INTRAVASCULAR ULTRASOUND AND MAGNETIC RESONANCE IMAGING OF THE PULMONARY ARTERIES IN PULMONARY HYPERTENSION

by

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Thesis submitted to the University of Edinburgh for the degree of MD, 1996

CONTENTS

ACKNOWLEDGEMENTS

I wish to acknowledge all those who helped with this thesis:

First, I would like to thank Professor Keith Fox, University of Edinburgh for his invaluable advice, encouragement and support. I would also like to thank Dr Gordon Williams for his support and supervision of the project at Killingbeck Hospital, Leeds. For additional help, advice and encouragement I am grateful to Dr David Dickinson, Dr John Gibbs and Dr John Parsons, Consultant Paediatric Cardiologists, Killingbeck Hospital, Leeds.

For help with the intravascular studies, special thanks to Dr Mike Blackburn, Dr Paul Brooksby and Mr Kevin Watterson, KIllingbeck Hospital, Leeds.

For help with the MRI studies, I wish to thank Dr M Sivananthran, Mr John Ridgeway and the staff of the MRI Department at St James' University Hospital, Leeds. Special thanks also to the patients and 'normal' volunteers who so enthusiastically participated in the MRI studies.

For help with the morphology studies I wish to thank Professor Robert Anderson and Dr Leon Gerlis, National Heart and Lung Institute, London, both for advice and help with preparation of the specimens. Thanks also to Professor Sheila Haworth, Great Ormond Street, London for helpful advice at

the outset of the study. Special thanks to Mrs Helena Wright, Killingbeck Hospital, who so patiently and expertly prepared all the histological specimens for me.

For help with preparation of the illustrations, I wish to thank Mrs Helena Wright, Dr Mike Blackburn, Mansfield Scientific, and the staff of the Medical Illustration Department at the Royal Hospital for Sick Children, Glasgow

For study leave to complete the writing of the thesis I am very grateful for the support of Dr Alan Houston, Dr Bill Doig and Dr Neil Wilson, Consultant Paediatric Cardiologists, Royal Hospital for Sick Children, Glasgow.

Finally, I would like to Acknowledge the financial support of the Children's Heart Surgery Fund without whom this thesis would not have been possible.

ABSTRACT

Two relatively new techniques by which the pulmonary arteries can be imaged in life are intravascular ultrasound and magnetic resonance imaging. The main aim of this thesis is to describe the changes which are detectable on intravascular ultrasound and magnetic resonance imaging in patients with pulmonary hypertension and to determine whether these imaging modalities could be of use for the clinical assessment of the condition.

Intravascular ultrasound was performed in 10 young adults with Eisenmenger's Syndrome and 4 infants with pulmonary hypertension secondary to a left to right shunt. Vasodilator studies were performed in 5 of the patients with Eisenmenger's. The vessel wall appeared as a single echogenic layer in all patients, making it difficult to define or measure medial thickness with certainty. Morphological changes of intimal hypertrophy and atherosclerosis were evident in patients with Eisenmenger's whereas in the infants the intima appeared thin and smooth, typical of normal artery. The technique gave excellent definition of the vessel lumen allowing continuous measurement of changes in luminal dimensions in response to vasodilators.

MRI of the pulmonary arteries was performed in 11 patients with Eisenmenger's and 6 normal controls. In patients with pulmonary hypertension the pulmonary arteries were found to be dilated with reduced distensibility

when compared with normals. Calculations of Qp:Qs by MRI in patients with systemic to pulmonary shunts and pulmonary hypertension did not correlate well with values from cardiac catheterisation in all patients.

As intravascular and magnetic resonance imaging are confined to the elastic pulmonary arteries, quantitative morphological studies were peformed on 24 post mortem specimens of lungs from patients who had died with pulmonary hypertension to determine whether there was any correlation between changes in the elastic pulmonary arteries and severity of pulmonary vascular disease. When compared with normals there was medial thickening in those with pulmonary hypertension but this was of an insufficient degree to be detectable by current ultrasound catheters. There was no correlation between degree of medial thickening in the elastic pulmonary arteries and severity of pulmonary vascular disease but intimal thickening and atherosclerosis were evident in those with more advanced disease.

In conclusion, magnetic resonance imaging was found to have limited role in the assesssment of pulmonary hypertension but with new technical developments could become a non-invasive method of studying pulmonary hypertension in the future. The morphological changes detectable by intravascular ultrasound tend to be in severe disease only but the technique provides a unique method of studying pulmonary vascular reactivity in life.

SUMMARY

A perplexing problem in congenital heart disease is that of pulmonary hypertension and the development of pulmonary vascular disease in patients with left to right shunts. First, the pathogenesis and physiology of pulmonary vascular disease is poorly understood and most of our understanding of the development and progression of the disease has come from the study of lung biospies. Second, the accurate assessment of the severity and reversibility of pulmonary vascular disease in life is limited and largely inferred from measurements made by methods such as Doppler or angiography. Third, our ability to modify the disease remains poor.

The study of the pathophysiology of pulmonary hypertensive vessels in life has been hindered by difficulty in imaging the vessels. The main method of imaging the pulmonary vessels in life remains angiography which merely provides a sillouette of the pulmonary tree.

Pulmonary vascular disease is essentially a disease of the peripheral vessels but post mortem studies show that hypertensive induced intimal and medial hypertrophy also occur in the larger elastic pulmonary arteries as well as in the peripheral vessels. Two relatively new techniques by which the elastic pulmonary arteries can be imaged in life are intravascular ultrasound and magnetic resonance imaging. Intravascular ultrasound images the vessel wall

layers from within the vessel lumen, theoretically allowing imaging of changes in vessel wall morphology as well as assessment of vessel physiology. Magnetic resonance imaging has been established as an important clinical tool in the diagnosis of congenital heart disease, particularly for assessing the pulmonary arteries. Recent advances in magnetic resonance techniques have made it possible to evaluate vessel pulsatilty and flow, potentially providing a noninvasive means of studying pulmonary arterial pathophysiology in life.

The main aim of this thesis was to describe the changes which are detectable on intravascular ultrasound and magnetic resonance imaging in patients with pulmonary hypertension and to determine whether these imaging modalities could be of use in the clinical assessment of the condition.

Intravascular ultrasound was performed in 10 young adults with Eisenmenger's Syndrome and 4 infants with pulmonary hypertension secondary to a left to right shunt. Vasodilator studies were performed in 5 of the patients with Eisenmenger's. On intravascular imaging, the vessel wall appeared as a single echogenic layer in all patients, making it impossible to define or measure medial thickness with certainty. Morphological changes of intimal hypertrophy and atherosclerosis were evident in patients with Eisenmenger's, whereas in the infants the intima appeared thin and smooth, typical of normal artery. Intravascular ultrasound was found to give excellent definition of the vessel lumen allowing continuous measurement of changes in luminal dimensions in

response to vasodilators.

MRI of the pulmonary arteries was performed in 11 patients with Eisenmenger's and in 6 normal controls. In patients with pulmonary hypertension the pulmonary arteries were found to be dilated with reduced distensibilty when compared with normals. Calculations of Qp:Qs by MRI correlated well with values at catheterisation in only 5 out of 7 patients with systemic to pulmonary shunts and pulmonary hypertension.

In order to determine the relation between morphological changes in vessels amenable to intravascular ultrasound and severity of pulmonary vascular disease, quantitative morphological studies were peformed on 24 post mortem specimens of elastic pulmonary arteries from patients who had died with pulmonary hypertension. When compared with normals there was medial thickening of the elastic pulmonary arteries but this was of an insufficient degree to be detectable by current intravascular transducers. There was no correlation between degree of medial thickening and severity of pulmonary vascular disease. Intimal thickening and atherosclerosis were evident in those with more advanced disease.

In conclusion, magnetic resonance imaging has little role in the clinical assesssment of pulmonary hypertension at present but with new technical developments could become a non-invasive method of studying pulmonary

hypertension in the future. The morphological changes detectable by intravascular ultrasound tend to be in severe disease only but the technique provides a unique method of studying pulmonary vascular reactivity in life.

CHAPTER 1

INTRODUCTION

PULMONARY HYPERTENSION

Normal Pulmonary Arterial Pressures

Pulmonary hypertension simply refers to an elevation in pulmonary arterial pressures above the normal. In the adult, normal pulmonary arterial pressure is around 15-30mmHg systolic and 5-10mmHg diastolic, with a mean of approximately 15mmHg. In the foetus, pulmonary arterial pressures are considerably higher than in the newborn or adult.[1] Pulmonary arterial resistance falls dramatically at birth with the onset of ventilation. Immediately following birth, pulmonary arterial pressure is equal to systemic but within hours to days the pressure falls to near normal adult levels and usually within two weeks mean pulmonary arterial pressure has fallen to approximately 15mmHg,[2] although is slightly higher (around 25mmHg) at high altitudes.[3]

The Morphology of the pulmonary arteries

Although pulmonary arterial pressures fall relatively quickly following birth, it takes longer for the morphology of the pulmonary vessels to regress to the appearances seen in adult vessels.[4] Morphologically the pulmonary arterial tree can be divided into three types of vessel; elastic pulmonary arteries, muscular pulmonary arteries and pulmonary arterioles. The elastic pulmonary

arteries include the pulmonary trunk and main pulmonary arteries. They are distinguished by their relatively thin media which has scant smooth muscle and is made mainly of elastin arranged in a loose network. The elastic pulmonary arteries generally extend to the 7th generation in the pulmonary tree (the segmental artery is considered as the first generation).[5] The muscular pulmonary arteries are smaller (generally less than 500μm in the adult) and are distinguished by a media which consists mostly of smooth muscle with little elastin. The arterioles are thin-walled vessels, consisting of a single layer of endothelial cells on a basal lamina. Pulmonary arterioles are the smallest vessels in the arterial tree and accompany the alveoli. Under normal conditions they have no medial layer.

Changes in pulmonary arterial morphology following birth

At birth the media of the pulmonary trunk has a configuration similar to that of the aorta, with a thick medial muscular coat and a dense network of interlocking parallel elastic fibrils (Fig1). As pulmonary arterial pressure falls, the media of the pulmonary trunk becomes thinner and the elastic fibres lose their parallel configuration to become disarrayed in a loose network.[6,7]
The media of the muscular pulmonary arteries also is significantly thicker in the newborn than in the adult. The percentage of medial thickness to total vessel diameter in the newborn approaches 20% but by age two months has decreased to near adult values of 5-10%.[6,7]

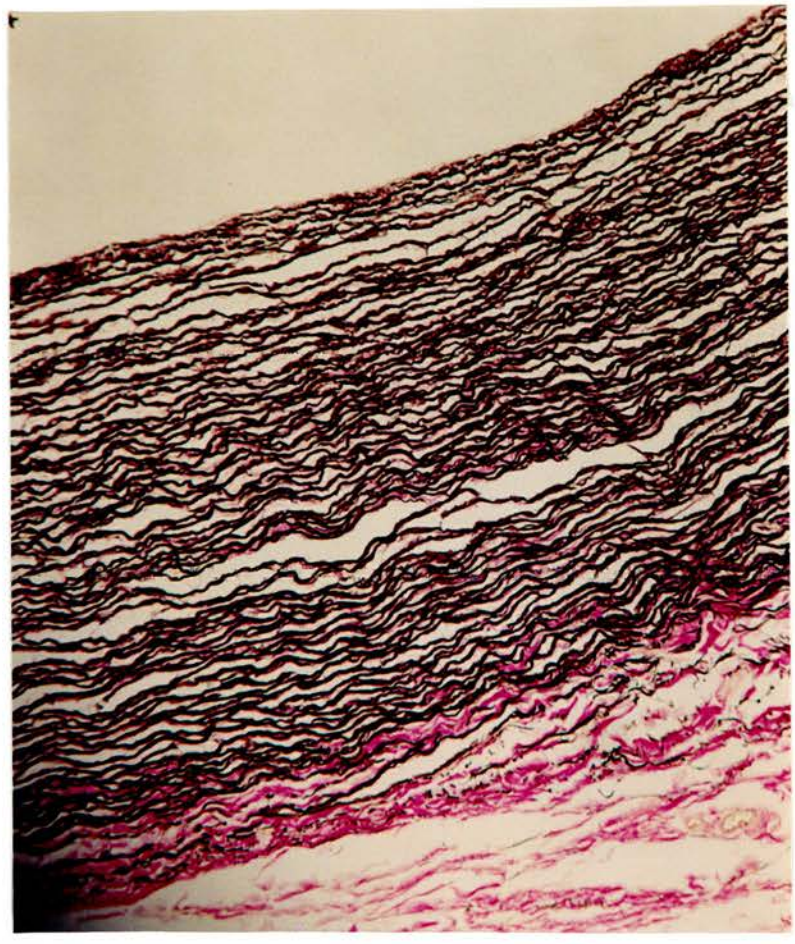


Figure 1.
Media of the pulmonary Trunk (x 25) (Elastin Van Giesen)
The media has a thick medial muscular coat with a dense network of interlocking parallel elastic fibrils.

Causes of pulmonary hypertension

Causes of pulmonary hypertension are listed in table A.

There are several causes of elevated pulmonary arterial pressures which can be divided into three broad categories:

1. Hyperdynamic pulmonary hypertension, secondary to increased pulmonary blood flow, e.g from a left to right shunt.

2. Passive pulmonary hypertension, secondary to increased back pressure from elevated pulmonary venous pressure or left atrial pressure, e.g mitral stenosis.

3. Reactive pulmonary hypertension secondary to an increase in pulmonary vascular resistance resulting from constriction of the muscular pulmonary arteries, e.g primary pulmonary hypertension.

It is rare to find any 'mechanism' of pulmonary hypertension in isolation. For example, in patients with left to right shunts, there are elements of hyperdynamic and reactive pulmonary hypertension and if left heart failure develops, also an element of passive pulmonary hypertension.

Table A
CAUSES OF PULMONARY HYPERTENSION

PASSIVE+/- REACTIVE
Left ventricular failure
Mitral valve disease
Cor triatriatum
Pulmonary veno-occlusive disease
Obstructed total anomalous pulmonary venous drainage

HYPERDYNAMIC +/- REACTIVE
Patent arterial duct
Ventricular septal defect
Atrial septal defect (rarely in childhood)
Total anomalous pulmonary venous connection (unobstructed)
Transposition of the great arteries
Truncus arteriosus
Common or single ventricle
High output states
Carcinoid syndrome

PURE REACTIVE PULMONARY HYPERTENSION
Cor pulmonale
Eisenmenger syndrome
Primary pulmonary hypertension

(From 'Heart Disease in Paediatrics', Jordan and Scott, Churchill Livingstone)

Pulmonary vascular disease

Elevated pressures in the pulmonary circulation have a deleterious effect on the pulmonary resistance vessels which can result in pulmonary vascular disease. Pulmonary vascular disease appears to develop most rapidly when the pulmonary circulation is subjected both to increased blood flow and elevated pressure, such as when there is a large ventricular septal defect, patent arterial duct, aortopulmonary window, truncus arteriosus or transposition of the great arteries.[8]

Pathology of pulmonary vascular disease

The major changes of pulmonary vascular disease occur in the small resistance vesels, i.e. the arterioles and muscular pulmonary arteries. In the initial stages there is thickening of the media of the muscular pulmonary arteries with extension of muscle distally into the pulmonary arterioles (Fig 2). This is followed by cellular intimal hypertrophy (Fig 3). As the disease progresses, cellular intimal proliferation gives way to intimal fibrosis, the vessel walls lose their elasticity and complex vascular lesions develop in the form of plexiform, angiomatoid, and cavernous lesions (Fig 4). The elevated pulmonary pressures result in chronic dilatation of these vessels, with eventual rupture of the thin walled arteriolar sacs, haemorrhage into alveoli and pulmonary haemosiderosis (Fig 5). The end result is a necrotising arteritis.[9]

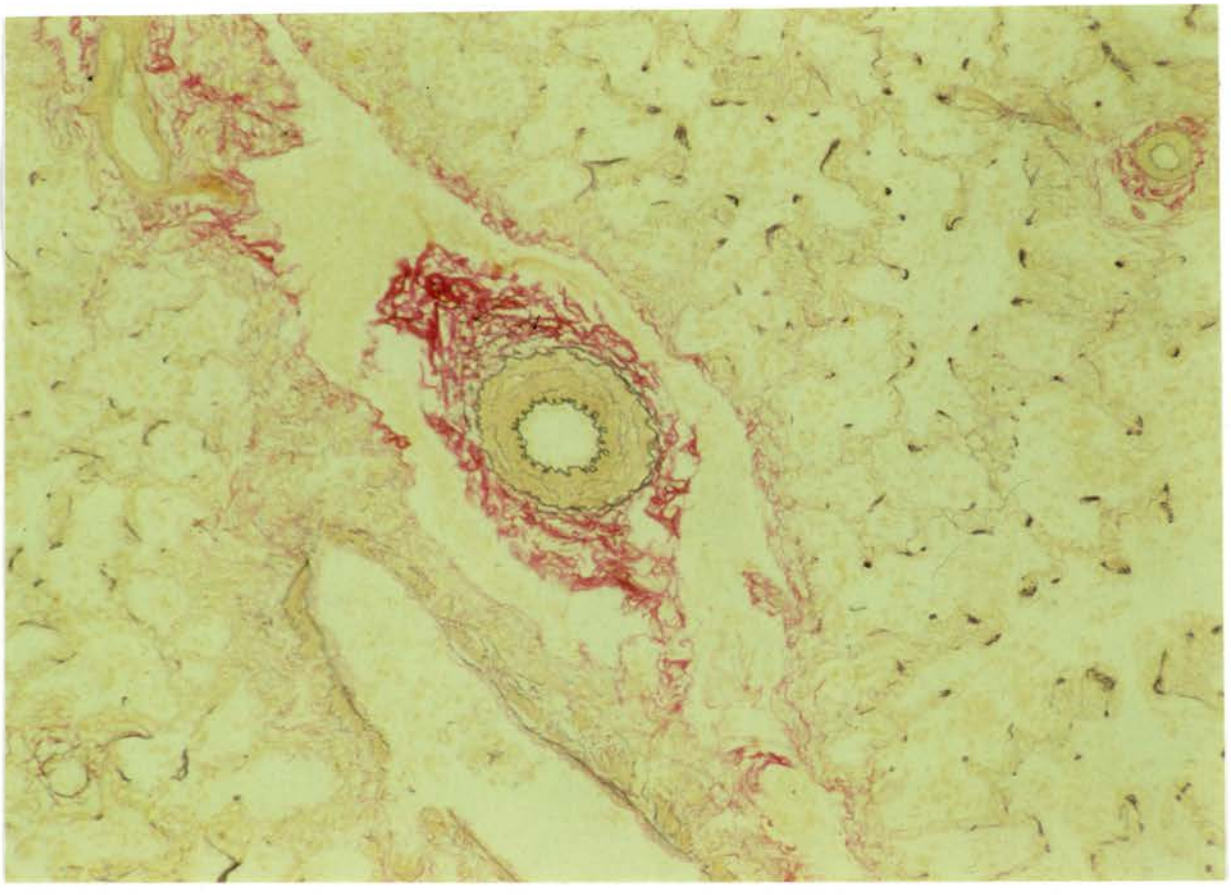


Figure 2.
Grade 1 pulmonary vascular disease (x 100) (Elastin Van Giesen)
There is medial thickening in the muscular pulmonary arteries.

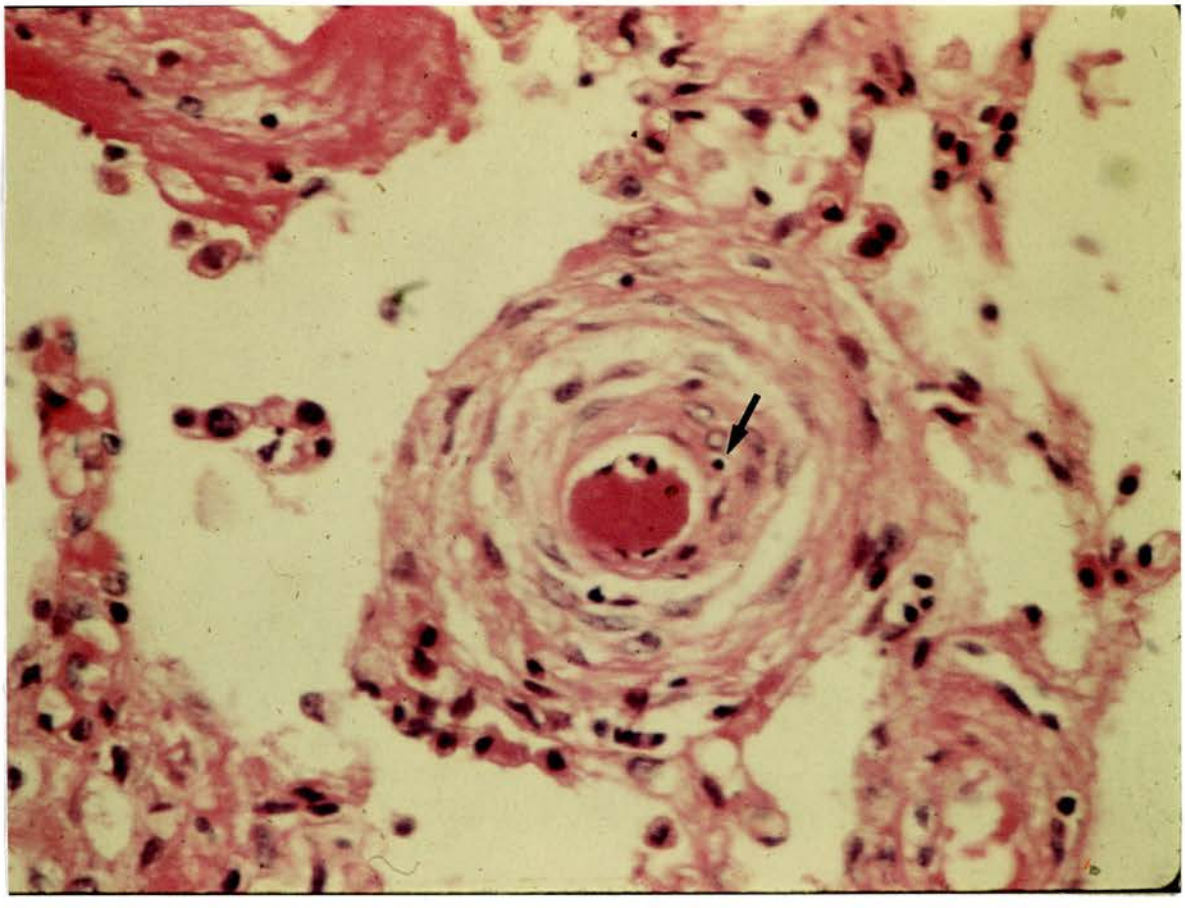


Figure 3.
Grade 2 pulmonary vascular disease. (x 200) (Haematoxylin and Eosin)
There is cellular intimal hypertrophy (arrow).

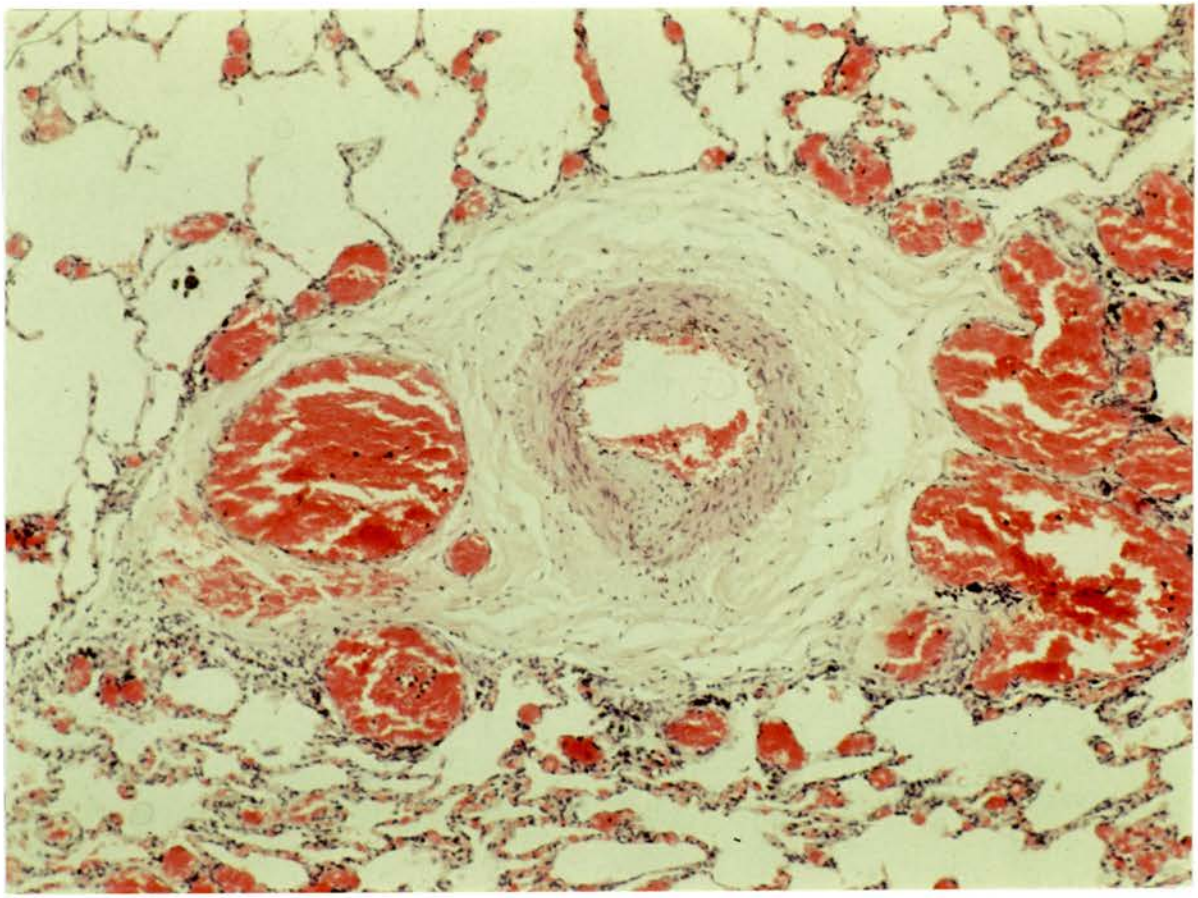


Figure 4.
Grade 4 pulmonary vascular disease. (x 100) (Haematoxylin and Eosin)
A Plexiform complex vascular lesion is shown.

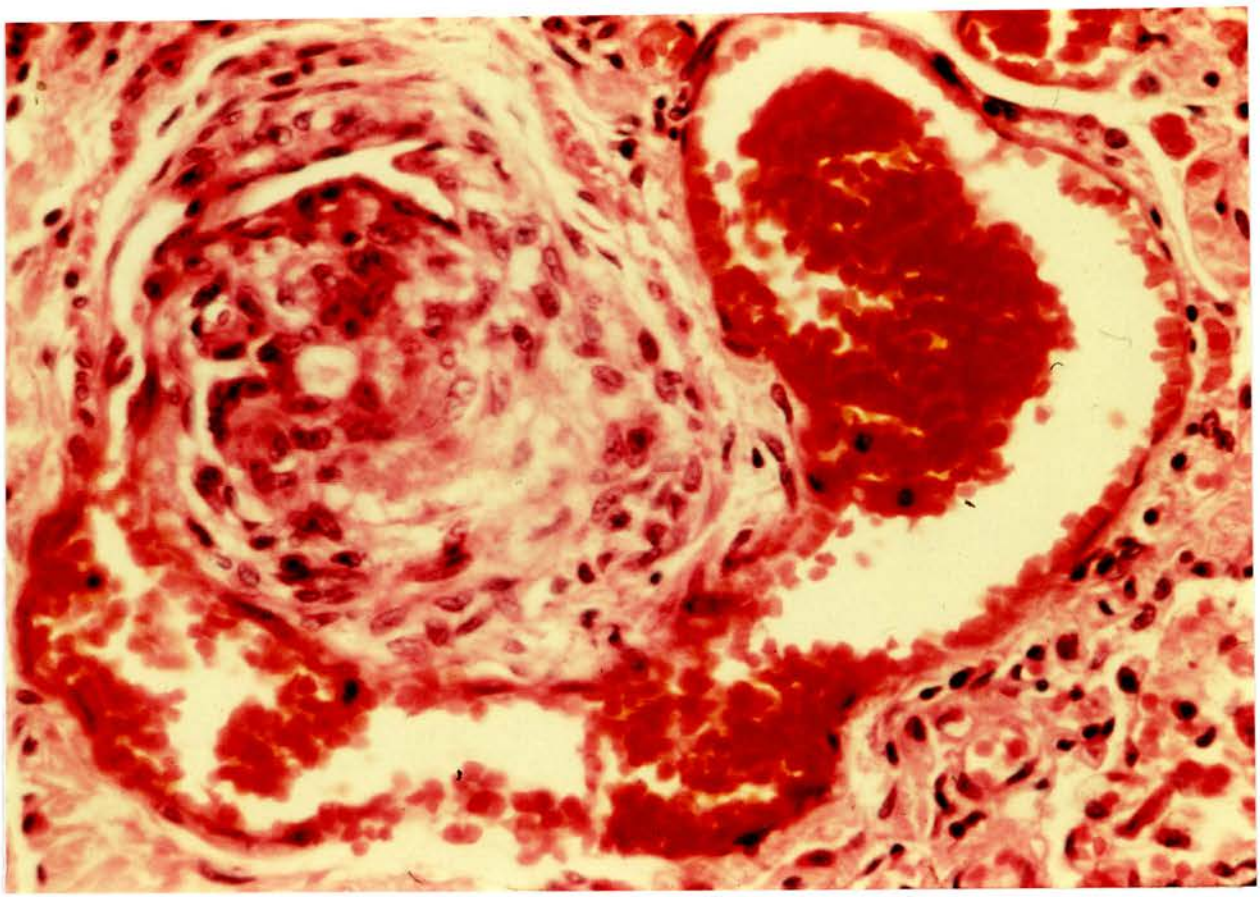


Figure 5.
End-stage pulmonary vascular disease (x200) (Haematoxylin and Eosin)
There is rupture of thin-walled arteriolar sacs, haemorrhage into alveoli and pulmonary haemosiderosis.

Morphology of the pulmonary trunk in pulmonary hypertension

Morphological changes are also evident in the pulmonary trunk in pulmonary hypertension. If pulmonary arterial pressures remain elevated after birth, the pulmonary trunk retains its thick muscular media as well as the parallel arrangement of the elastic fibres similar to that of the aorta, i.e. so-called 'aortification' of the pulmonary trunk.[6,7] If, however, pulmonary hypertension resolves following birth but then recurs later in life, the pulmonary trunk develops a thick medial muscular coat but the elastic fibres have had time to become disarrayed and have the normal 'adult' appearance.

Reversibilty of pulmonary vascular disease

One of the most crucial factors to be considered in the management of patients with left to right shunts is the progresssive nature of pulmonary vascular disease. If a defect is left uncorrected pathological changes can progress and become so advanced as to become irreversible. Closure of the defect at this stage can result in accelerated right heart failure. Assessment of the severity and reversibilty of pulmonary vascular disease is therefore of vital importance especially in the management of the older infant or child with a left to right shunt.

Heath Edwards grades

In an attempt to define the histological changes which correlate with clinically irreversible disease, Heath and Edwards in 1958, graded the histological

changes of pulmonary vascular disease from 1 to 6 according to increasing severity (Table B).[9] They found that the main histological features correlating with irreversibility were development of the complex vascular lesions and vessel dilatation (grade 4 in their grading system). The complex vascular lesions probably develop as the result of repeated microthrombosis and recanalisation of the arterioles. These plexiform lesions are proximal to most of the alveolar capillary bed and have a very high resistance to blood flow.

The rate at which pulmonary vascular disease develops may differ according to type of cardiac anomaly.[8] Whereas in an uncorrected large ventricular septal defect, irreversible vascular lesions may not develop until after the first few years of life, in infants with transposition of the great arteries and a ventricular septal defect, irreversible changes may develop as early as 2 months and almost always by 2 years. The reasons for this are unclear. In addition there are some patients with septal defects in whom pulmonary vascular resistance appears never to fall after birth and who never develop cardiac failure.[10]

Ventricular Septal Defects and Pulmonary Hypertension

Ventricular septal defects are the commonest of congenital heart lesions and can be used as a model to consider the development of pulmonary

Table B

HEATH-EDWARDS GRADES OF PULMONARY VASCULAR DISEASE

Grade 1

Thickening of the adventitia and media of the muscular pulmonary arteries with extension of muscle distally into the pulmonary arterioles which do not normally have a muscular layer.

Grade 2

Medial thickening as observed in grade 1 plus cellular intimal proliferation. In some cases the cellular intimal proliferation can be so marked as to occlude the arteriolar lumen.

Grade 3

Medial hypertrophy as observed in grade 1. The intimal cellular proliferation observed in grade 2 gives way to fibrosis. The changes of medial and intimal hypertrophy begin to extend into the larger muscular pulmonary arteries (100-500μm).

Grade 4

As a result of fibrosis the vessel intima loses its elasticity and complex vascular changes begin to develop in the form of plexiform, angiomatoid, and cavernous lesions.

Grade 5

At this stage the emphasis in histological features shifts from intimal and medial hypertrophy to vascular dilatation. The pulmonary arterioles and smallest muscular pulmonary arteries become greatly distended to form plexiform sacs with fragile walls. Chronic dilatation of the vessels occurs.

Grade 6

As a result of chronic dilatation, there is eventual rupture of the thin walled arteriolar sacs with haemorrhage into alveoli and pulmonary haemosiderosis. The end result is a necrotising arteritis.

vascular disease in individuals with left to right shunts. The development of pulmonary vascular disease in patients with a ventricular septal defect depends upon the size of the lesion and individual reactivity of pulmonary vessels. Approximately 50% of ventricular septal defects will close spontaneously or become smaller within the first few months or years of life.[11,12] In these patients pulmonary arterial medial thickening resolves and pulmonary vascular resistance decreases. In infants with large ventricular septal defects the pulmonary vascular resistance usually falls transiently after birth, resulting in an increase in left to right shunting and the development of heart failure. In most of those infants, there is a marked increase in the muscle mass of the small pulmonary arteries and this is associated with an increase in pulmonary vascular resistance.[13] If such large defects are left uncorrected, pulmonary vascular changes can progress.

Eisenmenger Syndrome

When the pulmonary vascular resistance becomes higher than the systemic vascular resistance there is shunt reversal and the patient becomes cyanosed. In 1987, Eisenmenger described the case of a patient who had been breathless and cyanosed since infancy and who died following massive haemoptysis at the age of 32.[14] At postmortem he was found to have a large ventricular septal defect. Eisenmenger realised that the pulmonary vascular resistance had been elevated but failed to identify this as the cause of the patient's right to left shunt and cyanosis. Since Eisenmenger's first case report the term

'Eisenmenger Complex' has been given to other patients with a ventricular septal defect and cyanosis secondary to shunt reversal.

In 1958, Paul Wood pointed out that other lesions resulting in left to right shunts could lead to an elevated pulmonary vascular resistance with eventual reversal of the shunt and cyanosis.[15] He defined such a combination as the Eisenmenger Syndrome. The natural history of the Eisenmenger Syndrome is one of increasing cyanosis and ultimately, heart failure. Patients usually survive to the third decade. Death is often sudden, from haemoptysis or syncope, the latter presumed to be secondary to arrhythmia or pulmonary hypertensive crisis. There is no known medical treatment to significantly influence the pulmonary vascular resistance in these patients. Surgical closure of the anatomical lesion responsible for the elevated pulmonary vascular resistance will only result in accelerated death from right heart failure. Cardiopulmonary transplant is the only therapeutic option currently available.

Clinical features of pulmonary hypertension

Clearly it is important to identify the presence of pulmonary hypertension before irreversible pulmonary vascular disease develops. The clinical signs of pulmonary hypertension include a prominent a-wave in the jugular venous pulse, a palpable right ventricular impulse at the left sternal edge and a loud pulmonary component of the second sound. A short ejection systolic murmur may be heard in the pulmonary area due to ejection of blood into the dilated

pulmonary artery. In some, an early diastolic murmur is audible down the left sternal border due to functional pulmonary regurgitation. The chest X-ray typically reveals a prominent right ventricle, a dilated pulmonary artery and pruning of the small peripheral vessels. On ECG there are peaked p-waves due to right atrial hypertrophy and tall R waves in V4R and V1, indicative of right ventricular hypertrophy.

Assessment of pulmonary hypertension and pulmonary vascular disease

The earliest and most established method of measuring the severity of pulmonary hypertension is cardiac catheterisation during which pulmonary arterial pressures can be measured and pulmonary vascular resistance calculated from the following equation:

Pulmonary vascular resistance =

$$\frac{\text{Pulmonary arterial pressure - left atrial pressure}}{\text{Pulmonary blood flow}}$$

where, *Pulmonary blood flow* =

$$\frac{\text{Pulmonary oxygen uptake}}{\text{Pulmonary venous oxygen content - pulmonary arterial oxygen content}}$$

Unfortunately the increase in pulmonary vascular resistance does not always accurately correlate with the severity or reversibilty of pulmonary vascular

disease which is the most important information required to determine the feasibilty of surgery. There is some evidence that pulmonary vascular disease is likely to be reversible if pulmonary vascular resistance is labile and falls during administration of vasodilators such as Oxygen and Prostacyclin, the assumption being that if the only structural change in the pulmonary vasculature is muscle hypertrophy, the circulation should still respond to vasodilators.[16] The ability of this technique to accurately predict the reversibility of pulmonary vascular disease, however, is poor.

Wedge Angiography

Wedge angiography has been used as a method to improve the correlation between structural and functional changes. In the normal lung the pulmonary arteries should taper towards the periphery but in elevated pulmonary vascular resistance, the vessels taper over a shorter distance (so-called 'pruning'). In a study by Rabinovitch and colleagues in 1978, the rate of tapering was found to correlate both with pulmonary haemodynamics at cardiac catherisation and severity of pulmonary vascular disease at biopsy.[17] The problem with wedge biopsy is that although it identifies patients with advanced pulmonary vascular disease it cannot differentiate between patients with less severe stages of diease who are potentially operable.

Doppler

The relatively recent introduction of Doppler into clinical cardiology has allowed

non-invasive estimation of pulmonary arterial pressures from measurement of tricuspid and pulmonary regurgitant jets. In pulmonary hypertension the velocity of the regurgitant jets is high. The pressure drop ($P_1 - P_2$) across the tricuspid valve can be calculated if the velocity of the jet (V) is measured in metres/second and the modified Bernoulli equation applied:[18]

$$P_1 - P_2 = 4V_{max^2}$$

Provided there is no pulmonary artery stenosis the right ventricular pressure can be assumed to equal pulmonary arterial pressure.[19]

Right atrial pressure is normally 5-10mmHg. If right atrial pressure is added to the pressure drop across the tricuspid valve an estimation of right ventricular systolic pressure and thus systolic pulmonary arterial pressure can be obtained.[20] Likewise by measuring the maximum velocity of the pulmonary regurgitant jet and applying the Bernoulli equation it is possible to obtain an estimation of pulmonary diastolic pressure. [21] Unfortunately, not all patients have measurable tricuspid or pulmonary regurgitation. [22] In addition, Doppler can only estimate pulmonary arterial pressure and not the severity or reversibility of pulmonary vascular disease.

Lung Biopsy

The gold standard for assessing the severity of pulmonary vascular disease is open lung biopsy where the pathological changes of pulmonary vascular disease can be observed and graded. A major drawback is that surgery is required and the changes may be patchy so that a single biopsy may not be

representative of the whole lung.[23] In addition, lung biopsy provides limited information regarding changes in vessel physiology secondary to pulmonary hypertension.

In-vivo Study of Pulmonary Hypertension

At present there is no satisfactory method of studying pulmonary arterial morphology and physiology in life. New in-vivo methods of investigating the pulmonary vessels in pulmonary hypertension would be useful, not only to help in the clinical assessment of disease but also to improve our understanding of the pathogenesis and physiology of pulmonary vascular disease and to aid research into identifying means of modifying the disease.

There are two relatively new imaging techniques which allow dynamic imaging of the pulmonary vessels; intravascular ultrasound and magnetic resonance imaging. Initial studies have suggested that these techniques could provide a means of evaluating pulmonary hypertension in life but to date their use in patients with pulmonary hypertension has not been established. [24,25]

The purpose of this thesis is to evaluate the use of intravascular ultrasound and magnetic resonance imaging in the study of pulmonary hypertension.

Aims

The aims of this thesis are as follows:

1. To evaluate the use of intravascular ultrasound as a method of imaging the morphological changes which occur in pulmonary hypertension.

2. To evaluate the use of intravascular ultrasound to study the effect of pulmonary vasodilators in pulmonary hypertension.

3. To describe the changes detectable by MRI of the pulmonary arteries in pulmonary hypertension.

4. To determine the ability of MRI to measure pulmonary arterial flow and Qp:Qs in patients with systemic to pulmonary shunts.

5. As intravascular and magnetic resonance imaging are confined to the elastic pulmonary arteries, to quantify the morphological changes in the elastic pulmonary arteries in pulmonary hypertension and establish their relation to the severity of pulmonary vascular disease.

6. To determine whether intravascular ultrasound and MRI could be of clinical use in the assessment of pulmonary hypertension.

CHAPTER 2

INTRAVASCULAR ULTRASOUND

History

Intravascular ultrasound is not a new concept. It was first described in 1960 by Cieszynski who introduced a single element catheter into the hearts of dogs to measure cardiac chamber sizes.[26] Similar studies were performed by a number of other researchers[27-29] but then interest waned somewhat in the technique, probably due to the development of transthoracic and transoesophageal echo. It has only been in the past five to ten years that there has been renewed interest in intravascular imaging, largely as a result of the increase in therapeutic intervention of coronary artery disease bringing with it the need to define as clearly as possible the nature and extent of atherosclerosis.[30]

Angiography versus ultrasound

Although angiography is considered the current gold standard for studying atherosclerosis, the technique only gives a sillouette of the vessel wall. As a result it may miss early disease, may underestimate the extent of disease and gives little information regarding plaque type and morphology or the effects of interventions on the vessel wall.[31,32] Intravascular ultrasound, on the other hand, potentially provides an ideal method for studying atherosclerosis. This is

because intravascular ultrasound images the vessel from within the vessel lumen itself, potentially allowing accurate measurement of luminal dimensions, of plaque size and morphology, of vessel wall morpholgy and also of the effects of interventions on the vessel wall itself.[33,34]

Intravascular Ultrasound Catheters

The concept of intravascular imaging is simple, i.e. a cardiac catheter with an ultrasound transducer built into the tip. Technically, however, such a catheter is difficult to produce as it must be small, flexible, easy to manipulate, but yet produce good quality images. It is largely thanks to the pioneering work of Bom and his colleagues in Rotterdam that we have the ultrasound catheters that are commercially available today (Fig 6).[35] These ultrasound catheters look very similar to ordinary cardiac catheters and are available in different sizes, ranging from 3 French (i.e. approximately 1mm in diameter) to 9 French. The ultrasound transducer is situated just proximal to the tip. The transducer itself may be mechanical, consisting of a single element with a rotating mirror, or be phased array, consisting of a circular array of elements built around the tip. In the mechanically rotated catheters the drive shaft is found within the catheter body itself. The non-imaging end connects to an ultrasound machine which has been adapted for use with intravascular imaging.

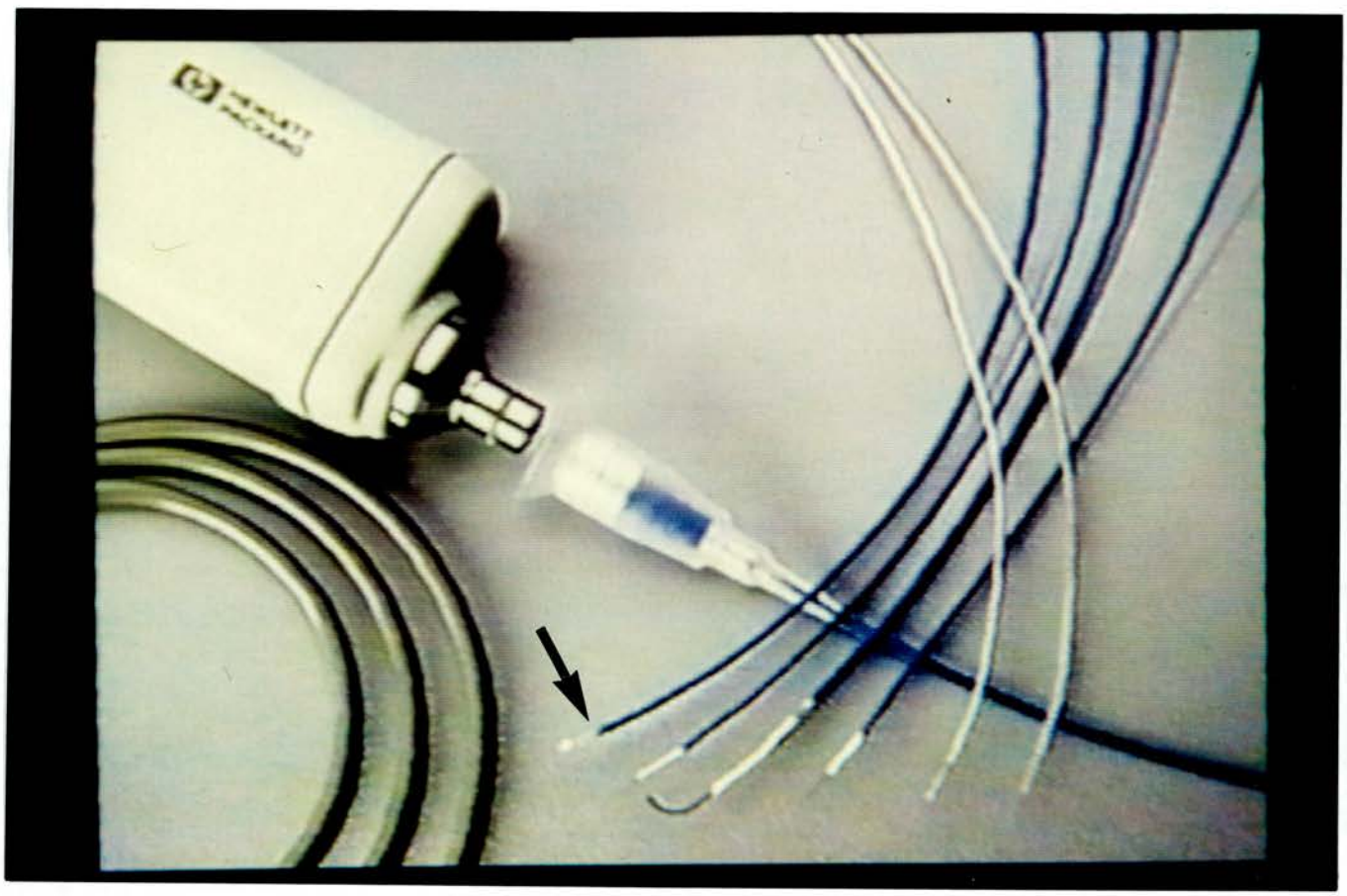


Figure 6.
Intravascular ultrasound catheters.
Catheter sizes range from 3 French to 9 French and frequency of transducer from 12.5MHz to 30MHz. The ultrasound tranducer is situated just proximal to the tip (arrow), the drive shaft is found within the catheter body and the non-imaging ends fit onto an ultrasound machine adapted for use with intravascular imaging.

The catheters are available in different frequencies; mainly 30MHz, 20MHz and 12.5MHz. The higher the transducer frequency the better the near resolution but less field of depth. The higher frequency probes, therefore, are most suited to studying the smaller vessels, whereas the lower frequency catheters are more suited to studying larger vessels or for intracardiac imaging.[36]

Intravascular Ultrasound Imaging

The catheters used for the studies described in this thesis were all mechanically rotated transducers (Mansfield Scientific, Boston USA). Figure 7 shows a diagramatic representation of such a catheter. To prepare the catheter for use it is necessary to eliminate the air between the ultrasound transducer and the catheter wall. This is achieved by injecting water into the port around the transducer. To ensure all the air is eliminated the catheter tip is twirled several times. The catheter is then ready for use and is introduced into the patient in a manner similar to introducing any cardiac catheter. To assist with catheter guidance and manipulation, some of the ultrasound catheters have a monorail for use with a guide wire, otherwise they may be introduced through a long sheath.

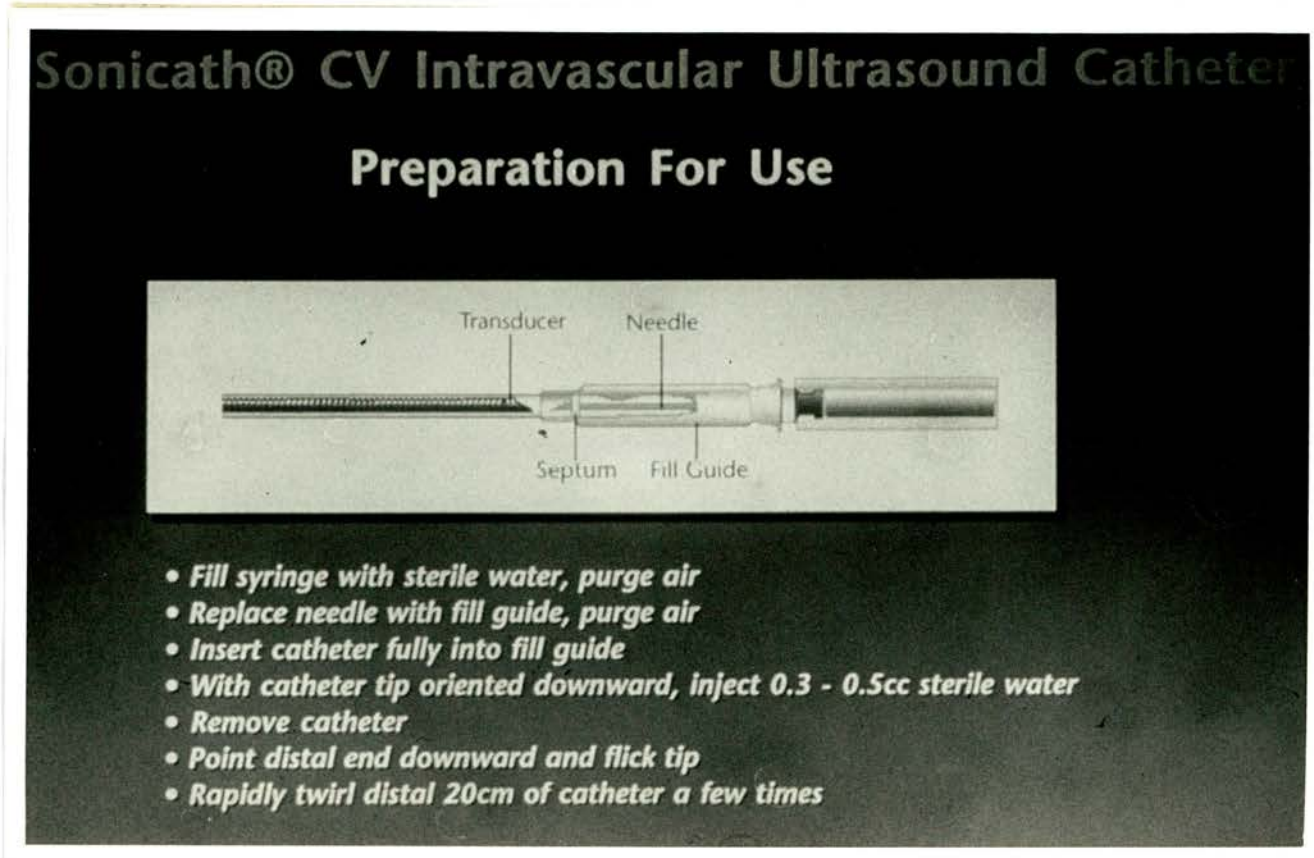


Figure7.
Diagram of an intravascular ultrasound catheter.
Water is injected into the port around the transducer to eliminate air.

Intravascular Ultrasound of a Muscular Artery

Imaging begins as soon as the ultrasound catheter is introduced into the patient. Figure 8 shows a typical ultrasound image of a muscular artery. Characteristically on intravascular imaging of muscular arteries the vessel wall has a trilayer appearance, consisting of an inner echodense ring, an outer echodense ring and a middle echolucent ring.[37,38] On initial in-vitro histological studies these three layers were identified as the three histological layers of the vessel wall, i.e the intima, the media and the adventitia.[39,40] It is believed that it is the elastin within the vessel wall which is echoreflective, thus the media (which is relatively elastin poor compared to the elastin rich intima and adventitia) is echolucent.[40,41] This theory is supported by the observation that the walls of elastic arteries, which have a relatively elastin rich media with scant smooth muscle, tend to appear as a single echodense ring on intravascular imaging rather than a three layered ring.[41]

The precise nature of the trilayer appearance is, however, controversial. Certainly it is not always seen on ultrasound imaging of muscular arteries in life, especially in younger patients. Some would argue that the process of tissue fixation of vessels for in-vitro histological studies alters the ultrasound characteristics of the vessel walls allowing a trilayer appearance to be seen.[42] Others argue that the trilayer apearance seen in life may simply be due to differences in mobility in different parts of the vessel wall resulting in reflection of echos at the interface of changes in mobility. [43] This theory would help

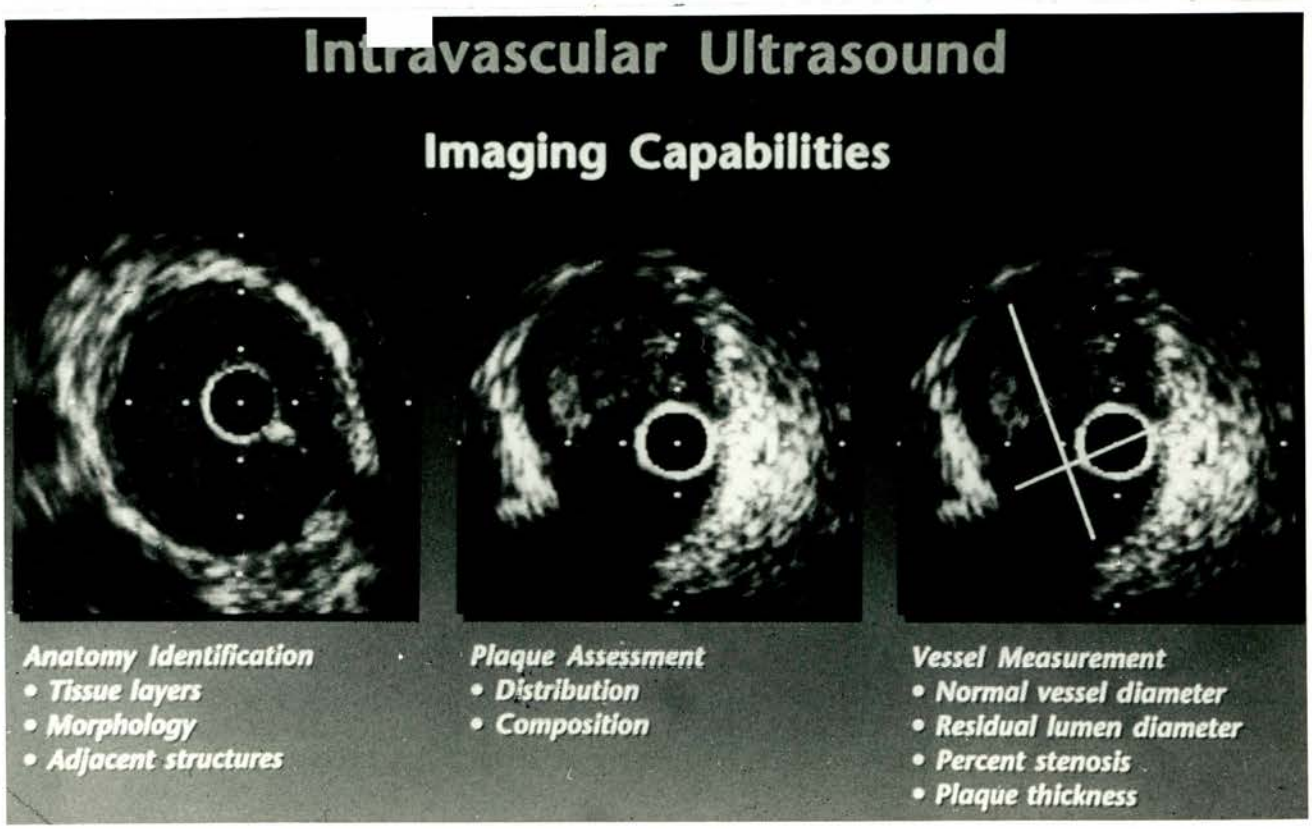


Figure 8.
Ultrasound image of a muscular artery (right). The ultrasound catheter is seen as a small circle within the vessel lumen. The outer white ring is the vessel wall and is seen here to have the characteristic trilayer appearance. The middle and left image show an atheromatous plaque.

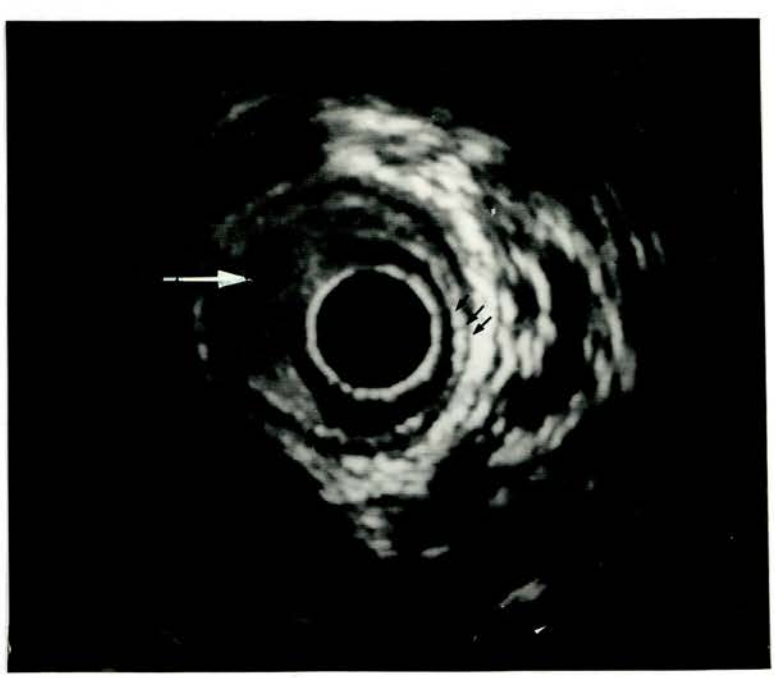


Figure 9.
Ultrasound image of crescentic atheromatous plaque (white arrow). The vessel wall has a trilayer appearance, consisting of an inner and outer echodense ring separated by a middle echolucent ring (black arrows).

explain the observation that the trilayer appearance is more commonly seen in vessels of older patients or in patients with diseased vessels who are more likely to have areas of altered compliance in the vessel wall. [44]

The precise nature of the trilayer appearance therefore remains controversial but there is agreement that intravascular ultrasound allows accurate measurement of luminal dimensions and visualisation of the intimal surface, thus providing a unique technique for studying atherosclerosis.[45,46]

Imaging of Atheroma

Figure 9 shows an intravascular image of an atheromatous plaque. Again the ultrasound catheter can be seen as a small echodense ring in the middle of the vessel lumen. The vessel wall is the outer white ring and in this image is seen as a trilayered structure, consisting of inner and outer echodense rings separated by a middle echolucent ring. These three layers may represent the three layers of the vessel wall. In addition a rather homogenous crescentic shaped mass can be seen impinging upon the vessel lumen and this is an atherosclerotic plaque. In this instance the plaque appears to consist of fibro-fatty material with very little calcium. It can be appreciated that with intravascular ultrasound it is possible to obtain accurate measurements of luminal diameter, plaque size, residual luminal diameter and percent stenosis as well as determine plaque type and morphology.

There have been numerous studies evaluating the use of intravascular ultrasound in assessing atherosclerosis and in 1991 it was estimated that over 140 centres throughout the United States and Europe were using the technique for clinical applications.[47] It is now established that with intravascular ultrasound it is possible to detect early disease which may be missed by angiography;[48] to measure the extent and severity of atherosclerosis often more accurately than by angiography;[49] and to evaluate the effects of interventions on atheromatous plaques and the adjacent wall which may not be appreciated by angiography.[50] As a result some enthusiasts have suggested that the technique should replace angiography as the gold standard for studying atherosclerosis.[51]

Whereas it is unlikely that intravascular ultrasound will replace angiography for the routine investigation of coronary artery disease, it is proving to be a useful adjunct to angiography in assessing plaque regression,[52] determining the suitability of different lesions for intervention, evaluating the effects of intervention,[53] and clarifying diagnosis in cases where coronary artery status remains unclear despite angiography.[49]

INTRAVASCULAR ULTRASOUND IN CONGENITAL HEART DISEASE

In contrast to the numerous studies in coronary artery disease there have been very few studies of the use of intravascular ultrasound in congenital heart disease. Most of the results of these studies have been published only in abstract form which probably witnesses to the rather disappointing findings. There are, however, four potential areas of application for intravascular ultrasound in congenital heart disease:

In studying:-

1. Intracardiac structures
2. Vascular interventions
3. Diseases of the pulmonary arteries
4. Endothelial function and vascular reactivity.

1.Intracardiac Imaging

The first 2-dimensional intracardiac ultrasound imaging was performed in the hearts of dogs using a 5 MHz transoesophageal probe.[54] Not surprisingly, using this probe it was possible to obtain excellent images of intracardiac structures, including a four chamber view and clear images of the valves, the outflow tracts and the coronary sinus. This raised hopes that intracardiac imaging held potential for guiding interventions within the heart, including closure of septal defects and radiofrequency ablations.[55,56]

Obviously it is not feasible to use transoesphageal probes in the hearts of humans, and therefore 20 MHz and 12.5 MHz ultrasound catheters have been employed.[57,58] These studies report that although it is possible to image intracardiac structures there are problems with limited depth of field and difficulty in maintaining stability of the catheter. [24,59]

During the period of research for this thesis, intracardiac ultrasound was performed in 12 young adults (aged 16-35) with congenital heart disease who were undergoing diagnostic catheterisation. 10 of the young adults were also undergoing pulmonary intravascular imaging and the intracardiac studies were performed at the same time. (See Chapter 3 and Table C, p66) The other 2 patients comprised a 19 year-old male with pulmonary arterial stenosis following previous repair of Tetralogy of Fallot and a 16-year old female with pulmonary atresia and ventricular septal defect. Informed consent was obtained from the patients prior to commencing the studies. 6 French, 12.5MHz mechanically rotated ultrasound catheters (Mansfield Scientific) were used for the intracardiac studies. Following the diagnostic catheter procedure, the femoral venous sheath was exchanged for an 8 French, long biopsy sheath. The biopsy sheath was introduced into the right atrium and the ultrasound catheter passed through the sheath and into the heart. Images were recorded with the catheter in the ventricle and while the catheter was being withdrawn through the tricuspid valve into the right atrium and inferior vena cava. The procedure was uncomplicated in all patients.

In all patients, despite the long sheath, it was difficult to keep the catheter stable within the chambers of the heart; the catheter tended to move widely to and fro with each heart beat, distorting images. Due to the limited depth of field of the transducer it was not possible to image the cardiac chambers or valves in their entirety.

Fig 10 shows an intracardiac ultrasound image of an atrioventricular septal defect. The catheter can be seen in the chamber of the right ventricle. the outer echogenic 'ring' is the surrounding myocardium and the gap in the myocardium represents part of the atrioventricular septal defect. The ventricle could not be imaged in its entirety.

Fig 11 shows an intracardiac image of the right ventricular outflow tract in a 19 year old male with a previous repair of Tetralogy of Fallot. The transannular patch is brightly echogenic. One of the leaflets of the pulmonary valve can be seen as an echogenic line but the valve could not be imaged in its entirety.

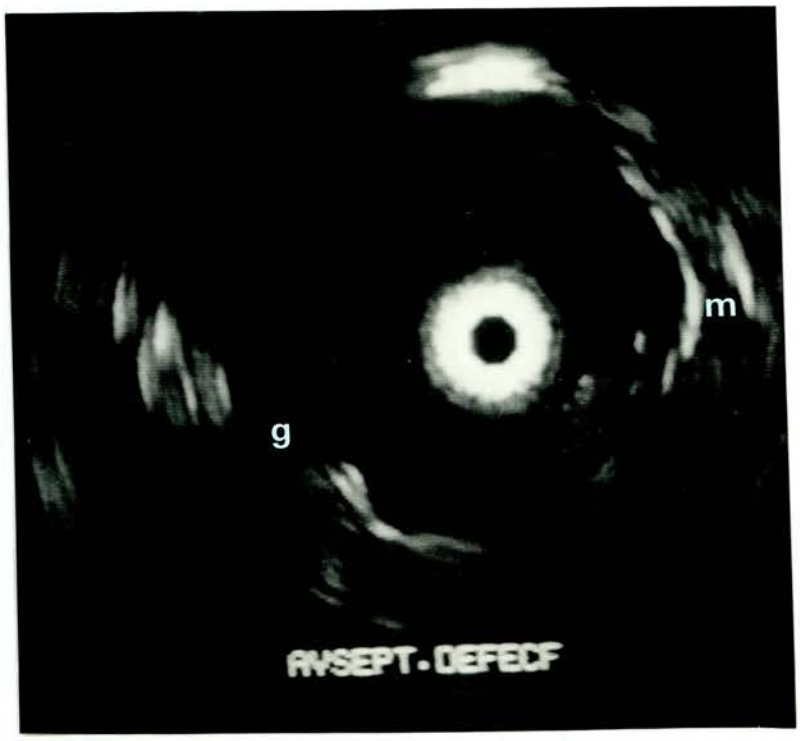


Figure 10.
Intracardiac Image of an atrioventricular septal defect.
The catheter can be seen in the chamber of the ventricle. The outer white 'ring' is the myocardium (m) and the gap in the myocardium (g) represents part of the atrioventricular septal defect.

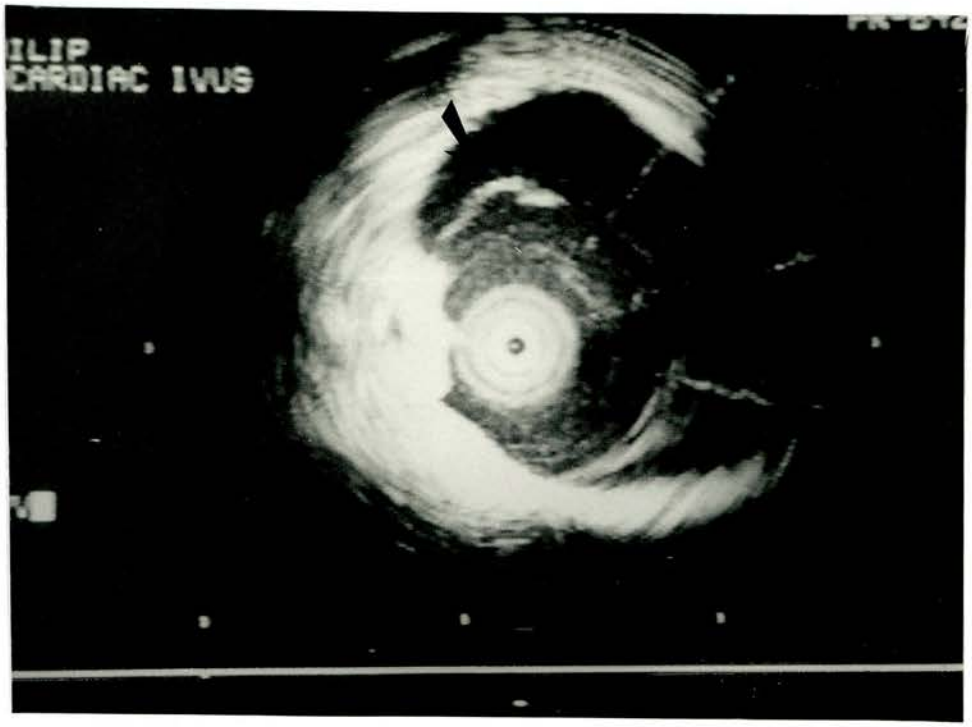


Figure 11.
Intracardiac image of the right ventricular outflow tract.
The transannular patch is brightly echogenic and calcified. One of the leaflets of the pulmonary valve can be seen as a thin echogenic line (arrow).

On analysis of the small group of patients studied, intravascular ultrasound proved more expensive, more invasive, less readily available, had less field of depth, produced poorer images and was more difficult to manipulate when compared with transthoracic and transoesophageal echocardiography for imaging of congenital heart defects. Certainly at present, it is difficult to see a clear role for intracardiac imaging of structural defects.

2. Vascular Interventions

Over the past decade, there has been rapid development of techniques and applications for interventional catheterisation. The main application has been in the management of atheroma which may be treated by techniques including angioplasty, atherectomy or stenting. In Paediatric Cardiology, atheroma is rarely a problem, but vessel stenoses, such as those which occur in the pulmonary arteries or aorta may be improved by angioplasty or stenting.[60,61]

Intravascular Ultrasound to Monitor Interventions of Atheroma

Intravascular ultrasound provides a unique method of monitoring the effect of catheter interventions on the vessel wall in life. Prior to intervention, the technique provides information regarding the severity of stenosis, the nature of the stenosis and the suitability for different types of intervention. Following intervention, the success of the procedure, the creation of any intimal tearing and the development of complications can be evaluated. Finally, perhaps if we understood more fully the nature of the lesion inflicted on the vessel wall, the

risk of restenosis could be predicted.[62,63]

There have been many studies of the use of intravascular ultrasound in monitoring interventions of atherosclerosis.[53,62-65] Fig.12 shows an atheromatous plaque as visualised by angiography and intravascular ultrasound. Prior to angioplasty the narrowing caused by the plaque can be appreciated on angiography but with intravascular ultrasound information can also be obtained about plaque morphology and percent stenosis. Following angioplasty, an improvement in luminal diameter can be seen on angiography, but with intravascular imaging it is possible to determine the effects on the atheromatous plaque.

Stent Deployment

Perhaps the most useful application of intravascular ultrasound in interventional catheterisation has been in assessing the deployment of stents. In 1994, Colombo and colleagues demonstrated that over 80% of stents may not be fully deployed when visualised by intravascular ultrasound and that inadequate stent deployment is frequently not detected by angiography.[66]

Fig.13 shows an intravascular image of a stent within a vessel. The catheter is seen as a small circle within the vessel lumen. The struts of the stent are brightly echogenic and there is a gap between the struts and the vessel wall. It is easy to appreciate that the stent is not fully deployed. Following further

balloon dilatation, the stent is seen to be closely adherent to the vessel wall and is now fully deployed.

Hybrid Catheters

The ability of intravascular ultrasound to monitor interventions has led to attempts to develop so called 'hybrid' catheters. Hybrid catheters essentially consist of a combination of an interventional catheter together with an ultrasound catheter.[67] Examples include the balloon ultrasound imaging catheter (BUIC), atherectomy ultrasound imaging catheter and laser ultrasound imaging catheter. [64,68,69] The BUIC has been the most successful to date. Fig.14 shows a diagramatic representation of a BUIC, which consists of a balloon catheter with an ultrasound catheter through the middle. Although the balloon material attenuates ultrasound to some degree it is not marked and using this catheter it is possible to image the site and size of stenosis, watch the vessel being dilated, and image the success and damage afterwards, including the degree of luminal widening and whether there has been any intimal tearing.

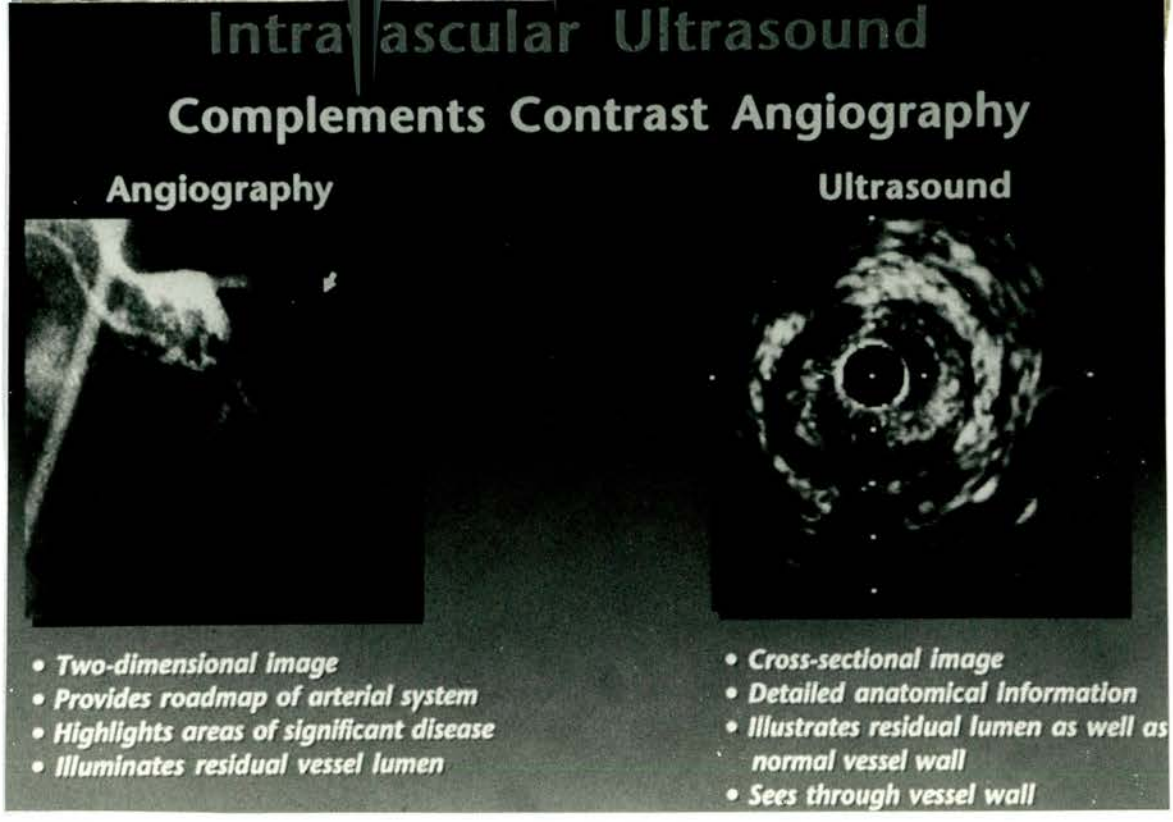


Figure 12.
Comparison of intravascular ultrasound with angiography. Whereas angiography shows the stenosis, intravascular ultrasound also gives information about plaque morphology, percent stenosis and the effects of angioplasty on the vessel wall.

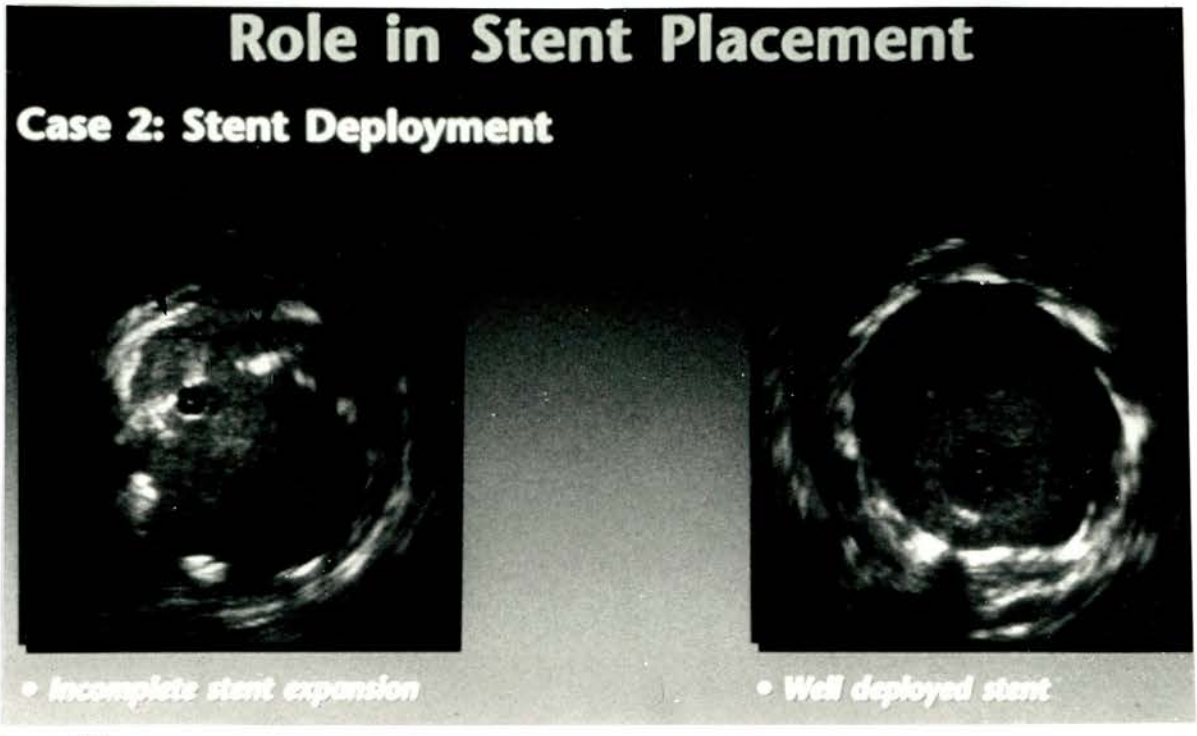


Figure 13.
Intravascular ultrasound of stent deployment.
The image on the left shows incomplete expansion of the stent (vessel wall - straight arrow, border of stent - curved arrow). Following further angioplasty, intravascular ultrasound confirms full expansion of the stent.

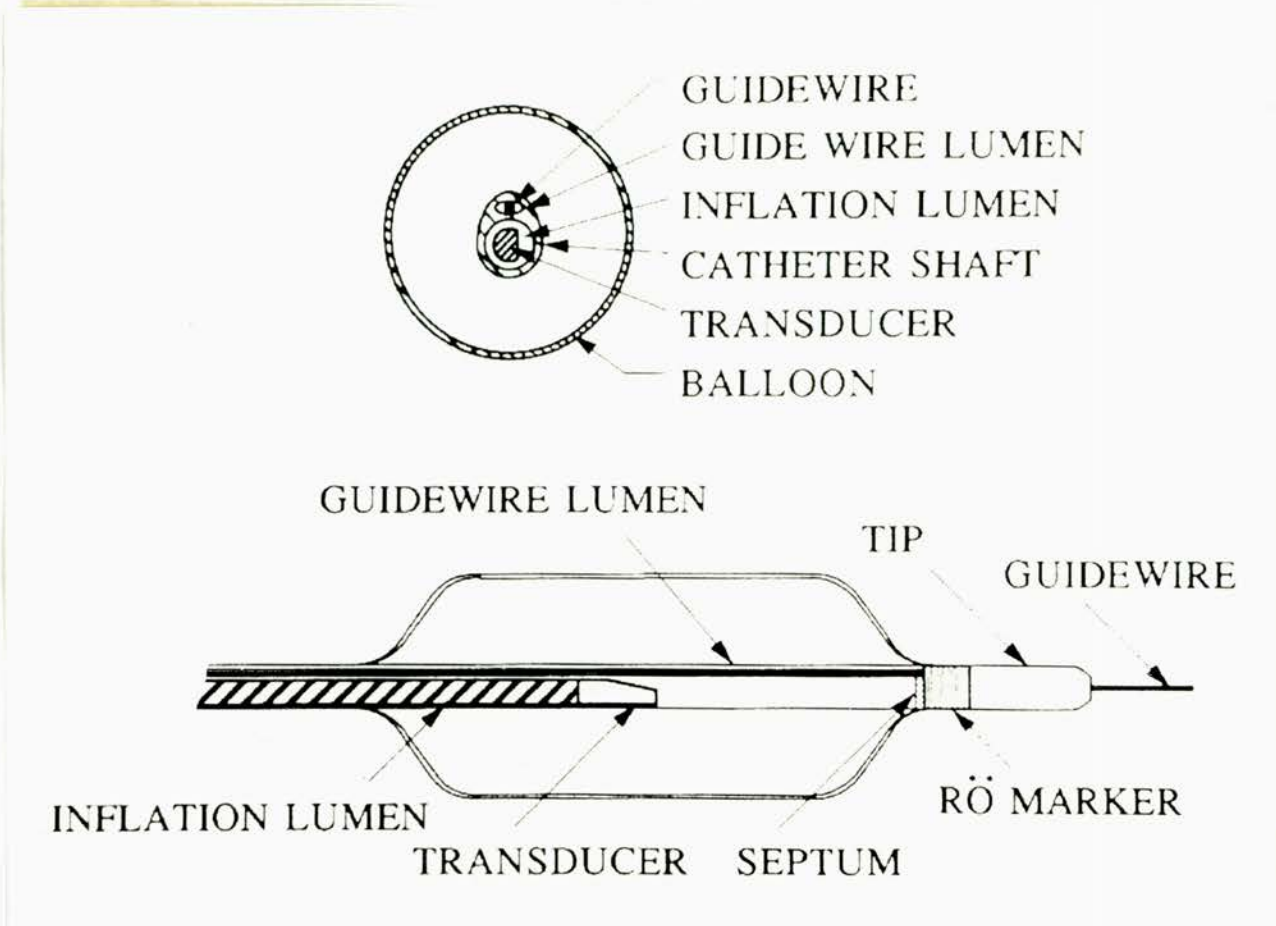


Figure 14.
Balloon ultrasound imaging catheter (BUIC).

Intravascular Ultrasound in Paediatric Interventional Catheterisation

Coarctation

In contrast to the numerous studies in ischaemic heart disease, there are no proper studies investigating the use of intravascular ultrasound to monitor interventions in congenital heart disease. There have, however, been two reports of the use of intravascular ultrasound to monitor balloon dilatation of the aorta, describing the ability of intravascular ultrasound to accurately measure the stenosis and detect intimal tearing and dissection.[70,71]

During the period of research for this thesis, intravascular ultrasound was performed on 2 male patients, aged 9 and 12 years, who underwent balloon dilatation of coarctation of the aorta. Following angiography and measurement of pre-angioplasty gradient, the diagnostic catheter was exchanged for a 6 French, 12.5MHz ultrasound catheter with a monorail. The ultrasound catheter was introduced along a guide wire positioned across the coarctation. Images of aorta distal to the coarctation site and images of the coarctation site were recorded. Measurements of luminal diameter were obtained both by intravascular ultrasound and angiography at the coarctation site and site of normal aorta.

In each patient, the coarctation was dilated with a balloon catheter, sized according to the measured diameter of the normal descending aorta.

Following balloon dilatation, a guide wire was left across the lesion, the post-angioplasty gradient was measured and an angiogram performed. The ultrasound catheter was then introduced along the guide wire across the coarctation site. Images were recorded of normal aorta and the site of balloon angioplasty.

Figure 15a shows the aortogram from the 12 year-old male with previous repair of coarctation. The site of recoarctation is easily appreciated. Figure 15b shows an intravascular image at the site of coarctation. The catheter is seen as a small circle in the middle of the vessel lumen and the outer white ring is the vessel wall. The Dacron patch used for repair can be seen as a brightly echogenic area on the vessel wall. Intravascular ultrasound allows accurate measurement of the luminal diameter at the coarctation site and comparison with the diameter of normal aortic lumen, aiding choice of correct balloon size. In both patients, before and after angioplasty, the measurements of lumenal diameter at the sites of coarctation and healthy aorta by angiography and intravascular ultrasound were within 5mm.

Following balloon dilatation the improvement in luminal diameter could be appreciated both by angiography and intravascular ultrasound, but intravascular ultrasound was also able to determine whether any intimal tearing had occurred (Figs 16a and 16b).

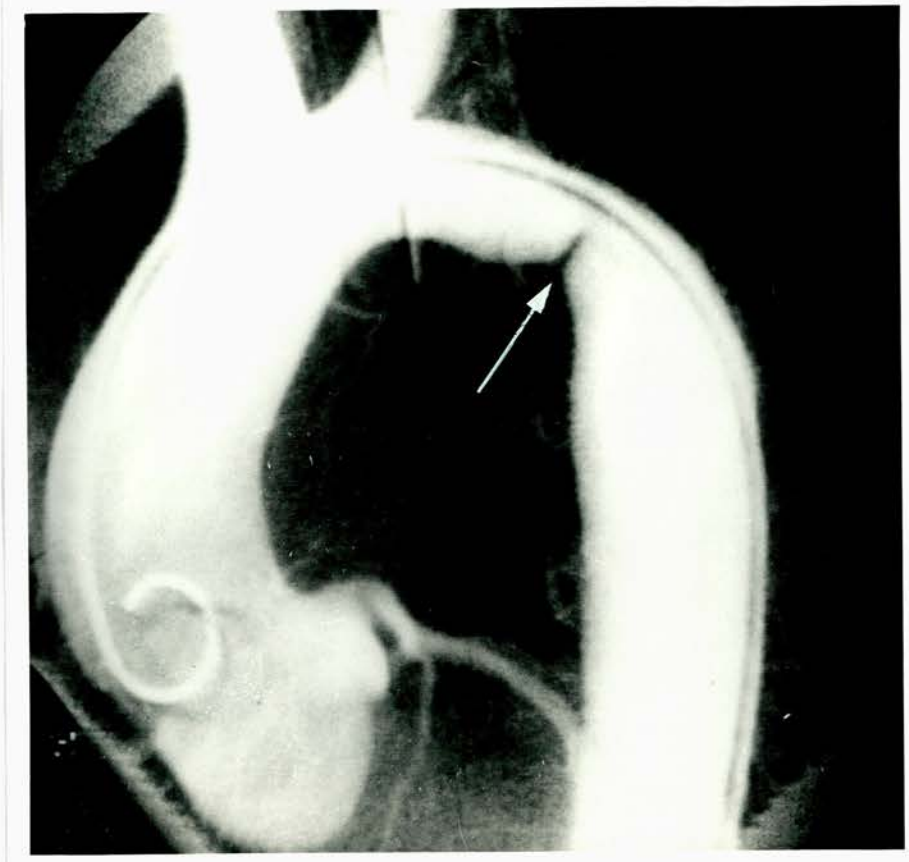


Figure 15a.
Aortogram from a 12 year old male with previous repair of coarctation.
There is significant narrowing due to recoarctation (arrow).

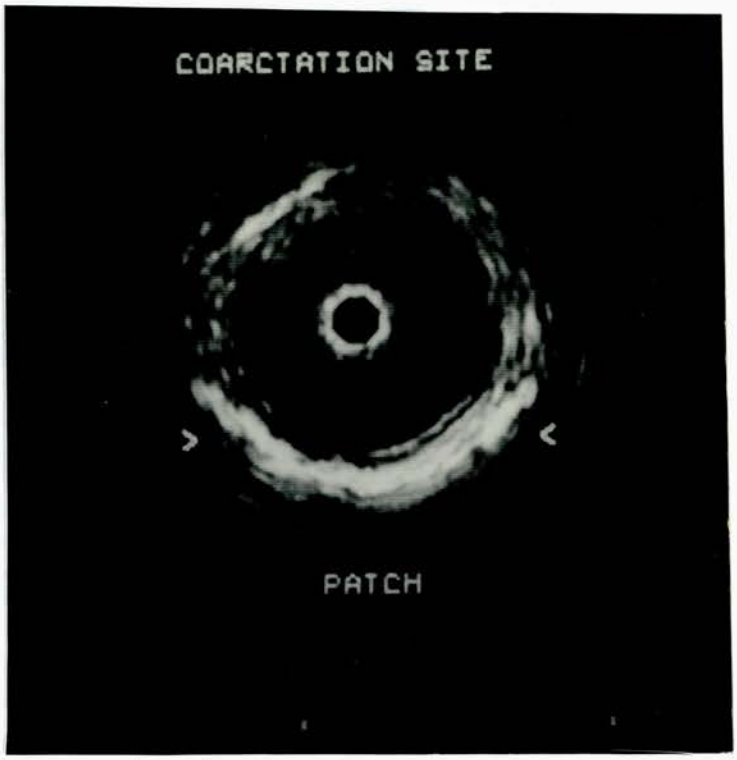


Figure 15b.
Intravascular ultrasound at the site of coarctation.
The Dacron patch used for the repair is calcified and brightly echogenic.

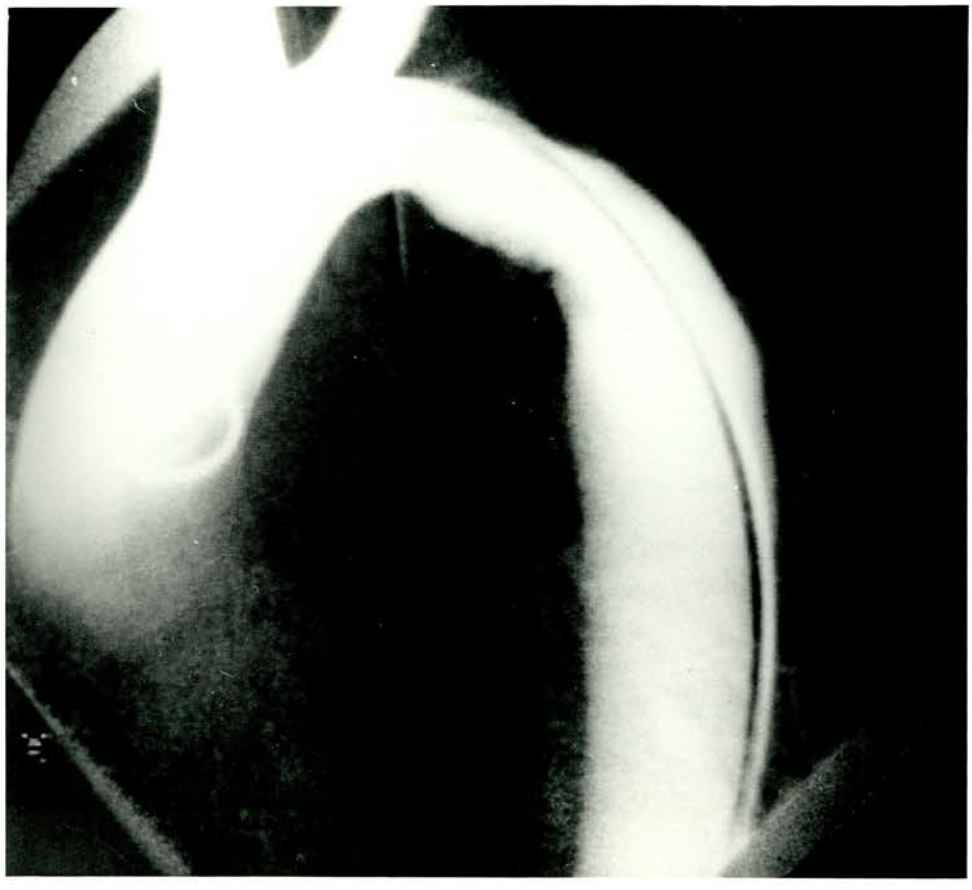


Figure 16a.
Aortogram following balloon dilatation of coarctation.
There is marked improvement in luminal diameter.

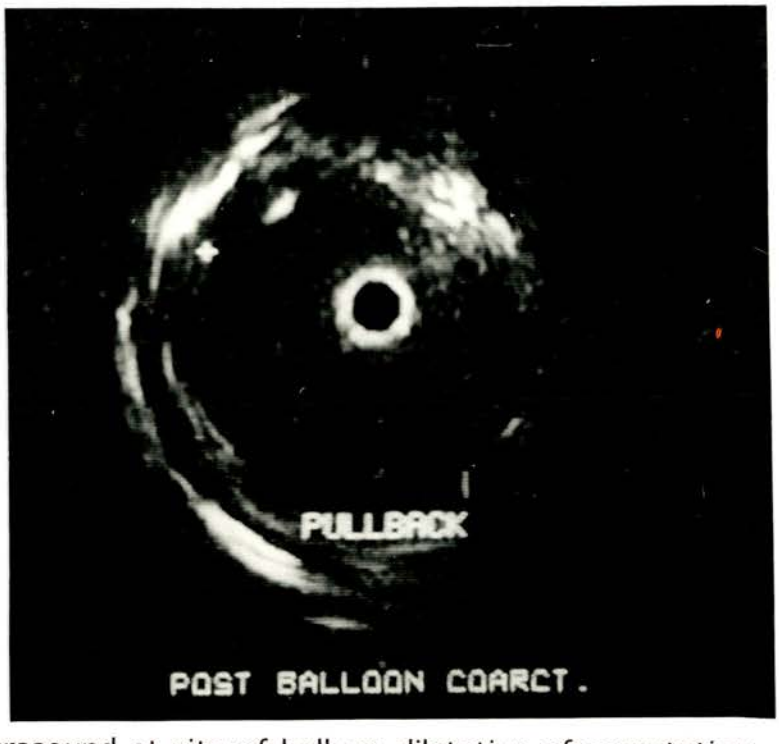


Figure 16 b.
Intravascular ultrasound at site of balloon dilatation of coarctation.
There is improvement in luminal diameter but no evidence of intimal tear.

Fig 17 shows the site of coarctation folowing balloon angioplasty in the 9 year-old patient. In this patient an intimal tear has been produced, which was not be evident on angiography. It would be interesting to know whether it is patients who sustain such tears who are more likely to develop aneurysms in the future. Perhaps intravascular ultrasound could help answer this question.

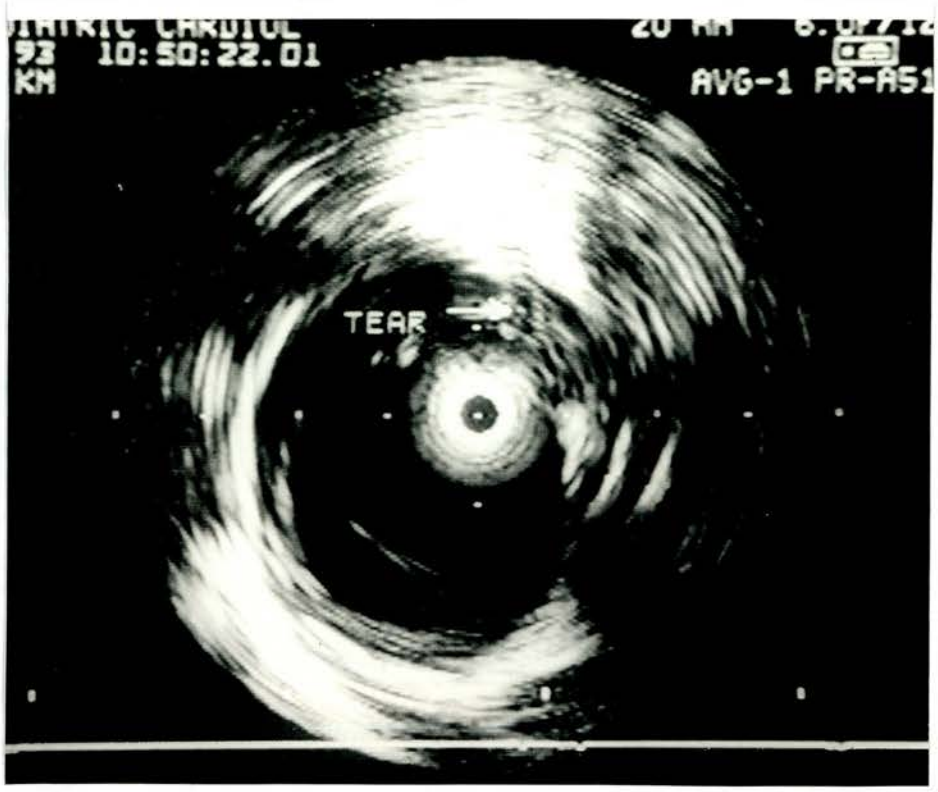


Figure 17.
Intravascular ultrasound following balloon dilatation of coarctation in a 9 year old male.
There is evidence of an intimal tear (arrow).

Pulmonary Circulation

There are no reported studies of the use of intravascular ultrasound to monitor interventions in the pulmonary circulation. During the period of study for this thesis, intravascular ultrasound was used to monitor a catheter intervention of a stenosed Blalock-Taussig shunt.

Fig18a shows the angiogram from a 19 year old male with tricuspid atresia, pulmonary atresia and stenosis of a classical right sided Blalock-Taussig shunt. On intravascular imaging narrowing at the site of stenosis was appreciated compared with the diameter at the area of luminal patency of the shunt (Fig 18b). Following angioplasty, although there was a loss of balloon waist, there was little improvement in luminal diameter due to the phenomenon of vessel recoil (Fig19a, 19b). A stent was therefore deployed, resulting in marked improvement in pulmonary flow (Fig20a). Full stent deployment can be confirmed by intravascular imaging (Fig20b). The stent is shown to be nicely adherent to the vessel wall.

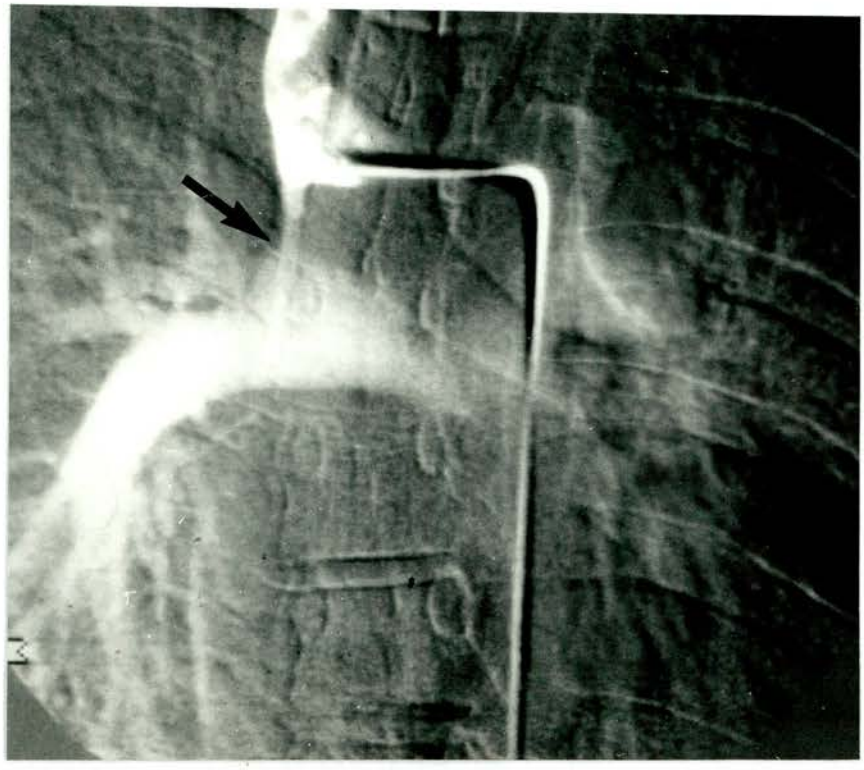


Figure 18a.
Angiogram of stenosed Blalock-Taussig shunt (arrow).

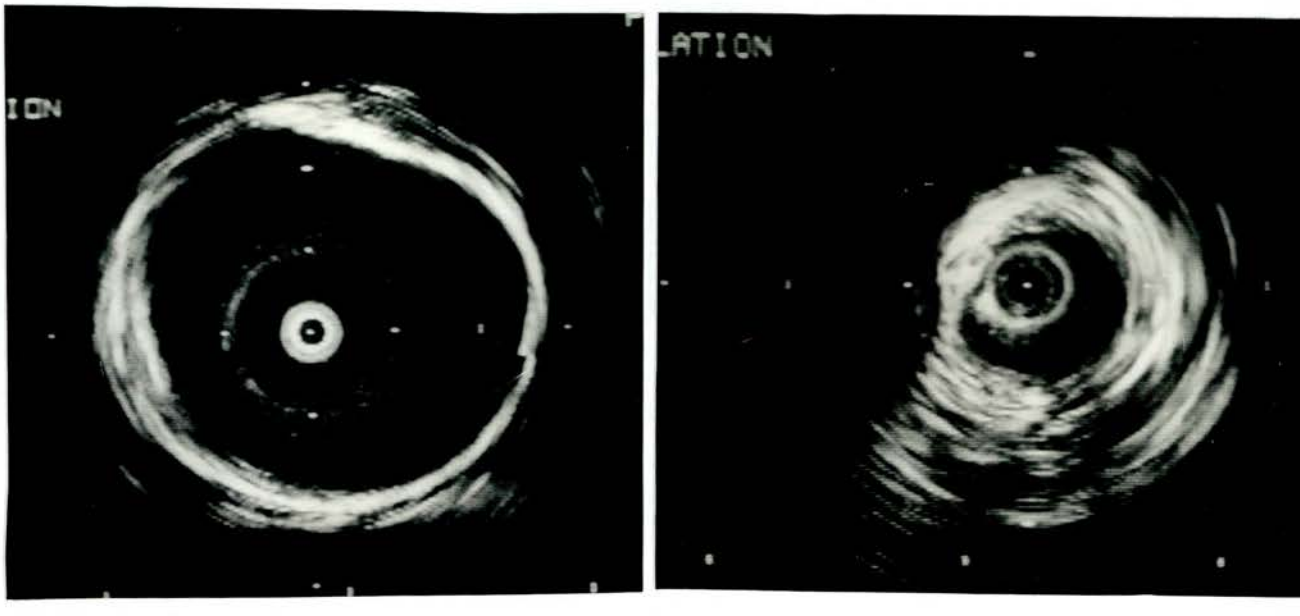


Figure 18 b.
Intravascular ultrasound of Blalock-Taussig shunt.
The image on the left shows the diameter of the shunt where it is well patent, compared with the image on the right where the shunt is stenosed.

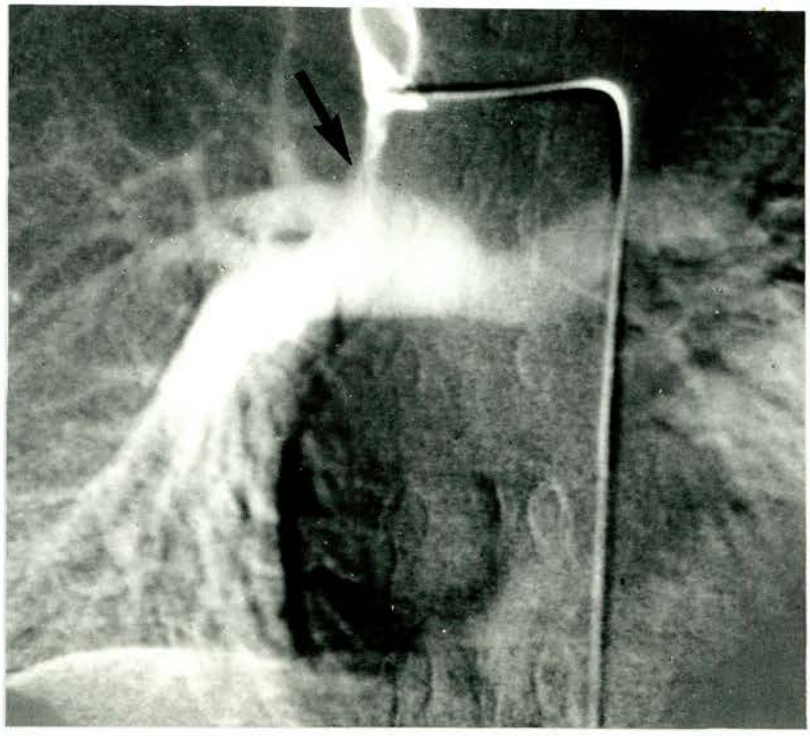


Figure 19a.
Angiogram following balloon dilatation of stenosed Blalock-Taussig shunt.
Although there was loss of balloon waist, due to vessel recoil there is minimal improvement in the diameter of the shunt or pulmonary blood flow.

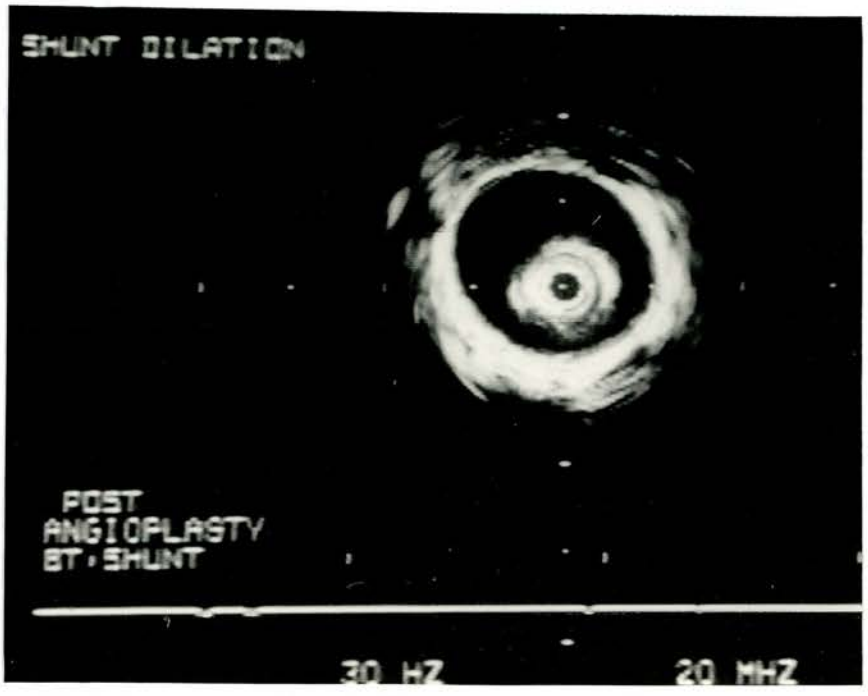


Figure 19 b.
Intravascular ultrasound following balloon dilatation of Blalock-Taussig shunt.
There is little improvement in luminal diameter.

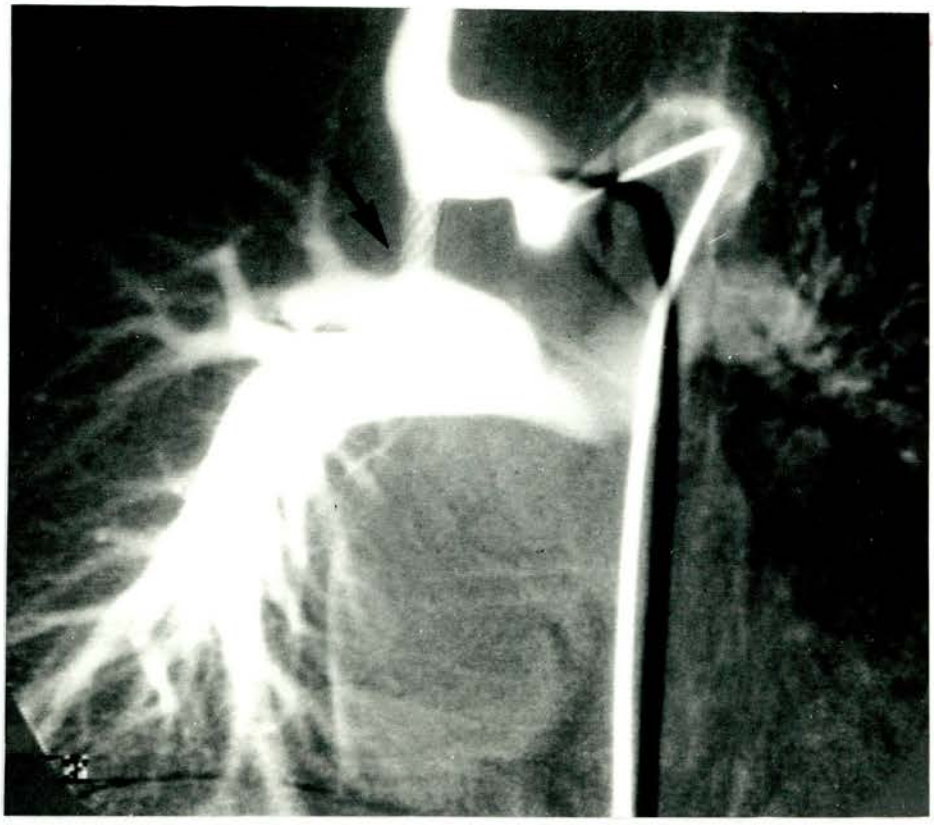


Figure 20a.
Angiogram following stent deployment in stenosed Blalock-Taussig shunt(arrow).The shunt is well patent and there is marked improvement in pulmonary flow.

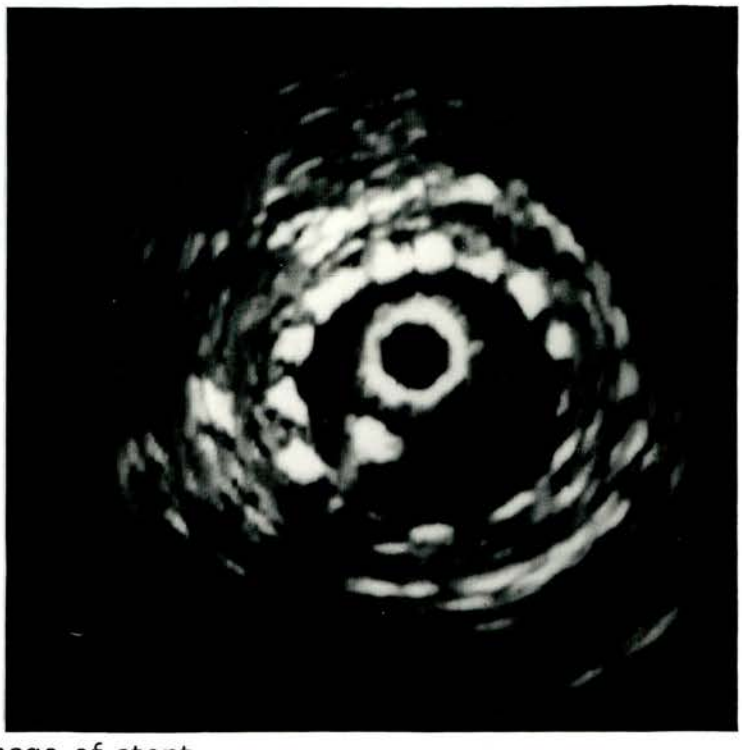


Figure 20 b.
Intravascular Image of stent.
The stent is seen to be fully deployed; the echogenic struts are nicely adherent to the vessel wall.

Occlusion Devices

Another potential application of intravascular ultrasound in Paediatric interventional catheterisations which has not been explored is monitoring the placement of occlusion devices. Fig.21 shows an intravascular image of an arterial duct. The ultrasound catheter is seen within the aortic lumen and the 'gap' in the vessel wall is the origin of the arterial duct. Following the deployment of one coil the duct is only partially occluded but after deployment of a second coil the duct can be seen to be fully occluded.

Whether intravascular ultrasound could actually add any useful information to angiography in Paediatric interventions is not certain, but its full role in monitoring Paediatric interventions can only be determined if critical studies are undertaken. Unfortunately studies in Paediatrics are more difficult than in the adult population due to smaller numbers, lack of sponsorship, unwillingness to prolong catheter procedure and screening times and difficulty in manipulating an intravascular catheter through an often complex cardiovascular system.

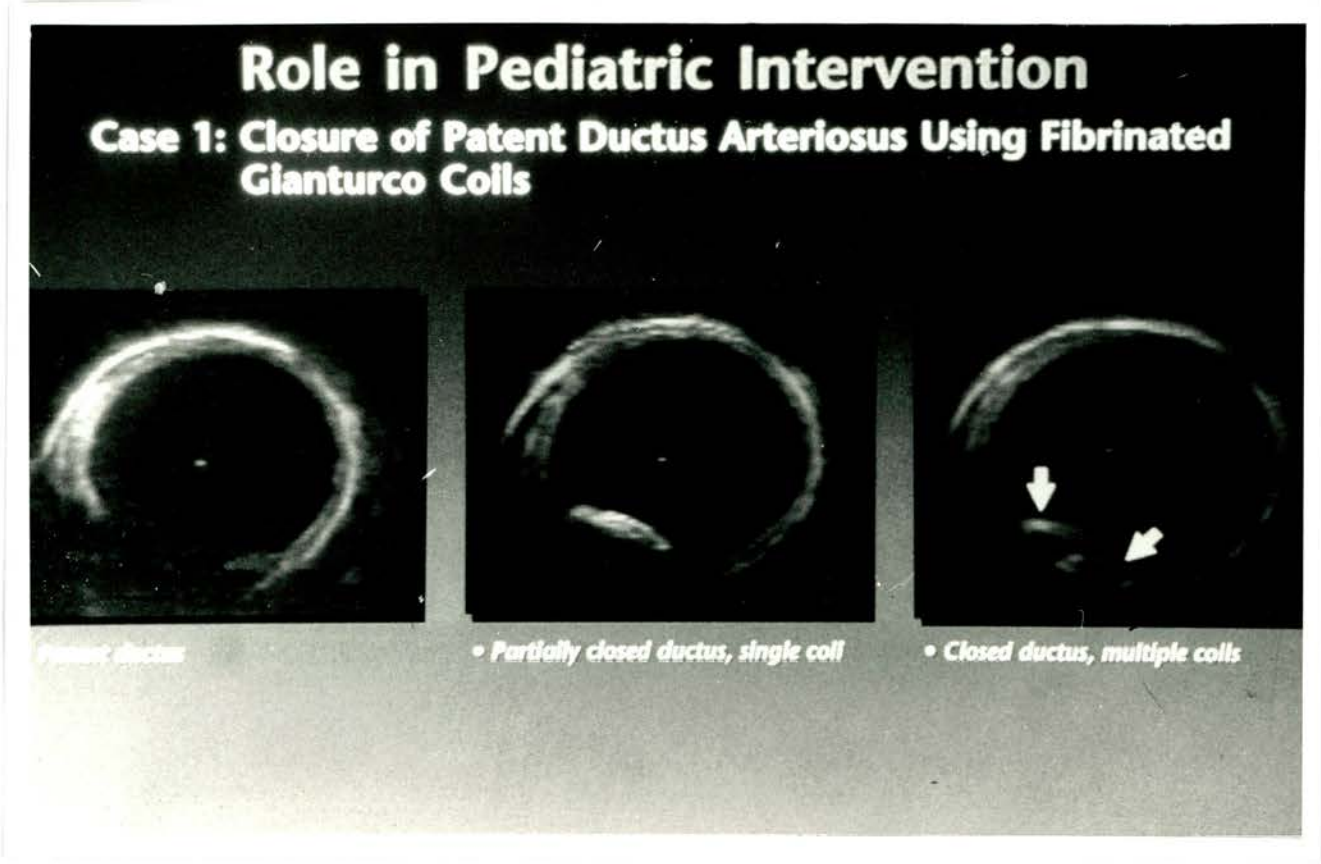


Figure 21.
Intravascular image of duct occlusion by Gianturco coils
In the image on the far left, the ultrasound catheter is seen within the lumen of the aorta. The'gap' in the wall of the aorta is the origin of the arterial duct.

In the middle image, the duct can be seen to be partly, but not completely, occluded by one coil.

In the image on the right, following deployment of a second coil the duct can be seen to be completely occluded.

3. Intravascular imaging of the pulmonary arteries

Intravascular ultrasound of the pulmonary arteries has not received much interest, probably because a useful application is not so immediately apparent and because commercial promotion of the technique for use in pulmonary vessels is not so financially lucrative as studying atherosclerosis. There are, however, three potential areas of application:

1. *Diagnosis of pulmonary thromboembolism*

In patients in whom a diagnosis of pulmonary thromboembolism remains unclear despite angiography, intravascular imaging may allow direct visualisation of thrombus, confirming the diagnosis (Fig. 22). There are a few case reports describing this application of intravascular ultrasound, but it is unlikely to be a major clinical use for the technique.[72,73]

2. *Evaluation of therapeutic catheterisation*

As described above, in subjects undergoing therapeutic catheterisation for dilatation of stenosed pulmonary vessels, intravascular ultrasound may help evaluate results, such as showing intimal tears or dissection secondary to angioplasty, or confirming adequate deployment of stents.

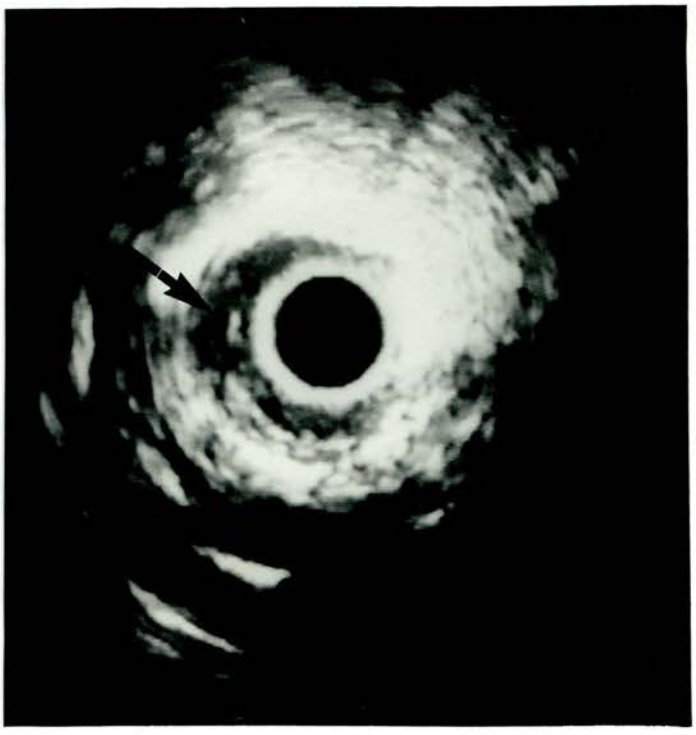


Figure 22.
Intravascular ultrasound within a pulmonary artery in a 9 year old male with pulmonary hypertension secondary to multiple thromboemboli from a ventriculoperitoneal shunt.

The catheter is seen within the vessel lumen. The echogenic homogenous material is thrombus(arrow).

3. *Assessment of pulmonary hypertension*

The third potential use of pulmonary intravascular ultrasound is in the investigation of pulmonary hypertension and pulmonary vascular disease. Initial studies of pulmonary intravascular imaging in patients with pulmonary hypertension have shown evidence of medial and intimal thickening, as well as atherosclerotic lesions very similar to those seen in coronary artery disease.[74,75] Such findings suggest that intravascular ultrasound may be of use in evaluating the morphological changes which occur in pulmonary hypertension and this potential application of intravascular ultrasound will be explored further in this thesis(Chapter 3).

4. Endothelial Function and Vascular Reactivity

Intravascular ultrasound gives excellent imaging of vessel luminal dimensions and therefore provides a method of studying vascular reactivity in life. There are surprisingly few studies involving this application of the technique and most of the studies have used intravascular Doppler to assess vascular flow rather than 2-D imaging to observe changes in luminal dimensions.[76] The use of intravascular ultrasound for the study of pulmonary vascular reactivity will be explored further in this thesis (chapter 4).

CHAPTER 3

INTRAVASCULAR ULTRASOUND

PULMONARY ARTERIAL MORPHOLOGY

Introduction

The initial studies of intravascular imaging in pulmonary hypertension have suggested that intravascular ultrasound can detect medial and intimal thickening as well as changes of atherosclerosis in the pulmonary arteries in pulmonary hypertension.[74,75] This raises the possibility that the technique may provide a method of evaluating pulmonary vascular morphology in life at the time of cardiac catherisation or surgery without the need for lung biopsy. Naturally using intravascular ultrasound to assess morphology in pulmonary hypertension could only be of clinical use if the changes in vessels accessible to the ultrasound catheters reflected the severity of pulmonary vascular disease. The relation between morphological changes in the proximal and peripheral vessels will therefore be explored later in this thesis(Chapter 6).

Aims

The purpose of this study was to evaluate the potential of intravascular ultrasound as a method of studying vascular morphology in life in pulmonary hypertension with reference to the following:

1. Safety and ease of use of the technique in studying patients with pulmonary hypertension.

2. Identification of technical and other problems.

3. Description and quantification of morphological changes evident on intravascular imaging of pulmonary hypertensive arteries.

METHODS

Approval for the study was granted by the Hospital Ethics Committee. Patients with endstage pulmonary vascular disease were chosen for study as pathophysiological changes were likely to be most evident in this population. In addition, the feasibilty of pulmonary intravascular imaging in infants with left to right shunts was evaluated as it is this group most likely to have modifiable disease.

Patients

Intravascular ultrasound was performed in 10 young adults (age 20-35 years) with endstage pulmonary vascular disease secondary to a left to right shunt and 4 infants (age 3-6 months) with a left to right shunt and reversible pulmonary hypertension.

Table C shows the clinical characteristics of the patients, including the pulmonary and systemic pressures in the four infants. Pulmonary arterial pressure was greater than twice systemic in three of the infants and less than one third systemic in one infant.

In the young adults intravascular ultrasound studies were done at the time of cardiac catheterisation which was being performed as part of an assessment for cardiopulmonary transplant. On the day prior to cardiac catheterisation, the procedure and potential risks of intravascular ultrasound were explained

Table C. Clinical characteristics of patients.

Patient	Age	Diagnosis	PAP	SAP	PVR
*GR	26	VSD, Eisenmenger's	110/60	120/65	12
*DT	34	VSD, Eisenmenger's	105/65	115/65	15
*NA	31	PDA, Eisenmenger's	95/60	110/60	12
*DB	22	VSD, Eisenmenger's	95/60	115/65	17
*SL	35	VSD, Eisenmenger's	90/60	110/65	15
KC	24	AVSD, Eisenmenger's	110/60	120/70	12
AT	32	WS, Eisenmenger's	110/65	110/60	12
DMB	28	VSD, TGA, Mustard's	110/60	105/65	12
JW	19	PDA, Eisenmenger's	110/55	105/60	8
SW	22	PDA, Eisenmenger's	110/65	110/65	9
DM	3 months	ASD	25/15	70/40	-
AS	4 months	AVSD	45/15	60/30	-
JH	5 months	VSD	45/17	70/35	-
CM	3 months	AVSD	30/15	65/40	-

PAP; pulmonary arterial pressure(mmHg), SAP; systemic arterial pressure(mmHg), PVR; pulmonary vascular resistance(Wood Units/m^2).VSD; ventricular septal defect, PDA; patent arterial duct, AVSD; atrioventricular septal defect, WS; Waterston shunt, TGA; transposition of the great arteries.

* = Patients in whom vasodilator studies performed.

and each patient given an information sheet to read. Informed consent for the intravascular imaging was obtained prior to commencing cardiac catheterisation.

In the infants, the studies were performed at the time of cardiac surgery since cardiac catheterisation is now rarely performed in very young infants with left to right shunts in our institution. The procedure and potential risks of intravascular ultrasound were explained to the parent/guardian and informed consent for the intravascular studies obtained from the parents prior to commencing surgery.

Intravascular Ultrasound

6F, 20MHz, mechanically rotated intravascular ultrasound tipped catheters (Mansfield Scientific) were used for the studies in the young adults and 3.5F, 30MHz mechanically rotated ultrasound catheters (Mansfield Scientific) employed for the studies in the infants. The axial resolution of the catheters was 0.1mm and lateral resolution of the order of 0.2-0.3mm depending on the gain setting. Images were displayed on a Sonos 100 (Hewlett Packard) or Diasonics ultrasound machine adapted for use with intravascular catheters. Prior to in-vivo use the function and calibration of each ultrasound catheter was tested in-vitro by inserting the catheter in a sterilised thin glass cylinder filled with water. The area as determined by ultrasound was validated against the measured diameter of the cylinder.

Intravascular Imaging in Patients with Eisenmenger's

In the patients with Eisenmenger's cardiac catheterisation was performed with the patient sedated (Diazepam 10mg orally 1 hour prior to procedure) and breathing room air. The right groin was infiltrated with Lignocaine 2% and the right femoral vein cannulated with a 7 French sheath with a haemostatic valve (Cordis) using the Seldinger technique.

Following routine right heart catheterisation during which measurement of pulmonary arterial pressure and calculation of pulmonary vascular resistance were obtained, the 7 French sheath was exchanged over a guide wire for an 8 French biopsy sheath (Cordis). The biopsy sheath was introduced into the pulmonary artery. The intravascular ultrasound catheter was then advanced into the pulmonary arteries through the biopsy sheath until almost wedged, avoiding contact between the probe and the vessel wall which would result in 'ring-down artifact'. Once the ultrasound probe was in a satisfactory and stable position, images were recorded. The procedure was repeated for more than one segment of lung. On completion of imaging of the pulmonary arteries, the ultrasound catheter and biopsy sheath were withdrawn through the right heart and inferior vena cava while still imaging. The sheath and ultrasound catheter were then removed and haemostasis obtained with simple local pressure.

Intravascular Imaging in Infants

The infants were anaesthetised for cardiac surgery. Following thoracotomy and prior to the infant going on cardiopulmonary bypass, the main pulmonary artery was cannulated with an 18 Gauge Vygon needle and exchanged over a wire for a 5F sheath (Cordis). A purse string suture was placed around the sheath. The mean pulmonary arterial and systemic pressures were recorded. The intravascular ultrasound probe was then advanced through the sheath and into the pulmonary tree until almost wedged. Images were recorded once the probe was in a stable position. Images were recorded on withdrawal of the catheter from branch pulmonary arteries to pulmonary trunk. All images were recorded on VHS video tapes. At the end of the procedure the catheter and sheath were removed and haemostasis was achieved by pulling tight the purse string suture.

Analysis of Results

Images were analysed at a later date using a Image-Vue Work Station to enable measurements to be made on the recorded video images. Images were analysed for the following:

1. The presence or absence of the characteristic trilayer appearance of the vessel wall.
2. The ability to distinguish and measure the media.
3. The presence of intimal thickening including atherosclerotic lesions.

Intravascular imaging in Patients with Eisenmenger's

Complications

There were no adverse effects due to intravascular imaging experienced by any of the patients. In two patients with Eisenmenger's the technique had to be abandoned; one due to failure to enter the pulmonary arteries with the intravascular ultrasound catheter (DMB) and the other due to the sharp angle of the branching of the pulmonary arteries causing 'binding' of the ultrasound catheter with loss of imaging (JW). Complete transducer failure occurred during imaging in four patients with Eisenmenger's and in one infant, requiring replacement with a new ultrasound catheter. It was unclear why the transducers failed, but probably simply reflected catheter fragility. A total of 21 catheters were used for 14 patients at a cost of £11,000.

Morphology

In the patients with Eisenmenger's it was possible to enter the third and fourth order branch pulmonary arteries. The catheter could be advanced until wedged but this resulted in marked 'ring down' artifact with merging of echo signals which completely obscured the layers of the vessel wall. To produce a satisfactory image the catheter had to be withdrawn until there was a distance of approximately 1mm between the external surface of the catheter and the vessel wall. This meant that the smallest vessels which could be

imaged were of the order of 4-5mm in diameter. An average of three lung segments was analysed for each of the patients.

A problem with imaging was that the echogenic density of the vessel wall tended to vary with vessel wall motion. As the vessel became more distended, areas of 'drop-out' would occur resulting in the illusion of gaps in the vessel wall.

In the patients with Eisenmenger's, none of the vessels imaged had the characteristic trilayer appearance normally described with intravascular imaging. Instead, the vessel wall consisted of a single echogenic layer (Fig 23,24) and it was not possible to sufficiently define the boundaries of the media in order to obtain measurements of medial thickness.

In all the patients with Eisenmenger's the luminal surface of the intraparenchymal pulmonary arteries was found to be irregularly thickened suggesting intimal hypertrophy. Atherosclerotic lesions similar to those described in systemic vessels were identified in all but one patient.

As the catheter was withdrawn from branch pulmonary arteries into right ventricle the main pulmonary arteries and pulmonary trunk were imaged. Despite using a biopsy sheath it was impossible to stabilise the catheter

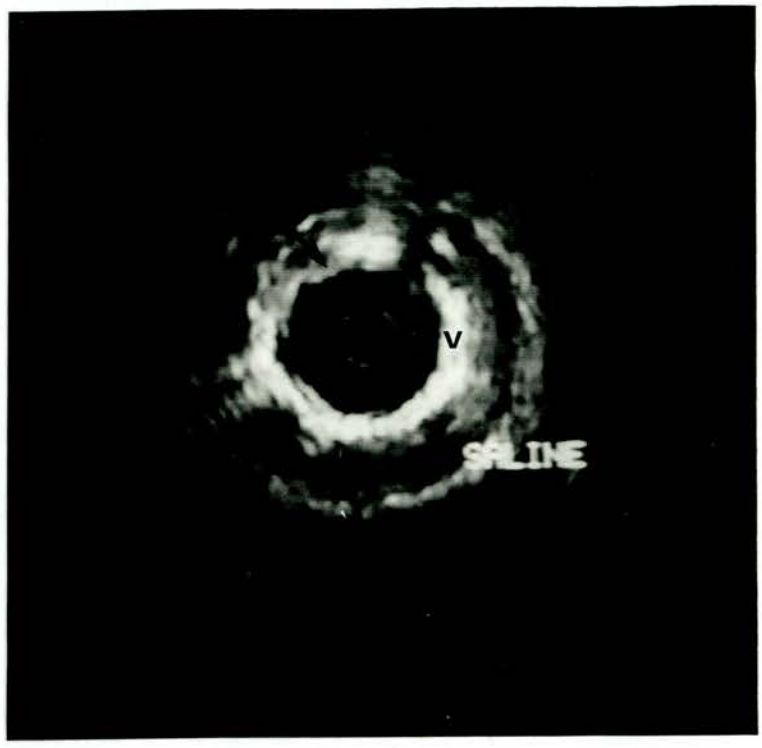


Figure 23.
Intravascular Image within the pulmonary artery of a 26 year-old male with a VSD and Eisenmenger's Complex.
The ultrasound catheter is seen as a small circle in the vessel lumen. The outer white ring is the vessel wall. The vessel wall (v) is seen as a single layer and it is not possible to define the media with certainty. The intima is thickened and irregular and there is atheromatous plaque (arrow) similar to that seen in peripheral vessels.

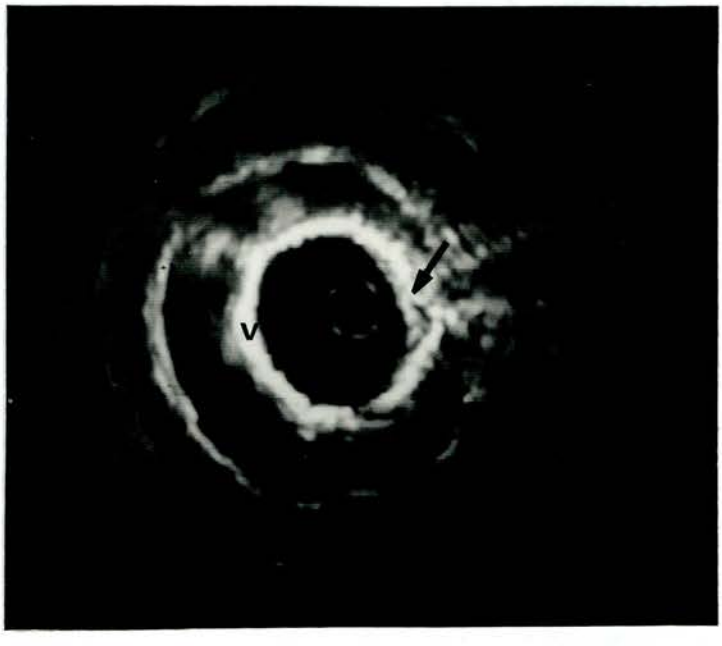


Figure 24.
Intravascular Image within the pulmonary artery of a 19 year-old male with a VSD and Eisenmenger's Complex.
The ultrasound catheter is seen as a small circle in the vessel lumen. The outer white ring is the vessel wall(v). The vessel wall (v) is seen as a single layer. The intima is thickened and irregular and there is atheroma (arrow).

centrally in the larger vessels. The catheter moved to and fro with each heart beat causing the imaged vessels to appear elipsoid. The main pulmonary arteries appeared as a single echodense layer typical of elastic arteries (Fig. 25).

As the transducer crossed the pulmonary valve the valve cusps were seen as thin mobile echogenic structures (Fig.26). The muscle of the right ventricular outflow tract was visualised but the whole ventricle could not be visualised in one image due to the high frequency of the transducer reducing available field of view.

Intravascular Imaging in Infants

Complications

One of the infants developed ventricular tachycardia when the ultrasound catheter was introduced into the right ventricular outflow tract. The arrhythmia resolved on immediate removal of the catheter. There were no problems of bleeding from the site of pulmonary arterial puncture in any of the patients. Postoperative course was uncomplicated in three of the infants but the fourth, DB, who had systemic pulmonary pressures at the time of surgery, suffered pulmonary hypertensive crises postoperatively and required 48 hours of prostacyclin. Subsequently his recovery was unremarkable. All four infants were discharged home within 10 days of surgery.

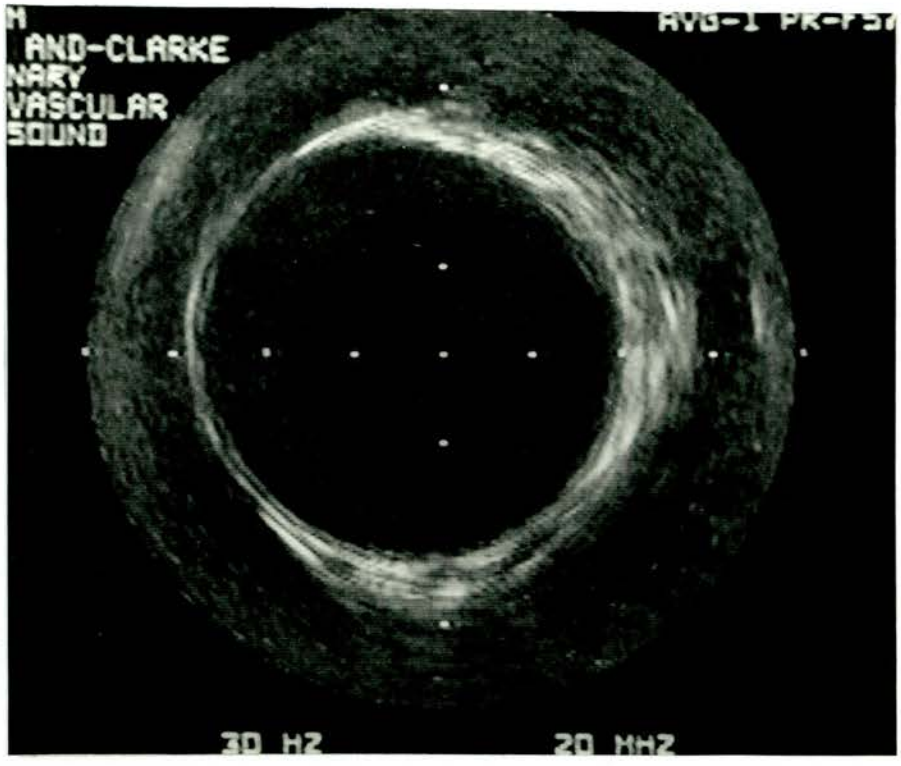


Figure 25.
Intravascular ultrasound within the pulmonary trunk.

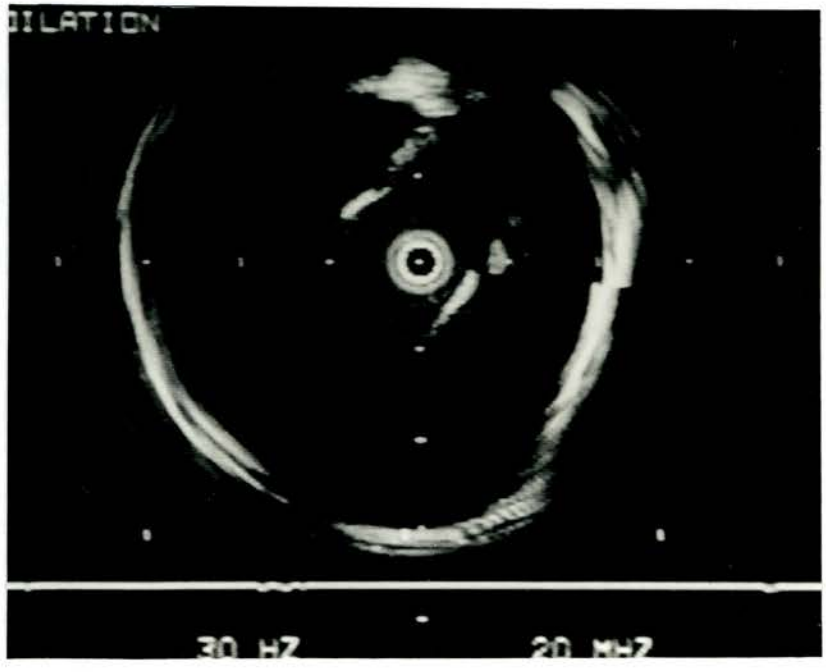


Figure 26.
Intravascular image of a pulmonary valve.
The valve leaflets are seen as thin echogenic lines on either side of the catheter.

Intravascular Imaging in Infants

As the ultrasound catheters were advanced into the pulmonary arterial tree without fluoroscopic screening, it was impossible to be certain about the exact position of the catheter. Direct palpation of the right and left pulmonary artery allowed determination of which lung was being catheterised. In all four infants the ultrasound catheter entered the left but not the right lung vessels, presumably due to the angle at which the sheath was positioned in the main pulmonary artery and the angle of origin of the left pulmonary artery. Without fluoroscopic screening it was deemed unsafe to use a guidewire or long sheath and this made it difficult to manouevre the catheter. Only in two infants was it possible to advance the catheter to a wedged position. In the other two it was impossible to advance the catheter farther than the left main pulmonary artery.

Morphology

In the infants the smallest vessels imaged were approximately 4-5mm; i.e relatively large elastic pulmonary arteries. The vessel wall appeared as a single echodense layer and it was not possible to accurately differentiate the three morphological components of the vessel wall. The intimal surface was thin and smooth, typical of normal artery and none had evidence of atherosclerosis(Fig 27).

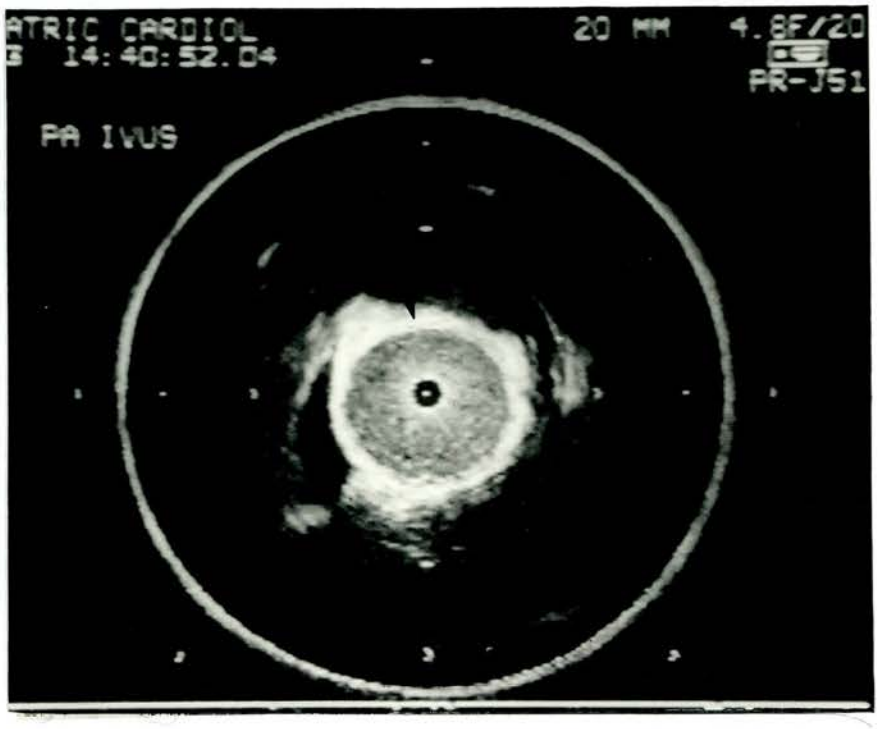


Figure 27.
Intravascular ultrasound of a pulmonary artery in a 4 month old infant with a ventricular septal defect and pulmonary hypertension. The vessel wall is indicated by the arrow.

DISCUSSION

Technical considerations in intravascular imaging

Transducers - mechanical versus phased array

Intravascular imaging is performed using a cardiac catheter with an ultrasound transducer built into the tip. For the ultrasound transducer itself there are two possible approaches. One is to use a mechanically rotated transducer or rotating mirror and the other is to use an electronic array. Both approaches have limitations which must be taken into account when interpreting images. Mechanical transducers are difficult to make within consistent mechanical specifications. As a result, the transducer rotation speed may vary due to mechanical drag, producing distortion of the image and affecting accuracy of quantitative measurements.[77] This is especially a problem when the drive shaft is bent by a tortuous vessel.

The main advantage of the multi element array system is that it overcomes the problem of non-uniform rotation. In addition, as there is no mechanical drive shaft required, the catheter is more flexible and able to negotiate tortuous vessels. The disadvantage of the multi-element system is that it requires complex hardware and software for image reconstruction which makes the transducers expensive.[78] The choice of mechanical as opposed to phased array transducers in this study was mainly influenced by commercial availablity and more affordable cost.

Imaging Artifacts

Ring down artifact

A major problem encountered when imaging small vessels with intravascular ultrasound is 'ring-down' artifact. This occurs secondary to high amplitude oscillations of the transducer piezoelectric material and results in a heaping up of echoes from structures located close to the transducer. The result is a bright echogenic image with loss of definition. The effect can be reduced in mechanical catheters by using a rotating acoustic mirror to produce a greater signal path length from transducer to vessel lumen. An acoustic mirror is not suitable for electronic array catheters as the transducer elements are surface mounted. Ring-down is eliminated in electronic array catheters by the process of digital subtraction. A reference image containing ring-down artifact is obtained while imaging a large vessel such as the aorta and thereafter the central portion of this image is subtracted from all subsequent frames.

Variations in acoustic reflectance

One of the problems frequently encountered in intravascular imaging is low acoustic reflectance from normal intima which results in echo 'drop-out' and gives the appearance of gaps in the vessel wall. Conversely, atherosclerotic or calcified intima is intensly echoreflective and may obscure imaging of underlying structures. Such problems were encountered in the patients with Eisenmenger's syndrome in whom the intima was thickened and atheroclerotic lesions common. As 'drop-out' makes accurate measurement of luminal area

difficult it is important to measure luminal area where the luminal circumference appears complete on imaging.

Manipulation of the Catheter

Catheter 'Binding'

In patients with complex congenital heart defects, manipulation of the soft floppy intravascular imaging catheters around sharp angles or across abnormal valves may be difficult. Such difficulties were experienced in one of the patients with Eisenmeneger's in whom it was impossible to enter the pulmonary arteries. A problem peculiar to the mechanical catheters is that the catheter drive shaft is situated within the body of the catheter and will 'bind' if required to negotiate too sharp an angle. Naturally, this results in loss of imaging as happened in one of the patients with Eisenmenger's.

Catheter Guidance

There are two methods employed to improve catheter guidance. One is to use a guide wire and many commercial catheters now have a guide wire monorail. An alternative method is to use a long sheath, such a myocardial biopsy sheath which can be introduced into the pulmonary arteries. It was found that for pulmonary arterial studies, superior catheter guidance and stability were obtained using a sheath. Catheter stability is of supreme importance to ensure that the catheter remains well centred within the lumen as the vessel lumen tends to appear ellipsoid when the catheter is not centralised, affecting

the accuracy of measurements of luminal area. In addition, as described above, 'ring-down' artifact occurs when the catheter is too close to the vessel wall.

Complications

Only one patient experienced complications related to intravascular imaging and in this patient the arrhythmia induced by the ultrasound catheter resolved on removal of the catheter. Intravascular ultrasound appeared to add no significant morbidity to either cardiac catheterisation or surgery.

Morphology of pulmonary arteries on intravascular imaging

In the patients with Eisenmenger's, the boundaries of the three mural layers of the pulmonary arteries studied could not be truly defined despite the claims from previous studies that medial thickening is demonstrable on intravascular imaging of pulmonary hypertensive vessels.[74,75] Instead, the wall of the pulmonary arteries studied was found to have a single echodense layer. This is not surprising as pulmonary arteries accessible to intravascular imaging are elastic arteries and therefore the media has more echodense elastin giving the vessel wall the appearance of a single echodense layer. Although, the muscular pulmonary arteries would be more likely to have a trilayer appearance, these vessels are too small to allow imaging by current intravascular ultrasound catheters.

Confirming the findings of others, the intimal layer was found to be irregular and thickened, and atherosclerotic lesions, similar to those found in systemic vessels were demonstrated in the patients with Eisenmenger's.[74,75] As previously mentioned, atherosclerotic lesions are found in postmortem lungs from patients with pulmonary hypertension as young as three years old.[79] Atherosclerotic plaques are also demonstrable in normal elderly individuals as part of ageing.[7] It is quite feasible that atherosclerotic lesions within a hypertensive pulmonary ciculation could behave as those in the systemic circulation with plaque rupture and formation of thrombi. Such thromotic episodes could then contribute to pulmonary hypertension and the progression of pulmonary vascular disease.

Intravascular Morphology in Infants with Pulmonary Hypertension

In the infants it was possible only to image relatively large vessels of around 4-5mm in diameter i.e 2nd order branch pulmonary arteries. As in the patients with Eisenmenger's it was not possible to distinguish a trilayer appearance on intravascular imaging. Unlike the older patients with Eisenmengers the intima in the infants was a barely visible thin layer as would be expected on imaging healthy intima.

In both groups of patients, in the intraparenchymal arteries, the vessel wall appeared to be surrounded by an echogenic ring. These outer echogenic rings are believed to be artifact caused by acoustic reflections from surrounding

lung tissue.[36]

Conclusions

Obviously a major limitation when studying pulmonary vascular morphology with intravascular ultrasound is that the smallest pulmonary vessels accessible to current imaging catheters are relatively large elastic pulmonary arteries (especially in infants), whereas pulmonary vascular disease is a disease largely affecting peripheral vessels. When imaging elastic arteries it is often not possible to define three vessel layers probably due to the echogeneity of the elastin rich media. In addition the echoreflectivity of a thickened intima may obscure underlying mural structure.

The pathological findings which could be demonstrated in the patients with Eisenmenger's were those of intimal thickening and atherosclerotic lesions and the suggestion of an overall increase in vessel wall size. Therefore, although such lesions may be found in the elderly as part of the normal aging process, the finding of pulmonary atheroma in a young patient is likely to indicate long-standing severe pulmonary hypertension.

In infants the boundaries of each vessel wall layer were not clear enough on intravascular imaging to allow meaningful measurements to be made. It could be argued, however, that if the intima and adventitia are thin walled as in normal vessels, measurement of the vessel wall itself would be representative

of medial thickness. Measurements of medial thickening in the elastic pulmonary arteries of patients with potentially reversible pulmonary hypertension would only be of use, however, if they reflected severity of pulmonary vascular disease. This will be explored later in this thesis.

In conclusion, intravascular ultrasound is able to detect changes of intimal thickening, atherosclerosis and vessel wall thickening in the elastic pulmonary arteries in patients with advanced pulmonary hypertensive disease. In infants, intravascular ultrasound allows measurement of vessel wall thickness which is likely to reflect medial thickness. If the degree of medial thickness in the elastic pulmonary arteries proved to reflect severity of pulmonary vascular disease and was of a magnitude to be detectable by intravascular imaging, the technique potentially could be used to assess pulmonary vascular morphology in this age group without the need to resort to lung biopsy.

CHAPTER 4

INTRAVASCULAR ULTRASOUND
PULMONARY VASCULAR REACTIVITY

History

As early as 1962, Dawes demonstrated that the high pulmonary vascular resistance in lamb foetal lung was mainly secondary to vasoconstriction rather than due to mechanical factors.[80] He also demonstrated that vascular resistance could be lowered by raising arterial pO_2 or giving injections of the vasodilator Acetylcholine.

In 1980 Furchgott and Zawadzki showed that healthy endothelium produced a relaxing factor which was important for the control of vasomotor tone.[81] This factor has now been identified as endothelial derived relaxing factor which has the same molecular structure as Nitric Oxide. Vasodilators are now often classified as endothelial-dependent and endothelial-independent. Endothelial-dependent factors exert their effect by inducing release of relaxing factors from the endothelium whereas endothelial-independent factors act direcly on the endothelium to cause vasodilation. An example of an endothelial dependent factor is Acetylcholine. Endothelial-independent factors include Prostacyclin, Nitric oxide and Adenosine.

Pulmonary vasoconstrictors

More recent studies have demonstrated that there may also be a constricting substance (or sustances) secreted by the endothelium under certain conditions, including hypoxia. This substance has been called Endothelin.[82] It has been postulated that Endothelin might have a role in the development of pulmonary vascular disease. A recent study by Haworth et al, however, showed that Endothelin does not appear to be elevated in the pulmonary blood of patients with pulmonary hypertension and its precise role in the development of pumonary vascular disease remains unclear.[83]

Persistent foetal circulation

There is much that remains unknown about the reactivity of lung vessels, but it appears that some individuals are particularly sensitive to factors causing vasoconstriction. For example, in some newborns, pulmonary vascular resistance fails to drop following delivery. This results in poor pulmonary blood flow, the arterial duct remains patent, there is a right to left shunt at ductal and atrial level, and the neonate becomes cyanosed and acidotic. The condition is known as persistent foetal circulation.[84] Many infants who develop persistent foetal circulation have a history of birth asphyxia or difficult delivery but many others have no apparent precipitating factor. The mechanism for the condition is unknown and mortality is high despite administration of vasodilators and ventilation.

Pulmonary reactivity in left to right shunts

In infants with a left to right shunt, it is unclear why, given a similar defect and shunt size, some appear to have a particular prediliction to developing pulmonary vascular disease. Patients with Down's syndrome appear particularly at risk.[85] Following surgery for left to right shunts a percentage of individuals develop pulmonary hypertensive crises during which there are sudden acute rises in pulmonary vascular resistance resulting in reduced pulmonary blood flow and hypoxia.[86] Again, the mechanism of pulmonary hypertensive crises is not clear, nor is it clear why certain individuals have such labile vascular reactivity.

Pulmonary reactivity at high altitudes

Individual differences in pulmonary vascular reactivity are also manifest at high altitudes. The reduction in inspired pO2 at high altitudes results in relative hypoxia which causes pulmonary vascular constriction. Subjects who live at altitudes greater than 30,000 feet have a higher mean pulmonary arterial pressure; approximately 25mmHg compared with 17mmHg at sea level. On ascending from sea level to high altitudes, pulmonary vascular resistance rises, but there are some individuals who appear to have particularly reactive vessels and develop pulmonary oedema. The only treatment is rapid descent but mortality is high.[87] At present there is no way of identifying the individuals at risk.

Pulmonary vasodilators

There is growing interest in the role of endothelial dysfunction and vascular reactivity in the development of cardiovascular diseases with a need to develop methods to study endothelial function in life. The evaluation of pulmonary vasodilators in-vivo has largely consisted of measuring changes in pulmonary vascular resistance following administration of vasodilators. More recently Celermajer et al used a combination of arteriography and Doppler flow to evaluate both local and peripheral vessel dilatation in response to vasodilators.[88]

Intravascular ultrasound to assess vascular reactivity

Intravascular ultrasound produces clear images of the lumen. In-vivo and in-vitro studies have shown that intravascular ultrasound gives accurate measurements of luminal size and is superior to angiography in this respect, particularly where intimal disease is present.[48-50] In addition, measurement of luminal area by intravascular ultrasound appears to be very reproducible (as demonstrated by studies of inter- and intra-observer variation) and changes in luminal diameter can be measured continuously during infusion of vasodilators, allowing immediate detection of any change.[89,90] Although intravascular ultrasound would appear to be an ideal method of measuring luminal diameter the technique has rarely been used in studies of vascular reactivity.[91,92,93]

Aims

The aims of this study are as follows:

1. To assess the effects of pulmonary vasodilators on local and distal pulmonary vessels in pulmonary hypertension using intravascular ultrasound to measure changes in local luminal dimensions.

2. To determine whether intravascular ultrasound is a useful and safe technique for the evaluation of pulmonary vascular reactivity.

MATERIALS AND METHODS

Approval for the vasodilator studies was granted by the Hospital Ethics Committee. Prior to cardiac catheterisation the nature, anticipated duration and potential side-effects of the studies were explained to the patients. Three patients refused to consent for vasodilator studies due to the anticipated length of the studies. In two patients it was not possible to image the pulmonary arteries for reasons described in Ch3, p64, therefore vasodilator studies were performed in only five of the young adults with Eisenmenger's syndrome.

Vasodilator studies were not performed in the infants as the effects of ventilation, oxygen and anaesthetic agents would have confounded interpretation. In addition it was felt by the surgeon that the anticipated length of the studies would have posed an unacceptable delay to proceeding with surgery.

Technique

Following completion of routine cardiac catheterisation, the cardiac catheter was exchanged for an 8F biopsy sheath which was advanced into the pulmonary artery as described in Ch3, p63.

A 22 gauge arterial catheter was inserted into the right femoral artery to allow simultaneous measurement of systemic arterial pressure and arterial

blood gas sampling. A second venupuncture was made in the right femoral vein and, using the Seldinger technique, a 6F sheath was introduced into the vein and a 6F multipurpose cardiac catheter (Cordis) was advanced through the sheath until positioned in the main pulmonary artery. The multipurpose catheter was used to sample blood for oxygen saturations and to measure pulmonary arterial pressures.

The intravascular ultrasound catheter was introduced through the cardiac biopsy sheath and into the pulmonary arteries until almost wedged. Once the ultrasound catheter was stabilised in a position where clear images of the lumen were obtained, the vasodilator studies were commenced. The choice of vasodilators for this study was largely influenced by availability. The equipment required for the administration of Nitric Oxide was not available and there were no facilities for measuring Acetylcholine levels. Oxygen, Prostacyclin and Adenosine were therefore chosen as pulmonary vasodilators. Oxygen was delivered by mask. Saline, Prostacyclin and Adenosine were infused through the side-arm of the biopsy sheath directly into the pulmonary vessel imaged.

Administration of vasodilators

The vasodilators were administered as follows:

Oxygen

100% oxygen was delivered by mask for 10 minutes.

Saline

A bolus of 50ml of Saline was infused directly into the pulmonary artery to investigate the effects of volume alone.

Adenosine

Adenosine was infused into the pulmonary arteries, at an initial rate of 50ug/kg/min and increased by 50ug/kg/min every two minutes until either a maximum dose of 500ug/kg/min, or the development of side effects, including a reduction in mean systemic blood pressure by 30%, chest pain, dyspnoea, tingling, parasthaesea or nausea.[94]

Prostacyclin

Prostacyclin was infused directly into the pulmonary arteries, at an initial rate of 5ng/kg/min and increased by 5ng/kg/min every 5mins until either a maximum of 25ng/kg/min or the development of side effects including a reduction in mean systemic blood pressure by 30%, headache, nausea or flushing.

An interval of 10 minutes was allowed between each vasodilator to allow haemodynamics to return to baseline.

Aortic and pulmonary arterial pressures were monitored continuously throughout the study.

Pulmonary vascular resistance

Pulmonary vascular resistance was calculated at the beginning of the administration of each vasodilator, following each increment in dose, and at the end-point of each study. Blood for oxygen saturations was taken from the pulmonary artery, superior and inferior vena cavae and femoral artery. Oxygen saturations were measured using a standard blood gas analyser. Oxygen consumption was measured simultaneously using a respiratory gas analyser (MC Horizon, Sensor Medics Ltd.) and cardiac outputs calculated from the equations:-

Systemic blood flow =

$$\frac{\textit{Systemic oxygen uptake}}{\textit{Systemic arterial oxygen content - Systemic venous oxygen content}}$$

Pulmonary blood flow =

$$\frac{\textit{Pulmonary oxygen uptake}}{\textit{Pulmonary venous oxygen content - pulmonary arterial oxygen content}}$$

Pulmonary vascular resistance was then calculated from the following equation:-

Pulmonary vascular resistance =

$$\frac{\text{Pulmonary arterial pressure - left atrial pressure}}{\text{Pulmonary blood flow}}$$

where, *Pulmonary blood flow* =

$$\frac{\text{Pulmonary oxygen uptake}}{\text{Pulmonary venous oxygen content - pulmonary arterial oxygen content}}$$

Measurements of luminal area

Images of luminal area were recorded at the beginning of each vasodilator study, following each increment in dose, and at the end-point of each study. Images were recorded on Super VHS video tapes for a minimum of 20 cardiac cycles.

Recorded images were analysed later using an Image-Vue work station. Measurements were made of percentage change in maximal luminal diameter following vasodilators.

RESULTS

Complications

Three patients experienced Adenosine related side-effects of chest pain and bradycardia but symptoms resolved within seconds of ceasing the infusion. There were no other complications experienced by any of the patients.

Vasodilator studies

Fig.28 shows the response of luminal area to administration of Oxygen, Prostacyclin, Saline and Adenosine. There was no significant change in luminal area or pulmonary vascular resistance in response to the administration of any of the agents in the group as a whole ($p>0.05$, Mann-Whitney U). A notable local vasodilator response to Prostacyclin and Adenosine was, however, observed in one of the patients (GR). The response to Adenosine was particularly marked but at a dose which also resulted in side effects(Fig 29). Side effects resolved within seconds of ceasing the Adenosine infusion. The local vasodilator response to adenosine was reproducible, but as the response was transient, there was not sufficient time to obtain samples to calculate any change in pulmonary vascular resistance. In the same patient, however, the calculated pulmonary vascular resistance fell from 12 Wood Units/m^2 to 9 Wood Units/m^2 in response to Prostacyclin.

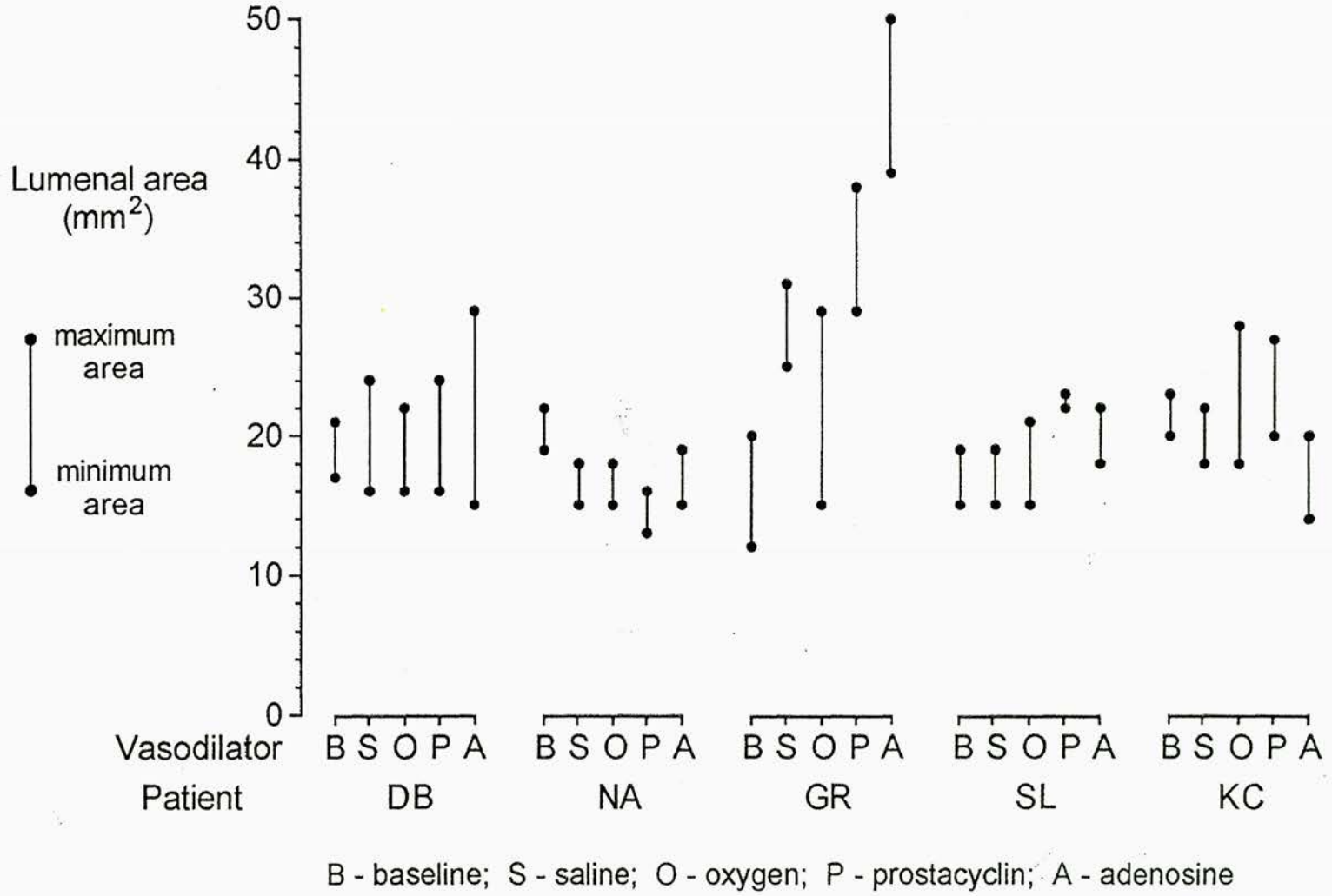
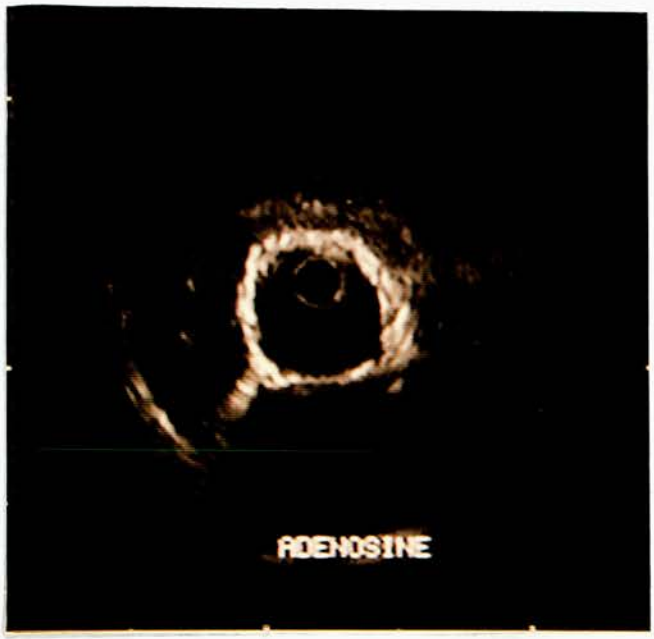
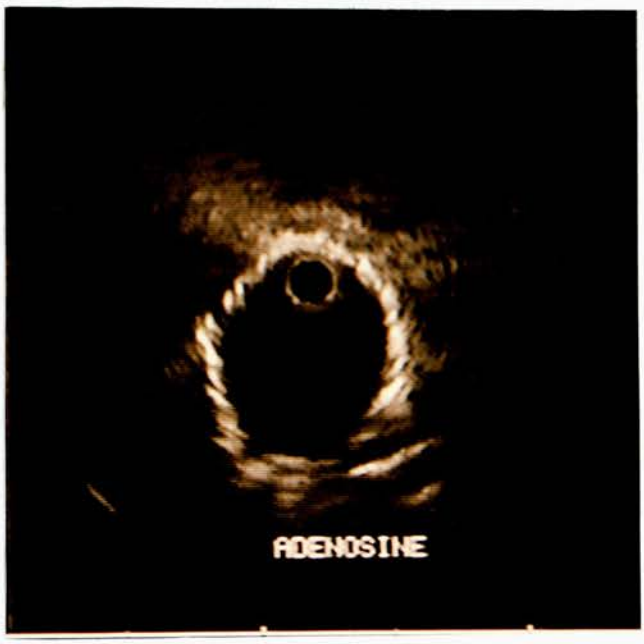


Figure 28.
Maximum and minimum luminal area at end-point of each vasodilator for each patient. There is no significant increase in luminal area in response to any vasodilator in the group of patients as a whole but one patient (GR) has a marked response to prostacyclin and adenosine.

Figure 29.
Intravascular ultrasound showing dramatic response of pulmonary artery to infusion of adenosine. The vessel can be seen to dilate. This effect was reproducible.





In the three patients who developed Adenosine related side effects, bradycardia was associated with marked local pulmonary vasoconstriction visible by ultrasound. This effect resolved with improvement of heart rate within seconds of ceasing the adenosine infusion.

DISCUSSION

The purpose of this study was to evaluate the potential of intravascular ultrasound as a method of studying vascular structure and reactivity in life in patients with pulmonary hypertension. As discussed previously, a major drawback in using intravascular ultrasound is that the smallest pulmonary vessels accessible to current imaging catheters are elastic pulmonary arteries, whereas pulmonary vascular disease is essentially a disease of peripheral vessels. Nevertheless, in-vitro studies of pulmonary arterial reactivity are usually performed on strips of elastic pulmonary artery, therefore it is not unreasonable to consider elastic pulmonary arteries as a model for changes in more peripheral vessels.

Evaluation of pulmonary vasodilators in-vivo mainly has consisted of assessing changes in pulmonary vascular resistance. More recently Celermajer et al used a combination of angiography and Doppler flow studies to measure both local and peripheral vessel dilatation in response to vasodilators.[88] The problem with angiography is that a single image may not be at the point of maximal vessel dilatation. Intravascular ultrasound, however, enables continuous and accurate measurement of luminal dimensions, allowing immediate detection of any change and measurement of maximal luminal area. Furthermore, the technique requires no contrast which may be hazardous in patients with pulmonary hypertension.

In keeping with the severe advanced pulmonary vascular disease in Eisenmenger's Syndrome, pulmonary vasodilators produced no significant response in the patient group as a whole. In view of the advanced disease in this population they were perhaps not the best group in which to study vascular reactivity, but for reasons discussed above, we were unable to study vascular reactivity in the infants who would have had more labile pulmonary haemodynamics. Nevertheless, Prostacyclin and Adenosine resulted in a notable increase in vessel luminal area in one patient with Eisenmenger's(GR). Although we were also able to detect a slight reduction in peripheral vascular resistance to Prostacyclin in the same patient (GR), our method of measuring pulmonary vascular resistance did not allow simultaneous detection of changes in peripheral vessels in response to Adenosine as the effects were too transient. The use of intravascular Doppler, as described by Calermajer et al, would have helped to overcome this problem by allowing continuous measurement of blood flow velocity and estimation of change in peripheral vascular resistance during infusion of Adenosine.[88]

It is not clear why the patient GR responded so markedly to Adenosine. The potency of Adenosine as a pulmonary vasodilator is well recognised and other researchers have found the drug to cause pulmonary vasodilation where other agents have failed.[94,95] The precise mechanism of action is not clear but it is believed to act on the A1 and A2 receptors on the endothelium to increase cyclic AMP.[96] A longer acting analogue with a better therapeutic ratio would be

required for its use in clinical practice but clearly the pulmonary vasodilator effects of this agent merit further investigation.

Adenosine induced bradycardia resulted in vasoconstriction visible by ultrasound. Although it has been believed that pulmonary hypertensive crises result from reactive constriction in the peripheral vessels it is possible that more proximal vessels also are involved. Vasoconstrictors such as Endothelin may play an important role in the development of pulmonary vascular disease[82] and intravascular ultrasound could provide a valuable technique for studying such vasoconstrictors in life.

Although intravascular ultrasound gives excellent definition of the vessel lumen, in the presence of luminal disease, such as occurs in atherosclerosis and hypertension, it may become more difficult to decide what to define as 'lumen', increasing inter and intraobserver variability. In addition, the smaller the vessel studied the more significant becomes observer error and therefore the use of intravascular ultrasound for determining the local effects of vasodilators is likely to be most accurate for measuring changes in larger vessels. Recently there has been increased interest in the role of the larger so-called 'capacitance' vessels in the development of cardiovascular diseases. In an article in the British Heart Journal entitled 'Large arteries are more than passive conduits', the authors, Ramsay and Jones suggested that for too long the large vessels have been forgotten and that diseases of these vessels result

in alterations of distensibility and pulsatility which can have a profound effect on the cardiovascular system.[97] Endothelial dysfunction of the larger vesels may contribute to reduction of arterial distensibility in hypercholesterolaemia[98] and hypertension.[99] Some medications known to be benefical in treating cardiovascular diseases, including ACE inhibitors, not only cause vasodilation of small vessels but also reduce vessel wall stiffness in larger vessels.[100] Intravascular imaging could provide an ideal technique for assessing the effects of vasodilators in these vessels.

In conclusion, intravascular ultrasound is a technique which may be used in the study of pulmonary hypertension in life either at the time of catheterisation or at the time of surgery, adding little morbidity to either procedure. The technique gives excellent definition of the vessel lumen, allowing measurement of vessel luminal area and assessment of local vascular reactivity to vasodilators and vasoconstrictors. Intravascular imaging thus provides a unique method of assessing vascular reactivity in life, not only in the pulmonary circulation but also in other vessels and should prove especially useful if combined with intra-arterial Doppler.

CHAPTER 5

MAGNETIC RESONANCE IMAGING

Principles

In 1944 Rabi won the Nobel Prize for the discovery of nuclear magnetic resonance. He observed that hydrogen atoms in a magnetic field could absorb radiofrequency electromagnetic energy at a sharply defined or "resonant" frequency.[102] The first clinical applications of nuclear magnetic imaging came in the 1970's due to the efforts of Damadian and Lauterbur who produced the first human images and used the technique for the detection of malignancy.[103,104] Since then magnetic resonance imaging has been used to study diseases of the brain, spinal cord, musculoskeletal system, abdomen and pelvis.[102] More recently magnetic resonance imaging has been applied to the cardiovascular system.

Cardiac Magnetic resonance imaging(MRI)

There are a number of features which make magnetic resonance imaging ideal for the clinical evaluation of cardiovascular diseases. The technique has a wide field of view, is able to image blood vessels with excellent spatial and temporal resolution and does not require intravascular contrast material or ionizing radiation.[102,105] Despite these attractions the technique has had a relatively minor role in cardiovascular medicine. This is largely because the information

obtained by echocardiography often obviates the need for magnetic resonance imaging. In addition, magnetic resonance imaging is expensive and not always readily available. Motion artifact and previously lengthy scanning times have also contributed to its slow clinical use. Recently, however, there have been a number of technological developments which have reduced scanning time and led to increasing application for magnetic resonance imaging in cardiovascular medicine.[102]

Cardiac applications of Magnetic resonance imaging

The development of rapid imaging techniques has now made it possible to define cardiac anatomy and connections, evaluate ventricular dimensions and function, and calculate blood flow velocities and shunts using magnetic resonance imaging.[105,106,107] In congenital heart disease, magnetic resonance imaging has proved particularly useful in defining the anatomy of complex defects; imaging patients with poor echocardiographic windows;[108] and imaging structures difficult to visualise by conventional echocardiography, such as the pulmonary arteries, pulmonary veins and the aorta.[107,108,109,110]

Basic cardiovascular imaging techniques

Due to the rapid motion of the heart relative to the time required to acquire an image, it is necessary to synchronise the MRI data-aquisition technique to a physiological trigger. Without such a trigger the image would be blurred beyond all recognition. The gating trigger normally used is the R wave of the

patient's ECG.[111] ECG-gated MRI can be used to obtain 'dark blood' or 'bright blood' static or cine images of multiple tomographic slices spanning the heart and great vessels in three dimensions. Contrast features depend on the techniques used to send and retrieve MRI signals and can be varied dramatically without the use of contrast agents. These MRI signal techniques are called sequences. Cardiovascular images usually are acquired using either spin-echo sequence or gradient-echo sequence. Spin-echo sequence is characterised by excellent soft tissue contrast, dark blood and a relatively slow acquisition time. Conversely, gradient echo sequence is characterised by poor soft tissue contrast, bright blood and faster acquisition times. Cine images are possible with either technique.[112]

Cine MRI

The anatomy of central pulmonary arteries and veins can be evaluated by conventional spin-echo magnetic resonance imaging (MRI).[113] Recently developed techniques of cine MRI and flow mapping, now make it possible to measure vessel pulsatility and flow.[114] MRI could thus provide a noninvasive means of evaluating pulmonary pathophysiology in pulmonary hypertension. A noninvasive method of evaluating pulmonary hypertension would be extremely valuable as invasive procedures carry a higher risk in pulmonary hypertensive patients, particularly contrast angiography. The attraction of MRI is that it also allows confirmation of cardiac anatomy and vascular connections, i.e. information useful for transplant assessment.

MRI of the pulmonary arteries in pulmonary hypertension

There are a small number of studies which have investigated the MRI features of pulmonary arteries in pulmonary hypertension. The findings have included dilated pulmonary arteries, reduced pulmonary arterial pulsatility and altered flow patterns.[115-117] These initial studies, however, have been on a small heterogenous population of patients with pulmonary hypertension secondary to a number of different causes, the majority being mitral stenosis. It is conceivable that a left to right shunt producing high pulmonary blood flow may result in different pathophysiological changes in the elastic pulmonary arteries compared with other causes of pulmonary hypertension.

The aim of this study was to determine the use of MRI in the assessment of pulmonary hypertension secondary to left to right shunts with reference to the following:-

1. The safety of the technique and acceptability to patients.
2. MRI features of pulmonary hypertension.
3. Clinical applications of the technique for the assessment of patients with pulmonary hypertension.
4. Whether the technique could be of clinical use as a noninvasive method of assessing pulmonary hypertension.

METHODS

The study was approved by the Hospital Ethics Comittee. The nature of the study and potential risks of magnetic resonance imaging were explained to the patients and volunteers and informed consent obtained before commencing the studies.

The pulmonary arteries of 11 patients, aged 18-34, with pulmonary hypertension secondary to a left to right shunt and established pulmonary vascular disease were studied by MRI.

Table D shows the clinical characteristics of the patients.

The control group consisted of 6 healthy, non-smoking individuals, aged 25-32.

Magnetic resonance imaging

Magnetic resonance Imaging was performed using a 1.0 Tesla SIEMENS MAGNETOM 42SP MRI system. Following a fast localising scan, contiguous 7mm-thick, axial slices through the great vessels and heart chambers were obtained, using an ECG-synchronised, T1-weighted spin-echo sequence (Fig. 30). The resultant images helped to establish anatomy and to define subsequent imaging planes. Further localising scans were then performed in two planes parallel to the left and right main pulmonary arteries respectively, using an ECG-synchronised gradient echo cine pulse sequence (Figs. 31a, 31b).

Table D. Clinical characteristics of patients - MRI

Patient	Age	Diagnosis	PAP	SAP	PVR
AT	32	Waterston shunt	110/65	110/60	12
DT	34	VSD, Eisenmenger's	105/65	115/65	15
LH	31	VSD, Eisenmenger's	95/60	110/60	12
DB	22	VSD, Eisenmenger's	95/60	115/65	17
SL	35	VSD, Eisenmenger's	90/60	110/65	15
KC	24	AVSD, Eisenmenger's	110/60	120/70	12
LG	22	VSD, Eisenmenger's	110/60	110/60	10
JS	23	PDA (closed)	90/60	100/60	9
JW	19	PDA, Eisenmenger's	110/60	105/60	8
CB	21	VSD, Eisenmenger's	100/65	100/60	10
*DM	28	TGA, VSD, Mustard's	110/65	105/60	12

PAP; pulmonary arterial pressure(mmHg), SAP; systemic arterial pressure(mmHg), PVR; pulmonary vascular resistance(Wood Units/m^2).

VSD; ventricular septal defect, PDA; patent arterial duct, AVSD; atrioventricular septal defect, TGA; transposition of the great arteries.

* = Unable to obtain satisfactory magnetic resonance images due to motion artifact.

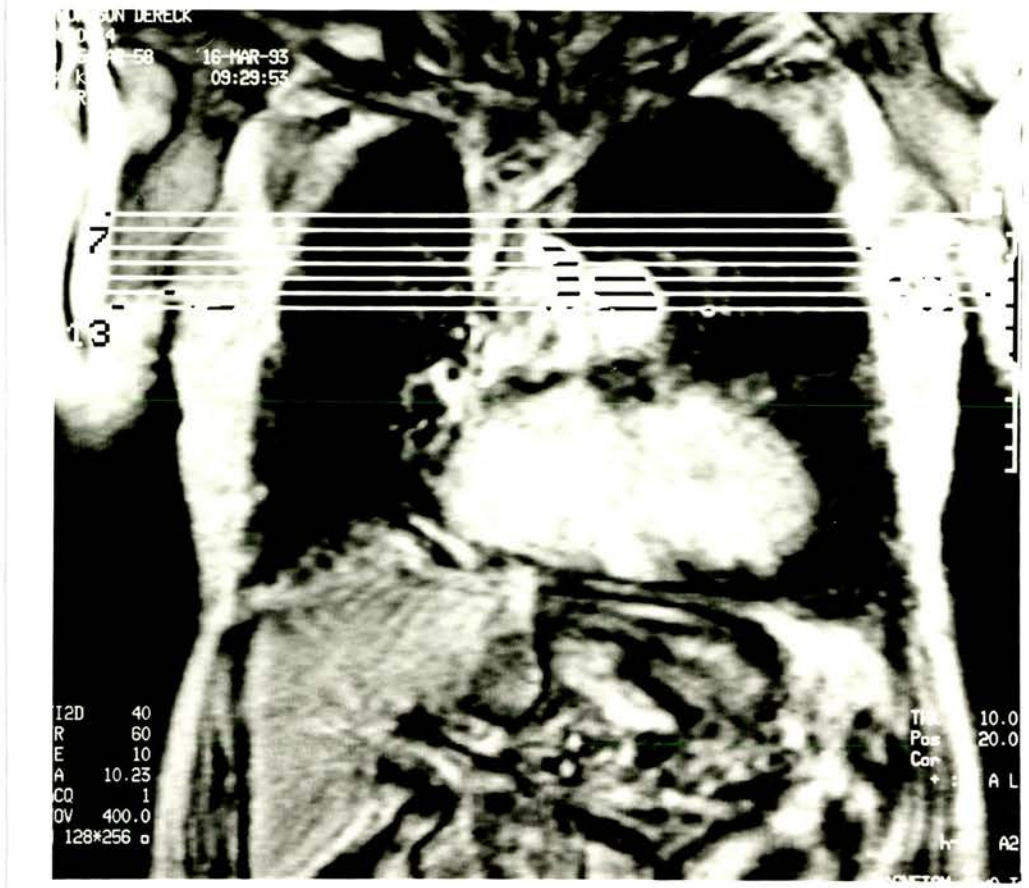


Figure 30.
MRI of thoracic cage and heart - localising scan.

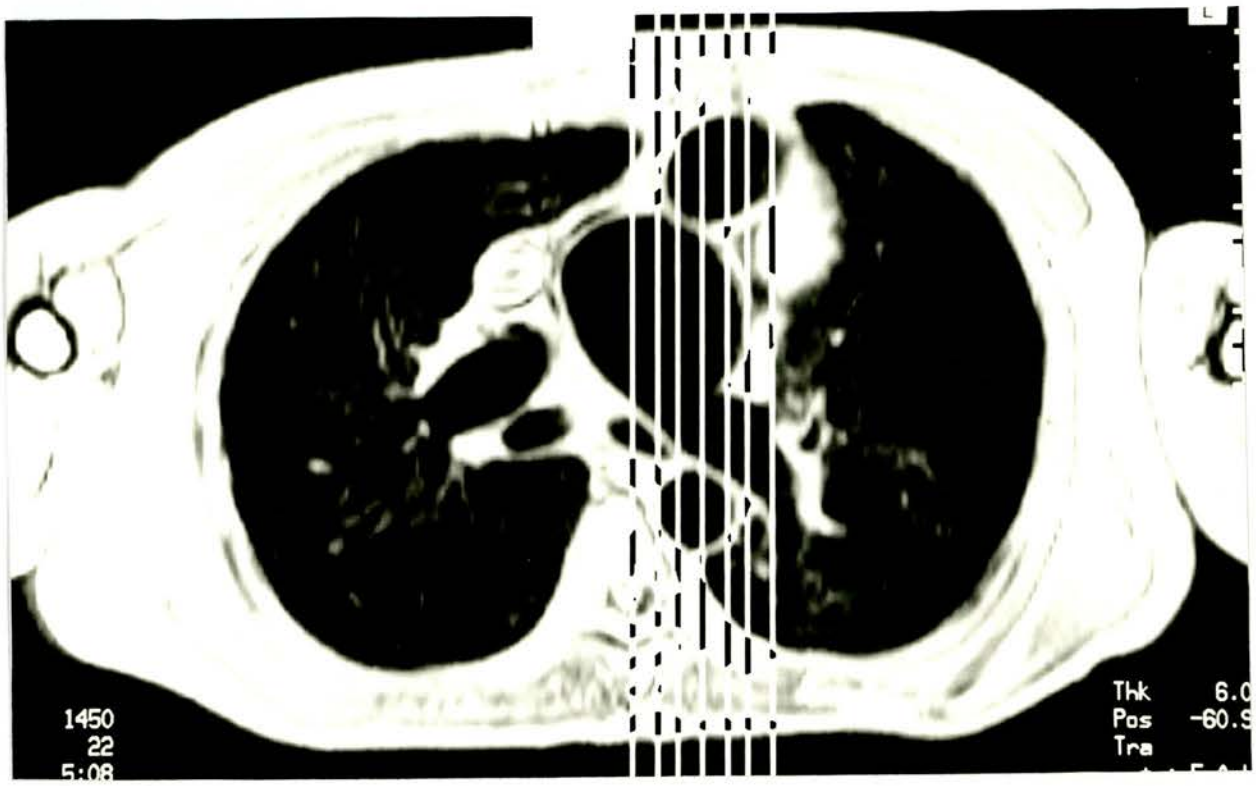


Figure 31a.
MRI - localising scan of left pulmonary artery.

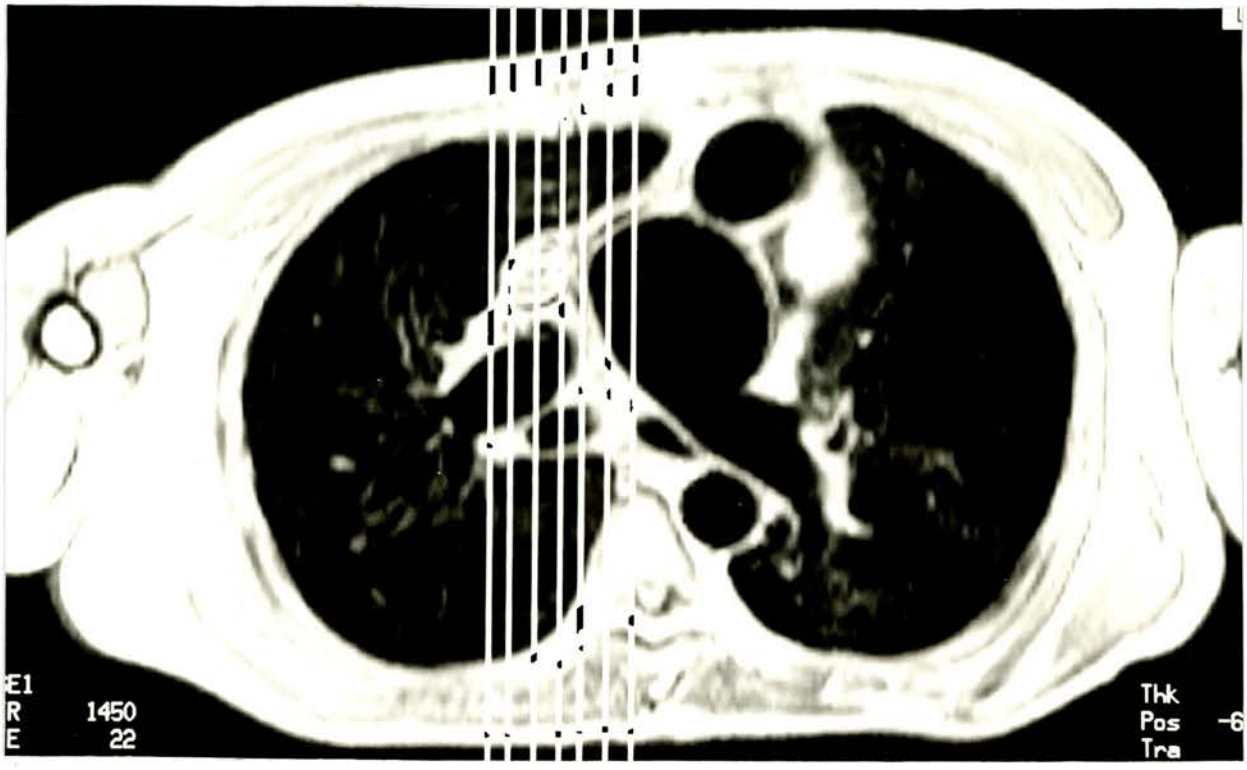


Figure 31b.
MRI - Localising scan of the right pulmonary artery.

These images were used to define separate planes which were truly perpendicular to the two arteries. Further ECG -synchronised, 4mm thick, gradient echo images were obtained at 50 millisecond intervals throughout the cardiac cycle in these planes at two locations along the left and right pulmonary arteries (Figs. 32a, 32b).

The cross-sectional areas at each location of the left and right pulmonary arteries were measured throughout the cardiac cycle using Region-of-Interest software.

Measurements

Regional pulmonary arterial distensibilty was calculated as the percentage of maximal area attained during systole minus the minimal area during diastole, divided by the maximal systolic area.

Pulmonary Flow

One further ECG-synchronised acquisition was performed through the mid-portion of the main pulmonary artery and ascending aorta to obtain velocity phase maps of blood flow throughout the cardiac cycle, the image intensity of the velocity phase maps being proportional to the velocity of flow. The images were displayed in a cine loop which allowed qualitative assessment of blood flow patterns in the main pulmonary artery and ascending aorta. The

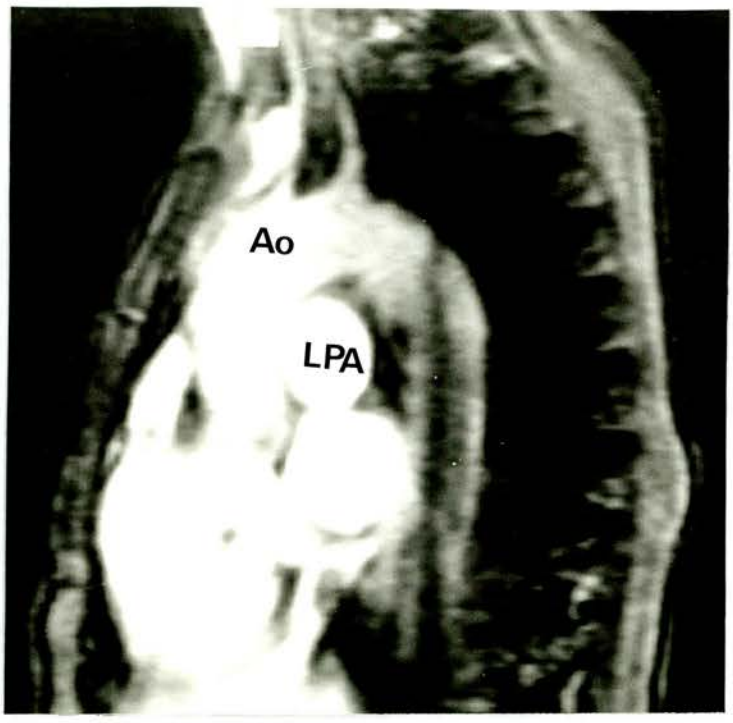


Figure 32a.
Cine MRI - left pulmonary artery (LPA); aorta (Ao).

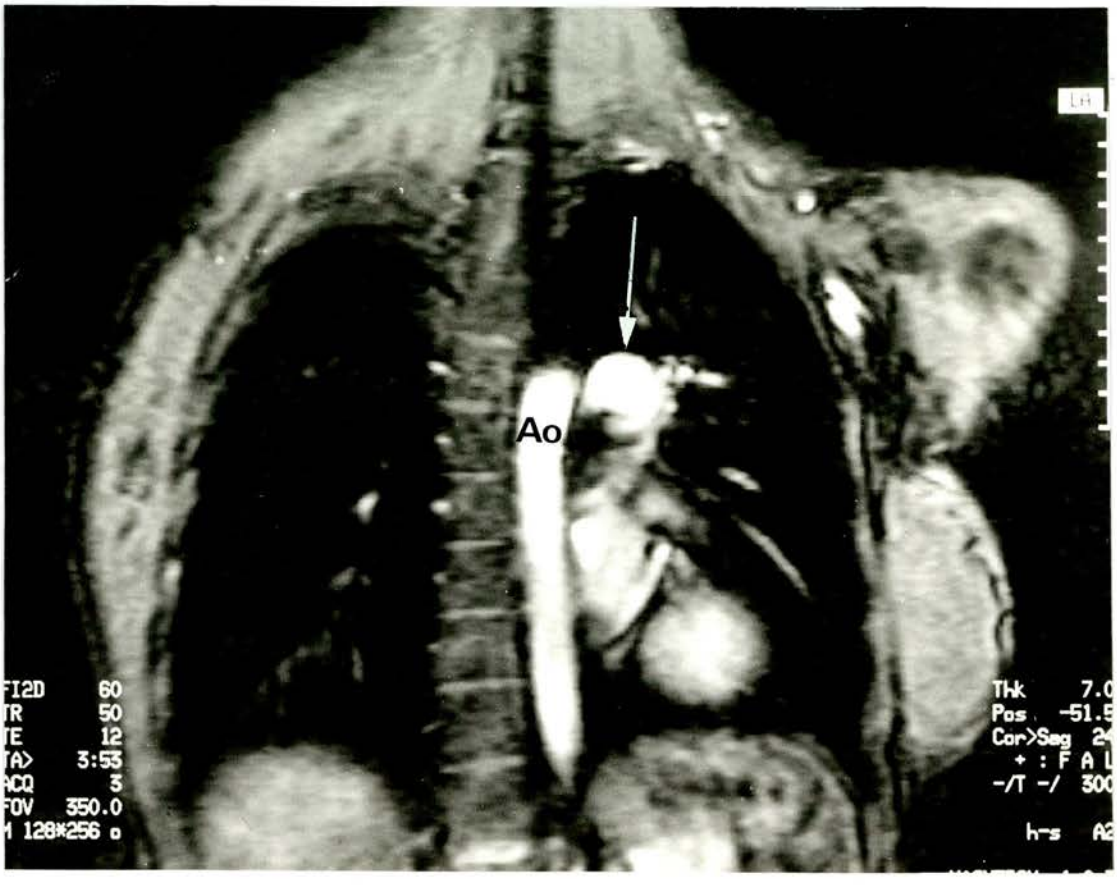


Figure 32b.
Cine MRI of right pulmonary artery (arrow); aorta (Ao).

diameters of the pulmonary artery and aorta were measured above the valve and an area for each calculated (Figs. 33a,33b). Using dedicated software, the resultant phase maps and vessel areas were used to calculate cardiac output from the right and left sides of the heart. The overall shunt or pulmonary to systemic flow (Qp:Qs) was determined from the values of aortic and pulmonary flow.

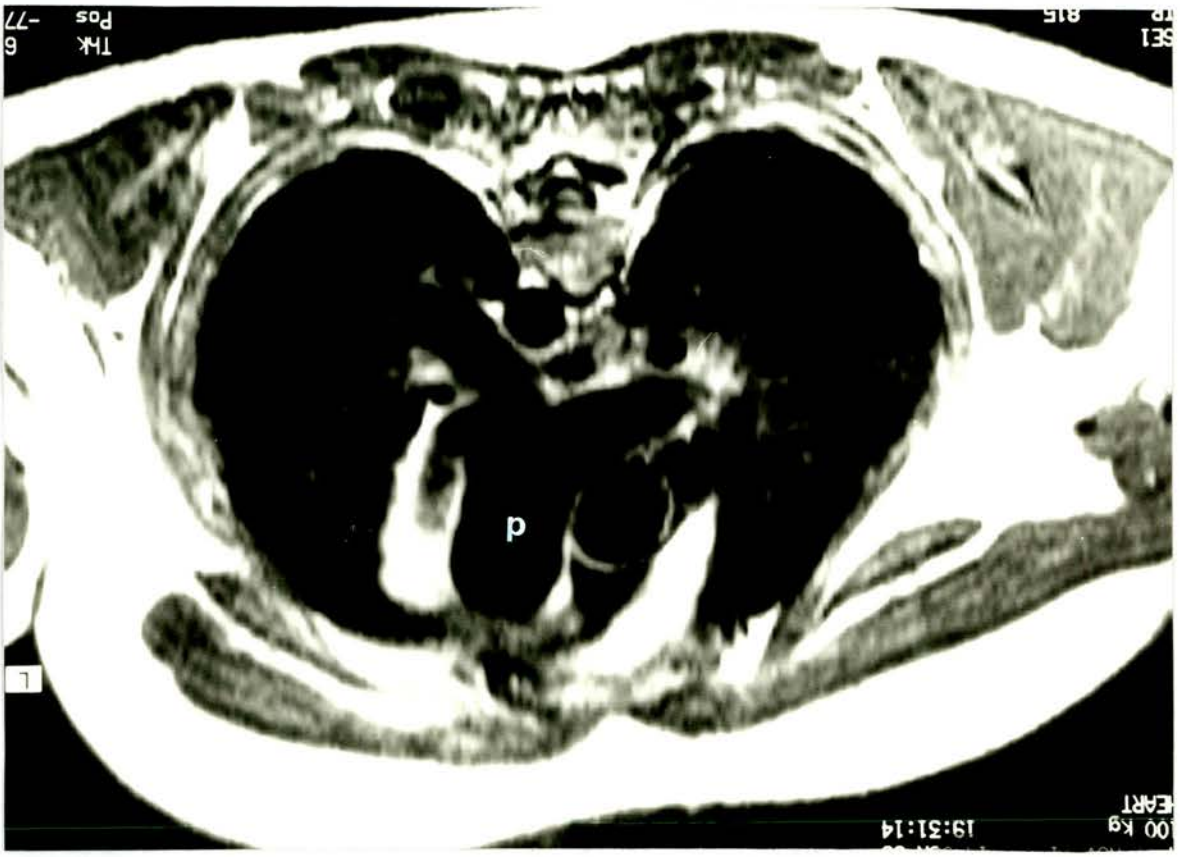


Figure 33a.
MRI of pulmonary trunk (p) and branch pulmonary arteries for flow measurements.

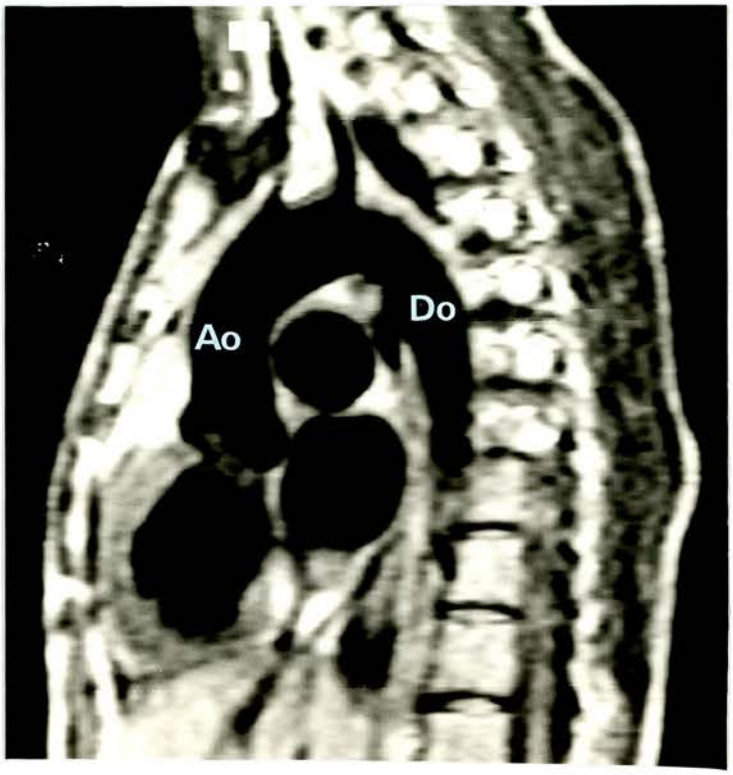


Figure 33b.
MRI of aorta for flow measurements; ascending aorta (Ao); descending aorta (Do).

RESULTS

All the patients tolerated the MRI examination well although two felt slightly claustrophobic. It was possible to obtain satisfactory images of the pulmonary arteries in all patients except one in whom movement artifact made interpretation impossible. Unfortunately due to clinical demands on the MRI equipment used for this study, flow studies were possible on only 7 of the patients with pulmonary hypertension and 3 of the normal subjects.

In all patients, the MR images clearly delineated the cardiac defects, defined pulmonary arterial anatomy and size, and allowed measurement of thoracic cavity size, assessment of systemic venous connections and evaluation of any spinal scoliosis (Figs. 33a, 34). There was excellent correlation between diagnosis made at MRI and that made at previous catheterisation. No MRI examination lasted longer than one hour in any subject and there were no side-effects.

Pulmonary arterial size

The values for pulmonary arterial luminal area are shown in figure 35. Although there is a tendency to increased pulmonary arterial size in the group with pulmonary hypertension when compared with the normal controls, this does not reach statistical significance ($p>0.05$, Mann-Whitney U). The size of the pulmonary artery in normal subjects was remarkably consistent between subjects but smaller in females than in males.

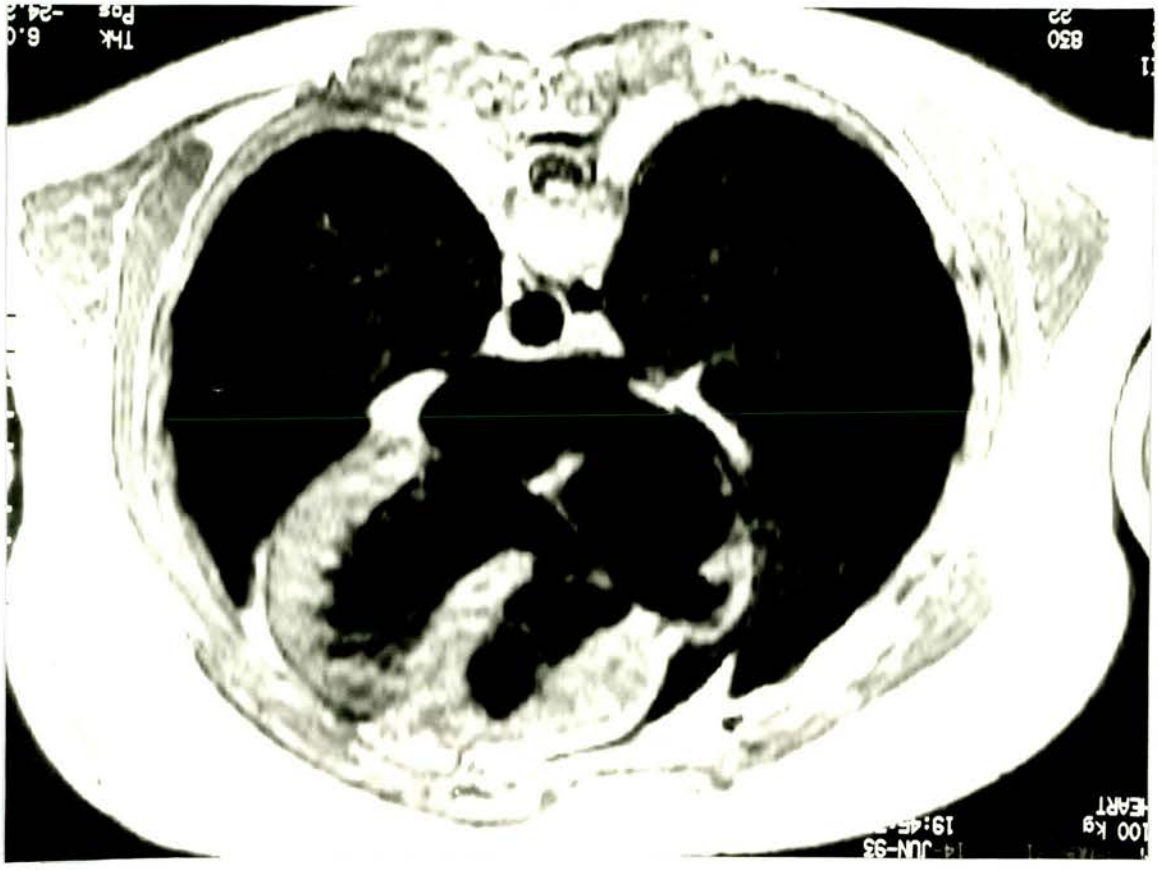


Figure 34.
MRI of heart in a 22 year old female showing a ventricular septal defect. The defect in the ventricular septum is clearly seen.

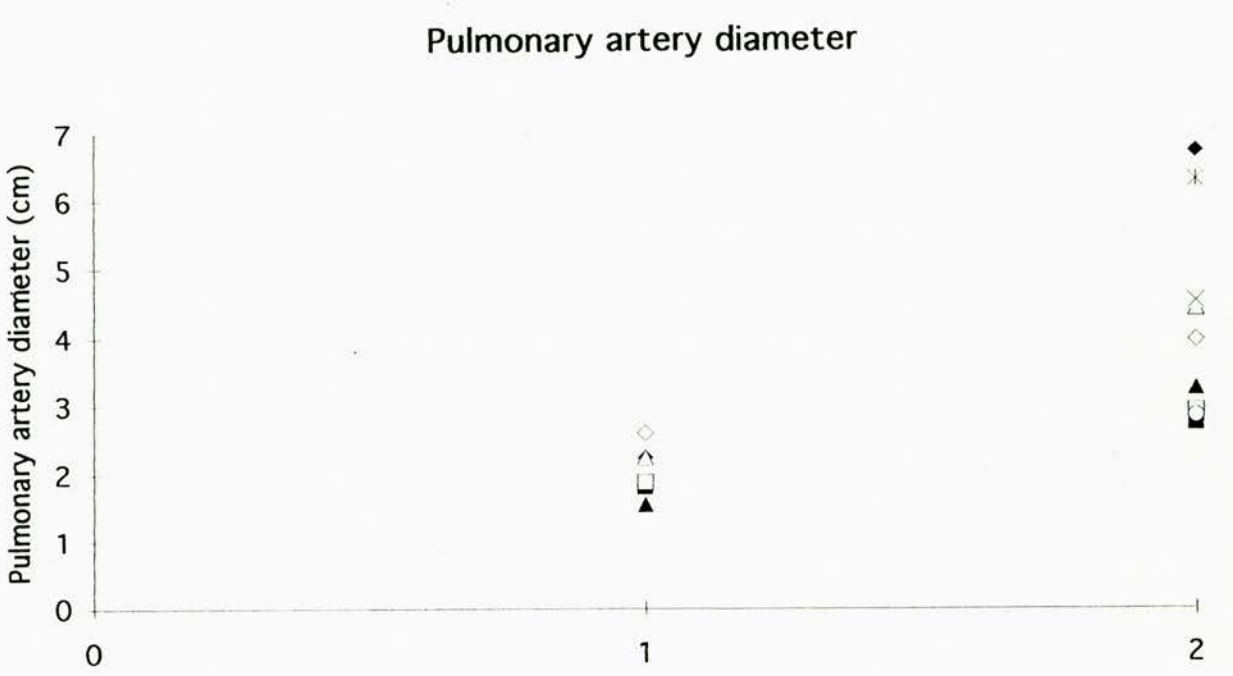


Figure 35.
Comparison of pulmonary arterial diameter between normal subjects (group 1) and patients with pulmonary hypertension (group 2).
There is a tendency towards increased pulmonary aterial diameter in the patients with pulmonary hypertension but this does not reach statistical significance ($p>0.05$, Mann-Whitney U).

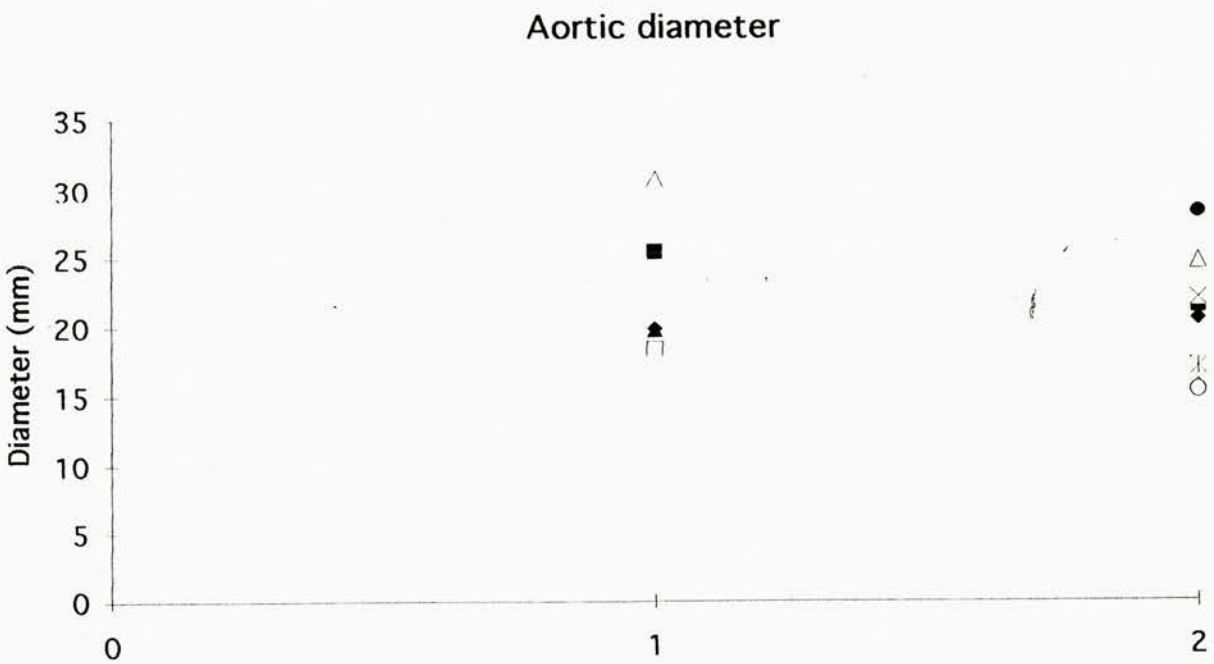


Figure 36.
Comparison between aortic diameter in normal subjects (group 1) and patients with pulmonary hypertension (group 2).
There is no difference between the two groups.

Aortic size

There was no difference in aortic diameter between normals and patients with pulmonary hypertension (Fig. 36).

Pulmonary arterial distensibily

The change in pulmonary arterial diameter throughout the cardiac cycle in the patients with pulmonary hypertension and normal subjects is shown in Figure 37. The time taken to peak distention in the normal subjects is approximately 125-150ms whereas in the patients with pulmonary hypertension the time to peak distention is delayed (approximately 225-250ms).

Figure 38 shows the comparison in maximum distensibility between the two groups. Although there is a tendency towards reduced pulmonary arterial distensibilty in the population with pulmonary hypertension, the results do not reach statistical significance ($p>0.05$, Mann-Whitney-U).

Aortic distensibilty

The results of aortic distensibilty are shown in Figure 39. There is no significant difference between aortic distensibility in the two groups ($p>0.05$, Mann Whitney-U).

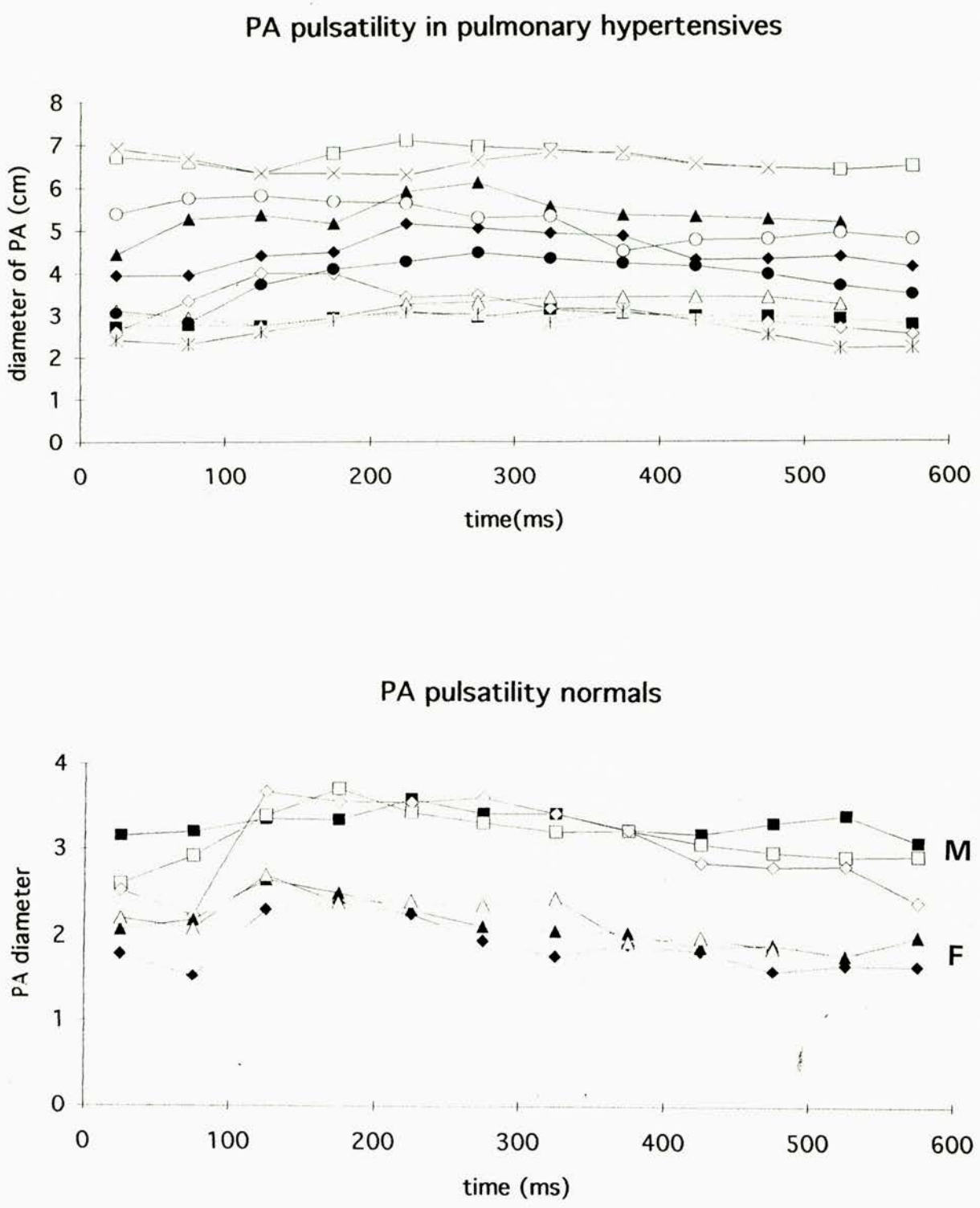


Figure 37.
Pulmonary arterial pulsatility in patients with pulmonary hypertension compared with normal subjects.
In the normal subjects the time to peak distention is approximately 125-150ms, whereas in the subjects with pulmonary hypertension, the time to peak distension is delayed (approximately 225-250ms).

(It can also be noted that in the normal subjects, pulmonary arterial diameter is smaller for females than for males).

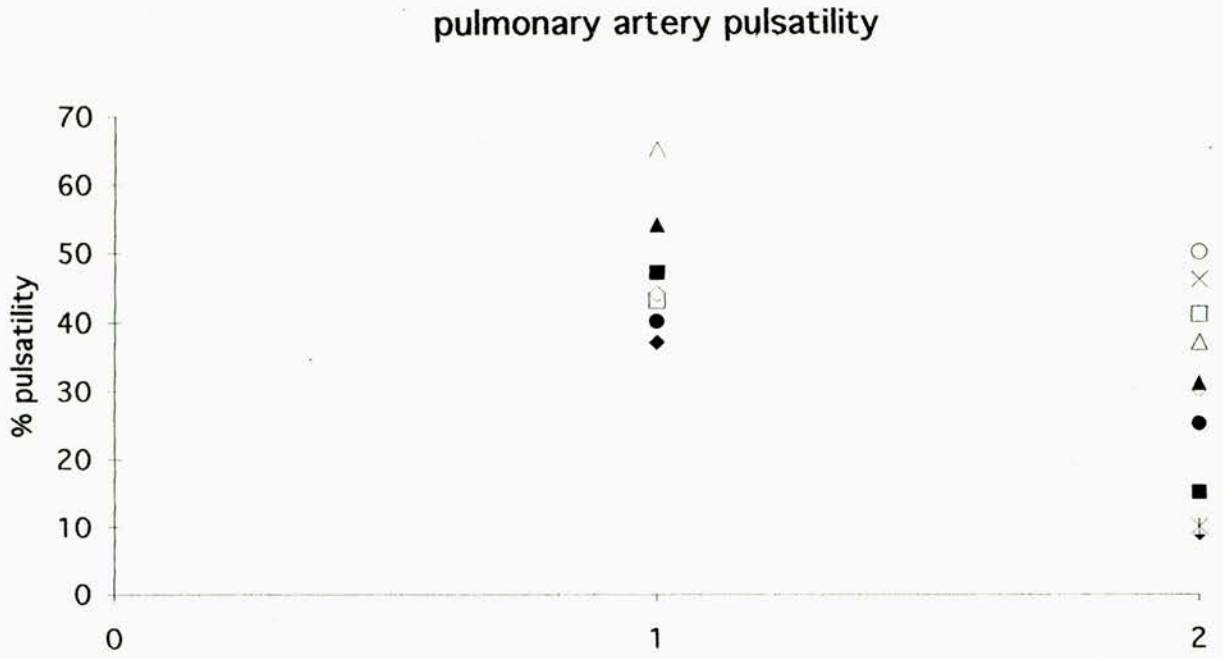


Figure 38.
Comparison of maximum distensibilty (% change in pulmonary artery size) between normal subjects (group 1) and patients with pulmonary hypertension (group 2).
There is a tendency to reduced pulmonary arterial distensibilty in patients with pulmonary hypertension but this does not reach statistical significance, ($p>0.05$, Mann-Whitney U).

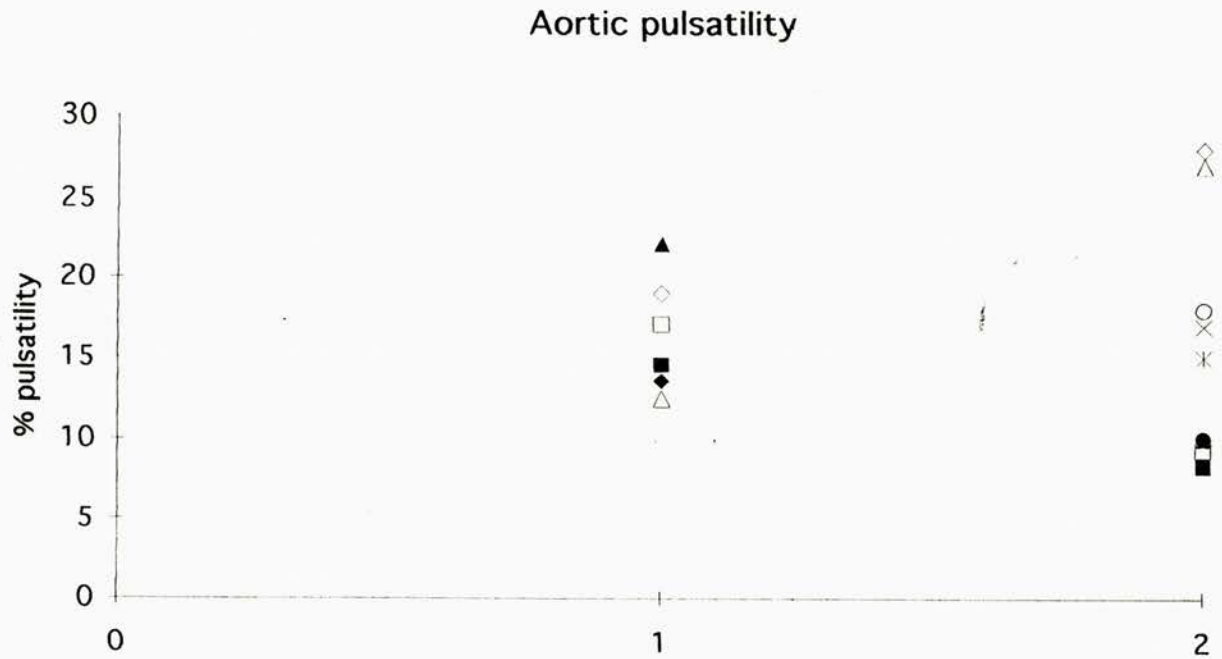


Figure 39.
Comparison between aortic distensibility in normals subjects (group 1) and patients with pulmonary hypertension (group 2).
There is no difference between the two groups.

Pulmonary arterial distensibilty and vessel diameter

There is a significant correlation between reduced pulmonary arterial distensibilty and increased pulmonary arterial diameter ($p<0.009$, Spearman Rank Correlation) (Fig. 40).

Shunt Measurements

Table E shows the values for pulmonary and aortic forward and regurgitant flow, estimated Qp:Qs by MRI and calculated Qp:Qs at catheterisation. The normal subjects have an expected Qp:Qs of approximately 1:1 as measured by MRI as does the patient JS, who had undergone surgical closure of shunt (patent arterial duct) in childhood.

In the patients with uncorrected shunts, there was overall poor correlation between values of Qp:Qs obtained at cardiac catheterisation and values obtained at MRI, mainly due to the marked overestimation of Qp:Qs in two patients by MRI (Table E and Fig. 41).

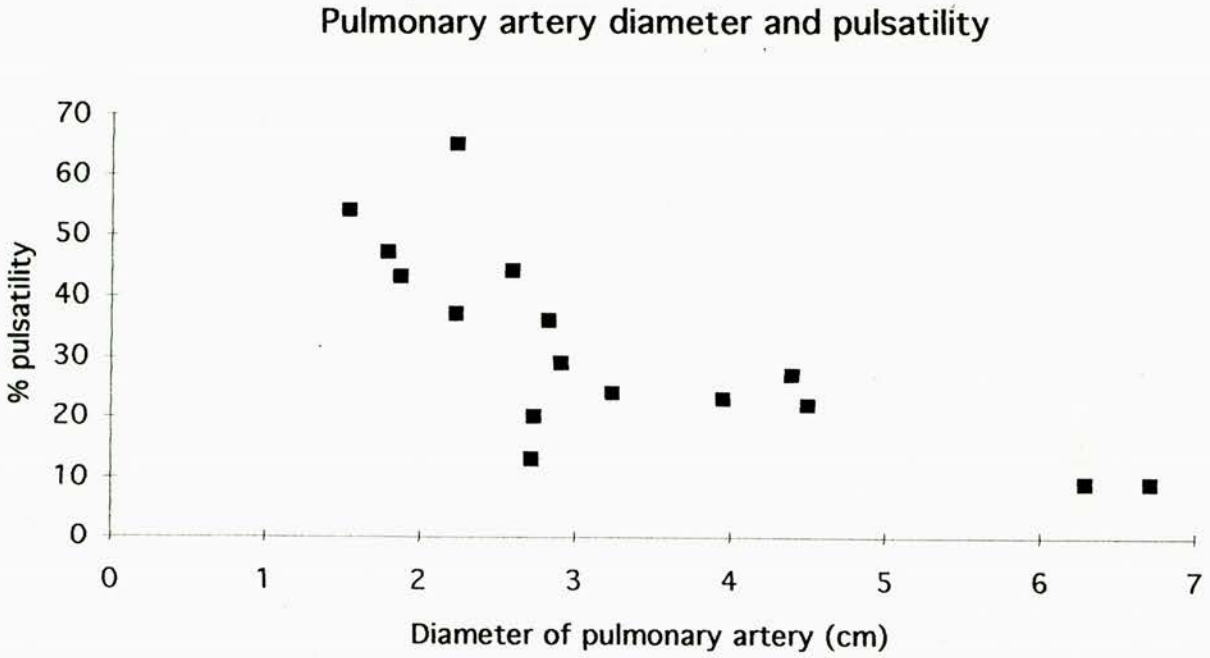


Figure 40.
Correlation between pulmonary arterial size and distensibility.
The greater the pulmonary arterial diameter, the less the distensibilty ($p<0.009$, Spearman Rank Correlation).

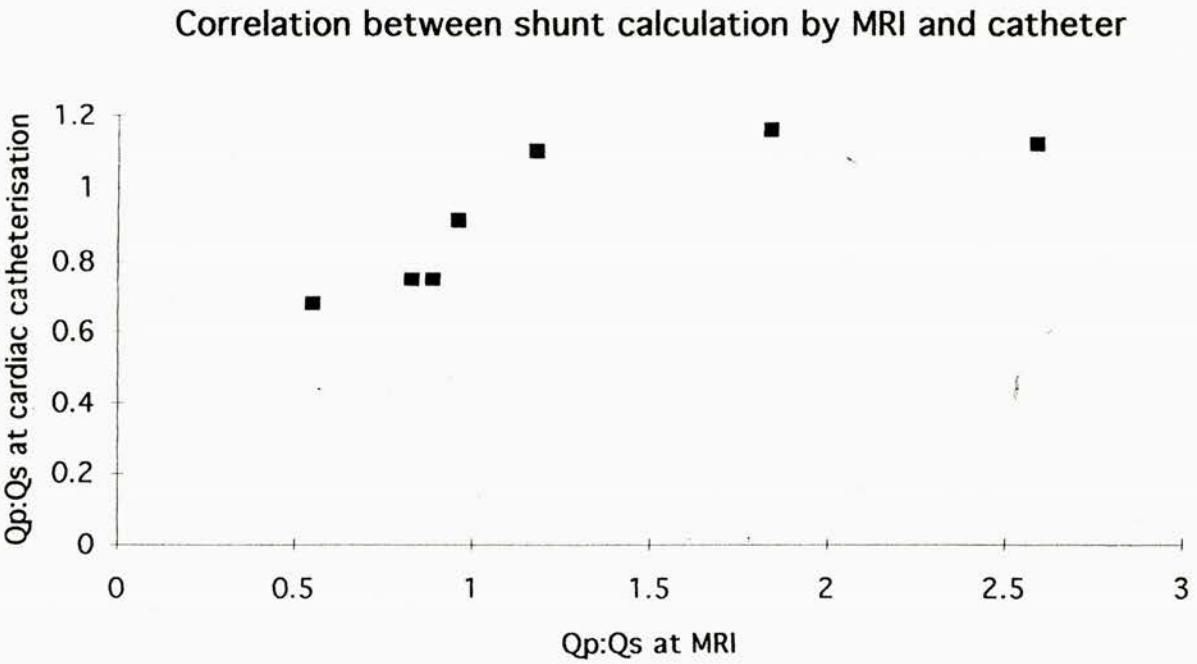


Figure 41.
Correlation between shunt calculation of Qp:Qs at MRI and cardiac catheterisation.
There is good correlation between methods of measurement in 4 patients but in the other 2 patients, Qp:Qs has been greatly overestimated by MRI, making overall correlation between the two methods poor.

Table E. MRI measurements of flow and shunts

Name	Ao flow	pulm flow	Qp:Qs(MRI)	Qp:Qs(cath)
SF(normal)	88	89.3	1.01	-
AH(normal)	83.3	75.9	0.91	-
AS(normal)	77.5	83	1.07	-
CB(PHT)	96.7	86.0	0.89	0.75
*JS(PHT)	80.7	95.5	1.18	1.1
KAS(PHT)	102.4	84.9	0.83	0.75
DB(PHT)	59.4	109.4	1.84	1.16
AT(PHT)	25.3	13.9	0.55	0.68
DT(PHT)	96.5	250	2.59	1.12
SL(PHT)	45.6	43.8	0.96	0.91

Ao flow; aortic flow (mls/s), Pulm flow; pulmonary flow (mls/s), Qp/Qs(MRI); pulmonary to systemic shunt measured by MRI; Qp/Qs cath; pulmonary to systemic shunt measured at cardiac catheterisation.

PHT; pulmonary hypertension.

* = Patient in whom shunt (patent arterial duct) had been closed surgically.

DISCUSSION

Technical considerations

The construction of an MRI image is dependent upon a series of acquisitions gated to the patient's ECG, therefore it is necessary for the patient to remain still or the effect of movement artifact will obscure images. This was a problem in two patients scanned who had a persistent cough.

The quality of MRI images is relatively operator independent but for studies to measure pulmonary arterial diameter it is important to obtain a clear cross sectional image parallel to each pulmonary artery and it requires a skilled operator to locate the sites. It is easier to obtain a satisfactory cross-sectional image of the left pulmonary artery as opposed to the right as the latter passes posteriorly beneath the aortic arch, whereas the left can be easily imaged in a saggital section (Figs. 32a, 32b). As measurements of pulmonary artery size and distensibility are likely to be more accurate and reproducible if the left pulmonary artery is used, the left was used for comparisons in this study.

An additional problem in the assessment of pulmonary arterial pulsatility using cine MRI is the effect of turbulent blood flow within vessels. Areas of turbulent flow at the edges of vessels result in loss of contrast and thus a tendency to underestimate vessel area.[116] This must be taken into consideration when measuring luminal area by MRI. The same artifact can lead to poor

reproducibility of measurements, but if the observers are aware of the problem, reproducibility is good.

Pulmonary artery dilatation

Postmortem studies on strips of artery show that the elasticity of a vessel diminishes the more it is stretched from its original size.[118] In patients with left to right shunts increased pulmonary blood volume results in pulmonary arterial dilatation. As pulmonary hypertension develops, increased intravascular pressure and resistance contribute further to dilatation of the pulmonary vessels. The influences of and individual responses to each of these factors will vary and is likely to explain the wide variation in pulmonary arterial diameter on MRI in pulmonary hypertensives, which ranged from upper 'normal' to markedly dilated. This would explain why although there was a definite trend towards increased pulmonary arterial diameter compared with normals the values did not reach statistical significance. An additional contributing factor to lack of statistical significance is the small sample studied.

Pulmonary arterial pulsatility

Our values for pulmonary arterial pulsatility were higher both for normals and pulmonary hypertensives than values quoted in previous studies.[115-117] In our study we measured pulmonary arterial luminal area throughout the cardiac cycle, calculating pulsatility from the maximum and minimum area measured during one cardiac cycle. All previous studies have calculated pulsatility from a

single systolic and single diastolic image timed from the patient's ECG. The latter method would not necessarily give the maximum and minimum luminal area and it is possible that pulmonary arterial pulsatilty would be underestimated. This is especially true as the the time to peak distention appeared to be delayed in pulmonary vascular disease, possibly due to the increased pulmonary vascular resistance.

Flow Studies

Studies using ultrasound and Doppler to measure cardiac output and calculate shunts have shown that in adults, measuring the aortic diameter above the valve tends to overestimate systemic cardiac output as the aorta widens above the valve.[119] More accurate measurements can be obtained if the aortic diameter is measured at the level of the valve leaflets or even in the left ventricular outflow tract.[119] As the difference is less significant in children and young adults,[120,121] in this study the aortic and pulmonary measurements were made above the valve. However, the pulmonary arterial dilatation which occurs in pulmonary hypertension could lead to overestimation of pulmonary flow.

Shunts

Calculation of Qp:Qs in the normal subjects gave the normal expected values of 1:1. In the subjects with pulmonary hypertension, however, the measurements of Qp:Qs at MRI correlated well with those at cardiac catheterisation for five

of the patients but very poorly for the other two patients. There are a number of factors likely to contribute to inaccuracies in shunt calculation using the MRI method described above. First, as described above, pulmonary arterial dilatation secondary to pulmonary hypertension may result in overestimation of pulmonary flow and right sided cardiac output.[122] Second the flow in the main pulmonary artery is unlikely to be laminar, due to the contribution of flow from the shunt itself and a variable degree of pulmonary regurgitation which is common when pulmonary arterial pressures are elevated. Third, pulmonary regurgitation itself is likely to cause overestimation of effective cardiac output. Thus, whereas MRI can provide a non-invasive method of estimating cardiac output in patients without shunts, in those with shunts, values obtained using the above techniques can be inaccurate.

Conclusions

This study shows that dilated pulmonary arteries, reduced pulmonary arterial pulsatility and delayed peak distention are features evident on MRI examination which are consistent with elevated pulmonary arterial pressures and pulmonary vascular resistance in patients with left to right shunts. MRI is a useful examination for the confirmation of cardiovascular anatomy, measurement of thoracic volumes and assessment of spinal scoliosis in patients considered for cardiopulmonary transplant. Pulmonary arterial studies to measure pulmonary arterial pulsatilty, size, flow pattern and time to peak distensibility help to confirm elevated pulmonary vascular resistance but cannot predict severity or

reversibility. If values of pulmonary vascular resistance and indices of reversibilty are required cardiac catheterisation is still necessary.

Nevertheless, MRI should not be discarded as a technique for measuring syystemic to pulmonary shunts and pulmonary vascular resistance. With new developments in magnetic resonance angiography, it may become possible to measure pulmonary blood flow in distal vessels. The distal vessels should be less subject to factors affecting flow measurement in the main pulmonary arteries. Using measurement of flow in peripheral pulmonary arteries MRI could become a noninvasive method of measuring systemic to pulmonary shunts and pulmonary vascular resistance as well as response to pulmonary vasoactive agents in the future. [123]

CHAPTER 6

MORPHOLOGY OF ELASTIC PULMONARY ARTERIES

A MORPHOMETRIC STUDY

Heath-Edwards Grades

The observation that pulmonary vascular disease was progressive led Heath and Edwards to grade the morphological changes according to severity (Table B)[9]. Following the introduction of routine cardiac catheterisation which allowed direct measurement of pulmonary arterial pressure, calculation of pulmonary vascular resistance and assessment of reversibilty, attempts were made to correlate histological changes with haemodynamic findings. Irreversibilty of pulmonary vascular resistance appeared to correlate with grade 3-4 on the Heath- Edwards grades (i.e., the development of complex vascular lesions), but the overall correlation between Heath-Edwards grades and pulmonary haemodynamics was generally poor.[8] In addition it was noted that the morphological changes of pulmonary vascular disease tended to be patchy, findings on a single biopsy were not necessarily representative of the the whole lung and that multiple biopsies were required for an accurate assessment of pulmonary vascular disease to be made.

Rabinovitch Grades

In 1978 Rabinovitch, Haworth and colleagues took a more morphological

approach to grading pulmonary vascular disease.[8] They assessed arterial size, muscularity and alveolar to arteriolar ratio in lung biopsies and developed a grading system, A to C. This grading system proved to have a good correlation with haemodynamic data .[8,124]

Grade A is extension of muscle into smaller and more peripheral arteries than normal. It is associated with an increase in pulmonary blood flow without an increase in pulmonary arterial pressure. In grade B, the changes of grade A are seen but there is also thickening of the medial muscular coat of the small intra-acinar arteries. If the thickening is mild, it is not associated with elevated pulmonary vascular pressures, but if the media is greater than twice normal, it is invariably associated with pulmonary hypertension. Grade A and B are refinements of Heath-Edwards grade 1 and 2. Grade C represents more severe disease. In addition to extension of muscle and medial thickening, there is reduction in the number of small arteries and increase in alveolar to arteriolar ratio. This change is associated with an elevation in pulmonary vascular resistance.

Quantitative Morphology of Elastic Pulmonary Arteries

Although it has long been recognised that medial thickening occurs in the larger elastic pulmonary arteries as well as the muscular arteries, the morphological changes in the elastic pulmonary arteries have not been quantified. [6,7] Until the advent of intravascular ultrasound with its ability to image the vessel wall, it

was only possible to examine the morphology of the vessel wall at post-mortem, which is of little use for making decisions about live patients. As it is now possible to image the vessel wall of elastic pulmonary arteries using intravascular imaging, it is useful to establish what morphological changes would be expected on imaging. In addition, if there proved to be a relation between degree of vessel wall thickness in the elastic pulmonary artries and severity of pulmonary vascular disease, intravascular ultrasound could theoretically provide a method of assessing pulmonary vascular morphology in infants without the need for lung biopsy.

Aims

The aim of this study was to quantify the degree of vessel wall thickening in the elastic pulmonary arteries in infants under the age of five and to determine:

1. Whether medial thickening of the elastic pulmonary arteries is a feature of infants with pulmonary hypertension.

2. Whether there is a correlation between degree of vessel wall thickening and severity of pulmonary vascular disease.

3. Whether the morphological changes in the elastic pulmonary arteries in pulmonary hypertension would be detectable by intravascular imaging in life.

METHODS

Specimens of lungs from infants and children who died with pulmonary hypertension were obtained from the Killingbeck Collection, which consists of specimens of intact heart and lungs from postmortems performed on patients with congenital heart disease during the period 1965-1989. Lungs studied were from infants and children less than age 10 with documented pulmonary hypertension.

Tables F_{1-3} show the clinical details of the infants.

Controls

Normal lungs were obtained from infants who died from sudden infant death syndrome, age 6 months to 2 years, in whom no pathological abnormality was detected at postmortem.

Preparation of specimens

The cardiac lesion was identified and noted. The lungs were dissected from the heart at the hilum. 4mm thick slices of lung tissue were cut from the hilum and periphery from upper and lower lobes of each lung, perpendicular to the line of the pulmonary vessels. The lingula was avoided as the muscle coat tends to be thicker in this region of the lung. Several 5μm sections were taken from each slice. Sections were stained with Haematoxylin and Eosin and Elastin Van Giesen and then examined by microscopy. Vessels of 500μm-3mm in diameter

Table F_1. Patient details, age 0-12 months.

Name	Age at death	Diagnosis	PAP	H/E	Ao	PA	PA/Ao	Med 1	Med 2
AS(m)	3 weeks	VSD, TGA, CoA	N/A	I	6	15	2.5	0.06	0.21
SS(f)	3 months	VSD	75%	I	6	13	2.1	0.04	0.18
EY(f)	3 months	VSD	N/A	I	10	15	1.5	0.03	0.16
KG(f)	4 months	CoA/PDA	75%	I	9	15	1.7	0.08	0.29
LJ(f)	4 months	VSD	N/A	I	10	12	1.2	0.05	0.19
GM(f)	5 months	VSD	75%	I	9	12	1.3	0.04	0.18
*LB(f)	5.5 months	Pulm vein stenosis	syst	I	10	10	1	0.04	0.18
*NC(f)	8 months	PDA	syst	I	10	10	1	0.06	0.26
JD(f)	9 months	VSD	N/A	II	8	12	1.5	0.05	0.19
PY(m)	10 months	DORV	syst	III	12	15	1.2	0.05	0.20
JB(f)	10 months	VSD	75%	I	6	15	2.5	0.06	0.19

Table F_2. Patient details, age 12-24 months

Name	Age at death	Diagnosis	PAP	H/E	Ao	PA	PA/Ao	Med 1	Med 2
MW(m)	13 months	DILV, DORV, CoA	syst	II	10	13	1.3	0.03	0.16
PR(f)	14 months	VSD	syst	II	8	13	1.6	0.06	0.26
DB(m)	15 months	VSD	50%	I	8	16	2.0	0.09	0.25
KW(m)	18 months	Multiple VSD's	syst	III	10	12	1.2	0.06	0.21
JR(f)	19months	AVSD, DORV, TAPVD	N/A	I	12	8	0.7	0.02	0.09
*JJ(m)	20 months	TGA, Mustard's	syst	IV	15	24	1.6	0.05	0.24
AA(m)	22 months	AVSD	syst	III	8	18	2.25	0.05	0.26

Table F_3. Patient details, age >2 years.

Name	Age at death	Diagnosis	PAP	H/E	Ao	PA	PA/Ao	Med 1	Med 2
JL(m)	2.5 years	Multiple VSD's	75%	II	12	14	1.2	0.04	0.21
CS(f)	2.5 years	AVSD, PAB	75%	II	10	10	1	0.04	0.18
CB(m)	3.5 years	TGA, VSD	75%	IV	12	25	2.1	0.04	0.15
DK(m)	7 years	TGA, VSD, TR	syst	IV	10	18	1.8	0.06	0.28
SF(m)	8 years	AVSD, MVR	syst	III	12	12	1	0.03	0.16
MM(f)	9 years	AVSD, MVR	syst	I	12	20	1.7	0.03	0.12

PAP; pulmonary arterial pressure compared to systemic pressure at catheterisation, H/E; Heath Edward's grade of pulmonary vascular disease, Ao; diameter of ascending aorta(mm), PA; diameter of pulmonary trunk(mm), Med 1; mean medial thickness(mm) of vessel 0.5-1mm, Med 2; mean medial thickness(mm) of vessels 3-3.5mm, N/A; data not available, m; male, f; female VSD; ventricular septal defect, AVSD; atrioventricular septal defect, TGA; transposition of the great arteries, CoA; coarctation, MVR; mitral valve regurgitation, PAB; pulmonary artery band, PDA; patent arterial duct, DORV; double outlet right ventricle, DILV; double inlet left ventricle, TAPVD; total anomalous pulmonary venous drainage, TR; tricuspid regurgitation.

were assessed. An average of 40 vessels was studied for each specimen of heart/lungs. The intima was examined for thickening and evidence of atherosclerosis. Using an image analyser, medial thickness was measured in 4 regions for each vessel and a mean medial thickness for each vessel obtained. The mean medial thickness was compared against total vessel thickness (Fig42).

Aorta and pulmonary trunk

The diameters of the aorta and pulmonary trunk were measured. Sections were then cut from the aorta and pulmonary trunk and the morphology of the media of the pulmonary trunk was compared to that of the aorta for 'aortification' of the pulmonary trunk.

Peripheral vessels

The peripheral vessels were graded according to the Heath Edwards grades by an experienced pathologist and compared with the values of medial thickness for the elastic pulmonary arteries.

Analysis of results

For each specimen, an average medial thickness was obtained for each vessel size. Vessel sizes were divided into the following groups:-

0.5-1mm; 1-1.5mm; 1.5-2mm; 2-2.5mm; 2.5-3mm; 3-3.5mm.

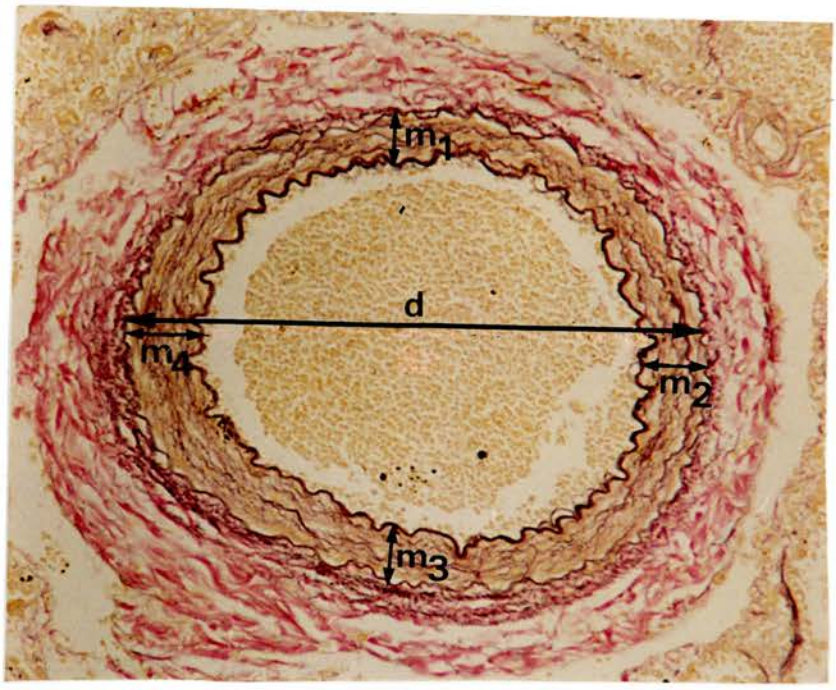


Figure 42.
Method of measuring medial thickness. (x25) (Elastin Van Giesen)
The thickness of the media is measured in four places (m_{1-4}) and an average medial thickness obtained. The maximum diameter of the vessel is measured (d). Medial thickness can then be expressed as a percentage of total vessel diameter.

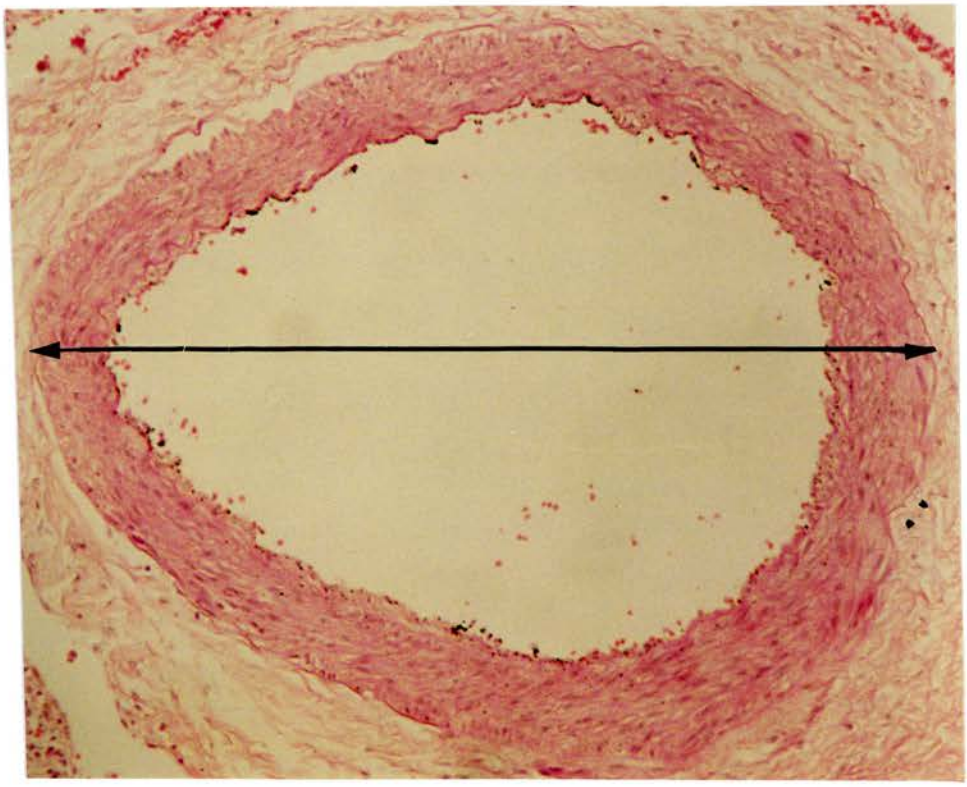


Figure 43.
Ellipsoid vessel. (x 10) (Haematoxylin and Eosin)
As a result of fixation without injection, vessels can collapse resulting in an ellipsoid shape. In such cases the maximum vessel diameter was measured (double headed arrow).

Patients were divided into the following age groups:-

0-6 months; 6-12 months; 12-24 months; >24 months.

For each patient age group the range of medial thickness for each vessel size was plotted on a graph. The results were compared with the values obtained from the normals and analysed for statistical significance using the Mann-Whitney U test.

RESULTS

Number of vessels analysed

An average of 40 vessels was analysed for each patient. The diameter of the vessels studied ranged from 0.5mm to 3.5mm.

Patient Age

24 (13 females) specimens of pulmonary hypertensive lungs and 8 specimens from children who died from sudden infant death syndrome were studied. The age at death for the children with pulmonary hypertension ranged from 3 weeks to 9 years, consisting of 7 less than 6 months old, 4 aged 6-12 months, 7 aged 12-24 months, and 6 over the age of 2 years. The age of death for the patients with sudden infant death syndrome ranged from 6-18 months.

Pulmonary arterial pressures

Data from cardiac catheterisation was available for 19 patients. In all of these patients pulmonary arterial pressure was at least half systemic and was systemic or suprasystemic in 11 patients (Table F).

Cardiac Diagnosis

The main diagnosis of those who died with pulmonary hypertension less than 6 months old was ventricular septal defect, but the older patients tended to have more complex lesions. All patients except three (marked by * in Table F) died following palliative or corrective cardiac surgery, most within 24 hours. Of

the three who died other than following surgery, one (LB) died at the time of diagnostic cardiac catheterisation, one (NC) died from progressive pulmonary hypertension and one (JJ) died a sudden death outside hospital.

Drugs

Most of the patients were prescribed Digoxin, Frusemide and Potasium Chloride. No other medications were documented.

Diameter of pulmonary trunk

All of the patients except one had a degree of dilatation of the pulmonary trunk when compared with the ascending aorta. In 6 patients the pulmonary trunk was at least twice the diameter of the ascending aorta. There was no correlation between dilatation of the pulmonary trunk and age at death or severity of pulmonary vascular disease. In one patient who had a degree of subpulmonary stenosis (JR) the diameter of the pulmonary trunk was less than that of the aorta.

Severity of pulmonary vascular disease

All the infants less than age 6 months had Heath Edwards grade I changes of pulmonary vascular disease. More severe changes were seen in patients over the age of 6 months. In patients over the age of 2 years only one had histological changes less severe than Heath Edwards grade II. This patient had undergone repair of an atrioventricular septal defect in the first year of life but

had severe residual mitral regurgitation. None of the infants less than two years old had evidence of atherosclerosis.

The three patients with the most advanced pulmonary vascular disease (Heath-Edwards grade IV) all had transposition of the great arteries; two also had a ventricular septal defect and one (JJ) who had previously undergone a Mustard's procedure, had severe baffle obstruction of the pulmonary venous channel. All three patients had evidence of atherosclerosis in the elastic pulmonary arteries.

Medial thickness

In the normals the range of medial thickness for each vessel size was remarkably consistent between individuals (fig. 44) but more variable in the infants with pulmonary hypertension for each age group. The mean medial thickness for each vessel size, however, was relatively similar between age groups.

There was no statistically significant difference between the mean values of medial thickness from normals compared with pulmonary hypertensives (Mann-Whitney U test). There was, however, an overall increase in medial thickness of approximately 0.02-0.03mm in vessels of 0.5-1mm and an increase of 0.03-0.05mm in vessels of 3-3.5mm, in patients with pulmonary hypertension when compared with normals.

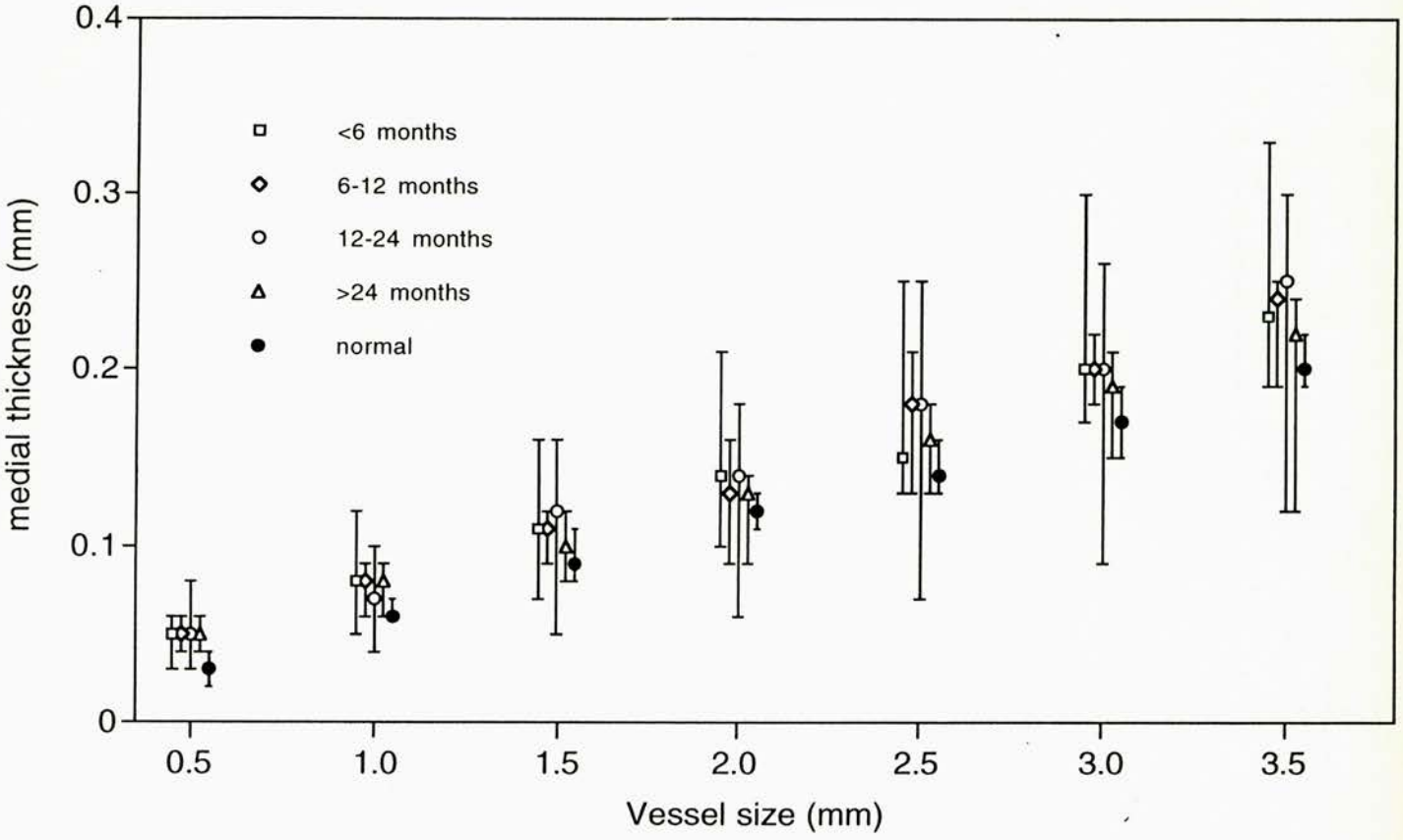


Figure 44.
Comparison of mean medial thickness between normal subjects and patients with pulmonary hypertension.

Between the normals subjects, the values of medial thickness for each vessel size are remarkably consistent.

In patients with pulmonary hypertension, there is a wide range of medial thickness for each vessel size in each age group.

In patients with pulmonary hypertension, *mean* medial thickness is similar for each vessel size between age groups.

Intravascular ultrasound - histological Correlation

There have been numerous studies attempting to correlate findings on imaging of vessels by intravascular ultrasound with findings at histology. All these studies have been of systemic vessels and there are no similar studies of the pulmonary arteries.[37,40,41]

There are several reasons why accurate in-vitro histological correlations are likely to be difficult in the pulmonary arteries. First, it would be difficult to simulate the effects of adjacent moving lung tissue which are likely to induce significant artifact and must be considered when imaging intrapulmonary vessels. In addition it would be difficult to identify the exact site of imaging for precise histological correlation when imaging vessels within the lung.

Initially, as part of this thesis an attempt was made to carry out in-vitro histological correlations using fresh pig lungs obtained from the local abbatoir. Pig lungs were chosen due to the similarity of their pulmonary arteries to humans'. The lungs were immersed in a water bath and the intravascular ultrasound catheter introduced directly into the pulmonary tree. Despite immersion in water, it was impossible to centralise the ultrasound catheter within the vessels. Due to the catheter's proximity to the vessel wall, problems of 'ring down' artifact were encountered and the vessel lumen appeared ellipsoid. In addition, there was poor imaging resolution with the production of

very poor images which were of insufficient quality for analysis. This is probably because our method of eliminating air from the pulmonary arteries was inadequate resulting in poor transmission of ultrasound.

Due to the difficulty in obtaining satisfactory in-vitro correlations it was decided to proceed first to study postmortem specimens of pulmonary arteries in patients with pulmonary hypertension to determine whether vessels accessible to intravascular imaging would have sufficient morphological changes to be detectable by the technique.

Patient population

Most infants with left to right shunts who develop pulmonary vascular disease (with the exception of those with atrial septal defects)[125] will have irreversible changes by the age of 5 years.[16] As the purpose of this study was to document the morphological changes in the elastic pulmonary arteries in patients with reversible compared to irreversible pulmonary vascular disease the age of population examined was 0-10 years. As most other non-cardiac infant deaths are likely to have some lung pathology, lungs from infants who had died as a result of sudden infant death syndrome were chosen as controls.

Limitations of Techniques

All lung specimens studied had been fixed in formalin. The process of tissue fixation in formalin results in a degree of tissue shrinkage of up to 30%, which will lead to some degree of underestimation of medial thickness. As all specimens were fixed in a similar manner they should be subject to similar degrees of shrinkage artifact. This is supported by the finding that medial thickness was remarkably consistent between specimens from normal subjects, however tissue shrinkage must be taken into consideration when estimating the degree of medial thickness which would be expected in life.

Ideally lungs should be injected with a distending medium at the time of fixation. Unfortunately none of the lung specimens in this study had been injected at the time of fixation. As a result the vessels tend to collapse and become more ellipsoid in shape (Fig 43). This can, of course, introduce errors in measurement of total vessel diameter and for this reason, in an attempt to overcome this error, the greatest diameter of each vessel was taken for comparison of medial to total vessel thickness.

Severity of pulmonary vascular disease

Irreversible pulmonary vascular disease is believed to occur between grade III-IV by the Heath-Edwards grading system. In this series of patients, the youngest with grade III changes was aged 18 months and the youngest with grade IV changes was aged 20 months. In a series of 90 patients,

Rabinovitch, Haworth and colleagues[23] found that progression of pulmonary vascular disease was more aggressive for certain cardiac defects, particularly transposition of the great arteries with ventricular septal defect. Certainly the patients with the most severe pulmonary vascular disease in this series all had a diagnosis of transposition of the great arteries, but it must also be taken into account that these patients were all older than 20 months.

Interestingly the patient (NC) who died from progressive pulmonary hypertension despite medical therapy had only grade I pulmonary hypertensive changes. The medial thickening was, however, very marked in both the muscular and elastic pulmonary arteries. This suggests that severe muscular hypertrophy without occlusive disease may be sufficient for irreversible pulmonary hypertension, possibly due to marked vasoconstriction.

Medial Thickness

Although the measurements of medial thickness for different vessel sizes were remarkably consistent between normal subjects, medial thickness in the pulmonary hypertensives was more variable. In addition, there was no direct correlation between the degree of medial thickening in the elastic pulmonary arteries and the severity of pulmonary vascular disease as determined by the Heath Edwards grades.

There are a number of factors which will influence overall medial thickness in the

elastic pulmonary arteries in patients with pulmonary hypertension. First, vessel dilatation occurs to a variable degree in pulmonary hypertension. This will affect the ratio between total vessel diameter and medial thickness and stretching of the vessel wall may result in a degree of medial thinning. Second, it is believed that high shearing stresses from elevated pulmonary flow and pulmonary arterial pressures result in endothelial damage. Platelets adhere to the damaged endothelium releasing mitogens which stimulate the proliferation of medial smooth muscle cells.[126] There are likely to be individual differences in the response of medial smooth muscle cells to mitogens. It is possible that patients with increased risk of platelet aggregation, including those with cyanosis and polycythaemia are at risk of developing more aggressive disease. This may partly explain why patients with transposition of the great arteries appear to develop more aggressive pulmonary vascular disease.

In the patients with pulmonary hypertension, although there was a wide range of values of medial thickness for each vessel size in each age group, the *mean* medial thickness for each vessel size was relatively similar between age groups. Compared with normals, there was an overall increase in medial thickness of approximately 0.2-0.3mm in the 0.5mm elastic pulmonary arteries and 0.03-0.05mm in the 3mm elastic pulmonary arteries (i.e. vessels accessible to current intravascular catheters). When shrinkage artifact is considered, this is a maximum increase in medial size by approximately 0.06-0.07mm in the 3mm vessels. Unfortunately this is outwith the resolution of the 30 MHz

intravascular transducers and thus it would be unlikely that intravascular ultrasound could differentiate this degree of medial thickening from normals.

Conclusions

From the above findings and the findings on intravascular ultrasound, morphological changes which are evident in the elastic pulmonary arteries in pulmonary hypertension include medial thickening, vessel dilatation, intimal thickening and atherosclerosis. The presence of atherosclerosis is associated with more advanced stages of pulmonary vascular disease and such changes are likely to be evident on intravascular ultrasound. Changes of medial thickening and vessel dilatation are too variable to be of predictive value in indicating the severity of pulmonary vascular disease and unlikely to be of a magnitude to be detectable by intravascular ultrasound. In conclusion, imaging of vessel wall morphology in life by intravascular ultrasound in patients with pulmonary hypertension may help to confirm advanced disease but cannot differentiate between less severe pulmonary hypertensive disease when the patient may still be operable.

CHAPTER 7

CONCLUSIONS

The main problem with attempting to study pulmonary vascular disease in life is that the significant changes mainly occur in the small resistance vessels of less than 500μm in diameter. Although there is no doubt that morphological changes and physiological changes occur in the larger elastic pulmonary arteries, as has been shown in this study, these changes do not directly reflect the severity of pulmonary vascular disease.

Although intravascular ultrasound has been used to study vessel morphology in the systemic circulation, when imaging the pulmonary arteries with intravascular ultrasound it is difficult to identify the three layers of the vessel wall, possibly partly because the vessels studied are elastic pulmonary arteries with an elastin rich media. In patients with longstanding advanced pulmonary vascular disease atherosclerotic lesions can be identified at post mortem and in life by intravascular ultrasound. In infants with earlier disease, the intima of the elastic pulmonary arteries is smooth and the vessel wall thickness largely reflects the thickness of the media. Medial thickening is evident in the elastic pulmonary arteries in infants and children with pulmonary hypertension but this is of a degree which is outwith the resolution of a 30MHz intravascular ultrasound transducer. It is unlikely, therefore, that such an increase in medial

thickening could be differentiated from normal by intravascular imaging. Even if it could, the clinical significance is limited as there is no direct relation to severity and reversiblity of pulmonary vascular disease.

The limited application of intravascular ultrasound in identifying morphological changes in pulmonary hypertension is disappointing but is of less importance as early surgery for infants with left to right shunts becomes normal practice. Advances in cardiac surgery together with improvements in cardioprotection and cardiopulmonary bypass have made it possible to perform corrective surgery even in very young infants, prior to the development of advanced pulmonary vascular disease and morphological assessment of pulmonary vascular disease is therefore less frequently required.

A subject now attracting greater interest than morphology is pulmonary reactivity and response to vasoactive agents in life. Post-operative pulmonary hypertension following cardiac surgery in neonates and infants remains a difficult problem for intensivists and cardiologists, and although the introduction of Nitric Oxide has enhanced the management of this problem a greater understanding of the nature of the condition as well as a method of identifying patients at risk is needed. This is true also for other conditions where pulmonary hypertension is poorly understood and controlled, including altitude sickness and primary pulmonary hypertension.

The study of pulmonary reactivity ideally should be performed in life. Intravascular ultrasound gives excellent definition of the vessel lumen and offers a unique method of studying larger vessels. If combined with Doppler, simultaneous study of the smaller resistance vessels should be possible. Intravascular ultrasound is relatively straightforward to learn and perform. It can be performed with minimal morbidity either at the time of cardiac catheterisation or surgery.

Magnetic resonance imaging is limited as a method of studying vascular reactivity as the technique is still confined to imaging extraparenchymal arteries, i.e large elastic pulmonary arteries. Unfortunately using current imaging techniques, measurements of pulmonary flow and pulmonary to systemic shunts can be inaccurate due to a number of confounding effects, including pulmonary regurgitation and vessel dilatation. Nevertheless, advances in magnetic resonance angiography raise the possibility that in the future flow in the intraparenchymal pulmonary vessels could be studied, potentially providing a noninvasive method of studying pulmonary vascular resistance in life.

In conclusion therefore, current MRI techniques have little to offer in the study of pulmonary vascular disease and pulmonary vascular reactivity. Intravascular ultrasound allows both imaging of vessel lumen diameter and vessel wall morphology. The morphological changes which are detectable on intravascular

imaging in pulmonary hypertension tend to be in severe disease and are not likely to affect clinical management. Intravascular ultrasound does, however, provide a unique method of studying pulmonary reactivity in life. If combined with Doppler, it could provide a useful method of studying vascular reactivity in life, not only in the pulmonary tree but also in other vessels.

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