# LIFE THREATENING HAEMOPTYSIS:

# A CLINICAL AND RADIOLOGICAL STUDY

by

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**DECLARATION**

This thesis represents original work by the author. Apart from assistance credited under Acknowledgements, it is based solely on my own unaided efforts.

This research was self funded and no sponsorship was obtained from any commercial company.

This work has not been submitted previously to the University of Natal or any other University.

Signed:.....

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## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **AFB** | ACID FAST BACILLI |
| **AIDS** | ACQUIRED IMMUNODEFICIENCY SYNDROME |
| **BAE** | BRONCHIAL ARTERY EMBOLIZATION |
| **C/S** | CULTURE AND SENSITIVITY |
| **CT** | COMPUTED TOMOGRAPHY |
| **ESR** | ERYTHROCYTE SEDIMENTATION RATE |
| **F** | FRENCH |
| **HB** | HAEMOGLOBIN |
| **HIV** | HUMAN IMMUNODEFICIENCY VIRUS |
| **hr** | HOUR |
| **HRCT** | HIGH RESOLUTION COMPUTED TOMOGRAPHY |
| **HU** | HOUNSFIELD UNIT |
| **MDR** | MULTI DRUG RESISTANCE |
| **PVA** | POLY VINYL ALCOHOL PARTICLES |
| **SD** | STANDARD DEVIATION |

## PUBLICATIONS

1. Pulmonary angiography and embolization for severe hemoptysis due to cavitatory tuberculosis S.Sanyika, P.Corr, D.Royston, D.Blyth. Cardiovascular & Interventional Radiology 1999;22:457-460.

2. Efficacy and cost effectiveness of bronchial arterial embolization for severe haemoptysis Corr P, Blyth D, Sanyika C, Royston D. S African Medical Journal 2001;91:861-864.

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**PRESENTATIONS**

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## DEDICATION

I dedicate this work to the memory of my parents whose love and encouragement have meant so much to me.

To my wife Dominique thank you for your love and understanding.

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## PREFACE

The study has been approved by the Ethics Committee of the Faculty of Health Sciences, Nelson R Mandela School of Medicine, University of Natal.

The research described in this thesis was performed in the Department of Radiology, University of Natal, under the supervision of Professor Umesh Lalloo.

**ABSTRACT**

The investigation and management of patients with life threatening haemoptysis is a common clinical problem in South African Hospitals. Establishing the aetiology and origin of the haemorrhage and treating these patients is both difficult and expensive in terms of human and financial resources. The purpose of this study was to identify common local aetiologies for severe haemoptysis, review the investigation and treatment of these patients at Wentworth Hospital, Durban and to formulate a plan of management. Retrospective and prospective studies of consecutive patients treated at Wentworth Hospital were performed. In the prospective study a new embolic material gelatin linked acryl microspheres (embospheres) was used for bronchial artery embolization (BAE).

The study demonstrated a change in the spectrum of aetiologies of haemoptysis, from bronchiectasis following tuberculosis to destructive pneumonias. The chest radiograph was always the initial imaging investigation but was found to be inaccurate in detecting the origin of the bleeding. High resolution computed tomography of the lungs (HRCT) was the single best investigation to detect the cause and origin of the haemoptysis. HRCT detected focal bronchiectasis and intracavitatory aspergillomas that were undetected on the chest radiograph. Pleural thickening detected on CT was a good indicator

of the presence of transpleural collaterals. The major limitation with HRCT was that it could not be performed if the patient was too dyspnoeic to co-operate during the scan.

The role of bronchoscopy appears limited in patients with severe haemoptysis to those patients who are potential surgical candidates. I found that bronchoscopy was not accurate in detecting the source of bleeding in the few patients in which it was performed. Bronchial arteriography remains the gold standard in the detecting the source of haemorrhage. Bleeding sites were detected on angiography in the presence of focal hypervascularity, neovascularity and the presence of broncho-pulmonary shunts. Bronchial arteries were hypertrophied in bronchiectasis but were normal in size in some patients who had acute pneumonias.

Bronchial artery embolization was the treatment of choice for severe haemoptysis in the patients studied. The use of gelatin cross linked microspheres has significantly improved the initial success rate following the procedure with less complications compared to the use of polyvinyl alcohol particles (PVA). It is important to identify systemic transpleural collaterals at arteriography and to embolize them to reduce recurrent haemoptysis. Patients with aspergillomas responded well to embolization. Recurrent haemoptysis remains the major limitation of BAE but is reduced with the use of microspheres as embolic agents and thorough embolization of systemic

collaterals on the affected side. Surgical resection was an option for a limited number of patients with focal disease in one lung and good respiratory reserve.

The major limitation of the study was the absence of long term follow up to detect those patients with late recurrent haemoptysis.

# CHAPTER 1

# INTRODUCTION

## 1.1 The Problem of Life Threatening haemoptysis

Life threatening haemoptysis is defined as the expectoration of 300mls of blood or more in a 24 hours period (White, 1999). Life threatening haemoptysis is a common medical emergency in developing countries (Abal, 2001). This is an especially common cause of morbidity and mortality in South African patients (Knott-Craig,et al, 1993). Untreated, life threatening haemoptysis has a mortality that ranges from 50 to 80% (Yoon, 2002). Haemoptysis can be life threatening as haemorrhage into the alveolar air spaces interferes with gas exchange and oxygen transfer into the blood. The causes of haemoptysis as described in the literature are extensive, however in South African patients bronchiectasis and destructive lung disease from tuberculosis, are the main causes (Knott-Craig et al, 1993). Acute pulmonary disease, especially in HIV positive patients, is becoming an important cause of life threatening haemoptysis in South African patients. The prevalence of acute destructive pulmonary disease in AIDS patients and underlying pathology in these patients has not been clearly established locally. This is due to the lack of pathological material from AIDS patients, as autopsies are not routinely performed.

The treatment of patients with life threatening haemoptysis depends on the

cause, extent of pulmonary disease, and severity of haemoptysis (Yoon, 2002). Current treatments that are available include: medical therapy, surgical resection and or bronchial artery embolization (BAE). The majority of South African patients are unsuitable for surgical resection of the bleeding lesion because the disease is often bilateral and they have poor pulmonary reserves (Knott-Craig et al. 1993). Bronchial artery embolization with medical therapy has been used extensively at Wentworth Hospital over the last 10 years to treat patients because surgery in patients with bilateral pulmonary disease and or pulmonary insufficiency is precluded (Corr et al. 2001). Although bronchial artery embolization has been described in the literature as a palliative or temporising treatment, bronchial artery embolization is used locally with medical therapy as a definitive treatment (Corr et al. 2001). This trend towards using BAE as a definitive treatment for haemoptysis in surgically untreatable patients appears to be receiving wide support amongst chest physicians (Haponik et al, 2000). One of the unresolved issues that needs to be addressed is the problem of recurrent haemoptysis which is recorded in up to 50% of patients at one year post BAE (White, Jr. 1999). Recurrence is typically bimodal, with the first peak within the first 30 days due to incomplete embolization of bronchial and systemic arterial collaterals and the second peak within the first year after embolization from recurrence of the underlying pathology. We do not really know the patient outcome following treatment locally as the follow up of patients suffering from haemoptysis is very short as many patients are lost to follow up.

### 1.2 Problems that Need to be Addressed

1. Which patients require urgent treatment and high care?
2. How to investigate patients in the most time and cost effective method to localise the origin of the bleeding most effectively?
3. How to determine the underlying pulmonary disease most effectively?
4. How to treat these patients to achieve the best outcome?
5. How to solve the problem of recurrent haemoptysis?

### 1.3 The aims of this study are:

a. To retrospectively review the case records and imaging of patients treated for massive haemoptysis at Wentworth Hospital to determine the current local aetiologies of life threatening haemoptysis, diagnostic work up and management of these patients.

b. To prospectively assess the efficacy of bronchial artery embolization using a new embolic material: gelatin cross linked acryl microspheres (Embospheres) as a treatment option in patients admitted to Wentworth Hospital with massive haemoptysis from January 2002 to February 2003.

c. To produce a treatment plan or algorithm to manage these patients more effectively in the future.

# CHAPTER TWO

# LITERATURE REVIEW

## 2.1 Definition

Massive or severe haemoptysis is described by most authors to be the production of more than 300mls of expectorated blood over a 24 hour period (Jean-Baptiste 2000;Marshall et al 1997). Various volumes of blood have been used in definitions, ranging from 100 to 1000mls over 24 hours have been used to describe massive or severe haemoptysis in the literature. Often a true reflection of the volume of the haemoptysis is not made as a significant volume of blood may remain within the bronchial tree and may not be expectorated (Wong et al. 2002). However what is probably more important is the ability of the patient to maintain a patent airway in the presence of on going pulmonary haemorrhage (Deffebach et al. 1987). Even a small haemoptysis can be life-threatening condition. A better description would actually be **life threatening haemoptysis** such that a decision to actively treat the patient is made (Yoon et al. 2002).

## 2.2 Aetiology of Life Threatening Haemoptysis

The aetiology varies depending on whether the patient is from the developed or developing world (Abal, Nair et al 2001;Syabbalo 1991). In the developed world, the most common cause is from bronchiectasis from cystic fibrosis,

followed by carcinoma of the bronchus (Brinson et al. 1998;Cipolli et al. 1995). In the developing world, the most common cause of haemoptysis is bronchiectasis from pulmonary tuberculosis, childhood measles and pertussis followed by intracavitatory aspergillomas (Abal, Nair et al 2001;Barker 2002). In South Africa, the prevalence of pulmonary tuberculosis is one of the highest in the world. There are an estimated 2 million adults co-infected with tuberculosis and HIV (Corbett et al. 2003). A recent investigation of HIV prevalence among adult medical inpatients in a Durban tertiary care hospital found 54% of patients were HIV positive, of whom 84% had AIDS (Acquired Immunodeficiency Syndrome) (Colvin et al. 2001).

The spectrum of aetiologies of life threatening haemoptysis appears to be changing, in that acute destructive pneumonias in patients who have the Acquired Immunodeficiency Syndrome (AIDS), is now a common cause of life threatening haemoptysis. This has surpassed bronchiectasis as the main cause for severe haemoptysis in the KwaZulu Natal region of South Africa (Corr et al. 2001). This is due to an increased prevalence of HIV infection in the population and the rapid coinfection with pulmonary tuberculosis in HIV positive patients.

## 2.3 Pathophysiology of Haemoptysis

The actual origin of life threatening haemoptysis is from the bronchial arteries

in more than 90% of patients (Uflacker et al. 1983;Uflacker et al. 1985). In only about 5% of patients the origin of bleeding is from the pulmonary circulation. In the remaining 5% of patients the bleeding may originate from the aorta from an aorto-bronchial fistula or from the systemic arterial supply to the lungs (Yoon et al. 2002).

The bronchial circulation has a marked ability to proliferate and undergo angiogenesis in response to chronic lung infection, pulmonary vascular occlusion and the presence of lung tumours (Charan et al. 1997). In patients with pulmonary disease the pulmonary blood flow is often reduced or occluded at the arteriolar level because of hypoxic vasoconstriction, thrombosis or vasculitis (Yoon et al. 2002). New bronchial vessels formed by angiogenesis can be detected within 5 days of occlusion of pulmonary blood flow in the rat model (Charan et al, 1997). Lung inflammation causes the accumulation of macrophages and neutrophils. Activated macrophages promote angiogenesis by producing tumour necrosis factor alpha, basic fibroblast factor growth factor and tumour necrosis factor beta (Carmeliet 2003). Neutrophils produce interleukin-8 II in the presence of infection. All these factors promote endothelial activity and angiogenesis in the bronchial vasculature (Carmeliet 2003;Charan et al. 1997) In chronic inflammation such as bronchiectasis, there is a marked increase in the bronchial circulation from a normal 1% of cardiac output up to 35% of cardiac output (Nakamura et al. 1968). This increased bronchial blood flow has a significant haemodynamic effect. The increased bronchial arterial blood flow is at systemic arterial pressures and systemic

arterial oxygen saturation draining into the pulmonary circulation via enlarged bronchopulmonary anastomoses.

Enlargement of bronchial arteries in pulmonary tuberculosis was first observed by Guillot in 1845 (Guillot et al.1845). The new bronchial vessels will supply a focal area of inflammation and are often fragile and will therefore easily rupture with resultant haemorrhage and haemoptysis (Yoon et al.2002). Transpleural collaterals from the intercostals, internal thoracic and inferior phrenic arteries enlarge to supply the parietal pleura (Wong, Szkup et al 2002;Yu-Tang et al. 2002). These collaterals enter the pulmonary lesions through pleural adhesions.

The capacity for the bronchial arterial tree to proliferate by angiogenesis and enlarge in response to inflammation, neoplasia and pulmonary vascular obstruction is unique and is not seen in the pulmonary arterial circulation (Uflacker et al. 1985, Deffebach et al, 1987). In chronic bronchiectasis the bronchial arteries enlarge significantly while in patients with acute destructive lung disease bronchial arteries are often normal in size proximally (Cipolli et al. 1995).

In patients with tuberculosis, pulmonary artery aneurysms are an uncommon but underdiagnosed cause of massive haemoptysis (Sanyika et al. 1999). The reason for this is that pulmonary angiography has never been a routine investigation in the diagnostic work of a patient with massive haemoptysis

(Wong et al. 2002). The pulmonary aneurysms or Rasmussen aneurysms are inflammatory aneurysms of peripheral branches of the pulmonary artery within the wall of tuberculous cavities. Haemorrhage is recurrent and massive. These aneurysms can be treated by pulmonary artery embolization (Patankar et al. 2000;Remy et al. 1980;Santelli et al. 1994).

## 2.4 Vascular Anatomy

### 2.4.1 Bronchial Artery Anatomy

Normally there are four bronchial arteries arising from the descending thoracic aorta at the level of the fourth thoracic vertebra adjacent to the carina and origin of the left main bronchus (Yoon et al. 2002). However the anatomy can be very variable in terms of origin, branching pattern, and course.

A common trunk from the aorta is not uncommon but its true prevalence is unknown.

Cauldwell et al reported four main branching patterns after performing post mortem dissections on 150 cadavers **(figure 1)** (Cauldwell et al. 1948):

Figure 1: Cauldwell EW, Siekert RG, Lininger RE, Anson BJ. The bronchial arteries: an anatomic study of 150 cadavers. Surg Gynaecol Obstet 1948;86:395-412.

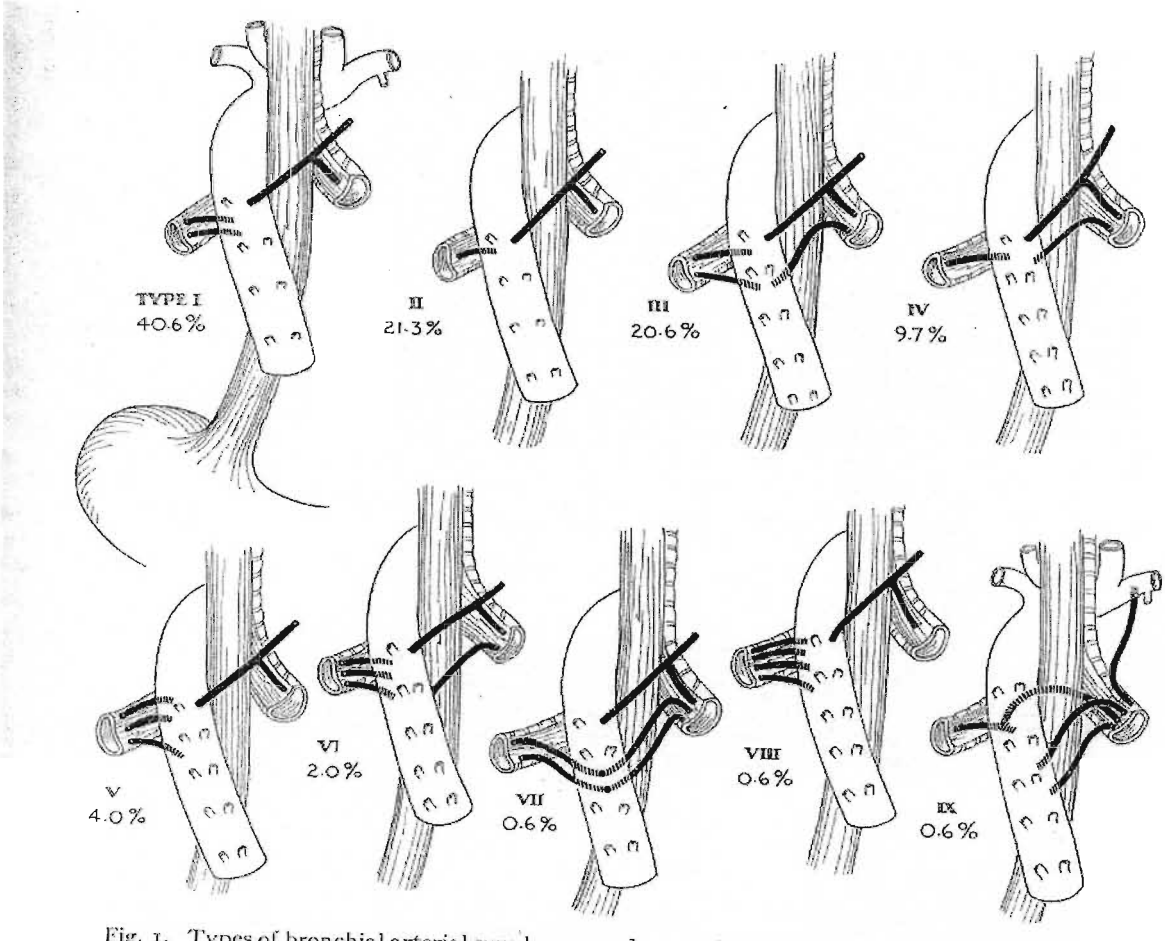



Fig. 1. Types of bronchial arterial supply, 150 cadavers; classification based upon origin, number, and course of the vessels. Semidiagrammatic; dorsal aspect.

**Type I:** two bronchial arteries on the left and one on the right that presents as an intercostobronchial trunk (ICBT) in 40% patients

**Type II:** one bronchial artery on the left and one ICBT on the right in 21% of patients

**Type III**: two bronchial arteries on the left and two arteries on the right (one ICBT and one bronchial artery) in 20% of patients

**Type IV**: one bronchial artery on the left and two on the right (one ICBT and one bronchial artery) in 9.7% of patients.

Botenga described the bronchial artery anatomy using selective arteriography as follows (Botenga SAJ 1970):

**Type I**: two bronchial arteries on the left and one ICBT on the right in 28% of patients.

**Type II**: one bronchial artery on the left and one ICBT on the right in17% of patients.

**Type III**: one bronchial artery one the left, one bronchial common trunk, and one ICBT on the right in 17% of patients.

**Type IV**: two bronchial arteries on the left, one bronchial artery on the right, and an ICBT on the right in 11% of patients.

**Type V**: one bronchial artery on the left, one on the right, and an ICBT on the right in 8.5% of patients.

**Type VI**: one common bronchial trunk to the left and right and one ICBT in 8.5% of patients.

**Type VII**: one bronchial common trunk to the left and to the right in 4.3% of patients.

Work performed by Uflacker et al. 1985 demonstrated that the intercostobronchial trunk (ICBT) was a constant artery in almost all of their 75 patients supplying the right upper lobe bronchus **(figure 2)**. He found that bronchial arteries arising from a common trunk from the aorta to be very common, in 43% of patients, the same as in Botenga's series. His angiographic study was very similar to the anatomy described Botenga and different from the dissection study of Cauldwell et al **(figure 3).**

**Figure 2: Uflacker, R., Kaemmerer, A., Picon, P. D., Rizzon, C. F., Neves, C. M., Oliveira, E. S., Oliveira, M. E., Azevedo, S. N., & Ossanai, R. 1985, "Bronchial artery embolization in the management of hemoptysis: technical aspects and long-term results", *Radiology*, vol. 157, no. 3, pp. 637-644.**

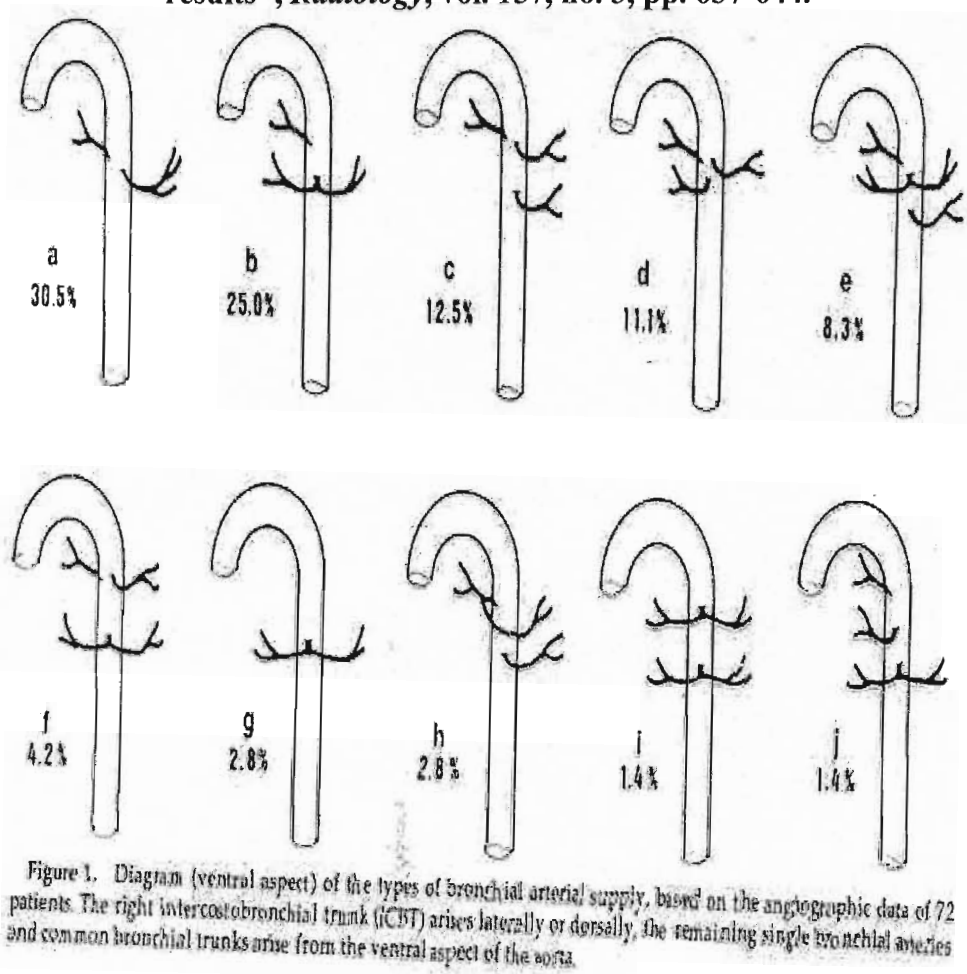
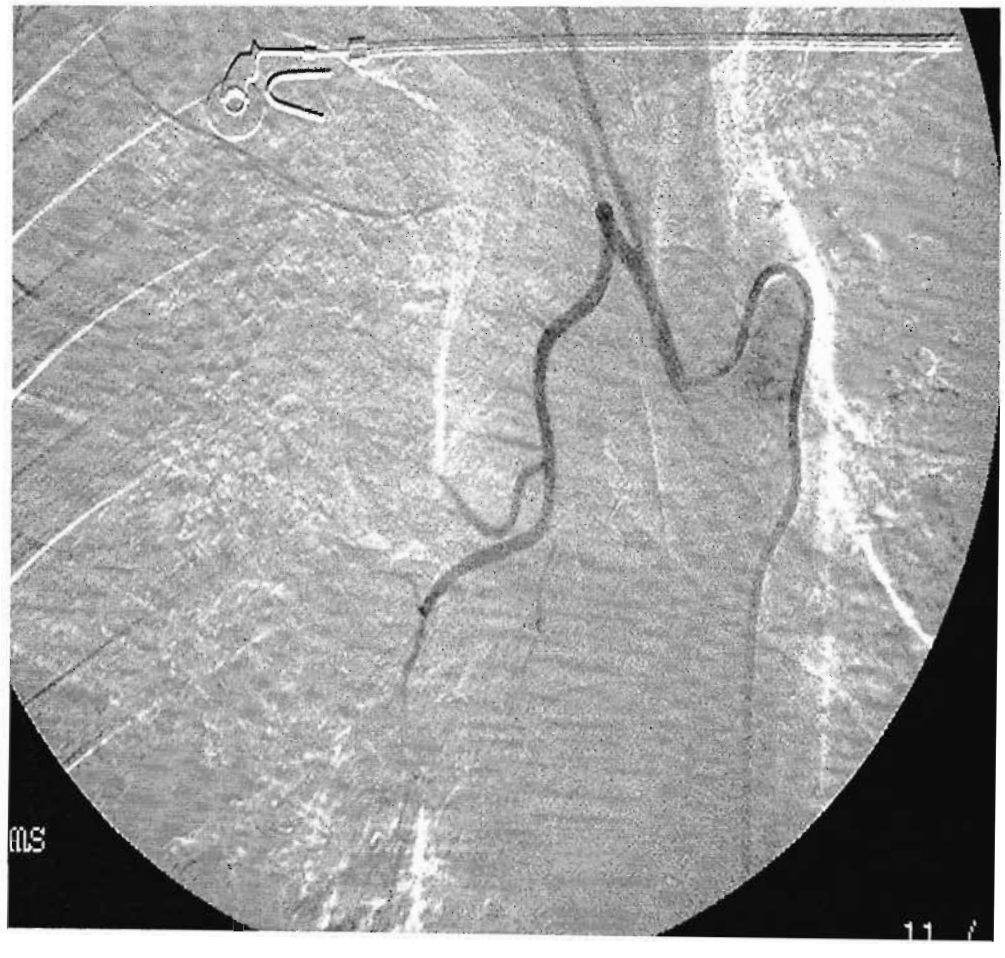



Figure 1. Diagram (ventral aspect) of the types of bronchial arterial supply, based on the angiographic data of 72 patients. The right intercostobronchial trunk (ICBT) arises laterally or dorsally, the remaining single bronchial arteries and common bronchial trunks arise from the ventral aspect of the aorta.

Figure 3: Normal Intercosto-bronchial trunk (ICBT) on selective bronchial arteriography



Liebow found that 43% of all right bronchial arteries were of intercostal origin usually from the first right intercostal artery, while 84% of left bronchial arteries arise directly from the aorta (Liebow 1965).

Bronchial arteries supply the trachea, the extra and intra pulmonary bronchi, the bronchovascular bundles, nerves, regional lymph nodes, the visceral pleura, oesophagus and vasa vasorum of the aorta, pulmonary artery and vein (Deffebach et al. 1987). The bronchial arteries enter the lungs through the hila and divide on reaching the main stem bronchus on each side in the peribronchial connective tissue and then follow the bronchial tree and airways as far as the terminal bronchioles. The branches freely anastomose with each other forming a vascular plexus in the peribronchial space. The arterioles also penetrate the wall to supply the bronchial mucosa and to form a submucosal plexus. Therefore there is both a peribronchial and submucosal plexus along the entire bronchial tree down to the terminal bronchioles. These vascular plexuses anastomose with the pulmonary microcirculation (Deffebach et al.1987). Some bronchial artery branches form anastomoses with pulmonary arterioles producing so called bronchopulmonary arteries. These are present in neonates but less commonly detected in adults (Wagenvoort & Wagenvoort 1967). The anastomoses appear coiled because of their spiral muscles and probably control arterial pressure between the bronchial and pulmonary circulations. Bronchial veins drain the proximal tracheobronchial tree for the first 3 subdivisions into the azygous and hemiazygous veins. The intrapulmonary bronchial venous flow is into the pulmonary circulation.

Bronchial arteries that originate outside the area between T5 and T6 vertebral levels are considered to be anomalous (Yoon et al, 2002). The reported prevalence of anomalous origins ranges from 8.3% to 35% (Cohen et al. 1990; Sancho et al. 1998). These bronchial arteries may arise from the aortic arch, internal thoracic artery, thyrocervical trunk, subclavian artery, costocervical trunk, brachiocephalic artery, pericardophrenic artery, inferior phrenic artery or abdominal aorta (Yoon et al. 2002). Most anomalous bronchial arteries originate from the aortic arch (Sancho et al. 1998). These arteries can be differentiated from systemic pleural collaterals in that they follow the bronchi into the lung while systemic collaterals enter the lung through the pleura or pulmonary ligament (Sancho et al 1998).The importance of these arteries is that they may be the cause of haemorrhage and be missed at angiography with the bleeding remaining undetected (McPherson et al. 1990).

The bronchial arteries normally measure 1.5mm in diameter at their origin in adults and 0.5mm at their point of entry into a broncho-pulmonary segment (Deffebach et al. 1987). A bronchial artery that measures more than 2mm in diameter at its origin on CT is most likely to be abnormal (Furuse et al. 1987). The bronchial arteries enlarge especially following chronic pulmonary infection such as bronchiectasis. Enlarged bronchial arteries may be detected on contrast enhanced CT of the mediastinum as tubular structures in the retro oesophageal and retro tracheal regions, the retrocarinal region and the azygo oesophageal window (Song et al. 1998). The enlarged bronchial arteries are often mistaken for mediastinal lymph nodes, an azygous vein or the oesophageal wall (Song et al.

1998).

### 2.4.2 Non Bronchial Systemic Arteries

The parietal pleural is supplied by systemic artery branches while the visceral pleura is supplied by the bronchial arteries. Systemic artery collaterals are an important source of bleeding in patients with pleural disease, especially tuberculosis. If the systemic collaterals are missed at the initial angiogram and only the bronchial arteries embolized, the patient may experience recurrent haemoptysis. An extensive search for systemic collaterals at angiography is necessary (Marshall et al. 1997). The most common arteries involved are: intercostals arteries, branches of subclavian and axillary arteries, internal mammary artery and inferior phrenic artery. They all supply the pleura and become enlarged and send collaterals out in the presence of a pulmonary inflammatory lesion adjacent to the pleura. The presence of pleural thickening on the chest radiograph suggests pleural collateral vessels (Tamura et al. 1993). Pleural thickening exceeding 3mm and the presence of enhancing vascular structures in the sub-pleural fat on CT have been found to be accurate indicators of the presence of systemic transpleural collaterals (Yoon et al. 2003).

## 2.5 Clinical Diagnosis

The diagnostic work up is to establish the cause and origin of the bleeding within the lungs. Investigations include chest radiography, bronchoscopy and high-resolution computed tomography of the chest and lungs (HRCT).

### 2.5.1 Chest Radiograph

A chest radiograph is the first investigation in a patient presenting with haemoptysis. The chest radiograph may demonstrate pneumonia, tuberculosis, pulmonary neoplasm, aspergillomas or lung abscess (Naidich et al. 1990). However the diagnosis and interpretation of chest pathology can be difficult in the presence of bilateral pulmonary disease. The chest radiograph is insensitive in detecting the cause of haemoptysis in 17-81% of all patients reported in the literature (Hsiao et al. 2001).

### 2.5.2 Bronchoscopy

Fibreoptic bronchoscopy is often considered to be the primary investigation to detect the cause and site of bronchial bleeding, especially to determine which lung the bleeding is originating (Jean-Baptiste 2000). The diagnostic accuracy of fibreoptic bronchoscopy in patients with haemoptysis is between 10% and 43%. The role of bronchoscopy when the chest radiograph is normal or non-localising is controversial as the diagnostic accuracy is low varying from 0-31% of patients

(Marshall et al 1996). Hsaio in a prospective study found that bronchoscopy is unnecessary prior to embolization if the chest radiographs can lateralize the bleeding origin to the left or right lung (Hsiao et al. 2001). Performing bronchoscopy in patients with massive haemoptysis is difficult and can cause the patient to become more restless and hypoxic (Jean-Baptiste 2000). A major problem with fibreoptic bronchoscopy is the inability to suction large amounts of blood adequately during the procedure. This makes fibreoptic bronchoscopy potentially dangerous during life threatening haemoptysis.

### 2.5.3 Chest Computed Tomography (CT)

CT of the chest has been demonstrated to be of considerable benefit in detecting the cause and origin of haemoptysis (McGuinness et al. 1994;Naidich et al 1995). CT can detect lesions not detected on chest radiographs. CT can suggest a specific diagnosis in 39-88% of patients in whom the chest radiographs were considered non diagnostic and in 50% patients of patients in whom the fibreoptic bronchoscopy findings were considered non diagnostic (Millar et al. 1992). However the interpretation of CT findings may be difficult in the presence of bilateral pulmonary disease. CT can also localize the site of bleeding in 63%-100% of patients with haemoptysis, which is much higher than bronchoscopy or chest radiographs (Marshall et al. 1996). Most researchers now believe that CT should be performed before fibreoptic bronchoscopy in all patients with massive haemoptysis to localize the site of bleeding (Hsiao et al.2001, Marshall et al.1996). Modern CT has the advantage that it is non invasive and fast and is

therefore a suitable investigation for critically ill patients. Yoon et al. 2003 in a prospective study of 27 patients has reported that enlarged bronchial and systemic arteries may be detected on modern spiral CT with intravenous contrast enhancement in 67% of patients with massive or life threatening haemoptysis.

## 2.6 Management of Life Threatening Haemoptysis

The management of life threatening haemoptysis is a medical emergency (Johnson 2002; Knott-Craig et al. 1993; Nath 1990). Patients are often debilitated with compromised respiratory reserve. Untreated, the patient with life threatening haemoptysis has a mortality rate varying from 58% to 80% depending on the rate of bleeding and the presence or absence of pulmonary malignancy (Najarian et al. 1998). Patients who bleed more than 1000mls per 24 hours are especially at risk of dying (Deffebach et al.1987). Therefore a well-coordinated management plan is necessary for a successful outcome following massive haemoptysis (Jean-Bapiste 2000).

Conservative treatment may have a role in certain rare causes such as Goodpasture's syndrome or coagulopathies where there is no focal pulmonary or bronchial lesion present. Knott Craig et al in the largest series reported from South Africa emphasise the point that unless the source of bleeding is identified and treated definitively during hospital stay the patient is at significant risk of recurrent haemorrhage. The risk of dying was 36.4% in their series, of which 45%

of these patients died from their recurrent haemoptysis (Knott-Craig et al. 1993). The patient with life threatening haemoptysis requires admission to a high care ward, resuscitation with intravenous fluids, cross match for blood and possible blood transfusion. Intravenous antibiotics are necessary if a lung abscess or destructive pneumonia is suspected. Careful monitoring of arterial $pO_2$ is mandatory as patients rapidly become hypoxaemic after a life threatening haemoptysis. Loss of 400mls of blood into the alveolar air spaces is all that is required to reduce $O_2$ transfer (Jean-Bapiste 2000). Blood in the bronchial tree also causes obstruction of the airways resulting in suffocation. Oxygen by nasal prongs and or ventilation may be necessary if there is hypoxaemia.

Once the patient is stabilised the treatment options are:

### 2.6.1 Bronchoscopy and Endobronchial Treatment

Hiebert in 1974 introduced endobronchial iced saline lavage and balloon catheter endobronchial tamponade (Gottlieb et al 1975;Jolliet et al 1992). He used a Foley catheter, which can only pass through a rigid bronchoscope to tamponade the affected bronchus. Newer 6F balloon catheters have been used through a flexible bronchoscope with promising results (Freitag 1993;Freitag et al. 1994). Fibrin products and laser photocoagulation have been reported as case reports with limited success (Morell et al. 1995;Tsukamoto et al 1989). In all of these endobronchial procedures a high degree of operator skill is required while

working on an ill patient who is dyspnoeic.

### 2.6.2 Surgery

Lobectomy or pneumonectomy were previously considered the treatment of choice once the bleeding site had been identified (Garzon et al 1978). However today surgery is one of a number of management choices. The surgical mortality rate, defined as death within 7 days of the operation, is reported in the literature between 1% and 50% (Corey et al 1987). Indications for surgery vary from series to series, however if a remediable surgical lesion can be detected, resection remains a good option. Contraindications for resection are poor respiratory reserve, bilateral pulmonary disease and inability to accurately localise the origin of the bleeding. Timing of surgical resection is critical according to Knott Craig et al. Patients undergoing emergency resection in the presence of active bleeding have a very high mortality. Postponing resection for 5 to 10 days after life threatening haemoptysis allows the airspace to clear the haemorrhage and pulmonary reserve to recover (Knott-Craig et al. 1983). Here bronchial artery embolization is used as a temporising procedure to prevent recurrent haemoptysis while the patient recovers sufficient pulmonary reserve to be fit enough for a surgical resection.

### 2.6.3 Bronchial Artery Embolization

#### a. History

Bronchial angiography was first described by Viamonte et al in 1964 (Viamonte et al. 1964 and 1965). Remy in France in 1973 described the first use of bronchial artery embolization (BAE) to treat severe haemoptysis in a large series of 45 patients (Remy et al. 1977). He used steel coils and cyano-acrylic glue as embolic agents. Uflacker et al from Brazil subsequently reported two series of patients treated by BAE, the first series in 1983 and a second series in 1985 (Uflacker et al. 1983 and 1985). He used steel coils and cyanoacrylate glue as the embolic agents. Most of their patients suffered from chronic bronchiectasis or cavitatory aspergillomas. Haemoptysis stopped in 82% and 77% of patients respectively. However there was a high recurrence of haemoptysis in 18% and 21% of patients respectively. He noted that there was an especially high recurrence rate from patients who had pulmonary aspergillomas. There were no serious complications from the procedure. Uflacker commented that BAE is an effective way to control life threatening haemoptysis with a low recurrence rate and reduced mortality among severely ill patients (Uflacker et al, 1985). BAE has been successfully used to treat haemoptysis from pulmonary infection including mycetomas, bleeding primary bronchial and metastatic cancers and bronchiectasis following cystic fibrosis (Akiyama et al. 1995;Antonelli et al. 2002;Hirshberg et al. 1997;Judson & Stevens 2001). Today BAE is regarded as the preferred initial treatment for life threatening haemoptysis when radiologists with interventional skills and equipment are available (Johnson 2002).

**b. Technique**

A standard Seldinger technique is used to access the femoral artery as in conventional femoral arteriography. A femoral artery sheath is placed in the femoral artery. Some radiologists prefer to demonstrate the number and origin of the bronchial arteries by performing a preliminary descending thoracic aortogram using a 5 French pig tail catheter (Phillips et al 2000). The advantage of this step is to detect any anomalous origins of the bronchial arteries and any systemic arteries causing the bleeding. Normally standard 5 French catheters are used for selection of the bronchial artery origins (Mikaelson catheter) although some authors routinely used a microcatheter. The advantage of using a microcatheter is that the catheter position is stable and safe for embolization and the catheter end hole is situated distal to any spinal cord branches thus preventing inadvertent spinal cord embolization (Marshall et al. 1997;Tanaka et al. 1997). After superselective catheterisation of the bronchial artery a hand injection of 2-5mls of iodine containing low osmolar contrast medium (300mg I/ml) is performed to produce a bronchial angiogram. Active contrast extravasation from the bleeding site is rarely detected. This sign occurs in only 3.6% to 10.7% of patients in the reported series (Keller et al. 1987;Ramakantan et al. 1996). Angiographic findings of bronchial artery bleeding include: hypertrophied bronchial arteries, neovascularity, hypervascularity, broncho-pulmonary shunts and rarely bronchial artery aneurysms (Yoon et al. 2002). The decision on which arteries to embolize is based on the presence of positive angiographic signs, the CT findings, chest radiographic and bronchoscopic findings (Yoon et al.2002).

Many different embolic materials have been tried in BAE. The ideal agent is a material that flows freely in the catheter but solidifies relatively rapidly once deposited in the artery. The embolic material must not solidify too fast so that the material can reach the bronchial arterioles and the bleeding lesion. It is critically important that the occlusion of the artery is permanent to prevent recurrent bleeding. The material must be sufficiently large not to pass through the broncho-pulmonary anastomoses. These anastomoses measure 325 microns in diameter in humans (Deffebach et al. 1987). If smaller particles are used pulmonary infarction may occur as the material occludes segmental pulmonary arteries (Pump 1972). It is also important to prevent the particles travelling distally into those branches supplying the oesophagus, bronchial wall, the vasa vasora of pulmonary arteries and aorta. Embolization of these branches may lead to wall necrosis (Marshall et al. 1997). The best particle size is between 500 - 750 microns in diameter. This is because the particles are too big to pass through the normal bronchopulmonary anastomoses. Initially gelatin sponge was used. However its lack of radio opacity and its temporary occlusive properties meant that re-canalisation of arteries and recurrent bleeding was a problem. Liquid materials such as isobutyl-2-cyanoacrylate were also used initially but there is a high risk of tissue necrosis because of capillary occlusion. Steel and platinum coils have also been used. Although providing permanent vessel occlusion, they only occlude the proximal artery thus allowing collateral vessels to feed the distal patent bronchial artery. This results in recurrent haemoptysis. Poly-vinyl alcohol particles are non-absorbable particles of the correct diameter and are probably the most common embolic material used today for BAE (Yoon et al 2002). PVA particles induce

marked thrombosis of the vessel but often only cause proximal occlusion of the vessel. This is thought to be due to the irregular size and shape of the particles.

Gelatin cross linked acryl microspheres (registered name: Embospheres) have shown promise in the embolisation of uterine fibroids, head and neck tumours and meningiomas (Bendszus et al. 2000;Pelage et al. 2003). These microspheres are spherical porous beads made from an acrylic co-polymer, which is cross-linked to gelatin. This means that they are of a precise size and are hydrophilic and do not clump together while in solution before delivery through the catheter. These particles are easy to deploy, have good radio opacity and result in a permanent occlusion of the artery. Microspheres are well tolerated by patients (Beaujeux et al. 1996;Laurent et al. 1996). These particles have not yet been used for BAE in a large series but their superior occlusive ability and good patient tolerance suggest they would be an ideal embolic material for BAE.

## 2.7 Results of Bronchial Artery Embolization

Bronchial artery embolization is very effective in reducing and even stopping life threatening haemoptysis in the acute emergency admission. BAE is successful in 73% to 98% of patients in the reported series with a mean follow up from 1 day to 1 month (Hayakawa et al. 1992;Jean-Baptiste 2000;Kato et al. 2000;Ramakantan et al. 1996;Remy et al. 1977;Uflacker et al. 1985). Long-term success rate is much lower and is reported to be from 10% to 70% in the literature with a follow up

ranging from 1 month to 46 months. Results are shown in **table 1**. Short term results in the first 30 days post procedure have improved with better techniques such as the use of microcatheters (White, Jr. 1999). Longer term results up to 1 to 2 years post procedure are more difficult to analyse because of a lack of consistent reporting or agreement about terms such as technical success or recurrence (White, Jr. 1999). Recurrence of haemoptysis is typically bimodal. The initial peak is 1 to 2 months post procedure and the second peak is 1 to 2 years post BAE (White, Jr. 1999). The initial peak of recurrence is due to incomplete bronchial artery embolization or the presence of transpleural collaterals while the second later peak is due to the recurrence of the initial vascular pathology.

The success rate can be improved if the BAE is repeated and systemic collaterals or pulmonary causes for the bleeding such as Rasmussen aneurysms can be identified and treated (Kato et al 2000). Haemoptysis will recur if the underlying pulmonary disease such as tuberculosis is not treated. Therefore in the past BAE has always been considered a palliative or temporising procedure that prepares the patient for elective surgical resection of localised disease or continued medical therapy with antibiotics or anti TB drugs.

### 2.8 Complications of Bronchial Artery Embolization

A number of complications following BAE have been reported. Chest pain immediately after the procedure is common with a reported prevalence of 24% to 91% of patients (Cohen et al. 1990;Ramakantan et al. 1996;Yoon et al. 2002).

Chest pain is probably caused by ischaemia to the pleura and is very transient lasting a few hours. The pain can usually be controlled with oral analgesics. Dysphagia is uncommon occurring in 0.7% to 18.2% of patients and usually resolves spontaneously. Dissection of the bronchial artery during catheter manipulation has been reported but is generally asymptomatic (Yoon et al. 2002).

Spinal cord ischaemia and infarction is very rare but can be clinically disastrous with the patient developing paraparesis or quadraparesis. The prevalence of this complication recorded in the literature is from 1.4% to 6.5% (Yoon et al. 2002). This is due to inadvertent embolization of spinal cord radicular arteries that arise from intercostals arteries or the ICBT (Cheng et al. 1996;Ramakantan et al. 1996;Tanaka et al. 1997;Wong et al. 2002). Often spinal cord branches are not detected on the initial selective bronchial or intercostals arteriogram. As the embolization proceeds and distal bronchial artery branches are occluded, reflux of embolic particles into undetected spinal cord branches occurs (Kardjiev et al. 1974;Najarian et al. 1998). As a rule if the anterior spinal artery is visualised at selective bronchial or intercostals angiography, embolization should not be attempted because of the risk of spinal cord ischaemia. The use of microcatheters will reduce the risk of spinal cord embolization by placing the catheter tip super selectively in the bronchial artery beyond the spinal cord branch (Tanaka et al. 1997).

Less common complications reported include: bronchial wall necrosis, aortic wall necrosis, broncho-oesophageal fistula and transient cortical blindness (Liu et al.

1998). These complications occur because of distal embolization of bronchial artery branches to the oesophagus and aortic wall.

**Table 1: Bronchial Artery Embolization Outcomes Reported in the Literature 1977-2002**

| Reference | Year | Number starting | Number completed (%) | Technical & Immediate Success (%) | 30 days (%) | Long Term Follow Up (%) |
|---|---|---|---|---|---|---|
| (Remy, Arnaud, Fardou, Giraud, & Voisin 1977) | 1977 | 76 | 49/76 (65) | 41/76 (54) | 41/76 (54) | 35/76 (46% *2-18months)* |
| Uflacker et al.1985 | 1985 | 75 | 64/75 (81) | 49/75 (65) | NS | 39/75 (52% *1-47months, median 24 months)*) |
| (Rabkin et al. 1987) | 1987 | 306 | 278/306 (91) | 278/306 (91) | 239/306 (78) | 242/306 (79% *3-14 months*) |
| (Hayakawa, Tanaka, Torizuka, Mitsumori, Okuno, Matsui, Satoh, Fujiwara, & Misaki 1992) | 1992 | 70 | 63/70 (90) | NS | NS | 36/70 (51% *mean 22months, median 14months*) |
| (Cremaschi et al. 1993) | 1993 | 209 | 205/209 (98) | 205/209 (98) | NS | 172/209 (82% *12 months*) |
| (Ramakantan, Bandekar, Gandhi, Aulakh, & Deshmukh 1996c) | 1996 | 140 | 102/140 (73) | 102/140 (73) | 72/140 (51) | 94/140 (67%*at 6 months )* 19/140 *(13.5% at 14 months)* |
| (Tanaka et al. 1997a) | 1997 | 47 | 47/47 (100) | 47/47 (100) | 43/47 (91) | NS |
| (Fernando et al. 1998) | 1998 | 31 | 26/31 (84) | 26/31 (84) | 26/31 (84) | NS |
| Kato et al 2000 | 2000 | 101 | 100/101 | 94/100 (94) | 94 (94) | 77.7% *1 year,* 70% *3 years* |
| (Mal et al. 1999) | 1999 | 56 | 46/56 (82) | 43/56 (77) | 36/56 (64) | 39/56 (70% *3 months)* 25/56 (45% *13 months)*) |
| (Swanson et al. 2002) | 2002 | 54 | 51/54 (94) | 51/54 (94) | 46/54 (85) | 43/54 (80% *12 months*) |

NS not shown

30 days patients who have been successfully treated without any haemoptysis

>30 days patients who have been successfully treated without any haemoptysis

# CHAPTER 3

# PATIENTS AND METHODS

## 3.1 Retrospective Study

### 3.1.1 Patients

Consecutive patients admitted to Wentworth Hospital for life threatening haemoptysis from 1st January 1997 to 31st December 1998 were included in this study. All patients were referred to the Department of Thoracic Surgery as emergencies from King Edward VIII, Addington, R K Khan's Hospital and King George V Hospitals in the Durban Functional Region (DFR). These are the main secondary and tertiary level hospitals in the City of Durban. Wentworth Hospital is the only referral centre for cardiothoracic patients in the province of KwaZulu Natal, which has an estimated population of 9 million. This represents 20% of the total population of South Africa.

Patients were included in the study if their haemoptysis were equal to or exceeded 300mls over a 24-hour period immediately prior to admission to hospital. Patients were asked how much blood was coughed up in the previous 24 hours in terms of "tea cups" assuming the average tea cup contained 100mls of fluid (3 "cup fills").

All patients were assessed by a thoracic surgeon. The surgeon decided whether

to admit the patient to the high care ward and whether the patient required bronchial artery embolization to stop the bleeding.

The intention to treat by performing bronchial artery embolization was made in the presence of:

1. Life threatening haemoptysis equal to or greater than 300mls over 24 hours immediately prior to admission.
2. Unilateral or bilateral pulmonary disease on the chest radiograph and or computed tomography (CT).
3. Poor respiratory reserve.

Patients were managed conservatively if the haemoptysis was small <150mls per 24 hours and the patient was haemodynamically stable. All patients were treated with intravenous antibiotics and anti TB drug therapy if clinically indicated.

### 3.1.2 The following data was recorded:

a. Demographic information
b. Length of hospital stay
c. Aetiology of pulmonary pathology
d. Haemoglobin level and white cell count on admission
e. Sputum analysis for acid fast bacilli
f. HIV status

g. Bronchoscopy findings

h. Surgical procedures-lobectomy, pneumonectomy, open lung biopsy

i. Clinical outcomes-success or failure or death

**j.** Complications of procedures

The procedure was considered technically successful if catheterisation and embolization could be safely performed.

The clinical outcome was considered as successful if the haemoptysis stopped or markedly decreased within 24 hours of the procedure being performed.

Embolization was considered a failure if the haemoptysis continued after 24 hours of the procedure or a surgical procedure such as lobectomy or pneumonectomy was performed to stop the haemorrhage.

### 3.1.3 Radiological studies assessed and recorded included:

a. Chest radiograph

b. HRCT chest

c. CT chest

d. Bronchial and systemic arteriography

### 3.1.4 Imaging Assessment

**a. Chest Radiograph**

All patients well enough had a frontal chest radiograph performed in the X ray department as an erect film. If the patient was too ill, a bedside unit supine radiograph was performed.

The following radiological signs were recorded:

Presence of pulmonary cavities

Masses within pulmonary cavities such as mycetomas or haematomas

Fluid level in pulmonary cavities

Infiltrates

Pulmonary opacification

Nodules

Masses

Lymphadenopathy

Possible origin of bleeding

**High Resolution CT Lungs (HRCT)**

HRCT was performed on some of the patients who were well enough to co-operate in this study. This was performed on the helical CT scanner Picker PQ

2000 at Wentworth Hospital. A 1mm slice width was used at 1 cm intervals using the bone algorithm of the scanner. The patient had to be able to co operate with suspended inspiration for a successful scan. Scans were photographed on the standard pulmonary window of 2000 HU and -700 HU level set by the scanner manufacturer.

**The following signs were recorded:**

Pulmonary cavities

Nodules

Alveolar opacification

Bronchiectasis

Mycetomas or intracavitatory haematomas

Possible origin of bleeding

**Definitions**

The following definitions, used in the detection of lung pathology using HRCT, are taken from High Resolution CT of the Lung by Webb, Muller and Naidich 1996.

**Pulmonary Cavity**

This is an air or air fluid containing area of destroyed lung with an irregular thickened wall (>5mm).

**Pulmonary Nodule**

A small nodular opacity varying in diameter from 1mm to 1cm. The opacity may be due to air-space opacification, peribronchial inflammation or interstitial granulomas or infiltrates.

**Alveolar Opacification**

Alveolar or air space opacification is the replacement of the air with the alveoli by oedema fluid, inflammatory exudate, cellular infiltrates or haemorrhage.

**Pneumonia**

Air space opacification with replacement of air within the alveoli by inflammatory exudates.

**Destructive Pneumonia**

Air space opacification with areas of breakdown within the opacification.

**Bronchiectasis**

Bronchiectasis was diagnosed according to the HRCT findings described by Webb, Muller and Naidich 1996.

**A**. Presence of bronchial dilatation. This occurs when the internal diameter of the affected bronchus is greater than the diameter of the adjacent pulmonary artery branch.

**B**. Bronchial wall thickening.

**C**. Visibility of peripheral bronchioles. Normally peripheral airways are invisible however the presence of peribronchial fibrosis and thickening make very small airways visible on HRCT.

**D**. Contour abnormalities. There is a lack of tapering of airways towards the periphery or a cluster of cysts with air fluid levels.

**E**. Fluid filled bronchi. Lobular or branching structures detected on HRCT due to mucus impaction.

**F**. Presence of atelectasis.

**Aspergillomas**

Fungal balls or mycetomas are diagnosed by the presence of:

**A**. Soft tissue density mass within a pulmonary cavity or cyst containing linear or branch intra-mass air density lucencies.

**B**. Mass moves position in the cavity on changing the patient's position while performing the CT scan from supine to prone.

**C**. Must be differentiated from intracavitatory haematomas, which do not have air lucencies and have blood densities.

**CT Chest**

This study was performed if the patient was too dyspnoeic to hold their breath during the scan for a high resolution CT of the lungs. Scans were performed on the Picker PQ 2000 CT scanner using 5mm slice width at 5mm intervals through the hilar regions. Scans were photographed on identical pulmonary windows and levels as with HRCT scans.

**The following signs were recorded:**

Cavities

Nodules

Alveolar opacification

Bronchiectasis

Mycetomas or intracavitatory haematomas

**Pleural Thickening**

The presence of pleural thickening >3mm thick has been demonstrated to be associated with significant transpleural systemic collaterals in inflammatory lung disease (Yoon et al 2003). Pleural thickness was assessed on the CT chest scans on soft tissue settings of 350 HU window and 40 HU level. Pleural thickening was measured tangential to the lung surface to the inner margin of the ribs.

**Arteriography**

Bronchial arteriography was performed on a Toshiba CASV 8000 angiography unit (Toshiba Inc, Japan) at Wentworth Hospital. The studies were performed by registrars (residents) from the Department of Radiology under the supervision of a consultant radiologist. Many procedures were performed as emergencies after hours or at weekends. A standard right femoral artery puncture was performed using the Seldinger technique. A 5 (F) French sheath was inserted into the femoral artery. Catheterisation of the bronchial arteries was performed using a 5F Mikaelson catheter. If the origin of the bronchial arteries could not be detected a pan-aortogram was performed with a long 5F

pigtail catheter in the aortic arch. Selective arteriography was performed with 5 ml of contrast medium containing nonionic iodine (iohexol 300mg Iodine/ml).

Bronchial arteries were assessed as normal or abnormal by the angiographer using the following criteria:

**i. Hypertrophied main bronchial arteries**

Bronchial arteries were considered normal if the artery origin was the same diameter as the catheter tip of the 5F Mickelson catheter on the arteriogram (1.2mm diameter).

Bronchial arteries were considered to be hypertrophied if the artery origin was greater diameter than the catheter tip.

**ii. Lung parenchymal hypervascularity**

This is detected as a pulmonary vascular "blush" on contrast injection.

**iii. Neovascularity**

New bronchial vessels are an indicator of angiogenesis and are detected as vessels of different calibres and configurations in a region of pulmonary hypervascularity.

**iv. arterio-venous shunting**

Shunts are detected as the opacification of branches of the pulmonary vascular tree on bronchial artery injection.

**v. Aneurysms**

Aneurysms are detected as localised collections of contrast arising from a bronchial artery.

**vi. Contrast medium extravasation (active bleeding)**

This rare sign is detected as free flowing contrast on bronchial artery injection.

Selective arteriography was also performed on both internal thoracic (mammary) arteries, both subclavian arteries, and intercostals arteries as a routine to detect the presence of abnormal vessels and collaterals supplying the pleura and contributing to the bleeding site on the affected side. Abnormal systemic arteries were diagnosed on angiography if there was enlargement of the artery, collateral vessels were detected supplying the pleura and lung and if there was persistent hypervascularity of the pleura and underlying lung.

The localisation of the bleeding site was made by reviewing the chest radiograph, CT chest, HRCT and the selective bronchial and systemic angiogram. By identifying areas of pulmonary hypervascularity, neovascularity, AV shunting and aneurysm formation on digital subraction angiography as sites of bleeding and then removing the digital subtraction "mask" on the monitor the bleeding site can be identified on the digital radiograph and correlated with the HRCT and CT scan.

### 3.1.5 Embolization Procedure

If abnormal bronchial arteries were detected on selective arteriography *in the lung suspected of bleeding*, they were embolised using polyvinyl alcohol particles (Contour, Nycomed, Paris and Trufill, Cordis, USA) of 500 to 750 microns diameter suspended in 5mls of dilute contrast medium. The decision to perform embolization was made in the presence of abnormal bronchial and systemic arteries on selective angiography and a focal pulmonary lesion on the chest radiograph, HRCT or CT chest. If the lesion could not be localised on imaging studies but the bronchial arteries were considered abnormal by the angiographer they were embolised. Embolization proceeded until there was marked slowing of blood flow in the bronchial artery but before complete cessation of blood flow. This was to prevent reflux of particles into the aorta. After waiting 2 minutes a gentle contrast injection of the embolized artery was performed to confirm occlusion of the vessel.

Embolization was considered to be technically successful if the abnormal bronchial artery was satisfactorily embolized without technical difficulty or complication. Failure was considered when the abnormal bronchial artery was not detected or could not be catheterised or could not be safely embolized because of catheter tip instability or the present of spinal cord artery feeders.

### 3.2 Prospective Study

#### 3.2.1 Patients

Consecutive patients admitted to Wentworth Hospital for massive haemoptysis over a 15 month period from 1st January 2002 to 31st March 2003 were included in this prospective study. All patients were referred to the Department of Thoracic Surgery as emergencies from King Edward VIII, Addington, R K Khan's Hospital and King George V Hospitals in the Durban Functional Region (DFR). The Ethics Committee of the Nelson Mandela Medical School approved this study.

This study was to determine the efficacy of a new bronchial artery embolic agent gelatin cross linked acryl microspheres (Embospheres, BioSphere Medical, Osaka, Japan http://www.biospheremed.com/) in the treatment of life threatening haemoptysis.

Patients with life threatening haemoptysis were treated as in the retrospective study with admission to the high care ward at Wentworth Hospital and full clinical assessment by a consultant thoracic surgeon.

The intention to treat by performing embolization was made in the presence of:

1. life threatening haemoptysis >300mls over 24 hours

2. unilateral or bilateral pulmonary disease on the chest radiograph and CT
3. poor respiratory reserve

Patients were managed conservatively if the haemoptysis was small <150mls per 24 hours and the patient was haemodynamically stable. All patients were treated with intravenous antibiotics if they were considered to have active pulmonary bacterial infection and anti TB drug therapy if they were clinically thought to have active pulmonary tuberculosis.

### 3.2.2 The following data was recorded:

a. Demographic information
b. Length of hospital stay
c. Aetiology of pulmonary pathology
d. Extent of disease on chest radiographs and CT scans
e. Haemoglobin level and white cell count on admission
f. Sputum analysis for acid fast bacilli
g. HIV status
h. Bronchoscopy findings
i. Surgical procedures-lobectomy, pneumonectomy, open lung biopsy
j. Clinical outcomes-success or failure or death
k. Complications arising from BAE.

Clinical outcome was considered as successful if the haemoptysis stopped or markedly decreased within 24 hours of the procedure being performed.

Embolization was considered a failure if the haemoptysis continued after 24 hours of the procedure or a surgical procedure such as lobectomy or pneumonectomy was performed to stop the haemorrhage.

### 3.2.3 Radiological studies assessed included:

a. Chest radiograph

b. High resolution CT lungs (HRCT)

c. CT chest

d. Bronchial arteriography and systemic arteriography.

### 3.2.4 Imaging Assessment

#### a. Chest Radiograph

The radiological signs recorded were the same as in the retrospective protocol.

#### b. High Resolution CT Lungs (HRCT)

We used a standard protocol for haemoptysis (Webb, Muller and Naidich 1996). This was performed on the helical CT scanner Picker PQ 2000 at Wentworth Hospital. A 1mm slice width at 10mm intervals was used using the bone algorithm from the scanner. The patient had to be able to co operate with suspended inspiration for a successful scan. Scans were photographed on the standard pulmonary window of 2000 HU and –700 HU level set by the scanner manufacturer.

**The following signs were recorded:**

Pulmonary cavities

Nodules

Alveolar opacification

Bronchiectasis

Mycetomas or intracavitatory haematomas

Pleural thickening >3mm thickness

**c. CT Chest**

This study was performed if the patient was too dyspnoeic to hold their breath during the scan. Scans were performed on the Picker PQ 2000 CT scanner using 5mm slice width at 5mm intervals through the hilar regions. Scans were reviewed on identical pulmonary windows.

**d. Arteriography**

Bronchial arteriography was performed on a Toshiba CASV 8000 angiography unit (Toshiba Inc, Japan) at Wentworth Hospital. Many procedures were performed as emergencies after hours or at weekends. Procedures were performed by the author, or by consultant radiologists experienced in the

technique or by senior registrars supervised by a consultant. A standard right femoral artery puncture was performed using the Seldinger technique. A 5 French sheath was inserted into the femoral artery. Catheterisation of the bronchial arteries was performed using a 5F Mikaelson catheter. If the origin of the bronchial arteries could not be detected a pan-aortogram was performed with a long 5 F pigtail catheter in the aortic arch. Selective arteriography was performed with 5 ml of non-ionic iodine containing contrast medium (iohexol 300mg Iodine/ml). The same protocol was used as with the retrospective study to determine whether bronchial arteries were normal or abnormal.

Selective arteriography was also performed on both internal thoracic (mammary) arteries, both subclavian arteries, and intercostals arteries routinely to detect the presence of abnormal vessels and collaterals supplying the pleura and contributing to the bleeding site.

The localisation of the bleeding site was made by reviewing the chest radiograph, CT chest, HRCT and the selective bronchial and systemic angiogram. By identifying areas of pulmonary hypervascularity, neovascularity, AV shunting and aneurysm formation on digital subraction angiography as sites of bleeding and then removing the digital subtraction "mask" on the monitor the bleeding site can be identified on the digital radiograph and correlated with the HRCT and CT scan.

### 3.2.5 Embolization Procedure

Abnormal bronchial and systemic arteries *in the lung suspected of bleeding* were embolized using gelatin coated acryl microspheres (Embospheres, Osaka, Japan) 500-700 microns diameter suspended in 5mls of dilute contrast medium. The decision to perform embolization was made in the presence of abnormal bronchial and systemic arteries on selective angiography and a focal pulmonary lesion on the chest radiograph, HRCT or CT chest. If the lesion could not be localised on imaging studies but the bronchial arteries were considered abnormal by the angiographer they were embolized. Embolization proceeded until there was marked slowing of blood flow in the bronchial artery but before complete cessation of flow. After waiting 2-3 minutes a contrast injection was performed to confirm vessel occlusion.

Embolization was considered to be technically successful if the abnormal bronchial artery was satisfactorily embolized without technical difficulty or complication. Failure was considered when the abnormal bronchial artery was not detected or could not be catheterised or could not be safely embolized because of catheter tip instability or the presence of spinal cord artery feeders.

If there was recurrent haemoptysis, the patient was re-embolized if the bronchial and systemic arteries supplying the pleura were still patent. A non selective pulmonary angiogram was performed at this time in some patients to detect the presence of pulmonary artery inflammatory aneurysms (Rasmussen

aneurysms). This was performed with a 5F catheter introduced via the right femoral vein and placed in the main pulmonary trunk. If an aneurysm from the pulmonary artery was detected embolization using steel coils or Goldvalve detachable balloons was performed (Cordis, USA).

**Analysis of Results**

A comparison of the results of treatment obtained from the retrospective and prospective studies was made using the chi-square test for non parametric data using SPSS for Windows 11 software (SPSS incorporated) and Epi-Info 2002 (CDC).

# CHAPTER 4

# RESULTS

## 4.1 Retrospective Study 1997/8

### 4.1.1 Patients

Eighty four patients were included in this study over a 24 month period from 1st January 1997 through to the 31st December 1988. There were 67 male and 17 female patients with a mean age of 29.7 years (standard deviation SD 11.7 years).

The mean number of haemoptyses in the 24 hours prior to hospital admission was 1.33 (range 1 to 4). The mean volume of the haemoptysis was 643mls (range 150 to 4000mls, SD 646 mls).

### 4.1.2 Aetiology of Pulmonary Disease

**Table 2: Aetiology**

| Aetiology | Number | Percentage |
|---|---|---|
| Pulmonary Tuberculosis | 47 | 56 |
| Bronchiectasis | 31 | 37 |
| Aspergillomas | 4 | 4.7 |
| Neoplasms | 2 | 2.3 |

Eighty one (96%) patients had a history of pulmonary tuberculosis. The diagnosis of active or reactivated pulmonary tuberculosis was made on clinical criteria of cough, fever, loss of weight and night sweats, radiological findings, as well as sputum positivity for acid fast bacilli (AFB'S). Forty seven (56%) patients were sputum positive for acid-fast bacilli (AFBs). Four patients (5%) were infected with multi drug resistant TB. Chronic pulmonary tuberculosis was the commonest aetiology for life threatening haemoptysis. Bronchiectasis and aspergillomas were confirmed on CT. The two neoplasms detected were bronchial carcinomas on histology.

### 4.1.3 HIV Status

A total of 40 (48%) patients consented to be tested for HIV. Thirty two patients (38%) were sero-positive for HIV, 10 patients in 1997 and 22 patients in 1998. Very few patients had their CD4 lymphocyte counts estimated because of cost.

### 4.1.4 Laboratory Parameters

The mean haemoglobin was 9.6 g/100mls on admission (range 4 to 14 g/100mls SD 2.6 g/100 mls). Twenty one (24%) patients required a blood transfusion.

The mean white cell count was 10 450 cells/$mm^3$ (range 3 000 to 34 000 cells/ $mm^3$ SD 6 270 cells/$mm^3$)

Sputum culture was positive in only 3 patients for Klebsiella, Pseudomonas and Serratia bacterial species.

### 4.1.5 Bronchoscopy

Rigid bronchoscopy was performed in 17 (20%) patients only, usually prior to surgery under general anaesthetic. In 9 (52%) out of the 17 patients the location of the bleeding was established at the time of the bronchoscopy.

### 4.1.6 Imaging

#### a. Chest Radiograph

In 50 patients (59%), the disease was bilateral on the chest radiograph and in 34 patients the disease was unilateral.

The origin of the haemorrhage was correctly identified in 20 patients when compared to the bronchial arteriograms. The accuracy of chest radiography in detecting the source of haemorrhage was therefore 25%.

#### b. CT of the Lungs

Limited CT examinations of the chest were performed during this period as the CT scanner at Wentworth Hospital had not been upgraded at this time so that

few high resolution scans (HRCT) were done. CT detected the bleeding source in 45 patients. The accuracy of CT in detecting the source of the haemorrhage using bronchial angiography as the gold standard was 56%.

**c. Bronchial and Systemic Arteriography**

The findings are demonstrated in **table 3.**

**Table 3: Angiographic findings in the retrospective study**

| FINDING | NUMBER | % |
|---|---|---|
| Enlarged BA | 74 | 88 |
| Normal size BA | 10 | 12 |
| Bleeding source | 80 | 95 |
| BP shunts | 15 | 18 |
| BA aneurysms | 5 | 6 |
| Contrast extravasation | 0 | 0 |
| Anomalous BA | 5 | 6 |

The bronchial arteries were enlarged in 74 (88%) patients and normal in calibre in 10 (12%) patients when compared to the calibre of a 5F Mikaelson catheter (1.5mm). As an indicator of a bleeding source, parenchymal hypervascularity and neovascularity was detected in 80 (95%) of patients (**figures 4a and b**).

No active contrast extravasation was detected in any arteriogram.

Bronchial artery aneurysms were present in 5 patients (**figure 5**).

Broncho-pulmonary shunts were present in 15 patients.

Anomalous bronchial arteries were detected in 5 (6%) patients, in all cases in the region of the aortic arch.

### 4.1.7 Patient Outcome

#### a. Bronchial Artery Embolization

Embolization was technically successful in 63 (75%) out of 84 patients who had the BAE performed. Seventy seven patients had one BAE procedure and 7 patients two BAE procedures. Embolization was unsuccessful in 10 patients due to the fact that the bronchial arteries were either too small to catheterise with 5F catheters, or the catheter tip could not be sited in a stable position to allow safe embolization. In one patient the bronchial arteries could not be detected and in the remainder of unsuccessful cases concerns about the presence of spinal feeders prevented the radiologist continuing with

Figure 4a: Left bronchial arteriogram demonstrates hypervascularity and neovascularity from a bleeding site in a LUL TB cavity

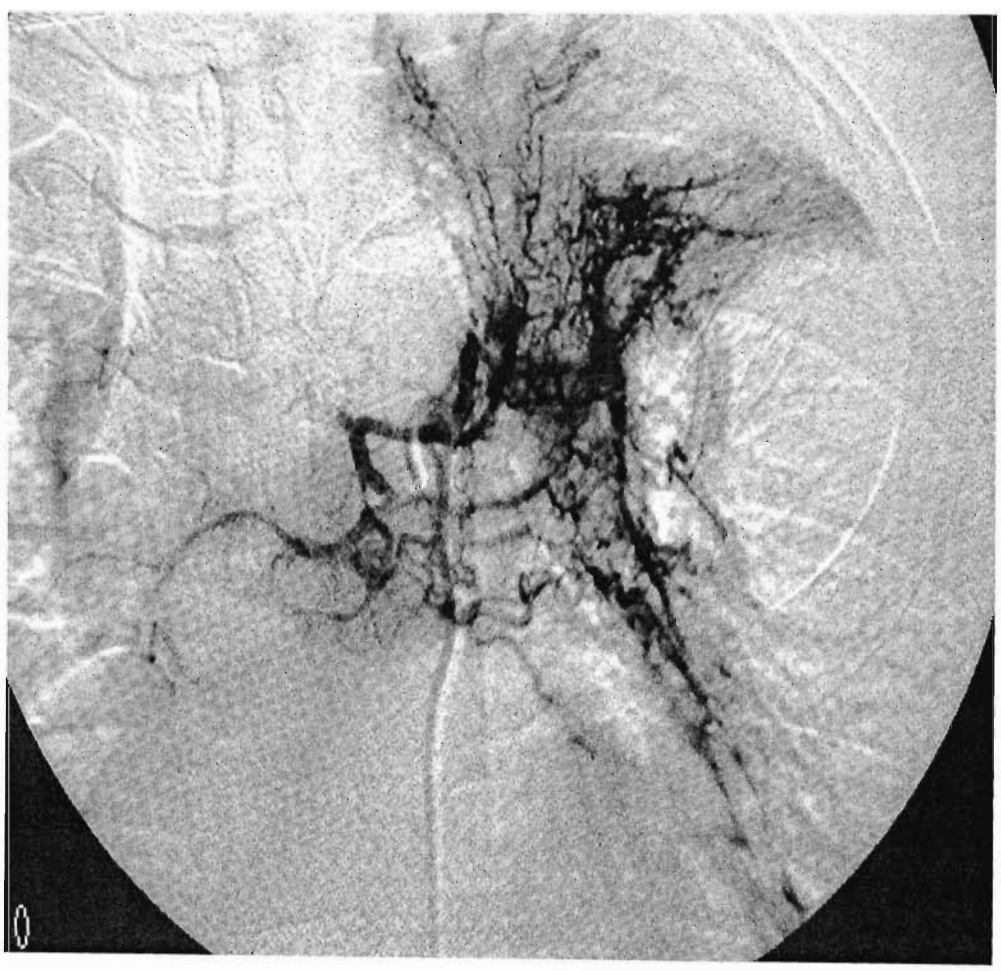


Figure 4b: Left bronchial arteriogram post embolization demonstrates complete occlusion of the bleeding artery.

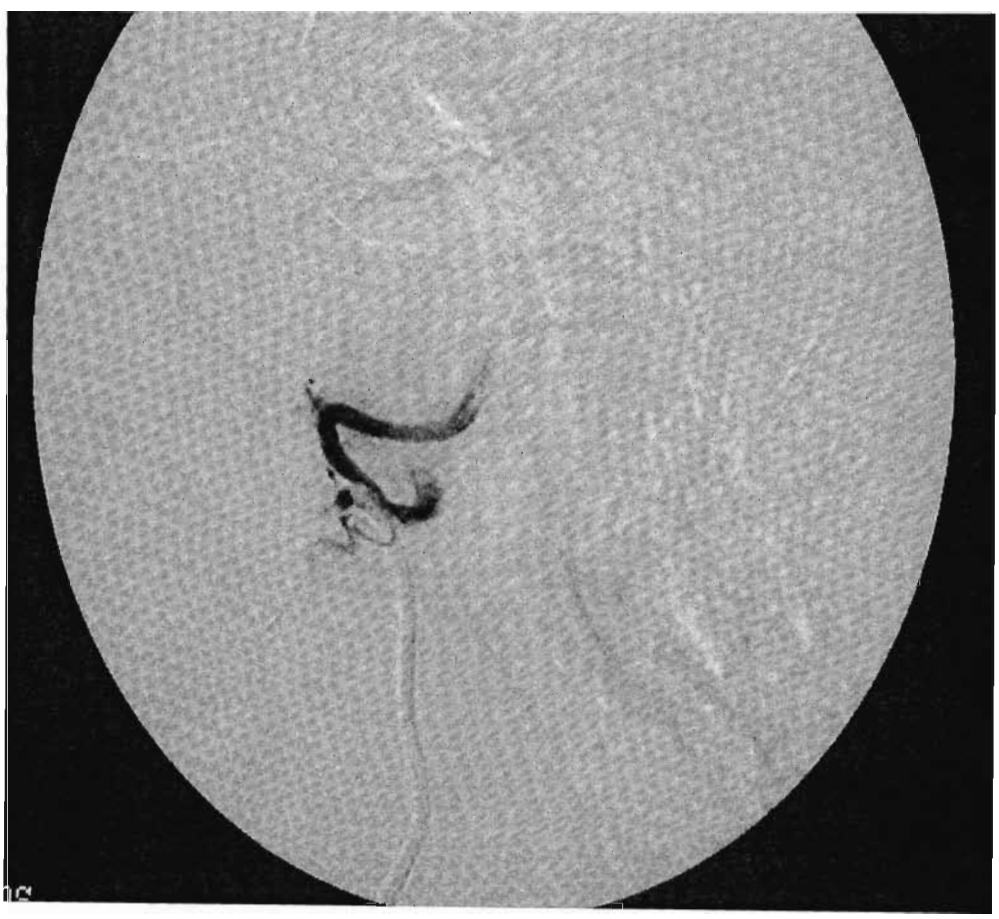
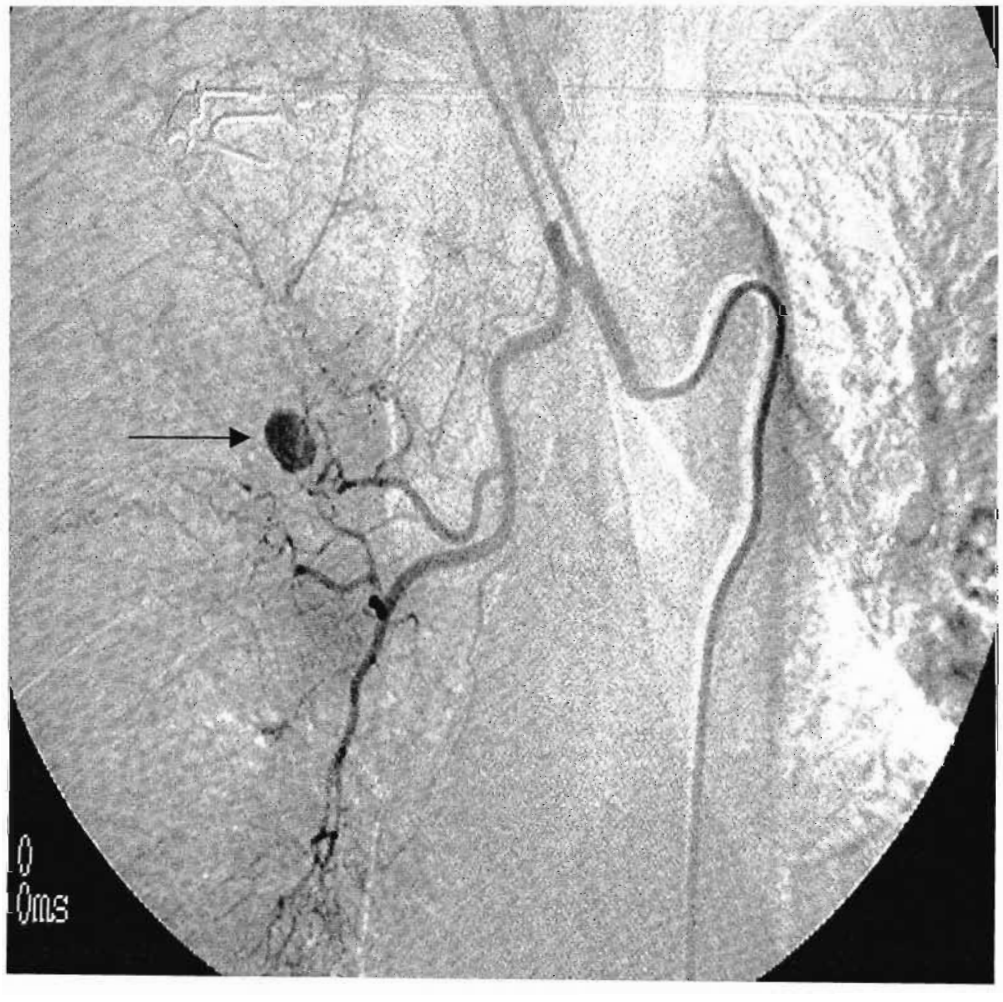


Figure 5: Right bronchial arteriogram with a bronchial aneurysm at the bleeding site (arrow)



embolization. There was one procedural complication due to an intimal flap created by catheter or guide wire manipulation in the lower lumbar aorta causing a localised aortic dissection extending into the right femoral artery. The dissection resulted in a diminished femoral pulse for a few hours, which then returned to normal without any long-term complication. Chest pain, which was transient, was recorded in 15 (17%) patients, usually resolving with oral analgesics.

Fifty seven patients (67.8%) had a successful outcome with haemoptysis resolving completely or almost completely within the first 24 hours.

Twenty seven patients (32%) continued to bleed with recurrent haemoptysis during the first week of hospital admission. Twenty of these patients were from the successfully embolized group (24%) and 7 were from the group of technical failures.

**b. Surgical Outcome**

Fourteen patients (16%) who continued to bleed after 24 hours required emergency lobectomy or pneumonectomy.

Sixteen patients were not offered any surgical procedure because of pulmonary insufficiency or bilaterality of disease.

### 4.1.8 Mortality

Four patients (4.7%) died and was from respiratory failure or recurrent pulmonary haemorrhage in 3 and disseminated cancer in 1 patient.

### 4.1.9 Hospital Stay

The mean stay for patients treated by BAE was 5 days (range 3-14 days, SD 3.3)

The mean stay for patients treated by pulmonary resection was 10 days.

### 4.1.10 Follow Up

A total of 32 patients (38%) were followed up at the out patient thoracic clinic at Wentworth Hospital usually within 2 weeks of the procedure. Haemoptysis had resolved in 20 patients completely and was reduced considerably in 12 patients.

Only 12 patients (14%) were followed up to 30 days post discharge.

## 4.2 Prospective Study 2002/3

### 4.2.1 Patients

Seventy patients were included in this study over 15 months from 1st January

2002 through to 31st March 2003. All patients signed informed consent for inclusion in the study.

There were 22 female patients and 48 male patients. Age range was from 17 to 62 years, with a mean age of 37 years (standard deviation SD10 years).

Patients had a mean of 4 episodes of haemoptysis (range 1 to 10) prior to admission to hospital. The mean volume of the haemoptysis in the 24 hours prior to admission was 424 ml blood (range 150 to 2000 mls, SD 313 mls)

### 4.2.2 Aetiology of Pulmonary Disease

**Table 4: Aetiology**

| Aetiology | N | % |
|---|---|---|
| Destructive Pneumonia | 19 | 27 |
| Chronic cavitatory TB | 19 | 27 |
| Single Destroyed Lung | 11 | 16 |
| Aspergillomas | 12 | 17 |
| Localised Bronchiectasis | 6 | 9 |
| Pulmonary Masses | 3 | 4 |

Sixty seven patients had a history of treatment for pulmonary tuberculosis. Nineteen patients (27%) had active chronic tuberculosis. The diagnosis of active tuberculosis was made on clinical grounds of cough, loss of weight, night sweats, radiological changes and positive sputum for acid fast bacilli. Nineteen patients were sputum positive for acid fast bacilli (AFB's). Eleven (16%) of these patients had developed multi-drug resistant tuberculosis (MDR) and were on treatment. Nineteen patients (27%) were diagnosed with destructive pneumonias. A destructive pneumonia was diagnosed clinically and radiologically in patients with a recent onset of cough, fever, chest pain and dypnoea who had air space opacification with areas of breakdown within the opacification on the their chest radiograph, CT or HRCT scans in the absence of clinical, bacteriological and radiological signs of pulmonary tuberculosis.

### 4.2.3 Haematological Measurements

The mean haemoglobin on admission to hospital was 9 g/100mls (range 1 to 15 g/100mls, SD 3.8 g/100mls). Twenty three patients (33%) received blood transfusions.

The mean full blood white count was 9 600 cells/$mm^3$ (range 1000 to 32 000 cells/$mm^3$ SD 5400 cells/$mm^3$).

The mean erythrocyte sedimentation rate using the Westergren method was 63 mm/hr (range 15 to 150 mm/hr, SD 55 mm/hr)

### 4.2.4 HIV status

Only 40 out of 70 patients (57%) were tested for HIV antibodies using the Western Blot test. All patients gave written consent and were counselled pre and post testing for HIV.

Twenty four patients (34%) were seropositive for HIV antibodies and sixteen patients tested seronegative for HIV antibodies. Very few patients had CD4 counts performed because of the cost of the test.

### 4.2.5 Sputum microscopy and culture

Eleven patients (16%) were sputum positive for acid fast bacilli on Ziehl Nielson stain. Only 4 patients had positive sputum cultures for bacteria: Haemophilius influenza, Actinobacter and Staphylococcus aureus were grown.

### 4.2.6 Imaging

#### a. Chest Radiograph

In 34 patients (50%) the disease was bilateral on chest radiography. Eleven patients had a completely destroyed lung and a normal contralateral lung (16%). Ten patients had right upper lobe disease, and five patients left upper lobe disease. Six patients had aspergillomas within upper lobe cavities (**figures**

**6a and 6 b)**. Three patients had solitary pulmonary masses.

Figure 6a: LUL cavity containing an aspergilloma (arrow)

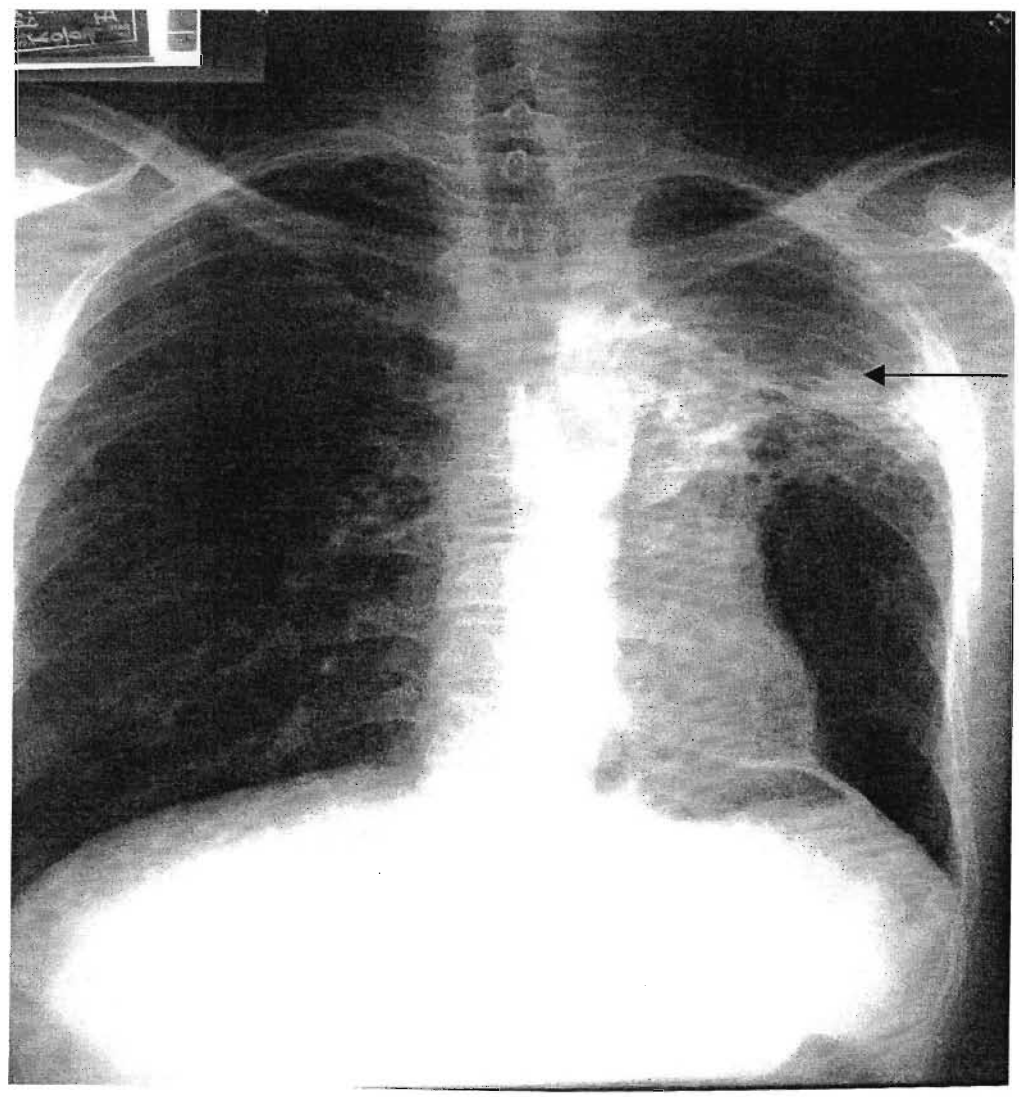
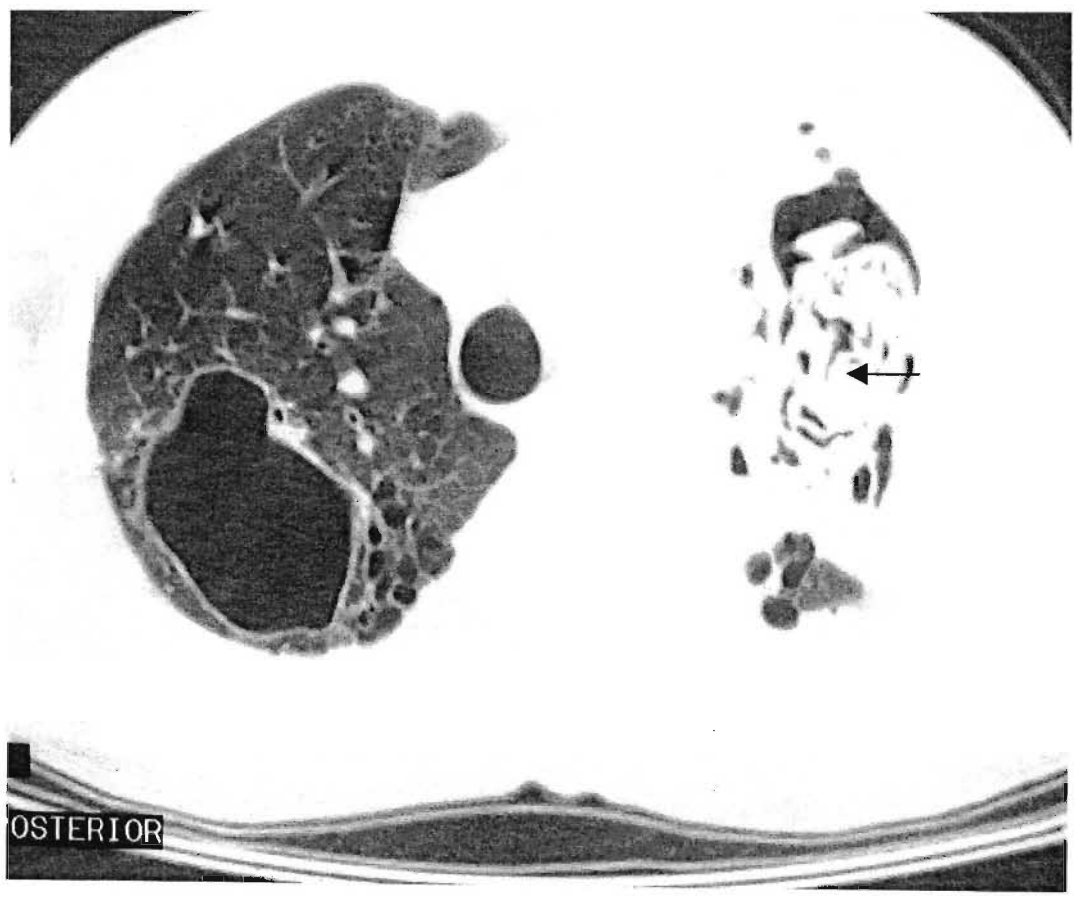


Figure6b:HRCTscan with an aspergilloma (arrow) in an LUL cavity



The origin of the bleeding was correctly recorded in 18 out of 70 (25.7%) patients. Using bronchial arteriography as a gold standard the accuracy of chest radiography to detect the origin of the bleeding was 27%.

**b. High Resolution CT of the Lungs**

Thirty four patients (50%) had HRCT scans performed. An additional 6 patients had aspergillomas detected on HRCT that were not evident on chest radiographs (**figure 7**). An additional 6 patients had lobar or segmental bronchiectasis detected that was not detected on the chest radiograph. In one patient the chest was reported as normal however segmental right middle lobe cystic bronchiectasis was present (**figure 8**). The origin of the bleeding was identified on HRCT in 30 out of 34 patients scanned. The HRCT scans were compared with the selective angiograms, and bleeding sites detected on angiography were compared with the lesions identified on HRCT. The accuracy of HRCT when compared to the gold standard of arteriography was 88% in detecting the origin of the haemorrhage in the lung. Pleural thickening greater than 3mm was present in 18 (53%) out of the 34 patients scanned.

Figure 7: HRCT of an aspergilloma (arrow) in an atelectactic lingula segment LUL that was not detected on chest radiograph. Focal RML bronchiectasis and left pleural thickening present

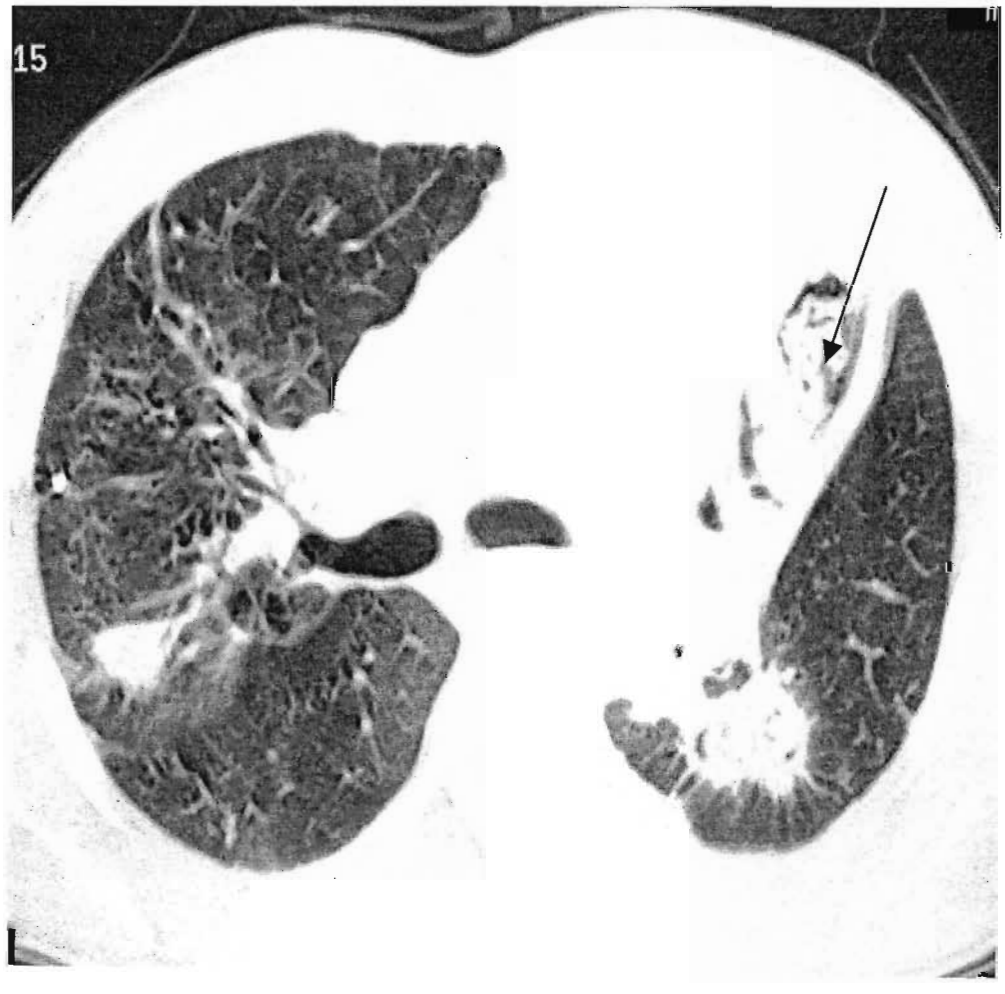
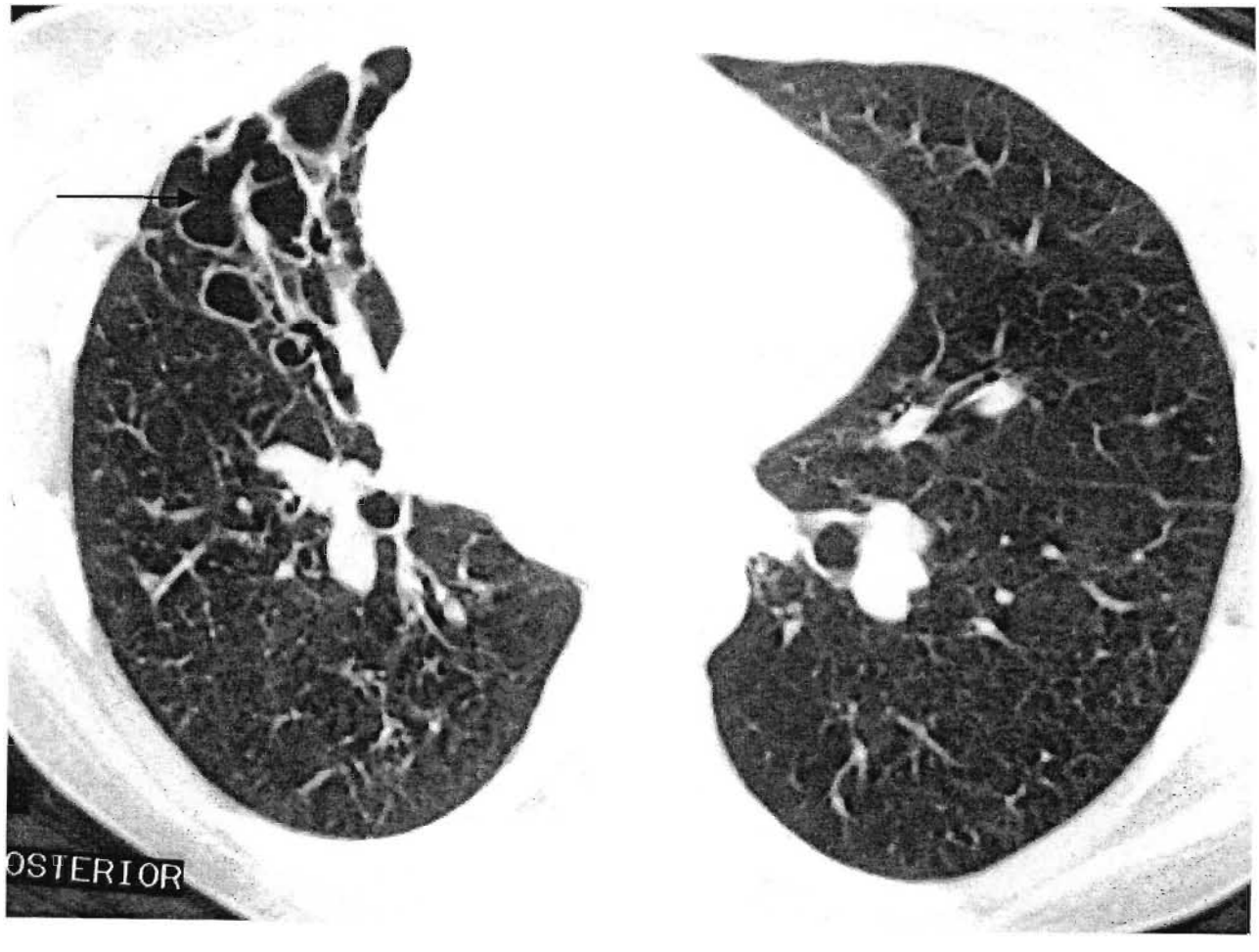


Figure 8: HRCT with RML focal bronchiectasis (arrow) in a patient whose chest radiograph reported as normal



### c. Bronchial and Systemic Arteriography

All patients had bronchial arteriography performed. 62 patients had a single procedure performed. 6 patients had two procedures and one patient each had 3 and 4 procedures for recurrent haemoptysis. The angiographic findings are demonstrated in **table 5**.

The bronchial artery patterns are demonstrated in **figure 9**. The commonest bronchial artery pattern was a right intercostobronchial trunk with two separate left bronchial arteries in 40% of patients, followed by a right intercostobronchial trunk and one left bronchial artery in 20% of patients, followed by a ICBT and separate bronchial on the right and two left bronchials in 20%, a single trunk dividing into left and right bronchial arteries in 10% of patients and a right ICBT and separate right bronchial and separate single left bronchial in 10% of patients. A right ICBT was constant in 90% of patients in this study. Anomalous bronchial arteries arising from the aortic arch were detected in 5 patients (7%).

## Figure 9: Bronchial Artery Variations Detected in the Prospective Study

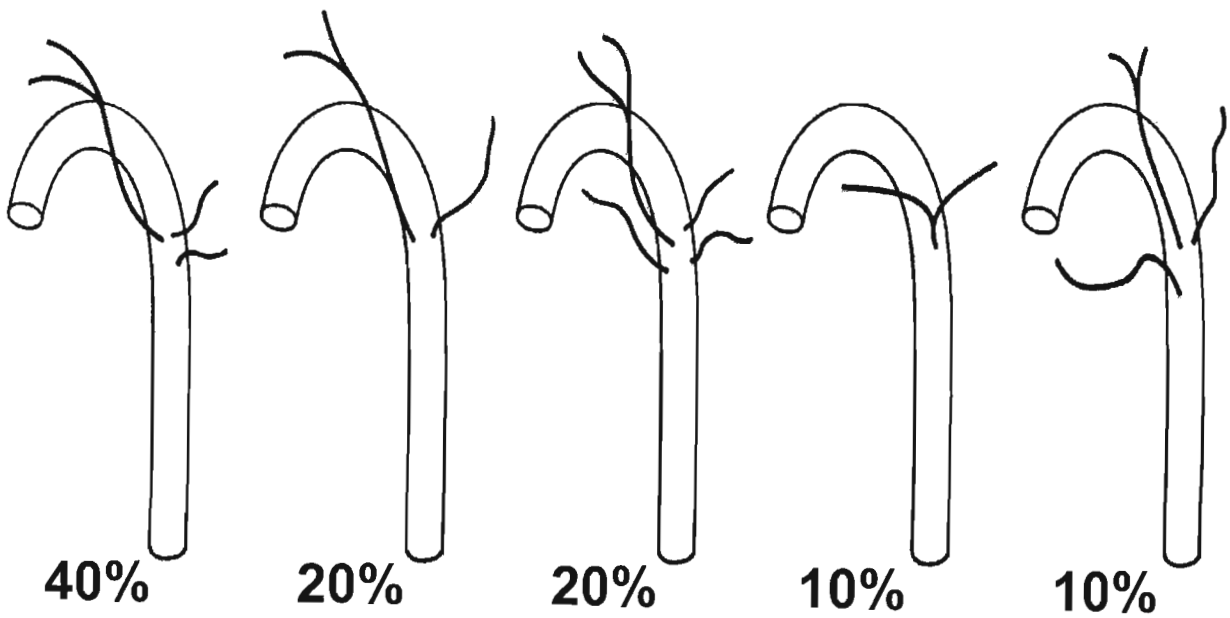


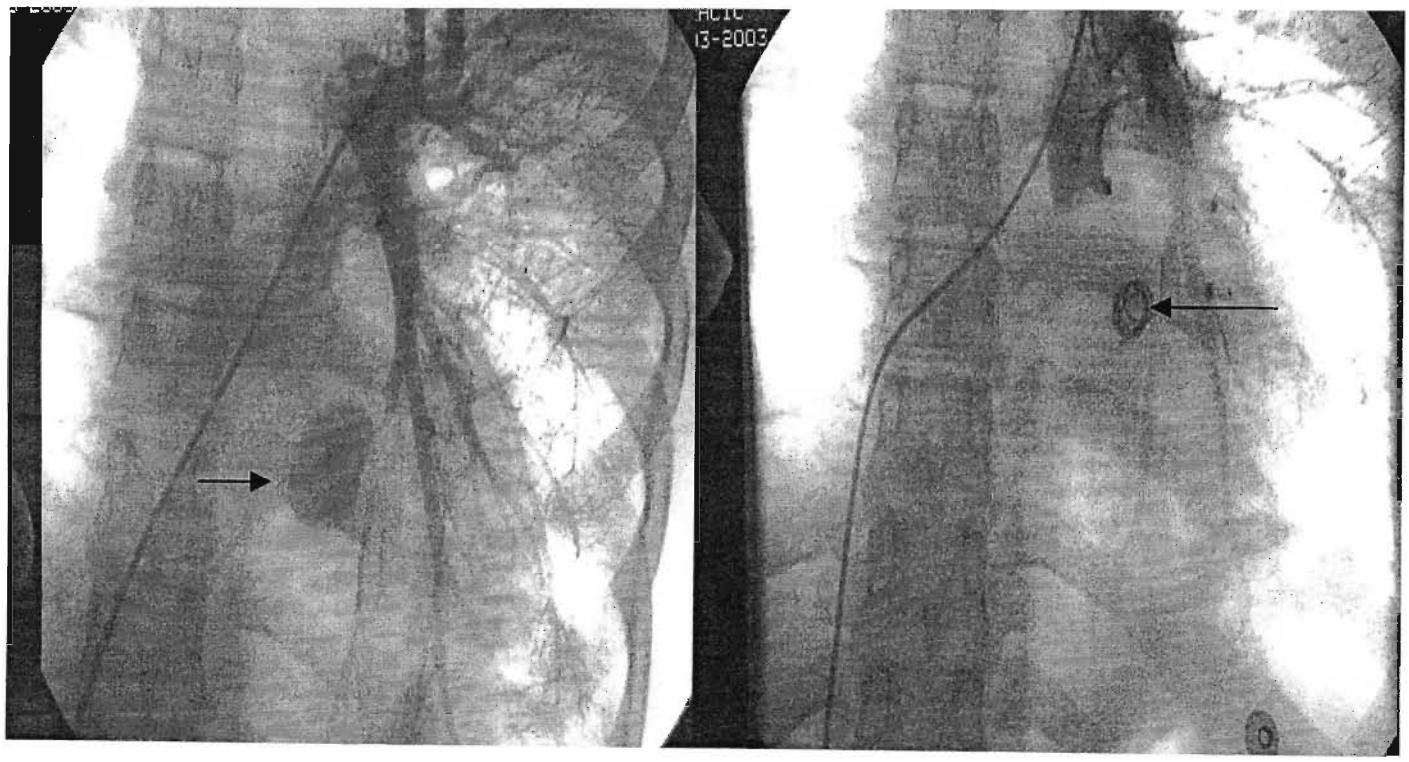
**Table 5: Angiographic Findings in the Prospective Study**

| FINDING | NUMBER | % |
|---|---|---|
| Enlarged BA | 50 | 71 |
| Normal calibre BA | 20 | 29 |
| Anomalous BA | 5 | 7 |
| Enlarged Intercostals and Internal Thoracic Artery | 28 | 40 |
| Bleeding Site Detected | 65 | 93 |
| Multiple Beleding Sites Detected | 11 | 16 |
| BA aneurysms | 3 | 4 |
| Pulmonary Aneurysm | 1 | 1 |
| Bronchopulmonary shunts | 10 | 14 |
| Contrast Extravasation | 0 | 0 |

BA-bronchial artery

Bronchial arteries were enlarged in 50 patients and of a normal size in 20 patients when compared to the 5F catheter tip. No active contrast extravasation was detected in any patient. The site of bleeding in the lung was detected by the presence of focal pulmonary hypervascularity and neovascularity in 65 patients (93%). (**figures 10a 10b and 10c**). In 28 patients (40%), in addition to enlarged bronchial arteries on the same side of the chest, the intercostals and/ or internal mammary arteries were enlarged with collaterals feeding the suspected bleeding lesion. In 11 patients (16%), more than one bleeding site was identified usually in the same lung. Bilateral bleeding sites were not detected in this study. Bronchial artery aneurysms were detected in 3 patients. One patient developed a left descending branch pulmonary artery aneurysm (Rasmussen's aneurysm) (**figures 11a,11b** ). Enlargement of the intercostal arteries and internal thoracic (mammary) artery was present in 28 (40%) patients in the study. Eighteen of these patients had pleural thickening greater than 3mm on CT or HRCT scans.

Figures 10 a&b:Pulmonary Aneurysm (arrow) arising from left lower lobe branch successfully embolized with a steel coil (long arrow)



A B

Figure 10c:Contrast Enhanced CT of the heart and central pulmonary arteries with enhancing pulmonary aneurysm (arrow)

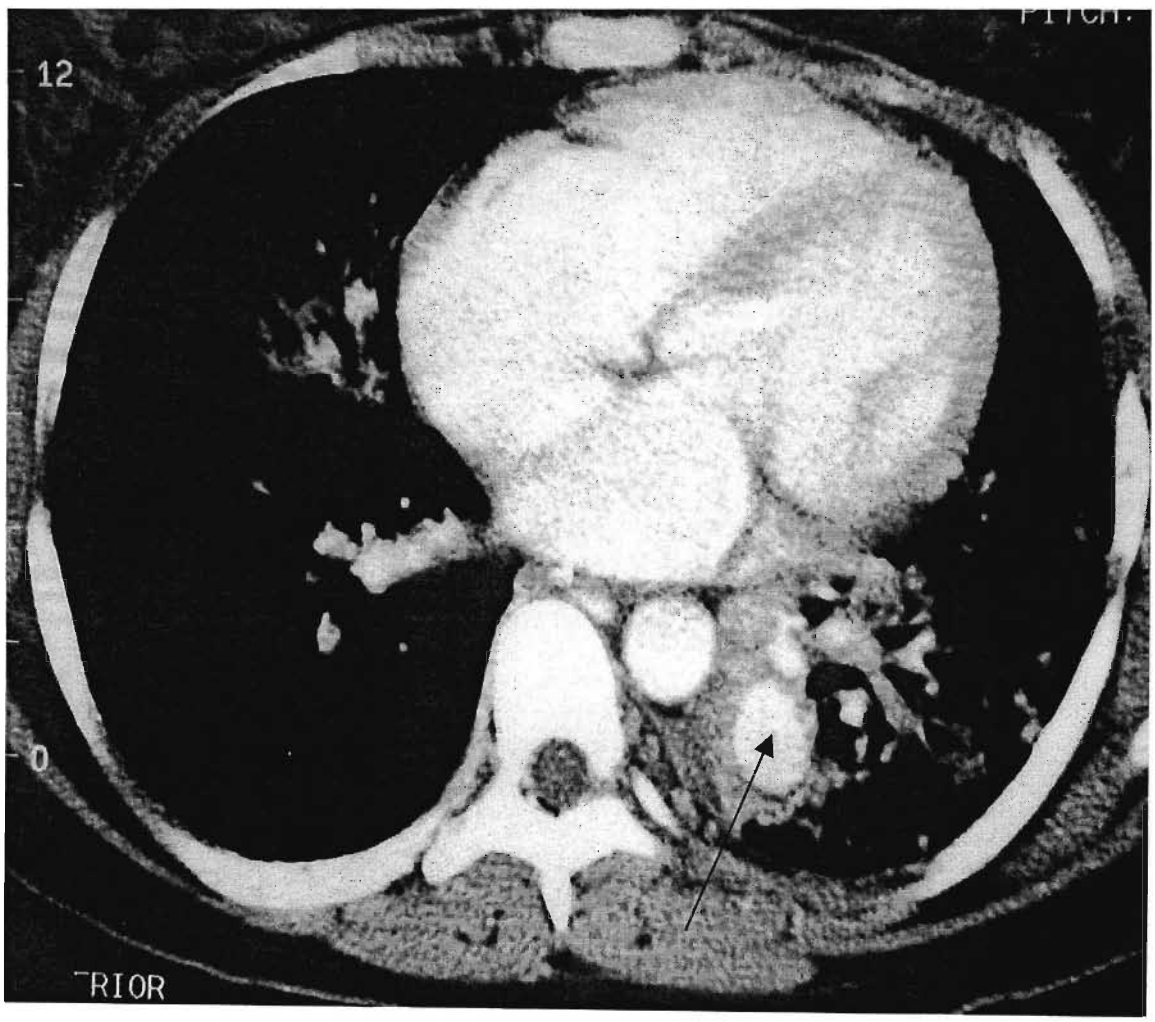


Figure 11a: Bronchial arteriogram demonstrates bronchial artery hypertrophy (arrow), pulmonary hypervascularity and bronchopulmonary shunting in the bleeding LUL

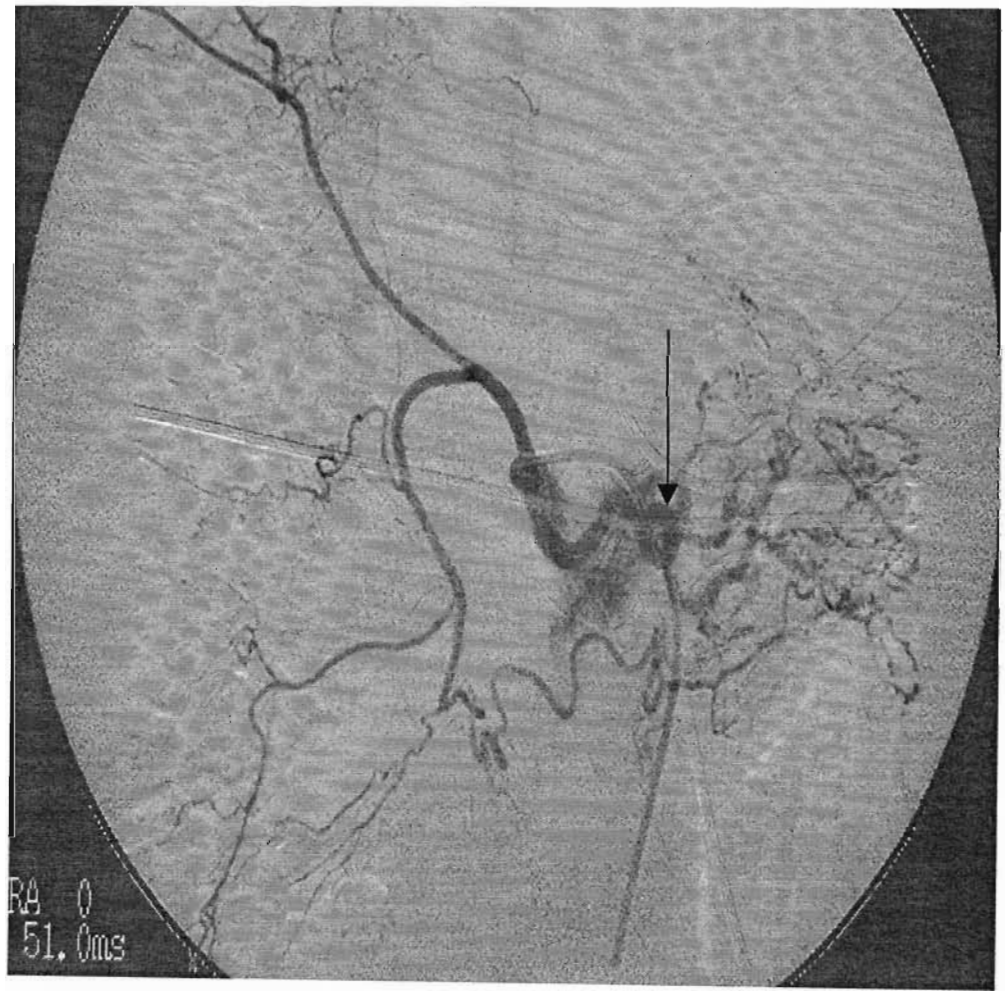
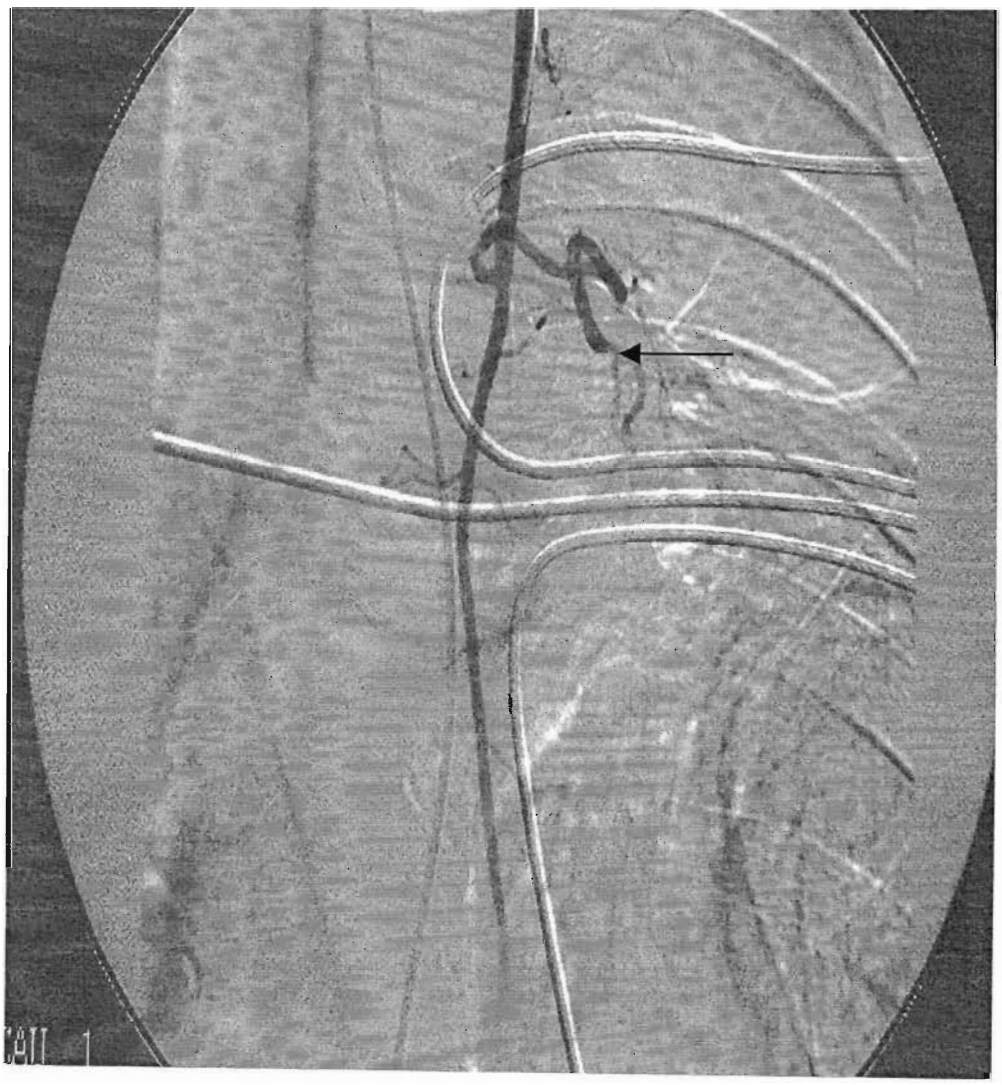


Fig 11b: Bronchial arteriogram post embolization with microspheres (arrow) demonstreates complete occlusion of the bleeding artery



### 4.2.7 Bronchoscopy

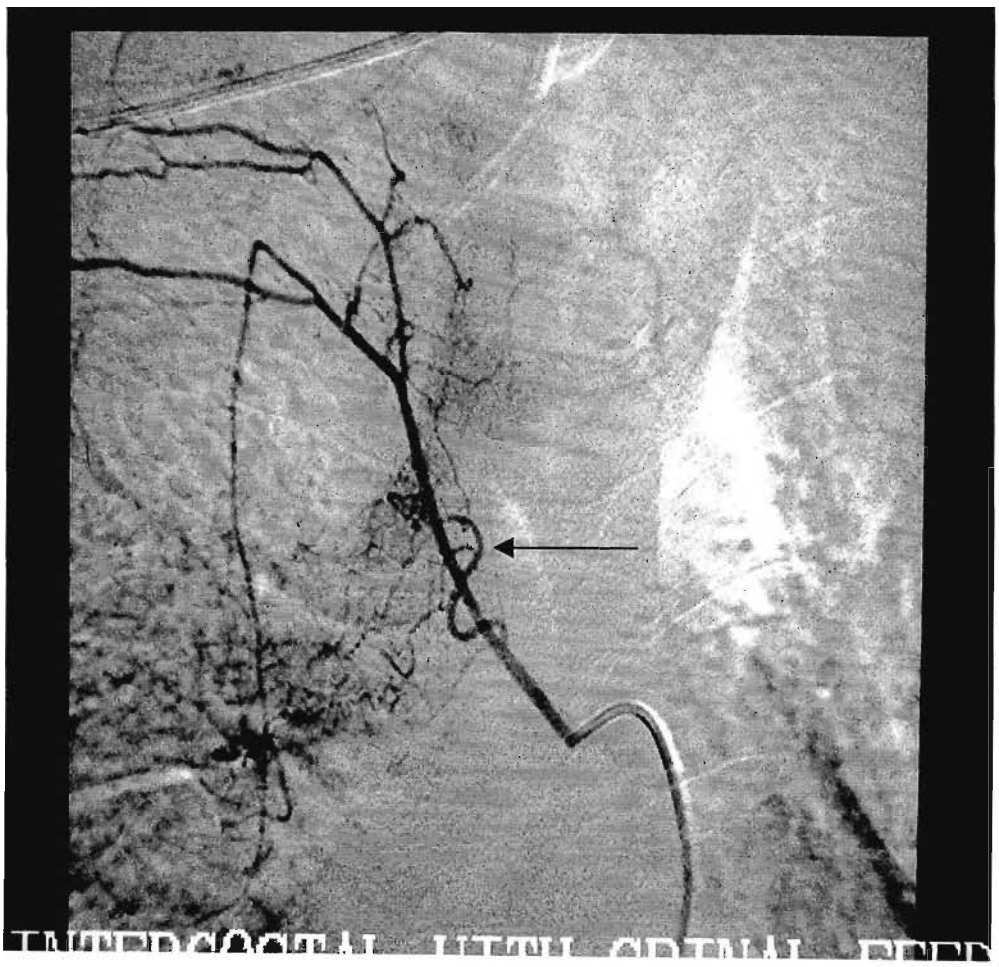
Bronschoscopy was performed in only 15 patients (21%). This was usually a prelude to surgery in 7 of these patients. Pus was noted arising from the bronchi in 2 patients and bleeding was detected from the affected bronchus in 5 (33%) patients only.

### 4.2.8 Outcome of Bronchial Artery Embolization

The procedure was technically successful in 63 patients (90%), unsuccessful in 6 patients (8.5%) and partially successful in 1 patient. The unsuccessful procedures were due to inability to correctly site the 5F catheter tip in the origin of the bronchial artery in 4 cases and because of the presence of spinal cord feeders arising from the bronchial artery in 1 case (**figure 12**).
Multiple bleeding sites were detected in 11 patients (16%) and embolization was performed in all patients.
The procedure including the selective angiography took a mean of 45 minutes to perform with a range from 30 to 90 minutes.

Twenty one out of 24 HIV positive patients (87%) responded successfully to initial BAE. There were 2 deaths and one patient developed recurrent haemoptysis in the first week in the HIV positive cohort as opposed to 5 deaths and 8 recurrent haemoptysis in those patients not tested for HIV who were HIV negative.

Figure 12:Right ICBT arteriogram with anterior spinal artery (arrow) demonstrated



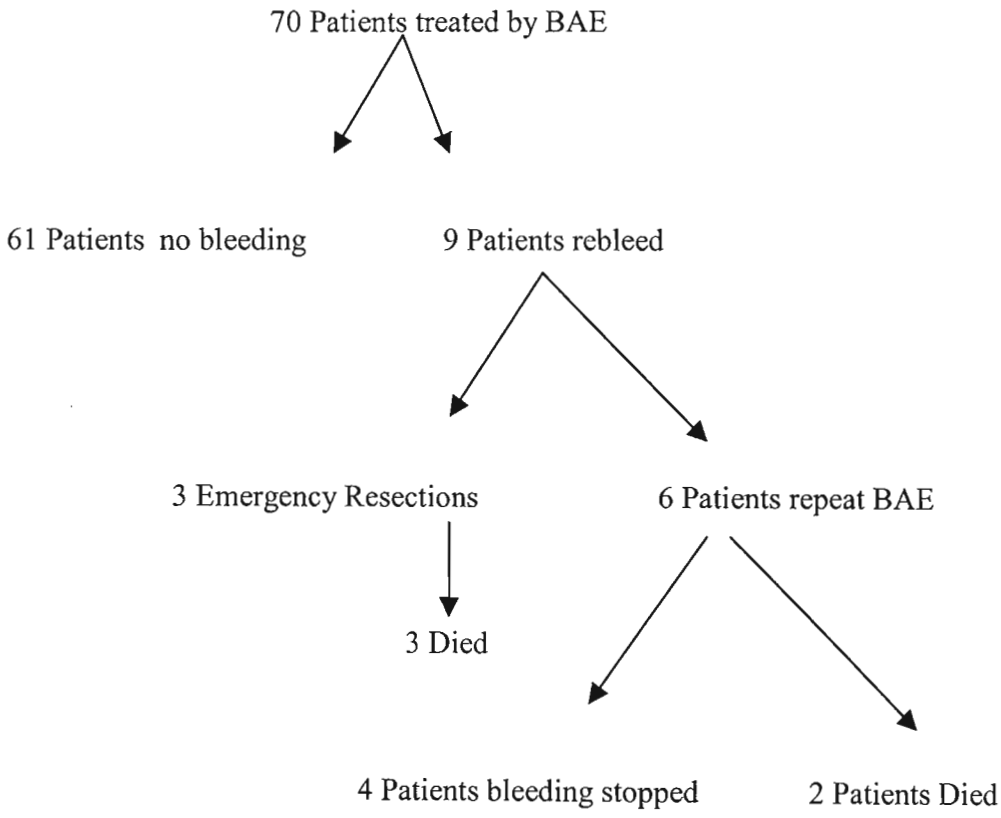
Haemoptysis stopped in the first 24 hours in 61 patients (87%) and was recurrent in 9 patients within the first week (13%). Patients with intracavitatory aspergillomas responded well to BAE with 11 out of 12 patients' haemoptysis stopping in the first week.

One patient developed a severe complication. This patient developed a stroke within 24 hours of the procedure. CT of the brain demonstrated a large middle cerebral artery infarct. This may have been due to inadvertent embolization in the aortic arch or due to pre existing vascular disease and catheter manipulation in the arch. Chest pain, which lasted less than 24 hours, was present in 5 (7%) patients.

### 4.2.9 Recurrent Haemoptysis

Nine patients (13%) developed recurrent massive haemoptysis within the first week. These patients all had significant upper lobe fibrosis and pleural thickening on CT. Three of these patients had emergency surgical resections performed (2 patients lobectomies and 1 patient a pneumonectomy). All 3 patients died from recurrent haemorrhage. In the remaining 6 patients BAE was repeated. In 2 of these patients repeat BAE was technically unsuccessful and both these patients died from recurrent haemorrhage. In the other 4 patients BAE was technically successful and all 4 patients recovered.

**Recurrent Haemoptysis following BAE**



### 4.2.10 Surgical Resections

Seven patients (10%) had surgical resections (4 patients pneumonectomies, 3 patients lobectomies). Three patients had emergency resections for recurrent haemoptysis and 4 patients for localised disease. One patient (14%) died following an emergency lobectomies for recurrent bleeding. The cause of death in this patient was exsanguination and respiratory failure. Only one of these patients was sufficiently fit for emergency pneumonectomy, but all died despite surgery.

### 4.2.11 Mortality

Seven patients (10%) died. Two patients died from primary lung cancers, the other 5 died from recurrent or persistent haemorrhage. Only one of these patients was sufficiently fit for an emergency pneumonectomy.

### 4.2.12 Hospital Stay

The mean hospital stay was 7 days (range 1 to 14 days, SD 3.3).

### 4.2.13 Follow Up

The mean follow up after hospital discharge was only 28 days with a median of 7 days (range 1 to 200 days, SD 42). Sixteen patients (23%) were followed up after 30 days (range 42-200 days, median 42 days).

## TABLE 6: COMPARISON OF RESULTS OF THE RETROSPECTIVE VERSUS PROSPECTIVE STUDY

| PARAMETER | RETROSPECTIVE | PROSPECTIVE |
|---|---|---|
| Study Duration | 24 months | 15 months |
| Patient Number | 84 | 70 |
| Mean Age | 30 | 37 |
| Haemoptysis Number | 1.3 | 4 |
| Haemoptysis volume mls mean | 643 | 424 |
| HIV positive prevalence % | 38 | 34 |
| Haemoglobin gm % Mean (SD) | 9.6 (2.6) | 9 (3.8) |
| White Cell Count cells/$mm^3$ | 10 450 (6 270) | 9 600 (5 400) |
| **Accuracy in detecting bleeding site:** Chest % | 25 | 27 |
| CT/HRCT % | 56 | 88 |
| Bronchoscopy % | 52 | 33 |
| **Embolization:** technical success % | 75 | 90 |
| Success at 24 hrs % | 68 | 87 |
| Complications chest pain | 17 % | 7% |
| Recurrent haemoptysis % in week 1 post BAE | 32 | 13 |
| Surgical Procedures % | 16 | 10 |
| Mortality % | 5 | 10 |

# CHAPTER 5:

# DISCUSSION

## 5.1.1 Demographic Profile

Both the retrospective and prospective studies have similar patient demographics. There has been an increase in the number of female patients over the 5 year period between the two studies although the mean age of presentation is similar. This patient profile is similar to that found in studies from other developing countries (Abal et al. 2001; Knott-Craig et al. 1993). These studies are composed of young adults who have underlying bronchiectasis following tuberculosis. Life threatening haemoptysis is a common clinical emergency in many developing countries that affects patients in the economically productive phase of their lives usually with families to support. This has implications both for health care costs and the economic cost to the country. In the developed world, life-threatening haemoptysis is uncommon. Most series consist of patients with bronchiectasis following cystic fibrosis (Cipolli et al. 1995).

## 5.2 Changing Aetiologies of Life Threatening Haemoptysis

### 5.2.1 Destructive Pneumonia

This study demonstrates an increase in prevalence of destructive or necrotising

pneumonias as a cause for life threatening haemoptysis between the retrospective and prospective studies. This increase in acute necrotising pneumonias is probably related to the fact that 10 out of the 19 patients with destructive pneumonia (53%) were HIV positive. Although there was no change in the HIV prevalence between the two studies, this may represent a false impression, as many patients in the prospective study did not consent to a HIV test so that the true prevalence is unknown.

The reason why HIV positive patients with pneumonia present with life threatening haemoptysis is unclear. Possible reasons include the patient's poor immune response to infection, the increased lung necrosis in bacterial infections, the presence of a coagulopathy, the presence of multiple pathogenic organisms or drug resistance to anti-TB treatment.

In my study patients with pneumonia, especially HIV positive patients, usually have normal sized bronchial and systemic arteries as opposed to enlarged bronchial arteries detected on arteriography in patients with bronchiectasis or chronic pulmonary disease. This may represent aggressive infection with rapid progression allowing insufficient time for the arterial supply to respond to the angiogenic triggers (Deffebach et al 1978). The other hypothesis is that immunosuppressed patients have insufficient lymphocytes and macrophages to provide angiogenic factors that would initiate angiogenesis in the lung (Charan et al.1997).

This is an important subgroup of patients to recognize clinically because of the

increasing incidence of HIV infection and AIDS patients in the community.

### 5.2.2 Bronchiectasis

Patchy and bilateral bronchiectasis is the most common cause of life threatening haemoptysis in most studies from the developing world (Abal et al. 2001, Knott-Craig et al. 1993, Uflacker et al. 1985). These patients are not suitable for surgery because of the multifocal nature of the bronchiectasis. Patients who are HIV positive are more likely to develop bronchiectasis following recurrent pulmonary infections and severe immunocompromise (McGuinness et al. 1993). This is confirmed in the HIV positive patients in the prospective study where 5 out of 24 HIV positive patients (20%) developed focal bronchiectasis. Often there is a combination of bronchiolitis and bronchiectasis in AIDS patients, which is best visualised on HRCT (McGuinness et al. 2002). Bronchiolitis is detected as nodular peripheral pulmonary densities with Y or V shaped configurations on HRCT scans (McGuinness et al. 1997).

In one patient who had a completely normal chest radiograph, HRCT detected focal segmental bronchiectasis in the right middle lobe as the cause of massive haemoptysis (**figure 8**). Naidich et al found that 8 out of 58 (17%) patients he studied with haemoptysis had normal chest radiographs but evidence of focal bronchiectasis on HRCT scans (Naidich et al. 1990). This confirms the importance of using HRCT scans to detect bronchiectasis when the chest

radiograph is normal as a possible source of the haemoptysis.

### 5.2.3 Aspergillomas

Mycetoma is the generic name for the fungal colonization of tuberculous pulmonary cavities. The most important pathogenic fungi are aspergillus species (Stevens et al. 2000). Aspergillus infection can present either as an aspergilloma or fungal ball in a pulmonary cavity, as a destructive parenchymal disease called chronic necrotising aspergillosis and as invasive aspergillosis in severely immune compromised patients (Soubani & Chandrasekar 2002). Aspergillus colonization of pulmonary cavities following pulmonary TB is common but often under recognized. The aspergilloma may exist for many years without causing symptoms but it can cause severe haemoptysis (Faulkner et al. 1978). Aspergillus infection is more common in HIV seropositive patients (Addrizzo-Harris et al. 1997). However only 4 out of the 12 patients (35%) with detected aspergillomas in the prospective study were HIV positive. Aspergillus infection tends to become progressive and invasive in HIV positive patients with a poorer prognosis than HIV negative patients (Addrizzo-Harris et al 1997). It is postulated that the aspergillus either invades blood vessels lining the tuberculous cavity or that endotoxins released by the fungus cause the haemoptysis (Addrizzo-Harris, Harkin, McGuinness, Naidich et al 1997).

Aspergillomas are detected by chest radiography as in intracavitatory mass, which is mobile with an air crescent. However aspergillomas are much more easily detected on HRCT **(figures 6a, 6b and 7)**. There are often small crescents of air within the aspergilloma, which is pathognomonic of an aspergilloma (Webb et al.1996). I found this sign useful in detecting aspergillomas on HRCT in the prospective study.

There was a three-fold increase in the number of aspergillomas detected between the two studies. The prevalence increased from 5% to 15%. This is due to their better detection using HRCT with eight out of the twelve patients' mycetomas being detected only by HRCT in the prospective study. The importance of detection of aspergillomas is that they often require surgical management. Treatment of aspergillomas is very difficult (Soubani et al 2002). Antifungal drugs, either inhaled or intracavitatory, are rarely effective as it is not possible to achieve sufficient drug levels within the cavities to kill the fungi. Amphotericin B and gelatin have been injected into pulmonary cavities containing aspergillomas under CT guidance with limited success (Munk et al. 1993). Surgical resection is associated with a high mortality of between 7% and 23% in published series (Daly et al. 1986). A recent report of 87 patients operated on for aspergillomas recorded a post-operative mortality of 5.7% (Regnard et al. 2000).

The presence of aspergillomas is an important cause for recurrent haemoptysis as these patients do not always respond to bronchial artery embolization

(Judson et al. 2001, Uflacker et al. 1985). In the largest series, Uflacker wrote that he believed BAE was only a temporising measure in treating patients with aspergillomas. All his patients with aspergillomas rebled after embolization, with a 25% mortality (Uflacker et al. 1985). My results in the prospective study using gelatin linked microspheres demonstrates that contrary to the results of Uflacker, bronchial artery embolization can be very useful in controlling haemoptysis in these patients but that recurrence of haemoptysis remains a problem. It is possible that the distal embolization achieved with microspheres in the cavity wall containing the aspergillus may be responsible for the improved results compared to the use of PVA particles for embolization.

### 5.2.4 Pulmonary Tumours

Bronchial neoplasms contribute between 5% to 44% of series of haemoptysis in the literature (Marshall et al. 1996). In my study pulmonary tumours were uncommon. In both cohorts pulmonary tumours or masses were noted in two patients each. The diagnoses were made on lymph node biopsy, bronchoscopy and mediastinoscopy. All four patients responded poorly to BAE. The arterial supply to pulmonary neoplasms is via the bronchial arteries (Charan et al 1997). Hayakawa et al. reported that their 63 patients with pulmonary tumour induced haemoptysis showed the highest initial failure rate of embolization and highest rate of recurrent haemoptysis when compared to inflammatory pulmonary lesions (Hayakawa et al. 1992). My results are consistent with those

reported in the literature where BAE has been found to be of very limited use in treating haemoptysis from tumour haemorrhage except as a temporising measure (Hayakawa et al. 1992, Swanson et al. 2002).

### 5.3 Laboratory and Haematological Parameters

Abal et al (2001) recorded the sequential haemoglobin levels of patients presenting with life threatening haemoptysis and concluded that, as in gastrointestinal haemorrhage, this may be of value in assessing the severity of the haemorrhage (Abal et al 2001). Wong et al found that the drop in haemoglobin during haemoptysis and the requirement for a blood transfusion as important parameters in their definition of "life threatening haemoptysis" (Wong et al 2002). In my study the haemoglobin was measured on admission and during the hospital stay however there was no correlation in my prospective study between the haemoglobin level and the patients' response to treatment or their outcome. In the retrospective study 25% and in the prospective study 32% of patients required blood transfusions. There was also no correlation between the white cell count or erythrocyte sedimentation rate and patient outcome.

Sputum culture for bacterial growth in these patients was generally unhelpful. This may be due to inadequate collection procedures or that patients were generally too ill to produce sputum.

### 5.4 HIV Status

As only 48% of patients in the prospective study were tested for HIV with their written consent, it is difficult to estimate the true prevalence of HIV seropositivity in the cohort. As the HIV positive patients had a history of

pulmonary TB they meet the World Health Organization's criteria for the diagnosis of AIDS (http://www.who.int/health_topics/hiv_infections/en/). I did not measure the CD4 lymphocyte levels because of cost and availability. In retrospect I believe the information of the degree of T cell immunosuppression may have provided useful information on the aetiology of pulmonary infections in these patients. Both HIV positive cohorts will represent varying degrees of immunosuppression but the important point of the studies is that BAE is effective in HIV positive patients for the treatment of massive haemoptysis. As far as I am aware this study is the only report that documents the effectiveness of BAE in treating HIV positive patients with massive haemoptysis.

### 5.5 Imaging Evaluation of Life Threatening Haemoptysis

#### 5.5.1 Chest Radiography

I found that the chest radiograph was of limited use in detecting the origin and cause of bleeding especially if the pulmonary disease was bilateral and diffuse as it was in 59% and 50% of the retrospective and prospective studies respectively. I correctly localised the bleeding origin in 24% and 27% of patients respectively. This is consistent with the previous studies which demonstrate that the chest radiograph was non localising for the detection of the source of bleeding in 17 % to 81% of patients (Hsiao et al. 2001). The limitation of chest radiographs in detecting the source of the haemoptysis needs to be recognised by both chest physicians and radiologists. The chest radiograph is however useful in providing an image of the global extent of the

pulmonary disease. The chest radiograph is easy to perform and relatively inexpensive and so will always remain the best initial investigation for haemoptysis.

### 5.5.2 High Resolution CT (HRCT) of the Lungs

Even though it was not possible to scan half the patients because they were too dyspnoeic to breath hold during the HRCT scan, the additional information obtained in those patients scanned was very valuable in localising the bleeding and determining the underlying aetiology. The results from the prospective study are similar to that of Haponick et al where CT correctly localised the cause of bleeding in 88% of patients scanned with haemoptysis when correlated with angiography (Haponik et al. 1987). The accuracy of CT was much lower in the retrospective study as HRCT scanning was not routinely performed at that time. In the series of Millar et al and McGuinness et al, CT detected the cause of bleeding in 50% and 61% of patients respectively (McGuinness et al. 1994;Millar et al. 1992). Both Naidich et al and McGuiness et al make the important point that a significant number of cases of bronchiectasis and aspergillomas were detected only on HRCT and not on the chest radiographs in their series (Naidich et al 1990). This finding is the same as in my study, where HRCT detected both additional cases of focal bronchiectasis and intracavitatory aspergillomas not detected on the chest radiographs. These results confirm the importance of performing HRCT scans on these patients where possible. Naidich recommends that the optimal HRCT

technique consists of 1-2mm thick sections obtained every 10mm from the thoracic inlet to the lung bases using a high frequency spatial algorithm for reconstruction such as a bone algorithm (Naidich, Funt, Ettenger, & Arranda 1990). I used this protocol in the patients scanned in the prospective series. The major disadvantage however is that many patients are too ill or dyspnoeic to breath held for the 15 seconds required to produce the scan. In these patients a conventional CT scan with 5mm thick sections is adequate.

### 5.5.3 Significance of Pleural Thickening

Pleural thickening greater than 3mm suggests the presence of a non-bronchial systemic arterial collateral supply in patients with life threatening haemoptysis (Yoon et al. 2003b). This was confirmed in the prospective study where 18 out of 34 patients scanned had pleural thickening greater than 3mm and all 18 patients had transpeural collaterals on angiography originating from systemic arteries that required embolization. Yoon et al found that in a prospective study of 40 patients with massive haemoptysis CT had a sensitivity of 80% and specificity of 84% in predicting the presence of intercostals, subclavian and axillary branch collateral supply to the pleural in the presence of pleural thickening. In our patients, especially with apical pleural thickening, enlargement of the intercostals, internal thoracic and axillary branches were found on selective angiography. Pleural thickening was especially common at the apex of the lung in those patients with chronic tuberculosis. The presence of pleural thickening on CT scan requires than a search be made for a collateral

pleural supply at the time of arteriography.

### 5.5.4 Detection of Enlarged Bronchial and Systemic Arteries

Contrast enhanced CT of the mediastinum on soft tissue settings (window 300 HU, centre 150 HU) can demonstrate enlarged right bronchial arteries as they originate from the aorta both in the precarinal space anterior to the carina and posterior to the proximal right main bronchus (Kuiper et al. 2003). Enlarged left bronchial arteries can be detected anterior and posterior to the proximal left main bronchus (Song et al. 1998). This was demonstrated in my study in those patients who had contrast enhanced studies.

I found that performing a thoracic panaortogram with a pigtail catheter at the level of the aortic arch proximal to the origin of the left subclavian artery to be very useful in detecting abnormal bronchial and systemic arteries that were supplying the pulmonary lesion that was bleeding. Aortography was performed prior to embolization in both studies in 10% of patients when there was a technical difficulty in finding the origin or selectively catheterising the bronchial arteries. Chun et al used aortography routinely post embolization to detect if any abnormal systemic arteries had been missed (Chun et al. 2003). They found that 14.5% of abnormal arteries had not been detected at the initial embolization but had been found after aortography. This included inferior phrenic and intercostal arteries in particular (Chun et al. 2003). The other value of performing aortography is to detect ectopic bronchial arteries, that

commonly originate from the superior aspect of the aortic arch (Sancho et al 1998, McPherson et al. 1990).

### 5.5.5 Bronchial and Systemic Arteriography

#### a. Bronchial Artery Anatomy

The bronchial anatomy in both studies is similar to the anatomy described by Botenga and Uflacker et al but differs from the patterns originally described by Cauldwell et al (Botenga 1969). Cauldwell et al. used microdissection techniques on cadavers while Botenga and Uflacker reported the angiographic anatomy. Given the small size of the bronchial arteries, the angiographic anatomical descriptions are probably a more accurate description of bronchial artery anatomy. The presence of a right intercostobronchial trunk was constant in 90% of the patients in my prospective study. This trunk arises from the posterolateral wall of the aorta as opposed to the left and right bronchial arteries, which arise from the anterolateral wall of the aorta. The origins and patterns of variation of the arteries are important for the radiologist to know when performing selective arteriography. I found that the origins of the bronchial arteries are close to the origin of the left main bronchus on fluoroscopy as described by Tanomkiat et al. (Tanomkiat et al. 2003) . This is a very useful radiographic landmark. The right intercostobronchial trunk is important as it supplies the right upper lobe bronchus and often gives radicular feeders to the spinal cord (Uflacker et al. 1985). The commonest pattern was a

right intercostobronchial trunk with two separate left bronchial arteries in 40% of patients, followed by a right intercostobronchial trunk and one left bronchial artery in 20% of patients, followed by a ICBT and separate bronchial on the right and two left bronchials in 20%, a single trunk dividing into left and right bronchial arteries in 10% of patients and a right ICBT and separate right bronchial and separate single left bronchial in 10% of patients.

**b. Bronchial Artery Size**

The normal bronchial artery diameter is small, measuring less than 2mm. The bronchial artery blood supply accounts for only 1% of normal cardiac output (Song et al. 1998a). The bronchial arteries hypertrophy in the presence of pulmonary diseases especially chronic inflammatory diseases, thromboembolic disease and chronic obstructive pulmonary disease (Deffebach et al. 1987, Charan et al. 1997). Hypertrophy of the bronchial arteries is far more pronounced with bronchial diseases such as bronchiectasis as opposed to alveolar air space or interstitial lung diseases (Liebow et al 1948). This is understandable considering that the bronchial arteries first supply the bronchial tree and only supply the diseased pulmonary parenchyma through broncho-pulmonary anastomoses (Deffebach et al 1987). Bronchial artery hypertrophy is however surprisingly rapid (Deffebach et al 1987). Work by Mathes demonstrated dilatation of the bronchial arteries and broncho-pulmonary anastomoses in 54 lungs with pneumonia at post mortem (Mathes et al 1932). They found obliteration of pulmonary arterioles in areas of consolidation.

Decreased pulmonary flow in pneumonia is well described and demonstrated non invasively today by perfusion lung scans using technetium 99m imaging. Mathes found, using a dog model, that bronchial arteries enlarge within days of an acute pulmonary infection (Mathes et al 1947).

Twenty eight per cent of patients in the prospective study had normal sized bronchial arteries although there was evidence of pulmonary hypervascularity. These patients had acute early pulmonary tuberculosis or bacterial infection. Many of these patients were HIV positive. It is possible that the absence of bronchial artery angiogenesis in these patients was due to their poor cellular immune response. Obviously because of normal size bronchial artery's small diameter, selective catheterisation with a 5F catheter is often difficult and the use of microcatheters would have been a better choice for safe embolization.

**c. Bronchial Artery Angiographic Findings**

The presence of bronchial artery hypertrophy, pulmonary parenchymal hypervascularity and neovascularity and bronchopulmonary shunting are all indirect signs of a focal pulmonary bleeding site. Bronchopulmonary shunts are commonly detected on bronchial arteriography in some series (Ramakantan et al. 1996, Osaki et al. 2000). Bronchopulmonary shunts are due to

hypertrophy of the bronchial artery-pulmonary artery anastomoses that occur naturally along the distal bronchial tree. These shunts are thought to contribute to haemoptysis by elevating the pulmonary pressure in the affected lobe to systemic arterial pressure (Liebow et al 1947). Osaki et al noted that the presence of shunts on angiography was an indicator of recurrent haemoptysis (Osaki et al. 2000). I did not find this correlation in my study. Contrast extravasation from an active bleeding site is rarely reported in any of the large series. I did not detect contrast extravasation in either of my studies. The presence of a bronchial artery aneurysm in 3 patients did not change the patient outcome either. Bronchial artery aneurysms are inflammatory false aneurysms usually associated with tuberculous cavities.

The results from my study demonstrate that bronchial artery arteriography with HRCT are the two most accurate methods to localise the bleeding site. It is important to correlate the angiographic findings of the site of bleeding with the anatomical level in the axial plane of the HRCT scan to identify the bleeding site especially in the presence of bilateral or diffuse pulmonary disease. HRCT will guide the angiographer to the affected lobe and is therefore an important complementary investigation to bronchial arteriography.

**d. Systemic Trans-Pleural Collaterals**

Collaterals from intercostals, internal thoracic and subclavian artery branches

are important arterial supplies to bleeding pulmonary lesions, especially in tuberculosis (Yoon et al. 2003). These anastomoses develop between the systemic arteries and pulmonary artery branches in the presence of pleural thickening and adhesions (Yoon et al 2003). There was good correlation between the presence of pleural thickening greater than 3mm especially at the lung apex on CT and presence of transpleural collaterals on angiography in the prospective study. The presence of pleural thickening warns the angiographer that a search for transpleural collaterals from systemic arteries must be made.

**e. Pulmonary Arteriography**

Pulmonary artery aneurysm (Rasmussen aneurysm) is an uncommon but rarely detected cause of recurrent haemoptysis in patients with inflammatory pulmonary disease especially pulmonary TB (Sanyika et al. 1999). These are inflammatory aneurysms that frequently remain undetected, as pulmonary angiography is not routinely performed in patients with life threatening haemoptysis. In the literature individual case reports are described involving cases of chronic pulmonary tuberculosis with Rasmussen aneurysms (Patankar et al. 2000;Santelli et al. 1994). Most aneurysms can be effectively treated by interventional techniques using balloons or steel coils (Sanyika et al 1999). The true prevalence of these pulmonary aneurysms is unknown because apart from contrast enhanced CT of the pulmonary arteries (CTA) there is no non-invasive method to examine the pulmonary arteries in these ill patients. I recommend

pulmonary angiograms be performed in patients with persistent recurrent haemoptysis to detect pulmonary aneurysms.

### 5.6 Role of Bronchoscopy

The local experience with bronchoscopy in patients with life threatening haemoptysis is limited. Only 21% of patients had bronchoscopy performed, usually using a rigid bronchoscope, in theatre under general anaesthetic. The origin of bleeding was detected in 33% of these patients in my prospective study. Bronchoscopy is viewed as a complementary investigation to HRCT in patients with haemoptysis (Marshall et al. 1996;Naidich et al. 1995). Bronchoscopy will allow examination of the bronchial mucosa and lumen and biopsy of any endobronchial lesion. The detection rate of focal lesions with fibre optic bronchoscopy in patients with haemoptysis, where the chest radiograph is non localising, is generally low in most series varying from 4 to 16% (Gong, Jr. et al. 1981;Jackson et al. 1985;Weaver et al. 1979). Fibreoptic bronchoscopy is both technically difficult and dangerous to perform during a life threatening haemoptysis because it is difficult to suction the airway adequately. Therefore only rigid bronchoscopy should be performed in this setting and should be limited to surgical candidates. Most authors believe than CT, or preferably HRCT, be performed prior to fibre-optic bronchoscopy so that the bronchoscopist can have a road map of where focal bronchial lesions are located and the origin of the bleeding can be detected accurately (Marshall et al. 1996). Other authors believe than bronchoscopy has a very limited role or

even no role, in the diagnosis of haemoptysis if the bleeding can be localised on chest radiograph or on HRCT (Hsiao et al. 2001;Snider 1979;Weaver et al. 1979).

In our setting bronchoscopy will probably remain as a second line of investigation following HRCT examination for preoperative assessment.

## 5.7 Patient Outcome following Bronchial Artery Embolization

Bronchial artery embolization was technically very successful in both studies and this is consistent with the results from all major series (**table 1**). A problem in a number of patients was that because the bronchial artery diameter was normal, satisfactory siting of a 5F catheter tip was difficult. As access to microcatheters was limited, because of financial constraints, these patients could not always be safely embolized. In one patient, detection of the anterior spinal artery feeders from the right intercostobronchial branch was the reason the procedure was abandoned. Tanaka however successfully used micro-catheters to superselect bronchial artery branches distal to the origins of the spinal feeders and embolize these vessels safely (Tanaka et al. 1997). If we had access to microcatheters on a regular basis, we would probably be able to improve our technical success rate.

There was only one serious permanent complication following the procedure in the prospective study. A patient developed a middle cerebral artery infarct

confirmed on CT a few hours after the procedure. This was probably due to cerebral thromboembolism of an aortic plaque during catheter manipulation in the arch.

No complications from spinal cord ischaemia were detected in either series in my study. The risk of spinal cord ischaemia has diminished over the years as ionic hyperosmolar contrast agents have been replaced with more physiological non-ionic iso-osmolar contrast agents and embolic material design has improved (Yoon et al. 2002). Special care is needed when embolizing collaterals from the right intercostobronchial trunk as this artery often provides feeders to the spinal cord.

Chest pain, which was transient, was present in a minority of patients and was less common in the prospective study using microspheres as the embolic material. The chest pain was always transient, settling within a few hours following the embolization procedure.

There was no statistical difference between the retrospective and prospective studies in the immediate technical success rate of embolization at the end of the procedure ($p=0.76$ chi square method with 1 degree of freedom). However at the end of the first 24 hours after embolization, the success rate was 87% for the prospective study vs 68% in the retrospective study. This difference was statistically significant ($p=0.0018$ chi square method with 1 degree of freedom). This demonstrates the value of using gelatin cross linked acryl

microspheres (Embospheres) as the embolic material of choice for BAE, both in terms of better initial success rate and less minor complications such as chest pain. Microspheres have been used successfully for embolisation of head and neck tumours, meningiomas and uterine fibroids. However this study is the first large series of its use to treat life threatening haemoptysis by BAE (Beaujeaux et al 1996, Bendszus et al 2000). Microspheres larger than 500 microns will not pass through bronchopulmonary anastomoses and result in a more uniform and total distal occlusion of the vascular bed than PVA particles.

### 5.8 The Problem of Recurrent and Persistent Haemoptysis

Recurrent haemoptysis is the major problem with bronchial arterial embolization. The recurrence rate within the first week after BAE in both series in this study were 34% in the retrospective study and 13% in the prospective study. Recurrent haemoptysis is initially due to incomplete embolization and the opening up of new transpleural and broncho-pulmonary collaterals. The recurrence rate was reduced in the prospective study by carefully demonstrating all systemic transpleural collaterals that were abnormal at the initial angiography and that could safely be embolized using microspheres. The use of post embolization panaortography to detect missed systemic feeders as proposed by Chun et al may reduce the rate of recurrent haemoptysis further (Chun et al. 2003). This result compares favourably with large series published where recurrence rates vary from 12% to 21% post BAE

(Osaki et al. 2000). Osaki et al emphasise that recurrence can occur up to 3 years post embolization, especially when there is bronchiectasis or when a broncho-pulmonary shunt can be demonstrated on angiography. Osaki followed up 22 patients up for 25 to 88 months (median 47 months) and found a 50% recurrence rate. Late recurrence is usually due to progression of the original pathology (White, Jr. 1999). In my cases this would be due to inadequate treatment of tuberculosis or the development of multi-drug resistant (MDR) tuberculosis.

Patients who have early recurrent haemoptysis in my study had a high mortality, 47% and 56% respectively in the retrospective and prospective series. These patients had compromised respiratory function as well as metabolic disturbances. Many patients underwent surgical resections. These findings are similar to those in large published series (Knott-Craig et al. 1993).

White makes an important point that the literature on patient results and outcome is confusing in that often the incorrect terminology is used to decide on what "successful" outcome means after BAE (White, Jr. 1999). There is a need for long term follow up of patients beyond 30 days to determining true recurrence rates for haemoptysis (Osaki et al. 2000). This is the major limitation of my study in that long term follow up of patients was not possible as patients were lost to follow up and could not be traced.

### 5.9 Surgical Resections for Haemoptysis

Pulmonary resections decreased from 16% to 10% of patients from the retrospective to the prospective study. This is probably due to the fact that the recurrence rate for haemoptysis decreased from 34% to 13%. Emergency resection has a high mortality often exceeding 50%. Patients are often haemodynamically compromised with poor respiratory reserves. Emergency pulmonary resection requires a high degree of expertise and experience from both the surgeon and anaesthetist for the best outcome. Often these procedures are performed after hours when this expertise may be unavailable. Most authors now agree that emergency resection should be avoided (Knott-Craig et al. 1993). Surgical interval resection following BAE is still considered to be the procedure of choice to treat severe haemoptysis in patients with focal disease in one lung (Garzon et al. 1982;Knott-Craig et al. 1993). However in my retrospective and prospective studies only 10 patients (11%) and 5 patients (7%) respectively were surgical candidates with focal pulmonary disease and good pulmonary reserves.

### 5.10 Mortality

There was an increase in mortality from 5.7% to 10% between the retrospective and prospective studies, this is probably due to the inclusion of patients with cancer. This difference was not statistically significant (chi square test pvalue 0.434 ). This compares favourably with reported series in the

literature. The causes of death in my series were persistent pulmonary haemorrhage, respiratory failure and metastatic pulmonary disease. In the non-neoplastic cases patients had prior recurrent haemoptysis.

### 5.11 Limitations of the Study

The major limitation of this study is the absence of long term follow up. This is due to the difficulty of tracing patients once they leave hospital.

### 5.12 Future Research

Although gelatin coated microspheres are an improvement in embolic material design making selective embolization easier, BAE requires considerable expertise and expensive infrastructure that is unavailable outside large tertiary care hospitals in South Africa. Newer embolic materials are constantly being developed. "Onyx" is an ethylene vinyl alcohol copolymer preparation in liquid form than is easier to use than cyano-acrylate glues and has shown promise as an embolic agent in the brain and spinal cord. It is possible likely that it may be effective in BAE if it does not cross bronchopulmonary anastomoses.

A better understanding of the factors that promote angiogenesis of the bronchial arteries in response to inflammation and neoplasia is likely to produce drugs that can inhibit angiogenesis (Charan et al.1997) . Not only

hypoxia but also infection is a potent stimulator of angiogenesis in the lung (Charan et al. 1997). Lung infections result in the accumulation of macrophages and neutrophils. Activated macrophages promote angiogenesis by producing tumour necrosis factor alpha, basic fibroblast factor growth factor and tumour necrosis factor beta (Carmeliet 2003). Neutrophils produce interleukin-8 II in the presence of infection. All these factors promote endothelial activity and angiogenesis in the bronchial vasculature (Carmeliet 2003;Charan et al. 1997). Integrins are natural anti-angiogenic factors produced by endothelial cells that diminish this pathological process (Carmeliet 2003). By stimulating anti-angiogenic activity in the bronchial artery vascular bed with drugs delivered by selective bronchial artery catheterisation, haemoptysis may be controlled more effectively in the future.

# CHAPTER 6

# PLAN FOR INVESTIGATING AND TREATING LIFE THREATENING HAEMOPTYSIS

## 6.1 Overview of the Problem

Life threatening haemoptysis is a major cause of morbidity and mortality in South Africa today. My study demonstrated that the aetiology of severe haemoptysis is changing with more patients presenting with acute destructive pneumonias than previously.

The treatment of haemoptysis locally is a major consumer of scarce financial, infrastructural and human resources in the public health system.

## 6.2 Major problems that need to be addressed are:

1. Which patients require urgent treatment and high care?
2. How to investigate patients in the most time and cost effective method to localise the origin of the bleeding most effectively?
3. How to determine the underlying pulmonary disease most effectively?
4. How to treat these patients to achieve the best outcome?
5. How to solve the problem of recurrent haemoptysis?

### 6.2.1 Which patients require urgent treatment and high care?

The main cause of death in severe haemoptysis is not haemorrhage itself but compromised respiratory function. Alveolar bleeding exceeding 400mls severely compromises alveolar gas exchange. Patients who have one or more haemoptyses greater than a total of 300mls in a 24-hour period require urgent treatment in a high care facility.

**High risk patients that require identification are:**

Patients who bleed more than 1000mls in a 24 period are at risk of dying.

Patients with bilateral pulmonary disease.

Patients with poor respiratory reserve.

Patients with intracavitatory aspergillomas.

Patients with recurrent or previous haemoptysis.

Patients should be transferred to a hospital where high care facilities and specialist care is available. Such a centre will require specialist physicians, surgeons, intensive care specialists and radiologists to be available on an emergency basis.

### 6.2.2. How to investigate patients in the most time and cost effective method?

Once a patient is resuscitated, an erect frontal chest radiograph should be the

first investigation. This can be a mobile radiograph with the patient sitting up in bed.

To determine the origin of the bleeding and underlying pulmonary disease a high resolution CT (HRCT) of the lungs should be the next investigation. If the patient is too dyspnoeic to co-operate with breathing to perform a HRCT scan, a conventional spiral CT of the lungs should be attempted.

If a focal bronchial luminal or wall lesion is identified on CT a rigid bronchoscopy is recommended if the patient can co-operate with the endoscopist to characterise and biopsy the lesion if possible. Fibreoptic bronchoscopy is not recommended because of the difficulty of suctioning the airway adequately during life threatening haemoptysis.

If the CT demonstrates diffuse or focal pulmonary disease, the patient should proceed to arteriography. It is important to identify all possible arterial feeders to the bleeding lesion, so that detecting the source of bleeding prior to angiography is very valuable so as to provide the radiologist with a road map. The presence of pleural thickening on the CT scan is a good indicator of the presence of trans-pleural collaterals. Arteriography must include selective bronchial, subclavian, internal thoracic and intercostals arteriography. If there is difficulty in detecting the origins of the bronchial arteries, an arch aortogram should be performed to detect any anomalous bronchial arteries. The angiographer must pay attention to the presence of bronchial arterial hypertrophy, parenchymal hypervascularity and the presence of broncho-pulmonary shunts. All these signs are indicators of

possible bleeding sites for embolization.

### 6.2.3. How to determine the underlying pulmonary disease most effectively?

The chest radiograph will provide a global image of the extent of pulmonary and bronchial disease. As most patients have diffuse or multifocal acute or chronic pulmonary disease, HRCT is particularly valuable in providing information on the underlying disease process. HRCT is especially useful to detect intracavitatory aspergillomas, focal bronchiectasis and bronchial wall lesions such as bronchial carcinomas. HRCT should be the investigation of choice when available and when the patient can co-operate with breathing to enable a scan to be performed.

It is important to obtain the following laboratory investigations: full blood count, INR (internationalised normalised ratio), sputum for microscopy, culture and sensitivity, sputum for acid fast bacilli and TB culture, arterial blood gas measurement and simple spirometry to determine pulmonary function and respiratory reserve.

For the surgical evaluation of the patient it is important to obtain a clinical history of the patient's effort tolerance to assess the respiratory reserve.

### 6.2.4. How to treat these patients to achieve the best outcome?

Bronchial artery embolization is the best treatment option available to patients locally. BAE has moved from being a temporising treatment in an emergency to

become the definitive treatment for almost all patients. Surgical resection should be reserved for patients with focal disease and a good pulmonary reserve. Most patients are unsuitable for surgery because of diffuse or multifocal pulmonary disease and poor respiratory reserve. Endobronchial techniques require a co-operative patient and a high degree of technical skill by the endoscopist and therefore should be used as a second line treatment. The key to improving the patient's outcome is to embolize all possible arterial feeders in the lung suspected of being the cause of the haemoptysis as completely as possible with a permanent embolic material in a patient who has been adequately resuscitated. There is no doubt that gelatin cross linked acryl microspheres (embospheres) are major advance in embolic material design compared to previously used embolic materials. The microspheres are easier to deliver through the catheter than polyvinyl alcohol particles and patients have less minor complications such as chest pain or discomfort after the procedure. We use particles larger than 500 microns so that they do not cross normal broncho-pulmonary anastomoses and infarct normal lung parenchyma.

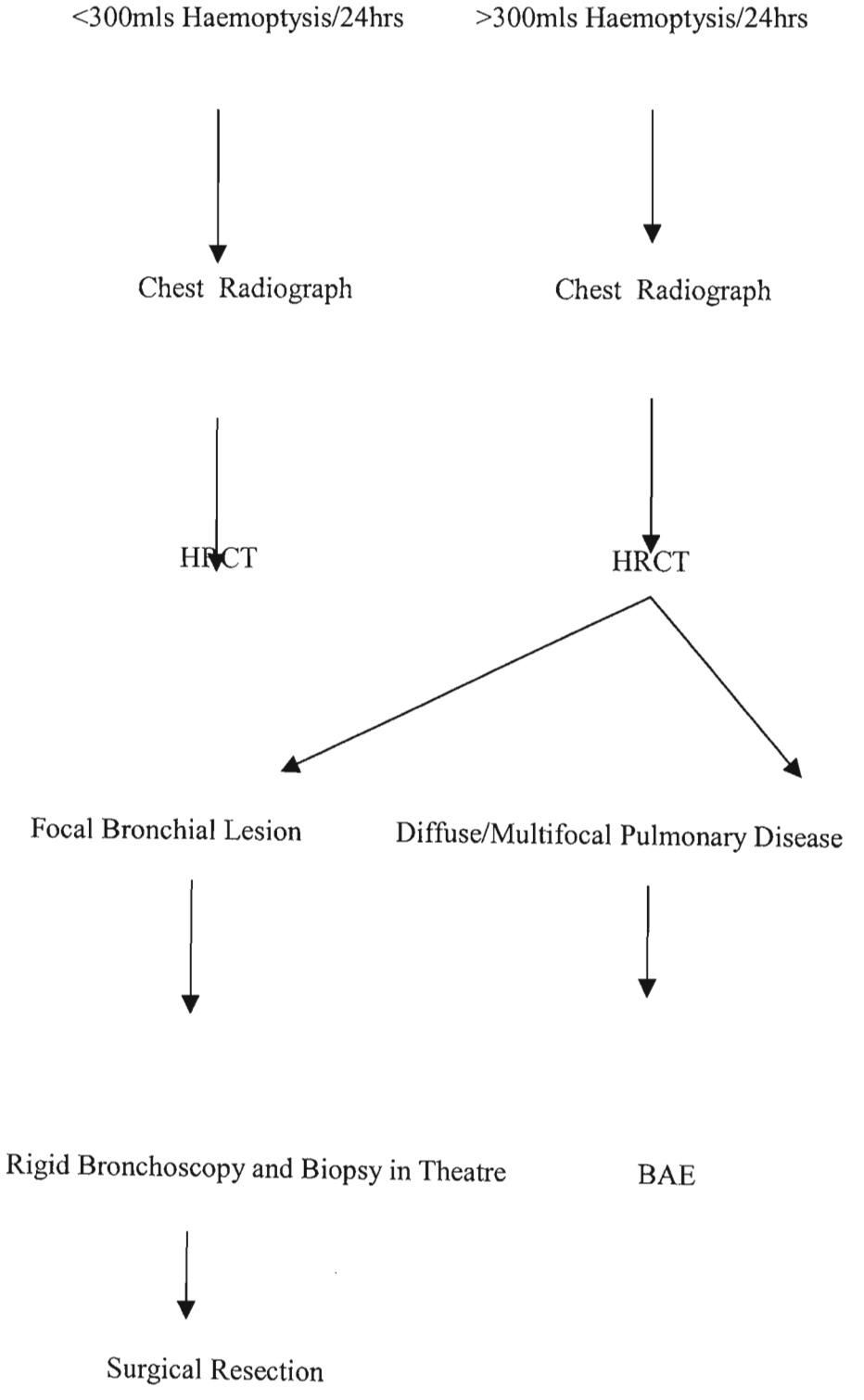
### 6.2.5. How to solve the problem of recurrent haemoptysis?

This is the most difficult problem to solve. Patients with recurrent haemoptysis have a high mortality and do not respond well to repeat embolization. It is important in these patients to exclude trans-pleural collaterals by performing a complete arteriographic investigation and embolizing all possible feeders and to exclude the possibility of a pulmonary artery aneurysm by performing a

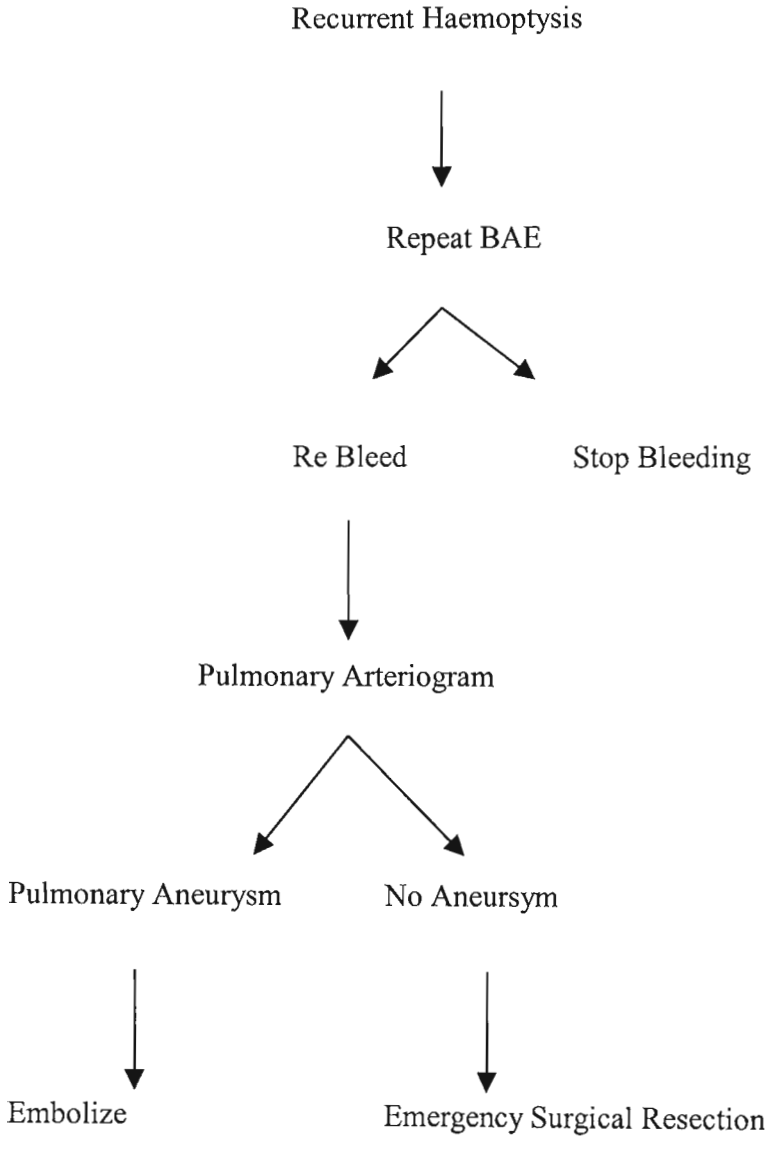
pulmonary arteriogram.

Further improvements in embolic materials are likely to reduce the rate of recurrence. Onyx is an ethylene vinyl alcohol copolymer preparation in liquid form than is easier to use than cyano-acrylate glues and has shown promise as an embolic agent in the brain and spinal cord. Patients with pulmonary TB or pyogenic infection must be on appropriate ant-TB treatment or antibiotics as incompletely treated infections are often a cause for recurrent bleeding.

**6.3 Plan of Investigation and Treatment of Life Threatening Haemoptysis**



### 6.4 Plan for Treating Recurrent Haemoptysis



# CHAPTER 7

# CONCLUSIONS

## 7.1 The Problem of Life Threatening Haemoptysis in South Africa

Life threatening haemoptysis is a common clinical emergency in South African hospitals. The investigation and management of haemoptysis and the underlying pathology is difficult and expensive in terms of health care resources. My study illustrates the changing aetiologies of life threatening haemoptysis over the last five years from bronchiectasis to acute destructive pneumonias. This may be due to the high prevalence of HIV/AIDS in the cohorts.

## 7.2 The Investigation of Life Threatening Haemoptysis

My study demonstrates the importance of the chest radiograph to give a global assessment of the extent of pulmonary disease. The chest radiograph should remain the initial imaging investigation; it is cheap and readily available. However it is inaccurate in detecting the origin of the haemoptysis. High resolution CT of the lungs (HRCT) is the best single investigation to demonstrate the cause and origin of the bleeding. My study demonstrates that aspergillomas and focal bronchiectasis were detected on HRCT scans that were

missed on chest radiographs. The presence of pleural thickening on CT, especially involving the lung apex, suggests the presence of transpleural collaterals and the need to perform systemic arteriography at the same time as bronchial arteriography.

The role of bronchoscopy in my study appears limited to the pre operative workup of those patients with focal disease who are surgical candidates. Bronchoscopy is very difficult to perform in sick dyspnoeic patients and diagnostic yield in my study was low.

Bronchial arteriography remains the gold standard to detect the bleeding source. No case of contrast extravasation from a bleeding bronchial artery was detected, however the presence of focal pulmonary hypervascularity, neovascularity and broncho-pulmonary shunts were good indicators of a bleeding sites. Knowledge of anatomical variations is important for the radiologist so that an adequate arteriographic study can be performed. Few anomalous bronchial arteries were detected on aortography in this study. Thoracic aortography is recommended if there is any technical difficulty in detecting the bronchial arteries. Bronchial arteries hypertrophy in the presence chronic pulmonary diseases such as bronchiectasis but often remain normal in diameter in acute pneumonias. This is especially common in HIV positive patients and may represent diminished angiogenic triggers from compromised macrophage and leucocyte function in these patients.

## 7.3 The Treatment of Life Threatening Haemoptysis

Bronchial and systemic artery collateral embolization on the side that is suspected to be bleeding is the treatment of choice for severe haemoptysis locally. Although recurrent haemoptysis remains a problem, the use of newer embolic materials such as gelatin coated acryl microspheres make embolization easier and safer for the patient compared to embolization with poly vinyl alcohol particles. The technical success rate is significantly higher ($p<0.01$) with microspheres compared to PVA particles. It is extremely important to perform a thorough embolization in the presence of transpleural collateral vessels. The role of BAE has moved from an emergency treatment to that of a definitive treatment in patients with bilateral pulmonary disease and or poor respiratory function.

In my prospective study patients with intracavitatory apergillomas responded well to microsphere embolization. Patients with upper lobe fibrosis and pleural thickening were however more likely to have recurrent haemoptysis. This presumably is due to undetected transpleural collaterals on the apex of the lung. Post embolization aortography may be useful here to detect collaterals that had been missed at embolization.

Surgical resection should be reserved for those patients with focal disease in one lung and good respiratory reserve.

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