.

(4) PAP at rest does not predict the change in PAP on exercise.

3.4.1 PAP Lying Awake

The higher values of PAP when lying awake compared with lying asleep suggest that the former may not truly reflect the basal state. Values when lying awake were always measured after at least 10 minutes at rest and this position was the first of the series of postures in which measurements were made after return to the main ward from the cardiac catheterisation laboratory. During the lying awake manoeuvre patients were

observed continuously and were discouraged from moving or speaking. At night they were asked to lie flat with the identical number of pillows as had been in place when lying awake, and were checked hourly by the nursing staff (when performing *in vivo* calibration of the catheter) who noted whether the patients were asleep or not. Despite these precautions, in the absence of continuous EEG monitoring it is not possible to say that these patients were asleep throughout the night.

3.4.2 Change in PAP with Posture

Micromanometer tipped catheter values also show a fall in PAP on sitting or standing. Doppler echo values (obtained in the semi-recumbent position) were also lower than the fluid filled catheter baseline values, but the Doppler measurements were not repeated in the lying position. This observation has been reported previously by Brecker *et al* (1994) who found that, in patients with severe pulmonary hypertension, Doppler echocardiography consistently underestimated systolic PAP by 20% when compared with high fidelity pulmonary artery catheters. Though Doppler values were lower in the results presented in this chapter, they were not significantly so, possibly because this patient group had milder pulmonary hypertension.

These differences may be explained by the fact that these two techniques are measuring different things; however, the lower values measured with Doppler echocardiography may be due to decreased venous return on sitting or standing, with a subsequent fall in right ventricular filling pressure, cardiac output and hence PAP.

Systolic pressure measured lying awake with the micromanometer tipped pulmonary artery catheter compared with the fluid filled pulmonary artery catheter in the same position was not significantly different. The values with the solid catheter were slightly higher; while this may be due to differences in the way these systems actually

measured pressure these measurements were not simultaneous. In all cases the micromanometer tipped pulmonary artery catheter measurements were made towards the end of the cardiac catheterisation by which time the patient had undergone a number of measurements and manoeuvres (e.g. exercise) and it is possible that the pressure measurement was affected by this.

3.4.3 Change in PAP with Exercise

PAP at rest did not predict changes in PAP with exercise in this group of patients. This is unlike the situation in patients with moderate or severe pulmonary hypertension in whom such a relationship is described (Reeves 1984). This anomaly may be due to the fact that the exercise workload at which pressures were measured differed between the subjects presented here.

Patients with similar lung function often have markedly dissimilar exercise tolerance and it may be that these differences exist because of variation in the response of the pulmonary circulation to increased cardiac output.

If the pulmonary circulation cannot accommodate the increased cardiac output of exercise by vasodilating or by recruiting additional vessels then the right side of the circulation is unable to transmit the additional venous return to the left side. This effectively places a brake on the increase in cardiac output required to respond adequately to the exercise stimulus. This leads to a slowing in the rate of rise of VO_2 and (because heart rate continues to increase despite this) a failure of O_2 pulse to rise on exercise. Patients with pulmonary vascular disease have a high physiological dead space to tidal volume ratio (V_D/V_T) and a positive value for arterial – end-tidal PCO_2 difference ($P(a\text{-}_{ET})\ CO_2$) suggesting poor perfusion of ventilated air spaces. Other abnormalities present where the main abnormality lies in the pulmonary circulation

include shortening of the red cell transit time due to loss of the pulmonary capillary bed, and the development of metabolic acidosis on exercise rather than the respiratory acidosis which accompanies respiratory disease on exercise. For these reasons limitations in exercise tolerance in patients with pulmonary vascular disease cannot be reliably predicted from resting measurements (Wasserman *et al* 1999).

Resting pulmonary artery pressures in patients with mild pulmonary hypertension may not be predictive of exercise induced changes in PAP; if so then earlier diagnosis of the development of changes in the pulmonary vasculature may be possible using the micromanometer tipped catheter than is the case with conventional methods of measurement.

In the 1980s there was a move away from single "office" readings of systemic blood pressure to the development of simple non-invasive systems for the measurement of 24-hour ambulatory systemic blood pressure as described in Chapter 1.4. The technique described in this chapter is not likely to gain widespread acceptance in the investigation of the pulmonary circulation because of its cost and invasiveness. However as a research tool it does offer a similar advantage to ambulatory blood pressure monitoring in the systemic circulation in that it can provide data about pressure in relation to daily activity and symptoms. The mean PAP over 24 hours can be accurately calculated and some additional insight gained into the chronic haemodynamic load faced by the right ventricle. This may allow the earlier identification of individuals at greater risk of subsequent right ventricular failure and consequently those with a poorer prognosis.

The advantages of ambulatory PAP measurement may also be relevant in the assessment of response to treatment. At present there is no completely selective pulmonary vasodilator and there continues to be debate about the appropriateness of

treatment in secondary pulmonary hypertension. There is, however, considerable evidence to support the use of vasodilators in primary pulmonary hypertension (Rubin *et al* 1993). Objective assessment of responses to these treatments will be required and, in addition to the information which may be gained by conventional catheter laboratory measurements of the pulmonary circulation, the micromanometer tipped pulmonary artery catheter described in this chapter can add measurements of 24 hour variations in PAP and the changes seen on exercise, and so possibly present a fuller picture of the continuing stresses faced by the right ventricle as well as responses to treatment. Furthermore, it is likely that treatment may be more effective early in the development of pulmonary vascular changes when single resting measurements may be normal (Salvaterra *et al* 1992) and the PAP response to exercise may reveal that these changes are taking place.

This chapter demonstrates some of the strengths and weaknesses of this technique in the assessment of the pulmonary circulation in patients with connective tissue disease. Although ambulatory monitoring of PAP has been extensively used in patients with heart failure and coronary artery disease (Chapter 1.5.4) it had not been used previously in patients with pulmonary vascular disease secondary to connective tissue disease and larger numbers of patients are required to assess its future role. However, ambulatory pulmonary artery pressure monitoring may have additional advantages alongside conventional systems in the assessment of the pulmonary circulation.

Chapter 4

Ambulatory PAP Monitoring During Sleep and Exercise in Normal Individuals and Patients with COPD

4.1 Introduction

In Chapter 3 it was shown that ambulatory pulmonary artery pressure monitoring provides useful data which is not obtainable using conventional methods of assessment of the pulmonary circulation. Furthermore it was suggested that conventional cardiac catheterisation has limitations which restrict its usefulness in certain patient groups. This is particularly true of COPD when, furthermore, echocardiography can be technically difficult. Pulmonary hypertension is a common complication of COPD and when severe implies a poor prognosis (Weitzenblum *et al* 1981). The signs and symptoms of COPD can be overwhelming and accurate measurement of pulmonary hypertension requires a cardiac catheter. Hence it is often difficult to diagnose and quantify secondary pulmonary hypertension and its role in morbidity of COPD is poorly understood. PAP may rise during sleep or exercise in patients with COPD (Riley *et al* 1948 and Boysen *et al* 1979). When this rise on exercise is excessive the future development of resting pulmonary hypertension is likely (Weitzenblum *et al* 1996). It has been shown that other routine daily activities are associated with a reduction in oxygen saturation in patients with COPD but normal resting saturations (Soguel Schenkel *et al* 1996) but the haemodynamic significance of this is more difficult to quantify. Conventional measurement of PAP is difficult during sleep, exercise or in ambulant patients, because of the nature of conventional fluid filled pulmonary artery catheters and in particular their dependence on external transducers. Chapter 3 described the use of a micromanometer tipped pulmonary artery catheter and data recording system to make continuous pulmonary artery pressure recordings in patients with pulmonary hypertension secondary to connective tissue disease.

In this chapter the use of this system to provide accurate measurements of PAP during daily activity, sleep or exercise in patients with COPD is described, thus providing information about the total haemodynamic burden faced by these individuals.

4.2 Methods

4.2.1 Patient Group

10 subjects were studied (5 male, 5 female) with a mean (±SD) age of 61 (±8) and an age range of 43-69 years. 5 patients had COPD defined as irreversible airflow obstruction as determined by their lung function testing (Table 4.1) and were receiving long-term oxygen therapy (LTOT) and 5 were normal. The latter group was referred with suspected pulmonary hypertension, usually because of misleading screening investigations (such as overestimation of PAP by echocardiography in 4 cases) or because of a strong clinical suspicion of pulmonary hypertension despite normal non-invasive tests of PAP. All of these patients had had alternative cardiac or pulmonary causes for their symptoms excluded by the referring hospital. In this group, where repeat screening investigations were normal, ambulatory pulmonary artery pressure measurement was performed to exclude exercise induced pulmonary hypertension.

Normal subjects were defined as those in whom there was no evidence of COPD or of pulmonary hypertension, neither in the cardiac catheterisation laboratory nor after 24 hours of ambulatory pulmonary artery pressure monitoring. All patients in the normal group had normal lung function and oxygen saturation. No alternative end diagnosis was reached in any of these patients.

Written informed consent was obtained for all patients. The study was approved by the West Glasgow Hospitals University NHS Trust Ethics Committee.

4.2.2 Measurements

All patients were referred for further investigation of suspected pulmonary hypertension and all underwent pre-catheterisation investigations as described in Chapter 2.2. These

Table 4.1

	COPD	*Normals*
Age	62 (3.9)	60 (11.4)
PAP (Cath. Lab.)	44.4 (5.5)	16.2 (4.3)
PVR (Woods Units)	5.5 (1.8)	1.6 (0.6)
PAP (mmHg)		
Mean total	50 (5.0)	13.8 (6.0)
Rest	55.9 (10.2)	14.8 (3.8)
FEV_1 *(Litres)*	0.99 (0.31)	
FVC (Litres)	2.24 (0.90)	
SpO_2 % *(on air)*	79 (3.44)	

Table 4.1 Patient Demographics and Resting Haemodynamics.

Patients were breathing oxygen during the first period of sleep and air during the second period. Normals were breathing air throughout. Rest refers to sitting at rest. Normals had normal lung function. All values are means.

PVR- pulmonary vascular resistance (Wood's Units)

PAP-pulmonary artery pressure

SpO2-oxygen saturation

Cath. Lab.-mean PAP measured supine in the cardiac catheterisation laboratory.

(±SD)- values in parentheses are standard deviations

included a chest radiograph, electrocardiogram, echocardiography and pulmonary function tests. A steady state exercise test was performed.

4.2.3 Cardiac Catheterisation

Conventional cardiac catheterisation was carried out as described in Chapter 2.4. Pressure values were recorded while patients breath held at functional residual capacity (to eliminate the effects of respiration on PAP). A mean of 6 beats was recorded and systolic and diastolic pressures were averaged.

4.2.4 Ambulatory PAP Monitoring

Ambulatory pulmonary artery pressure monitoring was carried out as described in Chapter 2.5. The catheter was left *in situ* for 24 hours.

Both groups had pulmonary artery pressure continuously measured during sleep in two 4 hour periods, from midnight to 4 am and from 4 am till 8 am. The COPD group was given continuous oxygen at their usual flow rate for the first period and remained off oxygen for the second period. Ward nursing staff were asked to confirm that the patients were asleep at the stated times.

4.2.5 Echocardiography

Echocardiography was carried out as described in Chapter 2.2.1. Data was obtained between 24 and 36 hours prior to cardiac catheterisation. Where echo measurements did not confirm pulmonary hypertension, ambulatory pulmonary artery pressure monitoring

was carried out to confirm normal resting PAP and to exclude exercise induced pulmonary hypertension.

4.2.6 Exercise Testing

All patients were exercised breathing air as described in Chapter 2.2.2.

A steady state workload of 30 watts was chosen because this was believed to be manageable for the patients with COPD and likely to allow reproducible and repeatable exercise data to be obtained by standardizing exercise protocols at this achievable workload.

4.2.7 Data Recording, Handling and Analysis

Data was recorded and processed as described in Chapter 2.5.1. Mean PAP during sleep was measured for the middle 2 hours of each nocturnal period. Exercise PAP measurements are the average, mean pressure recorded over 1 minute from the onset of the 4^{th} minute of steady state exercise.

4.2.8 Statistics

All data are expressed as mean ± standard deviation (SD) with 95% confidence intervals (CI) for all significant differences, unless otherwise stated. Statistical testing was by paired t-test. A p value of < 0.05 was considered to be statistically significant.

4.3 Results

4.3.1 Baseline Investigations

Baseline investigations for the control group were normal and are not shown. Pulmonary function tests for the COPD group were abnormal. Table 4.1.

The mean FEV_1 was markedly reduced, 0.99L (±0.31) as was resting oxygen saturation ($Sp0_2$) breathing air, $Sp0_2$ 79% (±3.44). These results reflected severe airflow obstruction in a group of patients receiving LTOT. Mean oxygen saturation measured asleep breathing air was 79% for the COPD group (Table 4.1) and remained above 92% for the normal group. Mean oxygen saturation measured asleep breathing oxygen was 90% for the COPD group and remained above 92% for the normal group. These results were recorded by nursing staff.

4.3.2 Mean PAP Measured in the Catheter Laboratory

- Group mean PAP in mmHg was 44.4 (±5.5) for the COPD group and 16.2 (±4.3) for the normal group. Table 4.1.

4.3.3 Mean PAP over 24 hours

- Group mean PAP in mmHg for the 24 hour period of pressure recording was 50.0 (±5.0) for the COPD group and 13.8 (±6.0) for the normal group. Table 4.1

4.3.4 Mean PAP at Rest

- Group mean PAP in mmHg sitting at rest was 55.9 (±10.2) for the COPD group and 14.8 (±3.8) for the normal group. Table 4.2.

Table 4.2

COPD Group	*Mean PAP mmHg (±SD)*		
Asleep breathing air	59.8 (8.1)		*Mean difference PAP mmHg (±SD)*
Asleep breathing oxygen	50.8 (5.5)	*Asleep breathing oxygen v asleep breathing air*	9.6 (5.32) (95% CI 4.9-14.3) p= 0.016
Exercise	59.0 (10.7)	*Exercise v asleep breathing air*	0.8 (8.93) (95% CI –7-8.6) p= 0.851
Normal Group			
Asleep breathing air	14.6 (5.9)		*Mean difference PAP mmHg (±SD)*
Asleep breathing air	14.6 (7.0)	*Asleep period 1 v asleep period 2*	0.0 (2.4) (95% CI –2.1-2.1) p= 1.000
Exercise	17.0 (4.0)	*Exercise v asleep breathing air*	3.3 (2.2) (95% CI 1.1-5.5) p= 0.061

Table 4.2 PAP asleep, breathing air and oxygen and during exercise for the COPD and normal groups

Patients were breathing oxygen during the first period of sleep and air during the second period. Normals were breathing air throughout.

Exercise refers to steady state exercise on the cycle ergometer at 30 watts. PAP: pulmonary artery pressure.

4.3.5 Mean PAP During Sleep

- Group mean PAP in mmHg for the COPD group was 59.8 (±8.1) asleep off oxygen and 50.8 (±5.5) asleep breathing oxygen. Table 4.2.
- Group mean PAP in mmHg for the normal group was 14.6 (±5.9) for the first nocturnal period and 14.6 (±7.0) for the second nocturnal period. Table 4.2.

4.3.6 Mean PAP During Exercise

- Group mean PAP in mmHg for the COPD group during exercise was 59.0 (±10.7).
- Group mean PAP in mmHg for the normal group during exercise was 17.0 (±4.0).

4.3.7 Within Group Comparison - COPD Group

- PAP asleep on oxygen is significantly lower than PAP asleep breathing air: mean difference (±SD) = 9.6 mmHg (5.32) (95% CI 4.9-14.3) p= 0.016 (Table 4.2) (Fig 4.1).
- PAP asleep breathing air remained significantly greater than 24 hour mean PAP: difference 9.8 mmHg (95% CI 0.2-19.4) ($p<0.05$). Figure 4.1.
- PAP during exercise is not significantly different from PAP asleep breathing air: mean difference (±SD) = 0.8 mmHg (8.9) (95% CI –7.0-8.6) p= 0.851 (Table 4.2.) (Fig 4.1).

Figure 4.1

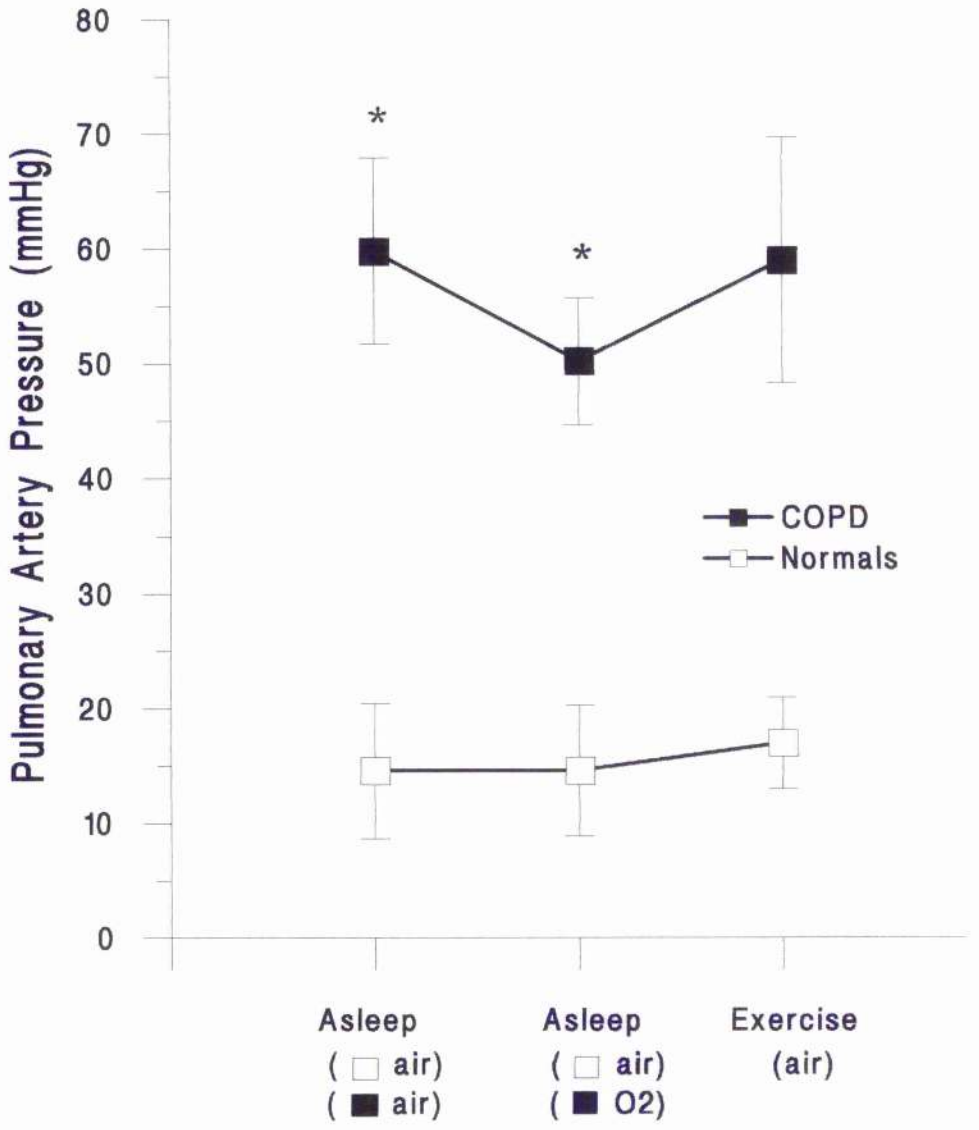


Figure 4.1 Mean PAP in Normals and Patients with COPD

Mean PAP for the COPD group and the normal group is shown during each activity. For the COPD group PAP was significantly lower breathing oxygen compared with air (* = $p < 0.05$)

4.3.8 Within Group Comparison – Normal Group

- PAP asleep breathing air for period 1 was not different from PAP asleep breathing air for period 2: mean difference 0.0 (2.4) (95% CI -2.1-2.1) p= 1.000. (Table 4.2) (Fig 4.1).
- PAP during exercise is not significantly different from PAP asleep breathing air: mean difference (±SD) = 3.3 mmHg (2.2) (95% CI 1.1-5.5) p= 0.061. (Table 4.2) (Fig 4.1).

4.3.9 Comparison between COPD and Normal groups

- Asleep on oxygen versus asleep on air for the COPD group compared with asleep on air for the normal group is significantly different: mean difference (±SD) = 7.6 mmHg (5.6) 95% CI 2.7-12.5) p= 0.039.
- Exercise versus asleep on air for both groups is significantly different: mean difference (±SD) = 5.0 mmHg (2.71) (95% CI 2.3-7.7) p= 0.034.

The PAP trace obtained from a patient with COPD during sleep is shown (Fig 4.2). This demonstrates the rise in PAP during sleep breathing air, which is abolished by breathing oxygen.

Figure 4.2

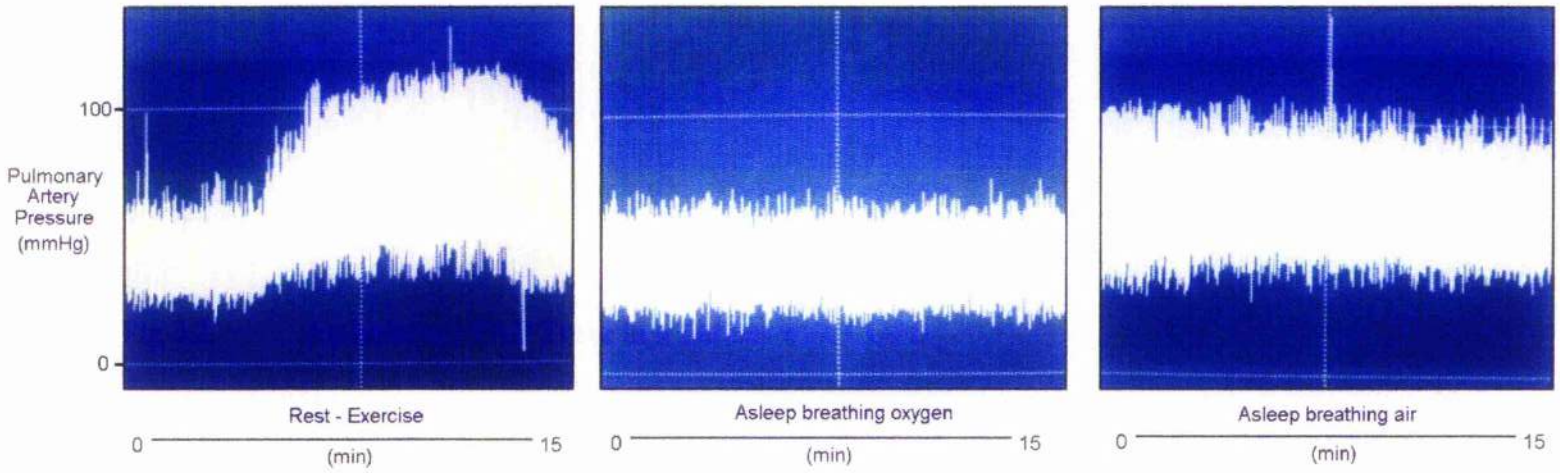


Fig 4.2 Ambulatory PAP Trace in a Patient with COPD

PAP tracings from a single patient with COPD during: rest followed by exercise (first panel); sleep breathing air (second panel); sleep breathing oxygen (third panel).

The rise in PAP during sleep is similar to that recorded during steady state exercise at 30 watts. Breathing oxygen abolishes this rise during sleep.

4.4 Discussion

This chapter has shown that patients with COPD receiving LTOT tolerate invasive haemodynamic assessment, including ambulatory pulmonary artery pressure monitoring and can safely perform cardiopulmonary exercise testing at a low workload. The number of patients discussed is small due to the difficulties encountered in recruiting frail patients in respiratory failure for invasive haemodynamic monitoring but nevertheless significant changes in haemodynamics were observed.

Previous studies of PAP in COPD have demonstrated that values are modestly elevated and progression slow (Weitzenblum *et al* 1979). However most of these measurements have been of resting pressure which has been shown to be of relatively poor prognostic value (Report of the Medical Research Council Working Party 1981). Furthermore it has also been shown that even routine daily activities in patients with mild COPD and normal resting oxygen saturations are associated with reductions in oxygen saturation (Soguel Schenkel *et al* 1996).

This chapter reports the measurement of PAP in a variety of situations in patients with respiratory failure receiving long-term oxygen therapy and the higher levels of PAP observed are therefore not surprising. These results demonstrate that patients with COPD receiving long-term oxygen therapy have levels of PAP, which are significantly higher than those of a control group when measured over 24 hours. These patients also have significantly higher PAP when the periods of sleep or exercise are excluded i.e. when performing normal daily activity breathing supplementary oxygen. Specific activities of daily living were not defined prior to these studies therefore this data is not presented. When studied during sleep without oxygen, the COPD group has a further rise in PAP,

which is greater than that measured on exercise and which is abolished by breathing oxygen during sleep. Others have previously reported increased pulmonary vascular resistance during REM sleep and the beneficial effects of oxygen in patients with moderate pulmonary hypertension and severe COPD (Fletcher and Levin 1984). However the extent of these rises compared to those seen during other activity has not been studied.

The normal group did not show any change in PAP during sleep (which is not surprising) nor did they demonstrate a significant rise during exercise as others have predicted (Riley *et al* 1948). This is probably because the workload chosen for the exercise test (30 watts) was too low to sufficiently stress the pulmonary circulation of normal individuals. Furthermore there was no variation in this group's PAP during normal daily activity.

There is no increase in pulmonary artery pressure on exercise compared with asleep breathing air in either within group comparison (section 4.3.7 and section 4.3.8 and table 4.2). In the COPD group this may have been due to restricted exercise capacity limiting the rise in pulmonary artery pressure combined with higher than expected pulmonary artery pressure asleep breathing air: in the normal group there was trivial rise in pulmonary artery pressure on exercise which was not significantly different from the pulmonary artery pressure measured during sleep.

The number of patients with COPD in this chapter is small and therefore it is difficult to reach firm conclusions. However, for these individuals, the rise in PAP seen during sleep may be an important contribution to the overall work facing the right heart and constitutes at least as great a haemodynamic burden as low level exercise.

This chapter has shown considerable variations in PAP during 24-hour ambulatory monitoring with normal daily activity, on exercise and during sleep and this may have implications for the way COPD is assessed. Measurement of PAP is difficult in ambulant patients because of the restrictions inherent in conventional cardiac catheterisation and may be unrepresentative because of the circumstances in which these are made i.e. at rest in the laboratory. Furthermore non-invasive measurement with echocardiography in COPD patients is often limited by the poor signal obtained.

The technique of ambulatory pulmonary artery pressure monitoring described in this chapter allows the time course and extent of rises in PAP to be measured and correlated with symptoms in patients with severe COPD carrying out normal daily activities.

Such knowledge of the pulmonary circulation under stress or during sleep in patients with COPD may be useful in assessing the contribution of pulmonary hypertension to overall morbidity and mortality. Transient rises in PAP have been observed and quantified during sleep and exercise during ambulatory monitoring in the hospital environment in patients treated with LTOT. It is possible that similar elevations in PAP may also be important in patients with milder COPD, which might have implications for future interventions.

Chapter 5

PAP Measurement During Exercise in Patients with Suspected Pulmonary Hypertension

5.1 Introduction

Chapter 4 has shown the usefulness of ambulatory pulmonary artery pressure monitoring to the study of sick patients with COPD and allowed measurement of PAP during sleep and exercise. In both cases this data about PAP would not have been easy to obtain using conventional methods of assessment.

Conventional methods of measurement in the pulmonary circulation may be invasive or non-invasive. Cardiac catheterisation with fluid filled, pulmonary artery catheters remains the gold standard method of haemodynamic measurement and is usually performed in supine patients at rest.

In the past secondary pulmonary hypertension has not been regarded as an important target for therapy and therefore few patients required multiple haemodynamic measurements. It is now realised that secondary pulmonary hypertension is relatively common and is a particular problem in connective tissue disease (Battle *et al* 1996). Furthermore, new treatment options are available and Prostacyclin and its derivatives have been shown to be beneficial long-term therapy for some patients (McLaughlin *et al* 1998), including those with severe pulmonary hypertension in association with connective tissue disease (De La Mata *et al* 1994 and Humbert *et al* 1998). Thus many more patients now require repeated haemodynamic assessment.

While cardiac catheterisation remains the assessment of choice, the increased demand on existing facilities suggests that additional methods of measurement might be useful.

Of particular interest in the study of the vasoreactivity of the pulmonary circulation is its response to the demands of exercise, when patients often report symptoms, and when abnormal levels of PAP may predict the subsequent development of pulmonary

hypertension (Weitzenblum *et al* 1996). Exercise testing of the pulmonary circulation can be performed with fluid filled, pulmonary artery catheters in the cardiac catheterisation laboratory (Ikram *et al* 1984), or alternatively by Doppler echocardiography (Winslow *et al* 1993) but there are technical difficulties inherent in both techniques.

Patients with pulmonary vascular disease often have limited exercise tolerance. This may be partly due to their prolonged adaptation to, and recovery from, exercise because of the limitations to blood flow imposed by the central circulation. This results in a reduction in oxygen uptake (VO_2) despite a greater than normal increase in ventilation (VE). Such patients have an oxygen deficit (i.e. require to perform work using preformed energy sources) and therefore perform exercise at a biological disadvantage (Sietsma 1992).

Ambulatory pulmonary artery pressure monitoring allowed measurement of gas exchange variables and PAP simultaneously during cardiopulmonary exercise testing in a group of patients with suspected pulmonary hypertension.

Correlations were sought between gas exchange variables and pulmonary artery pressure, measured simultaneously during cardiopulmonary exercise testing to assess whether these variables might then merit further study as potential non-invasive surrogate markers of the PAP response to exercise.

5.2 Methods and Equipment

5.2.1 Patient Group

This investigation was approved by West Glasgow Hospitals University NHS Trust Ethics Committee and all patients gave written, informed consent.

10 patients were studied of whom 7 had connective tissue disease, as defined by immunopathological patterns. (2 with CREST syndrome, 3 with positive autoantibodies and an undefined connective tissue disease, 1 with rheumatoid arthritis and 1 with features suggestive of a Scleroderma / Systemic Lupus Erythematosis overlap syndrome). Three had presumed PPH according to NIH criteria. There were 7 female and 3 male patients with mean age of 49 years (range 25-69 years). Table 5.1. All patients were considered capable of exercise at low workload on the cycle ergometer.

5.2.2 Measurements

Baseline investigations were carried out prior to cardiac catheterisation as described in Chapter 2.2. These routine investigations included electrocardiogram, pulmonary function testing, chest radiograph and Doppler echocardiography. High resolution CT scanning of thorax was performed to exclude interstitial lung disease.

5.2.3 Cardiac Catheterisation

Conventional cardiac catheterisation was performed as described in Chapter 2.4.

Pressures were recorded in the right atrium, right ventricle and proximal pulmonary artery and an estimate of pulmonary artery occlusion pressure was made with the catheter in the wedge position. Cardiac output was averaged over a minimum of three

Table 5.1

Patient No.	Age	Sex	Diagnosis	**FEV_1** (L), (% predicted)	**FVC** (L), (% predicted)	**KCO** (mol/min/kpa (% predicted)
1	36	F	CTD	**4.5** , (145%)	**4.9**, (123%)	**1.2**, (68%)
2	62	F	CREST	**2.2**, (105%)	**2.7**, (92%)	**1.2**, (72%)
3	67	F	CREST	**1.4**, (83%)	**2.0**, (84%)	**1.0**, (62%)
4	69	F	CTD	**1.4**, (80%)	**2.1**, (80%)	**0.9**, (56%)
5	40	F	SLE/SCL	**2.8**, (100%)	**3.6**, (102%)	**1.8**, (76%)
6	56	M	RA	**3.7**, (93%)	**5.0**, (94%)	**0.6**, (43%)
7	25	M	PPH	**3.9**, (95%)	**5.1**, (107%)	**1.5**, (77%)
8	54	F	PPH	**2.6**, (119%)	**3.2**, (113%)	**1.1**, (66%)
9	39	M	PPH	**3.5**, (99%)	**4.4**, (104%)	**1.4**, (80%)
10	41	F	CTD	**2.6**, (92%)	**3.3**, (93%)	**0.7**, (39%)
Mean (±SD)	48 range 25-69			**2.8**, (101.1%) **(1.1)**, (±18.9)	**3.2**, (99.2%) **(1.2)**, (±13.2)	**1.1**, (63.9%) (0.4), (±14.1)

Table 5.1 Patient Demographics, Diagnoses and Baseline Pulmonary Function

CTD; Connective tissue disease.

CREST; Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangectasia.

RA; Rheumatoid arthritis.

SLE/SCL; Systemic Lupus Erythematosis/ Scleroderma overlap syndrome.

PPH; Primary Pulmonary Hypertension.

FEV_1; Forced expiratory volume in one second.

FVC; Forced vital capacity.

KCO; Carbon monoxide transfer factor.

measurements using the thermodilution technique. In all patients the effects of exercise on pulmonary artery pressure was assessed by asking them to perform 3 minutes of straight leg raising. In the last 30 seconds of exercise measurements of pulmonary artery pressure, and cardiac output were repeated. Pulmonary artery occlusion pressure was not re-measured if the resting value had been normal, as was standard practice, as repeat measurement after exercise slightly increases the risk to the patient.

5.2.4 Ambulatory PAP monitoring

Ambulatory pulmonary artery pressure monitoring was carried out as described in Chapter 2.5.

5.2.5 Exercise testing

All patients were exercised breathing air as described in Chapter 2.2.2.

Formal exercise testing was performed after the micro-manometer tipped pulmonary artery catheter had been in place for almost 24 hours.

All the exercise variables presented are the mean of the values recorded for one minute from the onset of the 4th minute of exercise. This was based on the assumption that three minutes of constant workload exercise must have elapsed before steady state gas exchange kinetics will have become established (Sietsema *et al* 1989). Pulmonary artery pressures given are the mean pressures measured during the same period.

5.2.5.1 Protocol.

Exercise was performed on the electromagnetic, cycle ergometer and consisted of a

steady state exercise test at a workload of 30 Watts for a maximum of 8 minutes. This relatively low workload was chosen as manageable, and likely to be below the anaerobic threshold, for this group of patients with expected limited exercise capacity. Constant work rate testing was performed because exercise of this type is particularly suitable for measuring cardiovascular, ventilatory and gas-exchange kinetics (Nery *et al* 1982). Baseline values were measured over 2 minutes with patients sitting at rest on the cycle, before pedalling at 30 watts for a maximum of 8 minutes.

5.2.5.2 Cardiopulmonary exercise testing data

In each case breath by breath measurements of gas exchange were made. These included ventilation, tidal volume, respiratory rate, end tidal oxygen and carbon dioxide concentrations, oxygen saturations, oxygen uptake (VO_2) and carbon dioxide production (VCO_2). From these measurements other variables were derived including oxygen pulse (oxygen uptake / heart rate), and the ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) i.e. the ratios of ventilation to oxygen uptake and carbon dioxide output respectively. During exercise PAP was recorded continuously with the micro-manometer tipped pulmonary artery catheter.

5.2.6 Data Recording, Handling and Analysis

Data was recorded and processed as described in Chapter 2.5.1.

5.2.7 Statistics

All data are expressed as mean (± SD), unless otherwise stated. The strength of the correlation between the means was assessed by the Pearson correlation test. A p value of < 0.05 was considered to be statistically significant. Statistical analyses were

carried out using the OXSTAT package for personal computers (OXSTAT II, © 1983,1985 Holman, Jones, Walter & Wiggins; © 1986 Walter; © Microsoft Corp., 1982, 1983, 1984, 1985.).

5.3 Results

5.3.1.Relationship of PAP to Non-Invasive Variables Measured during Cardiopulmonary Exercise Testing

PAP measured with the micro-manometer tipped pulmonary artery catheter during the 4th minute of steady state exercise at 30 watts correlated with VE/VO_2 ($r=0.78$, $p=0.008$), and VE/VCO_2 ($r=0.80$, $p=0.005$). Figures 5.1 and 5.2.

There was no correlation between exercise PAP and other exercise testing variables. These included heart rate, oxygen pulse (O_2 Pulse), oxygen uptake (VO_2) and exercise time; nor did baseline line lung function (FEV_1, FVC and carbon monoxide transfer factor [KCO], Table 5.1) correlate with PAP, either at rest or during exercise.

The values for PAP, at rest and on exercise, measured with both the fluid filled, and micro-manometer tipped, pulmonary artery catheters are shown in Table 5.2. Patient 2 shows a considerable difference between resting and exercise measurements made with the two types of catheter. Patients 3 and 5 demonstrated a much higher pulmonary artery pressure on exercise measured with the micro-manometer tipped catheter than during straight leg raising measured with the fluid filled pulmonary artery catheter. Conversely patient 6 achieved a lower pulmonary artery pressure with the micro-manometer tipped catheter than fluid filled catheter. Table 5.3 shows the gas exchange variables recorded for each patient during steady state exercise testing.

5.3.2 Resting v Exercise Measurements made with the Fluid Filled, Pulmonary Artery Catheter

When patients were asked to perform three minutes of straight leg raising there was a correlation between resting and exercise values of mean PAP measured in the supine

Figure 5.1

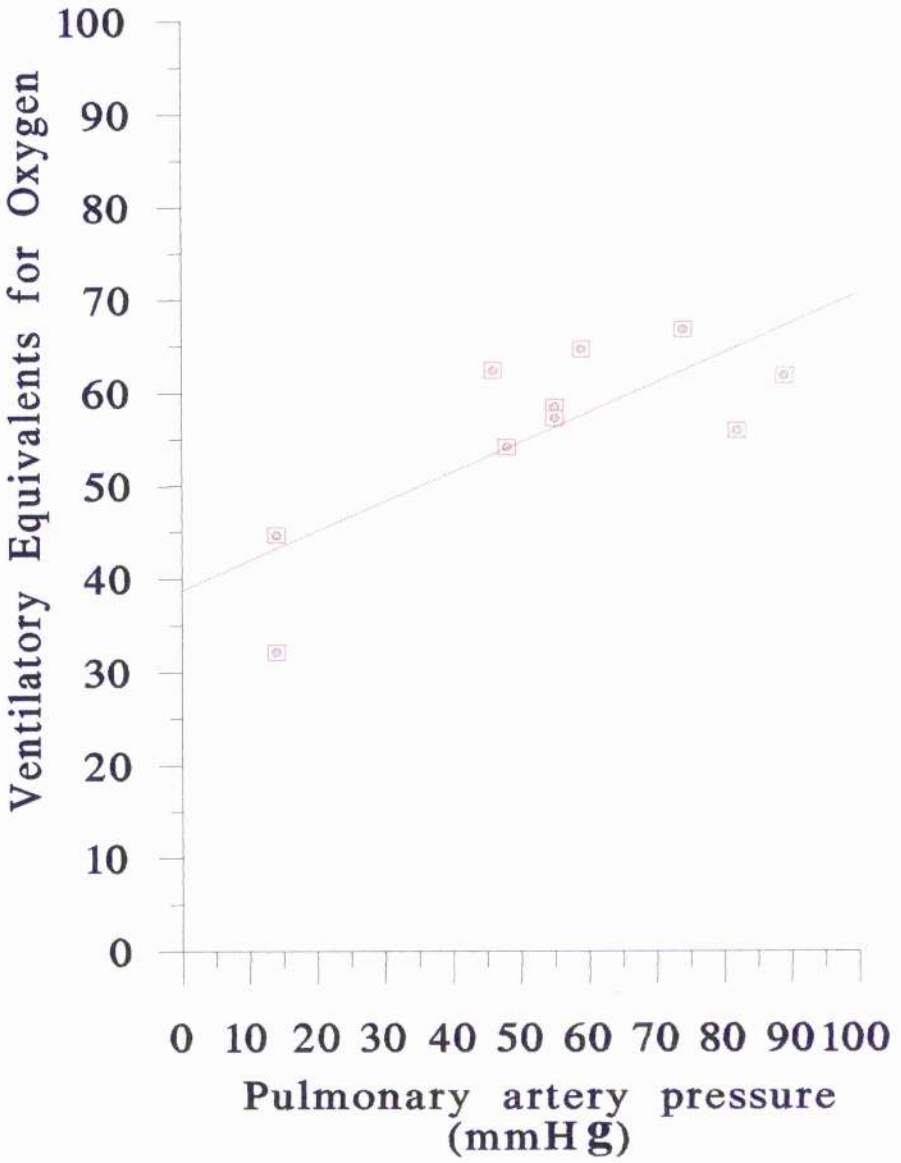


Figure 5.1 Ventilatory Equivalents for Oxygen

Ventilatory equivalents for oxygen measured during cardiopulmonary exercise testing (at a workload of 30 watts) from the onset of the 4th minute of exercise, for one minute, are shown plotted against the mean PAP recorded simultaneously. There was a significant correlation between the mean PAP on exercise and the mean value for the ventilatory equivalents $r = 0.78$, $p = 0.008$.

Figure 5.2

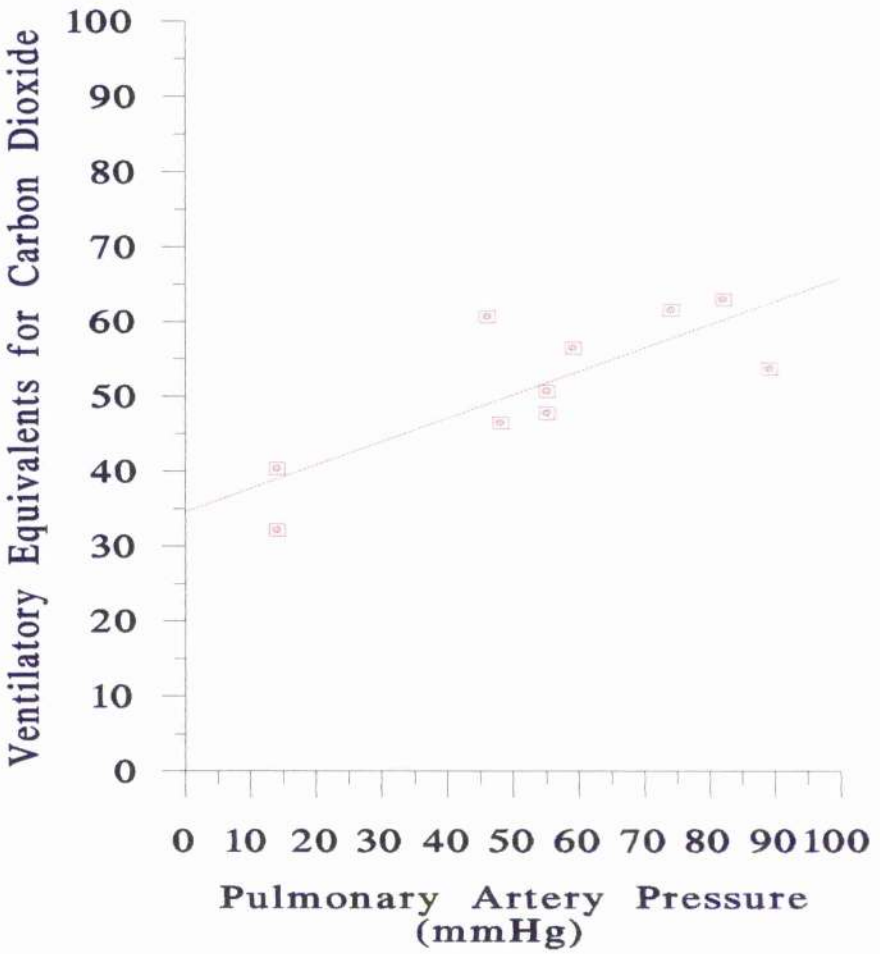


Figure 5.2 Ventilatory Equivalents for Carbon Dioxide

Ventilatory equivalents for carbon dioxide measured during cardiopulmonary exercise testing (at a workload of 30 watts), from the onset of the 4th minute of exercise, for one minute, are shown plotted against the mean PAP recorded simultaneously. There was a significant correlation between the mean PAP on exercise and the mean value for the ventilatory equivalents r=0.80, p=0.05.

Table 5.2

	Resting PAP (mmHg) [Cardiac outputs (L/min)]		**Exercise** PAP (mmHg) [Cardiac outputs (L/min)]	
Patient No.	Fluid filled	MM tipped	Fluid filled	MM tipped
1	13 [5.4]	13	14 [7.0]	14
2	20 [4.7]	8	39 [7.0]	14
3	40 [3.4]	29	56 [4.4]	48
4	33 [5.0]	33	43 [7.2]	55
5	47 [5.2]	45	65 [5.4]	46
6	40 [5.4]	42	45 [8.9]	59
7	54 [5.0]	42	61 [6.8]	55
8	48 [3.2]	48	60 [3.3]	82
9	55 [3.8]	73	70 [5.7]	74
10	71 [4.7]	69	90 [6.2]	89

Table 5.2 Mean PAP at Rest and on Exercise with the Conventional (Fluid Filled) and the Micro-Manometer Tipped (MM Tipped) Catheters

Fluid filled catheter: resting pressure and cardiac output measurements were made in supine subjects and are the mean of 6 beats, breath holding at functional residual capacity (FRC). Exercise pressure and cardiac output measurements were made during the last 30 seconds of 3 minutes of straight leg raising.

MM tipped catheter: resting pressure measurements in the sitting position on the exercise bike for 2 minutes immediately prior to the onset of exercise. Exercise values were measured from the onset of the 4th minute of steady state exercise (at a workload of 30 Watts) for one minute.

Table 5.3

Patient No.	HR (bpm)	VE/VO_2	VE/VCO_2	O_2 Pulse	VO_2 (l/min)
1	112	45	40	14.8	1.65
2	143	32	32	5.8	0.83
3	83	54	47	2.8	0.23
4	120	59	48	4.8	0.58
5	140	62	61	6.8	0.95
6	107	65	57	11.7	1.26
7	116	57	51	7.4	0.85
8	179	56	51	5.2	0.93
9	101	67	63	12.3	1.24
10	105	62	54	7.7	0.81

Table 5.3 Cardiopulmonary Exercise Testing Data

The mean values of gas exchange variables recorded during the 4th minute of steady state exercise at 30 watts

HR: Heart rate

VE/V_{O2}: Ventilatory equivalents for oxygen

VE/V_{CO2}: Ventilatory equivalents for carbon dioxide

O_2 pulse: Oxygen pulse

V_{O2}: Oxygen uptake

Ventilatory equivalents are the ratios of ventilation to oxygen uptake and carbon dioxide output respectively. The oxygen pulse is defined as the oxygen uptake divided by the heart rate.

position using the fluid filled catheter. ($r=0.96$, $p<0.001$). The mean increase in pressure was 12.2 (±6.3) mmHg.

5.3.3 Resting v Exercise Measurements made with the Micromanometer Tipped Pulmonary Artery Catheter

When patients exercised on the cycle ergometer at a steady state workload of 30 watts there was a correlation between resting (measured in the sitting position) and exercise values of mean PAP ($r=0.90$, $p=<0.001$). The mean increase in pressure due to exercise was 9.6(±10) mmHg.

Both resting and exercise measurements with the fluid filled catheter were made in the lying position, whereas with the micro-manometer tipped catheter both measurements were made in the sitting position. To determine whether this postural difference had influenced the results, PAP was also measured with the micro-manometer tipped pulmonary artery catheter in the lying position and this was compared with exercise in the sitting position. PAP measured supine with the micro-manometer tipped pulmonary artery catheter did correlate with the pressure measured on exercise in the sitting position with the same catheter ($r=0.92$, $p<0.001$). The mean increase in pressure was 7.3 (±11.9) mmHg.

5.4 Discussion

5.4.1 Exercise: Non-Invasively Measured Variables Of Gas Exchange And Pulmonary Artery Pressure

This chapter has shown that PAP measured during steady state exercise with the micro-manometer tipped pulmonary artery catheter correlates with VE/VO_2 and VE/VCO_2, but not with O_2 Pulse, or VO_2.

The PAP values represent the mean of more than 60 values. VE/VO_2 and VE/VCO_2 are also the mean of all the raw data for breath by breath values recorded for the same period of steady state exercise (1 minute) therefore the results are likely to be reliable. This is the first work to show that PAP on exercise correlates with simultaneously measured ventilatory equivalents for oxygen and carbon dioxide. The hypothesis is that these abnormal ventilatory equivalents on exercise are a result of increased physiological dead space ventilation, which is a consequence of the reduction in pulmonary capillary blood flow due to high pulmonary artery pressure.

These results are not surprising and have been predicted (Sietsema *et al* 1992, Manier and Castaing 1994) but it is surprising that no correlation between exercise PAP and VO_2 or O_2 pulse was seen. This may have been because the numbers of patients in this chapter was insufficient, or, more likely, because the chosen exercise protocol used too low a workload to allow these patients to demonstrate limitations in these variables and that we would have found a correlation between PAP and VO_{2MAX}. Another explanation may be that the abnormally high levels of PAP seen on exercise in some patients with pulmonary vascular disease which limit increases in cardiac output, also mask the change in oxygen pulse with exercise.

5.4.2 Pulmonary Haemodynamics During Exercise And Resting Pulmonary Function

Resting lung function (FEV1, FVC and KCO) did not correlate with exercise PAP in this chapter. It has been shown previously that lung function tests are often normal in pulmonary hypertension of various aetiologies (Gazetopaulos 1974), suggesting that pulmonary artery pressure per se has no effect on lung function. The patients discussed here had no radiological or clinical evidence of underlying lung disease therefore it was not surprising that this group had virtually normal spirometry. There was a reduction in the value of group mean KCO that would be explained on the basis of their pulmonary hypertension. This has also been described in pulmonary hypertension of a variety of causes (Romano *et al* 1993). It might therefore have been expected that this reduced KCO would have correlated with exercise levels of PAP but this was not the case. It would have been interesting to measure exercise KCO in this group of patients, but this was beyond the scope of this chapter.

5.4.3 Resting Vs. Exercise Pulmonary Haemodynamics.

This chapter shows that resting PAP measured in the supine or sitting position predicts PAP on exercise. Again this is not surprising and has been shown previously with fluid filled, pulmonary artery catheters (Lupi-Herra *et al* 1982) though this was not always the case in patients with milder degrees of pulmonary hypertension described in Chapter 3. Pulmonary artery occlusion pressure was not re-measured after exercise if the resting measurement was normal for the reasons previously discussed. It is likely that wedge pressure would have risen on exercise (Abdel Kafi *et al* 1998, Janicki 1985).

In this chapter the change in pressure on exercise was not predicted by the resting

value of PAP. Furthermore there are discrepancies in some patients between the values of PAP measured with the two types of catheter, which are not consistent (Table 5.2). However in each case the micro-manometer tipped pulmonary artery catheter reading taken in the cardiac catheterisation laboratory was consistent with the measurement of PAP which had just been obtained with the conventional catheter.

Patient 2 had results which were anomalous. This may have been because these measurements were not made simultaneously and it has been noted previously that there are significant intra-individual variations in pulmonary artery pressure measured at different times (Rich *et al* 1982). Alternatively it may be that the conventional cardiac catheterisation pressure measurement did not reflect the true resting state. However these differences seem too great to have been likely to have arisen physiologically and are more likely to have been due to technical error, probably with the zero levelling of the fluid filled pulmonary artery catheter.

Patients 3 and 5 had similar resting pressures measured with both types of catheter, but had much larger rises in pulmonary artery pressure on exercise when measured with the micro-manometer tipped catheter during the cardiopulmonary exercise test. These patients had moderate pulmonary hypertension and it is possible that the greater amount of work and greater pulmonary flow during the exercise test, when compared with simple straight leg raising, caused greater rises in pulmonary artery pressure. Patient 6 had severe rheumatoid arthritis and found cycling difficult. Consequently the rise in pulmonary artery pressure during the cardiopulmonary exercise test was less than that measured during straight leg raising.

Resting PAP measured with either fluid filled or micro-manometer tipped, pulmonary artery catheters did not correlate with cardiac output measured by thermodilution with fluid filled, pulmonary artery catheters, either at rest or after three minutes of exercise

(straight leg raising). Nor was there any correlation between exercise PAP (measured with the micro-manometer tipped pulmonary artery catheter) and the change in cardiac output from rest to exercise when measured with the fluid filled pulmonary artery catheter. However a trend was observed in that patients with higher levels of PAP tended to have lower resting values of cardiac output. The small numbers of patients in this chapter and the low level of exercise achieved make the interpretation of these observations difficult.

This chapter has shown that pulmonary haemodynamics on exercise can be measured by micro-manometer tipped pulmonary artery catheters, and that these haemodynamics correlate with ventilatory equivalents for oxygen and carbon dioxide measured non-invasively during a simultaneous cardiopulmonary exercise test. Accurate measurements of PAP on exercise in patients with mild resting pulmonary hypertension, or normal PAP who are symptomatic on exercise, may be useful in identifying individuals at risk of developing pulmonary hypertension.

Ventilatory equivalents merit further study as potential non-invasive surrogates of PAP on exercise.

Chapter 6

Oral Vasodilators in Patients with Pulmonary Hypertension Associated with Connective Tissue Disease: Assessment by Cardiopulmonary Exercise Testing

6.1 Introduction

In Chapter 3 the importance of background physiological variation in PAP was studied using the micro-manometer tipped pulmonary artery catheter; in Chapter 4 this method was used to study changes in PAP during sleep and exercise in a group of patients with COPD. In these situations such measurements could not have been made using conventional cardiac catheterisation. A perception of the growing need for repeated assessment of the pulmonary circulation led to work which attempted to identify surrogates of PAP measured non-invasively during cardiopulmonary exercise testing (Chapter 5).

Pulmonary hypertension is a life threatening complication of connective tissue disease (Hoeper *et al* 2002) and decisions about when to initiate specific therapy and how to evaluate responses remain difficult. In particular the point at which a patient may be deemed to have "failed" oral therapy and has become a potential candidate for parenteral treatment is controversial. The cost of such a decision, both to society and in terms of the impact on an individual patient's life, is considerable and therefore requires to be made in light of the best available evidence.

Chapter 5 described invasive measurement of PAP during exercise using a micro manometer tipped pulmonary artery catheter simultaneously with gas exchange variables, measured non-invasively during cardiopulmonary exercise testing. Some of these variables were shown to correlate with exercise PAP and may constitute a non-invasive surrogate of pulmonary haemodynamics on exercise (Raeside *et al* 1998). In this chapter the effects of treatment with oral vasodilators on these variables was measured by cardiopulmonary exercise testing.

Patients with connective tissue disease have been studied in Chapters 3 and 5 because they are analogous to PPH patients. The genesis of pulmonary hypertension in

connective tissue disease includes pulmonary vasospasm as one component and administration of intravenous vasodilators such as prostacyclin improves haemodynamic variables (Alpert *et al* 1991, Jolliet *et al* 1995, Menon *et al* 1998). Oral vasodilators have been used in PPH but the effect of these drugs on exercise variables in pulmonary hypertension associated with connective tissue disease is not known (Sanchez *et al* 1999).

PAP response to exercise has been shown to be abnormal in patients with connective tissue disease (Winslow *et al* 1993). Objective measurement of response to treatment with oral vasodilators using haemodynamic assessment may help in treatment decisions. Conventional cardiac catheterisation is an alternative but is invasive and can be used to measure haemodynamics on only very limited exercise.

6.2 Patients and Methods

6.2.1 Patient group

10 consecutive patients were studied. These patients had pulmonary hypertension secondary to connective tissue disease and had been commenced on treatment with diltiazem. The connective tissue disease diagnoses were as follows. 7 patients had CREST syndrome patients, 2 had SLE and 1 patient had Sjogren's syndrome (as defined by the American Rheumatology Association). All were female, mean age 63 years (range 33-75).

All patients were considered capable of exercising on the cycle ergometer without limitation from connective tissue disease.

All patients were treated with diltiazem, initiated in hospital and titrated to the maximum tolerated dose. Diltiazem was chosen because of previous experience with this drug in the treatment of PPH (Rich *et al* 1992). 6 of the 10 patients tolerated high dose diltiazem considered therapeutic for this indication. The mean, daily dose was 625 milligrams (range 480-750), (Table 6.1). Data is presented for these patients, 4 of whom had CREST syndrome and 2 who had SLE. The mean age of this group was 57 years (range 33-75).

All patients gave written informed consent. The study was approved by the West Glasgow Hospitals University NHS Trust Ethics Committee.

6.2.2 Measurements

All patients were referred for further investigation of pulmonary hypertension and had had pre-catheterisation investigations as described in Chapter 2.1.2. All patients underwent CT scanning to exclude interstitial lung disease. Echocardiography was

Table 6.1

Patient	*Age*	*Diagnosis*	*Resting PAPm (mmHg)*	*Diltiazem dose (mg/day)*	*Treatment duration (months)*
1	75	CREST	53	540	8
2	65	SLE	40	540	3
3	40	CREST	34	720	4
4	66	CREST	23	750	8
5	60	CREST	33	720	2
6	33	SLE	55	480	6

Table 6.1 Patient Demographics, Baseline Haemodynamics and Treatment Details

Baseline haemodynamics were measured in the cardiac catheterisation laboratory at rest with fluid filled, pulmonary artery catheters. Patient 4 had normal resting pulmonary artery pressure but developed significant pulmonary hypertension on exercise (PAP = 41 mmHg).
Diltiazem doses were the total daily amount taken for the duration shown in months.

PAPm: mean pulmonary artery pressure.
SLE: systemic lupus erythematosis.
CREST: Calcinosis, Raynaud's phenomenon, Oesophageal dysmotility, Sclerodactyly, Telangectasia.

performed to assess systolic PAP and to exclude significant left ventricular impairment. Serial measurements of PAP were made by echocardiography, by the same technician and at the same time of day (±2 hours).

6.2.3 Cardiac Catheterisation

All patients had previously undergone conventional cardiac catheterisation as described in Chapter 2.2. Supine PAP was measured at functional residual capacity with the catheter tip placed in the right, proximal pulmonary artery. Response to an acute intravenous vasodilator (Adenosine) was measured and all patients reported were "responders". A responder was defined as a patient in whom the administration of an intravenous vasodilator caused a reduction in pulmonary vascular resistance of >20% without a rise in PAP or a reduction in cardiac output. These patients did not go on to have ambulatory pulmonary artery pressure monitoring.

6.2.4 Cardiopulmonary Exercise Testing

All patients were exercised tested as described in Chapter 2.1.2.

Patients exercised at a steady state workload (30 watts) to a maximum of 8 minutes according to a standard protocol. The relatively low workload was considered appropriate for patients with presumed functional impairment both from their moderately severe pulmonary hypertension and underlying connective tissue disorder.

6.2.4.1 Measurements

A number of non-invasive variables of gas exchange were measured and derived. Ventilatory equivalents indicate ventilatory requirement for a given metabolic rate and oxygen pulse is the amount of oxygen extracted by the body from the oxygen

carried in each stroke volume. These variables were recorded from the onset of the fourth minute of steady state exercise for one minute.

- Ventilatory equivalent for oxygen (VE/VO_2) is calculated as the ventilation divided by the oxygen uptake.
- Ventilatory equivalent for carbon dioxide (VE/VCO_2) is calculated as the ventilation divided by the carbon dioxide output.
- Oxygen pulse (O_2 Pulse) is calculated by dividing the oxygen uptake by the heart rate
- Exercise time in minutes was measured from the onset of cycling at a constant workload of 30 watts up to a maximum of eight minutes.

6.2.5 Statistics

All data are expressed as mean (±SD) unless otherwise stated. The strength of the correlation between the means was assessed by the Pearson correlation test and a p value of < 0.05 was considered to be statistically significant.

6.3 Results

6.3.1 Patient Tolerability

4 patients could not tolerate diltiazem at the doses indicated for pulmonary hypertension secondary to connective tissue disease. This was due to unacceptable ankle swelling for 3 patients and excessive tiredness attributed to the drug in 1.

6.3.2 Cardiac Catheterisation

The groups mean PAP was 40mmHg (range 23-53mmHg), (Table 6.1).

6.3.3 Cardiopulmonary Exercise Testing

The mean interval between initiation of diltiazem and repeat cardiopulmonary exercise testing was 5 months (range 2 – 8 months (Table 6.1).

- *Exercise time*; group mean exercise time measured before and during treatment with diltiazem showed no improvement, 5.6 minutes (±1.9) to 6.5 minutes (±1.7), (Table 6.2 and Figure 6.1).
- *VE/VO_2;* group mean VE/VO_2 showed no change from baseline during diltiazem treatment, pre: 50.8 (±15.6) to post: 53.2 (±17.6). This change was not statistically significant (Table 6.2 and Figure 6.2).
- *VE/VCO_2;* group mean VE/VCO_2 showed a trend towards improvement from baseline during treatment with diltiazem, from 50.2 (±4.0) to 48.5 (±12.9), but this was not statistically significant (Table 6.2 and Figure 6.3).
- *O_2 pulse;* group mean O_2 pulse showed an improvement from baseline during treatment with diltiazem, from 5.5 (±1.9) to 8.2 (±1.7), ($p=0.03$), (Table 6.2).

Table 6.2

	Exercise time (min)		*VE/VO₂*		*VE/VCO₂*		*O₂ Pulse*	
Patient	*Baseline*	*On drug*	*Baseline*	*On drug*	*Baseline*	*On drug*	*Baseline*	*On drug*
1	4.4	4.2	72	70	61	53	3.5	5.4
2	3.9	7.2	53	60	54	59	6.8	9.8
3	8.0	8.0	31	28	33	30	6.9	9.9
4	5.3	7.2	35	34	33	35	6.0	8.6
5	4.0	4.5	62	63	66	53	2.8	7.4
6	8.0	8.0	52	64	54	61	7.0	8.0
Mean	5.6	6.5	50.8	53.2	50.2	48.5	5.5	8.2
SD	1.9	1.7	15.6	17.6	14.0	12.9	1.9	1.7
	p = 0.4		p = 0.8		p = 0.8		p = 0.03	

Table 6.2 Exercise Data

Variables measured and derived during cardiopulmonary exercise testing. Exercise variables are the mean values measured and derived, over one minute from the onset of the 4th minute of steady state exercise.
P values refer to baseline measurement compared with measurement on treatment.

Exercise time: during steady state exercise on the bicycle ergometer at 30 watts.
Baseline: before treatment with diltiazem.
On drug: during treatment with diltiazem.
VE/VO2: ventilatory equivalents for oxygen
VE/VCO2: ventilatory equivalents for carbon dioxide.
O_2 Pulse: oxygen pulse.

Figure 6.1

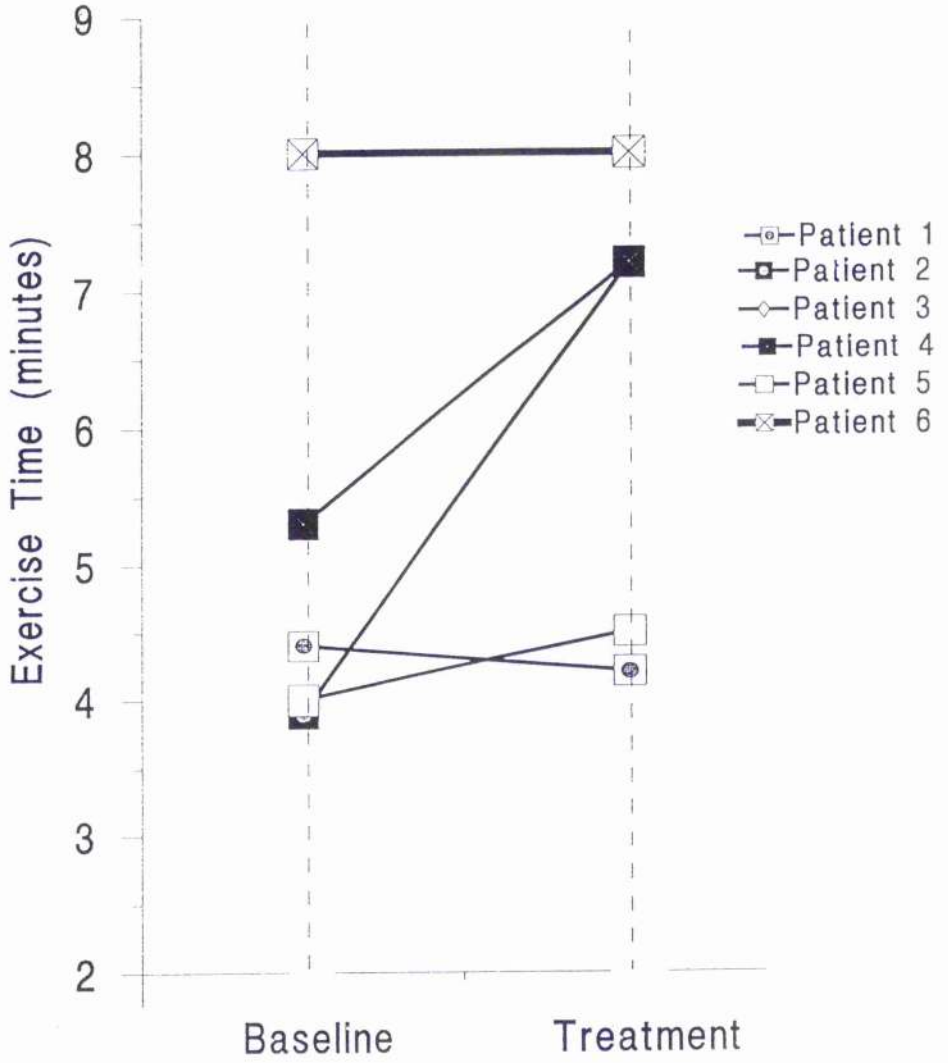


Figure 6.1 Exercise time

Steady state exercise times in minutes on the cycle ergometer (at 30 watts) are shown plotted before and during treatment with diltiazem for each of the six patients. There was no significant change in exercise time for the group (p=0.4).

Figure 6.2

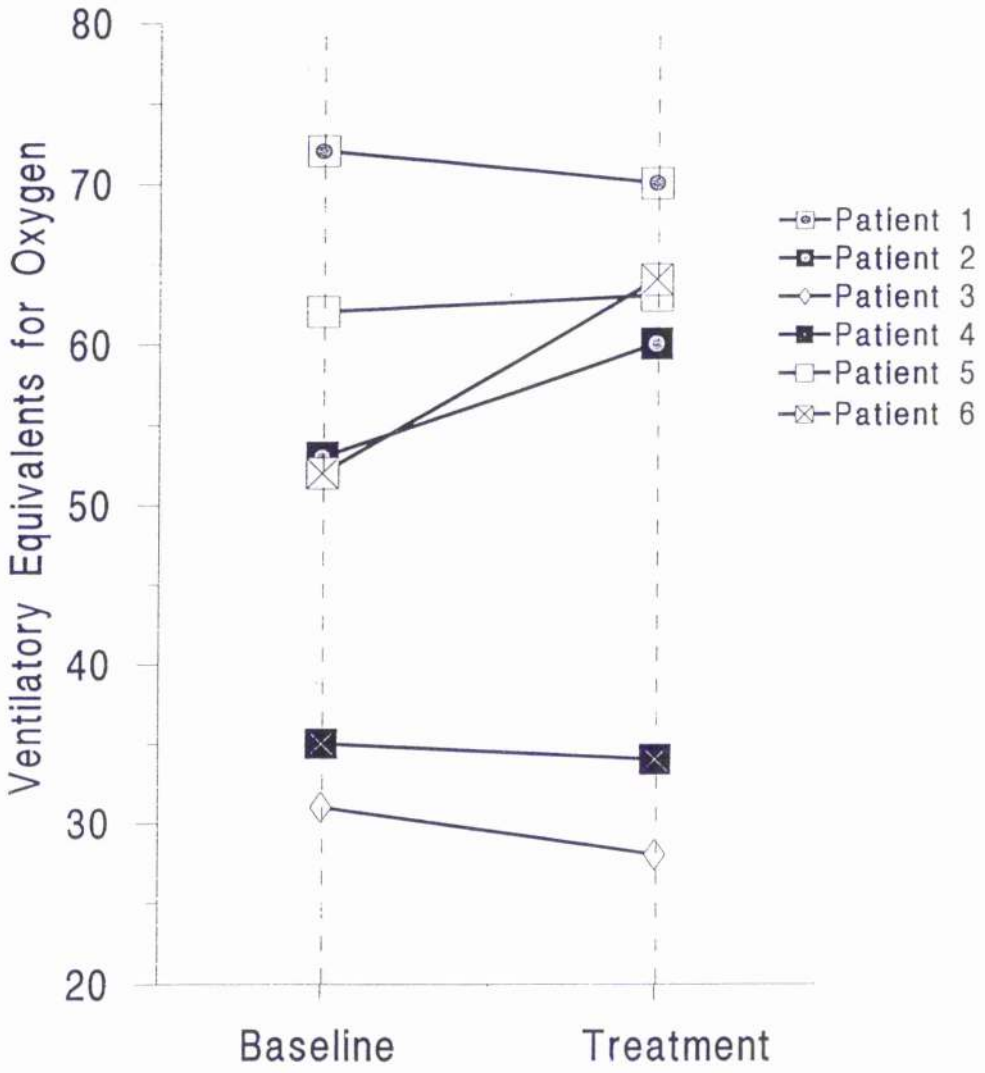


Figure 6.2 Ventilatory equivalents for oxygen

Ventilatory equivalents for oxygen (V_E/V_{O2}) are shown plotted before and during treatment with diltiazem for each of the six patients. There was no significant change in V_E/V_{O2} for the group ($p=0.8$).

Figure 6.3

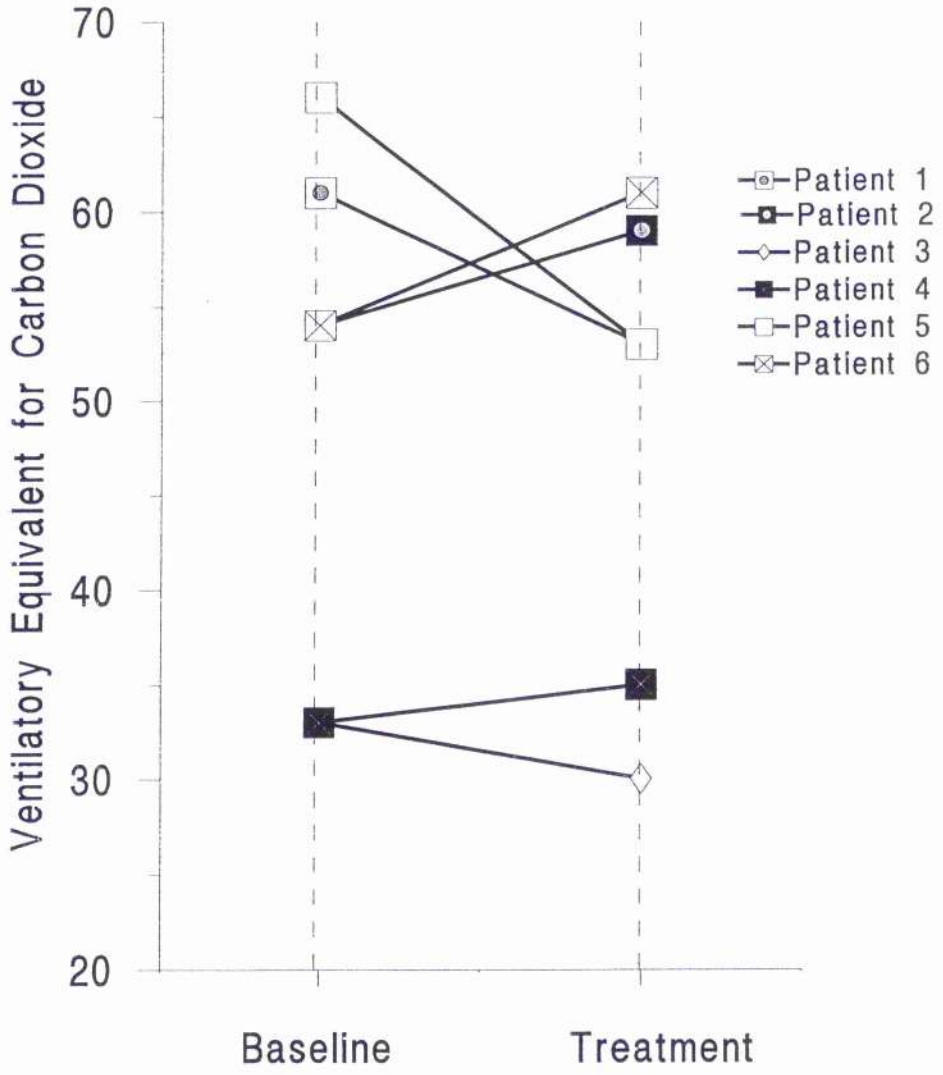


Figure 6.3 Ventilatory equivalents for carbon dioxide

Ventilatory equivalents for oxygen (V_E/V_{CO2}) are shown plotted before and during treatment with diltiazem for each of the six patients. There was no significant change in V_E/V_{CO2} for the group ($p=0.8$).

6.4 Discussion

In this chapter it has been shown that patients with pulmonary hypertension secondary to connective tissue disease are able to perform cardiopulmonary exercise testing at a low workload and that this is repeatable. No complication from cardiopulmonary exercise testing or cardiac catheterisation arose in the patients studied. Diltiazem in doses similar to those used to treat PPH was not well tolerated and 4 of the 10 patients intended to treat had to stop taking the drug because of unacceptable side effects. While it would have strengthened the study to continue them at the highest dose they could tolerate, we felt that it would have been unethical to so because there is no evidence of benefit from diltiazem in pulmonary hypertension at lower doses. Furthermore these were troublesome side effects which required withdrawal of the drug to resolve. Finally it was felt that this aspect of the study mirrored clinical experience when many patients cannot tolerate calcium channel blockers at the doses indicated for pulmonary hypertension.

In those who tolerated treatment, no objective improvement in gas exchange variables measured non-invasively during cardiopulmonary exercise testing could be demonstrated, i.e. variables which correlate with PAP on steady state exercise.

There was a slight improvement in exercise time during treatment, but this was not significant. This could be explained by a learning effect though interpretation of these results is further complicated by the fact that subjects 3 and 6 exercised for the maximum exercise time on both occasions. Patient 3 had mild pulmonary hypertension and although patient 6 had the highest level of PAP she was also the youngest. 8 minutes was chosen as a maximum exercise time as it was considered unlikely that this patient group would exceed this and further it was assumed that steady state exercise conditions have been reached by the onset of the 4^{th} minute of

exercise. Neither subject 3 or 6 reported any subjective improvement in exercise tolerance during their treatment period.

Exercise testing may be subject to a learning effect and it would have been desirable to repeat the baseline cardiopulmonary exercise test to exclude this. However all of the patients included in this section had been subject to cardiopulmonary exercise testing within the previous 6 months in the context of other studies. While this timescale is longer than desirable to eliminate any baseline learning effect, it was felt that previous testing may have reduced its likelihood. Furthermore this possibility (and the undoubted desirability of repeating the baseline exercise test) had to be balanced against subjecting this particular patient group to the demands of possibly excessive cardiopulmonary exercise testing which may have adversely affected recruitment of an already small number of patients.

No improvement in VE/VO_2 or VE/VCO_2 during treatment was observed. These patients had abnormally high ventilatory equivalents, at rest and on exercise. This may reflect increased dead space ventilation due to poor perfusion of ventilated lung caused by vascular restriction of blood flow, which worsened during exercise as ventilation increased. Ventilatory equivalents normally reach a nadir during progressive cardiopulmonary exercise testing. When this value is elevated it reflects increased dead space ventilation (Wasserman *et al* 1994). Thus it would be expected that successful vasodilator treatment would reduce ventilatory equivalents during steady state exercise by improving lung blood flow. These patients did not show any improvement ventilatory equivalents because their pulmonary hypertension did not respond to this vasodilator, although they had all previously been shown to respond to an intravenous vasodilator.

A significant change in O_2 pulse was observed, although this was not one of the variables previously found to correlate with PAP (Chapter 5). This might have been explained by the limiting effect of diltiazem on exercising heart rate. Oxygen pulse was defined as the amount of oxygen extracted by the body tissues from the oxygen carried in each stroke volume, and was calculated by dividing the maximal oxygen uptake by the heart rate. Therefore a reduction in heart rate alone may have suggested an improvement in oxygen pulse even when maximal oxygen uptake fell. However the fact that the O_2 pulse had not declined during treatment would also suggest a reduction in stroke volume did not occur, which might otherwise have been responsible for the lack of improvement in ventilatory equivalents.

These results are disappointing but not surprising. Pulmonary vasospasm is only one component of the vascular changes seen in connective tissue disease complicated by pulmonary hypertension (Stupi *et al* 1986). Acute vasodilator studies are even less likely to be positive in patients with connective tissue disease than in those with PPH (Sanchez *et al* 1999). This would suggest that only a minority of patients would have had vasoconstriction as the predominant cause of their pulmonary hypertension and most patients would have had at least some element of irreversible pulmonary hypertension.

6.5 Conclusion

In this chapter gas exchange variables were measured during cardiopulmonary exercise testing before and after treatment with oral vasodilator drugs in a group of patients with pulmonary hypertension secondary to connective tissue disease. These variables had previously been shown to correlate with steady state pulmonary artery pressure (Chapter 5). No improvement was demonstrated during treatment with diltiazem. These results suggest that there was no reduction in PAP on exercise in patients taking oral diltiazem who were known to be responders to intravenous vasodilators. Furthermore it was found that diltiazem in therapeutic doses for pulmonary hypertension was not well tolerated.

These results failed to demonstrate evidence for haemodynamic benefit from oral diltiazem in patients with pulmonary hypertension secondary to connective tissue disease. However the patient group was small (albeit due in part to side effects from diltiazem) and it is difficult to reach firm conclusions from these data. This chapter has demonstrated that gas exchange variables measured during cardiopulmonary exercise testing and simultaneous ambulatory PAP monitoring, merit further study as possible surrogates for PAP in exercising patients.

Chapter 7

General Discussion, Conclusions and Future Developments

7.1 Relevance of Secondary Pulmonary Hypertension to Mortality and Morbidity in Respiratory Disease and Connective Tissue Disease

The mortality of PPH is high with most patients dying within 10 years (Fuster *et al* 1984, D'Alonzo *et al* 1991). The importance of secondary pulmonary hypertension in the morbidity and mortality of respiratory disease is much less clear and the subject of debate (Weitzenblum *et al* 1996). Nonetheless if even the most conservative estimates of the incidence (Williams and Nicholl 1985) and progression (Weitzenblum1996) of pulmonary hypertension secondary to chronic lung disease are accepted then the size of the problem is considerable.

Many respiratory conditions can cause pulmonary hypertension, in particular COPD, interstitial lung disease, kyphoscoliosis and obstructive sleep apnoea. However although COPD constitutes more than 90% of pulmonary hypertension secondary to chronic hypoxic lung disease it is often misdiagnosed as other pathology such as congestive cardiac failure (Intersociety Commission for Heart Disease 1970); from the foregoing it is clear that the true incidence of pulmonary hypertension secondary to respiratory disease is unknown and possibly underestimated. What is clear from a number of studies in patients with COPD -whether receiving LTOT or not- is that the presence of pulmonary hypertension is a bad prognostic sign and that the higher the level of PAP the poorer the prognosis (Bishop and Cross 1984, Oswald-Mammoser *et al* 1995). These studies have shown that the 5 year survival rate in pulmonary hypertensive COPD patients is approximately 50%, rising to 62% in those on LTOT (Cooper *et al* 1987).

Pulmonary hypertension secondary to connective tissue disease is an easier problem to quantify, although the incidence varies considerably between different conditions.

In some connective tissue diseases, in particular the CREST variant (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangectasias) of systemic sclerosis, the prevalence may approach 50% (Yousem 1990) and PAH is the most important cause of mortality and morbidity in this condition. The frequency of PAH varies in the other collagen vascular diseases (Chapter 1.2.3.6) however because the pathology of PAH associated with collagen vascular diseases is similar to that in PPH it is usually of significance. Thrombosis *in situ* also occurs in pulmonary hypertension associated with collagen vascular disease (Welsh *et al* 1996, Hooper *et al* 1998) (Chapter 1.2.3.6) further complicating the management of systemic diseases.

In conclusion, whereas the presence of PAH in COPD is often considered an unremarkable finding whose presence extent and importance may be underestimated, in collagen vascular disease it is often sought and acknowledged as a serious complication which may prove difficult to control.

7.2 Limitations of Current Methods of Measurement in the Assessment of the Pulmonary Circulation

There is no easily applied sphygmomanometer for the pulmonary circulation and (until recently) no effective treatment for pulmonary hypertension has been available. The emergence of new treatments and a more rigorous approach to classification has renewed interest in making measurements in the pulmonary circulation and revealed deficiencies in many of the traditional methods of measurement. Non-invasive methods of measurement provide an indirect estimate of PAP (Chapter 1.3.1) but remain clinically very relevant and for most clinicians will be the only screening tools available to indicate individuals who should progress to invasive measurement of the

pulmonary circulation. The most widely used non-invasive method of measurement is Doppler-echocardiography. While this is an accurate and reliable tool in the assessment of PAP it is operator dependant and is not suitable for all patient groups, in particular those with COPD.

Cardiac catheterisation with fluid filled pulmonary artery catheters has long been considered the "gold standard" measurement in the pulmonary circulation. The principal limitations of such catheters are that they must be deployed in an unrepresentative environment (i.e. the cardiac catheterisation laboratory) in an unrepresentative position (i.e. supine) and in an unrepresentative state (i.e. resting). These are not usually the circumstances in which patients complain of symptoms.

There are also technical considerations which limit the usefulness of data obtained by conventional cardiac catheterisation. These mainly relate to the generation of artefacts in the pressure trace (in particular damping of the trace) and the inability to measure instantaneous pressures(Chapter 1.3.3.3). These disadvantages may be of limited significance in routine haemodynamic monitoring, but in studies of a low pressure system -such as the pulmonary circulation- where an intervention may cause subtle changes in PAP they can be significant.

7.3 Relevance of the Patient Groups Chosen for Study by Diagnosis

7.3.1 Connective Tissue Disease

PPH is the purest model for the study of pulmonary hypertension however is an extremely rare condition and it would have been ideal to assess the ambulatory pulmonary artery pressure monitoring system in patients with PPH. Patients with connective tissue disease were chosen for study as they often have few symptoms

(other than breathlessness) from their underlying lung disease (hence the symptoms experienced by patients with pulmonary hypertension secondary to connective tissue disease can be easier to identify) and because of increasing interest in the treatment of pulmonary hypertension associated with connective tissue disease. Finally, as connective tissue disease is commoner than PPH, they represent a suitable alternative group in which to identify the strengths and weaknesses of this measurement system.

Previously treatment of such patients was aimed at the underlying connective tissue disease or consequent hypoxia (e.g. secondary to pulmonary fibrosis) and pulmonary hypertension, if recognised, was considered untreatable. However, because the pathology of PAH associated with collagen vascular diseases is similar to that in PPH (Chapter 1.2.3.6) and because thrombosis *in situ* is an important feature of pulmonary hypertension associated with collagen vascular disease – as in PPH- (Welsh *et al* 1996, Hoeper *et al* 1998) advances in the treatment of PPH in recent years, have led to the belief that similar treatment should be offered to patients with pulmonary hypertension secondary to connective tissue disease.

In PPH the demonstration of vasoreactivity of the pulmonary circulation in the cardiac catheterisation laboratory is accepted as in indication for treatment with oral vasodilator drugs (Rubin *et al* 1993). Administration of vasodilators in patients with pulmonary hypertension secondary to connective tissue disease has also been shown to produce beneficial haemodynamic results (Alpert *et al* 1991, Jolliet *et al* 1995, Menon et al 1998 and Badesch 2000) suggesting that these patients should also receive treatment with oral vasodilators. Consequently, as in PPH, when they cannot tolerate them, or do not experience sustained benefit from them, they should then be offered continuous, parenteral vasodilators (Sanchez *et al* 1999). This is an expensive and inconvenient treatment and therefore before it is considered, it is necessary to

demonstrate objectively that treatment with oral vasodilators has failed. Pulmonary artery pressure is a physiological variable and hence subject to considerable variation. Stress testing would impose some uniformity of condition under which measurements might be made and when excessive elevations in PAP have been shown to be associated with diminished exercise tolerance in connective tissue disease (Winslow *et al* 1993).

Consequently we considered this patient group a suitable one to study with the micromanometer tipped pulmonary artery which allowed testing in a variety of situations including under controlled stress (exercise) and allowed us to assess the effects of posture and normal daily activity on the pulmonary circulation. Thus the ambulatory pulmonary artery pressure monitoring system offered significant advantages over conventional cardiac catheterisation. Furthermore we believed that this system might offer the opportunity to detect very early pulmonary hypertension (i.e. only present on exercise) with important treatment implications for a patient group at increased risk of pulmonary hypertension but with no clinical signs of it at rest.

7.3.2 Chronic Obstructive Pulmonary Disease

The commonest cause of secondary pulmonary hypertension by a large margin is chronic obstructive pulmonary disease (COPD); this patient group constitute a significant proportion (0.3%) of individuals in any industrialised community (Williams and Nicholl 1985) and constitute a major treatment challenge.

However there is considerable debate as to the importance of raised pulmonary artery pressure in this context as the actual increases in pulmonary artery pressure seen are small and progression is slow (Nacije 1992). While this is the case when these

pulmonary artery pressures are measured conventionally, one hypothesis of this thesis is that ambulatory measurement systems reveal a number of situations (i.e. with postural changes, on exercise or during sleep) where pulmonary artery pressures can be transiently much higher. Consequently it may be the case that conventional methods of measurement in the pulmonary circulation underestimate the variations in pulmonary artery pressure experienced by patients in the course of normal daily activity. It remains unclear whether these variations are haemodynamically important: this has been the case in the systemic circulation where ambulatory blood pressure monitoring has become a routine and useful clinical tool and it is the case that patients with COPD seem to experience markedly differing exercise limitations for similar levels of lung function. This raises the possibility that differing responses in the pulmonary circulation may be one part of the explanation for this.

Should these suspicions be borne out, this would have implications for the treatment of COPD, particularly in patients with mild or early pulmonary hypertension and the ambulatory pulmonary artery pressure measurement has significant advantages over the other available methods of measurement in the further investigation of this area.

7.3.3 Others

Various other patient groups with pulmonary hypertension are included in this thesis, including those with chronic thromboembolic pulmonary hypertension, pulmonary hypertension secondary to drugs and patients with PPH. These patients presented with suspected pulmonary hypertension and were studied in accordance with standard protocols. Where appropriate they were then included in studies reported here. Patients described as normals were individuals in whom pulmonary hypertension had

been wrongly suspected at rest and in whom ambulatory pulmonary artery pressure monitoring was carried out to exclude exercise related pulmonary hypertension.

7.4 Advantages of the Micromanometer Tipped Pulmonary Artery Catheter in the Assessment of the Pulmonary Circulation

In Chapter 1.3.3.5 the advantages and disadvantages of micromanometer tipped pulmonary artery catheters were described. The principal strength of such systems is the ability to make high fidelity pressure measurements in fully ambulant patients and to allow the correlation of symptoms and haemodynamic change in real time and with great accuracy. Chapters 3, 4 and 5 have shown that such solid state pulmonary artery catheters can be used safely (and are well tolerated) in patient groups with pulmonary hypertension of various aetiologies including frail patients with COPD on LTOT. Although the studies described previously never included periods of ambulatory pulmonary artery pressure monitoring greater than 24 hours there is no reason why this could not be done while accepting the increased risk of infection.

Chapter 3 has demonstrated that variations in PAP can be measured (using the micromanometer tipped pulmonary artery catheter) during changes in posture and activity in a group of patients with pulmonary hypertension secondary to connective tissue disease. This allows a more realistic appraisal of the haemodynamic burden facing these patients than that obtained by conventional measurements and consequently may give better prognostic information. If the abnormal rises seen in these circumstances portend the future development of resting pulmonary hypertension (and if early treatment is more likely to be beneficial) then this measurement system may also allow the identification of individuals who should be offered early treatment, or closely followed by conventional means.

Chapter 4 has shown that ambulatory pulmonary artery pressure monitoring was well tolerated in a group of patients with severe lung disease. In such patients the phenomenon of increased PAP during sleep and exercise has been demonstrated (Riley *et al* 1948, Boysen *et al* 1979) however ambulatory measurement permitted the extent of these rises to be fully appreciated. The observation that abnormal rises in PAP during exercise in patients with lung disease predicts the future development of pulmonary hypertension also suggests that the technique of ambulatory pulmonary artery pressure monitoring could be used to identify individuals at risk. Furthermore observations made in Chapter 4 suggest that PAP variation during activities of daily living may be greater that previously appreciated; if these were to be borne out by further study then this might have implications for earlier treatment (e.g. oxygen therapy) in COPD.

While there are undoubted advantages to ambulatory pulmonary artery pressure monitoring it is an invasive technique involving an element of risk and discomfort for the patient. The ability to carry out formal cardiopulmonary exercise testing (CPET) while simultaneously measuring PAP led to the hypothesis that CPET might provide non-invasively measured surrogates for PAP. Chapter 5 identified such variables and demonstrated that CPET at low workload was well tolerated by patients with pulmonary hypertension secondary to connective tissue disease.

Chapter 6 utilised these correlates of PAP measured non-invasively during CPET to assess the response to treatment in a group of patients with pulmonary hypertension secondary to connective tissue disease. No benefit was demonstrated following treatment with oral vasodilators. While this may confirm anecdotal clinical impression, the previous observation that such treatment failure will now lead to the introduction of further therapies (with additional inconvenience and cost) suggests

that a non-invasive, accurate and repeatable test of PAP under stress would be very useful. Such a test would allow clinical decision making to become more objective. The ambulatory pulmonary artery pressure monitoring is ideally suited to the study of the pulmonary circulation in such conditions and will permit the necessary further studies to confirm or refute the usefulness of non-invasive surrogates of PAP measured during cardiopulmonary exercise testing.

7.5 Conclusions and Future Developments

This thesis has demonstrated that ambulatory pulmonary artery pressure monitoring is safe and well tolerated in a variety of patients groups including those with multi-system disorders and in others with severe respiratory disease. Invasive haemodynamic assessment of patients with pulmonary hypertension and significant co-morbidity is challenging and it is difficult to conduct it on large numbers of patients. This leads to the possibility of type II errors where the study sample size has been too small to detect a difference between the two populations studied. While this is a very real concern it would not have been possible to recruit sufficient numbers of patients to power the studies reported in this thesis to exclude the possibility of type II errors arising. It is therefore necessary throughout this thesis to consider that such errors may have arisen.

This technique offers the opportunity to make very accurate measurements of PAP in patients carrying out their normal activities of daily living or in a variety of controlled circumstances including exercise. Such high fidelity measurements are likely to be very useful in making judgements about disease progression or the effectiveness of an intervention (and hence prognosis) in a low pressure system. Furthermore ambulatory pulmonary artery pressure monitoring permits the patient's symptoms to be directly

correlated with haemodynamic changes in the pulmonary circulation and consequently may allow us to achieve better insight into the total haemodynamic burden facing the right ventricle.

However even when safe and well tolerated, invasive procedures are time consuming, inconvenient for the patient and expensive for the investigator. An accurate, easily repeatable and hence non-invasive method of measurement in the pulmonary circulation remains an important goal, particularly as the options for the treatment of pulmonary hypertension increase. Chapter 5 described the simultaneous use of cardiopulmonary exercise testing and ambulatory pulmonary artery pressure monitoring in an attempt to define non-invasively measured surrogates for PAP. Further work is required to confirm the initial observation that cardiopulmonary exercise testing may provide these. An important strength of ambulatory pulmonary artery pressure monitoring is its ability to provide high fidelity PAP measured simultaneously with non-invasive methods of measurement.

If the burgeoning treatments for pulmonary hypertension lead to the anticipated increased diagnosis of this condition then resources and expertise are likely to become stretched. This possibility emphasises the need for new methods of measurement which have been proven to be reliable and accurate.

Furthermore if the emerging consensus that early treatment is more likely to be beneficial is proven, then screening susceptible individuals will be important. Ambulatory pulmonary artery pressure monitoring confers significant advantages over stress echo in the early identification of pulmonary hypertension in patients with normal resting pressure.

In this thesis ambulatory pulmonary artery pressure monitoring has been used to assess changes in PAP with posture and exercise patients with connective tissue

disease and during exercise and sleep in a group with COPD compared with normal individuals. These studies have shown that PAP varies considerably in these circumstances and that resting pressure does not always predict these variations. Changes in PAP have also been correlated with symptoms. These results suggest that the contribution of secondary pulmonary hypertension to morbidity and mortality in patients with connective tissue disease and COPD is considerable and underestimated by conventional methods of assessment.

The technique of ambulatory, high fidelity pressure measurement obtains a more complete picture of the haemodynamic variations induced by normal daily activity and under stress and contributes to our appreciation of the morbidity of pulmonary hypertension.

While it is unlikely ever to become commonplace it nonetheless offers a unique opportunity to measure the pulmonary circulation under conditions of "stress" (exercise, hypoxia etc). It seems possible that such measurements might allow earlier detection of abnormal pulmonary vascular responses and hence the earlier initiation of treatment. If (as seems likely) earlier treatment is more likely to be associated with a better outcome then prompt diagnosis would be worthwhile. As newer and more complex (and expensive) treatments are available for pulmonary hypertension then the greater is the need for assessment of their efficacy. Ambulatory pulmonary artery pressure monitoring offers a unique opportunity to assess the response to treatment in the circumstances in which a patient experiences symptoms as well as under conditions of controlled stress. Finally this new method of measurement may enable us to identify non-invasive methods of measurement of the pulmonary circulation which might be an advance on those widely available.

The pulmonary circulation is a stimulating and fast moving field; the emergence of effective treatments, improved understanding of the haemodynamics of raised PAP and the discovery of a possible genetic basis to abnormal responses in the pulmonary circulation demand improved pulmonary sphygmomanometers. Ambulatory pulmonary artery pressure monitoring is an important addition to this field.

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