Flow in the pulmonary collateral circulation: Novel measurements and clinical applications in cardiopulmonary disease.

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Statement of originality

I declare that this thesis, which I give for consideration of the degree of Doctor of Medicine (research), is my own original work. Any data, figure, or text deriving from published or unpublished work of others has been fully credited.

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Abstract

The pulmonary arteries carry deoxygenated blood at low pressure, supplying 99% of blood flow to the lungs. In health, the bronchial arteries account for less than 1% of cardiac output, carrying oxygenated blood at a pressure six times that of the pulmonary arteries.

In various respiratory conditions, pulmonary vascular remodelling occurs, and the contribution of bronchial arteries and other systemic vessels increases significantly. This circulation, often overlooked in the literature, becomes apparent in several clinical conditions as vessel hypertrophy and proliferation, observable on cross-sectional imaging. This recruitment process redirects more systemic blood flow to the lungs, increasing the shunt fraction (Qp/Qs ratio), which compares pulmonary arterial blood flow (Qp) to systemic (bronchial) vessel blood flow (Qs).

Studies suggest that the neurohumoral regulation of bronchial arteries is similar to other systemic vascular territories. In diseases causing systemic hypoxemia, alveolar hypoxia, pulmonary infarction, and chronic inflammation, bronchial artery hypertrophy and dilation deliver more oxygenated blood to ischemic lung tissue. Though studied in animal models and through invasive procedures, recent advancements in imaging technology have introduced non-invasive methods to assess this collateral circulation in humans.

Pulmonary vascular remodelling can cause various clinical manifestations, including haemoptysis. Most patients with haemoptysis and hypertrophied bronchial arteries at Royal Brompton Hospital have chronic bronchopulmonary inflammation secondary to cystic fibrosis (CF). Research on quantitative imaging measures in pulmonary vascular disease due to chronic respiratory conditions is limited. Systematic assessment of the shunt fraction in CF patients with bronchial hypertrophy has not been conducted.

MRI techniques have determined the Qp/Qs ratio in congenital heart disease patients, where differences in pulmonary and systemic circulation can be significant. In chronic respiratory conditions, this difference is likely small. This thesis evaluates MRI's precision and accuracy in calculating the shunt fraction, anticipating small shunts, marking the first systematic evaluation in respiratory patients.

Acknowledgement

Without the help, support, and guidance from many colleagues and friends at Royal Brompton Hospital, I would not have been able to complete this thesis.

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Scope of this thesis

At the outset it is important to recognise the limitations of this study due to small numbers and the significant impact the COVID-19 pandemic had on this study. Despite these challenges, the research team have demonstrated interesting observations that will act as reference for future larger studies

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List of abbreviations

AE	Adverse Event
AO	Aorta
AR	Adverse Reaction
BAE	Bronchial Artery Embolisation
BLS	Basic Life Support
CCT	Cardiac Computed Tomography
CI	Chief Investigator
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CMR	Cardiac Magnetic Resonance
CRF	Case Report Form
CVI	Circle cardiovascular imaging
CVS	Coronary venous system
EEBH	End Expiratory Breath hold
FB	Free breathing
GDPR	General Data Protection Act
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRAS	Integrated Research Application System
ISF	Investigator Site File
LA	Left atrium
LV	Left ventricle
MRI	Magnetic Resonance Imaging
NHS R&D	National Health Service Research & Development
PA	Pulmonary Artery
PASMCs	Pulmonary arterial smooth muscle cells

PC	Phase contrast
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RA	Right atrium
RBH	Royal Brompton Hospital
RCT	Randomised Control Trial
REC	Research Ethics Committee
RF	Radiofrequency
RV	Right ventricle
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SMC	Smooth muscle cells
SOP	Standard Operating Procedure
TOF	Time of flight
VENC	Velocity encoding

1 Introduction

This chapter is separated into two parts.

Part 1 -This includes sections 1.1 to 1.9

The initial sections describe what is already known and established in the literature and our current understanding of the bronchial circulation. In this section the pertinent background information relevant to the circulatory system, the pulmonary circulation to the lungs, and the functional and clinical consequences of an altered bronchial circulation are discussed. This section discusses in depth the embryology and anatomy of the bronchial circulation. In addition to tracing the evolution of our understanding of bronchial circulation over the past several centuries, this section examines the roles of several significant contributors to our current understanding. Also included in this section is a discussion on cardiac and extracardiac shunts and how these are potentially altered in respiratory patients.

Part 2 -This includes sections 1.10 to 1.12

In this section, the focus shifts to exploring imaging techniques aimed at measuring shunts, particularly within the context of bronchial circulation. The fundamental concept underlying magnetic resonance imaging (MRI) is discussed, with an emphasis on how phase-contrast velocity mapping techniques facilitate flow measurements. The current clinical practices regarding the assessment of shunts are summarised, highlighting the prevalent employment of MRI in diagnosing and monitoring such conditions. However, despite its widespread use, the discussion also illustrates the inherent pitfalls and limitations associated with MRI in accurately quantifying, in particular, small shunt fractions. The existing clinical configuration consistently falls short in providing the necessary level of accuracy and precision when assessing minor shunts. The aforementioned limitations arise from a multitude of factors, encompassing the technical intricacies inherent in magnetic resonance imaging (MRI), the complexities linked to flow dynamics, and the complex characteristics of the bronchial circulation. The concluding section of the chapter delineates the overarching objectives of the

thesis, which explicitly aim to address the deficiencies in our present understanding and clinical implementations related to the assessment of shunts.

1.1 Origins of this thesis

Evolution from a single-celled organism to mammals was only made possible by billions of years of morphological changes that enabled the performance of specific functions (1). Multicellular adaptations, for example, enabled a single-celled organism to develop a tube that eventually formed a bend in its morphology, laying the foundation for what we now recognise as the human heart. The 90-degree bend was necessary and without this essential morphological adaptation, organisms containing a myocardium would never have evolved (2). Dr. Philip Kilner also explains this beautifully in a letter published in Nature. Dr. Kilner used the term morphodynamics to describe the close relationship between flow and art (3). He implied that morphological characteristics in nature have evolved to facilitate functions (11). He described how the heart's inflow is constant, but its outflow is pulsating (Figure 1.1) He alluded to the fact that this has to do with a combination of morphology and elasticity, and that nature had evolved this mechanism for human functionality. Perhaps investigating the specific morphology of certain structures will shed light on their function.

At our institution we undertake bronchial artery embolisation (BAE) procedures for the treatment of acute and subacute episodes of haemoptysis. It has been observed that when radiographic contrast is injected into these vessels there is rapid transit of contrast material into the lung periphery (Figure 1.2), indicating there maybe vascular communications at a level that we are unable to discern using standard cross-sectional imaging techniques. Research and clinical practice have largely ignored the bronchial circulation however, the current evidence suggests complex microvasculature anastomoses are present in the pulmonary blood supply in both health and disease, and morphology may remodel in certain disease states (4). Bronchial artery remodelling, hypertrophy, and adaptation has been observed for decades, but the underlying drivers of this transformation remain elusive.

A better understanding of the bronchial arterial circulation will undoubtedly have clinical relevance. Despite the fact that physiology, morphology, and function are distinct entities, understanding one can potentially help us understand the others.



Figure 1.1 - A sculpture by Philip J Kilner at Royal Brompton Hospital, London.

The weight of the water building up in the pool is the 'gravitational analogue' of elasticity in vessel walls. Pulsatility develops spontaneously as the pool builds up. From Kilner, P. Science in Culture. *Nature* 442, 29 (2006) (3)

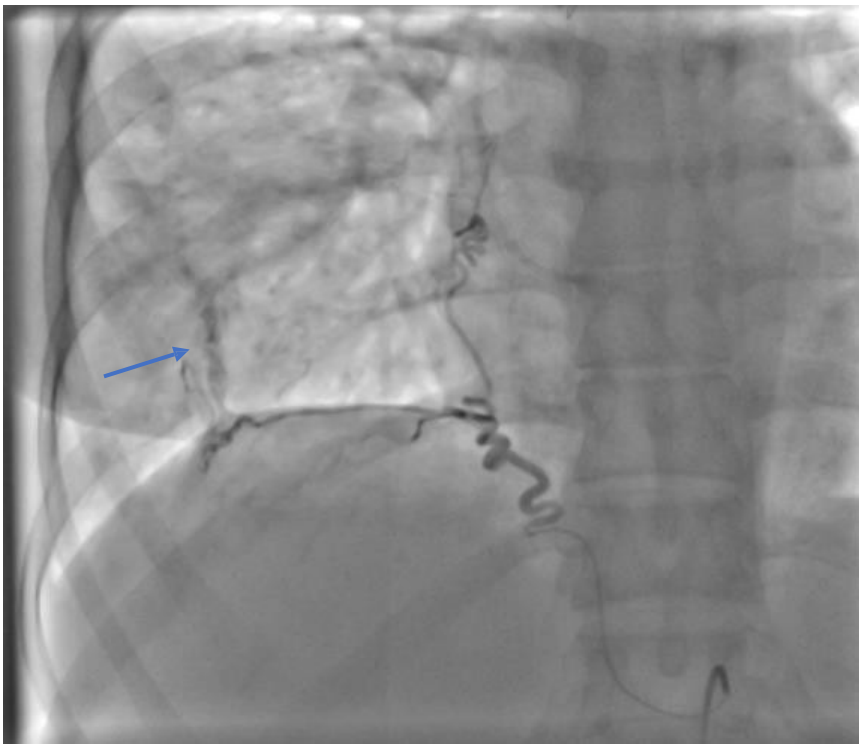


Figure 1.2 – Contrast in the periphery of the lung

Image shows rapid transit of contrast in the periphery of the lung (blue arrow) during a bronchial artery angiogram**.**

1.2 Features of the normal cardiovascular system

The cardiovascular system consists of the heart, blood vessels and circulating blood. This system is structured in a circuit comprising two distinct circulations: a systemic circulation and a pulmonary circulation (6). Before going into the details of the bronchial arterial circulation it is important to discuss some of the unique features of the cardiovascular system. Understanding how the circulatory system functions requires more variables than most pump, pipe, and fluid systems in machines. Some unique traits of the cardiovascular system are (6):

- The system is a closed circle rather than being open-ended and linear.
- The system is elastic rather than rigid.
- The system is filled with liquid at a positive mean pressure ("mean cardiovascular pressure"), which is independent to the pumping action of the heart.
- The right and left ventricles, which pump into and out of the same system, are connected in series with two interposed vascular beds (systemic and pulmonary).
- The heart fills passively, rather than by actively sucking.
- Due to the passive filling of the heart, the circulation rate is typically governed by peripheral-vascular factors rather than cardiac variables.
- The out flow from the heart is markedly pulsatile, while the inflow to it is relatively continuous.
- Ventricular capacity exceeds diastolic filling volume.
- The effect of vascular resistance on flow rate depends on its location in relation to upstream compliance and its magnitude.

In states of health, these specific traits allow the system to work in harmony. However, in the presence of disease these traits undergo adaptations of morphology in order to preserve function (6).

1.3 Why is bronchial circulation important?

The bronchial circulation is frequently overlooked; however, it has numerous important physiological roles and as such plays a significant role in a variety of pathologic conditions (5,7). A primary function of the bronchial circulation is the delivery of oxygen and nutrients to the various compartments within lungs (5).

The bronchial circulation is also crucial for acute airway responses and airway defence (5). Recruitment of inflammatory cells that participate in immune function to the airway mucosa also occurs via the bronchial circulation (13). Another key function of the bronchial circulation is airway clearance. Bronchial blood flow contributes to washout of bronchoconstrictors, proinflammatory mediators, and particulate matter from the airways (13). In instances where particulate matter causes pulmonary infarcts, the bronchial circulation also provides collateral blood flow to the lungs (10).

When bronchial arterial flow is altered, the function of bronchial circulation becomes more apparent. The bronchial arteries possess a remarkable capacity for remodelling, exhibiting both enlargement and angiogenesis depending on the underlying cause. For example, chronic infection is a common cause of bronchial arterial enlargement and increased blood flow (21). Unfortunately, this morphological adaptation often has undesired consequences and in patients with bronchial artery hypertrophy, there is often haemoptysis. Remodelling of the bronchial circulation also occurs in conditions where pulmonary gas exchange is compromised, as in the case of pulmonary atresia or chronic thromboembolic disease (12). While most of the gas exchange occurs via the pulmonary arteries, the bronchial circulation can contribute to gas exchange through anastomotic connections (21). In the absence of a normal pulmonary circulation, the bronchial arteries increase in number and calibre to provide the blood supply to the entire lungs (5,21). Upon restoration of pulmonary circulation, bronchial blood flow returns to normal and the expanded vasculature regresses partially (21).

During transplantation, the pulmonary arterial circulation is surgically restored, but not the bronchial circulation. Given that the bronchial circulation supplies approximately 50% of the airway wall perfusion and the pulmonary arteries supply the remainder, it is becoming increasingly clear that the bronchial circulation plays an important role in lung transplant and that loss of flow to the distal airways may result in further ischemia and hypoxic injury (14). In animal models, transplant with bronchial artery revascularisation improved airway oxygenation compared to standard transplant (21). Despite adequate pulmonary artery blood flow, it has been hypothesised that the loss of bronchial circulation in lung transplant patients results in airway hypoxia (15). In animal models, angiogenesis can gradually restore bronchial artery circulation after transplantation (16); however, imaging and post-mortem specimens of human transplanted lungs show a lack of identifiable bronchial arteries and/or severe microvascular loss around airways (17,18). These findings suggest that airway ischemia may contribute to airway fibrosis and poor transplant results (18).

Despite evidence suggesting the importance of bronchial circulation, its evaluation remains difficult. Understanding the structure and function of pulmonary circulation has made slow progress over the past century. However, with the recent advent of powerful imaging tools, the anatomy of the bronchial arteries can be observed (21). The application of these techniques to the study of the pulmonary and bronchial vasculature has yielded a plethora of knowledge. As researchers delve deeper into the cellular mechanisms that underpin genetic and phenotypic changes in lung circulations, and develop better models of pulmonary vascular disease, including lung injury and pulmonary hypertension, insights into both the physiology and contributing factors to pulmonary circulation pathology will undoubtedly be discovered. Translation of these results to clinical practice has the potential to improve patient outcomes. In 2018, Professor Andrew Bush from Imperial College, London wrote an article titled “Out of Sight, but Should Not Be Out of Mind: The Hidden Lung Blood Supply” in which he strongly argues the need to improve our understanding of the bronchial circulation (8).

It is clear the bronchial circulation plays an important role in health and disease. A study devoted to expanding our understanding of this circulation will improve patient outcomes over time. This project seeks to advance our understanding of this understudied circulation by employing novel

MRI imaging techniques to evaluate the systemic circulation to the lungs in cystic fibrosis (CF) patients with haemoptysis.

1.4 A historical perspective of the bronchial circulation

By the 1600s, it was clear that the lung had a second circulation, while the discovery of the bronchial circulation is attributed to a variety of people, including Galen, Domenici de Marchettis, and Leonardo da Vinci (21). In 1721, Frederich Ruysch described the bronchial circulation (Figure 1.3) and established the bronchial artery's aortic origin (19). Regardless of the original description, the role of the bronchial vasculature in health and disease is now well understood. The bronchial arteries distribute oxygenated blood from the systemic circulation to the airways, lymph nodes, nerves, pulmonary arteries, veins, and visceral pleura. The variation of this circulation in humans is still being investigated. In the third Century BE, the Museum of Alexandria provided fertile ground for anatomic observation through the practice of cadaver dissection. Erasistratus is credited with developing the concept of unidirectional blood flow to the lungs and subsequently the left ventricle (20). The discovery of aorta branches entering the human lung is attributed to him based on a reference by Galen, who visited Alexandria and carried this knowledge to Rome. Galen became physician and friend of the Emperor Marcus Aurelius. Miller, in his review of the history of the bronchial circulation, points out that Galen observed systemic blood vessels to the lungs but failed to name them.

In the Tractat de Arteria et Vena Dissectione he wrote (21): *"Arteries from the second thoracic vertebra emerge and are distributed to the adjacent lungs and break up into small branches which are then hard to see."*

Following the Middle Ages, Galen's anatomical technique experienced a decline in popularity. During the mid-13th century, Ibn-An-Nafis, a physician from Damascus, refuted the conclusions reached by Galen (21). It is not specified in Ibn An-Nafis' Commentary on Avicenna's Canon (21) how or via which pathways this nutrition enters the lung. After the Roman Empire's decline, the Byzantine Empire assimilated the majority of Greek knowledge that Western Europe had acquired.

Across Western Europe, Michael Servetus opposed Galen's theory throughout the early sixteenth century. Unfortunately, Michael Servetus failed to identify here the aortic branches to the lungs. Servetus communicated his ideas to Calvin, who rejected them. He was arrested, judged, and burned at the stake at Champel, outside Geneva on October 27, 1553, with a copy of his book attached to his arm. The sixteenth century is full of the rediscovery of Greek texts of the pulmonary circulation, culminating in the work and sacrifice of Michael Servetus, but no references are known at that time to have been made concerning the extraordinary efforts and description of the pulmonary and bronchial circulations by Leonardo da Vinci (22).

Leonardo da Vinci's contributions to the arts of painting and sculpture are well-known and will not be covered here, except for the fact that he created so much at once that even his finest works, including the Mona Lisa and the Last Supper, were unfinished (21). His scientific observations are likewise well-known. What is far from certain is our grasp of Leonardo's understanding of anatomy and physiology. There are detailed and contradicting versions of what happened to Leonardo's anatomic notes, which were arguably the most remarkable of their sort ever created (21).

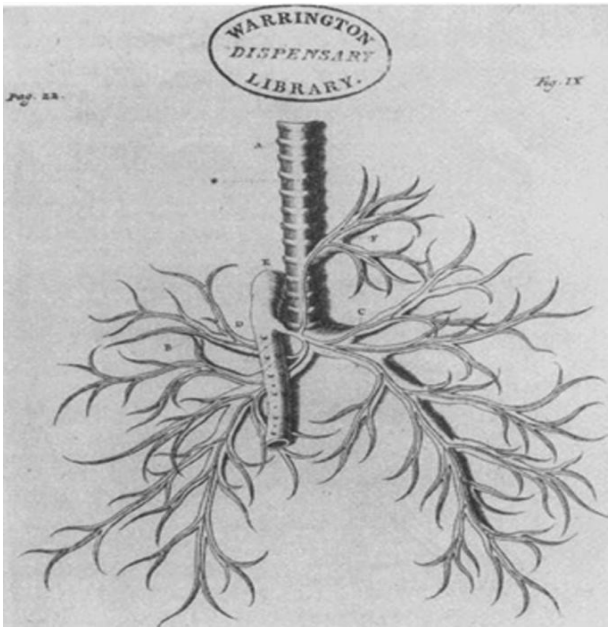


Figure 1.3 - Drawing by Fredrick Ruysch

The drawing illustrates bronchial circulation (19).

In an era before formalin or refrigeration, Da Vinci dissected around 30 human cadavers in Italy. It wasn't until the Quincentenary Exhibition devoted to Leonardo da Vinci's drawings at the Royal Academy in London in 1952 that his amazing anatomic insights could be placed in their proper historical context.

Much was published about bronchial arteries prior to the eighteenth century, but little mention is made of Leonardo da Vinci's key insights about the bronchial circulation made 500 years before (23). Leonardo da Vinci In the Quincentenary exhibition held in 1952 at the Royal Academy, London, and devoted to the drawings of Leonardo da Vinci, exhibit 301 showed a drawing from the Quaderni d'Anatomia Il.I.V. (Figure 1.4); in which Leonardo depicts the heart, the coronary arteries, the trachea, and the bronchial tree of a left lung with its accompanying bronchial arteries.

Bronchial circulation was not known until Leonardo da Vinci, according to most current physiologists and anatomists. William Harvey nearly discovered the secret of circulation, but he missed the terminal branches, the capillaries, in the lungs and periphery. This discovery required the microscope, and Marcello Malpighi may have completed the circle with its development (21).

The exact capillary link between bronchial and pulmonary circulations is still contested. Many have explored the mystery, yet doubt lingers. Harvey concludes: "Because the path is now clear, others with more fertile minds may seize the opportunity to do better and look into it further”.

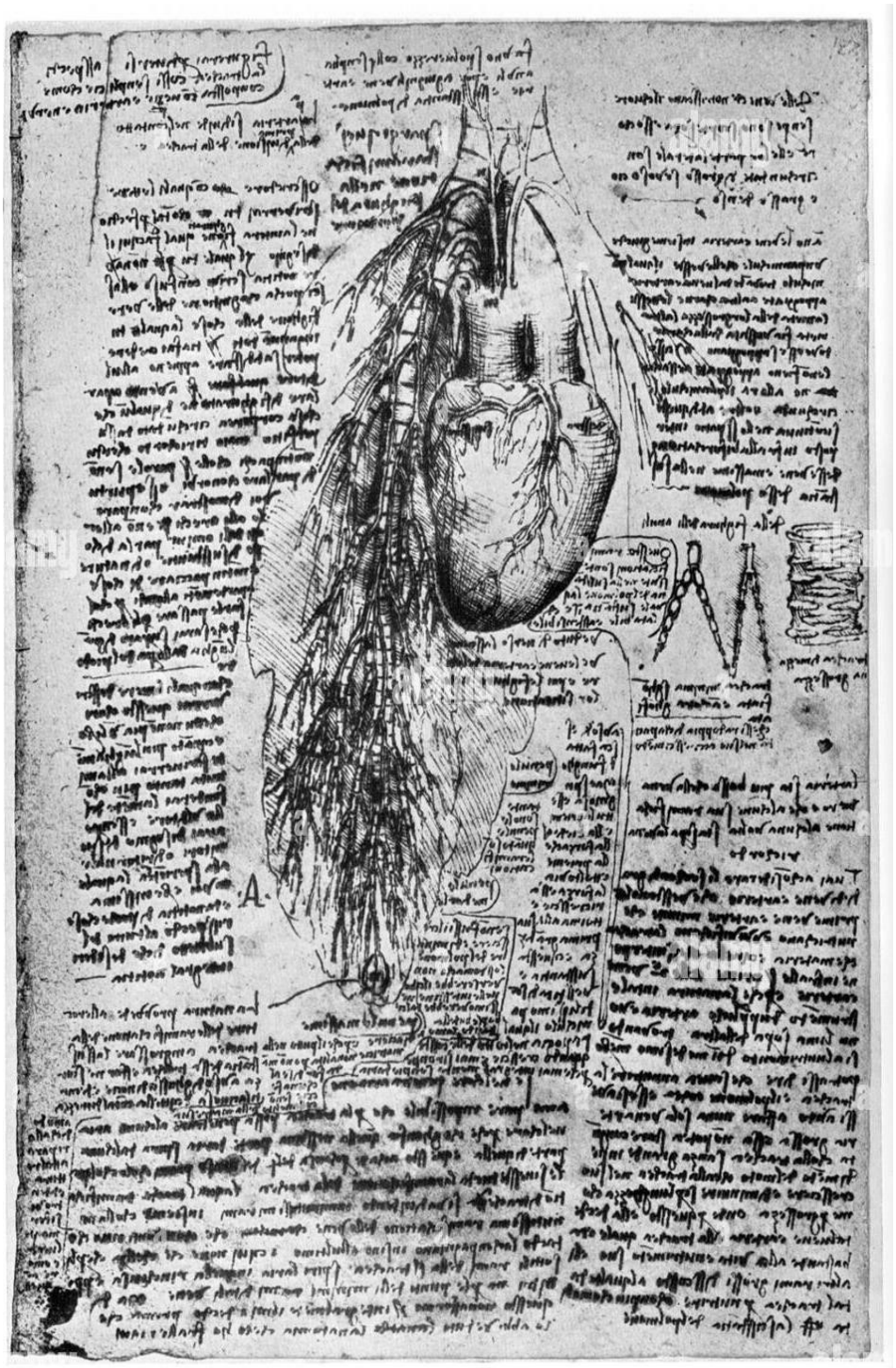


Figure 1.4 - Drawing by Leonardo da Vinci

Depicts the heart, the coronary arteries, the trachea, and the bronchial tree of a left lung with its accompanying bronchial arteries. From Leonardo da Vinci In the Quincentenary Exhibition held in 1952 at the Royal Academy, London (23).

1.5 Anatomy of the adult lung circulation in humans

1.5.1 The adult pulmonary circulation

The normal lung contains two distinct circulations of strikingly different origins, proportions, and functions (24). On the one hand is the large pulmonary circulation, which originates in the right heart and empties the entire de-oxygenated cardiac output into the lungs for gas exchange. On the other, is the diminutive systemic circulation, which delivers oxygenated blood to the lungs for the sustenance of its tissues, nerves, vessels, and conducting airways (25,26). In health, the bronchial arteries account for less than 1% of the cardiac output and carry oxygenated blood to the lungs at a pressure six times that of the pulmonary arteries (24,25).

During foetal life, the pulmonary circulation is a low flow, high-resistance circuit. With transition to postnatal life, the pulmonary vasculature dilates, accommodating the entire cardiac output, with high blood flow maintained at low intravascular pulmonary arterial pressure. As compared with the systemic circulation, pulmonary arteries have thinner walls with much less vascular smooth muscle and a relative lack of basal tone, likely a function of high production of endogenous vasodilators and low production of vasoconstrictors, resulting in a normal pulmonary vascular resistance that is approximately one-tenth that of the systemic circulation (24).

1.5.2 Pulmonary arterial circulation

During normal embryogenesis, the blood vessels of the lung divide into an arterial system that runs parallel to the airways, a capillary system that supplies the alveoli, and an irregular venous system that connects to the left side of the heart (24,28). (shown in Figure 1.5). The diameter of the main pulmonary artery in an adult lung is comparable to that of the aorta and varies with age, gender, and body size (24). The pulmonary artery wall is nearly as thick as the aortic wall during pregnancy and the first few days after birth. After birth, however, the elastic tissue gradually remodels, resulting in a significantly weakened pulmonary artery wall. When the principal pulmonary artery divides into its right and left main branches, the diameter of each branch is approximately half that of the parent artery (24). Before reaching the lungs, the right and left bronchial branches divide to nourish the different lobes. Each lobar artery divides into numerous variable branches that supply

the lung's bronchial tree (24). The proximity of the pulmonary arteries to the airways emphasises the need of matched ventilation and perfusion for optimal lung function. The tunica media of the big pulmonary arteries is mostly made up of elastic fibres and a little bit of smooth muscle, hence these arteries are categorised as elastic (24). These elastic arteries eventually give rise to vessels with a higher proportion of smooth muscle as the vascular diameter decreases (24). When compared to systemic arteries of the same diameter, pulmonary arteries are typically still thinner (24,28). In addition to endothelial cells, the pulmonary artery wall is made up of collagen and adventitial fibroblasts, an elastic lamina that allows for expansion during inspiration, and a thin intima (24).

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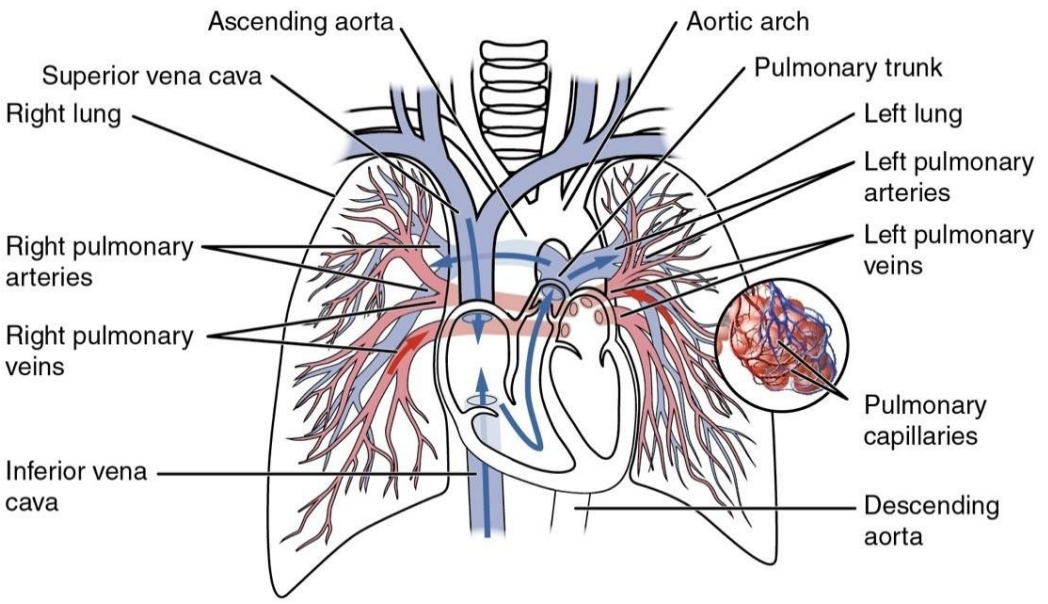


Figure 1.5 – Pulmonary arterial anatomy
Illustration of pulmonary arterial anatomy. The Lungs - Anatomy and Physiology 2e OpenStax. Available from: https://openstax.org/books/anatomy-and-physiology.

The small arterioles have a nonuniform layer of smooth muscle cells, which gives way to the small non-muscular pre-acinar arterioles, which are located near terminal bronchi (25). At the alveoli, terminal arterioles disperse into pulmonary capillaries within the alveolar walls (24,30).

Early in the 1950s, electron microscopy provided the first visual evidence of pulmonary capillaries, the tiny channels through which blood is transferred from arterial to venous circulation (31). The capillaries have a very thin wall composed of a single layer of endothelial cells and account for the majority of the pulmonary vasculature's surface area, which is estimated to be 126m^2 in an adult human (31). It should be noted that the thickness of pulmonary capillary walls is not uniform (30,31). For instance, the gas-exchange portion of the intra-acinar alveolar capillaries wall can thin to a layer of cytoplasm between two sections of plasma membrane, resulting in a thickness of 20 to 30 nm (32) with the cell contents and nucleus shifting to the "thick" side of the septum. Gas exchange between alveolar gas and blood occurs primarily in the pulmonary capillary bed, after which the blood flows into venules, whose gross structure is nearly identical to that of arterioles (32). While each small arteriole supplies a particular unit of respiratory tissue, the venules drain multiple lung regions. Venules do not follow the bronchiole tree and instead converge to form the pulmonary veins, which carry oxygenated blood to the left ventricle (24).

Anatomically, vessels are classified as either extrapulmonary or intrapulmonary (33). Extrapulmonary vessels are located in the mediastinum, which is outside of the lung, and the pressure surrounding these vessels is related to pleural pressures. The intrapulmonary vessels, including the capillaries, are subdivided anatomically and functionally into extra-alveolar or alveolar branches (33). Alveolar vessels consist of adjacent capillaries, whereas extra-alveolar vessels are larger and more proximal (33). Due to the differences in the tissues that surround them, these two types of vessels also have different perivascular pressures (24,33).

In humans, the systemic circulation relies on a high-pressure gradient to deliver cardiac output to the vascular beds of diverse organs with different blood flow requirements and located up to 180 cm apart (34). Thus, the vascular resistance of the systemic vessels is precisely controlled to maintain adequate pressure (34). While baroreceptors monitor pressure and utilise neural pathways to regulate intravascular pressure during changes in posture, physical activity, temperature, and blood volume, it is well recognised that the systemic vasculature also exhibits substantial autoregulation (24,34). This is in stark contrast to the adult pulmonary circulation, which is required to accommodate the total cardiac output and, thus, cannot actively adjust total blood flow (24,33,34). Instead, the adult pulmonary circulation is a low- resistance, highly compliant vascular bed whose properties are greatly influenced by external forces such as alveolar pressure,

cardiac output, and posture. In addition to serving as a conduit for blood and, in the case of the microvasculature, gas exchange, each segment of the pulmonary vasculature is unique in its responses to hemodynamic stress and is subject to a specific set of luminal and perivascular pressures due to the anatomic differences between the segments (35). Due to these differences, the reactions to mechanical stimuli like lung inflation are also distinct. The cardiorespiratory system is built to account for regional changes in structure, mechanical forces, ventilation, and gas exchange by incorporating compensating mechanisms for rearrangement that, to the greatest extent possible, synchronise blood flow with alveolar ventilation (24,30,35).

1.5.3 Bronchial arteries

In humans, bronchial arteries arise from the aorta or intercostal arteries (Figure 1.6) (28,36). Several researchers have examined the number of bronchial arteries in each lung, with varying conclusions.

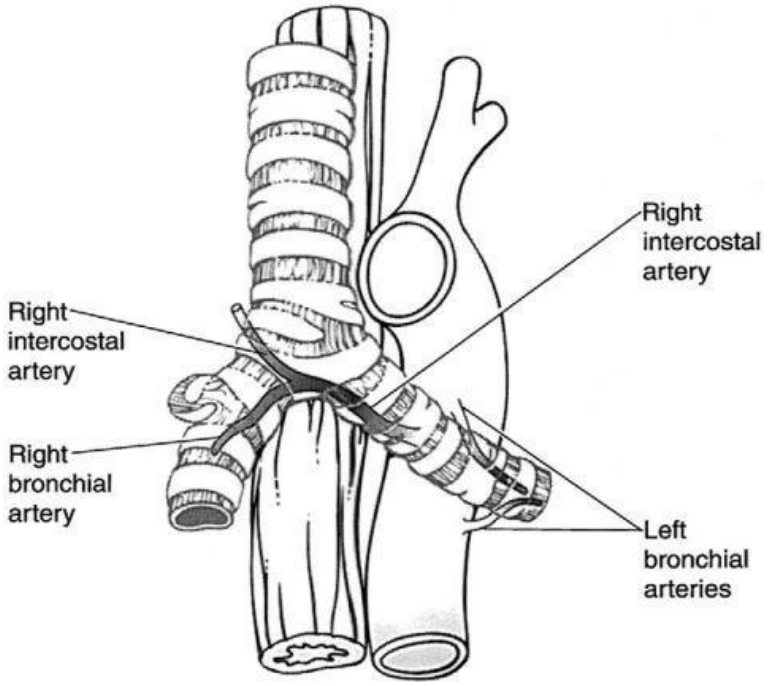


Figure 1.6 – Bronchial artery origin from aorta

Bronchial arteries typically originate from the aorta or intercostal arteries in humans. Image from Butler J. (ed.) (1992). The Bronchial Circulation. Marcel Dekker, Inc., New York.

The bronchial circulation provides systemic arterial perfusion to the trachea, upper airways, surface secretory cells, glands, nerves, visceral pleural surface, lymph nodes, pulmonary arteries, and pulmonary veins (24). The bronchial circulation perfuses the respiratory tract to the level of the terminal bronchioles. Lung structures distal to the terminal bronchioles, including the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli, are directly oxygenated by diffusion from the alveolar air and receive their nutrients from the mixed venous blood in the pulmonary circulation (24, 28, 36).

Bronchial blood flow accounts for only 1-3% of the output of the left ventricle. The bronchial arteries, typically three in number, arise either from the aorta and accompany the bronchial tree and divide with it. The pressure in the bronchial arteries is equal to the systemic pressure and is therefore much higher than the pressure in the pulmonary circulation (24, 39).

The return of venous blood from the capillaries of the bronchial circulation to the heart occurs either through true bronchial veins or through bronchopulmonary veins. In the region of the hilum, true bronchial veins are present and flow into the azygos, hemiazygos, or intercostal veins before entering the right atrium. The bronchopulmonary veins are a network of smaller blood vessels formed by the union of blood vessels from the bronchial and pulmonary circulatory systems. Through pulmonary veins, blood from these anastomosed vessels returns to the left atrium. Two-thirds of the total bronchial circulation is returned to the heart via the pulmonary veins and this anastomotic route, according to estimates and the remaining one third is to the right atrium via the bronchial veins (39). This deoxygenated blood, which mixes with oxygenated blood in the pulmonary veins, contributes to the small alveolar– arterial oxygen difference (Figure 1.7) in healthy individuals (39).

In 1948, Cauldwell et al. investigated the origin of the bronchial arteries in 150 human cadavers and found that the majority of the vessels originated directly from the aorta (38). They determined that two arteries to the left lung and one to the right lung were the most common presentation (41%). One artery to each lung was the next most common (21%), followed by two arteries to each lung (21%). The anatomical connections between the bronchial artery and other structures were not clearly documented, and cardiac abnormalities in these people were not ruled out (38).

For a better understanding of this blood flow, the map of the pulmonary circulation (Figure 1.8) gives a diagrammatic representation of the circulation to the lung. The Thebesian circulation, outlined in the Figure 1.8, is important in and discussed later in this chapter.

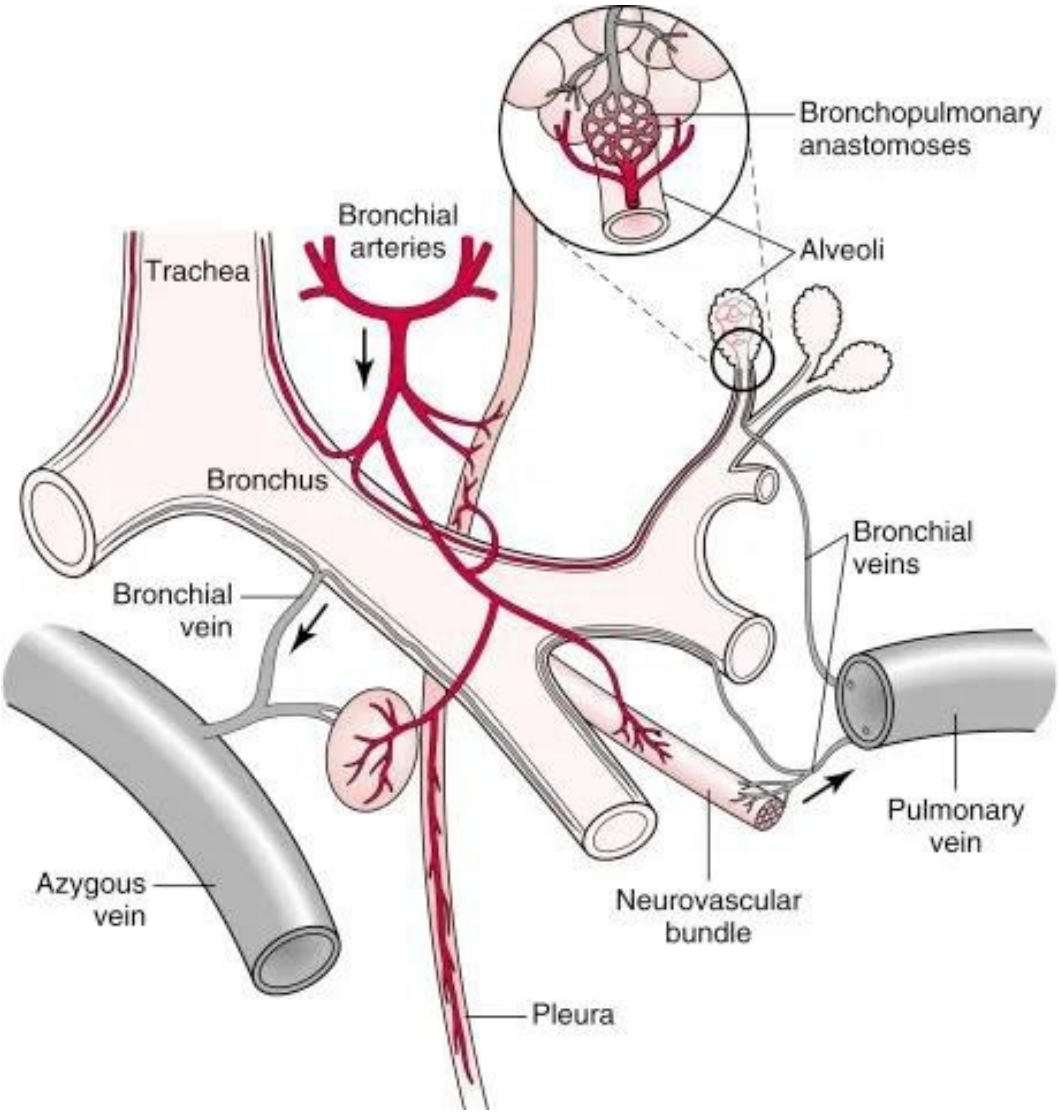


Figure 1.7 – The bronchial circulation

The anatomic features of the bronchial circulation. The bronchial circulation supplies blood to the trachea and airways to the level of the terminal bronchioles as well as to the pulmonary blood vessels, visceral pleura, hilar lymph nodes, and vagus nerve and its branches. Inset depicts a bronchopulmonary anastomosis. From Butler J. (ed.) (1992). The Bronchial Circulation. Marcel Dekker, Inc., New York (21).

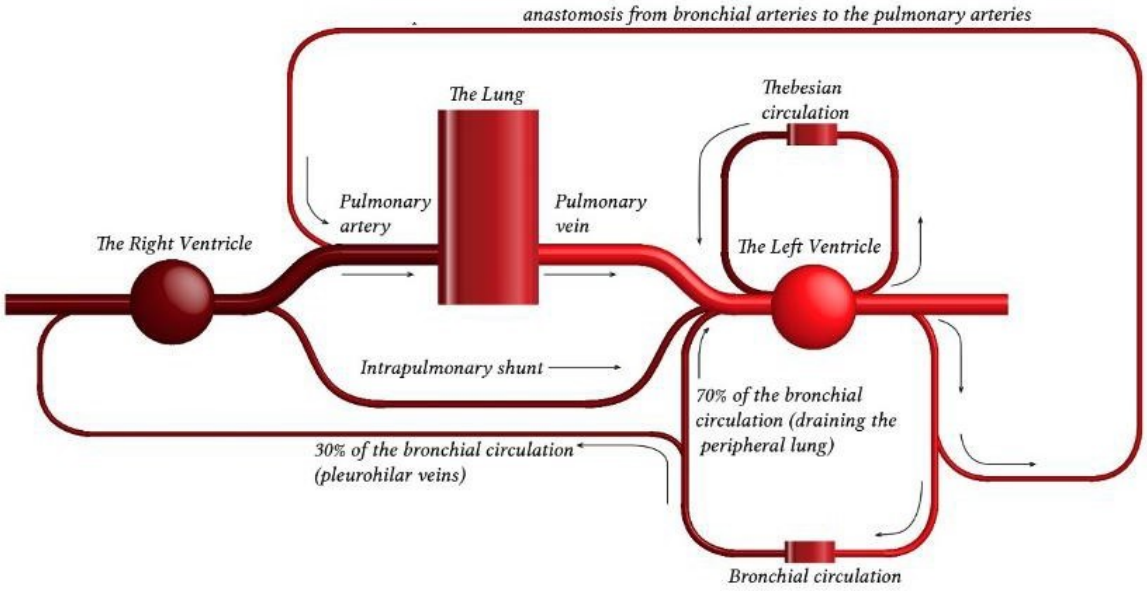


Figure 1.8 – Map of the pulmonary circulation

Map of the pulmonary circulation gives a diagrammatic representation of the circulation to the lung. From Anatomy of the pulmonary and bronchial circulation - derangedphysiology.com

In 1965, by infusing vinyl plastic into the aorta, Liebow analysed fifty normal human lungs. He confirmed that the major bronchial artery originated either directly from the aorta or through an intercostobronchial artery (40). He referred to these vessels as posterior bronchial arteries. In contrast, he referred to "accessory bronchial arteries" as blood vessels that reach the bronchi from aortic branches other than the aortic intercostal arteries (41). He determined that 30% of all specimens had two posterior bronchial arteries to each lung, which was the most frequent configuration. The 1979 investigation conducted by Kasai and Chiba confirmed this pattern (42). The superior right, inferior right, superior left, and inferior left bronchial arteries make up these four vessels. The arrangement of two left and one right bronchial arteries was deemed "classic" by Cauldwell et al. This configuration represented 20% of all occurrences (38). Liebow determined that the configuration of two right and one left bronchial arteries was nearly as prevalent as the conventional pattern, whereas in the Cauldwell series, it was only one-fourth as prevalent. Schreinemakers et al. examined 30 autopsy cases and discovered that one right and two left bronchial arteries was the most prevalent pattern, accounting for 26.6% of cases, followed by

two right and two left bronchial arteries (43). The fourth most common structure was a single main trunk to each bronchus. These four groups accounted for 76% of Liebow series specimens and 92% of Cauldwell et al. series specimens.

Furthermore, the origin of the bronchial arteries is quite varied. The posterior bronchial artery can originate either directly from the aorta or from a branch that also gives rise to the intercostal artery (intercostobronchial trunk). 66% of the specimens in Liebow's study had bronchial arteries originating from both the aorta and the intercostobronchial trunk, while 26% had only an aortic origin and 8% had intercostobronchial trunk-originating bronchial arteries. In an older series by Nakamura, the percentages were 80%, 18%, and 2%, respectively (44). 74% of the 50 specimens contained at least one intercostobronchial trunk. In 89% of Cauldwell's specimens, the intercostobronchial trunk was present, compared to 81% of Nakamura's specimens (38,43).

The most common arrangement of bronchial arteries is two on the right and two on the left, according to a Japanese study (42). The origin of the right superior artery was discovered to be the right first aortic intercostal artery. The right subclavian artery occasionally produced a tiny branch that connected to the right superior bronchial artery (42). The right inferior artery had the most complex course. It often originated directly from the aorta and travelled via the ventral route to the left bronchus (42). Over fifty percent of the time, a single trunk was established with the inferior left artery. The left superior artery originated from the aortic arch or the descending aorta near the left recurrent laryngeal nerve (42).

1.5.3.1 Anatomy of the bronchial arteries

It is evident from these various studies that the origin, branching pattern, and course of the normal bronchial arterial anatomy vary (25). Typically, bronchial arteries arise directly from the descending thoracic aorta, typically between the T5 and T6 vertebrae (36). Overall classification by Cauldwell et al is the most generally accepted and this work reported four classic bronchial artery branching patterns (Figure 1.9) (38):

Type I: Two bronchial arteries on the left and one on the right that manifests as an ICBT (Intercosto-bronchial trunk)

Type II: one on the left and one ICBT on the right

Type III: two on the left and two on the right (one ICBT and one bronchial artery)

Type IV: one on the left and two on the right (one ICBT and one bronchial artery)

The true prevalence of a common bronchial artery trunk is unknown.

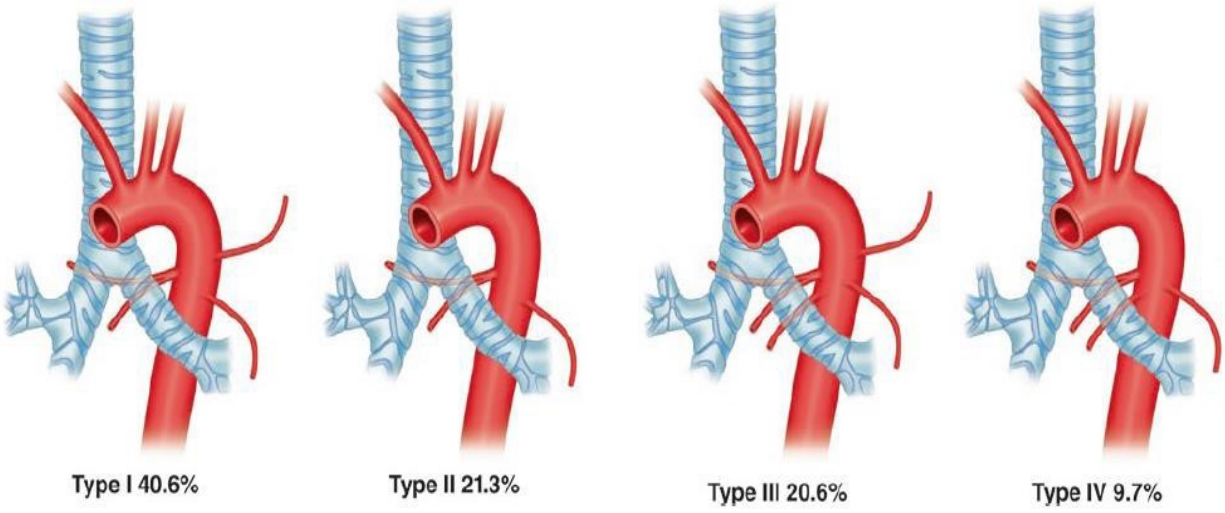


Figure 1.9 – Branching pattern of the bronchial circulation

Diagram shows normal variants in the bronchial arterial anatomy as described by Caldwell (46).

1.5.3.2 Function of the bronchial circulation in the normal lung

The physiologic function of the bronchial circulation remains somewhat of a mystery; lung transplant studies have demonstrated that adult lungs can function normally without a bronchial circulatory system. Therefore, in healthy individuals, these anastomoses likely have little importance. However, they may be important in neonates and young children for delivering nutrients to the developing lung, as well as in disease states where reciprocal changes in flow between the two circulations ensure a steady supply of nutrients (24). In individuals with a pulmonary embolus, for instance, the bronchial circulation increases to regions of the lung normally supplied by the pulmonary arteries; as a result, extensive pulmonary infarction is

uncommon, even with large pulmonary emboli (52). In individuals who have undergone lung transplantation in which the bronchial circulation has been removed, an increase in pulmonary circulation to these areas prevents necrosis of the airway cells and other structures supplied by the bronchial circulation (53).

Bronchial circulation may also play a key role in acute airway responses and airway defence. Inflammatory cells that participate in immune function are recruited to the airway mucosa via the bronchial circulation (54). Airway clearance is yet another important function of bronchial circulation. Bronchial blood flow aids in the removal of bronchoconstrictors, proinflammatory mediators, and particles from the airways (24). When particles cause pulmonary infarcts, the bronchial circulation also supplies collateral blood flow to the lungs (52).

1.5.3.3 Anomalous bronchial arteries

At the level of the major bronchi, bronchial arteries that originate outside the region between the T5 and T6 vertebrae are considered anomalous (48). The reported prevalence of bronchial arteries with an abnormal origin ranges between 8.3% and 35.0% (48). These aberrant bronchial arteries may originate from the aortic arch or from a number of major branches of the transverse arch (48). These may also originate from the abdominal aorta, the brachiocephalic and subclavian arteries or their branches, the intercostal arteries, the celiac artery branches, and the phrenic arteries (48). These are known as bronchial vessels because their course within the thorax parallels that of the bronchi. Anatomically and angiographically, aberrant bronchial arteries can be distinguished from non-bronchial systemic collateral vessels by their extension along the major bronchi. The majority of aberrant bronchial arteries originate from the aortic arch (48,49).

Normal bronchial arteries in adults have a diameter of less than 1.5 mm at their origin and 0.5 mm at their point of entry into a bronchopulmonary segment (50). A bronchial artery measuring greater than 2 millimetres in diameter on CT is most likely abnormal (Figure 1.10).

(51). On contrast-enhanced CT scans, hypertrophic bronchial arteries are readily visible within the mediastinum and around the central airway.

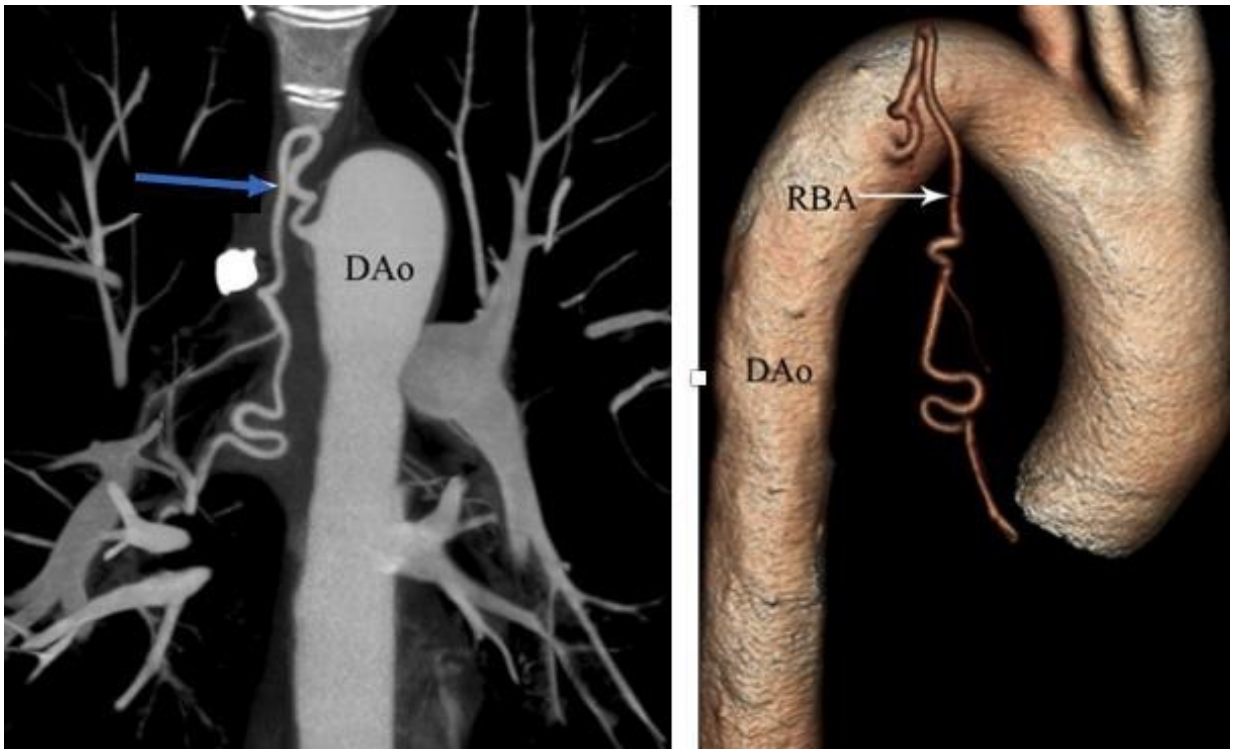


Figure 1.10 - MIP and volume rendered images of a dilated bronchial artery

The left panel shows a coronal MIP reconstruction, and the bronchial artery is depicted by the blue arrow. The right panel shows a volume rendered image from a CT study demonstrating an enlarged right bronchial artery (RBA). DAo: Descending aorta.

1.5.3.4 Anthropometric differences in arterial size

Anthropometric differences encompass variations in physical characteristics or measurements among individuals or populations, including differences related to gender (284). While there is literature available on anthropomorphic differences in arterial size in general, specific studies focusing on the bronchial artery across different demographic groups are relatively sparse. The 2mm cut-off is commonly used as a standard for bronchial artery size; however, academics have explored the range of arterial diameters across different populations to gain a deeper understanding of anatomical variations and their potential implications for clinical practice (285).

A study to assess the prevalence of anatomical variations of bronchial arteries using computed tomographic found similar anatomies of bronchial arteries between genders (286). Studies specifically exploring differences in bronchial anatomy by age, ethnicity and body compositions are limited in the literature.

1.5.4 Non-bronchial systemic arteries

Non-bronchial systemic arteries contribute to the pulmonary blood flow as well, and their sources vary (55). Non-bronchial systemic feeder vessels may arise from several arteries (e.g., the intercostal artery, subclavian branches, internal mammary arteries, and axillary arteries) (Figure 1.11). In contrast to bronchial arteries, non-bronchial systemic collateral vessels enter the pulmonary parenchyma through the adherent pleura or via the pulmonary ligament, and their course is not parallel to that of the bronchi (36). These collateral vessels may also hypertrophy in certain disease states (36). Pleural thickening or fibrosis is associated with an increased incidence of systemic collaterals (56).

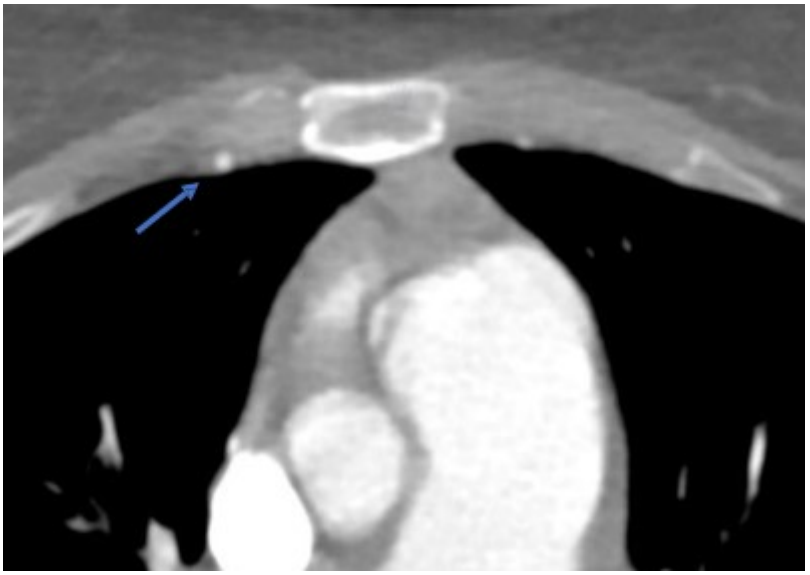


Figure 1.11 – Enlarged right internal mammary artery

Enlarged right internal mammary artery (blue arrow) compared to the left giving rise to a non-bronchial

1.5.4.1 Major aortopulmonary collateral arteries (MAPCAs)

In specific patient groups, major aortopulmonary collateral arteries (or MAPCAs) are also present (Figure 1.12). These arteries usually develop to perfuse the lungs when native pulmonary circulation is underdeveloped (57). Instead of arising from the pulmonary trunk, pulmonary blood supply develops from the aorta and other systemic arteries (57,58). MAPCAs develop early in embryonic life but regress as the normal pulmonary arteries develop (59). In certain congenital heart conditions, the pulmonary arteries do not develop, and the collaterals continue to grow and can become the main supply of blood to the lungs. MAPCAs are often found in association with congenital heart diseases with decreased pulmonary blood flow such as tetralogy of Fallot or pulmonary atresia (57). Rarely, MAPCAs may be seen in the absence of congenital heart disease, in which case they are termed as isolated aortopulmonary collateral arteries (60). In these cases, altered flow maybe a cause of congestive cardiac failure in neonates (59).

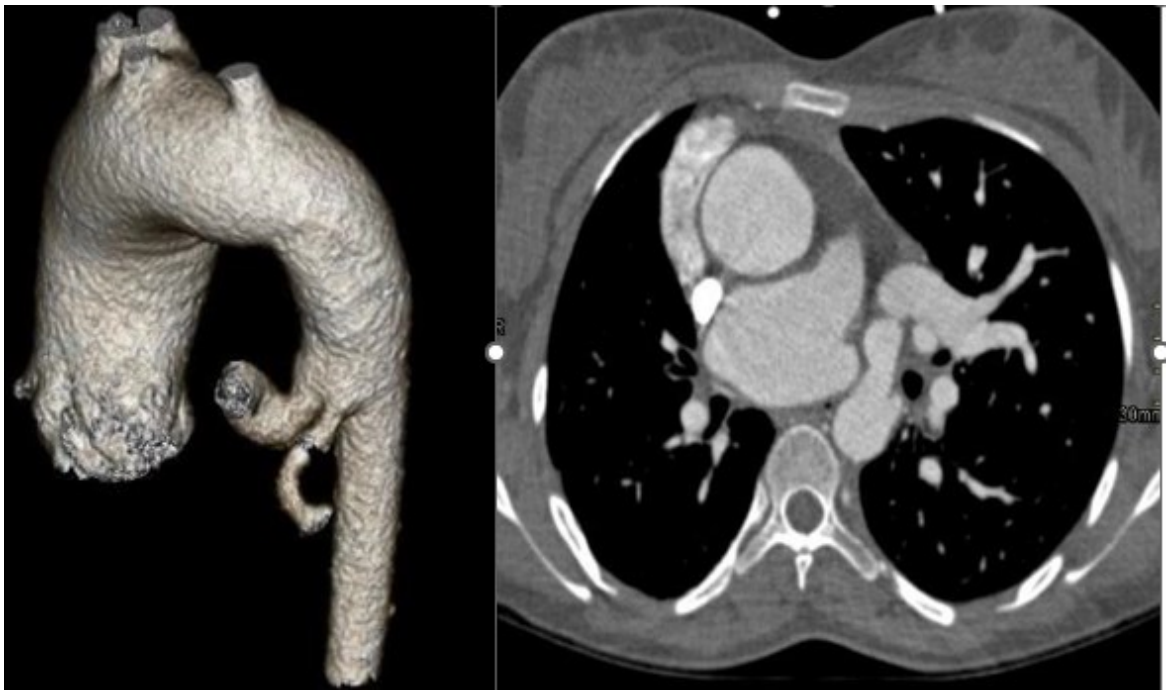


Figure 1.12 – Major aortopulmonary collateral arteries (MAPCA's)

Volume rendered image (left panel) and a trans axial CT image (right panel) of a patient with MAPCS in the context of a congenital heart disease.

A summary of key features and differences of the pulmonary arterial circulation and systemic circulation is provided in Table 1.1.

Table 1-1 Circulation to the lungs

Pulmonary arterial circulation	Systemic circulation
• Output of right side of the heart. • Carries deoxygenated blood • Returns oxygenated blood back to the heart. • Functions at lower pressure • Vessels have thin walls with little smooth muscle • Always accepts entire cardiac output • Symmetrical distribution of pressures • Hypoxia leads to vasoconstriction	• Output of the left side of the heart. • Carries oxygenated blood • Functions at higher pressure • Vessels have thicker walls with abundant smooth muscle • Cardiac output directed to numerous organs • Pressures vary according to distance from heart • Hypoxia leads to vasodilatation

A summary of key features of the systemic circulation to the lungs is provided in Table 1.2 respectively.

Table 1-2 Systemic circulation to the lungs.

Systemic circulation to the lungs			
Bronchial arteries	**Anomalous bronchial arteries**	**Non bronchial systemic arteries**	**MAPCAS**
• Originate directly from the descending thoracic aorta between the levels of the T5 and T6 vertebrae. • Four classic bronchial artery branching patterns are routinely seen.	• Originate outside the area between the T5 and T6 vertebrae • May originate from the aortic arch or many other major branches of the transverse arch	• Have variable origins • May originate from various arteries (eg, intercostal artery, branches of the subclavian, internal mammary arteries and axillary arteries)	• Develop to perfuse the lungs when native pulmonary circulation is underdeveloped. • Blood supply develops from the aorta and other systemic arteries MAPCAs are often found in association with congenital heart disease.

1.5.4.2 Debate in the literature around the systemic circulation to the lungs.

Norgaard et al make a case that the MAPCAs found in patients with pulmonary atresia with ventricular septal defect are in fact nothing more than dilated bronchial arteries (57). This theory however, has been argued against by Hanley in an editorial in which he states "to say that just because these two categories of arteries have some, or even significant, similarities, that they are the same entity is not accurate and the story is much more complex than that" (61). Hanley goes on to explain this further by using an interesting analogy. He says "Anyone with even a cursory understanding of natural history and human evolution understands that man is not descended from the monkey, but rather man and monkey are two separate differentiated

species with a common ancestor". Hanely continues his case by stating "that ancestor was neither man nor monkey, it was what it was, although it shares some features with both of its descendants, and both descendants also share some features. That is not to say that man and monkey are the same entity, not by a long shot".

He dismisses the claim made by Norgaard et al by saying "to claim that a MAPCA is nothing more than a jazzed up bronchial artery is the equivalent of saying a human is just a monkey on steroids. Most would agree that no amount of pharmacotherapy, or tutoring for that matter, could ever make a monkey write like Keats, compose like Wagner, or tell jokes like Seinfeld" (61).

It is evident that there is no consensus within the literature and that there is an ongoing debate in the nomenclature, origins and function of certain systemic collaterals to the lungs. Despite some of these uncertainties what we do know is that the systemic circulation plays an important role in various disease states (58).

In the literature, the terms "bronchial circulation" and systemic "pulmonary collateral circulation" are used frequently and often interchangeably to describe the non-pulmonary arterial circulation to the lung. It should be emphasised that the designation "bronchial circulation" is specific for bronchial arteries whereas systemic arterial vessels to the lung include arteries other than the bronchial arteries. In this thesis I will be describing systemic "pulmonary collateral circulation " to outline the variable routes of systemic blood flow to the lungs (62).

In thoracic disease processes that lead to patients experiencing systemic hypoxemia, alveolar hypoxia, pulmonary infarction, and chronic inflammation it is believed that the bronchial arteries undergo smooth muscle wall hypertrophy and dilate to direct more oxygenated blood to relatively ischaemic lung tissue (63). Significant remodelling of the systemic pulmonary collateral circulation can also occur in several clinical conditions and this can be observed morphologically on cross sectional imaging (49). On cross sectional imaging we routinely observe (64):

- Pre-existing vessels enlarge and become tortuous
- New vessels appear and join with the established to form bizarre vascular patterns.

In contrast to the normal lung, in which precapillary communications between the two circulations are difficult to demonstrate, the enlarged precapillary anastomoses between the pulmonary and systemic circulations are readily apparent on CT imaging.

This process of recruitment provides additional systemic circulation to the lungs and results in an increased proportion of cardiac output being diverted through the bronchial arterial system (62).

Depending on the severity of the underlying disease process the total systemic cardiac output to the bronchial arteries may increase from 1% to 18%–30% (62). Abnormal dilated bronchial arteries are large and often have a tortuous mediastinal course. Haemodynamics in such bronchial arteries have not been objectively investigated. Much of the research in the last decade has required the use of animal models and invasive procedures. More recently, non- invasive techniques for measuring bronchial blood flow have been developed and offer a new avenue for the study of this circulation in humans (65,66).

This process of recruitment provides additional systemic circulation to the lungs and results in an increased proportion of cardiac output being diverted through the collateral arterial system. The (Qp/Qs) ratio also known as the shunt fraction, allows us to assess any change in blood flow through pulmonary arteries (Qp) compared to the flow through systemic (including bronchial) vessels (Qs) (67,68). This is discussed in detail later.

Increased blood flow through the systemic collateral circulation can present with distinct clinical manifestations. These include, haemoptysis, most commonly encountered in patients with chronic suppurative lung diseases such as cystic fibrosis (69, 70). These patients demonstrate enlarged and tortuous bronchial arteries on cross sectional image.

1.6 Embryology

The embryological development of lung parenchyma and its accompanying vasculature are inherently linked (71). The three principal pulmonary vascular components are pulmonary arteries, pulmonary veins and bronchial arteries (72,73). An extra microvascular collateral circulation is present early on with systemic arteries, but its contribution reduces rapidly in the first few years; still, it remains a potential source of collateral circulation, albeit a weak one (72,73,74). A developmental error or injury in any of these components has major repercussions on the architecture and physiology of the pulmonary circulation as a whole (75,76). The arterial and venous systems are most often affected by the rare congenital disorders affecting the pulmonary circulation (75,76). Understanding the normal development of pulmonary circulation enables recognition of rare congenital abnormalities and related adaptive modifications (75,76).

From the initial stages of embryogenesis, the pulmonary circulation arises through a temporal and spatially controlled process linked to cardiovascular development. Pluripotent angioblast cells begin the process, which lays out the foundation for position and orientation of the cardiac chambers as well as their connection to the major vessels of the chest (75,76,77). By day 22, the primordial heart tubes show automatic and sustained contraction (beating), and by day 34, a circulation continuity exists between the heart and the primordial lung buds (72,76,78). The development of the pulmonary circulation is, with rare exceptions, characteristic. The development and growth of the pulmonary circulation take place along the 5 discrete stages of lung development

1. embryonic: first 1-7 weeks
2. pseudoglandular: 5-17 weeks
3. canalicular: 16-26 weeks
4. saccular: 24-38 weeks
5. alveolar: 36 weeks and beyond (72,78,79,80).

The embryonic and pseudoglandular stages of development of the macroscopic pulmonary circulation are of clinical importance to modern diagnostic imaging. During the pseudoglandular phase, the pulmonary macrovasculature (arteries and veins) develops independently from the microvasculature (capillaries) that connects the arterial and venous systems. By the mid-pseudoglandular stage, all the precapillary arteries and postcapillary veins that form in an individual would have developed (72).

The pulmonary arteries are derived morphologically from the truncus arteriosus (72), which originates from the ventricles and then separates into the ascending aorta and pulmonary trunk. During the pseudoglandular stage, the arteries and veins continue to develop in accordance with the branching patterns of the airways (72,73,74). Development of the pulmonary circulation down to the pre-acinar pulmonary arteries is complete by the 17th week of gestation (72,73,74).

During organogenesis, vascularisation can occur by vasculogenesis, angiogenesis, or both. Immunohistochemical analysis of foetal lung tissue to characterise the temporal and spatial expression of endothelial markers revealed that intrapulmonary arteries in humans develop largely through vasculogenesis, or the formation of new blood vessels from endothelial progenitor cells (248). Endothelial tubes carrying blood cells were found in the mesenchyme enclosing the airways and the foregut in these experiments (248).

As the pulmonary arteries and veins develop, the primitive vessels acquire a smooth muscle layer and extracellular matrix proteins are deposited to form a basement membrane that both separates different layers within the vascular wall and maintains the wall structure (81). In humans, the smooth muscle cells (SMC) surrounding the arteries appear to originate from three sites (81). Between 38 and 98 days of gestation, pulmonary artery smooth muscle cells (PASMCs) originate from bronchial smooth muscle in neighbouring airways. During this time frame, PASMCs appear to originate from the mesenchyme surrounding the arteries. Later in gestation (between 98 and 140 days), PASMCs co-express smooth muscle specific α-actin and endothelial markers, indicating endothelium to SMC transdifferentiation. Contrarily, venous SMCs originate from mesenchyme (82,83).

The pulmonary capillaries appear to arise separately from the arteries and veins, becoming connected to the more proximal vasculature during the pseudoglandular stage (82,83). As the

foetus enters the canalicular stage, the number of capillaries increases, a process believed to involve angiogenesis, vasculogenesis, and intussusception (creation of pillars within existing capillaries to expand their surface area) (84). At birth, the branching pattern of the pulmonary circulation is comparable to that observed in adults (265), although the size of the arteries increases as the lungs develop. Since the majority of alveolarisation of the human lung continues after birth, the postnatal capillary bed continues to expand through angiogenesis and intussusception, with gas exchange surface area increasing proportionally (82, 83, 84, 85).

1.6.1 Development of the bronchial circulation

The human bronchial circulation develops in two stages, with the creation of arteries beginning in the fourth week of gestation from the dorsal aorta. In the second trimester, these primitive arteries are replaced by bronchial arteries, which originate predominantly from the superior thoracic aorta (86, 87).

In the majority of cases, but not always, two bronchial arteries serve each lung, according to an analysis of human post-mortem specimens (87). The intrapulmonary bronchial arteries branch down the length of the bronchial tree to the terminal bronchioles, providing a huge network of capillaries that establish extensive anastomoses with other bronchial arteries and the pulmonary vasculature, forming bronchopulmonary anastomoses.

Due to these many connections with the pulmonary circulation, deoxygenated bronchial venous blood drains to the left heart via pulmonary veins, forming a plexus (86,88). This plexus gives rise to arterioles that penetrate the muscle layer to establish a submucosal microvascular network (89). Venous drainage of the proximal conducting airway (first two divisions) follows the same pattern as arterial supply, with the azygos and hemiazygos veins returning blood to the right heart. In addition to supplying the airways with systemic blood, these veins also feed systemic arterial blood to the walls of the pulmonary vessels, regional lymph nodes, nerves, and visceral pleura (90). In addition, the distal bronchial microvasculature forms anatomic right to left shunt often referred to as the “bronchopulmonary anastomotic” flow or the “pulmonary collateral” circulation. While bronchopulmonary anastomoses can occur anywhere in the vasculature (88,91,92), it is currently believed that bronchial venous blood drainage is largely a post-pulmonary capillary event (93).

1.6.2 Non-bronchial systemic circulation to the lungs

The network of microvasculature connections from transpleural–systemic to pulmonary artery anastomoses are also part of the pulmonary circulation, although their significance diminishes as an individual grows and develops (72,95,96). In pathologic situations, however, these lesser vascular networks may contribute significantly to the pulmonary circulation, particularly if the pathogenic process originates early in embryogenesis. In the case of major cono-truncal anomalies, such as Tetralogy of Fallot (TOF) with main PA atresia, which markedly impair pulmonary circulation, MAPCAs develop to provide pulmonary blood supply (97). Less dramatic changes can occur in agenesis of a right pulmonary artery (PA) or left PA, which more commonly lead to slow but progressive enlargement of the bronchial arteries in response to decreased lung parenchyma circulation and chronic ischemia.

Normal outcomes of pulmonary circulation embryogenesis include an arterial system network that closely matches the bronchial pathways and a venous system that parallels them up to the segmental level (98,99).

The timeline of the key stages of vascular development is summarised below (Figure 1.13).

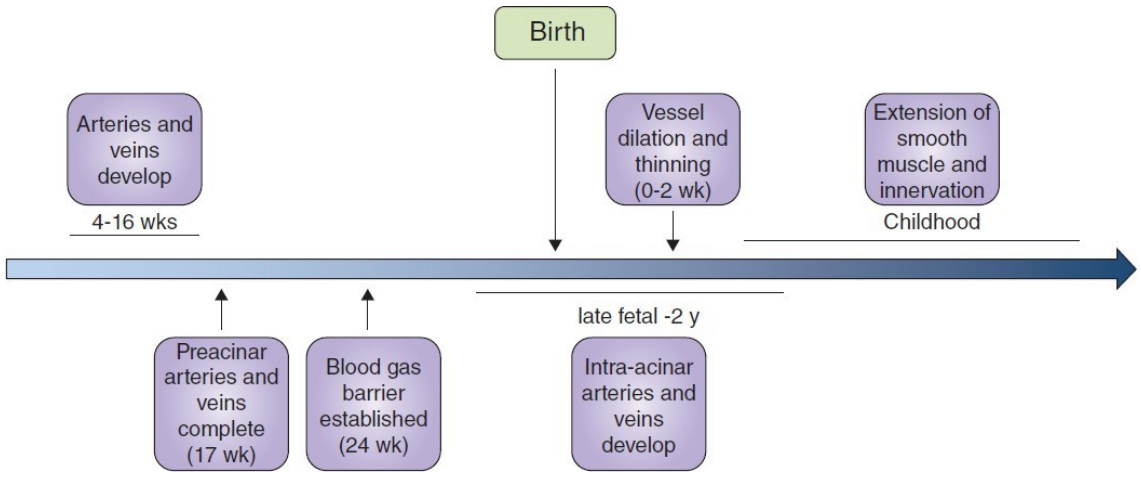


Figure 1.13 - Timeline of pulmonary vascular development.

1.7 The bronchial circulation: Histology and electron microscopy

Although the gross anatomy of the tracheobronchial circulation has been described by numerous authors, the detailed organisation and structure of the mucosal microvasculature has only been described a handful of times.

1.7.1 Macrovasculature vs Microvasculature

In general, macrovasculature refers to the vessels visible to the human eye (vessels greater than 100 um) (100). The microvasculature is a dense network of vessels with dimensions less than 100 um that are not visible to the naked eye. As one approaches the microvascular bed, the arteriole diameter decreases gradually (100). The network of microvessels that lies between the smallest detectable arteries and veins is composed of the branches of arterioles, capillaries, and postcapillary venules. The capillary bed is drained by venules, which are expanding-diameter channels (100). This microvascular network, which forms the terminal segment of the bronchial vascular system, facilitates the transport of gases, nutrients, and metabolic waste (100,101).

Using optical and electron microscopy on cross sections of airway mucosa from several species, it has been determined that capillaries are often less than 10 um from the epithelium (102).

1.7.2 Histology and ultrastructure

1.7.2.1 Arteries and arterioles

The bronchial arterial tree branches numerous times throughout the length of the bronchial artery, resulting in a large increase in the overall cross-sectional area of the arterial bed. The tunica media of arterioles measuring 100 um normally consists of two or more layers of smooth

muscle cells (102,103). As the diameter of the arteriole diminishes, so does the thickness of its three tunicae: intima, media, and adventitia. The terminal arteriole's tunica media comprises a single layer of smooth muscle cells (102,104). Thus, the distal section of the arteriolar stem is gradually shrunk to form terminal arterioles of capillary size. Except for connections formed with neighbouring smooth muscle and endothelial cells, medial smooth muscle cells are surrounded by a basal lamina (102,103,104). On the luminal side of the arteriole, the endothelial cells are flat and interconnected tightly. On the basal lamina, elastic and collagenous fibres separate these cells

from smooth muscle cells. In terminal arterioles, the endothelial cells are separated from the single layer of smooth muscle cells by a basal lamina

(105). By means of membrane-to-membrane interactions, smooth muscle and endothelial cells communicate (106). Adventitia, the outermost layer of the arterioles, is composed of fibroblasts and collagenous fibres. The adventitia contains unmyelinated neurons that can alter the contractile properties of the smooth muscle in the arteriolar wall and, consequently, the blood flow to the mucosa (102,106).

Electron microscopy reveals that two-thirds of the nerves to these vessels are positioned within 1 um of the artery wall smooth muscle. The nerves contain clear core vesicles with a diameter of 50 nm or a mixture of these and larger (80-100 nm) dense core vesicles, which are characteristic of cholinergic and peptidergic nerves. There are also nerves that resemble adrenergic nerves morphologically (106,107).

Histochemical evidence confirms that bronchial vessels are innervated by cholinergic, adrenergic, and peptidergic nerves (109). Neuropeptides such as substance P and calcitonin gene-related peptide, which have been linked to an afferent, sensory type of innervation, have also been detected near airway vessels (110). Nerves containing various types of vesicles have been discovered near the arteriolar smooth muscle in humans (109).

1.7.2.2 Capillo-venular plexus

The capillaries are derived from the terminal arterioles. They tend to run parallel to the long axis of the airway and are located just beneath the epithelial basement membrane (102). Using light microscopy, the total number of vessels within 200 um of the bronchial epithelial basement membrane in the submucosa of human airways has been determined (104). The capillary wall is composed of a single layer of flattened endothelial cells, a continuous basal lamina, and an incomplete layer of pericytes. Generally, the classification of various types of capillaries is based on the completeness of the endothelium (111,112). The structure of the endothelium in airway mucosal capillaries varies according to species. Some animals have endothelium that is continuous, while others, such as humans, have capillaries with fenestrations (113). In the cytoplasm and along the basal and apical surfaces of the capillary endothelium, there are numerous small vesicular invaginations measuring approximately 500- 700 um in diameter. These vesicles may be

responsible for fluid movement from one side of the cell to the other, according to Florey (114). Connecting the endothelial cells together are occluding junctions.

The capillaries give rise to a network of approximately 10-30 um postcapillary venules. These venules are situated deeper than the capillaries in the mucosa (102). Postcapillary venules receive connections from capillaries and other postcapillary venules, and they connect to larger collecting venules. Postcapillary venules are surrounded by a continuous endothelium, a continuous basal lamina, and a variable number of pericytes (115). The number of pericytes increases with vessel diameter, and they form a continuous layer around venules with a diameter between 30 and 50 um. In postcapillary venules, the intercellular junctions between endothelial cells are less tightly organised than in capillary walls (116,117). The junctions between venular endothelial cells are composed of discontinuous filaments of intramembranous particles in freeze-fracture replicas (117). The loose arrangement of endothelial cell junctions facilitates the separation of adjacent cells and may contribute to the increased susceptibility of these blood vessels to the effects of various inflammatory mediators (102,118). The pulmonary vessels, which do not respond to inflammatory mediators in the same way as the bronchial vessels, have a somewhat different vascular wall structure than the bronchial vessels. Endothelium is thicker, and there are more pericytes surrounding it (117,118). In the peri-endothelial layer of venules, cells with ultrastructural characteristics of smooth muscle begin to appear as vessel diameter increases. The larger bronchi return blood via bronchial veins to the azygos and hemiazygos veins (118). Blood from the peripheral airways is drained by pulmonary vein tributaries (118).

There is a paucity of quantitative data regarding the lymphatic vessels of the airway mucosa. In contrast to venules, these vessels have a thin endothelium, a discontinuous basal lamina, and no surrounding pericytes (119). This microanatomy and histology described above has been illustrated in Figures 1.14 to Figure 1.16.



Figure 1.14 – Microanatomy of the bronchial artery

Bronchial artery (arrow) accompanying the subsegmental bronchus (B) (21).

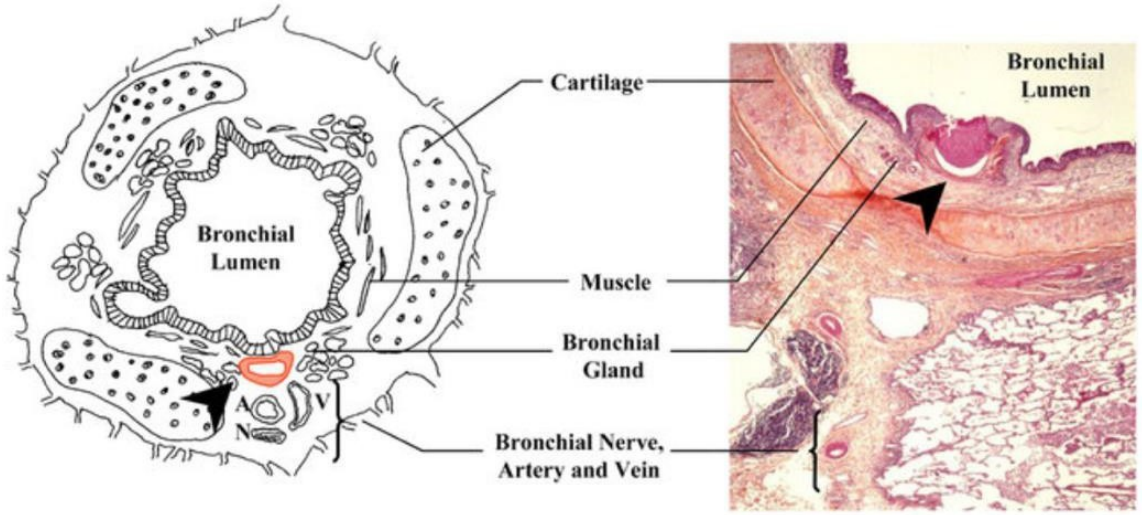


Figure 1.15 – Bronchial artery in relation to the bronchial lumen

Schematic showing bronchial artery (A) normally positioned in the bronchial mucosa, beneath the cartilage plates, near the bronchial vein (V) and nerve (N). Lung tissue section demonstrating ectopic superficial bronchial artery abnormally positioned under the bronchial epithelium (black arrowheads), with disruption of the artery muscular wall. (120)

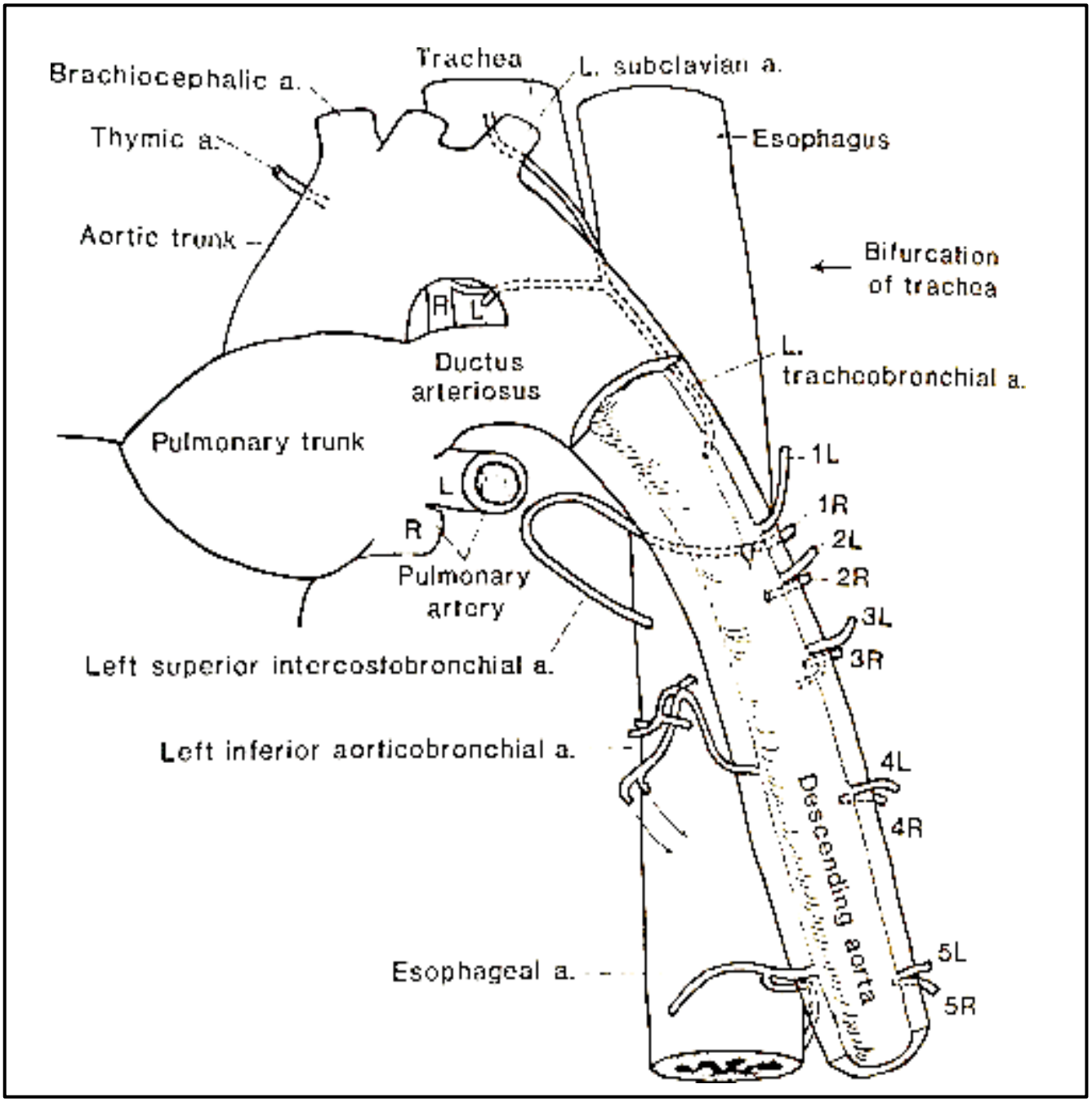


Figure 1.16 - Bronchial arteries of a 83 gestational day human foetus (85 mm length).

The numbering indicated order of paired intercostal arteries (L, Left and R, Right) From Butler J. (ed.) (1992). *The Bronchial Circulation*. Marcel Dekker, Inc., New York (21).

1.8 Clinical aspects related to the bronchial circulation

In various diseases, the bronchial circulation plays a key role. It is evident from earlier discussions in the anatomy section that the bronchial circulation plays an important role, and that abnormalities in the bronchial circulation associated with ill health can emerge in many anatomical compartments of the lungs. This section outlines how pathology may emerge in the major anatomical compartments and how chronic inflammation affects the bronchial circulation. Finally, the most significant and worrying symptom associated with the bronchial circulation, namely haemoptysis is discussed.

1.8.1 Airway disease

Increased blood flow to the bronchial mucosa is a defining feature of asthma (122). The hyperaemia causes oedema, mucosal thickening, and a rise in luminal secretion. This reduces the diameter of the airway, particularly if smaller airways are involved, hence increasing airway resistance and the effort required for breathing. This size reduction increases the effect of smooth muscle bronchoconstriction (122,123). The inflammatory response concurrently exacerbates airway inflammation and coughing. Interestingly, hyperventilation alone generates a similar mucosal hyperaemia in both healthy and asthmatic individuals (123). This is because air that has not been fully humidified and warmed to body temperature cools the mucosa and increases the osmolality of the mucus lining, which both increase bronchial blood flow (122,123). This response, which occurs in conjunction with exercise-induced tachypnoea, is thought to be the cause of exercise-induced asthma.

Acute bronchitis is linked to bronchial mucosal vessel dilatation (124) and can be caused by inhalation of toxic gases, notably cigarette smoke, aspiration of fluids, trauma, such as that produced by intubation, and infections, particularly viral infections of the upper respiratory tract. Persistent bronchitis causes more localised and chronic vasodilation and vascular hypertrophy (124). The dense and continuous vascular network of the airway mucosa provides a therapeutic advantage. If deposited anywhere on the mucosa, aerosolized drugs can reach every region of the bronchial tree (125). This is significant because, despite the possibility of higher concentrations at

the time of deposition, aerosol medications can reach airways that are blocked or poorly ventilated via the bronchial vasculature (125). Similarly, it is evident that inhaled therapeutic or harmful chemical aerosols or gases can reach the right heart despite the fact that the majority of an intrapulmonary dose is absorbed into the pulmonary venous circulation (125).

1.8.2 Parenchymal disease

Chronic inflammation of the parenchyma, regardless of the underlying aetiology, including infections, collagen diseases, immunological diseases, and "idiopathic" interstitial pneumonitis, is usually accompanied by an increase in flow in the bronchial circulation (126, 127). This includes patients with pneumonia (129). Hypoxic vasoconstriction, thrombotic blockage, and inflammation-induced pressure on the pulmonary arteries cut off the pulmonary circulation to the sick regions (129). Although the pulmonary circulation is responsible for the immediate leukocytic response in pneumococcal pneumonia, it appears that the bronchial circulation is responsible for the inflammatory response in aspiration-type acute lung damage

(127). Due to the high metabolic rate of the inflammatory, leukocyte-packed lung, any remaining pulmonary blood flow and bronchial blood flow become oxygen-depleted and, because they drain into the left atrium, generate a right-to-left shunt. Adult respiratory distress syndrome (ARDS) may manifest a similar abnormality (132).

The bronchial blood flow provides the necessary cells and other elements for persistent inflammation in the lungs. Occasionally, it expands to an unexpected degree in chronically inflamed regions (131). In bronchiectasis, for instance, the rate of bronchial arterial blood flowing through anastomoses into the pulmonary vascular bed may be adequate to lower or even reverse the local pulmonary blood flow. This helps route pulmonary flow to locations with appropriate ventilation (131). As bronchial circulation is crucial for the inflammatory response and subsequent healing of the lungs, therapeutic manoeuvres must not impede it. As positive alveolar pressure lowers bronchial blood flow, maintaining bronchial blood flow requires avoiding excessive positive end-expiratory pressure in circumstances such as acute respiratory distress syndrome (132). Since bronchial flow declines with decreasing blood pressure, systemic arterial pressures must be maintained using transfusions and similar methods (133). It terminates completely when systemic

arterial pressures fall below 40 mmHg. This may explain why a hypotensive or cardiac arrest period causes respiratory distress.

1.8.3 Vascular alterations in congenital heart disease.

When there is pulmonary artery atresia or stenosis because of congenital heart disease, systemic vessels from the aorta, including the bronchial arteries, enlarge, sometimes significantly (134). This ensures the nutrition of the lung parenchyma. Through anastomoses with the pulmonary vasculature, systemic blood in these vessels can perform some gas- exchange functions (135). These anastomoses are found between the bronchial vasculature, pulmonary arteries, capillaries, and veins. The ratio of ventilation to perfusion in these patients' lungs is consistently high, allowing CO2 to be removed from the systemic arterial blood (134,135). In cyanotic congenital heart disease, this systemic arterial blood is hypoxic, so O2 uptake can also occur. Surgical shunt operations, such as the Taussig shunt, may not be necessary in patients whose bronchial circulation is sufficiently developed to partially compensate for the lack of pulmonary inflow. To perform a comprehensive surgical repair, the patency of the central pulmonary arteries must be ensured.

Large left-to-right shunts, such as those found in ventricular septal defect, result in severe pulmonary vascular disease characterised by pulmonary hypertension and multiple obstructions of the small blood vessels (135). There is hyperplasia of the bronchial vasculature, and the proximal bronchopulmonary anastomoses become extremely apparent. Yaginuma et al. hypothesised that high-pressure pulmonary arterial blood flows through these anastomoses and then back into the pulmonary vessels downstream of the obstructing lesions to reach the alveolar capillaries (136). The most common cause of acquired pulmonary artery occlusion is embolism. As long as the airways remain patent, ventilation ensures tissue oxygenation, and bronchial circulation and, especially in the early stages, reverse flow in the pulmonary veins prevents substrate deficiency (137). Since bronchial flow is initially so low, it may be crucial to promote reverse pulmonary venous flow at this time through deep breathing. Acquired, chronic pulmonary artery occlusion results in hyperplasia of the bronchial circulation and an increase in systemic blood flow, which

adequately nourishes tissues and may participate in gas exchange. Nonetheless, the pulmonary vasculature distal to the obstruction is extremely abnormal, displaying the changes of severe pulmonary hypertension, including plexogenic arteriopathy (138).

The alterations in blood flow observed in congenital heart disease (CHD) offer valuable insights into the potential mechanisms underlying shunt formation in respiratory illnesses such as cystic fibrosis (CF) and bronchiectasis (135). In CHD, abnormalities in cardiac anatomy and physiology often lead to disruptions in pulmonary blood flow patterns, including increased pulmonary artery pressure, turbulent flow, and redirection of blood through intracardiac or extracardiac shunts (136). Similarly, CF and bronchiectasis involve pathological changes in lung structure and function, resulting in pulmonary vascular abnormalities and impaired gas exchange (217). These conditions can cause regional variations in lung perfusion and ventilation, creating areas of poorly ventilated or non-ventilated lung tissue (217). Consequently, blood flow may be redirected away from these regions through intrapulmonary shunts, bypassing the normal gas exchange areas of the lungs (271). Drawing parallels with CHD, where abnormal blood flow patterns contribute to shunt formation, these alterations in blood flow dynamics in CF and bronchiectasis may lead to the development of intrapulmonary shunts, exacerbating hypoxemia and respiratory compromise (21). Therefore, understanding the pathophysiological mechanisms underlying altered blood flow in CHD can provide valuable insights into the development and clinical implications of respiratory shunts in CF and bronchiectasis, guiding therapeutic strategies aimed at optimising lung function and patient outcomes.

1.8.4 Pleural disease

In humans, the visceral pleura is supplied by bronchial circulation. Additionally, the intercostal systemic circulation supplies the parietal pleura (139). Bronchial arteries may grow greatly in chronic pleural infections, such as empyema (139). Since this requires time, early decortication is significantly less likely to be compromised by challenging bleeding concerns (140). In the first phases of pleural infection, when the metabolic demands of the inflammatory response and the quantity of accumulated leukocytes are high, extra oxygen may improve bacterial clearance (140). It is

hypothesised that there is hypoxia within the bulk of leukocytes and that bactericidal power will increase if this oxygen deficiency is corrected, as oxygen is necessary for the "metabolic burst" of leukocytes when they destroy microorganisms (141).

1.8.5 Chronic lung infections

Bronchiectasis is frequently seen in patients with chronic lung infections and can be caused by a previous bacterial or viral infection, cystic fibrosis, tuberculosis, chronic airway inflammation, or impairment of the muco-ciliary clearance apparatus (e.g., ciliary dyskinesia or Young's syndrome) (142).

The bronchial circulation supplies the bronchial wall with blood flow and numerous studies have confirmed that the bronchial circulation becomes hypertrophied in certain chronic lung infections (143). Wood and Miller observed bronchial artery proliferation as early as 1938

(146). They carried out a series of post-mortem studies in humans with various lung diseases

(146). One bronchiectatic specimen from a young female adult in their series revealed an extensive network of new bronchial arterial branches along the course of the bronchi and bronchioles in the diseased lobe. This lobe's main bronchial artery was also slightly dilated and quite tortuous (146).

Numerous large anastomoses frequently develop between the bronchial and pulmonary arteries in patients with bronchiectasis (147,148). As a result, it is possible that systemic arterial pressure will be partially transmitted to the pulmonary arteries if bronchial blood flow is sufficiently increased in the affected lung regions (147). As a result, pressure in the pulmonary arteries may rise in areas of bronchiectatic lung tissue with large bronchopulmonary anastomoses. This could result in shunting of pulmonary arterial blood away from anastomotic regions and into normal lung areas. Indeed, in patients with bronchiectasis, Noszkov et al. measured vascular pressures and oxygen saturation in the pulmonary trunk and terminal branches of the pulmonary artery (149). They discovered 30-50 mmHg pulmonary artery occlusion (wedge) pressures in bronchiectatic

regions, but normal pressures in the pulmonary trunk and its main branches. The oxygen saturation measured with an unwedged catheter in the pulmonary artery supplying the bronchiectatic region was the same as that measured in the systemic arterial circulation, whereas the oxygen saturation measured in the pulmonary trunk was the same as that of venous blood (150).

The mechanisms underlying the formation of bronchopulmonary anastomoses in bronchiectasis are not completely defined (151). Bronchial artery enlargement in bronchiectasis is associated with the development of granulation tissue during the organising pneumonitis that precedes the changes of bronchiectasis. Granulation tissue production increases as the disease progresses (151). Because the bronchial circulation delivers blood to the airways, increased granulation tissue production in the bronchi results in increased bronchial blood flow (151,152). Through an increase in the number of bronchopulmonary anastomoses, bronchial blood flow drains into the pulmonary circulation (151). The functional significance of these bronchopulmonary anastomoses is unknown; most likely, changes in the vasa vasorum provide this drainage route for blood from the bronchial to the pulmonary circulations (152).

Bronchopulmonary communications are typically located on the walls of the bronchiectatic sac

(153). In fifty percent of instances, anastomoses can have a diameter of 1 mm (153). The bronchial arteries are spiral-shaped before they connect to the pulmonary arteries. It is possible that the spiral configuration of the bronchial arteries reduces the transmission of systemic arterial pressure to the pulmonary arteries, thereby preventing this factor from contributing to the development of pulmonary hypertension (154,155).

Darke and Lewtas investigated the bronchial arteries in various chronic lung disorders using both selective bronchial arteriography and thoracic aortography. A total of 23 bronchiectasis patients were studied (156). The contrast material was seen to pass from the aorta into the pulmonary artery via dilated bronchial arteries supplying the bronchiectatic segment (156). There were two major flow patterns that emerged. Initially, contrast material was freely injected into the pulmonary capillaries, then the pulmonary veins, and finally the left heart

(156). This was referred to as "forward flow." The second pattern, seen in only three patients, involved contrast flowing against the normal flow of the pulmonary artery and toward the lung's hilum, a condition known as "reverse flow." Such reverse flow was thought to be caused by increased vascular resistance in the pulmonary capillary bed caused by chronic inflammatory changes and an increase in bronchopulmonary blood flow (156). When pulmonary artery pressures in the pulmonary trunk were normal, this usually happened in unilateral bronchiectasis. On a pulmonary angiogram, reverse flow may appear as an occlusion of a lobar pulmonary artery and be misdiagnosed as a pulmonary embolism, a phenomenon not appreciated by clinical radiologists (282). In these cases, obtaining blood samples from the distal pulmonary artery for oxygen determination may be helpful in confirming that the angiographic abnormality is due to increased bronchopulmonary blood flow rather than a pulmonary embolism.

Selective pulmonary angiography may occasionally show rapid dilution of contrast material in the pulmonary artery in patients with severe bronchiectasis, indicating a flow of systemic blood into the pulmonary artery (157). Several researchers have attempted to estimate bronchial blood flow in bronchiectasis patients. The most common method has been to measure the outputs of the right and left ventricles. The difference in left ventricular output and right ventricular output is thought to be caused by bronchial flow returning to the left ventricle via the bronchopulmonary anastomoses.

Fishman and colleagues used the Fick principle to measure bronchial blood flow in two patients with bronchiectasis. They discovered that bronchial blood flow in these patients was 315 and 382 ml/min, or about 4% of cardiac output, whereas normal is less than 1% (158). Roosenburg and Deenstra, performed right heart catheterization in six patients with advanced bronchiectasis as part of a functional examination prior to resection. The catheter was inserted into the pulmonary artery that supplied the diseased portion of the lung, and the blood oxygen saturation was measured in that artery (159). They discovered that the oxygen saturation in the bronchiectatic lung was significantly higher than in the normal lung. The oxygen saturation was clearly higher than in mixed venous blood and, in many cases, equalled the oxygen saturation in systemic blood. These findings imply that functional bronchopulmonary anastomoses form on the pulmonary arterial side of pulmonary capillaries (159). In fact, when the artery to the affected bronchiectatic area was

occluded during catheterisation, an arterial pressure curve was often recorded. These pressure curves are most likely caused by partial transmission of systemic pressure through large anastomoses with the pulmonary arteries in the dilated bronchial arteries (159).

In chronic lung infection, there is sufficient evidence to suggest that the bronchial vasculature proliferates and hypertrophies. These mechanisms may be adaptive and play a role in the resolution and repair of lung infections. In fact, because pulmonary circulation is compromised in diseased regions, bronchial circulation could very well play an important physiological role.

1.8.6 Haemoptysis

The expectoration of blood from the pulmonary parenchyma or the infra-glottic tracheobronchial tree is haemoptysis (160). Tuberculosis, bronchiectasis, aspergillosis, and cystic fibrosis are among the most prevalent underlying causes (161).

1.8.6.1 Haemoptysis from bronchial arteries

As discussed earlier, the lungs have a dual vascular supply system including the pulmonary and the bronchial arteries, with multiple anastomoses providing an extensive collateral network between the two systems. The two systems communicate extensively via capillary beds near the alveoli and produce a right-to-left shunt that normally accounts for 1% of cardiac output (162).

Physiologically the entire cardiac output courses through the low-pressure pulmonary arteries and arterioles on route to being oxygenated in the pulmonary capillary bed. In contrast, the bronchial arteries are under much higher systemic pressure, but carry only a small portion of the cardiac output (162).

The bronchial circulation is responsible for 90% of cases of massive haemoptysis. Approximately 5% of cases are due to abnormalities of the pulmonary circulation and another 5% from systemic vessels or vessels directly arising from the aorta (163). Despite the quantitatively smaller contribution of the bronchial circulation to pulmonary blood flow, the bronchial arteries are generally a more important source of haemoptysis than the pulmonary circulation. In addition to

being perfused at a higher pressure, the bronchial arteries also supply blood to the airways and to lesions within the airways (161,162,163).

In primary bronchiectasis, cystic fibrosis, tuberculosis, and lung abscesses, granulomatous tissue ulcerates in continuity with the airways. Haemoptysis also occurs when the bronchial arterial bed, including that in the airway walls, is significantly enlarged because of absent or diminished pulmonary blood flow due to acquired or congenital heart disease. Bleeding in mitral stenosis and other causes of chronic pulmonary venous pressure elevation appears to originate from the airways' abnormally dense bronchial vasculature (164,165). In these conditions, the pulmonary veins impede the return of bronchial venous blood, causing it to reverse and flow into the right atrium, which has a lower pressure. It is believed that the increased bronchial venous plexus in the mucosa is the cause of the haemoptysis in these conditions (165). Other causes of bleeding in patients with mitral valve disease include frequent pulmonary infarctions and alveolar haemorrhage due to pulmonary oedema (165). Several possibilities for the pathophysiology of haemoptysis exist. The underlying initiating factor is abnormal decreased pulmonary arterial perfusion to the lung, secondary to occlusion or vasoconstriction, either in response to local lung parenchymal abnormality due to intrinsic abnormality of the pulmonary vessel (such as with thromboembolic disease or vasculitis) or due to congenital cardiac conditions resulting in decreased pulmonary arterial supply (such as tetralogy of Fallot) (167). The pre-existing collateral circulation to the lungs provided by the bronchial arteries, under the higher systemic arterial pressure, can enlarge to compensate for the decreased pulmonary arterial perfusion. In addition, there may be neovascularity and vascular remodelling associated with inflammatory processes (bronchiectasis, chronic bronchitis, and chronic necrotising infections) and neoplastic diseases. The bronchial arteries then form enlarged abnormal collateral vessels that, in the presence of inflammation or systemic arterial pressure, rupture into the airspaces, resulting in haemoptysis (167,168). Proliferation and enlargement of the bronchial arteries are the compensatory consequence of the expression of neo-angiogenetic growth factors in cases of restriction of pulmonary circulation caused by hypoxic vasoconstriction, pulmonary thromboembolism or thrombosis, vasculitis or chronic inflammatory lung diseases (169, 170, 171, 172). Since their walls are thinner and more fragile, and these vessels are subject to systemic arterial

pressure and are located in a region susceptible to chronic inflammation, they rupture more frequently with bleeding into the airways which is clinically exhibited as massive haemoptysis (173).

The exception is in the case of increased left atrial pressure, such as in untreated mitral valve stenosis; the aetiology is, rather, increased back pressure in the bronchial veins, which become variceal and can bleed, as in ‘‘cardiac apoplexy’’ (174).

1.8.6.2 Haemoptysis arising from the pulmonary artery

Less than 10% of all cases of haemoptysis originate from the pulmonary artery (175). The mechanism of this type of bleeding depends on the cause, and may be traumatic (Swan-Ganz catheter), inflammatory (Behcet’s disease or Hughes-Stovin’s syndrome), neoplastic (tumour necrosis and when the pulmonary artery is not encased in solid tumour), and infection (175). The most common causes of infections are predominantly tuberculosis (Rasmussen aneurysm), necrotic infectious pneumonias and other infections involving parenchymal necrosis such as invasive aspergillosis (175).

1.8.6.3 Definition of massive haemoptysis and indications for treatment

The most common definition of "massive haemoptysis" is bleeding greater than 240 millilitres per twenty-four hours (176). Recurrent bouts of mild haemorrhage (three or more bouts of 100 ml of blood per day within a week) are now regarded as a significant haemorrhagic event (177). In practice, however, the accuracy of patient measurement and reporting of expected blood volume may be limited (178).

When conservatively treated, massive haemoptysis carries a mortality risk between 50 and 85 percent (163). Aspiration of blood, which obstructs the airway, is the most common cause of death via asphyxiation (160). Less frequently, exsanguination and severe hypotension may cause mortality. This is because it requires approximately a volume of 150 – 200 ml in the tracheobronchial tree and 300 – 400 ml of blood in the alveolar space to significantly impair gas

exchange and cause death through asphyxia, long before blood loss results in volume deficiency shock (160,161).

1.8.6.4 Bronchial artery embolisation (BAE)

Bronchial artery embolisation (BAE) is a minimally invasive procedure that plays a crucial role in the management of haemoptysis, offering an effective therapeutic option to control and prevent recurrent episodes of bleeding (155). In BAE, selective catheterization of the bronchial arteries is performed, followed by the injection of embolic agents to occlude the arterial supply to the bleeding site within the bronchial circulation (155). By blocking the abnormal blood vessels responsible for haemorrhage, BAE effectively halts the source of bleeding while preserving the surrounding lung parenchyma. This approach is particularly advantageous in cases of haemoptysis associated with various underlying aetiologies, including bronchiectasis, tuberculosis, malignancy, and vascular abnormalities such as bronchial artery aneurysms or arteriovenous malformations (160, 161, 162). BAE offers several benefits, including high rates of technical success, low complication rates, and rapid cessation of bleeding, making it a valuable intervention in the management algorithm for haemoptysis (160, 161, 162). Additionally, BAE is associated with a lower risk of morbidity and mortality compared to surgical interventions, offering a less invasive and well-tolerated alternative for patients who are poor surgical candidates or have failed conservative management (169). As such, BAE represents a cornerstone in the multidisciplinary approach to the treatment of haemoptysis, providing patients with effective symptom control and improving clinical outcomes while minimizing the need for more invasive interventions. BAE is further discussed in Chapter 4.

1.9 Cardiovascular shunts

In clinical practice, a mechanical shunt is an abnormal conduit that permits fluid, typically blood, to travel from one area of the body to another. This may be a categorised by a number of ways for example (212):

- cardiac or extra cardiac shunt

- physiological and pathological shunt
- congenital or acquired shunt

1.9.1 Cardiac shunts

Intracardiac shunting lesions have emerged as perhaps one of the most recognisable characteristics of congenital heart disease in the field of cardiology. The majority of adult patients requiring therapy for adult congenital heart disease often present with a shunt (212,213).

In a healthy state, the heart distinguishes between oxygenated and deoxygenated blood flow. The systemic and pulmonary circulations of the heart operate in tandem to circulate blood throughout the body while maintaining a 1:1 ratio between the left and right sided cardiac outputs. The deoxygenated, systemic venous return to the right atrium is pumped to the lungs as the pulmonary blood flow (Qp). Once oxygenated, the blood returns via the pulmonary veins to the left atrium and is pumped into the aorta as the systemic blood flow or cardiac output (Qs). The term "shunt" refers to an abnormal connection allowing blood to flow directly from one side of the cardiac circulation to the other. Based on the direction of blood flow, it is right- to-left, left-to-right, bidirectional. On occasion the expression systemic-to-pulmonary, or pulmonary-to-systemic is utilised (212). Variations in pressure determine the flow direction

(212). A left-to-right shunt allows the oxygenated, pulmonary venous blood to return directly to the lungs rather than being pumped to the body. A right-to-left shunt allows the deoxygenated, systemic venous return to bypass the lungs and return to the body without becoming oxygenated. Overall, the circulation is impaired, placing extra strain on the overloaded ventricle. In most cases, the severity of symptoms is proportional to the amount of blood that has been diverted.

A schematic illustration of a normal heart, with the orientation of the arrows indicating the direction of blood flow, the length of the arrows representing the amount of blood flow, and the colour of the arrows indicating the saturation of blood in each chamber. Note that Qp = Qs in a normal heart, and that the diameters of the Qp and Qs arrows are equal. (Figure 1.17) (266).

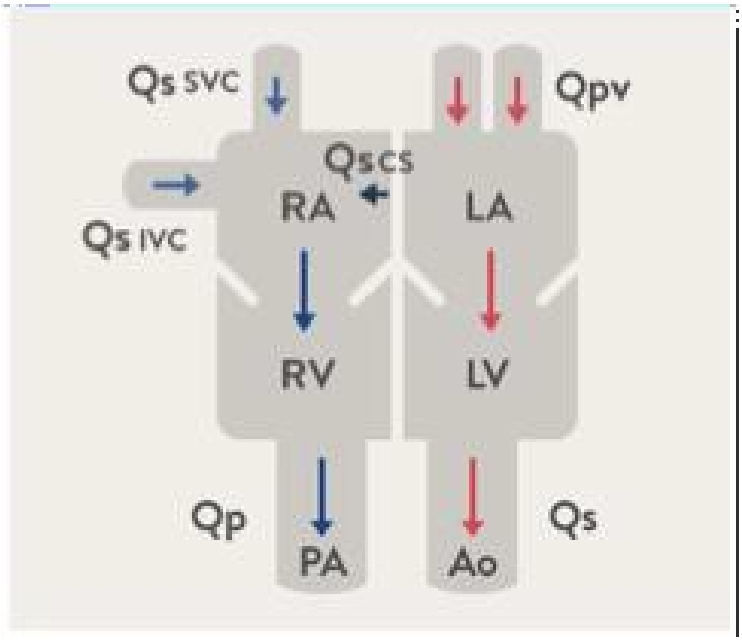


Figure 1.17 - A schematic illustration of flow in a normal heart

QsCS = coronary sinus flow, Qp = total pulmonary blood flow, Qs = total systemic blood flow Qpv = pulmonary venous flow.

RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, PA = pulmonary artery and Ao = aorta

1.9.2 Extra cardiac shunts

In certain chronic respiratory disorders, such as cystic fibrosis (CF), the systemic circulation responds to chronic lung changes by increasing blood flow through hypertrophied bronchial arteries. From clinical experience at our intuition requiring treatment of these pathologically enlarged bronchial arteries with bronchial artery embolisation (BAE) in patients with haemoptysis, it is postulated that these pathologically enlarged arteries alter the haemodynamics and cause a small but definite pathological shunt that increases overtime in step with the burden of airways disease as assessed by extent and severity of bronchiectasis, frequency of acute exacerbations and a variety of additional summative factors. This response to persistent hypoxia results in vascular

hypertrophy and hence blood diversion from the right to the left side of the circulation without gas exchange (217). The blood returning to the left atrium is not oxygenated, resulting in the same physiology as blood mixing from the right atrium to the left atrium. In CF, extensive systemic collaterals are frequently seen (217).

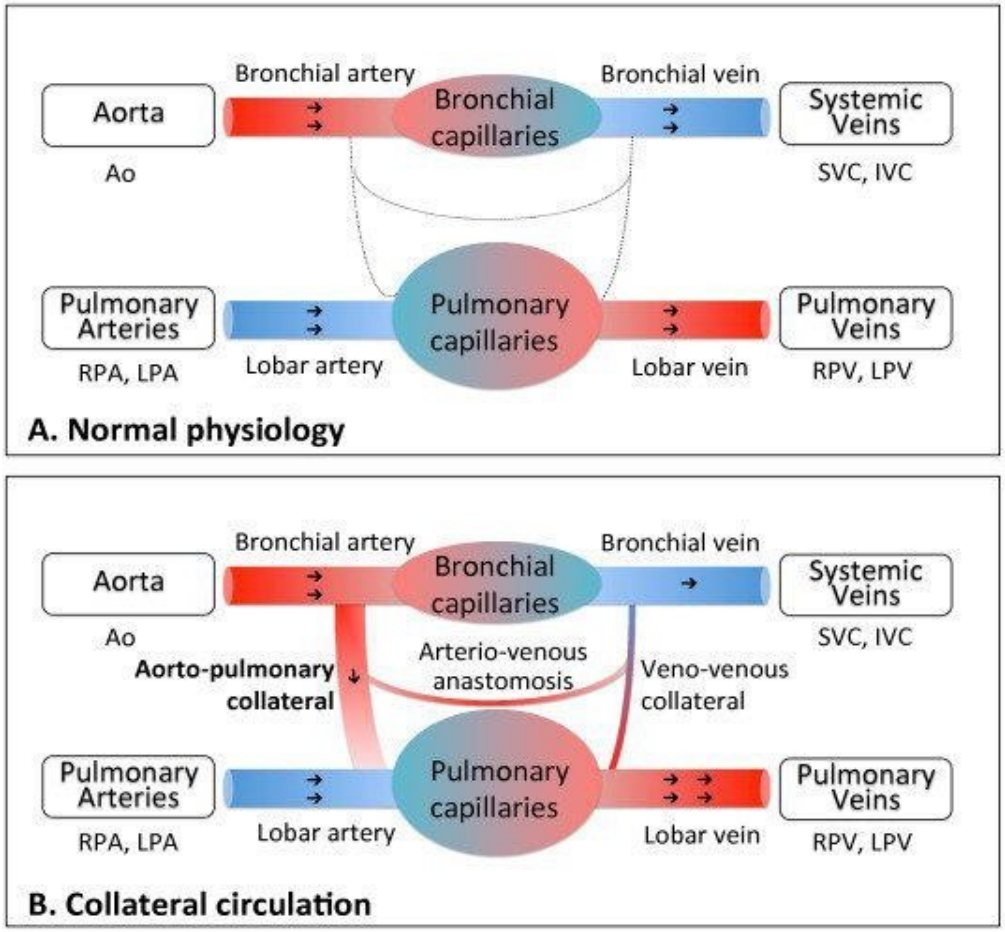


Figure 1.18 Bronchopulmonary collateral circulation

A) Normal physiology: The virtual network connections exist but do not significantly contribute to the lung blood flow.

B) Collateral circulation: The systemic and pulmonary circulatory systems are linked by a network of shunts. They include the aortopulmonary collaterals (between the bronchial artery and the pulmonary artery), veno-venous collaterals (between the bronchial vein and the pulmonary vein), and arterio-venous shunts (direct connections between the bronchial artery and vein circumventing the capillary network) (267)

As previously described in part 1 of this chapter, bronchial blood flow drainage is to both the systemic circulation and pulmonary circulation (via bronchopulmonary collaterals). The diagram below (Figure 1.18) illustrates the bronchopulmonary collateral circulation in normal physiology and the changes that occur to the collateral circulation in bronchial artery hypertrophy (267).

This increased blood diverted to the lungs via the systemic circulation may be enough to affect the shunt fraction. This extra cardiac shunting in respiratory patients has largely passed unnoticed in the literature. This thesis aims to shed some light on this circulation. It is important to note that these shunts are likely to be small and, as such, current routine clinical practice is unlikely to be sufficient to accurately measure this. This thesis examines the process of obtaining the shunt fraction in respiratory patients with precision and accuracy.

As alluded to previously, the degree of symptoms in patients with a shunt is proportional to the size of the shunt. This extracardiac shunting and the potential clinical implications on oxygen saturations is discussed further in chapter 6. The following section describes how these shunts are measured in clinical practice. This is prefaced by a brief section regarding the Thebesian circulation.

1.9.3 Coronary arterial and Thebesian circulation.

When assessing shunts, this coronary and Thebesian circulation must both be considered. Thebesian veins (named after Adam Christian Thebesius) are tiny veins without valves that drain venous blood directly from the myocardium into any of the four heart chambers (268,269, 270).

The coronary arteries supply the myocardium with oxygen and nutrients. The coronary venous system (CVS) has a significantly different macroscopic arrangement than the coronary arterial system, as well as a greater number of individual variants (268,269). The cardiac veins are divided into two primary categories by contemporary anatomical classification (268, 269). These two groups comprise of the tributaries of the greater CVS and the tributaries of the smaller CVS, comprising the Thebesian vessels. This is another example of a physiological shunt that exists in humans and allows deoxygenated blood to return to the left heart.

To facilitate understanding, the larger CVS is divided into two groups: coronary sinus (CS) tributaries and non-coronary sinus tributaries. Where both systems contribute equally to venous drainage, the name "compound CVS" has been coined. The bigger CVS drains the outside two-thirds of the ventricular myocardium, while the smaller CVS drains the inner third via its tributaries. CS tributaries drain the left atrium (LA), left ventricle (LV), and a portion of the right ventricle (RV), whereas non-CS tributaries drain the remainder of the RV and both atria. The veins of the bigger CVS reach their final destination in the right atrium. The bigger CVS drains both the right atrial appendage and the wall of sinus venosus, whereas the smaller CVS mostly drains the right atrial wing (268,269, 270). (Figure 1.19).

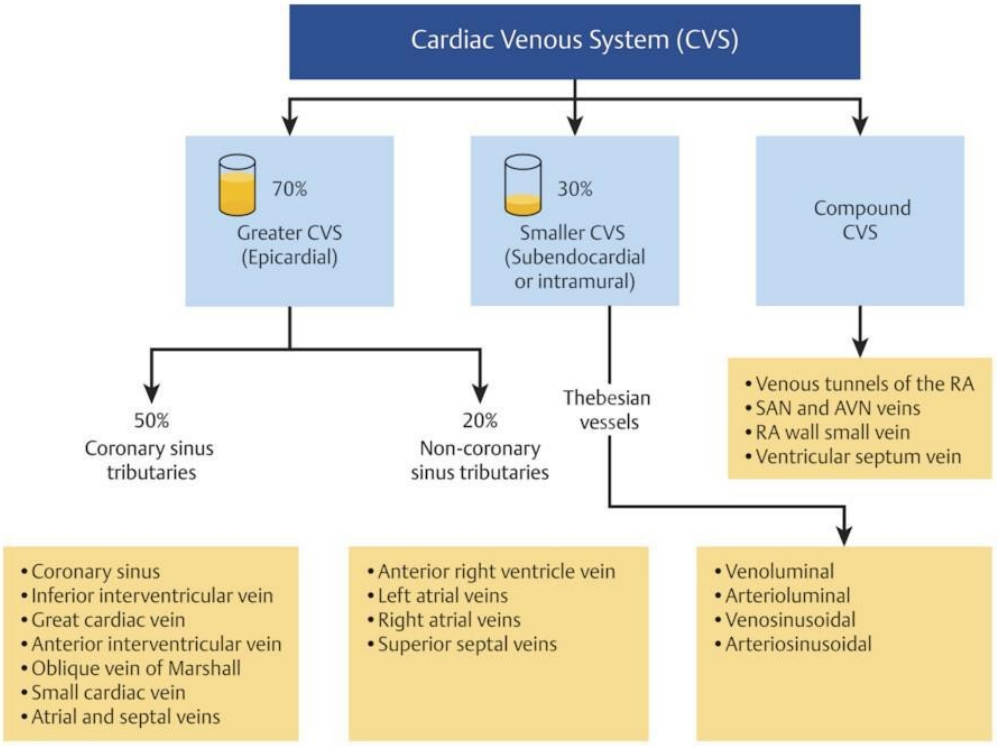


Figure 1.19 – Cardiac venous system

The flowchart explains how the cardiac venous system is divided. From radiologykey.com

1.9.3.1 Smaller cardiovascular system (Thebesian Vessels)

This subendocardial and intramyocardial bidirectional communication network consists of sinusoids, channels, and lacunae of varying widths, and travels in both directions to transport blood from the epicardial coronaries into the cardiac chambers to nourish the myocardium

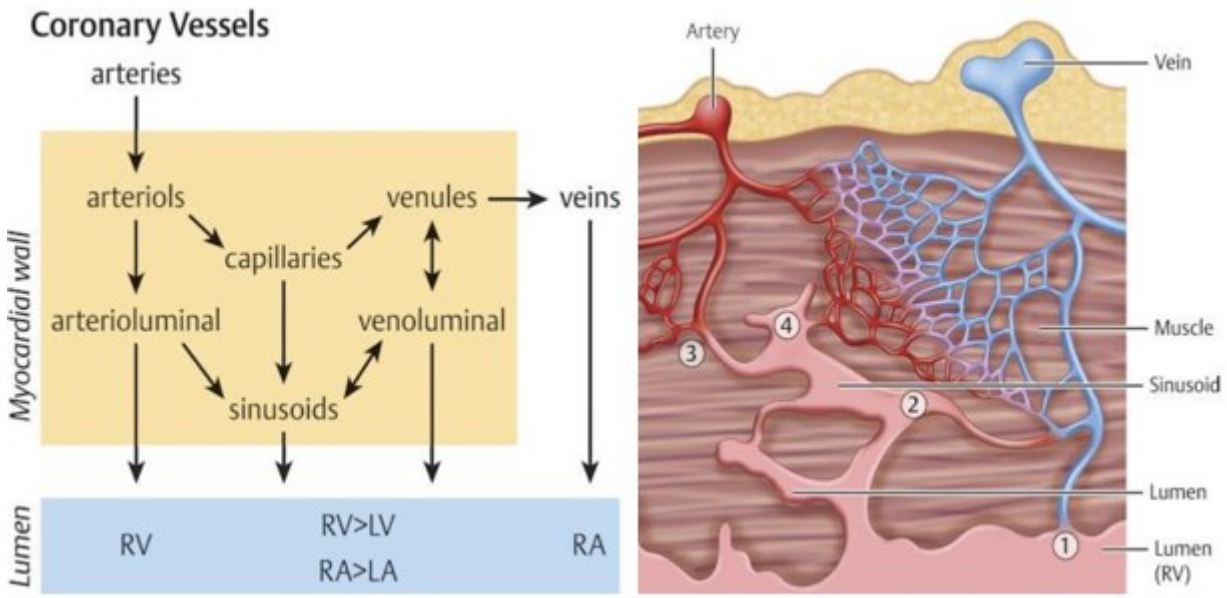


Figure 1.20 – Thebesian vessels

Left Panel -Schematic chart demonstrates extensive interconnection of the epicardial cardiac vessels through the intraluminal smaller cardiac venous system (CVS).

Right Panel -Tributaries of the smaller CVS (Thebesian vessels).

(1) Venoluminal vessels: connect intramural venules with the lumen of cardiac chambers

(2) Venosinusoidal vessels: connect intramural venules with subendocardial sinusoids and then the lumen;

(3) Arterioluminal vessels: connect arterioles with the atria or ventricles without traversing capillary beds; only exist in the right ventricle (RV);

(4) Arteriosinusoidal vessels: connect arterioles with sinusoidal spaces. RA, right atrium, LV, left ventricle, LA, left atrium.

From https://radiologykey.com

(270) (Figure. 1.20 - left panel). The vessels of the smaller CVS are collectively called Thebesian veins. However, in view of their arterial component, the term Thebesian vessels is preferred (270). Four separate sections are described (Figure 1.20 - right panel). Their orifices are located in cardiac chambers (mainly RA and RV) at the bases of the papillary muscles and are typically greater than 0.5 mm in diameter, but can be significantly larger, particularly in congenital heart disease with abnormal CS drainage (270).

1.9.3.2 The Thebesian circulation and impact on the shunt fraction

The Thebesian circulation presents a challenge in accurately assessing shunt fractions, particularly in patients with CHDs (215). Understanding the potential impact of the Thebesian circulation on hemodynamic measurements is essential for clinicians and researchers involved in the evaluation and management of patients with shunts.

The Thebesian circulation, plays a crucial yet often overlooked role in the assessment of shunt fraction (Qp/Qs) (237). While traditionally considered a minor contributor to overall cardiac output (~5%), the Thebesian circulation can introduce complexities in Qp/Qs calculations, particularly in conditions with intracardiac shunting or abnormal blood flow patterns (237). Since the Thebesian vessels return blood directly to the cardiac chambers without passing through the pulmonary or systemic circulation, they can introduce additional blood volume into the cardiac chambers without participating in gas exchange. Consequently, when assessing Qp/Qs using techniques such as MRI or angiography, failure to account for Thebesian circulation may result in overestimation of pulmonary blood flow and shunt fraction (237,270). Using MRI the Qs is usually at a slice downstream of the coronary ostia with corresponding consequences for the normal Qp/Qs ratio. Since the coronary and Thebesian circulation in a normal person is approximately 5% of the cardiac output (271) and the measurement of the systemic blood flow (Qs) is made downstream to the coronary ostia, the expected normal Qp/Qs is 1.05 when measured with this technique. In other words, in a normal healthy volunteer without a mechanical shunt a normal shunt fraction measured by CMR is a Qp/Qs 1.05 (accounting for the coronary/ Thebesian circulation) (237).

Understanding the presence and significance of the Thebesian circulation is therefore essential for accurate interpretation of Qp/Qs measurements and optimal management of patients with shunts.

Section 2

1.10 Measurement of bronchial blood flow in humans

The bronchial arteries are small in diameter (<1.5 mm at origin); consequently, the bronchial circulation is a high resistance, low-capacitance system (179). The vast majority of the lung blood flow passes through the pulmonary circulation, with only a small percentage carried by the bronchial circulation. Measuring the exact blood flow carried by the bronchial circulation is a difficult task, given its low flow, small size vessels, variable anatomic nature, and the fact that it represents such a small portion of the cardiac output. Several factors can influence bronchial blood flow and studies have shown that flow in the bronchial arteries is increased during alveolar hypoxia (133, 673), consistent with the response observed in most systemic vascular beds (180, 181). The mechanical effects of respiration also modulate flow in the bronchial circulation, with reductions in flow and increased draining via the pulmonary veins observed during lung inflation (181). It is likely that these inspiration induced alterations in bronchial flow are a consequence of changing lung volume and transpulmonary pressure compressing and/or stretching the systemic-to-pulmonary anastomotic bronchial blood vessels. Various vasoactive factors have also been shown to alter the pattern of blood flow in the bronchial arteries (182). Intravenous administration of acetylcholine also vasodilates the bronchial circulation (185,186) as does histamine (181).

Traditionally, invasive techniques have been used to measure the blood flow in patients with altered haemodynamics. Initial studies relied on animal model studies, and these provided important information that contributed to our current understanding. Current literature has established the significance of bronchial arterial blood flow and the occurrence of significant increases in bronchial blood flow in various disease states.

As discussed already the systemic collateral circulation to the lungs is complex and presents with varied anatomical, clinical and haemodynamic patterns. We know from earlier discussion that within the distal bronchial microvasculature, deoxygenated bronchial venous blood drains via

pulmonary veins to the left heart, producing an anatomic right to left shunt often referred to as the “bronchopulmonary anastomotic” flow or the “pulmonary collateral” circulation (91).

Several functional and quantitative MRI measures of pulmonary disease are emerging from the research setting into clinical practice that promise new methods for assessing changes in pulmonary and systemic collateral vasculature. MRI and in particular phase contrast sequences are a useful imaging technique that plays an important role in the morphologic and functional evaluation of cardiovascular shunts (187,206). In this thesis I have concentrated on this specific technique to assess flow in the bronchial circulation.

With improved cross-sectional imaging techniques and in conjunction with novel measures of assessing flow, a systematic assessment of this altered blood flow may reveal some of the mechanisms involved in the clinically observed proliferation of the systemic collateral circulation to the lungs. A better understanding of the change in the bronchial flow may also become a useful tool for an index of disease severity, monitoring therapy and prognostication.

1.11 Magnetic Resonance Imaging (MRI)

MRI is an excellent non-invasive imaging tool for examining circulatory shunts due to its ability to attain fine spatiotemporal resolution and (for cardiovascular work in particular) its fully variable FOV and oblique planar imaging capabilities. MRI can quantify big shunts (as important to cardiology), discover related anomalies, evaluate the pulmonary vasculature, and quantify ventricular size and function (189, 190). However, given the potential benefits, there are also associated challenges or pitfalls that should be understood and appreciated.

If we bring together a group of individuals involved in MRI and present them with an image, each will see something different in that image. Radiologists will home in on subtle pathology, technologists/radiographers may pick up on poor positioning, and physicists will evaluate signal-to-noise and detect artefacts. This demonstrates the fundamental need for multiple expertise to come together to acquire an optimised or importantly “diagnostic” image.

In order to achieve a diagnostic image, the following tasks must be accomplished (191):

- Ensure optimum patient co-operation and education of any breath hold manoeuvres.
- Resolving the tissues to unique locations in the image (spatial resolution)
- Detecting different signal amplitude (intensity) from the two tissues (contrast resolution).
- Resolving the cardiac and respiratory movements of tissues, by various methods

Artefacts are common in all diagnostic imaging modalities; however, MRI is particularly vulnerable. It is important to understand the mechanisms which lead to artefacts, so the diagnostic yield of the MRI study is not degraded (192).

1.11.1 Artefacts

Artefacts can degrade image quality, for example by interfering with spatial and contrast resolution (192). A detailed description of artefacts is beyond the scope of this thesis however it is important to recognise their occurrence and when these are expected, and if vigilance is applied their occurrence can be minimised. Some of these artefacts are more common in certain patient groups, such as those with underlying respiratory disorders, where patients' inability to hold their breath causes motion artefacts (192,193,194).

Common artefacts encountered in routine MRI methods are:

- Phase-encode ghosting caused by motion (cardiac and respiratory)
- Image resolution degrading (“blurring”) caused by motion
- Partial-volume artefact
- Under sampling (phase-encode FOV wraparound artefact)
- Truncation (Gibbs artefact)

MRI has many, even hundreds, of different acquisition methods, without standard terms across different vendors and software platforms. This causes confusion, especially when radiographers apply a method without any basic questioning of its limitations. The control software generally does not prevent attempted image acquisition with invalid parameters, possibly because there is no ionising radiation concerns with MRI imaging and so it is much less rigorously controlled than CT or other ionising radiation techniques. The radiofrequency (RF) power and nerve stimulation aspects are limited during each study, but generally there is no stringent limit on the total number of sequences nor time spent in the magnet.

The following section explains the basics of flow and how MRI protocols are specifically designed to assess this flow. The MRI physics of phase contrast imaging and its role in assessment of the shunt fraction (Qp/Qs) is also described. Chapter 3 of this thesis describes in detail the pitfalls/limitations that imagers need to be aware of when acquiring images and when evaluating the Qp/Qs ratio with a greater accuracy and precision, as required for this thesis compared to routine clinical practice.

1.11.2 Basics of Flow

There are four principal types of flow (Figure 1.21):

Laminar flow: Predictable flow velocities in coaxial cylindrical layers (laminae). This idealised flow develops after a sufficient straight length of steady flow in medium- and small- sized blood vessels, although it is further distorted because blood is not an ideal fluid. In a completely straight, nonbranching channel with non-pulsatile flow, velocity distribution should be parabolic, with peak velocities in the centre of the lumen. In real vessels of sufficient diameter for MRI studies, the velocity profile is usually more blunted ("plug flow") or offset due to upstream bends in the vessel and pulsatility, but the general laminar pattern may be established after a long enough section of straight vessel with low pulsatility (i.e. quite rarely in large vessels) (195, 196).

Turbulent flow: Chaotic fluid transport with random velocity fluctuations over position and time. When blood speeds exceed a certain threshold or vascular architecture sufficiently disrupts laminar flow, turbulence occurs. However, turbulence should not be confused with regions of flow recirculation ("complex flow", described next) in or downstream of bends in vessels, which are not randomly turbulent but may for example contain circulating regions of flow outside the

mainstream. Even under exercise, turbulent flow in the aorta tends to be provoked only by diseases, such as distal to stenoses. In ideal fluids, turbulence can be predicted using the Reynolds number (Re). Re values below 2000 predict laminar flow, while values above 2500 predict turbulent flow (195, 196). However, blood is far from an ideal fluid, and in curved elastic vessels bearing pulsatile flows (i.e. flow profile affected by the Womersley number), the Reynolds number is a stark oversimplification.

Vortex flow: (also known as complex flow) Localised whirling or sluggish blood flow that has detached from the vessel's core streamlines. These vortices, also known as flow eddies, are common at vascular bifurcations and distal to stenotic regions. Unlike turbulent regions, vortex flow zones are formed by currents and streamlines that move slowly, are not random, and frequently run counter to the main flow direction. Both turbulent and vortex flow pose difficulties for some methods of MR angiography (195, 196), which is why contrast-enhanced angiography is now dominant.

Stagnant flow: Flow where the velocity of flow slows to a point of stagnation. In other words, as far as some MRI acquisition methods are concerned it behaves like stationary tissue (195, 196).

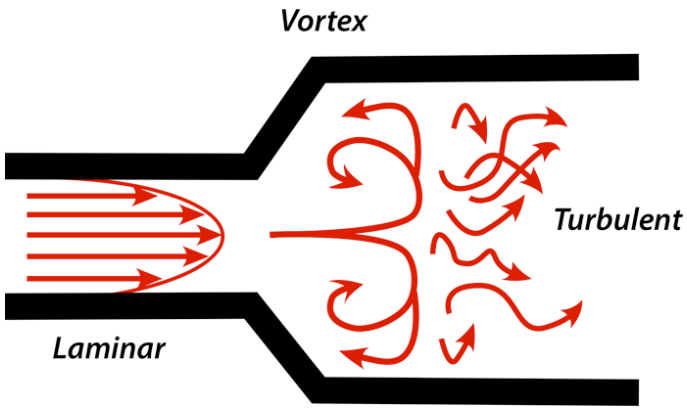


Figure 1.21 – Types of flow

Schematic showing different types of flow from https://mriquestions.com

1.11.3 MRI of flow

In this section, some of the basic principles of flow and its MRI assessment are described.

Flow is strictly defined as a volume of fluid per unit of time passing through a defined cross-sectional area (and is meaningless unless this area is specified or understood). For example, aortic flow is typically in units of ml/beat or litres/minute and is understood to be measured by adding up all the velocities of blood multiplied by the pixel area (the pixelwise instantaneous flows), which are summed over a cross-sectional area covering the ascending aorta, and secondly summed over the duration of the cardiac cycle. That area has to be adapted to the changing vessel size during the cardiac cycle, as will be apparent in more detail later in the thesis. Ironically, flow itself is not a vector quantity, and the area through which it was measured must be stated with it. Area is a vector quantity, so by stating this area with the volume flow, an understanding of the direction of the flow is assigned to the entire statement.

It is important to stress that blood flow is just a special case of motion. There is fundamentally nothing different about the flow of blood through an artery, a vein, urine through the ureters, or CSF through the cerebral aqueduct (198), except for vast variations in the volume, speed and complexity. The velocity of the moving fluid at each point in a vessel is depicted as a vector

(199). This vector describes both the direction (vector orientation) and speed (vector length) of the fluid's velocity at that location. If we observe a cross-sectional area of an artery, the net flow passing through the vessel at that location would be determined by the individual velocities of each image pixel each multiplied by (the same) pixel area, giving the pixelwise instantaneous flow, summed over the total cross-sectional area of the vessel. For pulsatile flows, this summation must be repeated for each time-point (cine frame or cardiac phase) imaged in the cardiac cycle, to obtain the total flow (ml/beat) per cardiac cycle, multiplied by heart rate to obtain cardiac output (litres/min).

Another aspect of flow, less often used in cardiology but applicable to non-pulsatile flows, is known as "instantaneous flow" and may occur in the literature just as "flow". It is the volume passing through the specified planar cross-sectional area, again per unit of time but now unrelated to the

cardiac cycle, and might be in units such as ml/second. The term “flow rate” also is used, but is perhaps superfluous as the “rate” of flow is already implicit to the basic definition of flow.

The term “volume flow” also occurs in the literature, where similarly the extra word seems superfluous. It is worth mentioning that in medicine “flow” is also used in perfusion measurements, for the supply rate of blood perfusing a given volume of tissue, typically stated in ml/g/min for so many ml of blood perfusing each gramme of the relevant organ per minute. This is not performed by phase-contrast and firmly outside the scope of this thesis. This usage of “flow” is even in physics terms an invalid definition of flow.

The MR signal has two components, namely, amplitude and frequency (leading to phase-shifts with time), both of which are used for image reconstruction (203) although the frequency (phase) information is not usually seen directly, as only the images showing magnitude (amplitude) in each pixel are normally viewed.

Leaving aside angiography, and concentrating on methods for MR flow measurement, there were originally 2 major classes of flow imaging methods (205). The time of flight (TOF) technique relies on flow dependent changes in longitudinal magnetisation, whilst phase- contrast techniques rely on velocity- dependent changes in the phase-shift of transverse magnetisation (205). In addition, for angiography not flow measurement, there are contrast enhanced MR techniques that employ exogenous contrast agents, such as gadolinium chelates, to provide strong vascular enhancement (205) although dependent on first-pass timing acquisition which is not trivial. Contrast-enhanced angiography is however related to shortening of the T1 properties instead of TOF effect and should not be confused with phase- contrast velocity mapping.

1.11.3.1 Phase-contrast velocity mapping

MRI is usually displayed as magnitude images; brighter pixels contain more signal. The signal is from the rotating transverse magnetisation in the pixel, which is a vector quantity (two properties: size and direction) (203). Although the direction is rotating, MRI detects how far it is running ahead or behind a reference rotating source (oscillator) in the scanner electronics (204,206). This ahead or behind quantity is known as phase (phase shift), used for position encoding in MRI because the

magnetic field gradients cause phase shifts depending on position-and also on a horde of other effects, among them velocity (187, 188, 203, 206) dependent on the gradient waveforms used to obtain the image. Phase has a 360° range, beyond which the same values repeat, causing wraparound (aliasing) (206). As mentioned, the phase of each pixel is affected by uncontrolled factors like main field non-uniformity and chemical shift, so the phase reconstruction (phase image) is usually confusing and not normally displayed (187,188,203, 206).

In the early 1980s, Paul R. Moran proposed the idea that blood flow speeds could be encoded by phase (207). Moran looked at how a pair of gradient pulses with zero total area (known as a bipolar gradient) affected the phase of both still and moving spins (207).

Conventional MR images show the amplitude of the regional signal at each pixel in the image (190,203,206). Techniques called phase shift or phase-contrast velocity mapping use velocity-induced phase shifts to tell the difference between moving blood and still tissue (190,203,206). When protons (or spins) move in the direction of a magnetic field gradient, they accumulate changes in phase, or phase shifts (8). A moving spin will experience a phase shift that depends on how fast it is moving, how strong the gradient is, and the duration of that applied gradient (190,203,206). Using an additional bipolar velocity-encoding imaging gradient, with zero total time-integral ("area" under the waveform), a precise and importantly reliably linear relationship between the velocity of moving spins and the phase shifts is created while stationary spins acquire zero phase shift (187, 188, 190,203,206).

Typically, two acquisitions are performed: one with velocity compensation and the other with velocity encoding (190,203,206). An additional bipolar gradient is introduced during the second acquisition (190,203,206). Each image is phase-reconstructed, and then the two-phase images are pixel-by-pixel subtracted to get the final velocity map (Figure 1.22). The objective of subtraction is to eliminate phase shifts that have nothing to do with flow (190,203,206). The phase subtraction image is sometimes thresholded by the normal magnitude image to eliminate random phase background pixels, such as air in the lungs, but the complexities of selecting the correct threshold are a barrier to widespread utilisation. The values of phase shifts are measured in degrees and range from -180° to +180° (190,203,206).

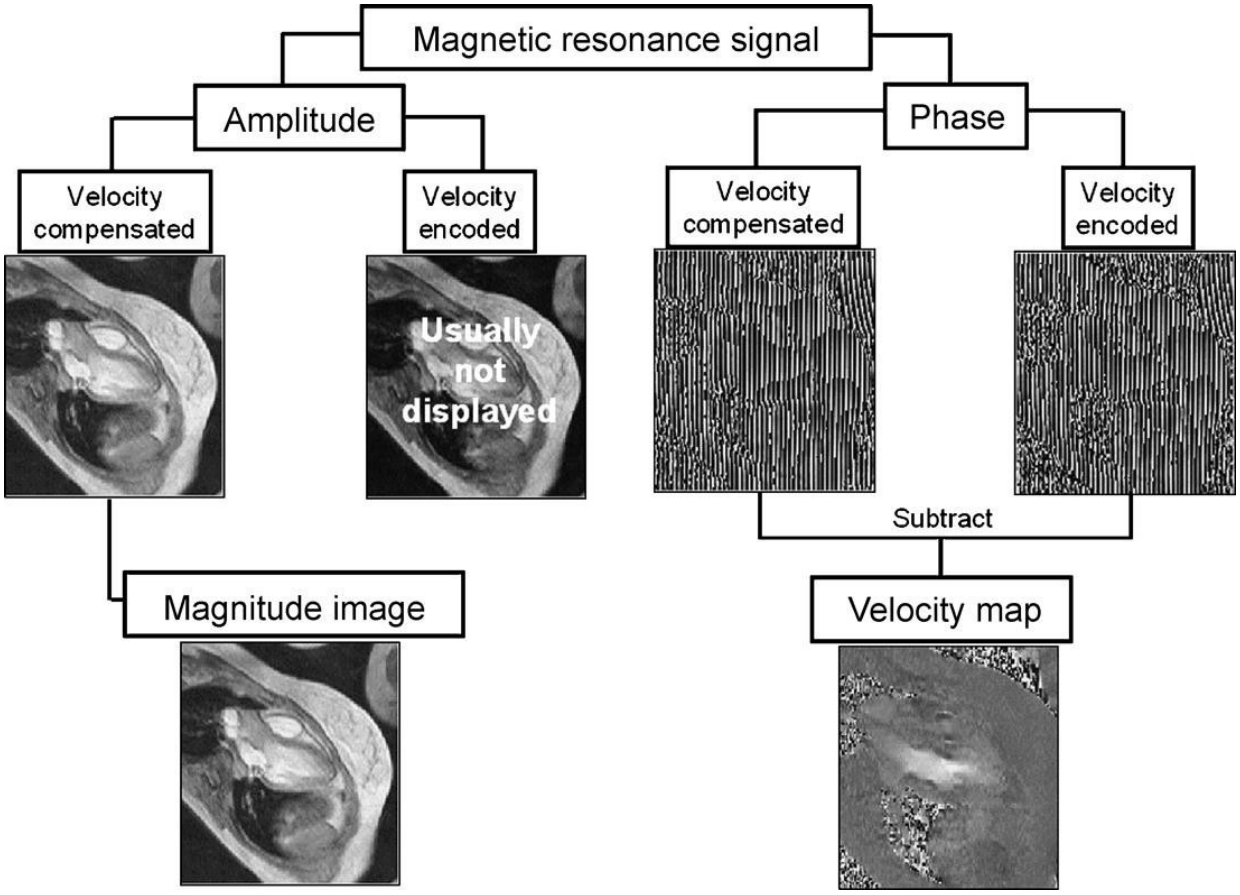


Figure 1.22 – Phase contrast velocity mapping

Diagram showing phase-contrast velocity mapping. Pairs of velocity compensated (reference) and velocity encoded datasets are acquired. The latter datasets are subtracted to yield a velocity or phase map with pixel values linearly related to velocity (203).

Quantitative flow measurement by phase-contrast has been used by MR imagers since the 1980s (200,201), and the potential of this technique has been known since 1960 (202). Assessment of blood flow forms an integral part of the overall assessment of cardiovascular function. MRI techniques offer several benefits, including fields-of-view unrestricted by windows of access, and the ability to measure velocities in any required direction. It is non- invasive and is associated with minimal risk (190), but is expensive, requires the ability to breath hold, be comfortable in a supine position and furthermore contraindicated by many devices , etc . The overarching major advantage of CMR is its ability to provide both anatomic and functional data in a single study. CMR

has become an important complement to echocardiography in the clinic, and in the evaluation of cardiovascular diseases.

With the increasing software and hardware capabilities of MRI units and a reduction in the time needed to complete a cardiac study, increasing indications are evolving for use of phase- contrast flow measurements (202, 205, 206). These indications have direct clinical roles and numerous research indications. Vital to the research of cardiovascular function and the clinical evaluation of cardiovascular disease is the monitoring of blood flow parameters. Evaluation of the heart valves requires detection and quantification of stenoses and regurgitation, while congenital cardiac anomalies necessitate identification and quantification of shunt flow (203, 206).

Additionally, there have been advancements in MRI technology aimed at improving imaging and understanding the impact of air on anatomical structures and physiological processes. Techniques such as Ultra-short echo time (UTE) MRI or PD weighted MRI have shown promise in addressing random effects like air in the lungs. However, it's worth noting that these techniques are still in the early stages of development and further refinement is ongoing (283).

1.11.3.1.1 Velocity encoding (VENC)

The velocity encoding, or VENC, is the constant that connects speed and phase angle (203,206). VENC adjusts for the expected flow speed in the vessels by controlling the amplitude, or strength, and timings of the bipolar gradient. This effectively tells the sequence the maximum flow speed that will be encoded correctly (190,203,206). The VENC changes the bipolar gradient so that the maximum speed chosen causes a 180° phase shift in the data. Aliasing can happen if the VENC chosen is lower than the speed of the vessel (190,203,206). In extreme situations such as turbulence or inter-beat flow instability, the signal from flow may be “accidentally phase-encoded” causing mis-mapping of the blood out of the lumen along the phase-encoding FOV direction (190,203,206). On the other hand, when the VENC settings are high, the intra-luminal signal is more reliably strong with little image contrast for the vessel wall delineation (190,203,206), but the phase-shifts used to derive velocity are smaller and therefore the “velocity-to-noise” ratio is weak. Generally, when measuring flow, the entire vessel cross-section is used, as fortunately the vessel wall is thin compared to the diameter of the great vessels and may partially saturate anyway

as it does not move much through-plane. For reliable flow calculation by summation of all the velocity pixels in the required vessel cross- sectional area, velocity aliasing of the fastest velocities must be corrected, usually by rescanning using a wider VENC. However, a very wide VENC should not be used as this degrades the signal-to-noise ratio of the velocity information compared to other sources of phase-shifts, both random and systematic. The VENC adjustment must be made at the time of acquisition and requires experienced radiographers.

1.11.3.1.2 Image generation

Usually the phase-contrast velocity acquisition generates two sets of cine images: magnitude images and phase images (Figure 1.23). The signal amplitude is shown on the magnitude images, which look like regular white-blood gradient echo images. They are used for anatomic orientation and to guide the delineation of the selected area for flow calculation during post-processing. On the phase images, each pixel shows how fast the spins in that pixel are moving on average. Because of this, the phase images are used to calculate flow by two stages of accumulation during post-processing (203, 206). The encoded range of speeds is usually shown in grayscale (but can also be colour-coded), and the software that runs the display can convert it into units of speed (203). Tissues that don't move, like the chest wall, are shown as a single mid-range grey colour. Pixels whose spins are moving in the direction of the velocity encoding look white, while pixels whose spins are moving in the opposite direction look black (203). Pixels with random

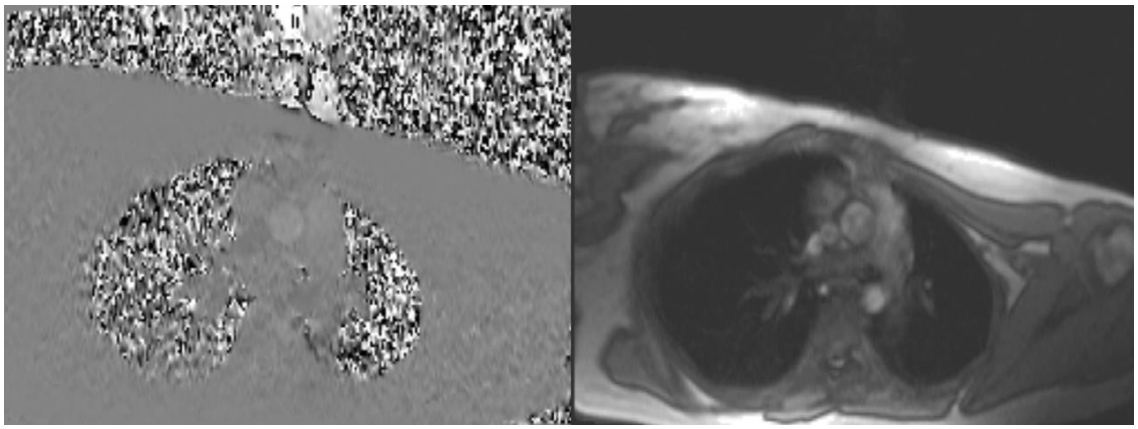


Figure 1.23 - Phase and magnitude images derived utilising phase-contrast velocity mapping.

A phase-contrast velocity mapping acquisition produces 2 cine images, a phase cine. (Panel 1) and a magnitude image (Panel 2)

phase information, as they have such low magnitude that they contain random noise, also called “salt and pepper” or "noise pixels," like those in the lung, look like they are a mix of white and black (203).

Usually, the bipolar velocity-encoding gradients are applied along only one direction to provide flow sensitivity in the clinically relevant direction, typically along a blood vessel, within a reasonable total imaging time. If the long scanning time is acceptable, velocity-encoding gradients can be used along two or even three directions during one longer scan to measure velocities in all directions. Thus the velocity data obtained from a phase-contrast (PC) study may obtained in any single direction or up to all directions, known as “4D Flow” in cardiac work because the fourth dimension of the pulsatile data is the time through the cardiac cycle. This technique can be used not only for blood flow measurements, but to depict the flow of any fluid such as cerebral spinal fluid (208,209).

In this thesis, the direction of velocity-encoding is always through the image slice so that the velocities of all the pixels multiplied by pixel area in the vessel cross-sectional area can be accumulated over the heartbeat to calculate flow. In- plane velocity encoding cannot support flow calculations (as the velocity distribution over the entire vessel cross-sectional area has not been imaged) but it is a common pitfall to attempt this.

In practice using simple bipolar gradients to measure flow velocities is not possible because magnetic field inhomogeneities create additional phase shifts that are indistinguishable from motion (203,206). To correct for these unwanted phase shifts, a subtraction technique is used to remove the background phase accumulation (this was covered earlier in the legend referring to Figure 1.18). In a modified form of the method, the bipolar gradients may be inverted instead of the Reference scan in Fig 1.18: (+/−) followed by (−/+) and subtracting the paired data. In theory it has been shown that this can reduce the accidental phase-encode ghosting problem, but that is important only in niche fields of work such as coronary velocity imaging next to far faster highly aliased velocities. This modification (sometimes known as “balanced velocity-encoding” was not used in this thesis.

Key Points (Figure 1.24):

A stationary spin exposed to a bipolar gradient pair will not experience a net phase shift, whereas a moving spin will experience a net phase shift linearly proportional to its velocity along the direction of the bipolar gradient

Accumulation of the pixelwise through-plane-encoded velocity phase shifts over the cross-sectional area of a vessel and with time through the cardiac cycle enables calculation of the flow through that slice of the vessel.

Spins flowing in opposite directions along the gradient acquire positive and negative phase shifts so both directions of motion (e.g. recirculating complex flows around a dominant forward flow stream) are vitally included in the linear response employed above for flow calculation.

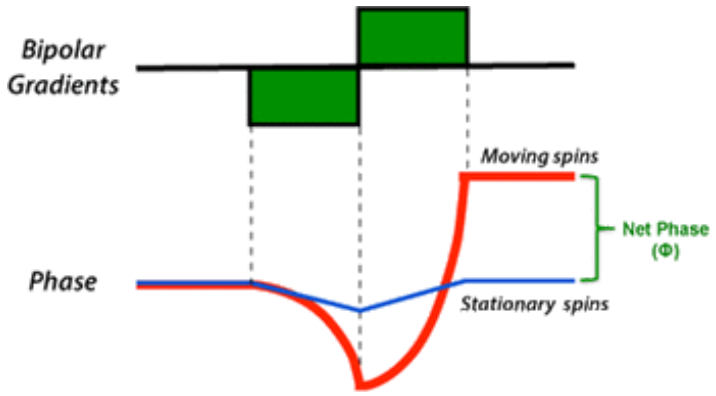


Figure 1.24 - Effect of bipolar phase-encoding gradients.

Net Phase is zero for stationary spins but positive for spins moving in the direction of the gradients. From https://mriquestions.com

1.11.3.1.3 In-plane versus through-plane velocity mapping

On modern scanners, it is possible to do both in-plane velocity mapping and through-plane velocity mapping. With in-plane acquisitions, velocity encoding can be in either the vertical or horizontal direction in the image. If one of these is encoded, it should be parallel to the flow in the vessel of interest. This can be done by rotating the field of view in the same plane as the flow (203).

However, it must be understood that in-plane velocity mapping fundamentally does not enable flow calculation.

Through-plane acquisitions are used to measure velocity and calculate the volume of flow. For an accurate assessment, the imaging plane should be perpendicular to the jet or vessel of interest (203). In-plane velocity mapping can help find the location of a through-plane acquisition allowing visualisation of the high-speed jet. But because of partial volume averaging or misalignment with the jet, in-plane acquisitions tend to underestimate the speed of a narrow jet. Correctly located through-plane velocity maps are more reliable as long as the imaging plane cuts through the core of the jet just downstream of the orifice, where it has the most speed. On traditional gradient echo images, the jet core has coherent laminar flow and can be seen as a central area with a high signal surrounded by darker areas with turbulent flow. On phase-contrast images, it is the area with the highest speed. It may take a series of cine and velocity acquisitions to find the jet core. Some narrow jets, like those caused by mitral, aortic, and mild tricuspid valve regurgitation, do not have a jet core that is coherent enough for phase- contrast velocity mapping (121) or it may change direction during the cardiac cycle

1.11.3.1.4 Electrocardiographic gating

For the highly pulsatile flows relevant to this thesis, a “cine” velocity map through the cardiac cycle is required. If possible, retrospective gating is superior as it covers the whole cardiac cycle. In older versions of MRI scanning, retrospective gating would also reduce artefacts caused by eddy currents that can happen when the regular application of a gradient is stopped, like in the older forms of prospective gating. In newer versions the gradients operate continually even if data is not being acquired. When an arrhythmia like atrial fibrillation varies the duration of the cardiac cycle during a breath-hold, prospective gating may need to be used (203).

1.11.3.1.5 Breath-hold versus non-breath-hold acquisitions

It is important to discuss the impact of breathing on flow measurement using phase contrast velocity mapping because some respiratory patients may have difficulty with breathing manoeuvres.

Phase-contrast velocity mapping can be performed either when the person is holding their breath or when they are breathing normally. Breath-hold acquisitions are faster and, provided that the

patient performs consistent end-expiration breath-holds, can position images more accurately than free-breathing. However, breath holding may have physiological impacts on blood flow (240). Using segmented FLASH sequences, it is possible to change elements like temporal resolution via the number of views (phase-encodes) per segment to get a short enough acquisition time (203) Additionally, one can reduce scan time by decreasing the number of phase encoding steps (reducing the phase field of view). This will result in phase wrap artefacts, which are acceptable so long as they do not overlap the region of interest (203)

- including the stationary background tissue of the thorax and abdominal walls required for corrections (Discussed in Chapter 3). For peak velocity measurements that require a rather precise location, breath-hold acquisitions are ideal, with exhalation halted at the more reproducible stage of exhalation. However, holding ones breath may alter the way your blood flows (210) and your heart rate (sinus arrhythmia). With averaged non-breath-hold techniques, which are typically segmented FLASH acquisitions, scan time is less important, but it should still be considered for the patient's comfort (203) and can be nearly as quick as breath-hold imaging when the breathing instruction times and patient recovery times are factored into the overall comparison of scanning duration.

A higher temporal resolution can also be achieved if required. As a rule, free breathing acquisitions are preferred for volume flow measurement with the caveat that some motion artefact maybe present in some cases with irregular breathing (203) and repeating these to optimise VENC or other factors can be too slow for the routine clinical service.

Many of the technical aspects of phase-contrast cine MRI for flow calculation are covered in much more detail in Chapter 3.

1.11.3.1.6 Phase offset error and background correction

Nearly all clinical MR imaging systems suffer from phase offset inaccuracy; whether this error is significant on a given machine depends on precise sequence timings and is still largely unresolved, more likely due to mechanical vibration than the well-corrected eddy currents typically cited. The phase offset is a systematic error in calculating the correct phase of both stationary and rotating spins (203). Occasionally, the issue can be resolved by discretely measuring and subtracting a fit to the background (228). This topic is elaborated upon in Chapter 3.

1.11.4 Assessment of shunts

Evaluation of shunt can be performed invasively through cardiac catheterisation, or non- invasively through imaging modalities. (214,215,216).

1.11.4.1 Fick Principle

The Fick principle states that blood flow is proportional to the difference in concentration of a substance in the blood as it enters and leaves an organ. This difference is used to determine cardiac output from the oxygen concentration in blood before it enters the lungs and after it leaves the lungs, knowing the rate at which oxygen is consumed (235). This principle is used to determine the Qp/Qs with oximetry via cardiac catheterisation. Several calculations may be performed on patients who have a communication between the two sides of the heart or between the aorta and the pulmonary artery, allowing a shunt to exist. Of these calculations, the only one that is of practical value is the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) — that is Qp/Qs (214,215). However, Qp/Qs can be considerably altered when a shunt is present. In minor left-to-right shunts (i.e., Qp/Qs < 1.5:1), the heart chambers and pulmonary vasculature are often normal and not markedly enlarged. With large shunts (Qp/Qs >2.0:1), left atrial and left ventricular volume overload develops, as well as raised right ventricular pressure and pulmonary arterial hypertension; these alterations eventually lead to Eisenmenger syndrome. (214,215,216)

1.11.4.2 Quantifying shunt volumes

A Qp/Qs ratio of 1, which is considered normal, implies no shunting in the system. The presence of a net left-to-right shunt is indicated by a pulmonary flow greater than systemic flow, as measured by the Qp/Qs ratio of greater than 1. A net right-to-left shunt is indicated by a Qp/Qs ratio of less than 1.

1.11.4.3 Imaging modalities to calculate the Qp/Qs

1.11.4.3.1 Nuclear Medicine techniques in assessment of the shunt fraction

Nuclear medicine was the first imaging modality to utilise Qp/Qs calculation through endovascular isotope injection and subsequent activity monitoring. Even though it provides accurate shunt measurements, it has a number of disadvantages, including ionising radiation. In addition, it lacks precision in determining shunt location (214).

1.11.4.3.2 Echocardiography in assessment of the shunt fraction

Echocardiography is the diagnostic modality of choice for the majority of cardiac shunts. It is accessible, inexpensive, safe, and painless, yet it provides a comprehensive look at the structure of the heart. Doppler ultrasound is commonly used for shunt quantification; however, there are limits to Qp/Qs ultrasound calculation due to operator reliance and a small acoustic window, respectively. It has no role in assessing the extra cardiac shunts pertinent to this thesis (214).

1.11.4.3.3 MRI in assessment of the shunt fraction

MRI imaging was first utilised to measure the Qp/Qs using phase contrast sequences in the 1990s (214). Quantification generated from MRI can be indirect or direct. Using velocity- encoded phase-contrast MRI or volumetric analysis of a ventricular stack of cine short-axis images, indirect quantification is possible (218). Using velocity-encoded phase-contrast MR images collected perpendicular to the ascending aorta and main pulmonary artery to estimate aortic (Qs) and pulmonary (Qp) flows, it is possible with expertise to reliably compute shunt volume and shunt fraction (Qp / Qs) (218).

MRI is now a well-established technique for assessing and quantifying moderate to large shunts that may present in patients with congenital cardiac disease; however, the assessment and quantification of tiny shunts in patients with respiratory disorders is definitely not well- established (214). In congenital cardiac disease, massive shunts and abnormally high shunt fractions are frequently observed. Given the large size of clinically important shunts, precision in image acquisition is not usually utilised, and significantly, this lack of precision has no routine impact on clinical care.

We now recognise that some respiratory disorders, such as suppurative lung conditions like CF, significantly alter the haemodynamics and subsequently may affect this shunt fraction; however, the amount of the shunt is substantially less, necessitating caution and accuracy to ensure a

genuine change is recognised (217). It is crucial to complete the examination precisely, acquiring the correct view, slice thickness, phase-encode resolution and cine temporal resolution, and last but not least the velocity-encoding range (VENC), combined with inspecting for R-R interval variations and breath-hold stability during the crucial two flow measurements needed. Most MRI systems do not routinely keep adequate records of R-R and BH for each scan. During the examination, the radiographer may modify these parameters, particularly for patient compliance with BH times, and an understanding of their significance and limitations ensures the data obtained is reliable.

1.12 Pitfalls of the MRI velocity-mapping methods and the need for a bespoke protocol

Assessing shunt fraction (Qp/Qs) using phase-contrast magnetic resonance imaging techniques is fraught with pitfalls, necessitating the development of a bespoke protocol tailored to accurately detect small shunts (220,221). While a valuable tool, MRI is susceptible to inherent limitations such as motion artefacts, signal loss, and phase wrapping, especially in regions with low flow velocities or complex flow patterns (221). In respiratory patients, factors like irregular respiratory motion, pulmonary vascular abnormalities, and variable blood flow dynamics exacerbate these challenges (220). Consequently, standard clinical MRI protocols are inadequate at capturing subtle shunts, leading to the underestimation or misinterpretation of Qp/Qs values (219). This knowledge gap underscores the need for further research to develop and validate specialised MRI protocols optimised for respiratory patients. By addressing these limitations and optimising imaging techniques the accuracy and reliability of Qp/Qs measurements in respiratory conditions can be improved. In clinical practice, shunt assessment predominantly focuses on cardiac patients, where shunts are typically larger. However, in respiratory patients, shunts are often smaller in scale. Hence, developing a meticulous protocol becomes crucial to ensure precise and accurate evaluation in this population. Overcoming these challenges necessitates meticulous attention to detail during data acquisition and analysis.

All known imaging methods utilised to measure blood flow in vivo have problems because they do not have a reference standard. Phantom experimental studies are used to obtain estimates for in-vivo flow measurements (221). As a result, it is challenging to quantify the error caused by phase

contrast measurements as a whole. Evans et al. found that in healthy people, the flow in the ascending aorta was 5% less than the flow in the pulmonary artery by CMR (219). Kondo et al. also found that the blood flow in the aortic and pulmonary trunks was not the same (220) informing us that difference in flow can occur and it is important to be vigilant to causes of this altered flow. When a non-breath-hold cine gradient-echo sequence with prospective gating is used, the technical error of a phase-contrast measurement is estimated to approach 5% (219) but is highly dependent on a series of factors discussed in depth next.

With commonly used sequences in clinical settings, phase-contrast measurements cannot provide real-time speed information. Instead, all measured speeds are averaged over at least a few heartbeats, or more if acquired during free breathing. Some centres advocate the use of free-breathing, as it may be advantageous when considering the flow over a longer period of time (e.g., to compensate for respiratory changes in venous blood flow returning to the heart during a BH manoeuvre).

1.12.1 Mismatch of encoding velocity

The measurement will be more precise if the encoding speed is close to the actual speed in the relevant region. Whenever calculating flow rates, background noise must be factored in (i.e., the random error of phases) (220).

The noise (σ) in the pixels of a velocity image is determined by the velocity-encoding range (VENC) and the signal-to-noise ratio (SNR) of the associated magnitude images reconstructed from the same acquired “raw data” (207).

This can be expressed as:

$$\sigma \sim \frac{V_{\text{enc}}}{\text{SNR}}.$$

Noise in velocity images increases with larger VENC values. Noise has less influence on estimation of flow because the noise is averaged over all of the voxels in the drawn vessel cross sectional area

ROI. Therefore, larger deviations from the ideal VENC can be tolerated as long as the peak velocity is not the main interest of the measurement.

Slow flow in the aorta, such as during diastole, may be inaccurately estimated if the VENC is too large (209,223). With sequences using VENC optimised for signal-to-noise ratio, however, the error drops below 10% (223). Since this error is not a major problem in routine clinical cardiology practice, more complex solutions, such as dynamic velocity encoding during the cardiac cycle (223), have not yet become commonly utilised (223). As can be seen in equation above, noise in a velocity image also depends on the signal-to-noise ratio of the magnitude image. An increased signal-to-noise ratio for magnitude images can be achieved by optimising sequence parameters like section thickness, flip angle, and receiver bandwidth. However, all of these parameters have associated trade-offs for accuracy, for example an increase in the section thickness may induce significant partial volume effects in smaller vessels like the branch pulmonary vessels or coronary bypass vessels (206).

1.12.2 Aliasing.

If the VENC is less than the fastest speed in the vessel of interest, then velocity-aliasing will occur (206). Aliasing has the potential to degrade the results of a flow measurement. This is usually readily evident to the operator when evaluating flow. This is evident in the velocity images, where voxels at the projected peak velocities have the opposite velocity value (206) in position and time than the surrounding voxels. Correction of such velocity aliasing is feasible only in very limited circumstances that are difficult to assess “on the spot” in all the relevant cardiac cine frames during scanning of a patient. However, rather than attempting to repair the aliased data set, it is safer and more effective to remeasure the flow using a slightly larger VENC (206) to ensure that no velocity pixels are aliased.

1.12.3 Misalignment of imaging plane

The imaging plane should be perpendicular to the direction of flow in order to obtain the most accurate readings of through-plane velocity, thereby enabling accurate flow computation

(203). In the calculation of flow, an error of up to 20 degrees is acceptable (203). Noting that the velocity decreases by cos(20deg), but the cross sectional area increases by 1/cos(20deg), this angulation does not by itself result in a flow calculation error. Possibly, the flow error is more closely associated with the partial volume of the angulated slice; these specifics have never been thoroughly investigated in vivo for the major cardiac vessels, perhaps because in clinical cardiology other physiological variations in flow are dominant. If a systemic artery appears to be elliptical on the magnitude image, it likely implies significant misalignment of the imaging plane during through-plane acquisition. The shape is far harder to assess for the lower- pressure pulmonary arteries that are frequently or even usually far from circular in cross- sectional shape.

1.12.4 Inadequate temporal resolution

Images or cine frames (also called cine phases) captured by phase-contrast velocity mapping reveal cardiac anatomy and velocity data at various stages (phases) of the cardiac cycle (206,203). If the temporal resolution (the number of frames or phases per heartbeat) is too coarse, then flow and maximum velocities may be underestimated. Depending on the patient's heart rate, the user can optimise the temporal resolution by modifying the repetition time, and, if k-space segmentation is employed, the number of views per segment (206,203). The scan time has to be considered in particular for breath-hold acquisitions. A faster scan can be achieved by acquiring more views each segment (number of phase-encode lines per cardiac cycle) (irregular naming), but this comes at the sacrifice of temporal resolution (206,203,225).

1.12.5 Inadequate spatial resolution

The velocity of a voxel is the average of its constituent velocities. This average phase- difference value is distorted due to the relative amplitude weighting (206). In other words, due to partial volume averaging, the voxel's flow will be underestimated if it contains a mixture of regions with extremely high and very low velocities, particularly at the vessel's edge, where it is uncertain what fraction of the pixel contains any flow. Noting that laminar flow is rarely fully developed in the large vessels close to the heart, it is often incorrect to assume that blood velocity is low near the vessel wall; in fact, blood velocity may actually accelerate around the outer edge of curved vessels.

If the pixel size exceeds approximately 25-30% of the vessel diameter, one can anticipate significant partial volume effects due to edge pixels (226,227). This error is typically insignificant (206) when measuring flow in the large vessels of the mediastinum, as a sufficient number (> approximately 16) of independent pixels are completely within the lumen.

1.12.6 Accelerated flow and spatial misregistration

The most accurate phase-contrast measurements are obtained when the flow is straight. In the presence of curved, complex, or accelerated flow, such as that resulting from turbulence or stenotic jets, it is more difficult to obtain accurate flow measurements (228). However, this source of error is mitigated by a short echo time, which reduces time-of-flight effects and turbulent signal loss, at the expense of a lower SNR and/or a reduction in frequency-encoding image resolution. Electrocardiographic gating and suspended breathing reduce spatial misregistration errors, except in cases of uncontrolled patient movement. The presence of coughing is potentially significant in patients with respiratory conditions. Artefacts of the ascending or descending aorta in the phase-encoding direction may also cause significant problems. These artefacts can be attributed to differences in blood flow through the arteries between the two overlapping data collections used in flow encoding and most noticeable in velocity images (206). In order to collect consistent raw data, the entire procedure relies on the repeatability of flow in successive cardiac cycles. This is not a simple averaging process and attempts to make it so through the use of real-time imaging are challenging for flow. However, in the future, this fragility may be alleviated. In cases of coughing or missed R-waves/irregular R-R intervals, it is necessary to retake the measurement (206) – assuming it was observed. This may be a problem as the patient is isolated in the scanning room and careful observation of the patient during each series is essential. However, operators are usually occupied preparing the next series required in the scanning protocol. The importance of attention to detail cannot be overemphasised and can be very challenging in busy cardiac MRI environments.

1.12.7 Signal loss

Two potential causes of signal loss are metallic prosthetic valve artefacts and irregular blood flow (203). This is due to turbulent flow, which occurs when the velocity of mesoscopic regions (relative

to the pixel size) of the flow varies randomly over time and space. Laminar or complex flows are ideal for phase-contrast velocity mapping (203), where "repeatable" refers to the pulsatility of the cardiac cycles required for one flow measurement. Modern scanners can now provide shorter echo times, which reduces signal loss caused by turbulence (230) and signal distortion caused by curved flows.

1.12.8 Phase offset errors and background corrections

The vast majority of clinical MR imaging systems have some degree of phase offset inaccuracy. This inaccuracy, known as the phase offset, is a systematic deviation from the correct phase of both stationary and moving spins (203). As the name implies, phase offset error is a consistent deviation from the correct phase of both stationary and moving spins. This error is highly problematic since it rarely occurs uniformly across the observer's whole range of view. If analysis software is utilised to provide a profile of the velocity images, the answer could be obtained. Phase offset errors can be corrected by skilfully measuring the background using stationary reference points, fitting and subtracting it (228).

Phase offset errors seem to be more pronounced with breath-hold acquisitions. While Maxwell gradients (231) are now routinely and analytically corrected, the more complex eddy currents and vibrations caused by the faster gradient switching of fast breath-hold scanning are probably less accurately corrected by the highly developed system "pre-emphasis" of all modern scanners (since about 1990), even for active-shielded gradients that are now standard hardware.

Manufacturers have reached a plateau in the hardware and software modifications to reduce these problems, to the extent that even the mechanical vibration of the gradient coils has now been shown to dominate the remaining errors in velocity-mapping backgrounds, extremely difficult to characterise and, much worse, even temperature-dependent as the water-cooled gradient-coil mountings warm up (changing their rigidity) during long scanning (274). This error is particularly deceptive because it rarely occurs uniformly across the whole viewing area (206,203). These offset errors are usually negligible for peak velocity estimation but may severely affect calculations of flows due to the integrations over area and time, (sometimes with serious consequences for valvular regurgitant fraction beyond the scope of this thesis). Phase offset errors can be corrected

for by applying simple background correction only if background phase varies linearly across the image, fortunately this is usually the case after Maxwell correction. Background correction should, be used with caution, after comprehensive training as incorrect utilisation may severely compound errors.

1.12.9 Potential errors during data analysis

There should be no noise or edge pixels in the vessel contours, as this would lead to incorrect summation of velocity information affecting the mean flow. Accurate vascular lumen contouring is necessary for flow quantification (203). Too small a contour results in underestimate of the total flow in the vessel. To make sure that extravascular noise pixels are not included in the ROI when using automated contour detection tools, the generated contours must be double-checked (203) for each cine frame.

1.12.10 Post processing

Special software is required to extract the information from the velocity images. This software can be obtained from the vendors of the MR imaging unit (with associated costs), it can also be obtained from third party vendors or developed in house (232). All these platforms usually support the drawing of contours (ROIs) into the vessel of interest and automatically copying those contours from magnitude to velocity images and vice versa (Figure 1.25 and Figure 1.26). In the commercial product used for this thesis (CVI42), the automatic contour detection works reasonably well with large vessels like the aorta, not quite so well for the less circular main pulmonary artery. The analysis program must allow ROI shape and position to be fluently adapted manually for each phase of the cardiac cycle. Generally, it is good practice to define contours in the magnitude images and cross-check them in the velocity images. Partial volume effects or large movements of the vessel may result in inadequate contour definition in the magnitude images. This problem may be easily corrected by looking at the velocity images. There is no consensus on this strategy. Some experiments have shown that the velocity images can be more reliable for estimation of vessel boundaries than the magnitude images (206,233), but that severely risks overestimation as the velocity-information of edge pixels that are only partially within the lumen may appear deceptively reliable (see Fig 3.4). In the diastolic frames, magnitude images seem to be more suitable for

definition of vessel boundaries. In the end, a combination of both magnitude and velocity images must be assessed by experienced operators with due care and attention.

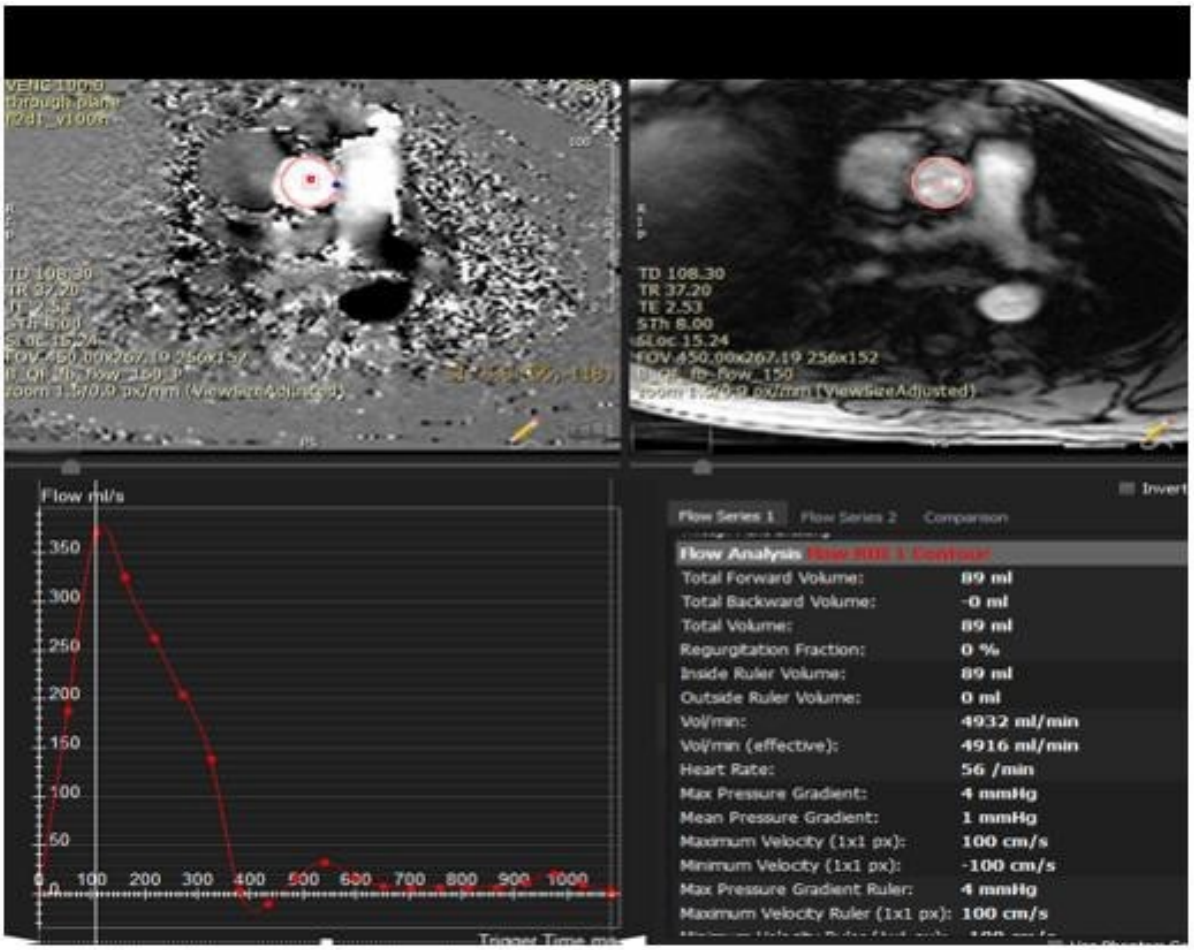


Figure 1.25 - Post processing of the aortic flow velocity.

Regions of interest drawn using semi-automatic vessel contouring for flow data analysis

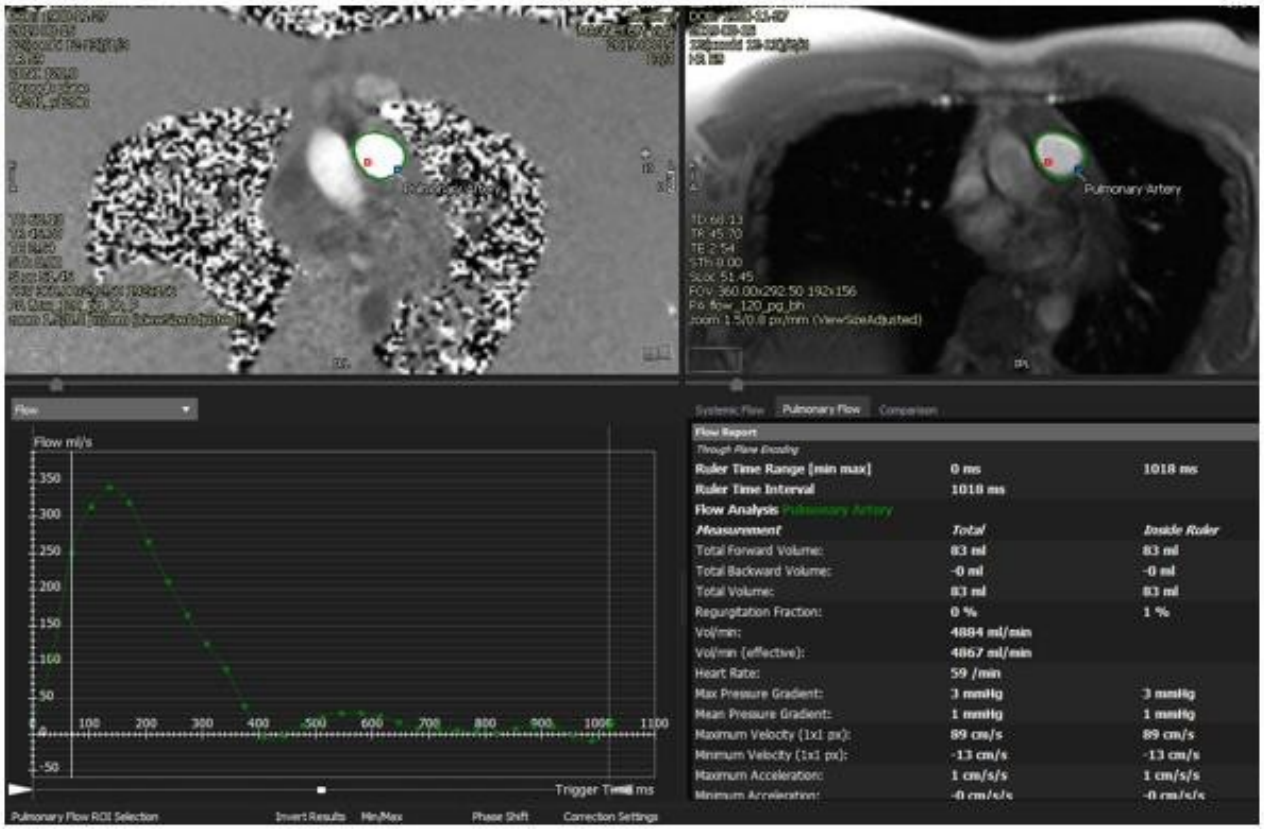


Figure 1.26 - Post processing of the PA flow velocity.

Regions of interest drawn using semi-automatic vessel contouring for flow data analysis

1.13 Aims of the thesis

This chapter has provided an overview of our current understanding of the bronchial circulation, highlighting the potential existence of shunts in respiratory patients, a phenomenon that remains relatively under-evaluated. Furthermore, the chapter has emphasised the foundational principles of MRI and PC MRI, as well as highlighted the notable challenges associated with measuring these shunts, with a specific emphasis on the imperative for optimising MRI techniques. Considering this knowledge gap, the aims of this thesis are delineated as follows:

- Develop a safe, novel MRI protocol to calculate the shunt fraction (Qp/Qs) with precision and accuracy.
- To determine whether CF patients presenting with haemoptysis have a measurable shunt.
- To determine whether this measurable shunt alters after bronchial artery embolisation.

2 General Methodology

In this section, the approach taken, and the common features of the projects included in this thesis are described. The demographic of the study participants and the recruitment methods are outlined, providing insight into the population under investigation. Additionally, the procedures for obtaining approval from the Health Research Authority (HRA) and other governance-related actions are discussed, emphasizing the ethical considerations and regulatory compliance involved in the research process.

2.1 Background

The Royal Brompton Hospital adult cystic fibrosis centre is one of the largest centres in Europe and treats approximately 1000 patients from diagnosis into adulthood. The service is highly rated and provides high quality, evidence-based treatment through a dedicated cystic fibrosis multidisciplinary team. Research, quality improvement, and service delivery are coordinated across the paediatric and adult CF centres at the Royal Brompton Hospital.

Patients with severe CF frequently experience haemoptysis. The prevalence intensifies with both age and the severity of the underlying pulmonary condition. There is a multifactorial mechanism that causes pulmonary vascular remodelling, which in turn causes bronchial arteries to become notably larger and tortuous. Typically, hypertrophied bronchial arteries are seen in CF patients who present with haemoptysis. After investigating the source of their haemoptysis, many patients are offered a procedure called bronchial artery embolisation (BAE). Despite its effectiveness in reducing haemoptysis symptoms, the impact on regional blood flow has not been rigorously studied.

Bronchial vascularity in CF has not been systematically investigated but is highly relevant due to the high morbidity and mortality associated with pulmonary vascular disease in this disorder (217).

BAE usually controls the symptoms of haemoptysis however, the alteration in the local haemodynamics is unknown. It is likely that the underlying pathophysiological mechanisms in CF alter the pulmonary blood flow significantly and in turn the shunt fraction also alters. MRI is a safe

and reproducible modality that has been shown to allow us to assess the Qp/Qs ratio in routine clinical practice for patients with congenital heart disease (214).

Over the past decade, a protocol for treating CF patients with small volumes of repeated haemoptysis by semi-elective embolisation of the bronchial arteries has been developed. Therefore, this procedure is performed under controlled conditions as opposed to as an emergency procedure. While this procedure is frequently successful in the short term, a significant number of patients re-present with a second episode of haemoptysis in the future, frequently several years later.

The ability to measure and interpret alterations in bronchial flow could have implications for the evaluation of illness severity, the tracking of therapeutic progress, and the prediction of future episodes of haemoptysis.

2.2 Management of potential study risks

Haemoptysis patients awaiting treatment with a BAE require close monitoring while they wait for treatment. This necessitates the care they receive as inpatients, where they may be closely monitored by medical professionals. As part of the study's design, I made sure a doctor with basic life support (BLS) training was with each patient the entire time they were in the MRI scanner, in case they experienced any severe bleeding. There were no risks associated with the MRI study itself.

2.3 Study objectives

2.3.1 Primary objective

Develop a MRI protocol to assess Qp/Qs with precision and accuracy ensuring appropriate use of background corrections.

2.3.2 Secondary objectives

To accurately quantify the (Qp/Qs) ratio in CF patients presenting with haemoptysis.

To assess if occlusion of the bronchial arteries results in measurable change in the Qp/Qs post bronchial artery embolisation.

To assess any physiological effect from this reduction in blood flow with standard assessments including bed side spirometry, resting oxygen saturations and quality-of- life questionnaires.

2.4 Study design

2.4.1 Overall design

This prospective pilot study developed a tailored MRI protocol to assess shunts with accuracy and precision.

The initial step involved developing an MRI protocol to quantify shunt fraction in healthy volunteers with accuracy and precision and subsequently this protocol was applied to a cohort of CF patients. The need to develop a robust protocol was discussed in the previous section.

2.4.1.1 Accuracy and Precision

Accuracy, in the context of science and technology, refers to how near a measurement comes to the actual value of a quantity being measured (273) (“bias”). The precision of a measuring system is the extent to which identical results are obtained from repeated measurements conducted under same conditions (273) (“scatter”). While precision and accuracy may be interchangeable in everyday conversation, in scientific endeavour there is a clear distinction between the two.

The difference between accuracy and precision is most often illustrated using the bullseye example. The objective is both precision and accuracy. Therefore, it is important to aim accurately as often as possible. To be merely accurate is to have darts that land relatively close to the bullseye, but not always. If you're just precise, your darts will land quite near to one other but not necessarily near the bull's-eye. However, in the best-case situation, your darts will always hit the bullseye due to a combination of accuracy and precision (Shown in Figure 2.1).

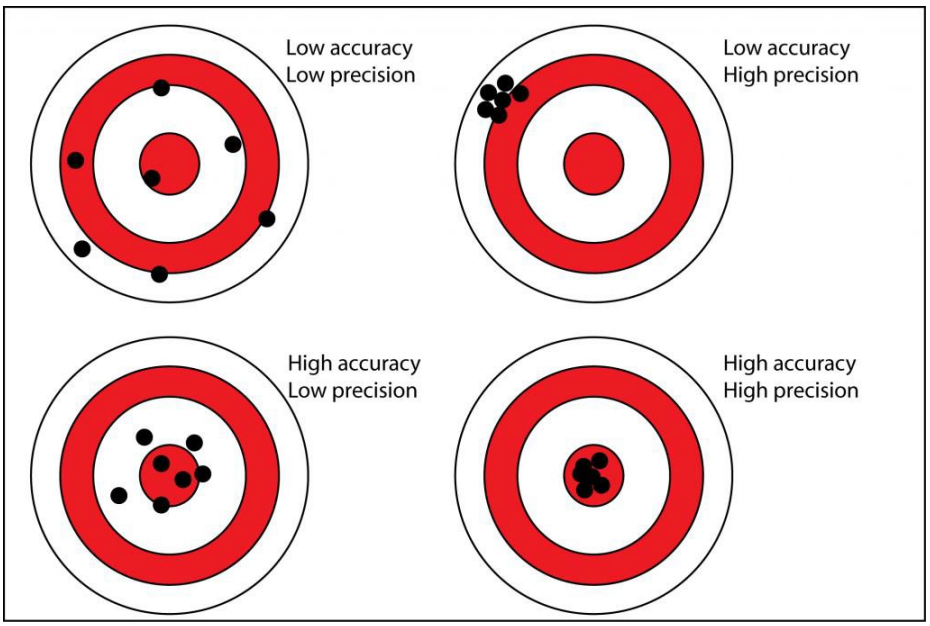


Figure 2.1- Precision vs accuracy

Accurate measurements fall in the bull's eye. Precise measurements are tightly clustered. Accurate and precise measurements are tightly clustered in the bull's eye.

Some other major differences between accuracy and precision are provided in Table 2.1

Table 2.1 Differences between accuracy and precision

Accuracy	Precision
Accuracy is closeness with the true value of the quantity being measured.	Precision is a measure of the reproducibility of the measurement.
Measurement can be accurate but not necessarily precise.	Measurement can be precise but not necessarily accurate.
It can be determined with a single measurement (although with no confidence unless precision is known).	It needs several measurements to be determined.
Accuracy may be affected with systematic error.	Precision may be affected with random error.
Accurate values have to be precise in most cases.	Precise values may or may not be accurate.
Degree of conformity.	Degree of reproducibility.

Clinical approaches that are currently in place often encounter difficulties in providing comprehensive assessments of shunt as a result of factors such as inherent measurement errors

and technical constraints. Therefore, it is critical to devise a novel method that can efficiently resolve these challenges and deliver improved levels of precision and accuracy in shunt measurement.

2.4.1.2 Volunteer study design

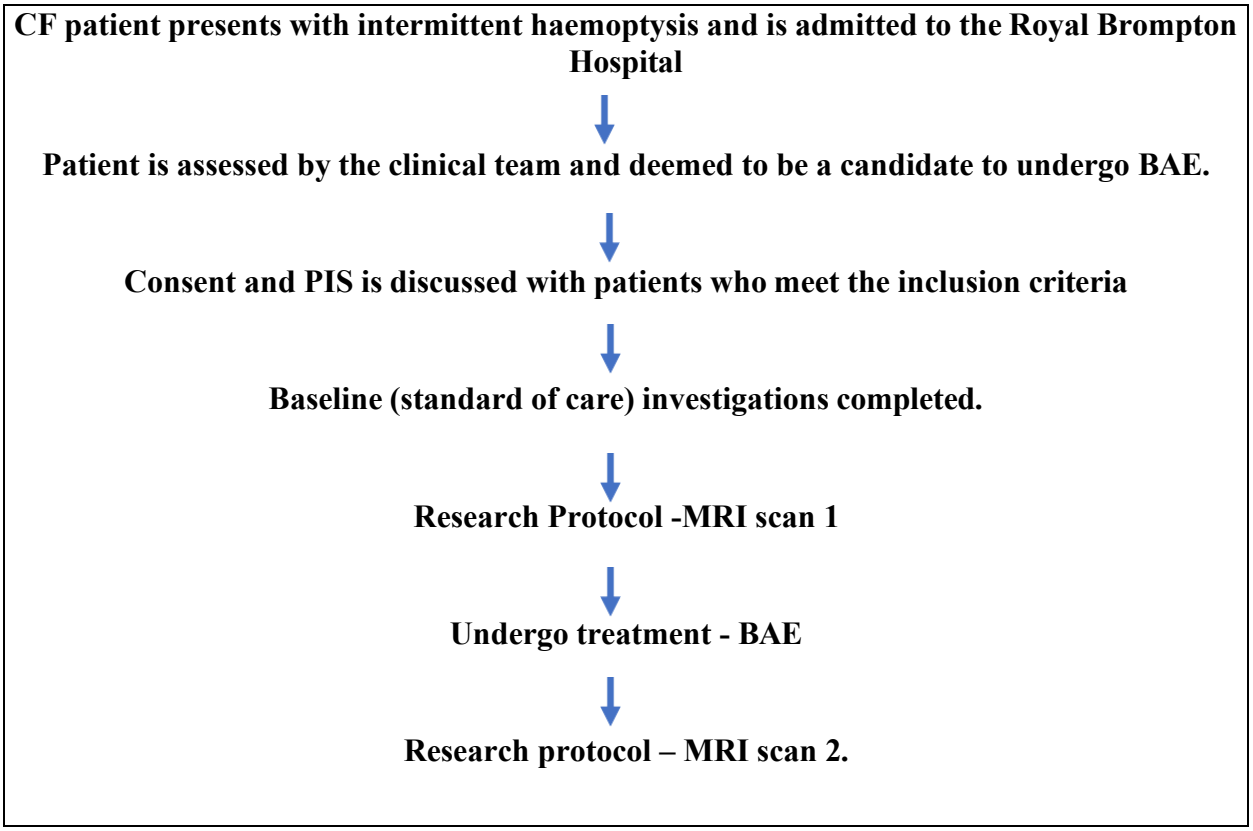
Ten healthy volunteers with normal cardiac function and no known shunts were imaged with a Siemens Vida 3T Numaris X VA11 scanner in order to develop a novel imaging protocol for assessing Qp/Qs with greater precision and accuracy than is required in routine clinical practice.

These images were acquired under the supervision of a physicist, an MRI radiographer, and an expert radiologist. Considering the ultimate application in CF patients, a custom MRI protocol was developed to accelerate the image acquisition process.

Interobserver and intermethod (breath hold and free breathing) variability were assessed to ensure precision. Volunteers were also removed from the table, and the entire process was repeated to evaluate intersession variability in light of reports of unreliability associated with scanner plane selection. Chapter 3 provides additional details.

2.4.1.3 Patient study design

The bespoke MRI protocol to assess Qp/Qs developed using healthy volunteers was applied to CF patients in this study. The flowchart describes the key stages involved in the study design.



2.5 Study location

The study was completed at the Royal Brompton hospital.

2.6 Discontinuation/withdrawal of participants

No subjects decided to withdraw from the study or expressed a desire to discontinue participation.

2.7 Subject/patient recruitment process

Patient recruitment at Royal Brompton commenced only once the following approval/essential documents were in place:

1.HRA approval

2.Local Site Delegation of Duties and Signature Log.

Signed Clinical study Site Agreement (CSSA) and confirmation of capacity and capability were also completed.

2.8 Study procedures

2.8.1 Informed consent

Informed written consent was obtained by the principal investigator (PI).

Consent to enter the study was obtained after receiving a thorough explanation of the nature, purpose, risks and potential benefits of the study and having the opportunity to deliberate.

The consent process took place on the ward where the participants were receiving medical care. Once a recommendation from the clinical team was obtained, patients were invited to participate. This provided patients the opportunity to ask questions and review the participant information sheet (PIS). Patients were given adequate time to decide (at least 24 hours).

The PI confirmed with all participants that inclusion in the research study was entirely voluntary, and they may withdraw from the study at any time without providing a reason.

The participants were given a copy of both the signed Informed Consent Form (ICF) and the approved Patient Information Sheet (PIS). The original signed consent form was retained at the study site (one filed in the medical notes and one field in the study master file). Additionally, a copy of the consent form was provided to the patient.

2.9 Study assessments

2.9.1 Screening assessments

All patients underwent standard routine care and baseline physical assessment.

These included:

- Bedside spirometry

- Body mass index (BMI)
- CT – Bronchial angiogram
- Standard of Care blood test – including CRP to assess inflammation.
- Cystic Fibrosis Questionnaire-Revised (CFQ-R)

2.9.2 Subsequent assessments

Patients underwent BAE after the first MRI scan. After receiving treatment (BAE) all participants had follow up MRI study within 7 days of the procedure while they were inpatients. If they would have been discharged, they would have been invited back to attend the hospital for the MRI study (as agreed during the consent process).

- After the post treatment MRI scan and completion of the CFQ-R, patients were not followed up as part of the research.

2.10 Radiology

MRI datasets were generated based on a unique study protocol. The research did not involve the use of ionising radiation.

The MRI studies were performed under the heading “research scan” and the findings were stored in patient PACS records.

The acquired images were post processed on validated post processing software (CVI42) by 2 trained practitioners.

The research studies did not uncover any incidental findings in the acquired images. If there were, they would have been investigated and the clinical team and patients would have been notified.

2.10.1 MRI Scanner specification

MRI scans were performed using a 3.0 Tesla scanner (Vida, Siemens, Erlangen, Germany) at the RBH site.

2.10.2 Bespoke MRI protocol

A brief outline is provided here. Further details are provided in Chapter 3.

1. Localisers

2.Limited views to localize the Aortic (Ao) and Pulmonary (Pa) flow planes

3.The views are LVOT, RVOT, enabling precisely cross-through- plane cines of the ascending Ao and MPA.

4.Positioning for flow, show where at the ascending Ao (STJ) and MPA

5.Repeat flow cines in free breathing and breath hold.

6.Once this has been acquired, obtain phantom correction scans using identical parameters as used for subjects (volunteers and patients).

The scan length was approximately 20 mins.

2.10.3 Post processing

This was performed by 2 trained users of Circle Cardiovascular Imaging (CVI42) software (Figure 2.2). Approximate time to complete measurements was 10 minutes.

Flow quantification post-processing of velocity encoded images requires:

1. Definition of vessel contour in all phases
2. Application of background correction

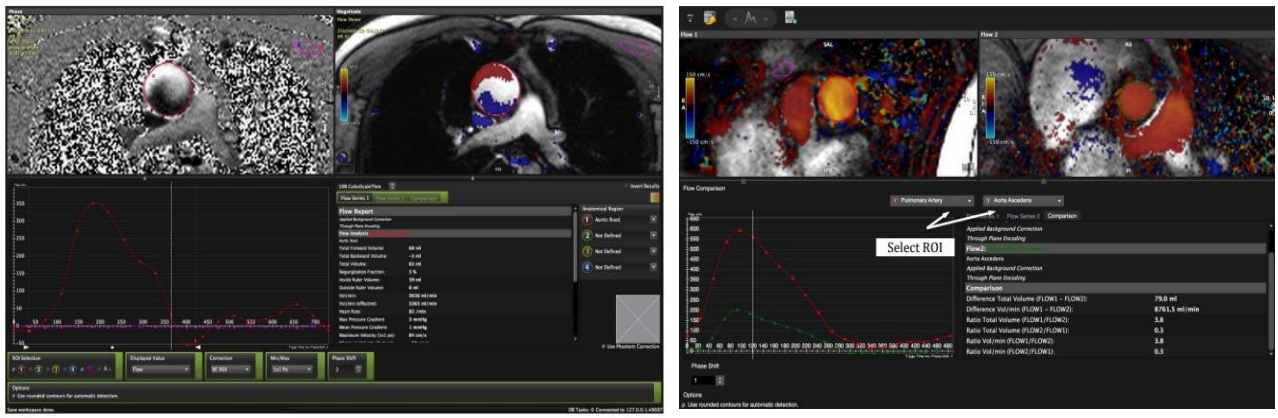


Figure 2.2 - A screen shot demonstrating vessel contouring on CVI42

2.11 Safety reporting definitions

The ICH GCP guidelines' definitions are provided here, and they were adhered to for this research.

2.11.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical study subject who is administered a treatment and which does not necessarily have a causal relationship with this treatment (*i.e.* any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

2.11.2 Serious adverse event (SAE)

A SAE is defined as an untoward occurrence that:

- Results in death or is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death).
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary

measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition).

- Results in persistent or significant disability or incapacity (substantial disruption of
- one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

Recording adverse events (AEs)

Provisions were in place to record all adverse events in the hospital notes and Case Report Form (CRF). There were no AEs in this study.

2.11.3 Serious adverse event (SAEs)

Provisions were in place for the Principal Investigator (PI) to report all SAEs to the Chief Investigator (CI) or a delegated individual in the research team. The PI and CI were responsible for reporting events to the research office immediately and/or within 24 hours of becoming aware of the event using the Sponsor's SAE reporting form. No SAEs were observed in this study.

2.11.4 Reporting of SAEs to the sponsor and the REC

Provisions were in place to record and report all AEs to the research office as well as the Research Ethics Committee (REC) that gave a favourable outcome of the study.

2.12 Data management and quality assurance

2.12.1 Confidentiality

All data was handled in accordance with the Data Protection Act 1998, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, 2nd Edition (2005).

The Case Report Forms (CRFs) did not bear the name of the subject or other personal identifiable data. The subject's initials, date of birth (DOB) and study identification number (ID), were used for identification.

2.12.2 Data collection tool

A CRF was used to record the data and stored in a safe place (locked cupboard in the Radiology research office). To ensure accuracy and efficiency participants were reminded to return the appropriate questionnaires and complete them in a timely manner.

2.12.3 Data handling and analysis

Data was stored and backed up on additional hard drives to allow recovery of data in case of a disaster such as fire/flooding/ theft. The PI was responsible for data entry and quality of data collection. Every patient received a numerical patient identifier. No data left NHS encrypted computers or was transferred outside the primary hospital. All data was handled in line with General Data Protection Act (GDPR) (2018).

2.12.4 Archiving arrangements

The study documents including CRFs, Informed Consent forms along with the study database will be kept for a minimum of five years, to be stored in locked offices within the Royal Brompton and Harefield NHS Foundation Trust (RB&HFT). The study database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

2.13 Statistical design

2.13.1 Sample size and recruitment

As this is a pilot study, with no pre-existing data, a formal sample size calculation was not made. The number of subjects to be included in the pilot study was determined by extrapolating data from the number of patients who have undergone a bronchial artery embolisation at the Royal Brompton hospital over the last 10 years. We anticipated recruiting up to 10 patients. The COVID-19 pandemic significantly impacted recruitment and by the end of the study a total of 5 patients underwent both pre and post BAE MRI scans.

2.13.2 Statistical analysis plan

Categorical data is presented as number (percentage). Continuous variables presented as mean (SD) or Median (IQR).

The Bland-Altman plot has been used to demonstrate the agreement of measurements obtained by two observers.

Formal testing for normality is a routine procedure in research studies. However, in this study, formal testing for normality was deemed unnecessary as normality has already been established in the literature, particularly in studies assessing flow measured by phase-contrast MRI imaging techniques (237). Established literature indicates that the flow volume data and subsequently the measured shunt fraction obtained from MRI is normally distributed. Since the data exhibits a normal distribution, a paired t-test was employed to assess the effect of the intervention and a 95% confidence interval was chosen to represent the data.

2.14 Ethics and regulatory requirements.

The Sponsor ensured that the study protocol, participant information sheet (PIS), informed consent form (ICF), GP letter and submitted supporting documents were approved by the Health Research Authority (HRA) which included Research Ethics Committee (REC) prior to any patient

recruitment taking place. The protocol and all agreed substantial protocol amendments, were documented and submitted for HRA approval prior to implementation.

2.14.1 IRAS and HRA application

The planning process of this prospective study took longer than initially anticipated as the clinical team raised concerns about these patients leaving the inpatient setting to have their research scans at an offsite facility within the trust. With this feedback and further discussions, a safe protocol was agreed. HRA approval was achieved, and Cambridge East research ethics committee (REC) approved the study protocol in May 2019.

IRAS project ID:	**256039**
Protocol number:	**N/A**
REC reference:	**19/EE/0154 (Cambridge East)**
Sponsor	**Royal Brompton and Harefield NHS Foundation Trust**

2.15 Finance

Funding for this study was provided by Chiesi Farmaceutici. This was through a competitive grant application process. Chiesi Farmaceutici were open to applications to support research specifically for CF patients. The research team applied for this and was awarded £12,000 to complete this research. The funds were used to pay for the MRI scans and other administrative costs of completing the study.

2.16 Insurance and Indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm was stated to the participants.

2.17 Statement of Compliance

The trial was conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

3 Development of a bespoke MRI protocol ensuring precision and accuracy in assessing the shunt fraction using MRI.

This chapter clarifies our methods and processes used to develop a tailored MRI protocol that measures the shunt fraction in healthy volunteers with precision and accuracy.

The entire image acquisition procedure was thoroughly evaluated to ensure that all potential pitfalls and limitations were identified and addressed. This level of precision is rare in routine clinical use of MRI, where much larger shunts are observed.

3.1 Introduction and Aims

Application of the Fick equation, derived by invasive oximetry, has been the gold standard for measuring Qp/Qs and intracardiac shunting in clinical practise (235). Even though echocardiography can be used to calculate Qp/Qs, it has several drawbacks (as explained in Chapter 1). CMR has emerged as a non-invasive alternative method for evaluating Qp/Qs over the years.

When pumping blood via its closed loop, which encompasses the pulmonary and systemic circulations, the heart functions as a cohesive structure. Qp/Qs = 1 when the amount of blood leaving the right and left ventricles are equal (ignoring the negligible Thebesian veins and the and coronary arteries depending on the location of the Qs and Qp measurements). Nonetheless, in CMR Qs is typically measured after the coronary ostia, yielding the accepted normal value derived by CMR in the region of approximately 1.05 (236,237).

Despite being the dominant clinical method for flow measurement during free breathing (FB) or breath holding (BH) in patients with congenital heart disease, phase-contrast cine flow imaging has not been tested for evaluating and quantifying small extra cardiac shunts that may be present in patients with respiratory diseases. For massive shunts that are clinically significant in congenital heart disease, it is not common practice to acquire velocity-mapping with greater precision than is required for overall shunt quantification. The routine setup, in clinical practice, is insufficient to determine small changes in respiratory patients where shunts are small compared to the large shunts associated with congenital heart disease.

A precise evaluation of systemic and pulmonary blood flow, allowing quantification of small shunts requires a dependable image acquisition process that provides consistency, repeatability, and mitigation of potential problems. This demands extra steps during study acquisition that are not supported in the standard clinical cardiac MRI practice, because there is no need for them. If small variations on accuracy are not addressed during the image acquisition process, the final evaluation may not be repeatable or trustworthy. Knowledge of these potential pitfalls will allow their elimination and increase confidence in the flow data authenticity and repeatability.

Several sources of error are apparent when utilising phase contrast velocity acquisitions to quantify the precise flow necessary for analysing shunts in respiratory patients. These can occur during image capture or can occur as a consequence of the design of the hardware itself. Overall, they can be separated into 3 subgroups namely patient, scanning and post processing factors (Table 3.1)

Accordingly, the aims of investigations in this chapter are as follows:

- Develop a MRI protocol to assess Qp/Qs with precision, ensuring appropriate use of background corrections.
- Test the novel MRI protocol for accuracy.
- Evaluate the effects of free breathing and breath holding on the projected capability to quantify small shunts

Table 3.1 Pitfalls of assessing shunt fraction on MRI

Patient factors
• Patient body habitus (extra BH time for larger Phase-encode FOV, especially for MPA plane) • Heart rate variability (severe arrhythmia may need FB flow scan supporting averaging and also rejection of highly abnormal R-R intervals) • Ability to breath hold (for accuracy aim for > ~12 R-R intervals BH) • Deep insp or exp BH may cause physiological flow variations - ensure BH instructions are understood, even rehearsed before scanning. • If FB flow, consider through-slice respiratory motion of vessel (especially the short MPA can be problematic) • Metallic prostheses (artificial valves, downstream positioning)
Scanning factors
• Operator concentration (prevent unnecessary disturbance of control-room) • Mismatch of encoding velocity (VENC) to peak vessel velocity. • Misalignment of imaging plane across vessel. • Phase-encode wraparound must not overlap static tissue (may be needed for background correction) (employ in plane rotation to require minimal PE FOV). • Image 'cropping' (FOV 'phase-encode oversampling') should not remove static tissue (may be needed for background correction). • Position vessel near as possible to isocentre reduces many errors (table move). • Inadequate temporal resolution in BH scans. • Inadequate phase-encode resolution in BH scans.

• Ghosting due to inadequate averaging of FB scans (each FB average can be quick as SNR is accumulated) (averages must be “long-term” so that they are respiratory uncorrelated). • Signal loss (defective valve – reduce TE, minimise voxel size, contradictory) • Monitor R-R intervals, scanner triggers, BH quality during flow scans (ideally scanner modifications could automatically record all of these). • Retrospective cine (ensure appropriate frame time is output from scanner). • Rescan if needed (fast transfer of images from scanner, assistant checking images while the operator is busy doing next scan)
Post-processing factors
• ROI errors (check all cine frames, tedious, needs concentration) • Background correction (static tissue mask or phantom correction) • Ensure velocity scale of images is correctly linked to VENC (pitfall) • Ensure R-R interval shown by image processing is reasonable (what averaging does it use?) • Qp/Qs derivation adds the percentage errors in Qp and Qs

3.2 Patients and Methods

The local research ethics committee approved this study, and a written consent was obtained from all volunteers. Ten healthy volunteers (mean age ± standard deviation: 38.0 years ± 12.9 range: 23-60 years. 5 male and 5 female) with normal cardiac function and no known shunts were scanned using a Siemens, Vida 3T Numaris X VA11 scanner to develop a novel imaging protocol to assess Qp/Qs with finer precision and accuracy than needed in routine cardiology. The methodology was designed to identify potential problems and technical issues, as well as correct and control variables that influenced shunt precision and accuracy.

To ensure participant safety, a questionnaire was given to each participant before the scan was performed. Blood pressure and heart rate was recorded for each individual at the start and end of the acquisition. The method of acquiring these images was overseen by a physicist, an MRI radiographer, and an expert radiologist. Each maintained a watch on their own area of expertise recording any issues as they were recognised. A tailored MRI protocol was designed to speed up the image acquisition process, bearing in mind the eventual application would be in respiratory patients, in our case CF. Prior experience has established that such patients may have trouble remaining still in MRI scanner for long periods of time. The same radiographer obtained images for all volunteers.

Cine phase-contrast velocity mapping was obtained perpendicular to the main PA and Ao at fixed resolution and timing in all subjects, while the phase-encoded FOV was enlarged if necessary (Figure 3.1). Flow measurements were obtained in end expiratory breath-hold and free-breathing, all with phantom scans replicating each patient scan for confirmation of the background correction (237).

To ensure precision we assessed for interobserver variability and intermethod (breath-hold and free-breathing) variability. The volunteers were also taken off the MRI table for 5 minutes. Subsequently the whole process was repeated to assess intersession variability.

The observed flow and shunt fraction measurements were tested for accuracy by comparing with the shunt fraction of 1.05.

The image acquisition protocol was as follows**:**

- Limited fast short BH cine scans to localise the Aortic (Ao) and Pulmonary (PA) flow planes
- The views are LVOT, Cross cut LVOT, RVOT, Cross cut of the RVOT, enabling precisely cross-sectional through plane cines of the ascending Ao and MPA. Through-plane retrospectively-gated cine phase-contrast velocity-mapping for volume quantification, based on through-plane velocity measurement.
    - The imaging parameters were as follows:

    - slice thickness 4-5 mm for cines, 7 mm for flow
    - velocity encoding 120 cm/s (PA), 150 cm/s (Ao)
    - Repeat flow cines in free breathing and breath hold.

- Optimise field of view: alignment with flow or vessel of interest, minimize phase-encode FOV wrap artefacts off the stationary tissue needed for optimal background-correction.
- Fixed parameters: number of frames/phases per cardiac cycle, repetition time, number of segments.
- Set velocity encoding range (VENC)
- Acquire images.
- Take the volunteer off the scanner couch, and then repeat the entire process.
- Once this has been acquired, obtain phantom correction images using identical parameters as used for both sets of the volunteer flow scans (Figure 3.2).

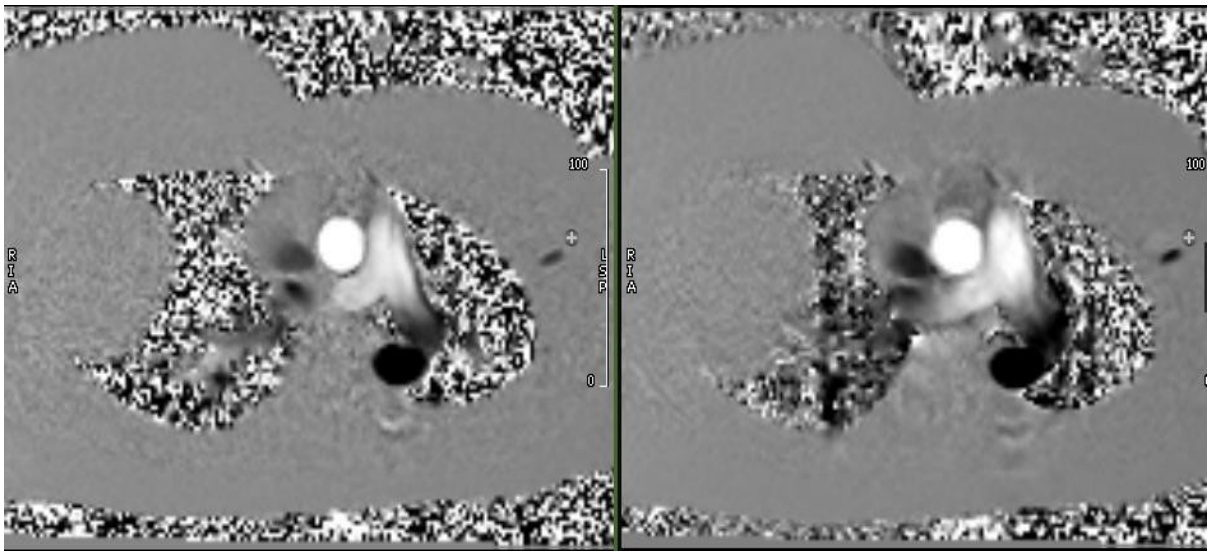


Figure 3.1 Examples of BH (Left) and FB (Right) phase-contrast images.

BH and FB used identical sequence parameters (8x1.9x1.9mm, TR/TE 4.6/2.5ms, 5 raw data lines per cycle, frame time 46ms, VENC 150/120 cm/s for AA/PA). For free-breathing, parallel imaging factor 1.7 was used to accelerate 5 outer-level averages, although blurring and through-plane motion of the vessel are problematic for FB especially for MPA.



Figure 3.2 – Setup for phantom images

Shows the setup for phantom images in this study to correct for phase offset errors.

3.2.1 Image analysis

The systemic and pulmonary flow volumes were measured by 2 independent observers applying the static tissue mask (to support linear order background phase fitting and subtraction) and phantom subtraction correction methods.

- Data post processing and analysis. (Performed by 2 separate readers)
    - Post Processing of the PA flow velocity and the aorta were at the MPA level (pulmonary flow) and sinotubular junction (STJ) of the ascending aorta (systemic flow)
    - The readers reviewed the drawn regions-of-interest (ROIs) on the vessel cross-sectional area for all cardiac phases of the cine velocity-map images and made sure the ROIs were placed accurately at the edge of the vessel. ROIs were drawn using semi-automatic vessel contouring initially (followed by manual checking) for flow data analysis.

3.2.2 Statistical Methods

Flows were calculated as the average of three measurements.

A Bland-Altman plot was utilised to display the agreement between two observers in measuring flow and subsequently the Qp/Qs.

A formal assessment of normality was not performed for flow measurements as previous research in the field has demonstrated the normal distribution of this parameter in similar populations (237). As such, we proceeded with the analysis under the assumption of normality, considering the established precedent in the literature.

A paired t-test was used to compare the differences in the flows of the great vessels and the shunt fraction obtained between two observers, between FB and BH and finally between sessions. In addition, Qp/Qs was calculated both before and after background correction. Since the coronary

circulation in a normal person is approximately 5% of the cardiac output (237) and the measurement of the systemic blood flow (Qs) is made distal to the coronary ostia, the expected normal Qp/Qs is 1.05 when measured with this technique. The results were compared to the expected Qp/Qs of 1.05 using paired t-test.

3.3 Results

Figure 3.3 illustrates the Bland-Altman plot, demonstrating good agreement in reporting flows between the two observers in this study, with a sample size of 264 paired observations. The mean difference between observers is calculated to be 0.69 mL, and the 95% limits of agreement are relatively narrow, ranging from -10.6 to 12.0 mL. These results indicate the absence of clinically important systematic bias in reporting the outcome between the two observers. Furthermore, there is no observable trend or variability in the plot as the mean of the observations increases, suggesting consistent agreement.

Table 3.2 displays the interobserver correlation, intersession correlation, and inter-method correlation, along with the corresponding statistical analyses. The table also includes 95% confidence intervals.

Table 3.3 shows the effect of background correction methods. Without background corrections, Qp/Qs differed significantly from 1.05. Only FB scanning with static mask or phantom corrections showed no significant difference from 1.05.

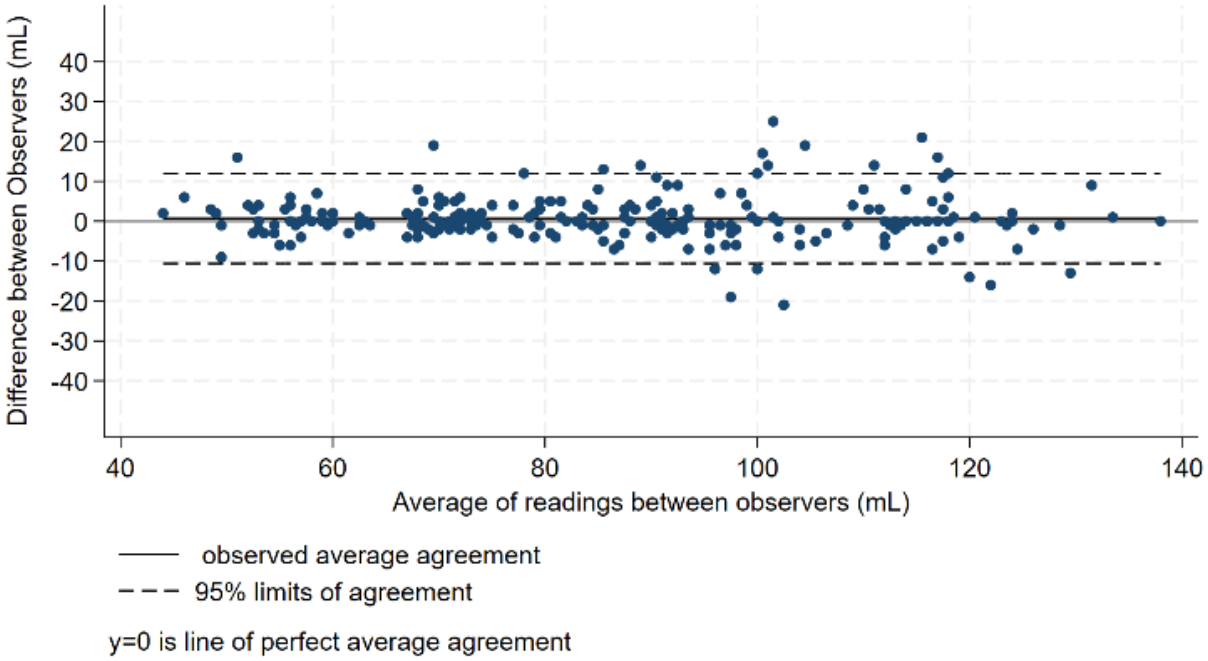


Figure 3.3 illustrates the Bland-Altman plot, demonstrating good agreement in reporting flows between the two observers in this study.

Table 3-2 Inter-observer, Inter-session and Inter-method flow and Qp/Qs measurements

Inter-observer (n=10, average of sessions)			
	Observer 1	**Observer 2**	**p**
	Mean +/- SD	**Mean +/- SD**	**Paired T-Test**
AO BH (ml)	81.3 +/- 22.1 (74.5, 88.1)	81.3+/-22.7 (74.4, 88.2)	p = 0.68
AO FB (ml)	80.8 +/-22.5 (73.8, 87.8)	81.2 +/-22.6 (74.3, 88.1)	p = 0.34
PA BH (ml)	81.4+/-24.3 (74.4, 88.4)	81.0 +/- 23.7 (74.2, 87.8)	p = 0.38
PA FB (ml)	86.1 +/-22.4 (79.3, 92.9)	83.4 +/-22.9 (76.6, 90.2)	p = 0.07
Qp/Qs BH	0.99 +/-0.05 (0.96, 1.02)	1.01 +/-0.04 (0.98, 1.04)	p = 0.32
Qp/Qs FB	0.94 +/- 0.08 (0.89, 0.99)	0.97 +/-0.05 (0.92, 1.02)	P = 0.06
Inter-session (n=10, average of observers)			
	Session 1	**Session 2**	**p**
	Mean +/- SD	**Mean +/- SD**	
AO BH (ml)	80.8 +/- 20.8 (73.9, 87.7)	81.35 +/- 20.36 (74.6, 88.1)	p = 0.97
AO FB (ml)	81 +/- 21.9 (74.1, 87.9)	80.85 +/- 20.6 (74.1, 87.6)	p = 0.90
PA BH (ml)	81.2 +/-23.4 (74.2, 88.2)	82.2 +/- 23.3 (75.3, 89.1)	p = 0.52
PA FB (ml)	84.8 +/-21.4 (78, 91.6)	83.9 +/-22.9 (76.9, 90.9	p = 0.60
Qp/Qs BH	0.99 +/-0.17 (0.92, 1.06)	0.99 +/-0.06 (0.96, 1.02)	p = 0.50
Qp/Qs FB	0.95 +/- 0.09 (0.88, 1.02)	0.96 +/- 0.04 (0.92, 1.00)	P = 0.41
Inter-method (n=10, average of sessions and observers)			
	BH	**FB**	**p**
	Mean +/- SD	Mean +/- SD	
AO (ml)	79.8 +/- 20 (73, 86.6)	79.3 +/-21.9 (72.4, 86.2)	P = 0.61
PA (ml)	80.9 +/- 23.1 (73.9, 87.9)	84.9 +/-22.2 (78, 91.8)	P = 0.06
Qp/Qs	0.98 +/-0.03 (0.94, 1.02)	0.93 +/- 0.05 (0.87, 0.99)	P = 0.04

Table 3-3 Effect of background corrections

Effect of background corrections (n=10, average of sessions and observers)			
	Uncorrected	Static mask	Phantom
	Mean +/- SD	Mean +/- SD	Mean +/- SD
AO BH (ml)	88.0 +/- 24.8 (75.3, 100.7)	81.5 +/-21.7 (70.4, 92.6)	81.3 +/- 23.6 (68.8, 93.8)
AO FB (ml)	87.9 +/- 24.4 (74.3, 101.5)	80.7 +/-20.4 (69.6, 91.8)	80.9 +/- 21.0 (68.8, 93.0)
PA BH (ml)	80.8 +/-20.8 (68.1, 93.5)	79.2 +/- 22.5 (66.1, 92.3)	81.7 +/-23.1 (68.0, 95.4)
PA FB (ml)	83.3 +/-19.9 (70.9, 95.7)	82.4 +/-22.4 (68.7, 96.1)	84.4 +/-22.2 (70.9, 97.9)
Qp/Qs BH	0.93 +/- 0.04 (0.91, 0.95)	0.97 +/- 0.04 (0.95, 0.99)	1.00 +/-0.05 (0.97, 1.03)
Qp/Qs FB	0.96 +/- 0.06 (0.90, 1.02)	1.02 +/-0.06 (0.96, 1.08)	1.04 +/- 0.04 (1.00, 1.08)
T-test * tested against 1.05 accepted normal			
Qp/Qs BH *	$p < 0.001$	$p < 0.001$	$p = 0.013$
Qp/Qs FB *	$p < 0.001$	$p = 0.11$	$p = 0.55$

3.4 Conclusion

For accuracy and reproducibility of Qp/Qs where small shunts are likely to be present, attention must be paid to the factors listed (Table 3.1). Failure to pay attention to any single one of the above may cause misleading Qp/Qs errors in this application to unusually small shunts.

The results show that FB with phantom correction came closest to Qp/Qs=1.05. The bias (underestimate) without correction, instead of wider scatter that might be expected, may arise from the fixed sequence parameters (akin to fixed setups in T1-mapping), and from similarities among the Ao and PA plane orientations (237). Applying first-order mask correction only partially reduced the error; spatial curvature (i.e. above first-order) of the static background error was noted in the phantom images. Assessing the optimal order of mask correction would be difficult without the phantom as guidance.

The differences between BH and FB using otherwise identical sequence parameters may comprise genuine flow changes with respiratory manoeuvres. Conversely, respiratory motion, of especially the PA, loses ROI clarity.

In this setup, Qp/Qs was under-estimated by an average of 8% (and as much as 22%) when it was not corrected. After phantom correction, this bias was no longer significant. For accuracy in small shunts (approximately below 20% of cardiac output), one needs a strict sequence setup and corrections that must be tested first by site normal data.

3.5 Discussion

In this chapter, the potential for error while utilising phase contrast velocity mapping images to quantify flow was investigated. This study draws attention to potential hazards, categorising them into patient factors, scanner factors, and post-processing factors. The assessment also stresses the importance of experienced staff across disciplines (physicist, radiographer, and radiologist) to ensure these pitfalls are recognised and mitigated. This stringent setup is necessary for the requirement of assessing small shunts (< 20% of the cardiac output) in respiratory patients.

3.5.1 Pitfalls

The pitfalls were introduced in the first chapter and this chapter has highlighted the significant challenges relating to Qp/Qs assessment by MRI and the need to be vigilant.

Assessing shunt fraction Qp/Qs using phase-contrast magnetic resonance imaging techniques is fraught with pitfalls, necessitating the development of a bespoke protocol tailored to accurately detect small shunts (220,221). While a valuable tool, MRI is susceptible to inherent limitations such as motion artefacts, signal loss, and phase wrapping, especially in regions with low flow velocities or complex flow patterns (221). In respiratory patients, factors like irregular respiratory motion, pulmonary vascular abnormalities, and variable blood flow dynamics exacerbate these challenges (220). Consequently, standard clinical MRI protocols are inadequate at capturing subtle shunts, leading to the underestimation or misinterpretation of Qp/Qs values (219). This piece of work has underscored the need for further research to develop and validate specialised MRI protocols optimised for respiratory patients. By addressing these limitations and optimising imaging techniques the accuracy and reliability of Qp/Qs measurements in respiratory conditions can be improved. In clinical practice, shunt assessment predominantly focuses on cardiac patients, where shunts are typically larger. However, in respiratory patients, shunts are often smaller in scale. Hence, developing a meticulous protocol becomes crucial to ensure precise and accurate evaluation in this population.

3.5.2 Accuracy and precision of the MRI protocol

The study in this chapter explored a novel MR protocol to accurately and precisely measure small shunts fraction This work demonstrated that for reliable quantification of small shunts (<≈ 20% of CO), rigorous sequence setup and background corrections are necessary.

As with most CMR, the undistracted vigilance of experienced staff regarding patient co- operation and correct sequence application is crucial for accuracy. The rigorously controlled sequence parameters and similarities among the AO and PA planes of normal subjects may explain the biased uncorrected result, rather than simply increased scatter without background correction, as the background error can depend on some sequence parameters which were held fixed (rather as in the fixed setups used for T1-mapping) (238). Spatially nonlinear static background error was noted in the phantom images but without the phantom images, assessing the optimal spatial order of mask correction would not be possible. Applying first-order mask correction to these flow images only partially reduced the error as shown. This highlights the need to acquire phantom images for the highest precision (precision, as the planes are generally similar, assuming a fixed sequence setup). Acquiring phantom correction images maybe impracticable in routine clinical practice however this study shows using them appropriately is possible and applying them in image processing was not too cumbersome.

The differences between end expiratory breath hold and free breathing using otherwise identical sequence parameters may include genuine flow changes with respiratory suspension (239), but conversely the respiratory motion of the proximal PA and aortic root loses ROI clarity.

Chernobelsky et al described that when flow is measured in the pulmonary artery and aorta (distal to the coronary artery origins), the corrected mean Qp/Qs is 1.05 (237). They explained that the measured Qp/Qs differs from 1 because of coronary artery blood flow, which is ∼5% of the total cardiac output. The need for attentiveness in obtaining flows in specific locations is brought to light. Sharing the locations from which flow measurements have been taken is vital. By describing the conditions of the Qp/Qs as measured by CMR with Qs downstream of the coronary ostia, potential ambiguities associated with phrases like "above the coronary ostia" for aorta flow can be avoided. In conclusion, for accuracy and precision (≈ <20% of CO) to measure small shunts,

rigorous sequence setup and correction methods, preferably proven by site normal data, are necessary.

3.5.3 Key Points

- Flow and velocity measurements are prone to inaccuracies and care is important especially when assessment involves small shunts as required for this thesis.
- Any research involving MRI must have a physicist at the centre of the protocol.
- Challenges inherent to the method can have a major impact on the final result.
- Precision is key for small shunts and is beyond the current clinical standard in cardiology.
- Acquiring phantom corrections are crucial for evaluating small shunts.

4 Novel application of the shunt fraction in cystic fibrosis patients with haemoptysis before and after BAE.

In the preceding chapter, the necessary steps for measuring the magnitude of small shunts was presented. Certain patients with underlying respiratory diseases such as cystic fibrosis (CF) may have such small shunts, and the size of these shunts will indirectly correlate with the amount and severity of the underlying suppurative airways disease. In this chapter the MRI protocol developed in the previous chapter was utilised to assess shunts in CF patients presenting to RBH with haemoptysis.

4.1 Introduction and aims

CF is a multisystem, progressive lung disease. As patients with CF advance in age the severity of their underlying chronic lung parenchymal disease such as bronchiectasis and chronic airway inflammation progresses (Figure 4.1) (252). Chronic lung disease invariably alters pulmonary haemodynamics. In patients with CF this often leads to vascular growth that results in markedly enlarged and tortuous bronchial/aortopulmonary collateral arteries and in some cases causes haemoptysis (Figure 4.2 and Figure 4.3) (243). At small volumes this is clearly alarming for the patient, but in larger volumes this can be life threatening. In patients with one or more episodes of life-threatening haemoptysis or with repeated episodes of smaller volumes of haemoptysis, bronchial artery embolisation (BAE) may be undertaken (252).

Haemoptysis is frequently attributed to abnormally large and fragile bronchial arteries. In health, the bronchial arteries deliver oxygenated blood to the lungs at a pressure six times that of the pulmonary arteries, accounting for less than 1% of cardiac output. Significant remodelling of the bronchial circulation can occur in CF and depending on the severity of the underlying disease process, the total systemic cardiac output to the bronchial arteries can increase by 1% to 18%. (62). This recruiting process increases systemic blood flow to the lungs and causes a greater proportion of cardiac output to be rerouted through the bronchial arterial system. It is postulated that the underlying pathophysiological mechanisms in CF alter the pulmonary and bronchial blood flow sufficiently to measurably alter the shunt fraction, and that the magnitude of this shunt may

correlate with disease severity, risk of bleeding or rebleeding, and survival indices. At RBH, we treat the biggest cohort of patients with CF in Europe, and BAE is frequently performed on these patients. This would be the first in the NHS study and could lead to a clinically applicable, non-invasive method for assessing the shunt fraction in CF patients. It could also give more evidence to support our proposed semi-elective intervention treatment strategy for patients with intermittent haemoptysis and CF.

Over the past few years, we have devised a technique for the semi-elective embolisation of the bronchial arteries in CF patients who produce small volumes of recurring haemoptysis. This is conducted in controlled conditions as opposed to as an emergency procedure. Under local anaesthesia and light sedation, arterial catheters are inserted into an artery in the patient's groin and then advanced to the bronchial arteries in the chest. Prior to the procedure, a CT angiogram is typically obtained to display the position and size of the bronchial and systemic arteries. Since the haemorrhage is intermittent, it is typically impossible to determine which abnormal artery caused earlier episodes of bleeding. Thus, the largest bronchial arteries are occluded by submillimetre particles (Figure 4.4). Even though this technique is frequently successful in the near term, a notable number of patients present with additional episodes of haemoptysis in the future.

A BAE is a safe procedure, but certain complications are possible, and the consent process needs to include these discussions. Pain and a burning sensation in the region of the body supplied by the embolised bronchial arteries are common minor effects. Rarely, significant consequences due to non-target embolisation include bronchial infarction, oesophago- bronchial fistula, myocardial or spinal cord infarction, ischemic colitis, transient cortical blindness, and stroke (253). Minor complications include temporary chest pain (in up to 91% of patients) and dysphagia, both of which are often self-limiting, but symptoms can continue up to two weeks (253). From clinical experience at our centre, we have also noted that patients sometimes express a feeling of increased breathlessness immediately after the embolisation procedure; the underlying mechanisms of this are poorly understood. At present there is no objective evidence that there is any deleterious effect from occluding these bronchial arteries, or any unintended impact on physiology that might explain this breathlessness. This is even though large bronchial arteries may supply a significant proportion of blood flow to the lungs.

The literature indicates that bronchial artery embolisation is an effective treatment for patients with severe haemoptysis, although outcomes can be variable (253). The alteration in local haemodynamics and the functional consequences of these changes have not been objectively investigated.

A better understanding of the change in the bronchial flow may also become a useful tool for index of disease severity, monitoring therapy and prognostication.

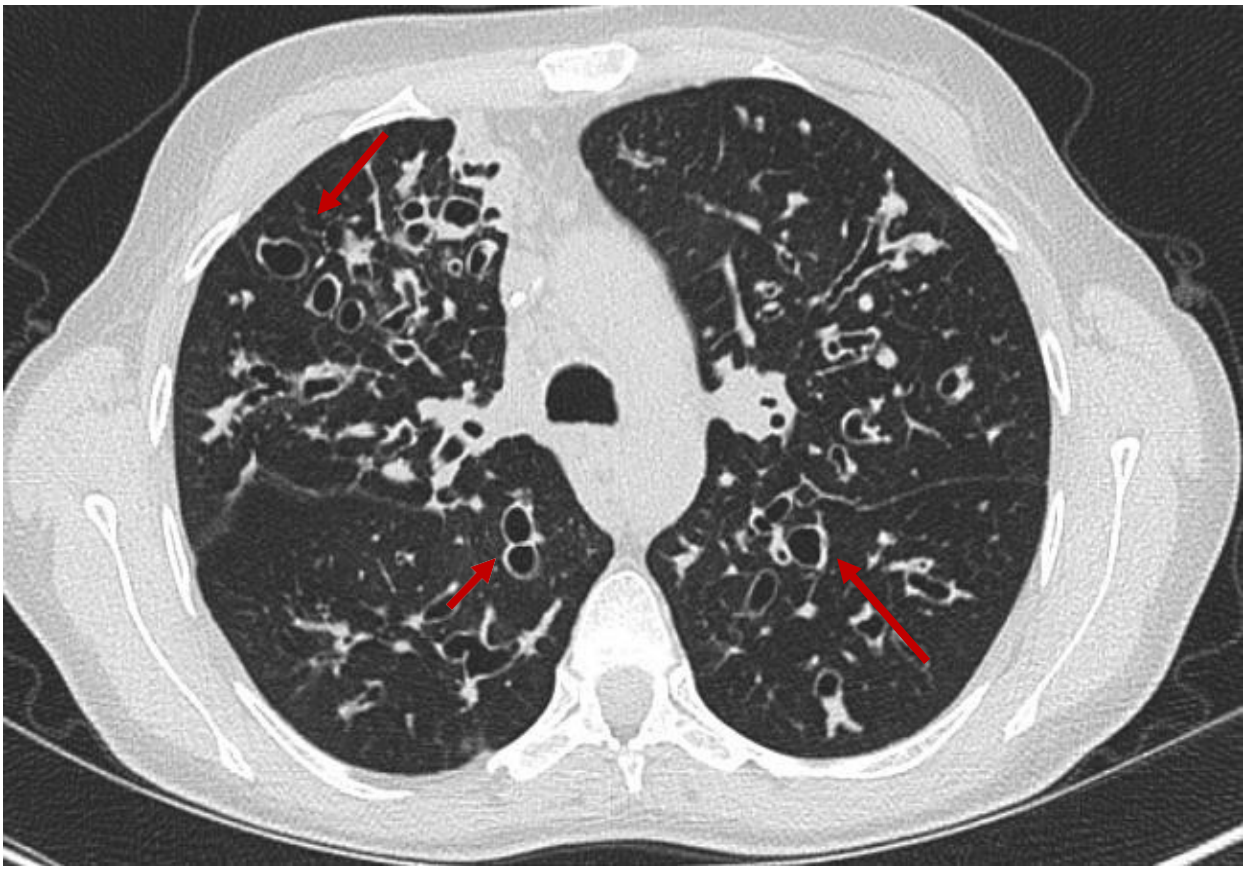


Figure 4.1 – CT image showing bronchiectasis

Trans axial CT of an adult CF patient shows extensive dilated airways (bronchiectasis) (red arrows)

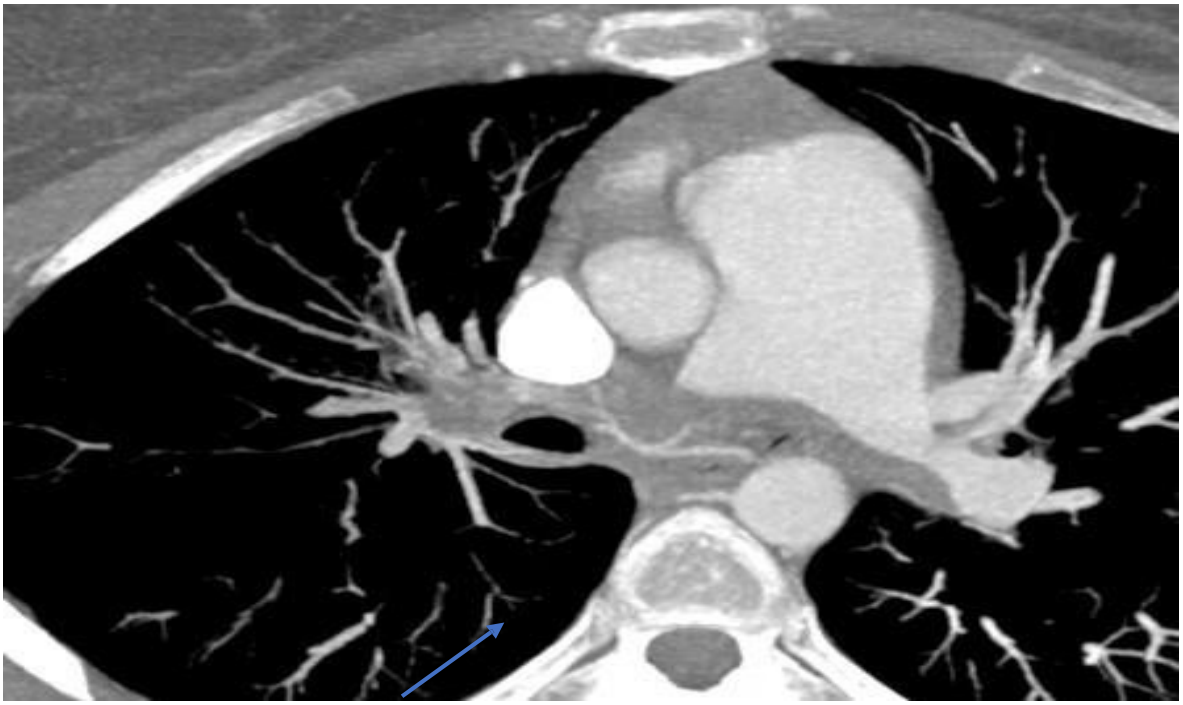


Figure 4.2 - CT image showing enlarged bronchial arteries

Trans axial CT of an adult CF patient shows enlarged bronchial arteries. (blue arrow)

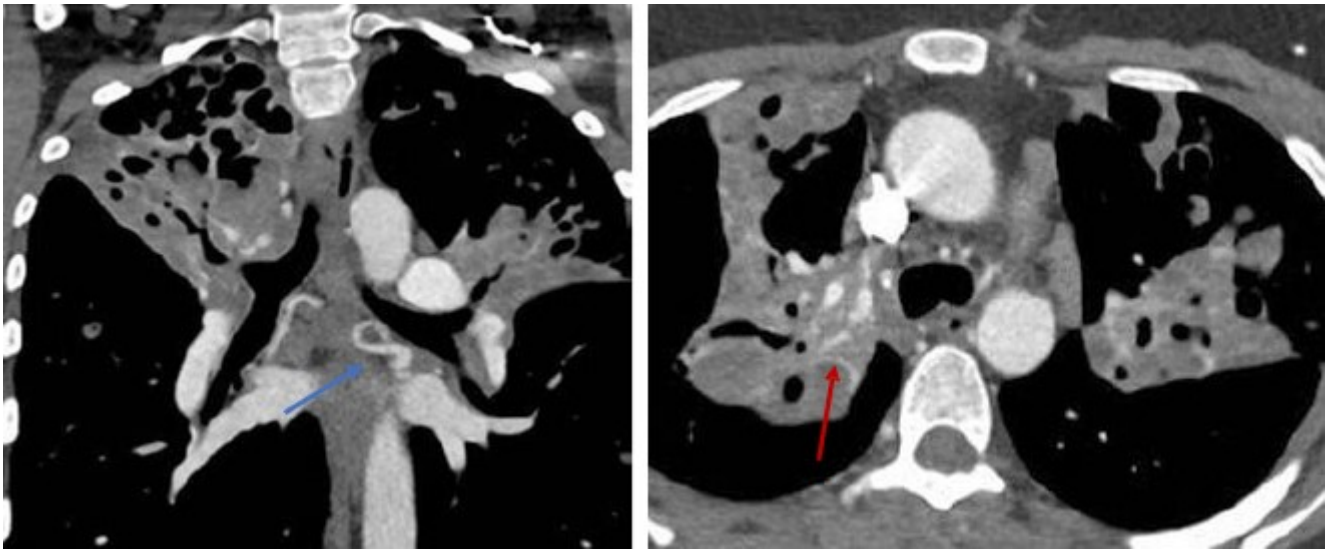


Figure 4.3 - CT showing MIP images of BA hypertrophy.

Coronal image (left panel) shows the origin of a large right intercostobronchial trunk arising from the thoracic aorta (blue arrow). Axial image (right panel) shows extensive areas of bronchiectasis with adjacent abnormal bronchial arteries (red arrow).

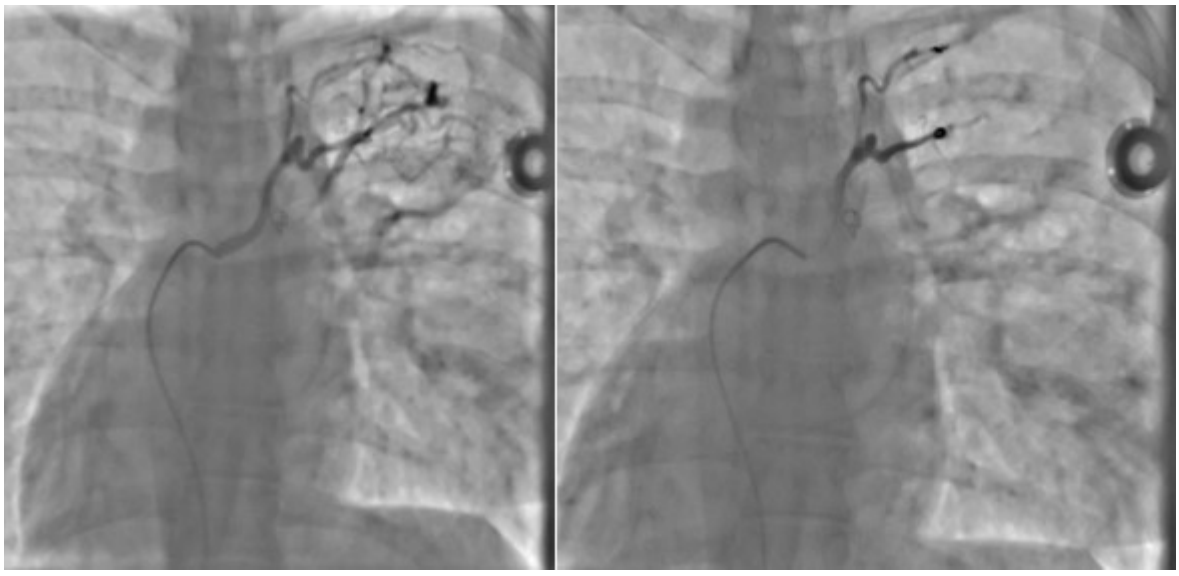


Figure 4.4– Bronchial artery embolisation.

Catheter directed bronchial artery embolisation in a patient with haemoptysis shows dilated and tortuous left bronchial arteries. This patient also had dextrocardia.

Aims of this chapter:

- To ascertain if it would be possible for CF patients with haemoptysis to go through a short MRI protocol developed in the previous chapter utilising healthy volunteers.
- To accurately quantify the (Qp/Qs) ratio in CF patients presenting with haemoptysis.
- To assess if occlusion of the bronchial arteries results in measurable change in the Qp/Qs post bronchial artery embolisation.
- To assess any physiological effect from this reduction in blood flow with standard assessments including bed side spirometry, resting oxygen saturations and quality-of- life questionnaires.

4.2 Patients and methods

HRA approval was obtained prior to the initiation of the study and informed consent was obtained for all study subjects. IRAS, REC reference and sponsor details are provided in Chapter

2. All subjects were provided research material which included participant information sheet (PIS), informed consent form (ICF), MRI safety questionnaire, 24 hours before recruitment.

In this prospective study 5 patients from RBH with CF who presented with intermittent haemoptysis and electively planned to undergo bronchial artery embolisation were recruited. Upon reaching adulthood, patients with CF frequently develop multiorgan involvement due to the underlying disease process. This may necessitate frequent hospital visits to monitor progress and, quite often, hospitalisation for intravenous therapy, which has a significant impact on the patient's lifestyle. Table 4.1 gives a summary of the five patients in this study and their important medical histories. Details regarding bronchial artery embolisation in these patients are also given.

The steps of recruitment are summarised below:

1. CF patient with significant and/or intermittent haemoptysis is admitted to the Royal Brompton Hospital

2. Patient is assessed by the clinical team and CT angiography requested as preliminary step prior to BAE.

3. ICF and PIS is discussed with patients who meet the inclusion criteria (see below).

4. Baseline (standard of care) investigations completed.

5. Research MRI Protocol - Qp/Qs assessment at baseline and then a post embolisation Qp/Qs assessment.

6. The patients were accompanied by a BLS trained doctor for their MRI assessments.

7. An experienced physicist, radiographer and a radiologist were present throughout both MRI acquisitions to ensure adherence to protocol.

8. Additionally, respiratory functional reserves before and after BAE by obtaining bedside spirometry FEV1 (volume and %) and FVC were assessed. The validated Cystic Fibrosis Questionnaire-Revised (CFQ-R) was also completed before and after BAE to ascertain quality of life.

4.2.1 Inclusion criteria

1. Adult patients >18 years

2. CF patients presenting with haemoptysis

3. Patients must be haemodynamically stable for the MRI study

4. No contraindications to MRI examination.

4.2.2 Exclusion criteria

1. Age < 18 years

2. Standard contra-indications to MRI (as per NHS MRI safety questionnaire).

3. Not medically fit for transfer to MRI.

4. Patient judged inappropriate for involvement in study by clinical team.

5. Pregnant (trying to become pregnant or lactating female)

4.2.3 Funding

Funding for the study was provide by Chiesi Farmaceutici and the funding covered the cost of scans and administration fees.

4.2.4 MRI protocol

The protocol developed in the previous chapter was used in these patients. The Qp/Qs was quantified in 5 CF patients before and after BAE. A brief summary of the protocol is provided below.

- All studies performed without sedation.
- Phase-contrast cines were obtained perpendicular to the main pulmonary artery (PA) and ascending aorta (AO) in end expiratory breath hold (BH) and free-breathing (FB), with background correction phantoms.
- Flow cines repeated (3 times) in free breathing and breath hold.
- After images from patients were acquired, phantom correction scans were obtained using identical parameters as used for the patient scans.

4.2.5 Post processing

Qp/Qs was calculated using CVI42 post processing software. Each vessel was contoured semiautomatically by two observers throughout the cardiac cycle, and then manually adjusted per cine frame for pulsatility and cardiac motion. The observers performed the contours independently. Flow measurements in the ascending aorta were obtained downstream of the coronary artery ostia.

4.2.6 Statistical methods

Given small sample numbers descriptive statistical analysis together with simple graphical analysis have been used to summarise findings in these 5 patients.

4.3 Results

As demonstrated in the normal volunteer study, FB and phantom corrected data was most accurate. Applying these metrics to the CF patient group, this study demonstrates a measurable shunt is present in all CF patient presenting with haemoptysis.

Table 4.2 summarises the median (min/max) phantom corrected flows of three repeat observations obtained by 2 observers in 5 patients. From the 5 patients the median phantom corrected FB Qp/Qs (min/max) was 0.84 (0.78/0.91). Figure 4.5 shows a graphical display of the Qp/Qs obtained in the subjects in this study.

Table 4.3 displays the Qp/Qs before and after bronchial artery embolisation. In all patients the Qp/Qs demonstrates a measurable change after treatment. Figure 4.6 illustrates this in a graphical display.

Bed side spirometry and resting oxygen saturations before and after BAE in these patients are summarised in Table 4.4.

CFQR scores in these 5 patients before and after BAE are summarised in Table 4.5.

Table 4.1 Patient demographics, medical history and BAE details			
Patient/ Demographics	**Details of the episode.**	**Significant medical history**	**BAE procedure details**
1 **Female** **35y**	Patient was admitted due to haemoptysis (1 egg cup) despite tranexamic acid. They also had reduced exercise tolerance, requiring more supplementary oxygen.	1. Cystic fibrosis F508 delta homozygous on Kaftrio 2. Pancreatic insufficiency 3. Liver transplant 2004 now under King's liver unit (On immunosuppression) 4. Recurrent moderate haemoptysis 5. Chronic rhinosinusitis 6. CF-related diabetes 7. Osteoporosis 8. Previous Mycobacterium abscessus treatment completed November 2019 9. Chronic infection with Pseudomonas aeruginosa 10. Lung transplant watch-and-wait list *11.* Renal impairment	Standard procedure, right groin access, conscious sedation, sterile conditions. An 0.035 " guidewire was passed through the needle and over this, a 5 Fr sheath was advanced, the 5Fr Cobra catheter was used as primary catheter, and a 2.4Fr Renegade catheter was used to localise the bronchial arteries, arising from the aorta. The Renegade was defective and exchanged out for a 2.4Fr Cantata. The large right bronchial artery, a subaortic bronchial artery, and a descending aortic bronchial artery, both IMAs the right subclavian and inferior phrenic arteries were interrogated. All but the inferior phrenic, the subaortic branches were embolised with 2 vials of contour < 500 micron particles and 3 cm x 3 mm Hilal coils platinum), haemostasis was achieved promptly. The descending aortic branch) was already occluded with a previously placed coil and so it was not embolised again. The sheath was removed, after placement of an angioseal device. .

2 **Female** **32y**	Patient admitted with significant haemoptysis approx 100-200mls. Haemodynamically stable on transfer.	1. Cystic fibrosis (F508del/R347P)- on Kaftrio 2. Pancreatic insufficiency 3. CF-related diabetes 4. Presumed fungal disease but normal serological fungal markers- off antifungal treatment 5. Epilepsy 6. Chronic rhinosinusitis 7. Chronic infection with Pseudomonas aeruginosa 8. Intermittent infection with Staphylococcus aureus 9. History of DIOS	Standard procedure, right groin access, conscious sedation, sterile conditions. An 0.035 " guidewire was passed through the needle and over this, a 5 Fr sheath was advanced, the 5Fr Sim 1 catheter was used as primary catheter, and a 2.4Fr Renegade catheter was used to localise the right bronchial artery, arising from the aorta. This was accessed, and treated with 1 vial of contour < 500 micron particles, haemostasis was achieved, two IMA branches were treated on the left and right with 1 vial of contour particles using an IMA catheter and a C1 catheter. A JR6 was not useful to access to the left IMA. The right and left subclavian and lower aortic bronchial artery collaterals were also accessed but a safe. Embolisation position was not achieved. The sheath was removed, after placement of a 6Fr angioseal device.

3 **Male** **36y**	Patient admitted with infective exacerbation and significant haemoptysis (250 mls)	1. Cystic fibrosis (homozygous F508del)- on Symkevi (Intolerant Kaftrio due to recurrent transaminitis) 2. Pancreatic insufficiency 3. Chronic Pseudomonas aeruginosa infection 4. S. aureus colonisation 5. Ambulatory and nocturnal oxygen requirement- 3L/min 6. Borderline respiratory failure - sleep study Feb 2022, hypercapnia (6.79 kPa) 7. On NIV for chest clearance 8. Recurrent haemoptysis 9. CF liver disease -Hepatic steatosis/mild fibrosis 10. Cystic fibrosis related diabetes 11. DIOS and recurrent constipation 12. CF bone disease - osteopenia 13. Ototoxicity affecting both cochlear and vestibular functions 14. Bilateral Sensorineural hearing loss with use of hearing aids 15. Temporomandibular dysfunction 16. Previous EBV and CMV infection 17. Chronic chest pain 18. Gastroesophageal reflux disease	Standard procedure, right groin access, conscious sedation, sterile conditions. An 0.035 " guidewire was passed through the needle and over this, a 5 Fr sheath was advanced, the 5Fr Cobra (1) and Simmonds (1) catheter were used as primary catheters, and a 2.4Fr Renegade catheter was used to localise the bronchial arteries, arising from the aorta. Both right and left were accessed, and treated with 2 vials of contour < 500 micron particles, haemostasis was achieved. The sheath was removed, an angioseal device was not placed as the sheath was clotted. There are two additional small left subclavian vessels which supply the left upper lobe, these were not accessed.

4 **Female** **33y**	Patient admitted with infective exacerbation and numerous intermittent moderate volume of haemoptysis (100 mls) not responding to conservative treatment - intravenous tranexamic acid, IV fosfomycin and colomycin.	1. Cystic fibrosis homozygous (F508del)- on Symkevi twice a week 2. CF-related diabetes 3. ABPA 4. Pancreatic insufficiency 5. Osteoporosis- on Denosumab 6. Previous sinus disease and nasal polyps 7. CT scan suggestive of fungal disease- previously adverse reaction to azoles- recently 8. Gastro-oesophageal reflux disease started Posaconazole	Standard procedure, right groin access, conscious sedation, sterile conditions. 5-French sheath, selective and subselective catheterisation of: 2. Common bronchial trunk, predominantly to the right lung, embolised to stasis with 710-1000 micron and 350-500 micron particles. Two large branches from the left internal mammary artery embolised to stasis. 3. Small branch from the left thyro cervical trunk embolised to stasis, including 2 x 20 mm x 2 cm embolisation coils. 4. Left axillary vessel, descending over the chest wall and shunting into the left mid zone, embolised to stasis with particles. 5. Right internal mammary artery with very large medial branches (x 2) embolised to stasis with a combination of particles and coils (3 cm x 3 mm x 2). Small branch from the right thyro cervical trunk embolised to stasis. No immediate complications.
5 **Female 31y**	Patient admitted with exhaustion and intermittent haemoptysis despite Septrin , IV Fosfomycin+ Caspofungin + Tranexamic acid	1. Cystic fibrosis (homozygous F508del) 2. Gastro-oesophageal reflux disease 3. Recurrent haemoptysis 4. Chronic Pseudomonas aeruginosa 5. Scedosporium with right-sided mycetoma 6. Previous empyema 7. Previous bronchial artery embolisation 8. PEG-fed 9. Pancreatic insufficient	Standard procedure, right groin access, conscious sedation, sterile conditions. 1. Large right phrenic was embolised to stasis, with two significant branches, one extending to the cavitating lesion in the right mid zone and a second in a paracardiac position. There is significant arterial - venous shunting evident at the initial assessment. 2. Large right bronchial, with two large branches, embolised to stasis with a combination of particles and then coils - marked shunting again noted at the microvascular level. 3. Small left bronchial embolised to stasis with particles. Extremely large right internal mammary branch and a small right internal mammary branch embolised to stasis with a combination of particles and coils.

Table 4-2 Phantom corrected flows obtained by 2 observers in the 5 patients and the Qp/Qs ratio

	AO BH (mls)	AO FB (mls)	PA BH (mls)	PA FB (mls)	Qp/Qs BH	Qp/Qs FB
Patient 1	73 (70/76)	77 (73/81)	59 (56/62)	60 (58/62)	0.81	**0.78**
Patient 2	76 (71/78)	80 (77/83)	65 (63/67)	67 (65/69)	0.83	**0.82**
Patient 3	125 (121/129)	124 (121/127)	92 (88/96)	99 (96/102)	0.73	**0.85**
Patient 4	91 (88/94)	93 (90/96)	66 (64/68)	78 (75/81)	0.73	**0.84**
Patient 5	109 (106/112)	108 (106/110)	91 (88/94)	98 (96/100)	0.83	**0.91**

*Median (Min/Max) summarises the phantom corrected flows of three repeat observations obtained by 2 observers in the 5 patients. Qp/Qs ratio based on phantom corrected flows is also provided.
AO = Aorta
PA = Pulmonary artery BH= Breath hold
FB = Free breathing

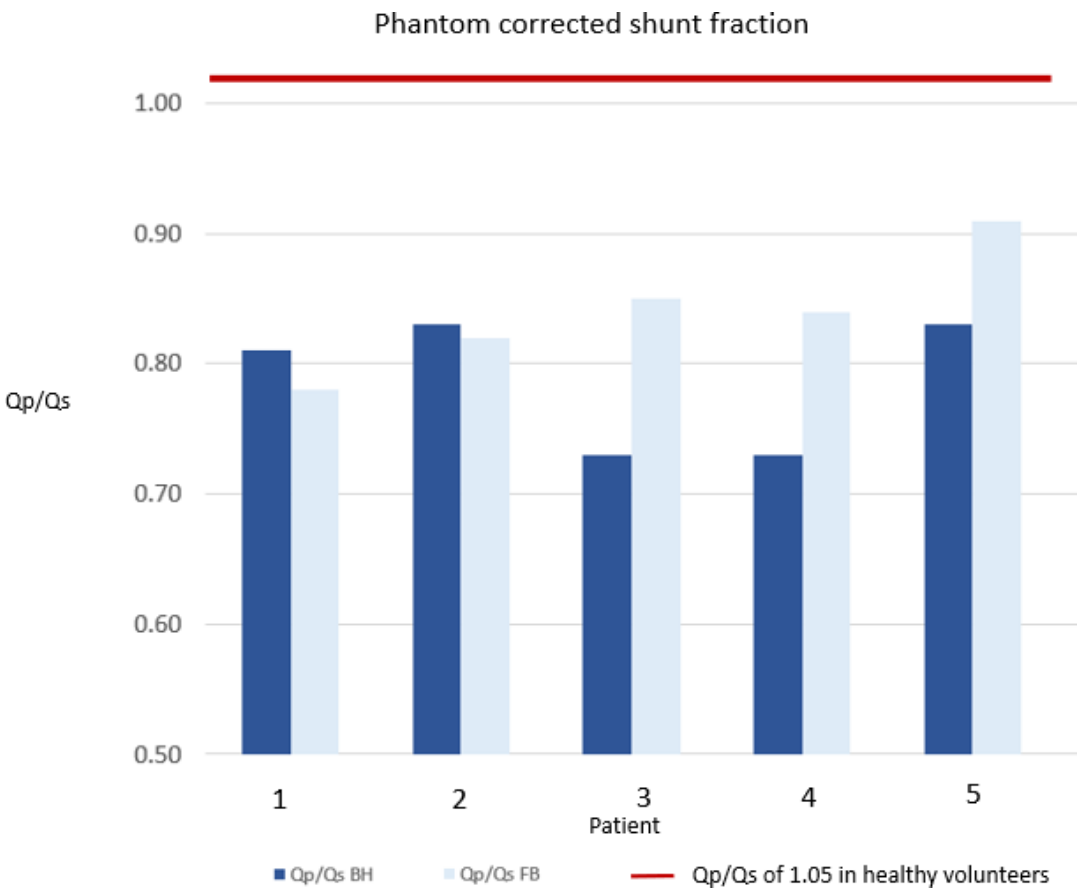


Figure 4.5 – Baseline phantom corrected Qp/Qs in all 5 participants

A graphical display of the Qp/Qs ratio obtained in all subjects in this study. All patients had a baseline Qp/Qs of below 1

Table 4.3 Phantom corrected Qp/Qs before and after BAE

		Before BAE	After BAE	Change as a percentage.
Patient 1	Qp/Qs BH	0.81	0.91	12.4 %
	Qp/Qs FB	**0.78**	**0.92**	**17.9 %**
Patient 2	Qp/Qs BH	0.83	0.85	2.4 %
	Qp/Qs FB	**0.82**	**0.88**	**7.3 %**
Patient 3	Qp/Qs BH	0.73	0.85	16.4 %
	Qp/Qs FB	**0.85**	**0.98**	**15.3 %**
Patient 4	Qp/Qs BH	0.73	1.01	38.4 %
	Qp/Qs FB	**0.84**	**1.04**	**23.4 %**
Patient 5	Qp/Qs BH	0.83	0.98	18.1 %
	Qp/Qs FB	**0.91**	**1.03**	**13.1 %**

Qp/Qs from 5 CF patients derived from the median phantom corrected flow measurements obtained by both observers.

Qp/Qs for Patient 2 did not demonstrate a major change pre and post BAE.
In this patient the bronchial arteries supplied critical structures and an extensive embolisation was not undertaken.

Table 4-4 Bed side spirometry and oxygen saturations before and after BAE

	Prior to BAE		Post BAE	
	Bedside spirometry	**Resting oxygen saturations**	**Bedside spirometry**	**Resting oxygen saturations**
Patient 1	FEV1 1.81 (59 %) FVC 2.62 (72 %)	94	FEV1 1.91 (62 %) FVC 2.72 (74 %)	94
Patient 2	FEV1 1.59 (51 %) FVC 2.55 (69 %)	96	FEV1 1.64 (54 %) FVC 2.69 (70 %)	97
Patient 3	FEV1 2.56 (57 %) FVC 4.3 (78 %)	96	FEV1 2.62 (60 %) FVC 3.89(71 %)	95
Patient 4	FEV1 1.52 (50 %) FVC 2.42 (67 %)	97	FEV1 1.53 (51 %) FVC 2.52 (70 %)	96
Patient 5	FEV1 1.83 (63 %) FVC 2.52 (71 %)	98	FEV1 1.75 (60 %) FVC 2.82 (73 %)	97
Bedside spirometry results (FEV1, FVC and the (% predicted) as well as the resting oxygen saturations are provided.				

Table 4-5 CFQ-R score before and after BAE

	CFQ-R score Pre BAE	**CFQ-R score 6 weeks Post BAE**
Patient 1	64	73
Patient 2	68	79
Patient 3	61	75
Patient 4	55	68
Patient 5	60	68
The CFQR- score is a score out of 100. The higher the score the better the quality of life. CFQ- R scores before and after BAE are provided.		

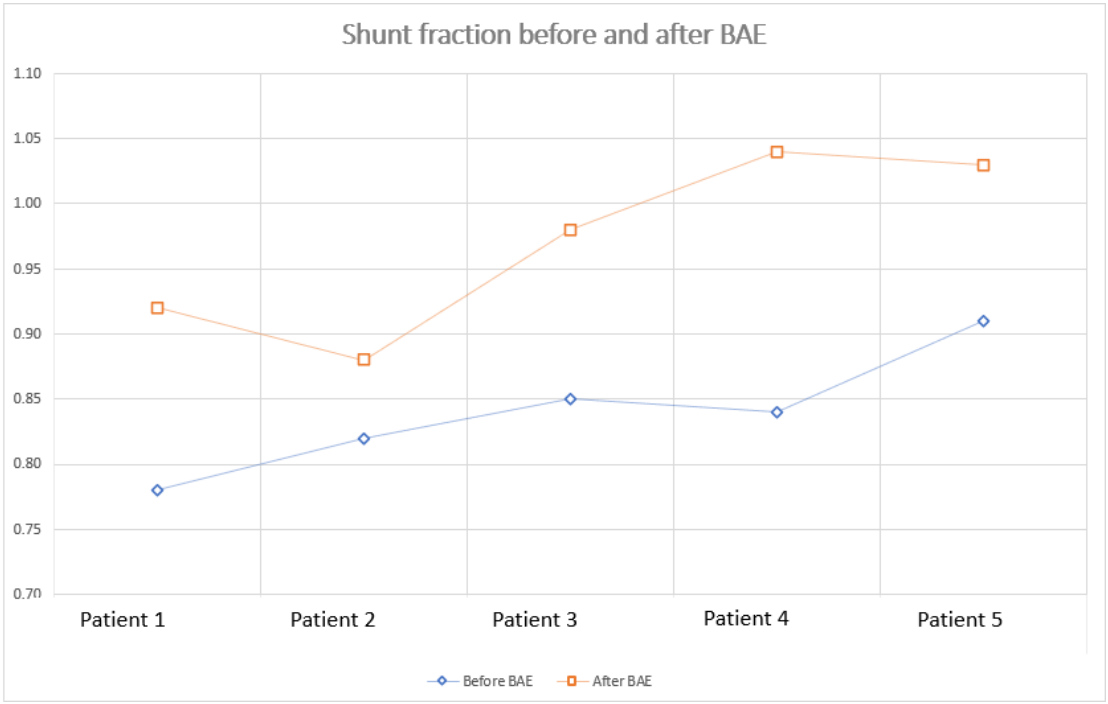


Figure 4.6 – Illustrates Qp/Qs FB before and after BAE in all 5 participants

4.4 Conclusion

This small study has identified that a bespoke MRI protocol to assess shunt fraction is feasible in CF patients presenting with haemoptysis. All 5 patients who underwent this MRI assessment completed it without difficulty. The protocol is designed to be efficient and ensure patients spend as little time on the scanner as possible. The acquisition which includes 3 sets of AO and PA flows in BH and FB acquisitions was achieved in less than 20 minutes in each patient. 20 minutes is a relatively short acquisition time to undergo an MR evaluation, especially since patients usually need more time for preparation and sometimes have trouble staying still, due to claustrophobia. As a comparison, an MRI of the spine or the liver can take up to 45 minutes.

The effect of breath hold and free breathing on Qp/Qs is important to recognise particularly in this patient population due to variable ability to sustain breath hold. As individuals with CF approach adulthood they are troubled by chronic coughing, recurrent wheezing, tachypnoea, and repeated lung infections. This can make breath holding extremely challenging and troublesome.

In the previous chapter it was established that FB data is the preferred technique due to increased reliability. This is especially the case in CF patients with inherent difficulty in breath hold. Using FB techniques with phantom correction I have demonstrated that there is a consistent finding of a Qp/Qs of less than one prior to embolisation in CF patients with haemoptysis.

I have also shown that BAE has a measurable effect on the shunt fraction. One patient within this study had complex anatomy that made it difficult to undertake an extensive embolisation. As a result, this single patient showed only a small change in shunt fraction. The remaining four patients were treated more extensively, typical of our institutional experience and these patients demonstrated a greater change in their shunt fraction. Indeed, the shunt fraction returned to the normal value (determined in the volunteer study) in two of the remaining four patients.

From our experience some patients report a sensation of breathlessness after BAE however in this small sample of patients the bed side spirometry results obtained before and after BAE did not demonstrate a substantial change.

There was a consistent improvement in CFQR scores after embolisation indicating possibly a better quality of life post embolisation compared to pre-embolisation.

4.5 Discussion

These findings provide novel insights into the pulmonary vascular haemodynamics in CF. The results indicate that phase-contrast MRI can be used to acquire measurements of the magnitude of the flow in the bronchial arteries, and that these values are reproducible.

According to the procedure reports, the embolisation was comprehensive in four out of five patients. The number of vessels treated and the size of the vessels treated were typical of the department's experience with over one hundred embolisation procedures over the past ten years. (Internal departmental audit data, unpublished). Due to unfavourable anatomy, a comprehensive BAE was not possible for the fifth patient. This patient demonstrated a smaller change in shunt fraction and as such indicates limited embolisation. Currently, there is no objective method for determining the efficacy of BAE, but this finding suggests that shunt fraction measurement may play a role in determining BAE efficacy.

In addition to demonstrating that a shunt exists in CF patients presenting with haemoptysis, these results demonstrate that embolisation reduces the flow sufficiently to have a measurable effect on the shunt fraction. This is the first time a measurable value has been obtained to assess pulmonary haemodynamics in BAE. This work indicates that change in shunt fraction correlates with number and extent of hypertrophied bronchial arteries treated however, more data is needed to confirm this.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a disease-specific measure of health- related quality of life (HRQOL) for children, adolescents, and adults with CF. It is a profile measure of HRQOL that includes multiple domains. It has undergone extensive reliability and validity testing. On a scale from 0 to 100, the CFQ-R application calculates the score derived from the CFQ-R, with higher scores indicating better HRQOL (255). Despite these small numbers, there is evidence that the CFQR score increases after BAE, indicating an overall improvement in quality of life. However, confounding factors are present. For example, patients often are treated with antibiotics in the period before BAE since it is often felt that infectious exacerbations may contribute to the occurrence of haemoptysis. This renders it impossible to determine whether BAE and subsequent decreased bronchial circulation or concurrent infection treatment improved CFQR.

Lastly, phantom corrections are often overlooked in clinical practice despite their importance when evaluating small shunts. Were it not for the phantoms used for corrections, the results would have been inaccurate.

4.5.1 Study Limitations

The primary limitation of this study is the small number of participants. To ascertain whether clinical conclusions may be made, a larger patient cohort must be evaluated. Nevertheless, important novel concepts have been demonstrated, and using this data as justification, future larger studies assessing shunts in patients with CF may improve our understanding of the pathophysiological process and provide more data from which valid clinical inferences can be drawn.

4.6 Key Points

To summarise, the shunt fraction is not part of routine assessment in patients with advanced CF. It is acknowledged that CF patients with advanced structural disease frequently demonstrate bronchial artery hypertrophy and exhibit haemoptysis.

This research has revealed that patients with hypertrophied bronchial arteries who present with haemoptysis have an abnormal shunt fraction and this shunt can be quantified by carefully optimised MRI. Furthermore, this technique can detect change following successful BAE. This novel finding may play a role in future risk stratification and the creation of a haemoptysis prediction score based on morphological and functional parameters.

5 Overall conclusions of the thesis

The first experiment examined the techniques required and the numerous pitfalls that can arise when assessing small shunts using MRI and categorised them into 3 subgroups (patient factors, scanner factors and post processing factors). This study established the importance of being vigilant when using MRI for assessing small shunts as even a small error can invalidate results. There are several pitfalls in patient co-operation, image acquisition, correction and analysis techniques that require mitigation to ensure reproducible and accurate results are obtained. Building on the knowledge of common pitfalls, a bespoke protocol was developed using healthy volunteers and the protocol was assessed for precision and accuracy. The findings highlight the importance of phantom corrections when assessing small (<20% CO) shunts. The method of phantom corrections is not used in clinical practice where shunts are larger and as such precise measurement is not always necessary. The importance of breath hold or free breathing and its effect on the shunt fraction was also evaluated in this study.

Once we were satisfied that we had an accurate and a reproducible method to assess small shunts with sufficient precision, the protocol was applied in 5 CF patients who presented with haemoptysis and quantified their shunt fraction. The findings demonstrated that it is feasible for CF patients to have an MRI while awaiting a bronchial artery embolisation. All 5 patients in the study showed a measurable shunt at baseline. This complements with other work that has recently been undertaken at the Royal Brompton Hospital where structural lung parenchyma appearances were assessed on MRI.

Finally, the shunt fraction was assessed after bronchial artery embolisation. This showed the shunt fraction changed in all patients after the bronchial arteries were targeted with embolisation and the shunt fraction returned towards the normal value.

The findings did not detect a deleterious effect of BAE on bedside spirometry. From clinical experience we have noticed patients sometimes express a feeling of increased breathlessness immediately after the embolisation procedure; the underlying mechanisms of this are poorly understood. At present there are no objective radiological measures that have been able to demonstrate a deleterious effect from blocking off these bronchial arteries to explain the cause

of this breathlessness. This is even though large bronchial arteries may supply a significant proportion of blood flow to the lungs.

Future research involving patients who may struggle with prolonged breath hold or require a timely assessment of the shunt fraction can use this work as evidence for proof of concepts to design and develop larger studies. This study also highlights the need to combine expertise of the physicist, radiographer and a radiologist in order to develop a streamlined bespoke protocol.

5.1 Summary of novel findings from this project

- Shunt fraction can be assessed precisely and accurately using a bespoke MRI protocol that is robust and precise enough to quantify small shunts.
- To assess small shunts (<20 % of cardiac output) phantom corrections are vital.
- In CF patients who present with haemoptysis the Qp/Qs at baseline is consistently < 1.
- After bronchial artery embolisation the Qp/QS returns towards the normal value of 1.05 (by CMR).
- Alteration in the Qp/Qs associated with BAE does not seem to have a deleterious effect on bed side spirometry and quality of life.

6 Discussion

This thesis has shown that there is a difference in the shunt fraction obtained in CF patients with haemoptysis compared to healthy volunteers. Furthermore, we have also identified that treating patients with haemoptysis via the means of a BAE alters the bronchial arterial flow and subsequently changes the shunt faction (towards normal). This change in the shunt fraction after embolisation of the bronchial arteries makes sense when we look at the anatomy of bronchial circulation (as explained in Chapter 1) and further discussed below.

This work also highlights numerous complex MRI physical principles and establishes the fundamental need for an experienced physicist to be involved in every step of establishing an MRI protocol to investigate a clinical question. Working closely with an expert physicist will increase the likelihood that the protocol is designed to mitigate potential problems that clinicians may not even be aware of, thereby decreasing the likelihood of obtaining inaccurate or even completely invalid results.

6.1 Nomenclature of a shunt

A specialist in congenital heart disease frequently utilises the terms right to left shunt and left to right shunt. Shunting outside the purview of congenital cardiac disease that occurs in respiratory disorders is a concept that is mostly overlooked, and whether the cardiology community would consider this shunt as a legitimate shunt is debatable. As previously mentioned to in the introduction, extracardiac shunting is significant in certain respiratory disorders and should be kept in mind while discussing shunts. This research contributes to our understanding of the anatomy of bronchial shunts.

Bronchial arteries originate from the descending aorta, and after supplying oxygen to various lung tissues, the blood eventually empties either to:

1. Small pulmonary arteries
2. Small pulmonary veins
3. To the azygos vein draining to the right atrium (11).

Measuring the aortic and pulmonary flow above the aortic and pulmonary valves in CF patients with haemoptysis revealed a median FB phantom corrected Qp/Qs (min/max) of 0.84 (0.78/0.91). When this shunt fraction is applied and extrapolated to known anatomy, it holds true. The bronchial circulation drains via the systemic azygous vein and back into the RA (proximal bronchial circulation) or to the LA via the bronchopulmonary anastomoses when the bronchial anatomy is normal. Additionally, in individuals with congenital heart disease who have large shunts (for the purpose of this discussion, defined as >2), we expect oxygen saturations to be abnormal.

Using diagrams (Figures 6.1 and 6.2) and scenarios, the clinical significance of extra cardiac shunting is illustrated below. I have used the Qp/Qs ratio of 0.8 to demonstrate the clinical applicability of this work. As an illustration, I will use an aortic flow rate of 5 L/min and a pulmonary flow rate of 4 L/min.

6.2 Scenarios

6.2.1 Flows

Scenario 1: Assuming blood is only returning from the bronchial arteries to the pulmonary arteries and pulmonary veins. No flow to the azygos (Figure 6.1).

In this case, of the 5 L/min entering the aorta, with 1L/min entering the bronchial arteries, if 0.5L/min going to bronchial arteries draining into the pulmonary arteries and 0.5 draining into the pulmonary veins, the effective flow to the body would be 4 L/min and the systemic venous return would be the same 4 L going to the right atrium, right ventricle and pulmonary artery. Therefore, any bronchial arteries draining either to the pulmonary arteries or pulmonary veins will have a similar effect on flow i.e. a QP/QS less than 1. This is a shunt from the aorta back into the pulmonary veins and left atrium. Whether it should be called left-to-right or right-to- left, is debatable and perhaps immaterial. The outcome of Qp/Qs by MRI is to document the volume of blood crossing the aortic and pulmonary valve. The altered flow however, may have an effect on systemic saturations, see below.

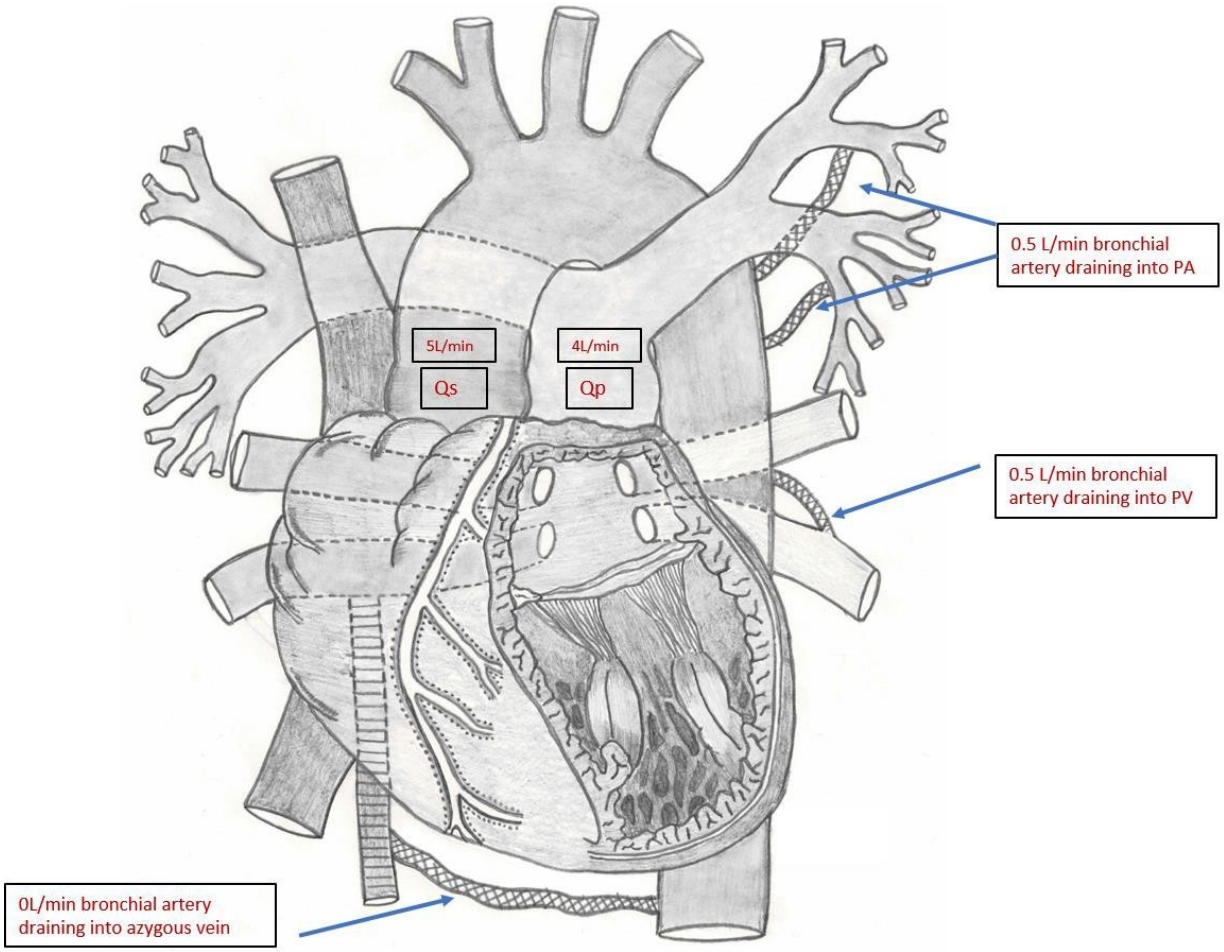


Figure 6.1 – Illustration of how a Qp/Qs of 0.8 is achieved when applied to anatomy (scenario 1) Assuming blood is only returning from the bronchial arteries to the pulmonary arteries and pulmonary veins. No flow to the azygos. This figure Illustrates how a Qp/Qs of 0.8 (obtained using the FB, phantom corrected measurements) makes sense when applied to anatomy. Image drawn by Image drawn by Dr Amina Khalil.

Scenario 2: Assuming there is also flow from bronchial arteries to the azygos vein, as well as into the pulmonary arteries and pulmonary veins (Figure 6.2).

In this case, of the 5 L/min entering the aorta, we assume 2L/min enters the bronchial arteries. Of this, 1 L goes to the pulmonary arteries and or pulmonary veins as above, but now another 1L

reaches the azygos vein via the bronchial circulation. Therefore, the effective flow to the body will be 3 L/min, which is also the systemic venous return until the mid SVC where 1 L will reach the SVC through the azygos adding itself to the 3 L, hence 4 L reaching the right atrium, right ventricle and pulmonary artery. Therefore, the shunt from bronchial arteries that returns via the azygos system will not modify the amount of blood reaching the right-sided chambers and main pulmonary artery for QP measurement by MRI. The QP/QS of 0.8 is still true.

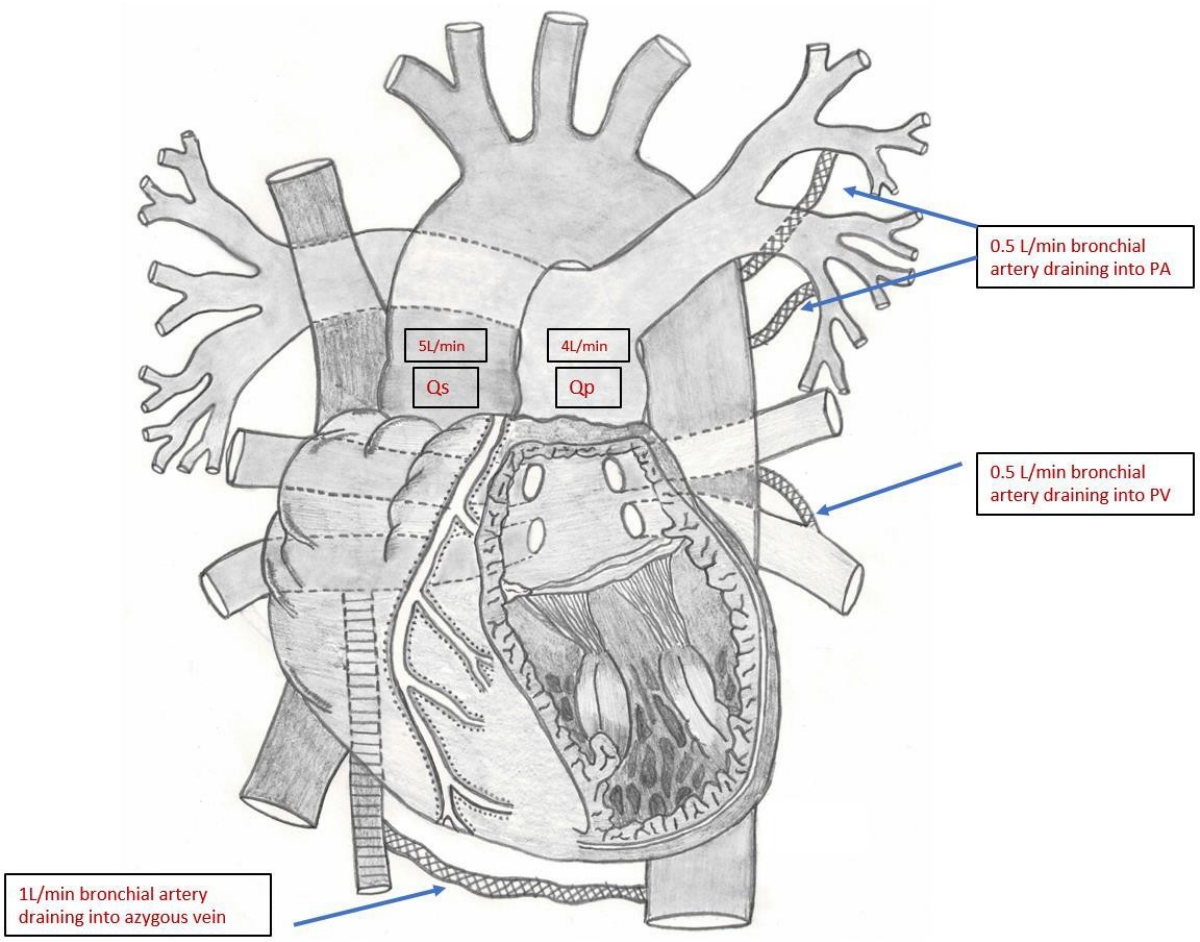


Figure 6.2 Illustration of how a Qp/Qs of 0.8 is achieved when applied to anatomy (Scenario 2) Assuming there is also flow from bronchial arteries to the azygos vein, as well as into the pulmonary arteries and pulmonary veins. This figure Illustrates how a Qp/Qs of 0.8 (obtained using the FB, phantom corrected measurements) makes sense when applied to anatomy. Image drawn by Dr Amina Khalil.

6.2.2 Saturations:

In congenital heart disease the degree of shunting is related to severity of symptoms and saturation.

Scenario 1: Assuming that bronchial artery blood desaturates to 60% as it provides oxygen to lung tissues, bronchial arteries draining to pulmonary arteries will not cause systemic desaturation as the desaturated blood from the bronchial arteries will join desaturated blood in the pulmonary arteries and then become saturated as it passes through the capillaries.

Bronchial arteries draining into the pulmonary venous system will however cause some desaturation which is proportionate to the volume of blood in the bronchial arteries and the oxygen saturation when reaching the pulmonary veins. It is predicted there will be a small degree of desaturation from 100% to 90-95%. This mildly desaturated blood reaches the left atrium, left ventricle and aorta. Hence the blood going into the bronchial arteries from the aorta will already be somewhat desaturated.

Scenario 2: Blood from the bronchial arteries will be desaturated when it drains into the azygos vein; however, this will have little effect on the saturations when this blood reaches the right atrium together with other systemic venous return and ultimately the pulmonary arteries. It will certainly not make any difference to systemic saturations.

Overall, it makes sense that shunt related to bronchial arteries produces a Qp/Qs of less than

1. There may be some desaturation related only to bronchial arteries draining into the pulmonary venous system, and subsequently into the left atrium and the aorta.

6.3 Limitations of this study

6.3.1 Small sample size.

The small sample size in this study is attributable to a few factors. Firstly, the opportunistic nature of recruitment made it difficult to anticipate when a patient with haemoptysis would present to the hospital and be enrolled for the study. Secondly, the recruitment criteria required that patients be hemodynamically stable; therefore, the study team relied on the clinical teams'

judgement to determine whether patients could be recruited. There were 3 patients who presented with haemoptysis during the recruitment period of this project who were deemed unsuitable for recruitment by the clinical team for various reasons. Lastly, and maybe most importantly, the COVID-19 pandemic had a substantial impact on the small sample size of this study. This is described in further depth in the subsequent section.

6.3.2 Lack of an established gold standard

The lack of a gold standard, such as in the case of the shunt fraction in respiratory patients, creates uncertainty and restricts the conclusions that can be derived from them.

Establishing a gold standard is crucial in medical research to ensure consistent and accurate findings as it provides a reference point against which the validity and reliability of alternative methods or measurements can be evaluated (287,288).

Despite novel findings demonstrated in this thesis in relation to MRI protocol for assessing shunt fraction in respiratory patients, it becomes apparent that further validation studies with larger sample sizes are necessary to strengthen the reliability of the findings. While the initial efforts have provided valuable insights into the accuracy of the new protocol, expanding the sample size will enhance statistical power and allow for a more robust assessment of its performance across diverse patient populations. Additionally, conducting more extensive validation studies will help to address any potential limitations or biases ensuring that the protocol can be confidently implemented in clinical practice and be a universally accepted technique for accurately quantifying pulmonary shunting. Furthermore, multicentre studies can also be used to encompass a broader spectrum of patients with various demographic, backgrounds and geographical locations (287, 288).

In addition to validation studies, conducting comparative studies is essential to mitigate the absence of a gold standard (289). Comparative studies involve the simultaneous evaluation of multiple methodologies for assessing the shunt fraction in respiratory patients, facilitating direct comparison to identify differences and limitations. By systematically comparing the performance of different methods under controlled conditions, researchers can elucidate the strengths and

weaknesses of each approach, aiding in informed decision-making about the optimal method for assessing the shunt fraction (289).

Additionally, another effective strategy to address the lack of a gold standard is through engaging in consensus-building activities (290). Consensus-building initiatives seek to achieve agreement on the most reliable and valid evaluation procedures by consulting a varied range of specialists (290). By engaging in thorough conversations, conducting systematic evaluations of current information, and organising consensus meetings, these initiatives help establish best practices and standardised methods. Consensus-building methods use the knowledge and expertise of experts to offer clear guidance when there is no definitive norm. Consensus-building methods leverage the knowledge and expertise of experts to provide clear guidance when there is no definitive norm.

In summary, while the absence of a gold standard presents challenges in research on shunt fraction in respiratory patients, employing a combination of strategies described above can mitigate its impact. Comparative analyses, validation studies, consensus-building, adopting a multimodal approach, and transparent reporting serve as indispensable tools for advancing research and addressing the challenges posed by the absence of a gold standard, ultimately enhancing the quality and rigor of scientific inquiry.

6.3.3 Patient acceptability/experience

The study found that patient accessibility and experience were positive, suggesting a successful recruitment strategy. It is important to recognise that, despite attempts to involve as many eligible participants as feasible, certain individuals were unable to participate in the study due to various factors. The reasons included medical contraindications, logistical problems and patient preferences. It is crucial to thoroughly document and report instances of non-participation in the study to facilitate necessary modifications. It is also worth noting that efforts should be undertaken to reduce obstacles to participation in further studies, guaranteeing that all qualified individuals can participate.

6.3.4 Impact of COVID-19 pandemic

The impact of COVID on this work has been substantial.

It was the beginning of the recruitment period for this work when the COVID pandemic was declared and its restrictions were introduced. The international community took drastic measures to stop the spread of the virus, including the closure of regular patient-facing clinics and the reassignment of personnel to higher priority sectors, such as intensive care units. Additionally, CF patients were considered particularly vulnerable, and as such, they were put under heightened shielding. These measures effectively paused recruitment for nine months. To counter these difficulties, I extended the recruitment period by 6 months; however, despite every effort, only 5 patients were recruited and completed the pre- and post-embolisation studies.

Concerns about the emerging virus's possible impact on the CF population emerged almost immediately after the pandemic was declared. Not only were there reports of worse outcomes in more vulnerable patients, but CF also has a long history of unfavourable outcomes associated with viruses (256).

Interestingly, however, as the pandemic progressed and more data became available, it was discovered that CF patients did not do as poorly as previously expected. A few explanations that have been proposed in the literature are:

1. CF patients are younger
2. CF patients have a lower prevalence of obesity.
3. CF patients are accustomed to infection preventive measures
4. Protective effects of CF cellular processes (e.g., dysregulated autophagy may counteract viral infection)
5. Protective effects of CF therapies(e.g., CFTR modulators or azithromycin) (257, 258, 259,260).

The lower number of CF patients who contracted the virus in the early stages of the pandemic is most likely attributable to improved infection control procedures and less exposure. Infectious exacerbations in patients with CF and the incidence of haemoptysis were also decreased by social isolation and better infection prevention strategies.

6.4 Future developments

Future applications of this work are now discussed under a few subheadings.

6.4.1 Non-CF bronchial artery hypertrophy.

This work will undoubtedly benefit CF patients but the potential to explore other patients that develop enlarged bronchial arteries and subsequently present with haemoptysis will be an interesting area to focus on in the future.

There are numerous mechanisms of proliferation of aortopulmonary collateral vessels. In CF there is chronic airway inflammation and bronchiectasis driving the proliferation of the bronchial circulation however there are other disease states where a separate mechanism is responsible (61, 62). Hypertrophied bronchial arteries are present in sarcoidosis, TB, aspergilloma, lung cancer, and chronic thromboembolic illness and other conditions associated with prolonged inflammation and infection (251). Similar to patients with cystic fibrosis, these patients often present with haemoptysis; however, it is unknown whether a shunt is present in these groups. In clinical practice, patients with interstitial lung disease have been seen to experience shortness of breath despite stable morphological fibrotic lung disease, and it is worth considering whether attention should be directed to bronchial circulation in these patients (262). It will be interesting to assess baseline shunt fraction in the non-CF patient population. To our knowledge this has not been performed yet.

For patients with certain congenital heart diseases, systemic-to-pulmonary collateral vessels are a relatively common finding because these conditions are frequently associated with reduced pulmonary perfusion (for example pulmonary atresia or unilateral lack of the pulmonary artery agenises (57, 60). CT studies frequently show larger bronchial arteries in patients with chronic thromboembolic disease and pulmonary hypertension (CTEPH) (251). More research is required to see if a shunt can be detected in these group of patients. Postulation drawn from our novel

findings is that patients with morphologically hypertrophied bronchial arteries will also have an associated abnormal shunt fraction.

Improved understanding of the disease processes involving the bronchial arterial circulation will allow improvements in patient care and shed light on to potential treatment options.

6.4.2 Development of a combined CT phenotype and Qp/Qs assessment to risk stratify for future haemoptysis.

This research indicates that CF patients with haemoptysis have a detectable shunt. It would be intriguing to determine if this shunt is also present in patients with an advanced phenotype on CT who have not presented with haemoptysis.

Combining the CT morphological features, specific clinical factors, and the shunt fraction (see below) could produce a combined score that could accurately predict the probability of future haemoptysis. A patient in this study who developed haemoptysis while hiking alone was understandably terrified by the ordeal. If a clinical risk score that incorporates morphological and functional data can be created, it would have the potential to improve risk classification. The three parameters that could be used to develop a haemoptysis prediction score are:

Morphology of lung CT phenotype. The Brody's scoring system is a lobar scoring system, which assigns a score to each lobe separately. This scoring system describes the following morphologic changes: bronchiectasis, peri-bronchial wall thickening, mucus plugging, air trapping and parenchymal involvement. This system has been validated and provides a reproducible method that could be used to evaluate the lobar location, severity, and extent of a broad spectrum of CT features of CF lung disease. The overall score is both sensitive to variation in the severity of lung disease and reproducible (275).

Specific clinical parameters (Haemoptysis grade, sputum cultures, spirometry, serum markers, frequency of admission and number of courses of antibiotics.

Shunt fraction as developed in this thesis.

Development of a single tailored MRI protocol to assess structural lung disease and shunt fraction in CF as part of annual assessment.

In patients presenting with haemoptysis and requiring inpatient admission, it is crucial that the protocols contain the necessary steps to ensure that patients are thoroughly monitored throughout the process and that the MRI protocol used to determine the shunt fraction is safe.

In this study, a physician with BLS training accompanied patients for both pre- and post-embolisation MRI assessments. With additional data, this work will help further streamline the process and possibly even incorporate the MRI-derived shunt fraction into the annual evaluation of advanced CF patients.

CT imaging is the gold standard for evaluating the morphology of the lungs and the degree of structural abnormalities in patients with advanced CF. Phase-contrast MRI could be a non- invasive supplement to the standard structural examination of these individuals. Despite MR imaging's inferiority to CT in terms of spatial resolution, it has the potential to shed light on the pathogenesis of chronic lung disorders by providing new functional and physiological information (without radiation exposure). Recently focus has shifted in the research community to determine the role of MRI in assessing lung structure in CF patients. This is predominantly to reduce radiation dose. With MRI offering further functional data eventually, one single examination may be able to assess both lung structure and function in these patients. The shunt fraction may also be utilised as a measure of disease severity and integrated into a morphological assessment for risk classification. Due to technical challenges such as low proton density and respiratory and cardiac motion, non-invasive airway and lung parenchymal assessment in CF has traditionally been beyond the scope of routine clinical imaging using chest MRI (276). However, technological advances have dramatically improved the quality of lung MRI (including signal-to-noise ratio, resolution, speed, and contrast). There is now consensus that lung MRI can be used clinically in CF to quantify the severity of lung disease. MRI can now achieve three-dimensional, high-resolution morphologic imaging, and in addition to this morphological information, MRI may be able to differentiate between active inflammation and scar tissue with sensitivity (276). Additionally, MRI could characterise various forms of inflammation for early treatment guidance. In addition, functional information from MRI can be used to evaluate regional, small-airway disease with the sensitivity to detect small changes in patients with mild CF. For a more objective and reproducible evaluation of disease severity, automated quantification methods have emerged as a complement to traditional visual analyses. Recently, work at RBH has been completed that evaluated MRI

assessment of structural lung disease in CF (277). The techniques described in this published thesis could be developed and incorporated into a new bespoke MRI protocol assessing morphology and function. This would offer CF patients one study to assess morphology and function as they move into their adult years.

6.4.3 CFTR modulators.

The symptoms of CF are managed with a variety of medications and treatments. It is recognised that new, highly effective medications (CFTR modulators) are now available to certain individuals with CF, and they are dramatically altering the disease's landscape (254).

CFTR modulators restore the function of damaged CFTR proteins by altering their structure. These medications are only effective if the faulty CFTR gene can produce CFTR protein. There are four medications that modulate the CFTR: ivacaftor, lumacaftor, tezacaftor, and elexacaftor

(278). They operate in various ways. Depending on their CFTR mutations, people with CF may take ivacaftor alone, also known as Kalydeco, or ivacaftor in combination with one or two other medications. Orkambi consists of ivacaftor and lumacaftor, Symkevi consists of ivacaftor and tezacaftor, and Kaftrio consists of ivacaftor, tezacaftor, and elexacaftor.

Several clinical trials of Kaftrio in individuals with CF have been conducted. In these trials, the effects of Kaftrio on individuals with different CFTR mutations (and different combinations of CFTR mutations) and on individuals with CF of varying ages were evaluated. Improvements in lung function (measured as percent predicted FEV1), number of exacerbations, overall CFTR protein function (measured as sweat chloride levels), and quality of life indicate that Kaftrio is beneficial for people with CF. In recent trials involving children aged 6 to 11 years, the Lung Clearance Index (LCI) and Body Mass Index (BMI) served as additional measurements (278, 279).

Perhaps in the future, we will no longer encounter such advanced morphological disease in CF. Nevertheless, the shunt fraction is an objective assessment of pulmonary haemodynamics and could serve as an additional tool for assessing physiology in these patients, with the caveat that the MRI technique must be carefully adapted for sufficient precision and accuracy. It would be fascinating to determine whether use of CFTR modulators modifies the shunt fraction before and after treatment initiation.

6.4.4 Lung transplantation

During lung transplantation the small bronchial vessels are not usually re-anastomosed. Instead, revascularisation is encouraged by pulling a loop of omentum through the diaphragm and wrapping it around the airway anastomotic site (263,264). In double-lung transplantation, the risk of ischemia associated with a tracheal anastomosis was contrasted with the success of anastomosing the airways closer to or within the lung tissue (265). These airways are nourished by larger pulmonary arterial contributions. Combined heart-lung transplantation has been associated with fewer airway necrosis problems, probably because nutritive bronchial vessels frequently arise from the coronary arteries (264). Emerging evidence links the development of bronchiolitis obliterans syndrome to airway ischemia, with some surgeons advocating bronchial artery revascularisation in an attempt to avert or delay the development of bronchiolitis obliterans syndrome (265). Perhaps the shunt fraction prior to surgery will aid decision making. (i.e. if a significant shunt exists prior to transplantation there may be a role for bronchial artery anastomosis).

6.4.5 Potential implications on physiology, disease pathogenesis and management.

The development of a novel MRI protocol for measuring the shunt fraction in CF patients, coupled with the observation that all patients presenting with haemoptysis exhibit a right-to-left shunt, holds significant implications for our comprehension of CF physiology, disease progression, and management strategies. Currently, only morphological changes are monitored through repeat CT studies (252). However, this thesis demonstrates that a surrogate physiological assessment derived from MRI allows for a functional evaluation of lung haemodynamics. This capability empowers clinicians to gauge if symptomatic decline may be attributed to a deteriorating shunt. As discussed earlier, worsening shunt may manifest as low saturations, providing additional support for decisions regarding oxygen therapy. Through further validation studies, MRI-derived measurements of shunt fraction could aid in risk stratification, identifying CF patients at higher risk of pulmonary haemorrhage and enabling early intervention. Additionally, MRI-derived quantitative data on pulmonary vascular function may inform treatment planning and decision-making regarding the timing and type of interventions, such as embolisation procedures or pharmacological therapies. Following extensive validation, this approach could be extended to all patients with hypertrophied bronchial arteries, potentially allowing intervention even before the

presentation of haemoptysis. Such proactive measures would undoubtedly benefit patients by alleviating the fear associated with symptomatic haemoptysis and reducing hospitalisations, leading to an improved quality of life and potentially reducing financial implications for the wider health service (295). Furthermore, the severity of shunt fraction measured by MRI may serve as a surrogate marker of disease severity and progression in CF patients, reflecting the extent of pulmonary vascular involvement and associated complications. Serial MRI assessments of shunt fraction could monitor the response to therapeutic interventions and guide adjustments in treatment strategies based on changes in pulmonary vascular physiology and disease progression. Integrating MRI-based assessment of shunt fraction into clinical practice potentially enables healthcare providers to predict the need for future interventions, stratify patients based on their risk of pulmonary haemorrhage, and tailor treatment plans accordingly. Overall, the novel MRI protocol developed in this thesis can eventually, after extensive validation offer a valuable tool for optimising patient care and improving outcomes in CF patients.

6.4.6 Non- CF patients presenting with haemoptysis.

Extending the MRI protocol developed in this thesis to include non-CF patients presenting with haemoptysis potentially broadens the applicability and its impact. Cohorts comprising patients with bronchiectasis or haemoptysis, irrespective of CF status, can undergo shunt assessment using the protocol developed in this study. Subsequently, this assessment has the potential to inform treatment decisions. Patients with bronchiectasis are known to be at increased risk of haemoptysis due to airway inflammation, infection, and structural lung damage (252). The information obtained from shunt assessment can theoretically benefit patients by guiding the decision for embolisation or non-interventional treatment. For instance, in cases where significant pulmonary shunting is identified, prophylactic embolisation may be considered to reduce the risk of recurrent or severe haemoptysis. Conversely, in patients with minimal or no pulmonary shunting, non-interventional treatments such as bronchial artery vasodilators or airway clearance techniques may be more appropriate. By assessing shunt fraction in these patients, clinicians can identify individuals at higher risk of haemoptysis and tailor management strategies accordingly. Similarly, in patients presenting with haemoptysis of unknown aetiology, the MRI protocol can help elucidate underlying vascular abnormalities or shunting, guiding appropriate interventions.

Overall, once validated, extending the application of the developed MRI protocol to non-CF patients with bronchiectasis or haemoptysis has the potential to improve risk stratification, guide treatment decisions, and optimise outcomes in these patient populations.

6.4.7 Artificial intelligence and MRI.

Artificial intelligence (AI) holds tremendous promise for the future of MRI technology. AI has the potential to revolutionise various aspects of MRI, including image acquisition, reconstruction, analysis, interpretation, and clinical decision-making (291,292).

One area where AI can significantly impact MRI is in image reconstruction and enhancement. AI algorithms can reconstruct high-quality images from under sampled or noisy data, reducing scan times and improving image quality. This can lead to faster scans, enhanced patient comfort, and more accurate diagnostic information (292,293).

Moreover, AI-powered image analysis tools can automate tasks such as image segmentation, and quantitative analysis of tissue characteristics. These tools can assist radiologists in interpreting MRI images more efficiently, leading to faster diagnosis and treatment planning (292,293).

Looking specifically at shunt fraction assessment AI algorithms can potentially enhance the accuracy and efficiency by automating the segmentation and analysis of MRI images, enabling rapid and precise quantification of blood flow (292,293). Machine learning models trained on large datasets of MRI scans can learn complex patterns and relationships, allowing for the development of predictive algorithms capable of predicting shunt fraction with high accuracy (292,293,294). AI has the potential to revolutionise MRI-based assessment, ultimately leading to better diagnosis, treatment, and management of respiratory conditions however, it is worth noting this will clearly take time while the hardware, software and data storage needs are met.

6.4.8 Final comments

Phase-contrast velocity mapping is a versatile method for measuring blood flow and velocity that can be incorporated into a comprehensive cardiovascular assessment. All elements, including hardware, software, patient cooperation, image acquisition, and data analysis, must be appropriately and meticulously optimised for precision. With experience, MRI can be utilised to obtain reliable Qp/Qs shunt data in respiratory patients, which may aid in the diagnosis, treatment, and follow-up of patients. This novel work will hopefully serve as a foundation for future, more extensive research.

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8 Appendix

8.1 Case Report Form

MR assessment of shunt fraction in CF patients before and after BAE

Study Reference: Insert study reference

Sponsor: Chiesi Farmaceutici

PRINCIPAL INVESTIGATOR: Dr Bhavin Rawal

Site ID/Number:

Participant Initials:	
Participant Trial Number:	

Date of Birth:

I hereby confirm that the information supplied in this CRF is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: _____

Date of Signature (dd/mm/yyyy): _____

SECTION 1: Eligibility Criteria -This section should list the eligibility criteria from the study protocol i.e.:

Inclusion Criteria	Yes	No*
1. Adults patients >18 years ?	☐	☐
2. Has the subject willingly given written informed consent?	☐	☐
3. No prior treatment by BAE	☐	☐
4. Patients is haemodynamically stable for the MRI scan?	☐	☐
5. No contraindications to have an MRI scan.		☐

*If any inclusion criteria is ticked no then the patient is not eligible for the study

Exclusion Criteria	Yes*	No
1. Age < 18 years	☐	☐

2. Standard contra-indications to MRI ☐ ☐

3. Not medically fit for transfer to MRI. ☐ ☐

4. Patient judged inappropriate for involvement in study by clinical team. ☐ ☐

5. Pregnancy ☐ ☐

*If any exclusion criteria are ticked yes then the patient is not eligible for the study

Eligibility confirmed by PI/delegated co-investigator:

Name: _____

Signature: _____

Date: _____

INFORMED CONSENT

Please note written informed consent must be given before any study specific procedures take place or any current therapy is discontinued for the purposes of participation in this study.

	Yes	No
Has the subject freely given written informed consent?	☐	☐

DEMOGRAPHIC DATA

D D M M Y Y Y Y

Date of Birth: ☐☐☐☐☐☐☐☐

☐

☐

Age (yrs): ☐☐ Sex: Female

Height (m): ☐.☐☐ Male

Weight (kg): ☐☐.☐

BMI: ☐☐ • ☐

Ethnicity: ……

SOCIAL HISTORY

Does the subject consume alcohol?	Yes ○ No ○
If yes:	
On average, how many units per week?	☐ units†

† Note units for exclusion criterion if applicable

Screening continued…

MEDICATIONS TAKEN

Is the subject currently or previously taking any medication including antibiotics, OTC, vitamins and/or supplements?

Yes ☐ No ☐

* Record all medication on Concomitant Medications Page

PREVIOUS MEDICAL HISTORY

Has the patient had any relevant medical history?	☐ **No** ☐ **Yes,** Complete below		
Condition / illness /surgical procedure (please consider using codes for relevant medical history)	**Start date** (DD/MMM/YY YY)	Stop date (DD/MMM/YY YY)	Or tick if ongoing at Screening g Visit?
	____/_____/____	____/_____/____	☐
	____/_____/____	____/_____/____	☐

	____/_____/____	____/_____/____	☐
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	____/_____/_____	____/_____/_____	☐
	____/_____/_____	____/_____/_____	☐

Analyte	Date of sample
Haemoglobin ☐ g/dL	_____

		Samples assumed to be taken on same date unless indicated otherwise
White cell count	$\times 10^9$ / L	
Platelet count	$\times 10^9$ / L	
Haematocrit		
Serum sodium	mmol/L	
Serum potassium	mmol/L	
Serum urea	mmol/L	
Serum creatinine	µmol/L	
Estimated glomerular filtration rate (if available)	mL/min	
Total bilirubin	µmol/L	DD/MM/YY







C-reactive protein	☐ mg/L
Random glucose	☐ mmol/L
Lactate	☐ mmol/L

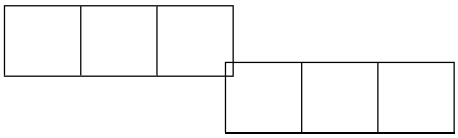
Are the analyses: Abnormal (clinically ◯ Abnormal (not clinically ◯ Norma ◯ Signature

*If abnormal and clinically significant, give details (clinically significant results may need to be entered on Adverse Event page, if they are serious or could be related to the study medicine)

BASELINE ASSESSMENTS PRIOR TO MRI (First scan)

VITAL SIGNS

Pulse rate: Bpm



Blood Pressure:

ECG

Is the ECG: Normal ☐ Abnormal* ☐

8.1.1.1.1.1 *Description:

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Spirometry

Date:

Results:

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Body mass index (BMI)

Date:

Results:

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CT – Bronchial angiogram

Date:

Results:

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Standard of Care blood Test – including CRP to assess inflammation. Date:

Cystic Fibrosis Questionnaire-Revised (CFQ-R) – Pre BAE Date:

QP/QS – Pre BAE

Date:

Pitfalls:

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CHECKLIST

Trial participant checklist

1.	Does the participant satisfy the inclusion and exclusion criteria to date?	Yes ○ No ○
2.	Have all screening procedures been completed?	Yes ○ No ○
3.	Is the subject willing to proceed?	

CRF completion:

Name: _____

Signature: _____

Date: _____

BAE Treatment:

Date of BAE (DD/MM/YYYY)	Procedure details (Material used, partial or complete)	Number of vessels Embolised	Patients symptoms before BAE	Patients symptoms after BAE
__/__/_____				

Visit Checklist:			
		Yes	No
1.	Have there been any new Adverse Events? (If yes, please record in Adverse Events Log)	☐	☐
2.	Have there been any changes in Concomitant Medications? (If yes, please record in Concomitant Medications Log)	☐	☐

ADVERSE EVENTS

Has the patient experienced any adverse events since informed consent? ☐ Yes ☐ No

Event details	Assessment of seriousness[2]	Relationship to study [3]
Onset: DD / MMM / YYYY **Resolution:** DD / MMM / YYYY **Intensity:**[1] mild ○ moderate ○ severe ○ Brief description: Outcome:	○ non-serious ○ serious* Initials _____ *Indicate reason: ○ resulted in death ○ life-threatening ○ required hospitalisation ○ prolonged hospitalisation ○ significant disability/incapacity ○ is a congenital anomaly/birth defect ○ other (state):	○ not related ○ possibly† ○ probably† ○ definitely† †Is the reaction: ○ expected‡ ○ unexpected ‡ Consistent with information about the IMP listed in the SmPC or clearly defined in the protocol.

Onset: DD / MMM / YYYY **Resolution:** DD / MMM / YYYY **Intensity:**[1] mild ○ moderate ○ severe ○ Brief description: Outcome:	○ non-serious ○ serious* Initials _____ *Indicate reason: ○ resulted in death ○ life-threatening ○ required hospitalisation ○ prolonged hospitalisation ○ significant disability/incapacity ○ is a congenital anomaly/birth defect ○ other (state):	○ not related ○ possibly† ○ probably† ○ definitely† †Is the reaction: ○ expected‡ ○ unexpected ‡ Consistent with information about the IMP listed in the SmPC or clearly defined in the protocol.

Onset: DD / MMM / YYYY **Resolution:** DD / MMM / YYYY **Intensity:**[1] mild ○ moderate ○ severe ○ Brief description: Outcome:	○ non-serious ○ serious* Initials _____ *Indicate reason: ○ resulted in death ○ life-threatening ○ required hospitalisation ○ prolonged hospitalisation ○ significant disability/incapacity ○ is a congenital anomaly/birth defect ○ other (state):	○ not related ○ possibly† ○ probably† ○ definitely† †Is the reaction: ○ expected‡ ○ unexpected ‡ Consistent with information about the drug listed in the SmPC or clearly defined in the protocol.

Post Bronchial Artery Embolisation

Spirometry – Post BAE

Date:

Results:

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CFQ- R score

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QP/QS

Date:

Pitfalls:

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Investigator Comments (for any comments not covered elsewhere in the CRF)

☐Yes ☐ No

Date	Comments	Signature

CRF completion:

Name: _____

Signature: _____

Date: _____

STUDY COMPLETION FORM and OFF STUDY Form

Did participant complete the trial?	☐ **Yes,** Please provide **date of last visit**: _____/ _____/ 2 0 _____ (DD / MMM / YYYY) ☐ **No,** Please provide **date of withdrawal** and complete below: _____/ _____/ 2 0 _____ (DD / MMM / YYYY)

Early Withdrawal: please tick most appropriate reason for participant not completing the trial:

☐ **Adverse Events related:** please state related AE: _____

☐ Participant's decision, specify: _____

☐ Investigator's decision, specify: _____

☐ **Sponsor's decision**

☐ **Lost to follow up**

☐ Other, specify: _____

CRF completion:

Name: _____

Signature: _____

Date: _____

8.2 Informed Consent Form

Royal Brompton & Harefield NHS
NHS Foundation Trust

REC Reference Number: 19/EE/0154

IRAS Number: 256039

Patient Identification Number for this trial: ___

Title:

Magnetic Resonance Imaging (MRI) derived measures of bronchial arterial flow in the assessment and follow-up of patients with Cystic fibrosis (CF) who undergo bronchial artery embolisation

Name of Researcher:

Dr Bhavin Rawal/ Professor Simon Padley

Please initial box

1. I confirm that I have read and understand the information sheet dated __/__/____for the above study and have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Royal Brompton and Harefield NHS Foundation Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

5. I agree my images can be stored for future research. ☐

6. I agree to my GP being informed of my participation in this study.

Name of Patient	Date	Signature

Name of person taking consent	Date	Signature

8.3 Participant Information Sheet (PIS)

Royal Brompton & Harefield NHS
NHS Foundation Trust

REC Reference Number: 19/EE/0154 IRAS Number: 256039

Study Title:

Magnetic Resonance Imaging (MRI) derived measures of bronchial arterial flow in the assessment and follow-up of patients with Cystic fibrosis (CF) who undergo bronchial artery embolisation

Invitation to participate in the above study:

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it will involve for you. Please take time to read the following carefully and discuss it with others if you wish. We will go through the information sheet with you and answer any questions you have. This should take about 5-10 minutes.

Part 1 of the information sheet informs you about the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear. Take time to decide whether or not you wish to take part.

Part 1

What is the purpose of the study?

This study is an educational project and will form part of an MD(Res) thesis.

You may be aware that the lungs receive blood supply from two separate circulations (pulmonary arteries and the bronchial arteries). In health, most of the blood is received from pulmonary arteries. In some patients the blood flow in the bronchial arteries is increased and sometimes this is responsible for distressing symptoms such as coughing up blood.

The purpose of this study is to assess the blood flow changes in enlarged bronchial arteries using MRI scans before and after bronchial artery embolisation (BAE). We would also like to assess if the lung function changes before and after the procedure.

Why have I been invited?

You have been invited to take part in this study because you have experienced coughing up blood and your doctors believe you will benefit from having treatment by an interventional radiologist. The treatment will aim to directly treat the bronchial arteries that are likely to be responsible for your symptoms.

Do I have to take part?

No. Taking part in this study is entirely voluntary and you can choose not to take part. If you decide to take part, we will go through what the study involves and get you to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or not take part will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part in this important study, you will have the following investigations in addition to the standard of care:

Undergo two separate research MRI scans. First scan will be before your bronchial artery embolisation (BAE) treatment and the second scan will be after your treatment (BAE).

Perform lung function test before and after bronchial artery embolisation (BAE) treatment.

Complete two short questionnaires, an MRI experience questionnaire and a Cystic fibrosis questionnaire-Revised (CFQ-R).

The MRI scans will take place at the Royal Brompton hospital. The scanning process will take up to 30mins. During the scan you will be asked to lie on your back in the scanner and stay still whilst images are being taken. You will have headphones to wear to block out the noise of the scanner and can have a choice of music to listen to. The scanner will take numerous images and for a detailed assessment of the blood flow we would like to give you contrast through an intravenous access route in your arm for some of these images. Intravenous contrast is routinely used in clinical practice and safety questionnaire will be completed prior to the study.

During the first MRI scan you will be accompanied by a doctor. If you feel unwell, we will not go ahead with the scan.

We will store all your personal information and scans in a safe place and ensure it remains confidential like any other test. We will inform you about the outcomes of the research once it is complete.

We will also be writing to your GP to inform them of your participation and we will give you our contact details so that you can contact us about any questions regarding this study.

Expenses and payments

All your investigations will be performed at the Royal Brompton hospital. We will endeavour to perform all your research investigations before you are discharged from hospital. If you do get discharged from the hospital before all your research investigations are completed we will cover the costs of transport to and from the hospital.

You will be able to have your medications before the research scans and this will not have any effect on the standard treatment you will receive.

What are the possible disadvantages and risks of taking part?

Some patients find MRI scans slightly claustrophobic and we will try and reduce this by making the scans as quick as possible or providing you with music during the study. Our staff are very experienced and are skilled at helping you complete the scan. As with any imaging study, there is a small risk of identifying incidental findings elsewhere in the body (for example a kidney or liver lesion). If this is the case, findings will be relayed to your doctor and further diagnostic tests may be arranged.

You will receive a water soluble contrast agent during the MRI study. This is routinely used in clinical practice but sometimes patients may not be able to have this, for example due to an allergy. We will complete a safety questionnaire prior to the study and if there are any concerns we will not give you the contrast agent.

Finally, lung function tests are relatively straightforward and generally considered to be very safe. Lung function tests are performed using a machine called a spirometer. By breathing into the spirometer, we can measure your lung volume and your ability to move air in and out of your lungs in a certain period of time. You may have previously undergone lung function tests as part of your routine annual review.

During the test, you will be seated and a soft clip will be placed on your nose to stop air escaping from it. The tester will explain what you need to do, and you may be asked to have a few practise attempts first.

When you're ready for the test, you'll be asked to:

inhale fully, so your lungs are completely filled with air

close your lips tightly around the mouthpiece

exhale as quickly and forcefully as you can, making sure you empty your lungs fully Overall, this should last around 15 minutes. Some people have experienced feeling sick or tired for a short period after the test. If this were to happen to you, we will ensure you are provided adequate assistance to recover and ensure a specialist nurse is available to accompany you. To reduce the likelihood of you feeling tired after the test we will aim to do the test when you are feeling well, and if there are any concerns we will delay the test until you are feeling better.

What are the possible benefits of taking part?

There will not be a direct clinical benefit to you by taking part in this study.

This study will help us quantify blood flow in the bronchial arterial circulation in patients who experience haemoptysis (coughing up blood) and assess if it changes significantly after treatment. We are hoping this will provide us with useful information about the changes that take place and whether or not these changes relate to your lung function tests.

We are hoping to get valuable information from this study to help design larger studies in the future to benefit patients with this clinical situation

What if there is a problem?

Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2

Will my taking part in the study be kept confidential?

Yes, we will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes we get new information from the research being performed. If this happens then your research doctor will tell you about any additional information and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study we may ask you to sign an agreement outlining the discussion.

What will happen if I don't want to carry on with this study?

If you would like to withdraw from the study at any stage, you will be able to do so. Information collected up to the point you were in the study may still be used however, any stored personal data or paperwork identifiable as you will be destroyed if you wish.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. They can be reached on E-mail: b.rawal@rbht.nhs.uk, Phone: 07983405204.

If you remain unhappy and wish to complain formally, you can do this through the Patient Advice and Liaison Service (PALS):

Royal Brompton Hospital Sydney Street

London SW3 6NP

Tel: 020 7349 7715

Email: pals@rbht.nhs.uk

In the event that you think you have suffered harm as a result of your participation in the study there are no automatic financial compensation arrangements. However, you may have the right to make a claim against the sponsor, the Royal Brompton Hospital. Where you wish to make a claim, you should consider seeking independent legal advice but you may still have to pay for your legal costs.

Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this due to someone's negligence, you may have grounds for a legal action against NHS England London, but you may have to pay your legal costs.

Harm:

If something goes wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action against the study sponsor, Royal Brompton and Harefield NHS Foundation Trust, but you may have to pay your legal costs.

The normal NHS complaints mechanism will still be available to you.

Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. If you do decide to participate you will be assigned a participant code, which will be used as a patient identifier. This will mean that all information that is collected about you during the course of the research will be anonymised. We will use information from you/or your medical records in order to undertake this study. The study doctor and staff; the study sponsor; the funder; and the research ethics committee may require access to your medical records and the information collected about you to check that the study is conducted correctly and to ensure the accuracy of the study data. These people are all obligated to maintain confidentiality by the nature of their work. Any information about you that leaves the hospital will also have all your personal details removed so that you cannot be recognised from it.

We will request your consent before informing your GP about your participation in the study.

General Data Protection Regulation (GDPR)

Royal Brompton hospital is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using

it properly. Royal Brompton hospital will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your at https://www.hra.nhs.uk/information-about- patients or by contacting Mr Patrik Pettersson, Interim Associate Director of Research, Royal Brompton and Harefield NHS Foundation Trust, Research office, Sydney street, SW3,6NP, Email: p.pettersson@rbht.nhs.uk, Phone:0207 352 8121 Ext 2610

The Royal Brompton hospital will collect information from you and/or your medical records for this research study in accordance with our instructions.

The Royal Brompton hospital will keep your name, NHS number, contact details and any other identifiable data confidential. The Royal Brompton hospital will use this information to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Royal Brompton hospital and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in Royal Brompton hospital who will have access to information that identifies you will be people involved in your clinical care and facilitating this study or who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Consenting to Future Research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this

organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

What will happen to the results of the research study?

Once we have concluded the research, we will write up our findings and share them amongst relevant health care professionals. The results of the study will form part of a thesis for a MD(Res) from Imperial College London entitled *"Flow in the bronchial arterial system: Novel measurements and clinical applications in cardiopulmonary disease"*. We will disseminate the information through presentations, educational publications and journal publications. We will inform you of the relevant findings.

During writing up of the research you will not be identified in any report/publication unless you have given explicit consent.

Who is organising and funding the research?

The research is being funded by Chiesi Farmaceutici and the Sponsor is Royal Brompton & Harefield NHS Foundation Trust. The doctors will not be receiving any additional pay. The doctors do not have any conflicts of interest.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC), to protect your interests. This study has been reviewed and given favourable opinion by Cambridge East Research Ethics Committee (REC).

Further Information and Contact Details

If you have any other questions or specific queries about the research please feel free to contact the Research team:

Dr Bhavin Rawal

Royal Brompton hospital Radiology Department Sydney Street

SW3 6NP

Email: b.rawal@rbht.nhs.uk, or Phone: 07983405204.

Professor S Padley

Royal Brompton hospital Radiology Department Sydney Street

SW3 6NP

Email:s.padley@imperial.nhs.uk or Phone:0207 352 8121 Ext.88381

1.1 GP Letter

Royal Brompton & Harefield NHS
NHS Foundation Trust

Royal Brompton Hospital
Sydney Street
London
SW3 6NP

REC Reference Number: 19/EE/0154

IRAS Number: 256039

GP LETTER

Study Title: Magnetic Resonance Imaging (MRI) derived measures of bronchial arterial flow in the assessment and follow-up of patients with Cystic fibrosis (CF) who undergo bronchial artery embolisation

Dr <name>

<
a

<date>

Re: Patient Forename SURNAME, DOB, Address

Dear Dr <name>,

We are writing to inform you that your patient has agreed to participate in the above research study at the Royal Brompton and Harefield NHS Foundation Trust. Your patient was enrolled into the study on **<date>**. We plan to recruit 10 patients into the study, and follow them up for a short period. Ethical approval for this study has been granted by <name of Research Ethics Committee>.

This pilot study will examine the role of MRI techniques to assess blood flow within the systemic circulation to the lungs, namely bronchial arteries. We will also evaluate the consequences of BAE including whether the flow within the bronchial arteries alters after embolisation and if the blood flow can serve as an index of disease severity.

Aims

1. Quantify the pulmonary blood flow to systemic blood flow (Qp/Qs ratio) in CF patients with haemoptysis before embolisation.
2. Quantify the alteration in systemic to pulmonary shunt after bronchial artery embolisation.
3. To correlate MRI derived bronchial blood flow with standard markers of disease severity and physiological impairment prior to treatment.

We shall inform you of any relevant medical changes in the patients' status that may occur during the course of the study and would appreciate if you would kindly inform us of any changes you make your patients medication. We may contact you to ask for information about significant medical events that may occur during the course of the study.

If you want any further details about the study, the involvement of your patient, or you wish to see a more detailed description of the study, please contact Dr Bhavin Rawal.

Enclosed with this letter is the study Patient Information Sheet for your reference. Yours

sincerely,

Dr Bhavin Rawal
Radiology Fellow
Royal Brompton Hospital
Sydney Street
SW3 6NP
07983405204

b.rawal@rbht.nhs.uk

8.4 MRI Safety questionnaire

Royal Brompton & Harefield NHS
NHS Foundation Trust

Cardiovascular Magnetic Resonance Unit
Tel: 020 7351 8800

Royal Brompton Hospital
Sydney Street
London SW3 6NP

Checklist & Information prior to having a Magnetic Resonance Scan

Name	Date of birth	Hospital Number	Height	Weight

As explained in the Patient Information Leaflet, we need to know about any metallic objects or implants in the body, and some other conditions.	Yes	No
Do you have a pacemaker, a defibrillator, or pacing wires in your heart?		
Do you have any other implants or metal in your body? eg: Hearing aid, ear implant, spine implant, programmable hydrocephalus shunt, others		
Have you had any operation on your head or spine?		
Have you had an injury to an eye which might have left metal in it?		
Have you ever had cardiac surgery?		
Do you suffer from epilepsy, diabetes, asthma or allergies (If yes, please circle which)?		
Are you wearing a drug-releasing patch?		
Are you aware of any problems with your kidneys or are you on kidney dialysis?		
Are you awaiting a liver transplant?		
Have you had recent major surgery or major illness?		
Are you pregnant?		
Are you able to lie flat? If not, please state why.		
Have you removed your watch, bankcards, spectacles, hearing aids, keys, coins, jewellery, and hairgrips? (Gold rings are not a problem)		
	Please tick	

Please note that this is a teaching hospital, and there may be doctors/staff in training observing the scan. You may need an injection of contrast agent during the scan, called gadolinium. Pictures may be taken using techniques developed by researchers at Royal Brompton Hospital that are only available here. These points are explained in detail on the Patient Information Leaflet which we ask you to read fully.

I have explained the procedure to the patient. In particular, I have explained the intended benefits, serious or frequently occurring risks. I have discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of those involved.

Consentor's Signature ..... Date: .....

By signing below you acknowledge that you have read the Patient Information Leaflet (overleaf), that the procedure has been explained to you by a qualified person, and that you have answered the above questions correctly.

Patient's Signature: ..... Date: .....

Witness' Signature: ..... Date: .....

PATIENT INFORMATION LEAFLET

Benefits of Cardiovascular Magnetic Resonance (CMR)
A CMR scan gives detailed information about the structure and function of the heart and blood vessels. CMR has many advantages including being non-invasive and not using x-rays.

Risks of CMR
CMR is thought to be one of the safest ways of imaging but there are a few, rare associated risks:

1. Strong Magnetic Field
A strong magnetic field is used to obtain images of your heart. It is not suitable for patients with some metal implants (for example cardiac pacemakers). Please remove all metallic objects and any clothing with metal fastenings before the scan, We will discuss these issues with you.

2, Contrast Agents
To gain extra information from the scan, we sometimes inject a ·contrast agent" into a vein in your arm using a small plastic tube. This usually has no side-effects, but problems may rarely occur:

- **Leaking.** Rarely, there can be leakage of the contrast agent from the vein into the surrounding tissues which can cause temporary discomfort.

- **Allergy.** Severe allergic reactions to a CMR contrast agent are very rare (1 in 100,000) and the doctor in charge of your investigation is trained to deal with this. Occasionally mild reactions are experienced (for example a metallic taste, a headache, or feeling sick}.

- **Nephrogenic systemic fibrosis (NSF).** This is an extremely rare side effect of some CMR contrast agents (less than 1 in a million). We use 'Gadovist" which has never been linked with NSF. NSF causes thickening of the skin, and sometimes the internal tissues. It only occurs in patients with severe kidney failure or those awaiting liver transplantation. Therefore we will check. your kidney function from your records before any injection of contrast, or ask you to have a blood test. If you have severe kidney failure, we will discuss the risks with you. You may consent to proceed with the CMR scan, or choose an alternative test

3, Stress Testing
If you are having a stress test, we exercise your heart by using a drug (adenosine or dobutamine). This is given into a vein in your arm using a small plastic tube. We will ask you questions to ensure it is safe for you to have this test.

- **Asthma.** Very occasionally, an asthma attack may be provoked by the use of adenosine. If this occurs, the drug is stopped immediately and we will treat you to dilate the airways. The doctor in charge is trained to deal with this situation.

- Heart rhythm disorder. Occasionally, adenosine or dobutamine causes the heart rhythm to become abnormal. If this occurs, the drug is stopped immediately and we will treat you to return the heart rhythm to normal. The doctor in charge is trained to deal with this situation.

4. Research Pictures
At Royal Brompton Hospital, through our research we develop special new techniques to take pictures of the heart and vessels, which may be used to give us extra information on how best to manage your health. These are non-standard but extremely safe and are not available elsewhere.

Risks of not having a Cardiovascular Magnetic Resonance Scan
If you decide that you do not want to have a CMR scan, it may be necessary to discuss other ways of looking at your heart. This could result in a delay in reaching your diagnosis and treatment.

Alternatives to Cardiovascular Magnetic Resonance (CMR)
If you feel you would rather not have a CMR scan, there are alternative ways of looking at the heart. However, other methods may not be able to provide exactly the same information as a CMR scan and will have their own risks. If you would like to discuss alternatives to a CMR scan, you may speak to your consultant or your general practitioner (GP).

Any questions:
If you have any questions, please do not hesitate to ask any member of staff