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*STUDIES OF EFFUSIVE
CONSTRICTIVE PERICARDITIS*

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Abstract

Tuberculous (TB) pericarditis is associated with a mortality rate of 17-40% despite treatment with anti-tuberculosis drugs. The complications of TB pericarditis that confer mortality and morbidity are pericardial tamponade, effusive constrictive pericarditis, and constrictive pericarditis. Whilst the diagnosis and treatment of pericardial tamponade and constriction are well established, there is a paucity of evidence on the frequency and significance of tuberculous effusive constrictive pericarditis.

The primary purpose of this work was to determine the prevalence, predictors, fractal (geometric) structure, biomarker signature, and outcome of effusive constrictive TB pericarditis. An invasive hemodynamic study of 68 patients with TB pericardial effusion showed that effusive constrictive disease was common, affecting about 50% of cases. Pericardial tamponade, which was previously considered to be uncommon in TB pericarditis, occurs in a similar proportion of cases but, contrary to previous reports, is not linked to the occurrence of effusive constrictive disease. The combination of pericardial tamponade and effusive constrictive disease occurred in about a quarter of cases.

Furthermore, I have shown through a series of studies that: (1) TB effusive constrictive pericarditis is predicted by a high right atrial pressure (> 15 mmHg); (2) the fibrin strands seen on echocardiography have a fractal geometry as opposed to a euclidean dimension, and that this fractal dimension is indistinguishable between pure effusive and effusive constrictive disease; and (3) that effusive constrictive disease is characterized by a cytokine profile that is distinct from pure effusive disease. In addition, this cytokine profile suggests that it is tissue inflammation and not fibrosis which distinguishes effusive constrictive from pure effusive tuberculous pericarditis; and that IL-10 is a candidate biomarker for the diagnosis of effusive constrictive physiology in patients with TB pericarditis. The study of the outcome of TB effusive constrictive pericarditis showed no significant increase in the frequency of constrictive pericarditis at 6 months of follow-up compared to cases with pure TB effusive disease. There was also no difference in 6-month all-cause mortality rate between the two groups.

Finally, TB pericarditis is associated with a significantly lower level of N-acetyl-Ser-Asp-Lys-Pro [AcSDKP] (an anti-fibrotic biomarker) in the pericardial fluid than in normal controls. The anti-fibrotic effect of angiotensin-converting enzyme (ACE) inhibitors is mediated partly by increasing the levels of AcSDKP in tissues. Therefore, this study has identified AcSDKP as a novel therapeutic target for the prevention of pericardial fibrosis through the use of ACE inhibitors.

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ABBREVIATIONS

AcSDKP	N-acetyl-Ser-Asp-Lys-Pro
AIDS	Acquired Immune Deficiency Syndrome
ADA	Adenosine deaminase
CI	Confidence Interval
CT	Computed Tomography
CPK	Creatine phosphokinase
CKMB%	Creatine Kinase MB %
CXR	Chest x-ray
ECG	Electrocardiogram
ECP	Effusive Constrictive Pericarditis
Gal-3	Galectin-3
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IFN- γ	Interferon gamma
IMPI	Initiative for the Investigation and Management of <i>Pericarditis</i>
IL-1 β	Interleukin-1beta
IL-6	Interleukin-6
IL-10	Interleukin 10
IL-17	Interleukin 17
IL-22	Interleukin 22
IPP	Intra-pericardial pressure
IQR	Inter-quartile range
LDH	Lactate dehydrogenase
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
<i>MTb</i>	<i>Mycobacterium Tuberculosis</i>
NT-pro BNP	N-terminal Pro Brain Naturetic Peptide
NYHA	New York Heart Association
OR	Odds Ratio
TB	<i>Tuberculosis</i>
RAP	Right Atrial Pressure
RR	Risk Ratio
SD	Standard Deviation
Th1	Tcell helper-1
Th2	Tcell helper-2
TGF- β	Transforming growth factor beta
TNF- α	Tumor Necrosis Factor-alpha
WHO	World Health Organization
ZN	Ziehl-Neelson

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Chapter 1

BACKGROUND TO THE THESIS

1.0 The anatomy, physiology and functions of the pericardium

The pericardium is a thin avascular two-layered fibro-serous sac, which surrounds the heart, proximal aorta, pulmonary artery, vena cava and pulmonary veins. The visceral layer is a serous single layer of ciliated mesothelial cells while the fibrous outer layer is made up predominantly of interwoven collagen and elastin (Hutchison 2009). During embryological development, as the heart tube grows into and invaginates the pericardial sac, the serosal layer surrounds the myocardium to form the epicardium [or visceral pericardium] and then folds back on itself to line the inner portion of the outer fibrous membrane (Manner, Perez-Pomares et al. 2001; Hutchison 2009). The 2 mm thick parietal pericardium receives its blood supply from branches of the internal mammary artery and is innervated by the phrenic nerve (Spodick 1997) while the epicardium is also innervated through sympathetic afferent fibers (Hutchison 2009).

Under normal conditions the pericardium is separated by a potential space that contains 10-50 ml of an ultrafiltrate composed of high amounts of phospholipids, albumin and surfactant-like prostaglandins (Spodick 1992). This pericardial fluid is produced by the serous layer and drained by the thoracic and right lymphatic ducts (Spodick 1992) and serves to lubricate and minimize friction between the parietal and visceral pericardial surfaces. The normal pressure within the pericardium is similar to pleural pressure and ranges between -5 mmHg at the end of inspiration and +3 at the end of expiration (Fowler, Shabetai et al. 1959; Spodick 1992). The difference between the pressure within the right ventricle at end-diastole and the intrapericardial pressure is called the transmural filling pressure and is the major determinant of cardiac filling in diastole. The lower intrapericardial pressures during inspiration result in an increase in the transmural pressure and accounts for the increased filling of the right ventricle during that phase of respiration.

Although a small fraction of the population is born without a pericardium (see below), it does serve a number of important functions. These include: 1] anchoring the heart within the mediastinum; 2] preventing spread of infection and malignancy from surrounding structures; 3] limiting the

acute dilation of cardiac chambers, particularly the right atrium and right ventricle; and 4] balancing right and left ventricular compliance, interactions and output (Troughton, Asher et al. 2004; Hutchison 2009).

1.1 The pericardium as anchor

The parietal pericardium and the underlying heart are anchored in place by ligamentous attachments to the sternum, vertebrae and diaphragm. These attachments prevent the heart from moving within the chest during forward and backward motions making it less prone to the acceleration or deceleration injuries seen with the descending aorta (Hutchison 2009).

1.12 The pericardium as a barrier to the spread of disease

Infection and malignancies are able to spread by a number of mechanisms including hematogenous spread, metastases, spread by the lymphatic system and contiguous spread. The pericardium is able to act as an effective barrier to the heart by contiguous spread.

1.13 The role of the pericardium in limiting cardiac chamber dilatation and maintaining optimal pressure volume relationships

The normal pericardium is an important determinant of cardiac filling. Abrupt stretching of the myocardium has the potential to disrupt myofibril overlap and the stress strain relationships that allow for optimal myocardial contraction (Smiseth, Frais et al. 1986; Tyberg, Taichman et al. 1986). The elastin component of the pericardium can stretch to accommodate an increase of approximately 15-20% beyond normal cardiac filling. The inelastic non-compliant collagenous component of the parietal pericardium limits the amount of acute dilation and thus is able to protect the heart by limiting sudden increases in volume related distention. Once pericardial compliance is exceeded, any increase in myocardial volume leads to a rapid increase in pressure, limiting any further filling (Smiseth, Frais et al. 1986; Tyberg, Taichman et al. 1986). Inflammation and edema of either layer of the pericardium can and lead to acute or subacute decrease in compliance, resulting in a significant shift to the left in the pressure-volume relationship of the underlying cardiac chambers (Sagrista-Sauleda, Permanyer-Miralda et al. 1987).

1.14 The pericardial contribution to ventricular interdependence

The pericardium provides the heart with a single overall cardiac volume that is determined by the limited ability of the parietal layer to stretch (Spodick 1997; Hutchison 2009). The result is that exceeding the volume of one cardiac chamber will have a significant impact on the ability of the remaining chamber to fill. This phenomenon is called ventricular interdependence or coupling and is particularly important in a number of disease states and less so under normal conditions (Hoit, Dalton et al. 1991).

The extra volume that the pericardium is able to stretch before normal pericardial compliance is exceeded is referred to as the pericardial reserve volume (Hutchison 2009). After the pericardial reserve volume has been exceeded pressure increases in a J shaped fashion, where small changes in volume can lead to large increases in pressure compromising the ability of the cardiac chambers to fill (Holt, Rhode et al. 1960).

1.15 Chronic pericardial remodeling

The pericardium is able to remodel to allow it to adapt to increases in intra-cardiac or intra-pericardial volume without rapid increases in pressure and impairment of cardiac filling (Hutchison 2009). Remodeling of the pericardium increases the pericardial reserve volume. The first and more common setting in which pericardial remodeling occurs is when there is chronic dilation of the underlying cardiac chambers. Under these circumstances the fibrous connective tissue matrix of the parietal pericardium is replaced with a new collagen matrix. This allows the pericardium to be more compliant at the higher volumes and the underlying heart to manage chronic volume overload conditions. The second setting is encountered when there is chronic accumulation of pericardial fluid. The pericardial remodeling in this setting, mimics that in the first setting, and also results in an increase in pericardial compliance and an increase in the capacity of the pericardium to hold larger volumes without significant alterations in the intra-pericardial pressure (Hutchison 2009). A third pattern of pericardial remodeling is maladaptive and results in increased fibrosis, thickening and scarring of the pericardium leading to significant reduction in pericardial compliance and reserve volume. This latter form of remodeling usually occurs in response to chronic inflammation (Hutchison 2009).

1.20 The symptoms and physical signs of pericardial disease

Abnormalities of the pericardium may cause symptoms and signs by one of four mechanisms: 1] stretching of the pericardium and inflammation or irritation of tissue that is innervated by both somatic and visceral nerves may cause chest pain, non specific chest discomfort and hiccups; 2] pressure on the lungs, bronchi and surrounding mediastinum exerted by increased pericardial pressure can result in reflex cough, dyspnea and dysphagia; 3] disease caused by mycobacteria, bacteria and other causes of purulent fluid may lead to fever and constitutional symptoms similar to that seen with empyema; 4] as the pressure in the pericardium rises, cardiac filling is compromised, stroke volume and cardiac output is reduced and unless appropriate compensatory reflexes such as tachycardia and increase in venous pressure are adequate, cardiac tamponade and or heart failure may ensue (Wood 1956).

1.21 Physical signs

A unique aspect of the physical signs of pericardial disease is that they are closely linked to and influenced by the respiratory cycle.

1.22 The jugular venous pressure

Appreciable waveforms in the jugular venous pressure in pericardial disease include: a prominent x descent alone; prominent x followed by a y descent; and/ or a prominent y descent alone. The x descent is produced by the combination of systolic retraction of the atrioventricular plane during ventricular contraction and atrial relaxation (Hutchison 2009). The y descent results from the combination of pericardial and myocardial recoil in early diastole and passive early ventricular filling from atrial emptying. A fall in the elevated mean central venous pressure during inspiration leads to an exaggeration of these descents. The x descent is the dominant waveform in tamponade while the y descent dominates in constrictive pericarditis (Wood 1956; Hutchison 2009).

1.23 Pulsus paradoxus

In healthy individuals, venous return to the left ventricle varies with the respiratory cycle. During inspiration pooling of blood in the pulmonary venous system decreases venous return while the opposite occurs during expiration. As a result, stroke volume and cardiac output fall marginally

leading to a drop in systemic arterial pressure of less than 10 mmHg and no appreciable change in the pulse volume. Pulsus paradoxus is defined as a fall in the systolic blood pressure of greater than 10 mmHg or an appreciable decrease in the pulse volume during normal inspiration (Wood 1956; McGregor 1979).

1.24 Pericardial friction rubs

Inflammation within the pericardium can generate high-frequency intermittent sounds known as friction rubs. Rubs may be mono, bi or tri-phasic corresponding the cardiac motion during ventricular systole, early diastole and atrial systole (Little and Freeman 2006). In addition they may be transient and can vary with the position of the patient during examination. Although there isn't consensus on the position in which they are best heard, many experts advocate listening during expiration, with the patient leaning forward and the stethoscope placed over the left lower sternal border where and when, contact of the pericardium with the chest wall is at its maximum (Hutchison 2009). The loudest component occurs during ventricular systole when the motion of the heart is greatest (Hutchison 2009).

1.25 Kussmaul sign

During normal spontaneous inspiration, as intra-pericardial pressure falls, the transmural filling pressure increases and central venous pressure falls (Spodick 1997). Kussmaul's sign is defined as the inability of this inspiratory fall in central pressure to occur. In the setting of pericardial disease, this failure of the venous pressure to fall results from impaired right atrial and ventricular filling due to disease induced abnormal pericardial physiology (Hutchison 2009).

1.26 The pericardial knock

A stiff non-compliant pericardium may lead to the abrupt cessation of rapid early diastolic filling of the ventricles generating a loud early diastolic third sound or pericardial knock (Wood 1956)

1.30 Special investigations for the assessment of pericardial disease

Abnormalities and diseases of the pericardium can present with compatible symptoms and signs or may be an incidental finding in an asymptomatic patient undergoing investigation for alternative complaints.

Investigation of patients with suspected pericardial disease involves a history and physical examination, followed by specific ancillary tests. These tests may include: the electrocardiogram [ECG], imaging of the pericardium, pericardiocentesis and analysis of pericardial fluid, pericardial biopsy; right and left heart catheterization, and analysis of peripheral blood or tissue from outside the pericardium.

1.31 The ECG in pericardial disease

Pericardial disease can lead to abnormalities of the QRS voltage, the ST segments, PR segments and T waves. QRS abnormalities encountered in pericardial effusion include: 1] voltage less than 10 mm in the precordial leads; 2] voltage less than 5 mm in the limb leads; and 3] a peak to peak variation in the QRS amplitude by greater than 10mm in any two sets of simultaneously recorded leads or electrical alternans (Usher and Popp 1972; Unverferth, Williams et al. 1979; Meyers, Bagin et al. 1993). This phasic variation in amplitude is usually best seen in the precordial leads.

Inflammation of the epicardium can lead to a current of injury pattern characterized by widespread elevation of ST segments. The ST segment elevation occurs at the J point, usually maintains its normal concavity and rarely rises above 5 mm. Reciprocal ST segment changes are not a feature (Surawicz and Lasseter 1970).

Inflammation and current of injury over the atria may affect atrial repolarization leading to PR segment elevation in lead AVR and depression in the other limb leads and most frequently in limb lead II (Surawicz and Lasseter 1970). Widespread T wave inversion and non-specific changes are a fairly common feature of pericardial disease.

1.32 Imaging of the pericardium

The main imaging modalities used in the assessment of the pericardium are the chest x-ray [CXR], fluoroscopy, trans thoracic and transesophageal echocardiography, computed tomography [CT] and magnetic resonance imaging [MRI].

1.33 The chest x-ray and fluoroscopy

The normal pericardium cannot be visualized by plain CXR. Features indicative of disease include: a flask-like cardiac silhouette when there is

greater than moderate effusion; calcification of the pericardium suggestive of pericardial constriction; and rounded opacities in the midline that may indicate the presence of a cyst (Hutchison 2009). CXR may contribute to establishing an etiological diagnosis to pericardial disease by identifying associated lung parenchymal disease, pleural disease or lymphadenopathy. Although pericardial calcification can be detected on fluoroscopy, this is not considered a primary diagnostic tool for this purpose (Hutchison 2009).

Figure 1

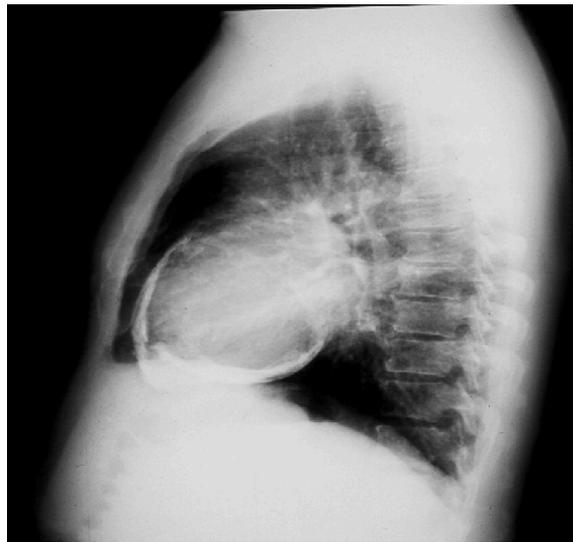


Fig 1. A lateral view of a chest radiograph showing pericardial calcification in a patient with presumed tuberculous constrictive pericarditis (courtesy of Prof PJ Commerford, University of Cape Town).

1.34 Echocardiography

Many experts and authorities consider echocardiography as the imaging modality of choice for the initial evaluation of patients with suspected pericardial disease (Chandraratna 1991; Maisch, Seferovic et al. 2004). The tool is particularly valuable for: 1] identifying the presence and hemodynamic impact of pericardial effusion; 2] assessing the presence of constrictive physiology; 3] identifying intrapericardial thrombus; and 3] assessing underlying myocardial function (Chandraratna 1991; Hutchison 2009). Echocardiography does have limitations in the assessment of pericardial disease. These include a limited acoustic window in some patients and difficulty assessing pericardial thickness in some areas of the pericardium.

1.35 Computed Tomography

CT scanning is considered a valuable test to investigate pericardial disease. It has the added benefit of being able to provide valuable information about associated pathology in the chest, such as pleural effusions, masses, lymph nodes aortic dissection and pathology in the lung parenchyma (Hutchison 2009). CT is most useful for providing anatomical detail and information on the presence of pericardial thickening, calcification and cysts. It lacks the ability to provide important physiological information (Hutchison 2009).

1.36 Magnetic resonance imaging

Cardiac MRI has the advantage of being able to provide high quality anatomical detail and functional information in pericardial disease in addition to assessing the presence and degree of tissue inflammation (Wang, Reddy et al. 2003). For these reasons MRI is particularly strong at: 1] detecting fluid when there is doubt or it is unclear by echocardiography; 2] characterizing pericardial cysts; 3] assessing pericardial inflammation and measuring thickness; 4] integrating these findings with functional and physiological information (Wang, Reddy et al. 2003; Hutchison 2009).

1.37 Pericardiocentesis and pericardial fluid analysis

Pericardiocentesis describes the removal of pericardial fluid that can be performed either surgically or percutaneously for diagnostic and/or therapeutic purposes. Indications for pericardiocentesis include hemodynamic compromise, suspected infectious etiology or effusion of uncertain etiology (Spodick 1995). Percutaneous pericardiocentesis can be performed via fluoroscopic guidance, echocardiographic guidance or blindly under rare circumstances (Spodick 1995; Maisch, Seferovic et al. 2004). Fluoroscopically guided pericardiocentesis is performed in a catheter laboratory with ECG monitoring and is usually via the sub-xyphoid approach. Echocardiographically guided pericardiocentesis can be performed at the bedside. Access to the pericardium by this method follows identification of the shortest route to the pericardial fluid, which is often through the sixth or seventh intercostal space in the anterior axillary line (Maisch, Seferovic et al. 2004).

The initial step in the analysis of aspirated pericardial fluid is aimed at establishing whether the fluid is a transudate or exudate. Transudates generally result from impaired drainage of the pericardium due to a raised right atrial pressure and exudates result from increased production of fluid following pericardial inflammation (Burgess 2004). Further analysis of exudative fluid is aimed mainly at investigating for the presence of infection and malignancy and should always include cultures and cytology in addition to biochemical markers of these disorders and gram stains (Maisch, Seferovic et al. 2004). The definitive diagnosis of most systemic diseases that have pericardial involvement, such as renal failure and rheumatoid arthritis, is infrequently confirmed by pericardial fluid analysis. In the majority of such cases the diagnosis is evident by other means prior to investigating the pericardium (Hutchison 2009).

1.38 Pericardioscopy and pericardial biopsy

The pericardium can be accessed for biopsy via open thoracotomy and subxiphoid pericardiotomy, both of which are usually performed by surgeons, or by pericardioscopy which involves the use of a rigid or flexible thoracoscope. Pericardioscopy does not require a general anesthetic (Seferovic, Ristic et al. 2003). Biopsy and analysis of tissue may provide a greater etiological diagnostic yield than pericardial fluid analysis alone. Biopsy is reserved for cases where previous tests have proved inconclusive and concern remains about infection or malignancy (Maisch, Seferovic et al. 2004). The method of attaining the pericardial samples may alter this yield. It appears that pericardioscopy with multiple sampling using either a rigid or flexible thoracoscope to obtain samples under direct visualization may provide the best results (Seferovic, Ristic et al. 2003).

1.39 Right and left heart study

Cardiac catheterization remains a very important means of assessing cardiac hemodynamics in suspected pericardial disease particularly where there may be several possible causes of heart failure or fluid retention. Rarely, it is required to diagnose tamponade in the presence of an effusion when the clinical evaluation and imaging tests are inconclusive (Hutchison 2009). More commonly the test is performed to look for evidence of constrictive physiology when other tests have been unhelpful and or to help

differentiate heart muscle disease from pericardial disease (Hurrell, Nishimura et al. 1996; Talreja, Nishimura et al. 2008).

1.40 Abnormalities and diseases of the pericardium

There is a spectrum of abnormalities and diseases of the pericardium that include congenital defects, pericarditis, pericardial cysts and pericardial tumors. The term pericarditis is all encompassing and refers to a number of syndromes including: acute pericarditis; effusive pericarditis or pericardial effusion; pericardial tamponade; effusive constrictive pericarditis and constrictive pericarditis.

1.41 Congenital defects of the pericardium

Congenital abnormalities of the pericardium comprise various degrees of absence of the pericardium. The most common variant is partial absence of the left pericardium, followed by partial absence of the right pericardium. Total absence of the pericardium is rare (Maisch, Seferovic et al. 2004). Although the majority of patients with absence of the pericardium are asymptomatic, the resultant loss of the anchoring effect increases the risk for traumatic aortic dissection (Meunier, Lopez et al. 2002). The only abnormal finding on physical examination is a systolic ejection murmur at the left upper sternal border although the mechanism of the murmur is not clear (Hutchison 2009) It is not known what the etiology of his condition is, but a leading hypothesis is that premature involution of the duct of Cuvier which supplies blood to the developing pericardial membrane results in the defect (Nasser, Helmen et al. 1970). One third of patients with congenital absence of the pericardium have other developmental abnormalities including tetralogy of fallot, patent ductus arteriosus, pulmonary sequestration and bronchogenic cysts (Nasser, Helmen et al. 1970).

Chest radiograph findings consistent with this diagnosis include: leftward displacement of the heart; leftward displacement and prominence of the main pulmonary artery; interposition of lung parenchyma between the aortic arch and the main pulmonary artery; and interposition of lung parenchyma between the heart and diaphragm on the left (Hutchison 2009). The ECG has poor sensitivity and low specificity. Right axis deviation, right bundle branch block and late transition of the R wave in the precordial leads are common findings (Gatzoulis, Munk et al. 2000). Absence of the

pericardium cannot be demonstrated echocardiographically. Unexplained displacement of the heart to the left, and unexplained or apparent right ventricular dilatation should alert the echocardiographer to the possibility of this diagnosis (Gatzoulis, Munk et al. 2000). Interposition of lung parenchyma between the main pulmonary artery and the aortic arch, and heart and diaphragm may be visualized better on CT but the imaging modality of choice for this diagnosis is cardiac MRI (Hutchison 2009).

1.42 Pericardial cysts

Cysts of the pericardium can be congenital or inflammatory and are uncommon. They are thin walled structures, containing clear fluid lined by a single layer of serosal cells. The majority are believed to be the result of defective development of the pericardium (Hutchison 2009). Most, are unilocular and are located at the cardio-diaphragmatic angles where they present as incidental findings on an imaging study. Echinococcal or hydatid cysts are the main form of inflammatory cysts comprising 1-2% of all cysts. Pericardial involvement usually follows rupture of hepatic or pulmonary cysts (Maisch, Seferovic et al. 2004).

1.43 Pericardial tumors

Primary tumors of the pericardium are very uncommon (Maisch, Seferovic et al. 2004). Mesothelioma is the most common of these rare neoplasms. Secondary tumors that frequently involve the pericardium include lung cancer, breast cancer, malignant melanoma and lymphoma. Pericardial tumors can involve either the visceral or parietal pericardium and they may occur as solitary or multiple tumors and may even fill the pericardial space (Hutchison 2009).

1.44 Intrapericardial thrombus

Thrombus or clot in the pericardium may arise following trauma to the thorax, aortic dissection, open-heart surgery, post-infarction myocardial rupture and as complications of procedures such as device insertion. Thrombus may accumulate anywhere in the pericardium including recesses that are difficult to visualize by means of echocardiography. As a result, the clinical manifestation of significant cardiac compression may be atypical, and the diagnosis may require CT, MRI or direct inspection by a surgeon.

Hypotension and low cardiac output without clinical evidence of elevation of the central venous pressures is common unless the clot accumulates directly over the right atrium (Hutchison 2009). Pericardial thrombus is most common after cardiac surgery and requires a high index of suspicion and a low threshold for intervention, It is important to recognize because the only effective means of relief of compression is surgical removal (Hutchison 2009).

Despite its limitations, echocardiography remains the initial investigation of choice in suspected cases particularly as it can readily be used even in unstable patients. In addition to identifying the presence of clot, assessment for evidence of compression of the surrounding cardiac chambers and great vessels is important (Hutchison 2009). Where clinical suspicion is high because of the pretest probability, such as after cardiac surgery, no imaging study excludes the diagnosis and surgical inspection is essential. .

1.50 Pericarditis syndromes

Pericardial syndromes are classified by the predominant mode of clinical manifestation, their duration, or by their etiology. These classification systems are not mutually exclusive and are often used concurrently. Classification by mode of presentation includes dry [acute] pericarditis, effusive pericarditis, effusive constrictive pericarditis and constrictive pericarditis. Classification by duration is arbitrarily divided into acute pericarditis when the duration is less than three weeks, sub-acute when the duration is greater than three weeks but shorter than three months and chronic when for greater than three months. The etiological classification may be divided into: infections pericarditis, pericarditis in systemic autoimmune diseases, immune mediated pericarditis, neoplastic pericarditis and pericarditis in non-autoimmune systemic disease (Maisch, Seferovic et al. 2004).

1.51 Acute pericarditis

Acute pericarditis is characterized by the rapid onset of inflammation of the pericardium that occurs as either a manifestation of systemic disease or as a localized clinical problem. When, as in the majority of cases, inflammation occurs in the absence of a readily identifiable cause, it called idiopathic pericarditis but is thought to be a post-viral phenomenon (Maisch, Seferovic et al. 2004; Troughton, Asher et al. 2004). A comprehensive

summary of potential causes of acute pericardial inflammation is provided in table 1.

Table 1: A summary of selected causes of pericarditis by etiology

INFECTIOUS PERICARDITIS	PERICARDITIS IN SYSTEMIC AUTO-IMMUNE DISEASES	IMMUNE RELATED PERICARDITIS	PERICARDITIS IN SYSTEMIC DISEASES
Viral	Systemic Lupus Erythematosus	Rheumatic fever	Acute myocardial infarction
Bacterial	Rheumatoid arthritis	Dressler's syndrome	Perimyocarditis
Fungal	Systemic Sclerosis	Postcardiotomy syndrome	Neoplastic
Parasitic	Dermatomyositis	Autoreactive	Paraneoplastic
			Uremic
			Trauma
			Myxedema

The classic triad of chest pain, pericardial friction rub and typical ECG changes characterizes acute pericarditis. The diagnosis requires two out of three of these features (Zayas, Anguita et al. 1995). The characteristic symptom of acute pericarditis is severe precordial pain that is usually sharp in nature, is made worse by cough, deep inspiration, and lying flat. Sitting forward relieves it. Irritation of the phrenic nerve results in pain which may be constant or intermittent and that is often referred to the scapular ridge (Little and Freeman 2006). In a minority of cases the sympathetic nerves that innervate the visceral pericardium mediate the pain and the pain is "visceral" rather than somatic. Under these circumstances the pain is described as dull or pressure like, making it almost indistinguishable from myocardial ischemia. Finally, in some cases, such as after open heart surgery, acute pericarditis may be asymptomatic (Hutchison 2009).

The distinguishing feature of acute pericarditis on physical examination is a pericardial friction rub. Found in about 35% of patients, the pericardial friction rub is described as a velcro -type scratchy sound with one, two or three components that correspond to the motion of the heart in ventricular systole, early diastole and atrial systole (Little and Freeman 2006). The friction rub can be transient and positional, making it a highly specific but insensitive physical finding (Hutchison 2009). Other typical findings include fever and tachycardia in an otherwise hemodynamically stable patient (Little and Freeman 2006). ECG abnormalities are noted in 90% of cases and classically evolve through four progressive stages. Stage one is characterized by diffuse ST-segment elevation and PR-segment depression. In stage two there is normalization of the ST and PR segments. Widespread T-wave inversions are typical of stage three and the ECG reverts to normal in stage four (Surawicz and Lasseter 1970). The role of the chest radiograph is to assess the lung parenchyma, the pleura and the aorta for any evidence of disease which may explain the source of pericardial inflammation (Hutchison 2009).

Echocardiography is recommended in all cases of suspected pericarditis, as part of the initial investigation and work up. Given its relatively low specificity and sensitivity for the diagnosis of acute pericarditis, its main role is to exclude potential complications such as cardiac tamponade (Maisch, Seferovic et al. 2004; Hutchison 2009). Most cases of pericarditis do not develop a sizeable pericardial effusion and therefore echocardiography lacks specificity and sensitivity for the diagnosis of acute pericarditis. Echocardiography may also occasionally assist in demonstrating the underlying cause of acute pericarditis such as myocardial infarction and aortic dissection (Hutchison 2009). Although other imaging modalities such as cardiac MRI are currently being used with increasing frequency for the assessment of acute pericarditis their diagnostic utility remains unknown when used routinely. Findings that are suggestive of acute pericarditis on MRI include pericardial thickening and delayed gadolinium hyperenhancement (Bogaert and Francone 2009). Pericardial thickening is not a universal finding in acute pericarditis and the diagnostic utility of delayed hyperenhancement remains unknown (Hutchison 2009)

The majority of patients have some evidence of systemic inflammation that may include a low-grade temperature, and elevated markers of inflammation. In addition to the clinical evaluation, ECG and echocardiogram, useful routine diagnostic tests include a full blood count, renal function and electrolytes, erythrocyte sedimentation rate and a measure of biomarkers of myocardial injury such as creatine kinase or troponin (Hutchison 2009). The yield from routine pericardiocentesis with or without pericardial biopsy in the setting of uncomplicated acute pericarditis is low; pericardial fluid or tissue analysis rarely alters management and the overall prognosis of acute pericarditis is good. As a result, most experts do not advocate the invasive diagnostic procedure unless a purulent etiology is suspected, the patient is very ill, or there is hemodynamic compromise from compressive pericardial fluid (Spodick 1997; Hutchison 2009).

Complications of acute pericarditis are infrequent. They include recurrent pericarditis, pericardial effusion and tamponade atrial tachyarrhythmias and constrictive pericarditis. If there is significant myocardial injury as part of a perimyocarditis, heart failure may ensue.

The treatment of acute pericarditis depends on the etiology. In the vast majority of cases, treatment is symptomatic and includes bed-rest, anti-inflammatory medications and analgesics. Corticosteroids are also effective for pain relief but, appear to increase the rate of recurrences if taken for greater than a week. There is evidence that colchicine given for three months in addition to aspirin for a month reduces subsequent recurrences by two thirds and reduces the duration of symptoms (Imazio, Bobbio et al. 2005).

1.52 Pericardial effusion

When the amount of fluid in the pericardial space exceeds the normal 15-50cc, a pericardial effusion is present. This increase in fluid usually occurs when fluid formation from inflammation or infection exceeds removal or when hydrostatic forces lead to a much slower removal of fluid than formation (Hutchison 2009). Fluid removal from the pericardium usually takes place via the azygos and hemi-azygos veins at a steady state that matches fluid formation. Right atrial pressure elevation from any cause can impair this venous drainage. Pericardial effusions can be serous, serosanguinous, purulent, lymph or blood. In addition to all cardiac causes of

fluid retention and systemic congestion the majority of causes of acute pericarditis listed in Table 1 can also cause a pericardial effusion (Soler-Soler, Sagristá-Sauleda et al. 2001).

By convention, pericardial effusions are classified as small moderate and large but in general the assessment of effusion size is imprecise and has an indirect correlation with hemodynamic sequelae. Effusions are arbitrarily considered small when they are less than 1cm posteriorly with little fluid anteriorly. Effusions that are greater than 1cm posteriorly and less than 1cm anteriorly are considered moderate and large effusions are greater than 1cm throughout (Hutchison 2009). Many effusions remain asymptomatic independent of size and are only discovered incidentally. The biggest determinant of the relationship between amount of pericardial fluid, and the hemodynamic effect is the rate at which the effusion accumulates (Ivens, Munt et al. 2007). For the pericardium to be able to stretch beyond its compliance limit, it requires time to remodel. Small effusions that accumulate rapidly can cause significant hemodynamic embarrassment and tamponade, while large chronic effusions [typically described in myxedema] may be completely asymptomatic (Ivens, Munt et al. 2007; Hutchison 2009).

Excess fluid in the pericardium may cause chest discomfort, cough and dysphagia, or exertional dyspnea. Other symptoms may be present which are usually determined by the etiology of the effusion. Symptoms of "right heart failure" are not common and suggest the presence of severe compression or tamponade.

The pulse may be normal, small or paradoxical depending on intra-pericardial pressures and the rate at which fluid accumulated within the pericardium. As the transmural filling pressure reduces and the stroke volume diminishes, the pulse volume decreases and a pulsus paradoxus may become evident. The central venous pressure also varies and depends on the intra-pericardial pressure. Effusions larger than 200-300 ml may be detected by dullness to percussion in the second left intercostal space and to the right of the sternum in the fourth and fifth intercostal space with the patient lying supine (Wood 1956). The heart sounds may be distant on auscultation and very rarely a friction rub and an early S3 may be heard. Compression and

collapse of the lung base can occasionally be detected as dullness to percussion and bronchial breathing [Ewart's sign](Wood 1956).

The main complication of pericardial effusion is pericardial tamponade. A proportion of patients develop constrictive pericarditis as a long-term complication at a rate that is determined by the underlying etiology (Ivens, Munt et al. 2007).

The management of pericardial effusion is determined by two factors: the etiology and the presence of symptoms. Idiopathic asymptomatic effusions can be treated conservatively with close follow up of patients for evidence of clinical deterioration (Ivens, Munt et al. 2007). Infections or other systemic conditions that require specific treatment should be treated accordingly and pain can usually be treated with medication. Symptoms that are due to compression of either the underlying heart or surrounding structures requires relief by evacuation of the pericardium (Hutchison 2009).

1.53 Pericardial tamponade

Cardiac tamponade is a pathophysiological phenomenon with a wide spectrum of hemodynamic and clinical severity. The hemodynamic hallmark of tamponade is the equalization of the intrapericardial, right atrial and pulmonary wedge pressures with the diastolic pressures of the left and right cardiac chambers (Shabetai, Fowler et al. 1970; Shabetai 2004). The onset of tamponade begins with a pericardial fluid induced rise in intra-pericardial pressure, leading to a reduction of the transmural filling pressure to near zero, and a compromise of cardiac chamber filling such that a number of physiological compensatory mechanisms are triggered in order to maintain cardiac output and blood pressure. The mechanisms include activation of the sympathetic nervous and rennin-angiotensin systems, fluid retention, tachycardia and an increase in the systemic vascular resistance (Spodick 1998). When these compensatory mechanisms are exceeded, heart failure and hemodynamic collapse ensue (Shabetai, Fowler et al. 1970; Shabetai 2004). Any cause of a pericardial effusion can also cause pericardial tamponade. However, it occurs more frequently with purulent, tuberculous and malignant pericardial effusions than with idiopathic or post viral pericarditis (Permanyer-Miralda 2004). The severity and rapidity of the onset of tamponade dictate the pattern of clinical presentation of tamponade.

Symptoms include fatigue and dyspnea with exertion and at rest; cough and dysphagia from mass effect; syncope and presyncope when standing and with exercise; peripheral edema and shock (Hutchison 2009).

The central venous pressure can be normal in early tamponade or be so high as to not be recognized in severe tamponade. An elevated jugular venous pressure is recorded clinically in less than 75% of echocardiographically confirmed cases (Merce, Sagrista-Sauleda et al. 1999). Compression of the cardiac chambers throughout systole and diastole leads to loss of the y descent in the jugular venous waveform and a prominent x descent. Kussmaul's sign is typically absent. The explanation for this latter observation is that intra-thoracic pressure variations with the respiratory cycle continue to be transmitted to the pericardium despite the presence of tense fluid (Hutchison 2009). Pulsus paradoxus is a "classic" physical finding but it is neither sensitive nor specific. A rub may occasionally be heard and frequently the heart sounds are distant on auscultation when the volume of pericardial fluid is moderate or large (Ivens, Munt et al. 2007)

The two ECG abnormalities that are most specific for tamponade are electrical alternans and low voltage (Bruch, Schmermund et al. 2001). Both are relatively insensitive with electrical alternans reported in only 20% of cases and rarely in acute tamponade (Hutchison 2009). The CXR is useful to suggest that a sizeable pericardial effusion is present and occasionally to provide clues about etiology. Echocardiography allows for rapid confirmation of the presence of pericardial tamponade and the safest method of pericardiocentesis (Maisch, Seferovic et al. 2004). Features of tamponade include: collapse of any of the cardiac chambers, a swinging heart, failure of inspiratory collapse of a distended inferior vena cava, and marked respiratory variation of the Doppler ventricular inflow velocities across both the mitral and tricuspid valve (Maisch, Seferovic et al. 2004). There is an inverse relationship between the thickness of the wall of the chamber and the likelihood that it collapses during tamponade. Therefore left ventricular collapse is rare and right atrial collapse is frequent (Hutchison 2009). Interpretation of the echo features of tamponade and the predictive value of any of the sign for confirming pericardial tamponade should always be in the

context of the clinical assessment (Eisenberg and Schiller 1991; Eisenberg, Oken et al. 1992; Fowler 1993)

Figure 2

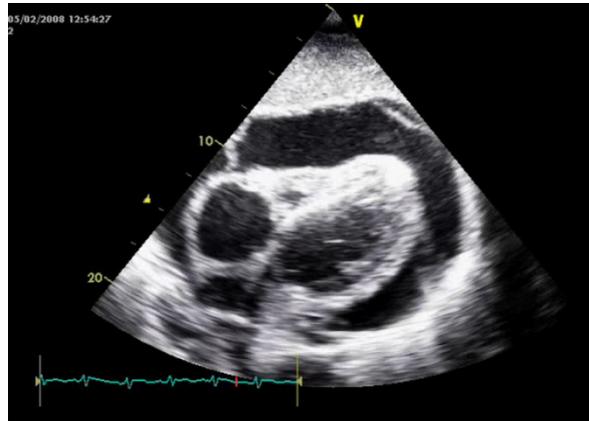


Fig 2. A subxiphisternal echocardiograph demonstrating diastolic collapse of the right ventricle with a large pericardial effusion (courtesy of Professor PJ Commerford University of Cape Town)

Right and left heart study are rarely required or performed to confirm the diagnosis of tamponade but on the rare occasions when hemodynamic assessment is required, the characteristic findings are diagnostic. The two important catheterization findings are: 1] equilibration of the mean chamber pressures in diastole; and 2] the inspiratory reduction in left sided systolic pressures and increase in right sided systolic pressures that are responsible for pulsus paradoxus (Shabetai, Fowler et al. 1970). CT and MRI are rarely performed in patients with clinical or echocardiographic evidence of tamponade. Features that are consistent with the diagnosis include: evidence of chamber collapse, engorgement of the inferior vena cava and hepatic veins; and bowing of the interventricular septum in the presence of a pericardial effusion (Restrepo, Lemos et al. 2007).

Once there is clinical evidence of significant hemodynamic compromise from tamponade the only effective treatment is prompt evacuation of the pericardium by either surgical or percutaneous drainage. Medical management, which includes measures to maintain or enhance systolic pressures such as the use of fluid and inotropes, is controversial and

may provide temporary relief at best (Kerber, Gascho et al. 1982; Spodick 2003).

1.54 Constrictive pericarditis

Constrictive pericarditis is a clinical syndrome characterized hemodynamically by: equilibration of elevated mean diastolic pressures of the cardiac chambers; rapid filling of the ventricles in early diastole followed by sudden arrest in diastole (Oh, Hatle et al. 1994); and evidence of ventricular interdependence (Hurrell, Nishimura et al. 1996; Talreja, Nishimura et al. 2008). Maladaptive remodeling of the pericardium, usually in response to inflammation, leads to the structural hallmark of the syndrome: a stiff, inelastic and non-compliant pericardium (Hutchison 2009). Pathologically there may be evidence of thickening, scarring, fibrosis, calcification or varying degrees of inflammation of both the visceral and parietal pericardium. The inelastic pericardium results in a fixed overall volume or box within which the heart must function (Myers and Spodick 1999). The more encasing and non-compliant the “box”, the more restricted is the filling of the cardiac chambers in diastole and the more severe the constrictive hemodynamics.

A number of important observations contribute to constrictive physiology and hemodynamics: 1] because of the limited available volume within the pericardium, ventricular interdependence is enhanced. Increased filling of one ventricle occurs at the expense of the other; 2] variations in intra-thoracic and intra-pericardial pressures during the respiratory cycle are dissociated. During inspiration the usual fall in inspiratory intra-thoracic pressure is not mirrored in the intra-pericardial space, the transmural filling pressure is not increased and the “suction pressure” which contributes to an increase in venous return during inspiration is not as prominent as it is in tamponade. Therefore changes in stroke volume and systolic pressure in constriction are due mainly to variations in the pressure gradient between the pulmonary veins and left ventricle during the respiratory cycle (Oh, Hatle et al. 1994) ; 3] unlike pericardial tamponade where chamber compression occurs throughout the cardiac cycle, in constrictive pericarditis compression does not occur until the cardiac volume reaches the pericardium induced ceiling in diastole. Therefore the bimodal venous return to the right atrium is

preserved in systole and early diastole (Myers and Spodick 1999; Hutchison 2009); and 4] at the beginning of diastole, the stiff inelastic pericardium recoils outward in a forceful abnormal manner, contributing to the accelerated early diastolic filling that is characteristic of the disorder (Hutchison 2009).

Peripheral edema, manifested as swelling of the distal extremities, and exertional fatigue or dyspnea are the most common symptoms (Ling, Oh et al. 1999). Chest discomfort and abdominal symptoms are less prominent but do occur in a minority of patients. Features which may help distinguish constrictive pericarditis from other pericardial syndromes on physical exam include: an elevated jugular venous pressure in which the x and y descents are prominent and the y descent is the dominant wave; Kussmaul's sign; a pulsus paradoxus that may be palpable for only a single beat and is infrequently measurable or detectable by blood pressure; and a pericardial knock which is sometimes palpable (Wood 1956; Myers and Spodick 1999). Other common important physical findings include hepatomegaly, ascites and a pleural effusion (Ling, Oh et al. 1999).

No ECG finding is specific for constrictive pericarditis. Atrial fibrillation and low voltage occur in approximately 30% of cases and non-specific ST and T wave changes occur commonly (Chesler, Mitha et al. 1976; Talreja, Edwards et al. 2003). The most specific radiographic finding is pericardial calcification. However, calcification of the pericardium occurs in a minority of patients and while it may provide clear evidence of a diseased pericardium, not all patients have corresponding compressive or constrictive physiology (Hutchison 2009).

The main imaging tools useful in this syndrome are echocardiography, CT and MRI. These tests contribute to the diagnosis of constriction to varying degrees by being able to demonstrate the following:

- 1] The presence of pericardial thickness or scarring. The normal pericardium is less than 2mm thick. Pericardial thickness is a common precursor to the pericardial constriction. However the presence of pericardial thickness does not confirm the presence of constrictive physiology and up to a quarter of patients can have constrictive pericarditis without imaging evidence of pericardial thickening (Talreja, Edwards et al. 2003; Hutchison 2009).

- 2] Evidence of constrictive physiology, which rests predominantly on the ability to detect phasic and exaggerated flow into the ventricles in diastole
- 3] Evidence of ventricular interdependence, which rests on being able to demonstrate abnormalities of septal motion in early diastole and flow reversal in the hepatic veins during inspiration.
- 4] Dilation and or congestion of the inferior vena cava and hepatic veins with diminished collapse on inspiration as evidence of significantly elevated central venous pressures.
- 5] Finally, the imaging studies are able to provide important structural and functional data about the underlying myocardium and valves (Hutchison 2009).

Left and right heart catheterization remains an important means to establish the diagnosis, particularly where clinical suspicion is high and the imaging data is inconclusive (Hurrell, Nishimura et al. 1996; Talreja, Nishimura et al. 2008). Cardiac catheterization is the only means to definitively demonstrate that: 1] there is elevation and equalization of the mean diastolic pressures across chambers; 2] that there is a dip and plateau in the diastolic filling pattern 3] that the right ventricular diastolic pressure is greater than one third the systolic pressure; and 4] that there pulmonary arterial pressures are not greater than 50 mm Hg (Hutchison 2009). While these findings are found in the majority of patients with constrictive pericarditis they may not differentiate the syndrome from other disorders with similar hemodynamics (Hurrell, Nishimura et al. 1996). The most useful hemodynamic signs with the best predictive value are those that demonstrate the presence of ventricular interdependence. These include: a simultaneous increase in the right ventricular systolic pressure and decrease in the left ventricular systolic pressure; an increase in the early transmitral pressure gradient as determined by the difference between the pulmonary wedge pressure and left ventricular diastolic pressure during the rapid early filling phase of diastole, of greater than 5 mm Hg; and analysis of the ratio of the area under the right ventricular pressure trace to the area under the left ventricular pressure trace in inspiration compared to expiration (Hurrell, Nishimura et al. 1996; Talreja, Nishimura et al. 2008).

Virtually any inflammatory cause of pericarditis can progress to pericardial constriction. Not surprisingly the biggest determinant of the etiology of constriction is the background prevalence of purulent and malignant pericarditis. Where these are common, they are a frequent cause of the syndrome. In most of the developing world tuberculosis remains the most common cause whereas in the developed world idiopathic and post-surgical cases dominate.

The accepted standard of care for the management of constrictive pericarditis is surgical pericardiectomy with as much stripping of the pericardium as is technically feasible (Ling, Oh et al. 1999). Pericardiectomy is a technically challenging procedure with peri-operative mortality rates between 5 and 15%. Predictors of a high complication rate include symptoms and signs of advanced heart failure, a prolonged duration of symptoms, a high right atrial pressure, and evidence of concomitant myocardial dysfunction (Seifert, Miller et al. 1985).

1.55 Unusual variants of constrictive pericarditis

A number of variants of the classical form of constrictive pericarditis have been described. These include: transient constrictive pericarditis and effusive constrictive pericarditis

1.551 Transient constrictive pericarditis

Constrictive pericarditis is not a progressive disorder with clinical deterioration in all patients. A small but important subset of patients, respond to medical treatment or undergo spontaneous resolution (Sagrasta-Sauleda, Permanyer-Miralda et al. 1987; Haley, Tajik et al. 2004). Transient constriction occurs most often following cardiac surgery but has also been reported following viral and idiopathic pericarditis (Haley, Tajik et al. 2004). The suggested mechanism for the constrictive physiology is loss of pericardial compliance and elasticity due to edema, fibrin deposition and or inflammation (Sagrasta-Sauleda, Permanyer-Miralda et al. 1987). Resolution can occur following a period ranging from two months up to two years. Resolution has been reported following no therapy, as well as treatment with diuretics, steroids, non-steroidal anti-inflammatory drugs antibiotics and following chemotherapy (Haley, Tajik et al. 2004). There are no variables that predict resolution in patients with newly diagnosed constrictive pericarditis.

This has prompted some experts to recommend a trial period of conservative treatment for two to three months prior to pericardiectomy in patients with minimal symptoms (Hutchison 2009). Occasionally pericardiectomy in the acute setting is necessary to manage heart failure if it is intractable to medical therapy (Anderson, Rodriguez et al. 2009).

1.552 Effusive constrictive pericarditis

Another small subset of patients develop cardiac compression from both pericardial fluid and the visceral pericardium simultaneously, resulting in the unusual combination of tamponade and constriction in the same patient. The diagnosis of effusive constrictive pericarditis requires the demonstration of three hemodynamic features: 1] evidence of pre-pericardiocentesis tamponade; 2] the normalization of the post pericardiocentesis intra-pericardial pressures; and 3] persistent elevation of the right atrial pressure (Hancock 1971; Hancock 2004). Effusive constrictive pericarditis is rare in idiopathic pericardial effusions (Sagrista-Sauleda, Angel et al. 2004) and thought to be much more common in highly inflammatory disease such as tuberculous and purulent pericarditis (Commerford and Strang 1991). The prevalence and natural history of effusive constrictive tuberculous pericarditis are the subjects of chapters five and nine this thesis.

1.60 Tuberculous pericarditis

The incidence of tuberculous [TB] pericarditis is related to the overall prevalence TB in a given populations. In parts of the world where *Mycobacterium tuberculosis* [MTb] the causative pathogen is endemic, such as Africa and much of Asia, it remains the most common cause of pericardial disease (Mayosi 2003). Tuberculosis also remains an important clinical problem in the Middle East and the formerly socialist republics of the Eastern block (Syed and Mayosi 2007). On the other hand, in the developed world where the prevalence of TB is low in non-immigrant populations, it now accounts for less than 4% of cases (Sagrista-Sauleda, Permanyer-Miralda et al. 1988; Syed and Mayosi 2007). TB pericarditis occurs in 1-2% of cases with pulmonary TB (Larrieu, Tyers et al. 1980) and is found in an equal proportion of autopsied cases of TB (Fowler 1991). The Human immunodeficiency virus [HIV] pandemic has seen a significant rise in the incidence of pericardial TB over the last few decades (Cegielski, Ramiya et al. 1990). A recent study from

South Africa showed that approximately 70% of pericardial effusions are due to tuberculosis (Reuter, Burgess et al. 2005).

The spread of TB to the pericardium occurs via three main mechanisms. Retrograde spread from mediastinal peritracheal and peribronchial lymph nodes and hematogenous spread during primary tuberculosis are the main methods via which the mycobacterium accesses the pericardium. Direct spread from lung parenchymal or pleural involvement is much less common (Heimann and Binder 1940; Peel 1948).

Protein antigens related to viable acid fast bacilli trigger an intense delayed hypersensitivity response. The subsequent activation of lymphocytes, macrophages and complement fixing antibodies leads to intense inflammation, granuloma formation, cytolysis and the production of a fibrinous exudate within the pericardium (Maisch, Maisch et al. 1982; Commerford and Strang 1991). In keeping with the delayed type hypersensitivity response that is characteristic of TB pericarditis cytokines that have been identified in the pericardial fluid of patients with the disease include Interferon-gamma [IFN- γ], Tumor Necrosis Factor alpha [TNF- α], and the following Interleukins [IL]: IL-1, IL-2, IL-6 and IL-10 with low levels of IL-4 (Burgess, Reuter et al. 2002).

Four stages of tuberculous pericarditis have been described: a dry stage, an effusive stage, an absorptive phase and a constrictive phase (Heimann and Binder 1940). The early dry phase is characterized by a neutrophil predominant fibrinous exudate, while serosanguinous lymphocyte predominant fluid with monocytes and foam cells is typical of the second stage. In the third stage, absorption of the effusion begins. This is associated with caseous transformation of the fluid and the onset of thickening and fibrotic scarring of the pericardium. The progressive maladaptive remodeling of the pericardium progresses into the fourth stage in which the fibrotic thickened pericardium loses its elasticity and compliance and compresses the underlying cardiac chambers resulting in pericardial constriction.

1.61 The clinical manifestations of tuberculous pericarditis

The clinical presentation of tuberculous pericarditis is highly variable (Sagrasta-Sauleda, Permanyer-Miralda et al. 1988). The duration of pericardial TB and how far advanced the disease is at onset of symptoms may influence

the presentation (Commerford and Strang 1991). Two general modes of presentation have been described (Peel 1948). In the first group the pericarditis is asymptomatic and is an incidental finding in patients who usually have active symptomatic TB elsewhere in the body (Peel 1948). In the second group, inflammation and compression from fluid, the diseased pericardium itself, or both, cause the typical constellation of symptoms associated with pericardial effusion, constrictive pericarditis or effusive constrictive pericarditis (Peel 1948). The typical syndrome of acute pericarditis characterized by chest pain, ECG changes and a friction rub without a sizable pericardial effusion is rare (Hageman, D et al. 1964; Desai 1979).

1.62 Tuberculous pericardial effusion

Tuberculous pericardial effusion develops slowly in the majority of patients although a fulminant course has been described (Ortbals and Avioli 1979). The typical presentation is that of symptoms of systemic infection with low-grade fever, malaise loss of weight and night sweats. If the slowly accumulated fluid does not cause any cardiac compression patients may have no symptoms referable to the effusion itself. In patients with compression, symptoms and signs may include exertional dyspnea, swelling of the abdomen or legs and a full heavy discomfort over the chest accompanied by tachycardia, pulsus paradoxus raised jugular venous pressure, edema, ascites, increased cardiac dullness to percussion and hepatomegaly. Findings on auscultation may include a friction rub in the minority of patients and soft or distant heart sounds in the majority (Ortbals and Avioli 1979). In Africa, patients presenting with the syndrome of heart failure from chronic cardiac compression is a common manifestation (Desai 1979; Mayosi, Burgess et al. 2005). In some parts of Africa such as the Eastern Cape Province of South Africa heart failure from compressive TB pericardial effusion is a more common presentation than hypertensive heart disease or idiopathic dilated cardiomyopathy (Mayosi, Burgess et al. 2005).

1.63 Tuberculous constrictive pericarditis

Constrictive pericarditis occurs in 25% of patients with TB pericarditis and one of the most serious sequelae of the condition. Clinical presentation is highly variable and depends on: a] the severity of cardiac compression caused

by the non-compliant pericardium; and b] whether or not there is active TB induced inflammation (Commerford and Strang 1991). Patients with minimum compression and no evidence of active inflammation may be completely asymptomatic, while those with severe constriction often present with symptoms and of systemic and pulmonary venous congestion and the typical signs of constriction (Commerford and Strang 1991) .

1.64 Tuberculous effusive constrictive pericarditis

Because tuberculous pericarditis is such a highly inflammatory condition associated with a high incidence of constrictive pericarditis, tuberculous effusive constrictive pericarditis is thought to be a common manifestation of TB pericarditis (Commerford and Strang 1991). To date there are no published studies to confirm this. The condition is often suspected at the bedside in a patient with suspected TB pericarditis who has physical findings which are typical of both compressive effusion [i.e. tamponade] and constriction. Specifically, these patients may have: a] a measureable pulsus paradoxus, which is unusual in constriction; b; prominent X and Y descents in the jugular venous pressure with a dominant X descent; and an audible or palpable pericardial knock (Commerford and Strang 1991).

1.65 The diagnosis of tuberculous pericarditis

The diagnosis of TB pericarditis requires a two-pronged strategy aimed at confirmation of pericardial disease and confirmation of the tuberculous etiology (Syed and Mayosi 2007). The approach to the diagnosis of pericarditis is similar to that for other causes of pericardial disease. Clinical evaluation, ECG, CXR and echocardiography are an important part of the initial assessment. Clues to the possibility of a tuberculous etiology include: the presence of prominent constitutional symptoms of weight loss, fever, drenching night sweats and malaise (Peel 1948); intra-pericardial echocardiographic abnormalities such as fibrin strands (Liu, Li et al. 2001; George, Salama et al. 2004); lung parenchymal changes or large pleural effusion suggestive of active tuberculosis (Reuter, Burgess et al. 2005); and evidence of enlarged mediastinal and tracheobronchial adenopathy on chest CT or MRI (Cherian, Habashy et al. 2003).

Diagnostic pericardiocentesis is recommended in all patients suspected of having a tuberculous pericardial effusion. Where there is evidence of

tamponade, evacuation of the pericardium is considered mandatory (Mayosi, Burgess et al. 2005). A bloodstained serosanguinous or straw colored exudate with high protein and an increased leukocyte count is typical. The leukocytes are usually predominantly lymphocytes and monocytes (Mayosi, Burgess et al. 2005). A search for acid and alcohol fast bacilli in the fluid or pericardial tissue is the only method of establishing a definitive diagnosis of tuberculosis. The sensitivity of fluid smear and microscopy is below 40%, but can be increased to over 50% by routinely adding fluid culture to the work up (Reuter, Burgess et al. 2006). The yield from culture can be increased from less than 55% to 75% by inoculating pericardial fluid directly into double-strength liquid Kirchner medium at the bedside (Strang, Latouf et al. 1991). The role of the polymerase chain reaction (PCR) in fluid remains hampered by the poor sensitivity and false positive rates found in some studies (Cherian 2004).

The contribution of pericardial biopsy to the diagnosis of TB is not clear in patients presenting with an unexplained effusion. Comparisons of tissue histology and fluid culture in TB endemic areas suggest that the latter test may be more sensitive although both are highly specific (Strang, Kakaza et al. 1988; Mayosi 2003). Where tissue is sampled, culture and PCR analysis in addition to histology may increase the diagnostic yield (Seferovic, Ristic et al. 2003; Maisch, Seferovic et al. 2004).

Tuberculin skin testing is not included in most diagnostic algorithms for pericardial effusion (Maisch, Seferovic et al. 2004) as they have a low negative and positive predictive value (Sagrsta-Sauleda, Permanyer-Miralda et al. 1988; Fowler 1991; Reuter, Burgess et al. 2006) for a tuberculosis etiology. Long culture periods and the low sensitivity associated with smear and microscopy may lead to potentially harmful delays to diagnosis and incorrect diagnosis with potentially harmful or fatal consequences (Mayosi, Burgess et al. 2005). As a result indirect methods of establishing a diagnosis of tuberculosis have become very important. These indirect methods include, adenosine deaminase [ADA], gamma interferon [IFN- γ], and clinical criteria

ADA is a polymorphic enzyme that catalyzes the deamination of adenosine to inosine and ammonium [Barton 1979]. ADA activity reflects a T-cell mediated cellular immune response and is greatest in activated T - lymphocytes (Ocana, Martinez-Vazquez et al. 1983). Where TB is endemic,

elevated pericardial ADA activity is suggestive of the diagnosis (Reuter, Burgess et al. 2006). The usefulness of ADA activity for this purpose is independent of HIV status (Reuter, Burgess et al. 2005). A pericardial ADA level of 40 IU/l or greater has a sensitivity and specificity of 88% and 83% respectively (Tuon, Litvoc et al. 2006). IFN- γ is an immuno-stimulatory and immune-modulating cytokine that is directly involved in the innate immune response to intracellular organisms such as MTb (Flynn, Chan et al. 1993). Levels of IFN- γ in pericardial fluid offer another way of making an indirect diagnosis of tuberculosis. Using a cutoff value of 50 pg/l the sensitivity and specificity of IFN- γ is 92% and 100% respectively (Burgess, Reuter et al. 2002). In light of the difficulty in establishing a definitive diagnosis of tuberculosis in some patients, a good response to empiric therapy has been used as an acceptable indirect method of establishing the diagnosis (Mayosi, Burgess et al. 2005).

There are two important aspects to the treatment of TB pericarditis. These are: 1] mechanical relief of cardiac compression from fluid, the pericardium or both; and 2] chemotherapy aimed at MTb. In the majority of patients who present with effusive disease, the main aims of treatment are to reduce the risk of death and progression to constrictive pericarditis. Prior to the introduction of effective anti-tuberculous therapy case fatality rates were close to 90% (Wood 1951). The incidence of constrictive pericarditis was also very high (Wood 1956; Schrire 1959). With use of the four available first line anti-tuberculous chemotherapeutic agents [pyrazinamide, ethambutol, rifampicin and isoniazid], the current mortality rates amongst immune competent patients is between 10% and 20% (Long, Younes et al. 1989) and rates of constrictive pericarditis are less than 25% (Strang 1984; Sagrista-Sauleda, Permanyer-Miralda et al. 1988). The recommended duration for medical therapy is usually six months (Combs, O'Brien et al. 1990).

The effectiveness of corticosteroids for TB pericarditis remains controversial. Although data from published trials suggest that there is a definite trend towards benefit for the reduction of mortality and morbidity, this data remain inconclusive (Mayosi, Ntsekhe et al. 2002; Ntsekhe, Wiysonge et al. 2003). What is less in dispute is that corticosteroids provide faster resolution of effusion, quicker relief of symptoms and signs and

improve functional status more than anti-tuberculous chemotherapy alone (Mayosi 2003).

Surgical pericardiectomy offers the most definitive form of treatment and best chance of cure for patients with established constrictive pericarditis (Maisch and Ristic 2003). There are no randomized studies to address the issue of optimal timing of the procedure. The following three strategies are often employed: 1] empiric administration of a six month course of anti-tuberculous chemotherapy followed by pericardiectomy in those with persistent symptoms; 2] a trial anti-tuberculous chemotherapy for a minimum of three months prior to planned pericardiectomy followed by completion of the course post-operatively; and 3] administration of pre-operative chemotherapy only in those patients with suggestive evidence of active TB such as compatible symptoms or raised inflammatory markers (Sagrista-Sauleda, Permanyer-Miralda et al. 1988; Maisch, Seferovic et al. 2004; Mayosi, Burgess et al. 2005). In those patients with advanced chronic constrictive pericarditis, pericardiectomy carries a considerable peri-operative risk and should be considered with caution (Maisch, Seferovic et al. 2004).

HIV has altered the epidemiology, clinical presentation, and natural history of TB. HIV induced rapid depletion of TB-specific T helper cells leads to a significant increase in the risk of developing TB (Wood, Maartens et al. 2000). This risk is estimated to be 20-fold higher early in the course of HIV and up to 120 times in patients with acquired immune deficiency syndrome [AIDS] (Zumla, Malon et al. 2000). The risk of disseminated and extra-pulmonary disease also increases as immune function declines. The most common sites of extra-pulmonary involvement are lymph nodes and pleura, but pericardial involvement is also a common site of disease (Barnes, Bloch et al. 1991; Shafer, Kim et al. 1991; Maher and Harries 1997).

Co-infection with HIV may alter the clinical presentation, immunopathology and natural history TB pericarditis. Whereas the pericardial T-cell lymphocytes in the pericardial fluid of HIV uninfected individuals are predominantly CD4 positive cells, they are predominantly CD8 positive cells in HIV infected patients (Reuter, Burgess et al. 2006). The histopathology of the pericardium is also different with less granuloma formation (Reuter, Burgess et al. 2006). Clinically, perimyocarditis, which is very unusual in

immunocompetent individuals is more common (Mayosi, Wiysonge et al. 2006) . This presents with a higher prevalence of exertional dyspnea, ECG abnormalities, cardiomegaly and hemodynamic instability and less emphasis on typical “right sided” features such as peripheral edema and ascites (Mayosi, Wiysonge et al. 2006). Co-infection with HIV may also increase the risk of death (Wiysonge, Ntsekhe et al. 2006) and may reduce the incidence of constrictive pericarditis (Ntsekhe and Hakim 2005).

1.70 The burden of tuberculosis and HIV in South Africa

The World Health Organization (WHO) estimates that over a third of the world’s population is presently infected with MTb. Approximately nine million new cases of tuberculosis occur globally each year and 1.7 million people die of tuberculosis annually. Africa is the region with the highest tuberculosis incidence rate per capita (363 per 100 000 population), with South Africa leading the way at 718 per 100 000 (Dye 2006; Abdool Karim, Churchyard et al. 2009).

South Africa is one of the major epicenters of the dual burden of TB and HIV infection, which have become major health problems worldwide (Lawn and Churchyard 2009). It is estimated that half of all tuberculosis patients in South Africa are co-infected with HIV (Abdool Karim, Churchyard et al. 2009). Furthermore, in communities where the seroprevalence of HIV is highest annual TB notification rates exceed 1500 per 100000 (Lawn, Bekker et al. 2006). 2007 the estimated number of people living with HIV worldwide was 33.2 million, there were 2.5 million new cases [an average of 6800 new infections each day], and 2.1 million people died of the acquired immunodeficiency syndrome (AIDS). Sub-Saharan Africa accounted for 70% of the world’s HIV burden and despite harboring only .7% of the world’s population South Africa accounted for 17% of the burden.

1.71 The pathogenesis of tuberculosis

Mycobacterium tuberculosis is a slow growing aerobic intra-cellular bacillus. The bacillus enters the human body via the respiratory tract through the inhalation of droplet nuclei. The immune response against TB plays a fundamental role in the outcome following exposure to the bacilli. There are three potential outcomes for organisms that make their way to the lungs (SCHLUGER and ROM 1998): 1] an effective host response can eliminate the

organism such that there is no chance of infection in the future; 2] primary tuberculosis characterized by multiplication, spread and clinical disease can develop; and 3] latent infection may develop in which bacilli do not replicate and there is no clinical disease but skin tests such as the PPD are positive. Latent disease has the potential to reactivate, multiply and cause clinical disease. Immunocompetent individuals with latent disease have a 5-10% lifetime risk of developing reactivated TB (Comstock 1982; Horsburgh 2004). In immunocompromised people such as those infected with HIV the risk rises to greater than 10% per year (Lawn, Bekker et al. 2006).

1.80 An overview of the adaptive and innate immune response with relevance to tuberculosis

The host immune response to TB consists of an interaction between the innate immune system, the adaptive immune system and cytokines. Ninety percent of immunocompetent individuals who become infected with TB will never develop clinical disease indicating that this response is quite effective (Comstock 1982). MTb has evolved to avoid destruction by innate and adaptive immune responses and to induce pathology that will ensure its transmission by infectious aerosol for long periods of time. This chronic immunopathology begins with accumulation of macrophages at the sites of disease. After the initial tissue inflammation at the site of primary infection, infiltration with neutrophils, monocytes and macrophages, is followed by the gradual arrival of T and B-lymphocytes and fibroblasts at the periphery and culminates in the formation of the classic TB granuloma. Although some bacilli may remain viable within it, the TB granuloma is considered as the end product of the host response to primary infection (Segovia-Juarez, Ganguli et al. 2004).

1.81 The innate immune response

Important role players in the innate immune response to TB include neutrophils, mast cells, macrophages, dendritic cells, epithelial cells and natural killer cells (Urban, Lourido et al. 2006) Other important aspects of the innate immune response are that there is no creation of a memory to the TB bacilli such that future responses are more efficient and there is no mechanism via which the response is specific for tuberculosis. As a result, while often effective in protecting the host, innate immunity is associated

with damage to host tissue in the context of providing defense.

Neutrophils are amongst the first cells to arrive following tuberculosis induced injury and activation of inflammation. They contribute to the control of infection by producing cytokines, interacting with macrophages and participating in granuloma formation. However they may also be involved in tissue damage and development of pathology rather than host protection (Tan, Meinken et al. 2006).

Following invasion of the host by TB, mast cells, which are found the mucosa of the respiratory tract, are activated to release their pro-inflammatory mediators. Among these pre-formed mediators are tumor necrosis factor alpha [TNF- α], transforming growth factor beta [TGF- β], fibroblast growth factor 2, and interleukins IL-2, IL-4, IL-5 and IL-8 (Muv \pm oz, Hern ν ndez-Pando et al. 2003)

Macrophages play an essential role in the host interaction with MTb via a number of receptors. These include Fc receptors, complement, mannose and members of the Toll-like receptor family. After they are phagocytosed the macrophages can kill the bacilli by phagosomes-lysosome fusion, generation of toxic reactive oxygen species and generation of nitric oxide (Kaufmann 2002). However the bacilli are able to survive and evade macrophage killing by inhibiting phagosomes acidification and their fusion with lysosomes. Surviving pathogens are transported to draining lymph nodes where they are presented to the adaptive immune system. In this way macrophages are responsible for eliminating and containing the infection within the host (Kaufmann 2002)

Dendritic cells are recruited from blood to the site of disease where they are able to recognize, capture and process MTb antigens. After undergoing maturation at the site of disease they migrate to peripheral lymph nodes to present internalized antigens to cells of the adaptive immune system (Banchereau and Steinman 1998). Dendritic cells induce the maturation of T cells towards a T helper 1 [Th1] profile by secreting cytokines IL-2, IL-18 and IL-23. The mature Th-1 cells are then able to release IFN- γ , activating and recruiting more macrophages (Humphreys, Stewart et al. 2006).

Natural killer cells may not be essential for host resistance against TB but they are amongst the early cells of the innate system to respond (Junqueira-Kipnis, Kipnis et al. 2003). The main functions of these cells are production of IFN- γ , cytotoxicity for macrophages infected with tuberculosis, and optimization of the ability to CD 8⁺ cells to lyse TB infected cells (Vankayalapati, Klucar et al. 2004).

1.82 The acquired immune response

The adaptive immune response to tuberculosis is much slower than the innate response. However, it provides two main features that innate immunity lacks: specific antigen recognition and memory that allows rapid recall of original antigen exposure. There are two major arms of the adaptive response: cell mediated and humoral immunity. The humoral response to tuberculosis plays a relatively minor role in the host defense against TB (Kaufmann 2002). The primary protective immune response is cell mediated because tuberculosis is an intracellular infection. TB antigens are presented by major histocompatibility complex [MHC] class II molecules to CD4⁺ T lymphocytes (Kaufmann 2002). CD4⁺ cells recruit and activate macrophages, promote killing and apoptosis of infected cells and are important for CD8 T cell function (Kaufmann 2002). CD8⁺ cells are able to recognize antigens presented by MHC class I molecules and their main function is lysis of infected cells and cytokine production (SCHLUGER and ROM 1998; Kaufmann 2002)

There are a number of distinct CD4 + helper T cell subsets involved in the response to tuberculosis. These subsets include Th1, Th2, Th17, and regulatory T cells (SCHLUGER and ROM 1998; Hougardy, Place et al. 2007; Scriba, Kalsdorf et al. 2008; Miossec, Korn et al. 2009) Th1 cells promote cell-mediated immunity and are responsible for delayed type hypersensitivity responses and granuloma formation through secretion of IFN- γ and IL-2. Th2 responses enhance the humoral immune response by the production of IL-4, IL-5 and IL-10. Th17 cells play a role in initiating neutrophil dominated inflammation. The major function of T regulatory (Treg) cells appears to be coordination of the suppression of the immune response and down regulation of inflammation (Scriba, Kalsdorf et al. 2008).

1.83 The role of cytokines

Cytokines are hormone-like glycoproteins that allow the cells of both arms the immune system cells to communicate; they are critical to the initiation, perpetuation, and subsequent downregulation of the immune response. They can be produced by non-immune cells, such as fibroblasts and endothelial cells, as well as most cells of the innate immune system and T lymphocytes. The nature and magnitude of the cell mediated immune response depends in large part on which cytokines are released (Belardelli 1995).

The role of cytokines in the control and resistance to TB is complex. Although there appears to be a degree of overlap, the cytokine responses can be categorized into pro-inflammatory, anti-inflammatory or regulatory mediators and those that do both. Pro-inflammatory cytokines include IFN- γ , TNF- α , IL-2, IL-1 β , IL-6, IL-17, IL-22 and the superfamily of IL-12, (Law, Weiden et al. 1996; Roach, Bean et al. 2002; Khader, Bell et al. 2007; Scriba, Kalsdorf et al. 2008). In general these cytokines play an important role in initiating and perpetuating immune responses that result in killing, tissue inflammation and granuloma formation (Flynn, Chan et al. 1993). In the attempt to kill eliminate and contain infective bacilli, tissue necrosis and damage may result. Therefore regulation of the immune response and prevention of excessive tissue injury and necrosis may be equally important to host survival. Important regulatory and anti-inflammatory cytokines include transforming growth factor-beta (TGF-beta), IL-4, IL-5 and IL-10 (Wallis and Ellner 1994). These mediators act by deactivating macrophages and are potent suppressors of T cell activation and proliferation (Moore, O'Garra et al. 1993; Gong, Zhang et al. 1996; Toossi and Ellner 1998). They result in increased antibody production and an inhibition of the delayed hypersensitivity response and its consequences (Wallis and Ellner 1994). IL-4, IL-5 and IL-10 are produced predominantly by macrophages and T lymphocytes helper cells. They down-regulate MTb induced Th1 responses by inhibiting IFN- γ production, natural killer cells (Barnes, Lu et al. 1993; Gong, Zhang et al. 1996). IL-10 is important for the prevention of excessive tissue damage and immunopathology that is associated with unbalanced cell mediated responses (Barnes, Lu et al. 1993). In addition to its anti-

inflammatory properties, there is some evidence to suggest that IL-10 plays a regulatory role in fibrosis: elevated levels have been associated with both suppression and upregulation of fibrosis (Nelson, Lauwers et al. 2000; Bergeron, Soler et al. 2003; Mu, Ouyang et al. 2005).

IFN- γ is one of the major effector inflammatory cytokines in the delayed type hypersensitivity response to TB. It is the main mediator of macrophage activation, is required for production of nitric oxide and stimulates natural killer cells, which in turn produce more IFN- γ (Wallis and Ellner 1994). TNF- α is also released in large amounts in response to TB. The role of this cytokine appears to be very dependent on the balance of other cytokines around it and the phenotype of the T-cell response (Hernandez-Pando and Rook 1994). In the setting of predominantly a Th1 response TNF- α may serve as an activator of macrophages and other cells where as in mixed Th1 and Th2 responses it may play a more active role in inflammation and tissue damage (Hernandez-Pando and Rook 1994). Other inflammatory cytokines involved in the response to TB, are IL-22, IL-6 and IL-1 β (Law, Weiden et al. 1996; Chizzolini, Chicheportiche et al. 1997). IL-6 is a multifunctional pro-inflammatory cytokine that potentiates the activity of IFN- γ . TNF- α , IL-6 and IL-1 β levels correlate with the TB disease activity; they are high when TB is active and fall in response to treatment (Tsao, Hong et al. 1999; Djoba Siawaya, Beyers et al. 2009).

1.84 Inflammation, immunopathology and fibrosis

The immune response to TB has been described as a “double edged sword”(Barnes, Lu et al. 1993) and is characterized by an attempt to balance inflammation and pathogen elimination on the one hand and tissue damage and necrosis on the other. Whether the outcome is one of protective immunity or significant immunopathology, is determined by the pattern of the immune response and the balance of cytokines (Fenton and Vermeulen 1996; Rook and Hernandez-Pando 1996; Bachmann and Kopf 2002). As an example, the role of TNF- α varies significantly depending on the balance of cytokines (Hernandez-Pando, Orozcoe et al. 1996). In predominantly Th1 responses, it results in minimum tissue damage and cytotoxicity, but in mixed Th1 and Th2 responses it is highly cytotoxic (Hernandez-Pando, Orozcoe et al. 1996).

Acute inflammation of any etiology is characterized by rapidly resolving vascular changes, edema and infiltration by neutrophils. Chronic inflammation such is as seen with TB, on the other hand, is characterized by mononuclear cellular infiltrate, tissue destruction and repair processes occurring simultaneously (Wynn 2004). Following prolonged inflammation, complete healing is unusual and some replacement of normal tissue by fibrosis and scar tissue is inevitable (Wynn 2008). Depending on the amount of this maladaptive type of tissue remodeling [fibrosis] the result can lead to organ dysfunction or failure (Wynn 2008).

After tissue damage has taken place and the repair process begins, one of two outcomes is possible. In ideal circumstances cells of the same morphology and function replace the injured tissue leaving no evidence of damage. On the other hand, connective tissue can replace the damaged tissue resulting in fibroplasia or fibrosis. Activation of the collagen and extra-cellular matrix secreting myofibroblast is one of the key steps in this latter process. A number of mesenchymal cells can be transformed into myofibroblasts in addition to fibroblasts (Hinz 2007; Hinz, Phan et al. 2007). CD4⁺ T helper cells and a host of cytokines including IL-4, TGF-beta IL-13 are potent activators of myofibroblasts and have all been implicated as important mediators of fibrosis (Wynn 2007). Although IL-10 has traditionally been classified as an anti-fibrotic cytokine, under specific conditions it too can be pro-fibrotic (Sun, Louie et al.).

Two novel mediators involved in inflammation healing and tissue remodeling are Galectin-3 and N-acetyl-Ser-Asp-Lys-Pro [AcSDKP](Liu, Hsu et al. 1995; Sharma, Pokharel et al. 2004; Sharma, Rhaleb et al. 2008). Galectin-3 is a ubiquitous β -galactoside binding animal lectin, which is found in the nucleus, cytoplasm and cell surface of macrophages (Henderson, Mackinnon et al. 2008). It interacts with a number of ligands within extracellular matrix such as collagen, laminin, and integrins, facilitates cell-cell interactions (Ochieng, Furtak et al. 2004) and plays a critical role in myofibroblast activation. Upregulation of galactin-3 expression has now been demonstrated in animal models of hepatic, pulmonary cardiac and renal fibrosis (Kasper and Hughes 1996; Sharma, Pokharel et al. 2004; Henderson, Mackinnon et al. 2006; Henderson, Mackinnon et al. 2008).

AcSDKP is a mammalian tetrapeptide which is released from its precursor thymosin β 4 (Rossdeutsch, Smart et al. 2008). It is ubiquitous in cardiac, renal, pulmonary, and other organ tissue and circulates in plasma monocytes (Azizi, Ezan et al. 1997). The tetrapeptide reduces inflammation and fibrosis in a number of settings (Masse, Ramirez et al. 1998; Cavasin, Liao et al. 2007; Sharma, Rhaleb et al. 2008). The anti-inflammatory and anti-fibrotic effect of this compound are mediated at least in part by counterbalancing the effects of galectin-3 and TGF- β on fibroblasts and collagen deposition (Rossdeutsch, Smart et al. 2008).

Post tuberculous fibrosis is a well-described outcome of active TB in several tissues and organs including the lungs, kidneys, retroperitoneum and pericardium (Becker 1988; Vaglio, Salvarani et al. 2006). Persistence of TB antigens, failure of immune resolution and down-regulation of inflammation, and excessive tissue damage all play an important role in triggering fibrosis (Ayala, Chung et al. 2003; Wynn 2004). Whether or not fibrosis is reversible is controversial. Evidence suggests that severe or advanced fibrosis is irreversible (Wynn 2008), but early on particularly when there is still active inflammation, resolution and reversal of the tissue remodeling can take place (Wynn 2008). To date no relationship between inflammation, immunopathology, or tissue remodeling related to TB and either galectin-3 or AcSDKP has been published.

CHAPTER 2

INTRODUCTION TO THE THESIS

2.1 General Introduction

The first case series of patients with effusive constrictive pericarditis was reported in 1971 (Hancock 1971). Thirteen cases were identified from patients presenting for surgical pericardiectomy to Stanford University Hospital over a period of ten years between 1960 and 1969. Until this publication, compressive pericardial disease was classified into one of two distinct syndromes: pericardial tamponade and constrictive pericarditis. In the former, cardiac compression resulted from fluid that had collected under tension in a free pericardial space (Spodick 1967; Spodick 2003). In the latter, cardiac compression resulted from constriction by fibrotic fusion of the two pericardial layers (Evans and Jackson 1952; Wood 1961). Sporadic case reports of a mixed “effusive-constrictive” condition characterized by visceral pericardial constriction in the presence of a tense effusion had been recognized (Burchell 1954; Spodick and Kumar 1968) but no definition of the clinical features, diagnostic approach, etiology and natural history of the syndrome was available (Hancock 1971). The Hancock case series aimed to address at least some of these unknown factors.

The Hancock paper was important for a number of reasons despite the obvious limitations of a small case series of patients collected over a decade. Perhaps of most significance was the fact that it expanded our understanding of the spectrum of pericardial disease by giving better definition to a compressive pericardial syndrome, which was neither classic tamponade nor constrictive pericarditis. Just ten years prior to its publication, the American Journal of Cardiology had devoted the entire January edition to a symposium on pericardial disease in which the syndrome was not mentioned (Am J Cardio Jan 1961). Secondly, Hancock’s paper suggested that the “natural history of effusive constrictive pericarditis appears to be the progression into non-effusive chronic constrictive pericarditis usually in less than a year” (Hancock 1971). Furthermore, he observed that this outcome was not influenced by medical therapy, including corticosteroids (Hancock 1971). The implication of these observations was that pericardiectomy with an emphasis on removing the visceral layer during the “active effusive constrictive” phase

was advisable particularly if the diagnosis could be confirmed hemodynamically during pericardiocentesis (Hancock 1971). Finally, Hancock: a) provided a description of the clinical, electrocardiographic and chest x-ray features of the disorder, which were an insensitive and non-specific mixture of features of both constriction and tamponade; and b) suggested the following method for the diagnosis of effusive constrictive pericarditis which has become the 'gold standard': during pericardiocentesis, "If the right atrial or central venous pressure remains elevated after reduction of the intra-pericardial pressure to normal there must be a disorder in addition to cardiac tamponade, and often this will be visceral constrictive pericarditis" (Hancock 1971).

It took 33 years before another major attempt was made to expand our understanding of the syndrome of effusive constrictive pericarditis. In 2004 Sagrista-Sauleda published the results of a prospective cohort of 15 patients with hemodynamically confirmed effusive constrictive pericarditis collected over a 15 year period of systematic evaluation of patients presenting to a single Spanish center with pericarditis (Sagrista-Sauleda, Angel et al. 2004). This important publication added four major insights to the body of knowledge. First it confirmed that effusive constrictive pericarditis was uncommon in patients with idiopathic pericardial effusion. Over 15 years, 1.2% [15] of 1184 consecutive patients evaluated and 6.8% [15] of the 218 with clinical evidence of tamponade had effusive constrictive pericarditis (Sagrista-Sauleda, Angel et al. 2004). Second was the observation that, although patients with effusive constrictive pericarditis do frequently progress to develop constrictive pericarditis, some cases may resolve spontaneously. Third was the confirmation that for those patients who require early surgery "extensive epicardiectomy" was the procedure of choice. Finally, Sagrista-Sauleda confirmed the limitations of attempting to make a diagnosis by clinical and echocardiographic methods and the essential role of measuring intra-pericardial and intra-cardiac pressures in cases of suspected effusive constrictive pericarditis; only 7 of the 15 cases were suspected clinically prior to pericardiocentesis (Sagrista-Sauleda, Angel et al. 2004).

2.2 Rationalé for the thesis

The Sagrista-Sauleda publication raised further questions about our understanding of effusive constrictive pericarditis and pericardial disease in general. Is the prevalence of effusive constrictive pericarditis the same for different causes of pericardial effusion such as tuberculosis? If effusive constrictive pericarditis is truly a distinct clinical entity, is its pathogenesis different from pericardial effusion without visceral constriction and if so how? Does it have distinct biomarkers that confirm its uniqueness? What is different about those patients who experience resolution of their constrictive hemodynamics without surgery from those who progress to non-effusive constriction? Are there unique clinical variables, which determine whether one is likely to develop visceral constriction such as duration of the effusion or the volume the pericardial fluid?

2.3 Structure of the thesis

To address these questions, I followed two steps in the development of this thesis. The first step was to conduct a systematic review of the literature to summarize the current state of knowledge about effusive constrictive pericarditis with regard to its prevalence, the influence of etiology on the prevalence and to delineate the outcome of effusive constrictive pericarditis.

The second step was to use an ongoing prospective registry of patients with tuberculous pericarditis to classify the participants into two groups: those with effusive constrictive pericarditis and those with effusive pericarditis. Using variety investigative tools, including novel mathematical methods and biomarkers, I performed clinical studies to investigate the clinical epidemiology, pathogenesis, diagnosis and outcome of tuberculous effusive constrictive pericarditis. The *Initiative for the investigation and Management of Pericarditis in Africa* [IMPI] began a prospective registry of patients with tuberculous pericarditis in 2003 (Mayosi, Wiysonge et al. 2006) In 2006 we began to systematically phenotype all patients in the registry by performing a right heart study and obtaining intra-pericardial pressures before and after pericardiocentesis in order to identify those patients with effusive constrictive pericarditis. The IMPI registry was used to address five questions related to the syndrome of effusive constrictive pericarditis in patients with tuberculous pericarditis.

2.4 Questions addressed in the thesis

I first conducted a systematic review of the literature to determine what is known about the prevalence, etiology and outcome of effusive constrictive pericarditis in general. This review addressed in particular the question of whether the etiology of the pericardial disease influenced the prevalence and outcome of effusive constrictive pericarditis.

The second question required the determination of the prevalence of effusive constrictive pericarditis in patients with tuberculous pericardial effusion. If Hancock's observation that effusive constrictive pericarditis is a precursor to non-effusive constrictive pericarditis is accepted (Hancock 1971), and given that the frequency of non-effusive constrictive pericarditis is higher in tuberculous pericarditis (25-30%) (Bhan 1980) than in idiopathic pericarditis (less than 10% of patients) (Kwon 2009) then it may be hypothesized that the prevalence of tuberculosis-associated effusive constrictive pericarditis would be significantly higher than the 8% reported for idiopathic pericarditis. The third question addressed whether there are any clinical variables, available when patients first present with a symptomatic pericardial effusion, which may predict the presence of visceral constriction and therefore identify patients as being at high risk for having effusive constrictive pericarditis. Eight such variables were selected on the basis that these factors may be important predictors of constrictive pericarditis. These were:

1. Duration of symptoms longer than 2 weeks as opposed to shorter than 2 weeks
2. Culture positive pericardial fluid for tuberculosis compared to culture negative pericarditis
3. Size of the pericardial effusion as determined by volume drained at pericardiocentesis
4. The height of the opening right atrial pressure
5. The presence versus absence of hemodynamically defined cardiac tamponade
6. The presence or absence of underlying myocardial injury as determined by the serum creatine kinase MB fraction [CK MB%]
7. Low voltage on ECG
8. The presence of atrial fibrillation on the ECG

The fourth question was whether there were distinct serum and pericardial fluid biomarkers, which define effusive constrictive pericarditis as a clinical entity with unique biological correlates. In the Hancock series, the histopathology of the resected pericardium showed that the process of pericardial fibrosis (Hancock 1971) was present in patients with effusive constrictive pericarditis despite the presence of pericardial fluid. Immunological models of fibrosis suggest that there are a number of factors which determine whether injured tissue heal by regeneration of healthy tissue or by fibrosis (Wynn 2004). Amongst these factors are the absolute and relative levels of T helper-1 [Th-1] and T-helper-2 [Th-2] related cytokines and activators of myofibroblasts (Henderson, Mackinnon et al. 2006). I hypothesized that there would be a significant difference in the levels of Th-1 and Th-2 related cytokines (e.g., higher levels of transforming growth factor beta [TGF- β]) (Wynn 2004), and a prominence of activators of myofibroblasts involved in inflammation and fibrosis, such as galectin-3 (Henderson, Mackinnon et al. 2006; Farnworth, Henderson et al. 2008; Henderson and Sethi 2009).

The fifth question was whether the quantification of the roughness and texture of pericardial fibrin strands seen on ultrasound imaging could be used to differentiate effusive constrictive from effusive pericarditis. This investigation was conducted in two stages. First, I tested whether echocardiographic fibrin strands have a fractal geometry that is quantifiable using fractal dimensions. Assuming I could demonstrate that pericardial fibrin strands have a fractal geometry, I sought to test if there are significant differences between the fractal dimension of fibrin strands found in tuberculous effusive constrictive pericarditis and those found in effusive tuberculous pericarditis.

Finally, I determined whether or not tuberculous effusive constrictive pericarditis was associated with the major adverse outcomes of death and the composite of clinical and subclinical constrictive pericarditis at 6 months of follow-up compared with effusive tuberculous pericarditis without constrictive physiology. Table 1 provides a summary of the aims of the thesis.

Table 2: Questions addressed in the thesis

1. What is known about the prevalence and outcome of effusive constrictive pericarditis in different etiological forms of pericardial disease?
2. What is the prevalence of effusive constrictive pericarditis in patients with tuberculous pericardial effusion?
3. What are the predictors of tuberculous effusive constrictive pericarditis?
4. Do echocardiogram-derived fibrin strands have a fractal as opposed to a euclidean geometry and if so can the fractal dimension be used to distinguish effusive constrictive from effusive tuberculous pericarditis?
5. Does tuberculous effusive constrictive pericarditis have a unique biomarker profile?
6. Is tuberculous effusive constrictive pericarditis associated with a higher a) mortality rate and b) incidence of constrictive pericarditis relative to effusive tuberculous pericarditis?

Chapter 3

METHODS

The methods of the systematic review are described in Chapter 3. In this chapter, I describe the methods of the IMPI Registry, which is used to address the five major questions (Questions 2-6 in Table 1, Chapter 1).

3.1 Background to the Initiative for the Investigation and Management of Pericarditis in Africa [IMPI] prospective registry

The decade after the publication of two of the largest ever studies on pericardial tuberculosis (Strang, Kakaza et al. 1987; Strang, Kakaza et al. 1988) witnessed a large increase in the incidence of cases of the disease (Cegielski, Ramiya et al. 1990; Maher and Harries 1997). This increase in case load, which was driven mainly by the HIV and AIDS pandemic that has plagued the African continent, cast doubt on the applicability of much of what was known about the pathogenesis, natural history and outcome of tuberculous pericarditis in the pre-HIV era. Three examples illustrate this point:

1. While there was consensus that the predominant mechanism of spread of tubercle bacilli to the pericardium in immune-competent individuals was from mediastinal and paratracheal nodes (Commerford and Strang 1991), it has been suggested that the predominant mechanism of spread in HIV-infected individuals may be dissemination by hematogenous spread (Pozniak, Weinberg et al. 1994). The implications for the clinical manifestations, diagnosis, treatment and outcome of this observation are unknown.

2. By the end of the 1980s the mortality rate of patients with tuberculous pericarditis was as low as 8% (Strang, Kakaza et al. 1988). However data from the West where the HIV epidemic began a decade earlier, indicated that any pericardial effusion in HIV-infected patients significantly reduced survival (Heidenreich, Eisenberg et al. 1995). Whether or not these observations would apply to the setting of HIV-associated tuberculous pericarditis was not known.

3. Finally, although the efficacy data are inconclusive (Ntsekhe, Wiysonge et al. 2003), the use of steroids for tuberculous pericarditis is considered safe in immune-competent patients (Hathirat, Vathesatogkit et al.

1980; Wijesundere and Siribaddana 1994). By contrast, whether adjuvant steroids are safe in HIV-infected patients, particularly those with advanced immune suppression, remains untested outside of a single small study of 58 participants from Zimbabwe (Hakim, Ternouth et al. 2000).

3.2 Establishment of the 1st phase of the IMPI registry

In 2002 a group of clinicians from around the African continent with an interest in tuberculous pericarditis held a meeting in Durban to outline a strategy to determine which of the many questions about tuberculous pericarditis in general and HIV-associated tuberculous pericarditis in particular could be answered in a trans-continental collaborative effort. The result of the meeting was the establishment of the *Initiative for the investigation and Management of Pericarditis in Africa* [IMPI] registry in 2003. The main aims of the first phase of this registry, involving 15 centers across sub-Saharan Africa, were to collect data about: a] the burden of disease; b] its clinical manifestations and outcome; c] the use and usefulness of a range of diagnostic tools; and d] to document the manner in which physicians diagnose and manage the disorder (Mayosi, Wiysonge et al. 2006; Mayosi, Wiysonge et al. 2008; Ntsekhe, Wiysonge et al. 2008) in the HIV era. The first phase of the IMPI registry ended in early 2005 after 185 patients were enrolled continent-wide.

3.3 Establishment of the 2nd phase of the IMPI registry

Several important insights from the first phase of the registry informed the design and conduct of the second phase which began in 2006. Amongst these were the observations that: a] only a small proportion of patients was diagnosed as having tuberculous pericarditis on the basis of microbiological or biochemical grounds (Mayosi, Wiysonge et al. 2006), raising questions about available diagnostic tools and the potential implications of treating patients with only a presumptive diagnosis; b] a very small proportion of patients underwent pericardiocentesis (Mayosi, Wiysonge et al. 2006) despite its diagnostic and therapeutic potential; c] the HIV status of the participants appeared to have a significant impact on the incidence rate of constrictive pericarditis (Ntsekhe, Wiysonge et al. 2008), implying that there may be an important message about pericardial constriction and fibrosis to be gained by further study; d] the clinical syndrome of effusive constrictive pericarditis

was diagnosed in 15% of patients (Mayosi, Wiysonge et al. 2006), a figure higher than the 3-8% that had been recorded in previous studies of patients with effusive pericarditis (Sagrasta-Sauleda, Angel et al. 2004; Reuter, Burgess et al. 2007). These observations raised questions about the true prevalence of the syndrome, our ability to diagnose it accurately and its relationship to non-effusive constrictive pericarditis. Finally, despite the fact that patients with HIV-associated tuberculous pericarditis were sicker and had more evidence of heart failure relative to their HIV un-infected controls (Mayosi, Wiysonge et al. 2006) there was reluctance to use adjunctive corticosteroids by their physicians (Wiysonge, Ntsekhe et al. 2008).

The second phase of the registry began in 2006 to address the questions and hypotheses generated by the first phase of the IMPI registry. The second phase differed significantly from the first phase in that the entire registry was conducted at the University of Cape Town's main teaching center, Groote Schuur Hospital. This was done for a number of reasons. To begin with, the Western Cape Province of South Africa has one of the highest incidence rates of tuberculosis in the world (i.e., over 1000 new cases per 100,000 per year) (Badri, Wilson et al. 2002). Assuming that up to 8% of patients with tuberculosis present with pericardial disease (Syed and Mayosi 2007) we anticipated that the case load of tuberculous pericarditis would be high enough in Cape Town to obtain large numbers of participants in order to get meaningful results from the questions we sought to have answered. Secondly, during the first phase of the registry [2003-2005] we established a referral system within the Cape metropole whereby patients with suspected tuberculous pericarditis presenting to surrounding public health care facilities were routinely referred to Groote Schuur Hospital for comprehensive evaluation including diagnostic pericardiocentesis. In the 3 years prior to the commencement of the registry the hospital performed between 50 and 70 pericardiocenteses per year. Thirdly, and perhaps most importantly, at this single center, there was a multi-disciplinary team of epidemiologist [Charles Shey Wiysonge], statistician [Motasim Badri] radiologist [Mojalefa Steyn], chemical pathologist [Tahir Pillay], microbiologist [Andrew Whitelaw], virologist [Craig Corcoran], infectious disease specialist [Robert Wilkinson], immunologist [Katalin and Robert Wilkinson], cardiologist [Mpiko Ntsekhe] led by the chief of medicine, Bongani Mayosi, all interested in pericardial

tuberculosis and keen to cooperate and collaborate in order to find answers about some important unknown facts relating to this common disorder which affects poor and vulnerable South Africans. The second phase of the registry was designed as a prospective cohort study whereby consecutive participants would undergo comprehensive clinical evaluation, pericardiocentesis, and close, careful supervised clinical follow-up.

3.4 Methods

3.41 Conduct of the study

Between March 2006 and May 2008 consecutive patients with symptoms and signs of large pericardial effusion, suspected of being tuberculous in etiology, referred to Groote Schuur Hospital for either diagnostic or therapeutic pericardiocentesis, were admitted for full evaluation and management. Patients were evaluated clinically (i.e., history and physical examination), had an ECG, CXR, echocardiogram (echo) and blood drawn for microbiological, hematological, immunological, and biochemical assessment. The clinical and echocardiographic assessment was conducted by one of several members of the pericarditis clinical team, which consisted of Faisal Syed, James Russell, Jens Hitzeroth, Usim Usim, led and supervised by myself. Two dedicated clinical cardiology technicians [Carolise Lemmer and Lerato Motete] performed follow up echocardiograms.

Patients with a confirmed large symptomatic effusion [$>500 \text{ cm}^3$ as determined by an echo free space of $>10 \text{ mm}$ at its greatest width (Maisch and Ristic 2003)], underwent fluoroscopically guided pericardiocentesis. Intra-pericardial and right atrial pressures were measured simultaneously before and after evacuation of the pericardial fluid. An attempt was made to evacuate the pericardium to dryness in all cases or to drain the fluid until the intra-pericardial pressures had been normalized if evacuation to dryness was not feasible. Following pericardiocentesis, patients returned to the ward for re-evaluation by clinical assessment, ECG, CXR and repeat echocardiography.

Pericardiocentesis was performed via a sub-xyphisternal approach under fluoroscopic guidance using the Seldinger technique, electrocardiographic monitoring and a 6 French (F) pigtail catheter. The right heart study was performed from the right femoral vein in the majority of patients using a 6F multipurpose catheter. Given that in the absence of any

organic tricuspid disease the right atrial mean pressure closely approximates the right ventricular end diastolic pressures (Reddy, Curtiss et al. 1978), in the majority of patients only the right atrial pressure was obtained and used as an estimate of the right ventricular end diastolic pressure. The pre and post pericardiocentesis pressures were obtained by connecting the fluid-filled catheter within the fluid-filled pericardium to a manometer via a calibrated transducer (Sutton and Gibson 1977).

3.42 Patient selection

Patients were included in the study if the following criteria were met:

1. Age \geq 18 years.
2. Tuberculosis confirmed as etiology of the pericardial effusion, as defined in section 2.4.3 below.
3. Size of the pericardial effusion estimated as $>500 \text{ cm}^3$ by echocardiography.
4. Right atrial and intra-pericardial pressure determination was available pre and post pericardiocentesis.
5. Written informed consent was given.

Patients were excluded if any of the following were present:

1. Refusal of patients to grant consent.
2. Pre-pericardiocentesis clinical examination and/or echocardiographic evidence of significant valvular heart disease
3. The hemodynamic data suggested that there was a significant discordance between the elevated right atrial pressure and the intra-pericardial pressure implying that the latter was not the cause of the former.

All patients who participated in the prospective cohort study signed an informed consent form in the language of their preference. The study received approval from the University of Cape Town Health Sciences Faculty Human Research Ethics Committee.

3.43 Definition of tuberculous pericarditis, effusive constrictive pericarditis and pericardial tamponade

Patients were considered to have tuberculous pericarditis if they had either or both of the following criteria:

1. A microbiological or molecular [polymerase chain reaction] confirmation of tuberculosis.
2. An elevated pericardial fluid adenosine deaminase [ADA] level or gamma-interferon level in patients with exudative effusions and no evidence of infection by other bacteria (Mayosi, Burgess et al. 2005; Reuter, Burgess et al. 2006). In parts of the world where tuberculosis is endemic, a pericardial fluid ADA value of $>40\text{U/L}$ has a sensitivity and specificity of 88% and 83% respectively (Tuon, Litvoc et al. 2006) while a gamma interferon level $>50\text{pg/ml}$ has a sensitivity and specificity of 92% and 100% (Burgess, Reuter et al. 2002).

A diagnosis of effusive constrictive pericarditis was made if all of the following criteria were met (Sagrista-Sauleda, Angel et al. 2004; Hutchison 2009):

1. The pre-pericardiocentesis right atrial pressure was elevated [$>8\text{mmHg}$].
2. The pre-pericardiocentesis right atrial pressure was elevated as a result of elevated intra-pericardial pressure as determined by a trans-mural pressure of $\leq 4\text{mmHg}$.
3. Failure of the right atrial pressure to fall by $\geq 50\%$ or to a level below 11 mmHg despite the normalization of the post-pericardiocentesis intra-pericardial pressure to zero or near zero.

Pericardial tamponade was diagnosed if the difference between the right atrial pressure and the intra-pericardial pressure was \leq two [2] mmHg during expiration (Sagrista-Sauleda, Angel et al. 2004).

The definition of effusive constrictive pericarditis was derived from that of Sagrista-Sauleda and colleagues (Sagrista-Sauleda, Angel et al. 2004), and modified in one important way to ensure stringent definition of pericardial disease, as follows:

Although the Sagrista-Sauleda definition required “tamponade that evolved into constriction (Sagrista-Sauleda, Angel et al. 2004)”, in their study 40% of the patients had an initial trans-mural filling pressure gradient which exceeded 6 mmHg (Sagrista-Sauleda, Angel et al. 2004), and approximately 25% had a initial gradient greater than 10 mmHg. These values are not in keeping with the previously defined hemodynamic characteristics of

pericardial tamponade (Reddy, Curtiss et al. 1978). To ensure that there was little doubt that the cause of the right atrial pressure elevation was due to the elevated intra-pericardial pressure and not due to right ventricular non-compliance from other causes, in this study we required that the two pressures (i.e., intra-pericardial and right atrial pressures) more closely approximate each other as shown by a trans-mural pressure gradient of ≤ 4 mmHg (Reddy, Curtiss et al. 1978; Boltwood 1987).

Patients diagnosed with tuberculosis were referred to a tuberculosis clinic and started on anti-tuberculosis therapy as per the guidelines of the South African National Tuberculosis Control Programme (Department of Health 2004). Those patients who tested positive for HIV after counseling were referred to an HIV clinic. The participants were followed up at the Cardiac Clinic of Groote Schuur Hospital at 2 weeks, 4 weeks, 12 weeks and 24 weeks from the time of enrolment in the registry.

I was provided with the opportunity to answer important questions about the prevalence, predictors, pathogenesis and prognosis of tuberculous effusive constrictive pericarditis through the establishment and implementation of the second phase of the IMPI prospective cohort study.

Chapter 4

The prevalence and natural history of effusive constrictive pericarditis: A systematic review of the literature

4.1 Introduction

Effusive constrictive pericarditis is believed to be a rare manifestation of pericardial disease (Cameron, Oesterle et al. 1987). The outcome of effusive constrictive pericarditis, with regard to the development of constrictive pericarditis, pericardiectomy rates and death, is not well defined (Hancock 2004). In the only prospective study of effusive constrictive pericarditis, the prevalence was 6.8% of patients undergoing pericardiocentesis and 1.2% of all patients referred with effusive pericarditis (Sagrista-Sauleda, Angel et al. 2004). In the same study 46.7% of participants with the diagnosis underwent pericardiectomy within four months and the mortality rate was 60% over the subsequent seven-year mean follow up period (Sagrista-Sauleda, Angel et al. 2004).

There are a number of reasons to question the generalizability of these findings. First, the influence of the etiology of pericarditis on the prevalence and outcome is not known. For example, tuberculous pericarditis is associated with significant inflammation (Reuter, Burgess et al. 2006), relative chronicity (Mayosi, Burgess et al. 2005), and a high rate of development of constrictive pericarditis in about 25% of cases (Schrire 1959; Desai 1979; Mayosi, Burgess et al. 2005). It is likely therefore that the prevalence of effusive constrictive pericarditis in patients with tuberculous pericarditis may be much higher than seen in acute forms of pericardial disease such as idiopathic or viral pericarditis, which have formed the basis of the previous studies of effusive constrictive pericarditis. With regard to the natural history, in the Sagrista-Sauleda study, those with neoplastic disease had a high mortality and low pericardiectomy rate whereas those with idiopathic disease had a low mortality rate but high pericardiectomy rate. The impact of the etiology of pericarditis on these outcomes amongst patients whose life expectancy is not severely limited by malignant disease is not known.

Secondly few investigators routinely use the 'gold standard' to establish the diagnosis of effusive constrictive pericarditis, which is invasive measurement of intra-pericardial and intra-cardiac pressures before and after

pericardiocentesis (Hancock 2004). Even though non-invasive tools, such as echocardiography and magnetic resonance imaging are gaining wider acceptance as methods for establishing the diagnosis (Zagol, Minderman et al. 2007), none has been compared to invasive hemodynamic diagnosis of effusive constrictive pericarditis (Zagol, Minderman et al. 2007; Grizzard 2009).

Data about the prevalence and outcome of effusive constrictive pericarditis are particularly important in the developing world where tuberculosis is the most common cause of pericarditis (Mayosi, Burgess et al. 2005). Currently there are no recommendations on the diagnosis and management of the syndrome, which some experts believe is the most common manifestation of tuberculous pericarditis (Commerford and Strang 1991).

We have conducted a systematic review of the literature to determine the prevalence and outcome of effusive constrictive pericarditis due to viral, tuberculous, uremic, purulent and idiopathic causes. Furthermore, we determined whether the etiology of the effusion had a significant impact on the prevalence and the outcome of effusive constrictive pericarditis. We limited the review to observational studies of pericarditis due to these non-neoplastic medical conditions that commonly progress to constrictive pericarditis (Cameron, Oesterle et al. 1987).

4.2 Methods

MEDLINE, EMBASE, and Google Scholar were searched for English language publications of observational studies of effusive constrictive pericarditis that were conducted from inception of the respective database through to July 2009. Search terms included: acute pericarditis, pericardial effusion, effusive constrictive pericarditis, pericardial tamponade, cardiac tamponade, tuberculous pericarditis, uremic pericarditis, purulent pericarditis, idiopathic pericarditis, viral pericarditis, and constrictive pericarditis. Limits included: the English language, human beings and the following MeSH terms ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Retrospective Studies"[MeSH] OR "Prospective Studies"[MeSH]). In addition to searching the databases, we contacted

researchers in the field, and searched the bibliographies of published reviews and studies on pericardial disease for relevant studies.

The eligibility criteria for inclusion and exclusion from the study, which are based on the Loney criteria for critical appraisal of research articles on prevalence of disease, are shown in Table 1 (Loney, Chambers et al. 1998). To be included in the review, a study had to provide sufficient information to enable determination of the proportion of study participants diagnosed with effusive constrictive pericarditis and at least six other eligibility criteria.

Studies where malignancy was the predominant cause of pericarditis were excluded from this systematic review because patients with this diagnosis generally do not survive long enough to develop constrictive pericarditis (Cameron, Oesterle et al. 1987; Colombo, Olson et al. 1988). Studies of patients with pericardial effusion that resulted from aortic dissection, myocardial infarction, medical procedures and trauma to the thorax were also excluded because pericardial sequelae are uncommon amongst long-term survivors of these conditions (Cameron, Oesterle et al. 1987; Correale, Maggioni et al. 1993; Correale, Maggioni et al. 1997; Ling, Oh et al. 1999).

After the relevant studies were selected, individual patient data were extracted and reviewed in order to exclude patients with malignancy associated effusive constrictive pericarditis. We conducted a meta-analysis of the individual patient data using the StatsDirect software (www.statsdirect.com). We used the Cochran Q test to assess statistical heterogeneity between studies and, in the absence of significant heterogeneity ($P > 0.1$), combined the data using a fixed-effects method. Otherwise, we used the random-effects method. In addition, we used Higgins I^2 statistic to quantify inconsistency across the studies included in the meta-analysis. The test statistic describes the percentage of the variability in effect estimates that is due to true heterogeneity rather than chance. The closer the I^2 value is to 100%, the more likely it is that true heterogeneity exists and therefore the less reliable the combined estimate becomes.

I conducted the electronic searches, selected the studies, all of which were reviewed by Drs Charles Wiysonge and Bongani Mayosi. The reporting of the systematic review is in keeping with standard recommendations for

reporting systematic reviews of observational studies (Stroup, Berlin et al. 2000).

Table 3: Eligibility criteria for inclusion in the systematic review

Inclusion criteria
1] The study design was observational [case control, cross sectional and cohort]; cross sectional studies were accepted for the determination of prevalence.
2] An acceptable definition of the syndrome of effusive constrictive pericarditis was given
3] The inclusion and exclusion criteria for the studies were clearly stated
4] There was a clear description of the number of participants in the study
5] The number or proportion of participants in the study with effusive constrictive pericarditis was clearly stated
6] The method of diagnosis of effusive constrictive pericarditis was described and determined in an unbiased manner
7] There was an adequate description of the study setting
8] There was an adequate description of the study population
Exclusion criteria
1] The number or proportion of participants with effusive constrictive pericarditis was not available
2] The etiology of pericarditis was neoplasia, myocardial infarction, aortic dissection, trauma or iatrogenic injury.
3] The diagnosis of effusive constrictive pericarditis was based on clinical assessment only

4.3 Definitions

Effusive constrictive pericarditis was classified as definite, probable or rejected based on the methods used to establish the diagnosis (Hancock 2004; Zagol, Minderman et al. 2007).

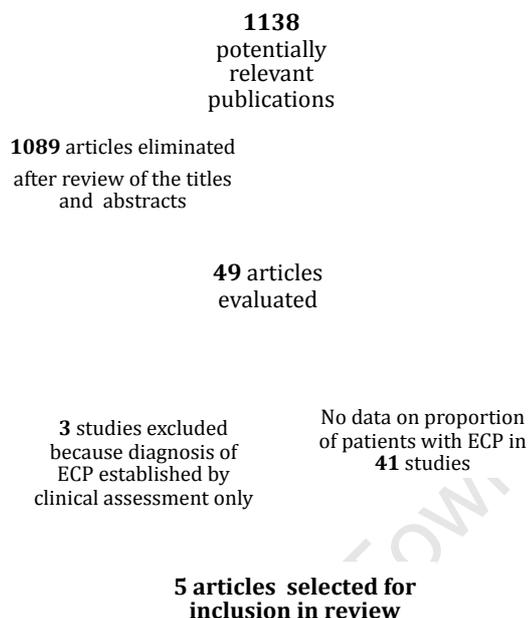
Patients were classified as having effusive constrictive pericarditis if the diagnosis was based on intra-pericardial and intra-cardiac hemodynamics determined before and after pericardiocentesis. This hemodynamic definition required that: a] the pre-pericardiocentesis transmural filling pressure i.e. the difference between the intra-pericardial pressure and the right atrial pressure

was less than 2 mmHg; b] the post-pericardiocentesis intra-pericardial pressure fell to near 0 mmHg; and c] the post-pericardiocentesis right atrial pressure failed to fall by 50% or to a level below 10 mm Hg (Sagrista-Sauleda, Angel et al. 2004).

The diagnosis of effusive constrictive pericarditis was considered probable if it was established on the basis of echocardiography or magnetic resonance imaging even though there are no published prospectively derived consensus diagnostic criteria by these imaging modalities. Widely accepted criteria include evidence of the following features in a patient with pericardial effusion: a] pericardial thickening; b] abnormal or paradoxical movement of the interventricular septum; c] a plethoric dilated inferior vena cava with reduced narrowing during inspiration; and d] marked respiratory variation of the mitral inflow doppler pattern (Zagol, Minderman et al. 2007)

4.4 Results

A flow chart for the selection process is provided in Figure. 1. Five studies were included in the systematic review (Nugue, Millaire et al. 1996; Tsang, Barnes et al. 2003; George, Salama et al. 2004; Sagrista-Sauleda, Angel et al. 2004).

Figure 3: Flow chart for the selected studies

4.41 Quality and characteristics of the included studies

A summary of the study design and strength of diagnosis of effusive constrictive pericarditis in the five studies is provided in Table 4. One of the three prospective cohorts was a single center South African study, designed to determine the 30 day and one year outcomes of consecutive patients with predominantly tuberculous pericarditis, who were each given a standardized therapeutic protocol, which included pericardiocentesis (Reuter, Burgess et al. 2007). The proportion of those with effusive constrictive pericarditis was 2.6% based on clinical and echocardiographic criteria.

The second prospective cohort study was a single center French study designed to determine the role of surgical pericardioscopy as a diagnostic tool among patients with large pericardial effusion of uncertain etiology (Nugue, Millaire et al. 1996). The proportion of patients diagnosed with effusive constrictive pericarditis is reported as 1.4%. All patients underwent pericardiocentesis, and echocardiography was used to assess pericardial physiology and content.

The third prospective cohort study was a single center Spanish study, which aimed to determine the prevalence of effusive constrictive pericarditis and to determine the incidence of pericarditis-related outcomes over a median follow up period of seven years (Sagrista-Sauleda, Angel et al. 2004). Consecutive participants presenting with a diagnosis of pericardial tamponade over 15 years underwent measurement of the pre- and post-pericardiocentesis intra-pericardial and right atrial pressures. The prevalence of non malignant effusive constrictive pericarditis was 5.8 % of those patients undergoing combined cardiac catheterization and pericardiocentesis, 5% of those with clinical tamponade and 1% of patients with any pericardial disease (Sagrista-Sauleda, Angel et al. 2004).

Table 4: The study, strength of ECP diagnosis, and study design

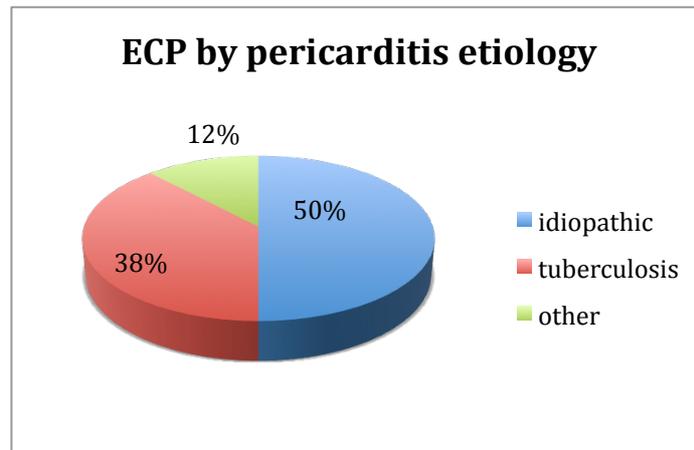
Study	Strength of ECP diagnosis	Study design	Number and Prevalence of non-neoplastic ECP cases
Reuter '07	Probable ECP	Prospective cohort	5 [2.6%]
Sagrista-Sauleda '04	Definite ECP	Prospective cohort	11 [5.8%]
Nugue '96	Probable ECP	Prospective cohort	2 [1.4%]
George '04	Probable ECP	Cross-sectional	4 [14.8%]
Tsang '03	Probable ECP	Retrospective	4 [4.3%]

The remaining two studies of patients with a probable diagnosis of effusive constrictive pericarditis were designed to a) determine the long term outcome of patients with symptomatic effusion (Tsang, Barnes et al. 2003) and

b] compare echocardiographic differences between tuberculous and idiopathic pericardial effusions (George, Salama et al. 2004). The prevalence rate of effusive constrictive pericarditis in these two studies was 4.3% and 14.8% respectively.

Figure 4 provides the etiology of pericarditis of the 26 patients with effusive constrictive pericarditis in the five studies.

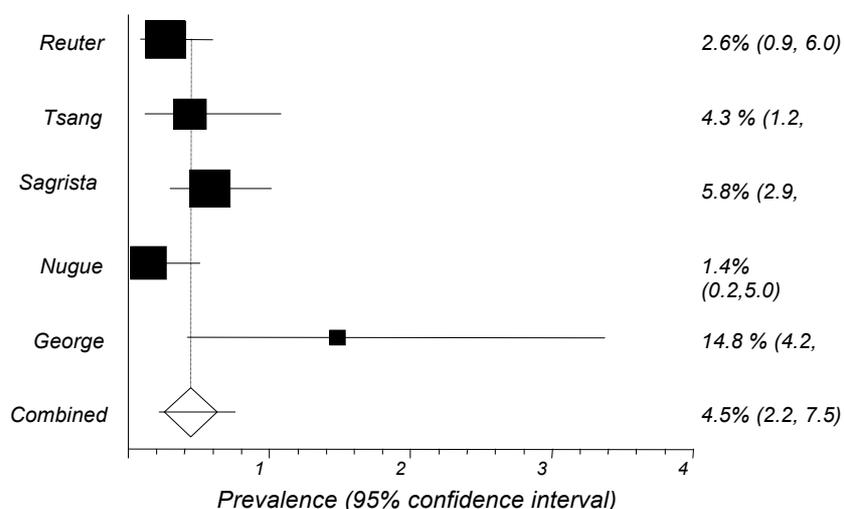
Figure 4



Overall there was significant variability in the prevalence of ECP across the five studies ($P = 0.04$; $I^2 = 61\%$), therefore we used a random-effects meta-analysis to combine the prevalence rates. The pooled prevalence of effusive constrictive pericarditis in the five studies was 4.5% (95% confidence interval 2.2% to 7.5%). The prevalence rates across the studies and confidence intervals are provided in Figure 5.

Figure 5

Forrest plot for the prevalence of effusive constrictive pericarditis

Test for heterogeneity

Cochran Q = 10.3 (df = 4), P = 0.04

I² = 61%

Pooled prevalence [random-effects] = 4.5% (95% CI = 2.2 to 7.5)

Table 5: Outcomes of patients with effusive constrictive pericarditis

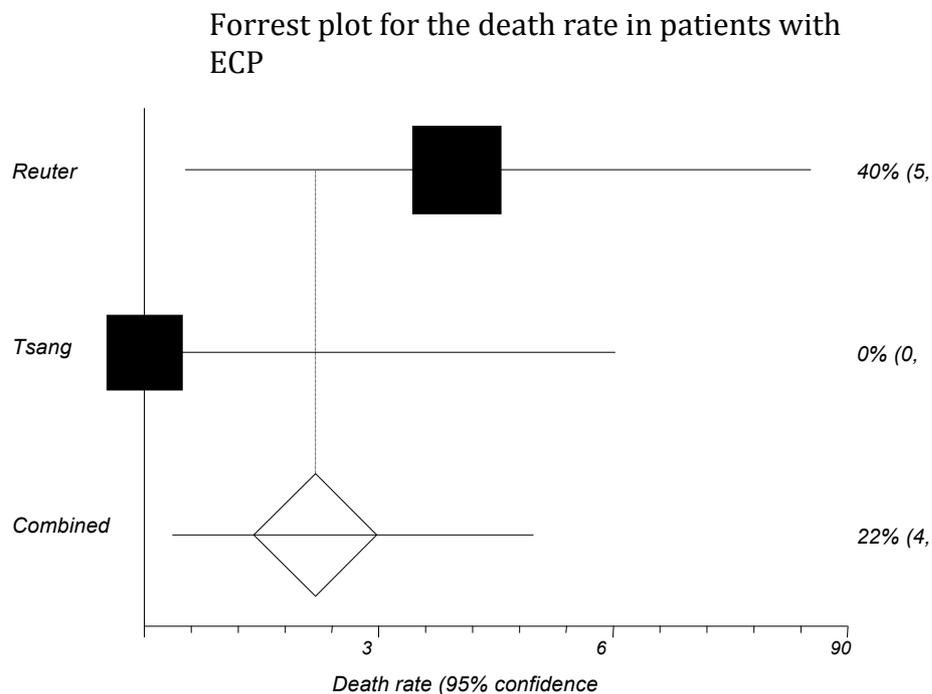
Study	Absolute number of study participants with non-neoplastic ECP	Number of patients with ECP who underwent pericardiectomy within 12 months	Number of patients with ECP dead at 12 months
Sagrista-Sauleda '04	11	7/11 [64%]	Mortality data at 12 months not available for all patients
Reuter '07	5	2/5 [40%]	2/5 [40%]
Tsang '03	4	4/4 [100%]	0/4 [0%]
Nugue '96	2	Pericardiectomy data not available	Mortality data not available
George '04	4	Pericardiectomy data not available	Mortality data not available
Total	26	13/20 [65%]	2/9 [22%]

Table 5 abbreviations key

ECP: effusive constrictive pericarditis, TB: tuberculosis

One-year mortality data was available for only nine participants with non-malignant disease from two studies (Tsang, Barnes et al. 2003; Reuter, Burgess et al. 2007) [Table 5]. Of the two deaths, one was from peri-operative complications and the other patient died while awaiting surgery. The combined death rate across the studies was 22%, with wide 95% confidence intervals (4% to 50%) due to the small numbers involved (Figure 4). Six patients did not have the operation. One patient with tuberculosis died from heart failure while awaiting surgery and two participants, also with tuberculosis, did not consent to the procedure. A conservative “wait and see” approach was adopted with 3 participants with idiopathic disease. These five participants who survived the early stages of their illness were alive and well at their last follow up visit.

Figure 6



Test for heterogeneity

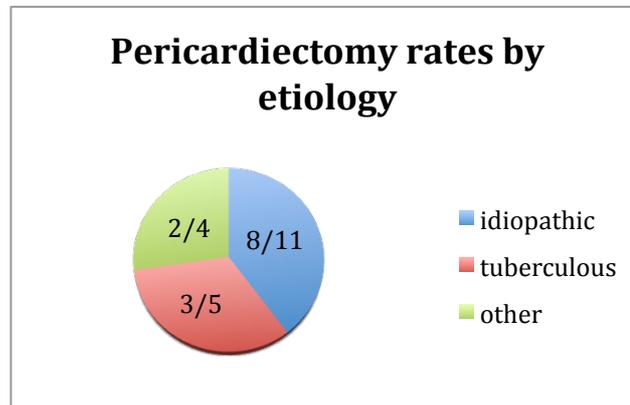
Cochran Q = 4.6 (df = 2), P = 0.10

I² = 56%

Pooled rate [random-effects] = 67.8 (95% CI = 36.1 to 92.3)

Only three of the studies provided data on the pericardiectomy rates (Tsang, Barnes et al. 2003; Sagrista-Sauleda, Angel et al. 2004; Reuter, Burgess et al. 2007). Figure 7 provides a breakdown of the pericardiectomy rates by etiology of pericarditis.

Figure 7



Overall 65% of participants underwent pericardiectomy within the first year. The persistence of heart failure was the reason for surgery in 54% of cases, making it the most common indication followed by prophylaxis against progression to fibrous constrictive pericarditis in 23%. Recurrence of pericardial effusion was an indication in 15%. In only 8% was the operation performed because of progression to non-effusive fibrous constrictive pericarditis.

4.5 Discussion

This systematic review highlights that there are very few prospective studies of the prevalence and outcome of non-malignancy associated effusive constrictive pericarditis. The prevalence of this syndrome in the available studies ranges from 1.4 to 14%; there was too little information to ascertain the mortality rate reliably, and the pericardiectomy rate was high [44-100%].

There were a total of 10 participants who had tuberculous effusive constrictive pericarditis in this review. Commerford and Strang have suggested that it is a common form of presentation of tuberculous pericarditis, it frequently progresses to fibrous constrictive pericarditis and may be amenable to treatment with corticosteroids (Commerford and Strang 1991). By contrast, the IMPI Africa Registry has suggested that using clinical criteria alone, effusive constrictive pericarditis is present in only 15% of cases

of tuberculous pericarditis (Mayosi, Wiysonge et al. 2006). The results of this comprehensive review show a low prevalence of effusive constrictive pericarditis in patients with tuberculous pericarditis that ranged from 3-14%. There is therefore a need for a definitive study of the prevalence of effusive constrictive pericarditis that is based on invasive hemodynamic methods for the diagnosis of the disease.

Although the pericardiectomy rate across the studies was high, the indications for the surgical intervention were not uniform amongst the 13 participants who had the operation. A significant proportion of patients who were managed conservatively had complete resolution of their constrictive physiology. This suggests that there is room for a study to test a strategy of watchful waiting compared to prophylactic pericardiectomy in those without persistence of heart failure.

Finally, the mortality rate for tuberculous pericarditis in the HIV era is as high as 40% in patients with AIDS at the end of 6 months of treatment with anti-tuberculosis medication (Mayosi, Wiysonge et al. 2008). Despite the absence of data on mortality in patients with non-malignancy associated effusive constrictive pericarditis, it is possible that because of its well documented hemodynamic sequelae (Hancock 2004), the pericardial syndrome is associated with a higher mortality rate than those without the syndrome.

In conclusion, in light of the lack of clarity on: a] the prevalence of effusive constrictive pericarditis amongst patients with tuberculosis and other non-idiopathic causes of pericarditis; b] the role of prophylactic pericardiectomy; and c] the impact of the syndrome on mortality, a study of well characterized participants with adequate follow up and clearly defined outcomes may have an important impact on clinical practice. The results of such a study will go a long way to informing current guidelines on the approach to effusive pericarditis, the need for routine invasive hemodynamic assessment of patients in order to look for effusive constrictive pericarditis and the management of patients when a diagnosis is established.

In this thesis, the IMPI registry has been used to determine the prevalence (chapter 4), predictors (chapter 5), mathematical form (chapter 6),

biomarker profile (chapter 7) and outcome (chapter 8) of effusive constrictive pericarditis in patients with tuberculous pericardial effusion.

Chapter 5

The prevalence of effusive constrictive pericarditis and pericardial tamponade in patients with tuberculous pericardial effusion

5.1 Background

The majority of patients with tuberculous pericarditis present with one of two distinct pericardial syndromes; effusive pericarditis and constrictive pericarditis (Commerford and Strang 1991; Mayosi, Burgess et al. 2005). Acute pericarditis, characterized by the triad of chest pain, ST and PR segment deviation on the ECG and a pericardial friction rub is said to be rare in pericardial tuberculosis (Schrire 1959; Strang 1984). Amongst those patients who present with effusive pericarditis, two complications may be evident. The first is significant cardiac compression associated with hemodynamic compromise (i.e., pericardial tamponade). The second is a combination of cardiac compression from the effusion and visceral pericardial constriction (i.e., effusive constrictive pericarditis) (Commerford and Strang 1991; Mayosi, Burgess et al. 2005). The two complications are not mutually exclusive and may occur in the same patient (Sagrasta-Sauleda 2004). The reported prevalence of effusive constrictive pericarditis and pericardial tamponade in patients with tuberculous pericardial effusion varies widely, and depends on the definitions and diagnostic methods used in the various studies of this question (Long, Younes et al. 1989; Commerford and Strang 1991; Hugo-Hamman, Scher et al. 1994; Mayosi, Wiysonge et al. 2006; Reuter, Burgess et al. 2007).

The clinical manifestations of pericardial tamponade are variable with the symptoms and signs being both non-sensitive and non-specific (Reddy, Curtiss et al. 1978; Guberman, Fowler et al. 1981; Wayne, Bishop et al. 1984; Brown, MacKinnon et al. 1992; Roy, Minor et al. 2007). This has been attributed to several variables that can influence the clinical manifestations including: the rate of accumulation of pericardial fluid, a patient's intravascular fluid status, the baseline blood pressure and the underlying cardiac function (Guberman, Fowler et al. 1981; Spodick 2003; Sagrasta-Sauleda, Angel et al. 2006). That there is no consensus on the role of echocardiography in the definition and diagnosis (Fowler 1993) compounds the issue, leading to some studies using a clinical definition (Strang, Nunn et

al. 2004) while others have incorporated an echocardiographic definition of pericardial tamponade (Reuter, Burgess et al. 2007)

As opposed to either a clinical definition or echocardiography-based definition, a hemodynamic definition of tamponade has an evidenced-based physiological basis (Reddy, Curtiss et al. 1978; Boltwood 1987) that is widely accepted (Spodick 2003). It recognizes that while there may be a spectrum of clinical severity of tamponade, the defining event or onset of tamponade occurs when the transmural filling pressure [i.e., the difference between the right atrial pressure and intra-pericardial pressure] averages zero (Fowler, Shabetai et al. 1959; Shabetai, Fowler et al. 1970; Boltwood 1987; Shabetai 2004). The widely accepted prevalence rate of tamponade in patients with tuberculous pericarditis as determined from large cohorts is approximately 10% (Fowler 1991; Strang, Nunn et al. 2004). However it is important to note that the diagnosis of tamponade in these studies was not established using hemodynamic definitions but rather using clinical and echocardiographic criteria.

Over the years, effusive constrictive pericarditis has been described as rare, with only sporadic case reports and a few small case series being published (Spaulding 1967; Rasaretnam and Chanmugam 1980; Santarone, Corrado et al. 2000). Difficulty in recognizing the syndrome and being able to establish a diagnosis has been an important reason for the paucity of data on its epidemiology and prognosis (Hancock 2004). Central to the diagnosis of effusive constrictive pericarditis from any cause is confirmation that the right atrial pressure remains elevated after fluid has been evacuated from the pericardium despite the fact that the intra-pericardial pressure has returned to normal [mean pressure -2 to +2 mmHg] (Hancock 2004). Clinical and non-invasive methods such as echocardiography, while helpful in providing clues to the diagnosis are inadequate, in part because of their inability to accurately assess intra-pericardial pressures (Sagrista-Sauleda 2004; Sagrista-Sauleda, Angel et al. 2004).

Establishing whether or not a patient with a sizable symptomatic tuberculous pericardial effusion has either pericardial tamponade, effusive constrictive pericarditis or both may be clinically and prognostically important (Mayosi, Burgess et al. 2005). Both are associated with a higher

incidence of the major adverse outcomes of death and constrictive pericarditis (Hancock 1971; Suwan and Potjalongsilp 1995; Hancock 2004). An early diagnosis of either may influence management. In the case of pericardial tamponade, even in the absence of overt shock, immediate pericardiocentesis may improve the symptoms and signs of heart failure and may be lifesaving (Spodick 2003). In the case of effusive constrictive pericarditis there may be a role for early pericardiectomy in those with persistent heart failure or close follow up for those whose symptoms resolve (Hancock 2004; Sagrista-Sauleda 2004).

Given that establishing a diagnosis may have management and prognostic implications it would be important to know the prevalence of the pericardial tamponade and effusive constrictive pericarditis in patients presenting with moderate or large pericardial effusions of tuberculous etiology. If either or both syndromes are rare, recommending routine measures to establish the diagnosis may be a waste of resources and time. If however either or both are more common than previously suspected investing in time to establish a diagnosis and treat appropriately may significantly alter outcomes in a large number of patients. This is particularly relevant in sub-Saharan Africa where tuberculous pericarditis is common, resources are limited and interventions such as pericardiocentesis are infrequently performed in patients presenting with large effusions suspected to be tuberculous in origin (Mayosi, Wiysonge et al. 2006).

5.2 Hypotheses

Given that the most common cause of constrictive pericarditis in the developing world is tuberculosis (Myers and Spodick 1999), that approximately 25% of patients with tuberculous pericarditis progress to develop constrictive pericarditis (Desai 1979; Bhan 1980) and assuming that tuberculous constrictive pericarditis is preceded by effusive constrictive pericarditis in a significant proportion of patients we hypothesized:

1. that the prevalence of tuberculous effusive constrictive pericarditis may be significantly higher than the 6.8% described in patients with idiopathic effusions; and
2. that the prevalence of hemodynamically confirmed pericardial tamponade would be significantly greater than the 10% that has been

described for tuberculous pericarditis previously using clinical criteria (Fowler 1991; Strang, Nunn et al. 2004)

5.3 Diagnostic criteria for effusive constrictive pericarditis and pericardial tamponade

The definitions of effusive constrictive pericarditis and pericardial tamponade were provided in Chapter 2 [section 2.4.3]. The criteria for establishing the hemodynamic diagnosis are summarized in Tables 6 and 7.

Table 6: Criteria for the hemodynamic diagnosis of effusive constrictive pericarditis

<p>1) The pre-pericardiocentesis right atrial pressure was elevated [$>8\text{mmHg}$]</p> <p>2 The pre-pericardiocentesis right atrial pressure was elevated as a result of elevated intra-pericardial pressures as determined by a trans-mural pressure gradient of $\leq 4\text{mmHg}$.</p> <p>3 Failure of the right atrial pressure to fall below 11 mmHg despite the normalization of the post-pericardiocentesis intra-pericardial pressure to zero.</p>

Table 7: Criteria for the hemodynamic diagnosis of pericardial tamponade

<p>1) The pre-pericardiocentesis right atrial pressure was elevated [$>8\text{mmHg}$]</p> <p>2) The difference between the right atrial pressure and the intra-pericardial pressure was \leq two [≤ 2] mmHg during expiration (Sagrasta-Sauleda, Angel et al. 2004).</p>

5.4 Study design and methods

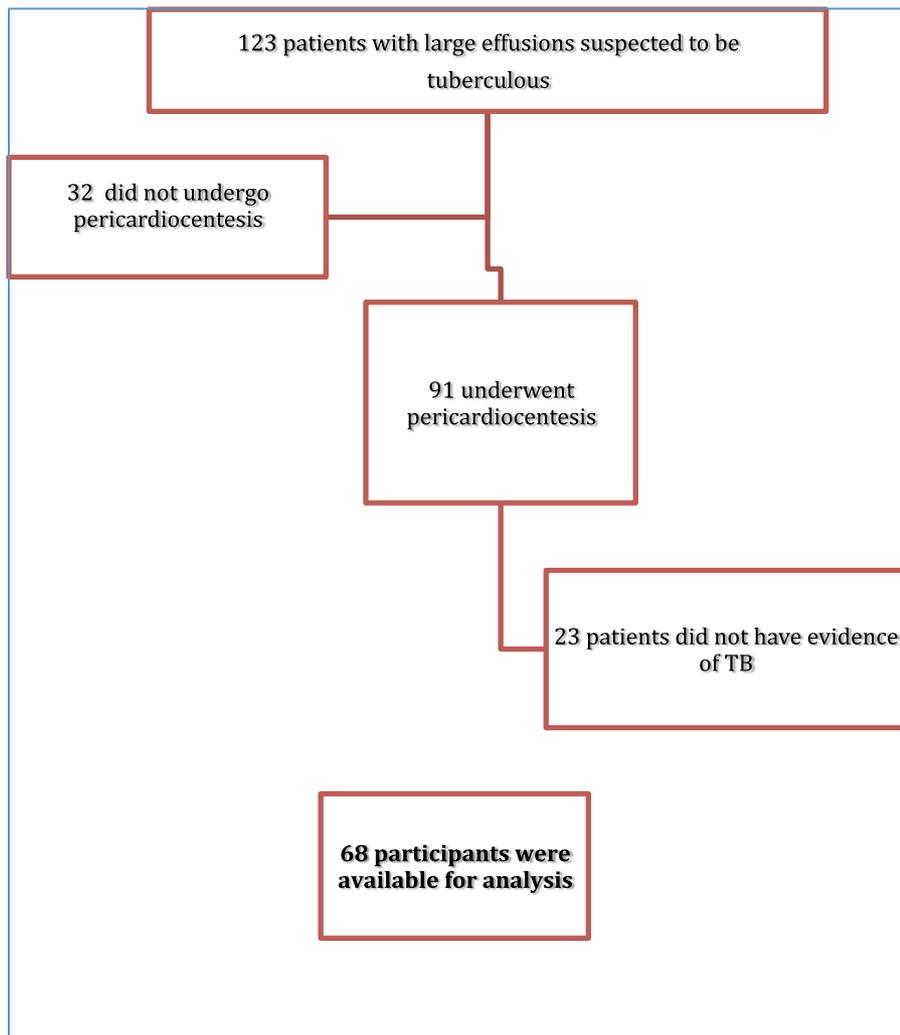
The methods (including details of the design, inclusion, and exclusion criteria) of the IMPI tuberculous pericarditis prospective cohort study are provided in Chapter 2 [2.4.1 and 2.4.2]. For the purpose of determining the

prevalence of pericardial tamponade and effusive constrictive pericarditis in patients with tuberculous pericardial effusion a cross sectional analysis of consecutive patients enrolled in the prospective registry was conducted. Over the 3 years prior to the onset of the study an average of 53 patients referred to our center with large pericardial effusions underwent either a diagnostic or therapeutic pericardiocentesis. Using this number as the population, and using the reported prevalence rate of effusive constrictive pericarditis of 8% in unselected patients with pericardial disease and pericardial tamponade of 10% in patients with tuberculous pericarditis and aiming for a precision of 5%, the calculated number of patients required to determine the prevalence rate was 54.

5.5 Results

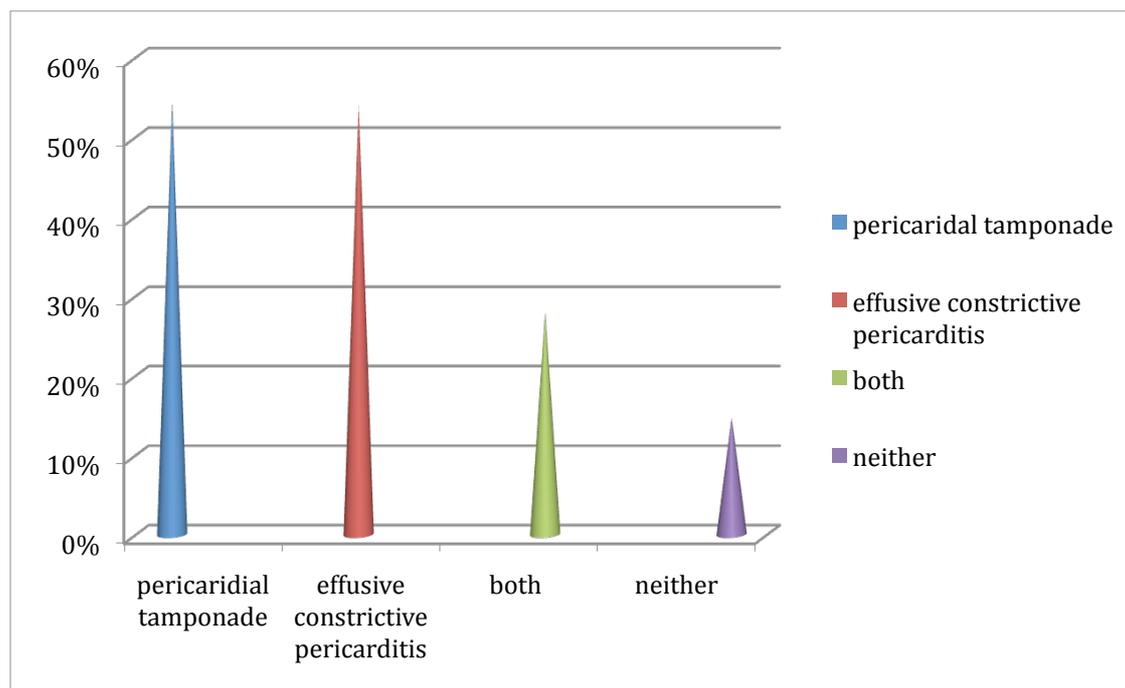
One hundred and twenty three patients were referred for assessment over the given period and 91 of them underwent pericardiocentesis. Sixty-eight patients met the inclusion and exclusion criteria and were available for analysis. Fifty five patients were excluded from the study for the following reasons: 8 participants refused consent, 18 had small hemodynamically insignificant effusions that were not amenable to safe sub-xyphisternal access and 6 patients were found to have alternative diagnoses such as cardiomyopathy and valvular heart disease. Twenty-three of the patients who underwent pericardiocentesis were subsequently found to have no evidence of tuberculosis by culture, PCR or biochemical analysis [Figure 8].

Figure 8: Flow diagram of 123 referrals to the IMPI study



Of the 68 participants who met the inclusion criteria, 36 met the definition of effusive constrictive pericarditis and 32 were classified as purely effusive pericarditis. Thirty-seven patients met the hemodynamic criteria for pericardial tamponade, 19 participants met the hemodynamic criteria for both pericardial tamponade and effusive constrictive pericarditis and 10 patients had large effusions with no evidence of significant cardiac compression or visceral constriction. Amongst patients with large tuberculous pericardial effusions, the prevalence of effusive constrictive pericarditis was therefore 52.9% [CI 41.2-65.4] and that of pericardial tamponade was 54.4% [CI 42.5-65.9] [Figure 9]. The presence of pericardial tamponade was not associated with a diagnosis of effusive constrictive pericarditis [$p=0.77$]

Figure 9: prevalence of pericardial tamponade and effusive constrictive pericarditis



5.6 Discussion

The main finding from this study is that the majority of patients with tuberculous pericardial effusion present with a significant cardiac compression manifest by pericardial tamponade in 54%, effusive constrictive pericarditis in 53% or both in 28%. There are only three observational studies of patients with tuberculous pericarditis that have provided data on the proportion of participants with effusive constrictive pericarditis since 1940 (Hugo-Hamman, Scher et al. 1994; Mayosi, Wiysonge et al. 2006; Reuter, Burgess et al. 2007). The prevalence rates in these studies ranged from 6.8% to 25%, but significant limitations in the methods used to establish the diagnosis rendered most of this information difficult to interpret. To the best of my knowledge, this is the first study that has used invasive hemodynamic measurements to determine the prevalence of pericardial tamponade and effusive constrictive pericarditis in patients with tuberculous pericardial effusion.

The prevalence rate of effusive constrictive pericarditis of 53% challenges the belief that that this syndrome is “rare” (Hancock 2004) and

validates the hypothesis that the frequency may vary depending on the etiology of the pericardial effusion. The finding that the prevalence rate of pericardial tamponade is approximately 54% is equally important. It validates the hypothesis that tamponade is more prevalent than suggested by clinical assessment alone (Strang, Nunn et al. 2004) and supports those who place a greater reliance on an echocardiography to look for tamponade (Reuter, Burgess et al. 2007).

Furthermore, I show for the first time that in approximately 50% of those with pericardial tamponade the hemodynamic insult is twofold: a) compression of the underlying heart from the pericardial fluid; and b) inflammation and insult to the visceral pericardium with evidence of loss of compliance and elasticity leading to visceral constriction of the underlying myocardium. In these patients evacuation of the pericardium by pericardiocentesis improves the transmural filling pressure and relieves the tamponade in the short term. In those without pericardial tamponade, pericardiocentesis is still important. It allows for the recognition of the significant proportion of patients who have effusive constrictive pericarditis and who may need close monitoring because they are at high risk of progression to fibrous constriction and heart failure. Whether or not pericardiocentesis itself reduces the incidence of subsequent constriction by physically removing pro-fibrotic cytokines from the pericardium is an intriguing hypothesis that requires further study.

5.61 Limitations of the study

Referral bias was an important potential limitation of this study. Although all patients with suspected pericardial tuberculosis were supposed to be referred for investigation and management, it is possible that doctors referred only those patients who they felt were sick enough. Given the data from the first phase of the IMPI registry of patients with suspected tuberculous pericarditis which showed that the majority of patients [64%] are started on anti-tuberculous therapy with little evidence for tuberculosis and a small minority [<35%] undergo pericardiocentesis (Mayosi, Wiysonge et al. 2006) it is possible that this referral pattern may have continued despite our attempt to avoid it. Prior to and during the study we conducted clinical workshops on tuberculous pericarditis with referring doctors, emphasizing

that the condition carries a high mortality and highlighting the need for all patients to be referred for appropriate diagnosis and management.

5.62 Implications for clinical practice

Current evidence is that a minority [$<35\%$] of patients with suspected tuberculous pericardial effusion undergo therapeutic or diagnostic pericardiocentesis in routine clinical practice (Mayosi, Wiysonge et al. 2006). Possible explanations for this include: a) the assumption that the etiology is not in question and therefore a diagnostic tap is not required; and b) under-recognition of the compressive effect of both the fluid and visceral pericardium on the underlying myocardium in about 50% of cases. This prevalence study suggests that half of patients with tuberculous pericardial effusion are likely to benefit both symptomatically and potentially prognostically from relief of the pericardial collection. In other words, patients with suspected tuberculous pericardial effusion may benefit from early referral for pericardiocentesis, contrary to current practice of conservative non-invasive management.

5.63 Implications for research

These observations have important implications for research related to the diagnosis, treatment and prognosis of tuberculous pericardial effusion. It is unlikely an invasive diagnosis of pericardial tamponade and effusive constrictive pericarditis will be widely available in clinical practice. There is therefore a need to replicate the findings of this work through the use of non-invasive modalities such as echocardiography.

It is not known whether the routine treatment of pericardial tamponade and effusive constrictive pericarditis when diagnosed by invasive hemodynamic means (such as in this study) requires treatment by pericardiocentesis or not. It is possible that the evacuation of the pericardial fluid in patients with these compressive pericardial syndromes may improve clinical outcomes. There is therefore a need for clinical trials of routine pericardiocentesis in patients with the compressive pericardial syndromes compared to routine practice.

The impact of pericardial tamponade and effusive constrictive pericarditis on the important outcomes of death and constrictive pericarditis is not known. This question is addressed further in Chapter 8 of this work.

Chapter 6

The predictors of tuberculous effusive constrictive pericarditis: right atrial pressure, not tamponade, predicts effusive constriction in tuberculous pericarditis

6.1 Introduction

The approach to the investigation and management of patients with suspected tuberculous pericarditis has been reviewed previously (Mayosi, Volmink et al. 2002; Maisch, Seferovic et al. 2004; Syed and Mayosi 2007). Emphasis is placed on the need to perform a thorough history and physical examination; echocardiography should be performed to confirm clinically suspected pericardial effusion and to look for features of tamponade; an exhaustive search should be done for evidence of tuberculosis, both within the pericardium and at other sites; and investigations should be performed to exclude alternative diagnoses such as purulent pericarditis and malignant effusion. This approach generates numerous patient-related variables that, either singularly or in combination, may help to identify those patients likely to have the visceral pericardial constriction and compressive pericardial fluid diagnostic of effusive constrictive pericarditis.

In addition to this routinely sought information, several additional variables may be important risk markers for effusive constrictive pericarditis. Assuming that effusive constrictive pericarditis represents a stage between effusive pericarditis and fibrotic constrictive pericarditis, the duration of pericardial tuberculosis prior to institution of therapy may be associated with the syndrome. Large effusions such as those seen with tuberculosis accumulate gradually over time (Henderson, Mackinnon et al. 2006), and the measured volume of fluid within the pericardium may be a surrogate marker of duration of disease.

Given that effusive constrictive pericarditis is characterized both by cardiac compression and constriction, it is possible that patients with this syndrome have a higher opening right atrial pressure than patients with cardiac compression from fluid alone. In the original Hancock series, patients with effusive constrictive pericarditis had higher opening pressures compared to controls with constrictive pericarditis and effusive pericarditis (Hancock 1971) but the number of participants was too small for significant

inferences to be made. Measurement of the opening right atrial pressure in a much larger prospective cohort may therefore provide important insights and clarify whether or not there is indeed a relationship.

The correlation of the clinical assessment of the jugular venous pressure and measured central venous pressure is poor (Stein, Neumann et al. 1997; Demeria, MacDougall et al. 2004) and unlikely to provide reliable estimation of the right atrial pressure. NT-pro brain natriuretic peptide [BNP] is a rapid bedside assay which reflects atrial stretch and the presence of heart failure (Levin, Gardner et al. 1998; Maisel, Krishnaswamy et al. 2002). It has been shown in small studies to correlate with the right atrial pressure (Raine, Erne et al. 1986; Gan, McCann et al. 2006). A small Korean study suggested that NT-pro BNP could be used as a marker of disease severity in patients with pericardial effusion as reflected by tachycardia, pulsus paradox and tamponade. Analogous to a possible association with the height of the right atrial pressure, there may be an important association between NT-pro BNP and effusive constrictive pericarditis.

Early case series and reports of effusive constrictive pericarditis suggested that it only occurred in patients with clinically defined tamponade (Hancock 1971; Rasaretnam and Chanmugam 1980). However the clinical assessment of tamponade in medical causes of pericardial effusions is insensitive (Reddy, Curtiss et al. 1978) and it is possible that patients with pericardial effusions who do not have tamponade may have clinically significant visceral constriction. Using one of the most accurate measures of the presence of tamponade [by measuring intra-pericardial pressures and right atrial pressures](Fowler, Shabetai et al. 1959; Boltwood 1987; Roca, Dominguez de Rozas et al. 1989) would allow for a more precise determination of the relationship between the presence of tamponade and effusive constrictive pericarditis.

Finally a small but significant proportion of patients with pericarditis present with elevated biomarkers of myocardial injury, a syndrome called perimyocarditis (Imazio, Cecchi et al. 2007; Imazio and Trincheri 2008). It is possible that evidence of myocardial injury in the setting of pericarditis is a marker of the severity of the visceral pericardial injury and that severe

visceral pericarditis is associated with early visceral constriction and a diagnosis effusive constrictive pericarditis.

Given a) that identifying patients with effusive constrictive pericarditis may have important prognostic and therapeutic implications, and b) the current limitations of clinical evaluation and non-invasive tools in making the diagnosis, a reasonable alternative may be to identify patient-related variables, that are strongly associated with effusive constrictive pericarditis and can help identify patients with tuberculous pericarditis who are likely to have the condition. The IMPI tuberculous pericarditis prospective registry provided a unique opportunity to identify these variables.

6.2 Study objectives

To determine whether any clinical variables predict a diagnosis of effusive constrictive pericarditis in patients presenting with moderate and large tuberculous pericardial effusions

5.3 Methods

For the purposes of determining the predictors of effusive constrictive pericarditis, the baseline variables and clinical characteristics outlined in Table 8 were collected from each participant enrolled in the prospective cohort.

Table 8: Variables that were tested in the search for independent predictors of tuberculous effusive constrictive pericarditis

DEMO-GRAPHICS	CLINICAL HISTORY	CLINICAL EXAMINATION	ECG	CXR	Serum analysis	Pericardial fluid analysis	HEMO-DYNAMICS
Age							
Sex	History of TB	JVP	Rate	Pleural effusion		ADA	Pericardial fluid volume
	Duration of symptoms	Heart rate	Rhythm	Compatible with active Tb	CPK	LDH	IPP pre-pericardiocentesis
	NYHA CLASS	Pulsus paradoxus	Chest lead voltage	Compatible with previous Tb	CK MB%	Protein	IPP post pericardiocentesis
	HIV status	Peripheral edema			NT-pro BNP	Albumin	RAP pre pericardiocentesis

Tamponade	CD4 cells	ZN stain	RAP post pericardiocentesis
	LDH Protein	Tb culture Tb PCR	Tamponade

Abbreviations key for table 8 in alphabetical order

ADA: adenine deaminase, CPK: creatine phosphokinase, CK MB%: creatine kinase MB subunit, CXR: chest x-ray, ECG: Electrocardiogram, HIV: human immunodeficiency virus, IPP: intra-pericardial pressure, JVP: jugular venous pressure, LDH: lactate dehydrogenase, NYHA: New York Heart Association, PCR: polymerase chain reaction, RAP: right atrial pressure, TB: mycobacterium tuberculosis, ZN: Ziehl-Neelson

6.4 Statistical considerations

The number of patients enrolled in this study was based on the sample size required to determine the prevalence rate of effusive constrictive pericarditis. Approximately 53 patients underwent pericardiocentesis annually for suspected tuberculous pericarditis over the 3 years prior to the onset of the study. With an anticipated prevalence rate of 8%, a minimum number of 54 would allow the determination of the prevalence with an acceptable precision.

Descriptive and summary statistics were calculated for all the recorded variables. Differences between groups were tested using the Student's *t* tests for continuous variables and the χ^2 test for categorical variables. The available data were first included in univariate logistic regression models to determine the association between patient variables and effusive constrictive pericarditis. Factors that were significant by univariate analysis were then included in a final multivariate logistic regression model for analysis. All tests were two sided and a p-value <0.05 was considered significant.

6.5 Results

Of the 68 participants who met the inclusion criteria, 36 met the definition of effusive constrictive pericarditis and 32 were classified as purely

effusive pericarditis. Table 9 provides the summary statistics for the baseline variables

By univariate logistic regression analysis only age OR 1.06 [95% CI 1.01-1,11] $p=0.02$), opening intra-pericardial pressure OR 1.35 [95% CI 1.17-1,56] $p=0.0001$ and the opening right atrial pressure OR 1.45 [95% CI 1.23-1.72] $p=0.0001$ were associated with a diagnosis of effusive constrictive pericarditis. The closing intra-pericardial pressure and right atrial pressure were also associated with effusive constrictive pericarditis but were excluded because they were an integral part of the definition of effusive constrictive pericarditis. In the final multivariate regression model only the opening right atrial pressure remained statistically significant OR 1.48 [95%CI 1.07-2.05] $p=0.02$

The relationship between the opening right atrial pressure and effusive constrictive pericarditis was re-analyzed by looking at the right atrial pressure as a categorical variable. Using a cutoff value of 15mmHg the odds ratio was 15.36 [CI 2.37-99.6] $p=0.004$, and the positive predictive and negative predictive values were 84.2% [CI 69.6-92.3] and 86.7% [CI 70.3-94.7] respectively. The overall diagnostic accuracy was 85.5% [CI 75-91.8].

Table 9: Effusive constrictive pericarditis by baseline demographic and clinical characteristics

Variable	Effusive pericarditis [32]	Effusive constrictive pericarditis [36]	p-value
Age: median [IQR]	29(26-34.5)	37(29-53)	0.02
Gender: number [%]			0.71
Male	21(65.6)	22(61.1)	
Female	11(34.4)	14(38.9)	
HIV status: number [%]			0.42
Positive	25(78.1)	25(69.4)	
Negative	7(21.9)	11(30.6)	
CD4 count cells/μl			

<200	20(62.5)	17(47.2)	0.69
≥200	12(37.5)	17(47.2)	
Previous TB: number [%]			0.11
Yes	6(24)	2(7.7)	
No	19(76)	24(92.3)	
Durations of symptoms (wks)	4.0(3.0-7.0)	4.0(2.75-5.75)	0.62
NYHA: number [%]			0.44
II	1(3.3)	0	
III	13(43.3)	19(52.8)	
IV	16(53.3)	17(47.2)	

VARIABLE	Effusive pericarditis	Effusive constrictive pericarditis	P-value
O-IPP mean [SD]	9.7 [4.65]	16. [5.1]	<0.0001
O-RAP median [IQR]	10.0 [8.3-13.0]	17.0 [15.0-20.0]	<0.0001
C-IPP	0.00 [0-1.75]	2.0 [0.0-4.0]	0.001
C-RAP	6.0 [4.0-8.0]	14.0 [12.0-15.75]	<0.0001
Hemodynamic Tamponade number [%]			0.77
Yes	18 [56.2]	19[52.8]	

No	14 [43.8]	17[47.2]	
Cardiac Variables	No-ECP	ECP	P-value
Heart rate >115bpm: number [%]			0.79
Yes	16(53.3)	18(50)	
No	14(46.7)	18(50)	
Clinical tamponade Number [%]	7 [21%]	5 [13.8%]	0.58
Jugular venous Pressure [mean \pm SD]	7.7 [\pm 3.1]	8.4 [3.3]	
AF: number [%]			0.52
Yes	9(29)	8(22.2)	
No	22(71)	28(77.8)	
Low QRS voltage: number [%]			0.56
Yes	3(13.6)	6(19.4)	
No	19(86.4)	25(80.6)	
NT P-BNP: median [IQR]	1228(527-1681)	573(355.25-810.5)	0.62
CKMB: median IQR]	19(12-23.5)	16.5(9.75-25.5)	0.29

Abbreviations key for table 9 in alphabetical order

AF: atrial fibrillation, BPM: beats per minute, CK MB%: creatine kinase MB subunit, C-IPP: closing intra-pericardial pressure, C-RAP: closing right atrial pressure, HIV: human immunodeficiency virus, NT P_BNP: N-terminal pro brain natriuretic peptide, TB:

Mycobacterium tuberculosis, IQR: inter-quartile range, SD: Standard deviation

6.6 Discussion

There are two important findings of this study of predictors of tuberculous effusive constrictive pericarditis. First is the observation that a high [$>15\text{mmHg}$] opening right atrial pressure is a specific hemodynamic marker of effusive constrictive pericarditis. Second is the finding that, contrary to prior understanding, pericardial tamponade does not predict effusive constrictive pericarditis.

Since the first case series of patients with effusive constrictive pericarditis, it has been assumed that pericardial tamponade is a precondition for the presence of effusive constrictive pericarditis (Hancock 2004). This study documents for the first time that although the two conditions frequently co-exist [28% of cases], more often than not they occur independently of each other.

The finding that the opening right atrial pressure in effusive constrictive pericarditis is significantly higher than it is in tamponade confirms that patients with large effusions may have significantly impaired cardiac filling in the absence of tamponade. This observation is relevant to clinical practice because it suggests that patients with tuberculous pericardial effusion should be considered for pericardiocentesis even in the absence of clinical signs of tamponade; pericardial fluid evacuation improves the hemodynamic compromise and identifies patients with effusive constrictive pericarditis who may be at risk of adverse outcomes.

Furthermore, the study findings may have implications for the diagnostic approach to tuberculous pericarditis. Non-invasive methods of diagnosing effusive constrictive pericarditis such as echocardiography and magnetic resonance imaging have been improving over time but remain limited (Zagol, Minderman et al. 2007). As an example, the echocardiographic diagnosis of effusive constrictive pericarditis was suspected in less than 50%

of confirmed cases in the study by Sagrista-Sauleda and colleagues (Sagrista-Sauleda, Angel et al. 2004). Given the significant improvement in the non-invasive estimation of the right atrial pressure using echocardiography, ultrasound and strain gauge plethysmography (Ward, Tiba et al. 2006; Brennan, Blair et al. 2007; Simon, Kliner et al. 2010), adding non-invasive right atrial estimation to routine echocardiography may significantly improve non-invasive diagnostic accuracy.

In view of the potential for the findings of this study to be integrated into clinical practice, a prospective study of participants with tuberculous effusive constrictive pericarditis designed to test the utility of right atrial pressure estimation for diagnosis and management is required. If such a study could provide evidence that a widely available non-invasive tool can enhance our ability to make an early accurate diagnosis of effusive constrictive pericarditis it may have a significant impact on the investigation, management and long-term outcomes of patients with effusive constrictive pericarditis.

Chapter 7

Fibrin Strands and Fractal Geometry in Tuberculous Pericarditis

7.1 Background and rationalé

Band-like fibrin strands and other intra-pericardial echocardiographic abnormalities have been noted in patients with pericardial effusion since the introduction of two-dimensional echocardiography over 30 years ago (Martin, Bowden et al. 1980). What these abnormalities represent remains unclear but they are a consistent echo finding in inflammatory conditions such as malignancy, bacterial infections and tuberculosis, and may reflect fibrinous pericarditis (Martin, Bowden et al. 1980; Chia, Choo et al. 1984). Several authors have suggested that band like fibrin strands may be helpful to differentiate tuberculous from idiopathic pericardial effusion (Martin, Bowden et al. 1980; Liu, Li et al. 2001). Others have argued that in patients with pericarditis, band-like fibrin strands are a marker of the severity of pericardial injury and may be a predictor of long-term complications such as recurrent pericarditis and constrictive pericarditis (Alio-Bosch, Candell-Riera et al. 1991; Suwan and Potjalongsilp 1995; Kim, Song et al. 2008).

Whether or not echocardiographically detected band-like fibrin strands can be used as predictor of effusive constrictive pericarditis is unknown. No validated methods exist to measure or quantify fibrin strands detected by two-dimensional echocardiography (Hinds, Reisner et al. 1992) limiting their use as a diagnostic tool. Given the possibility that band-like fibrin strands are: a) a marker of the degree of pericardial injury (Alio-Bosch, Candell-Riera et al. 1991); b) may predict subsequent constrictive pericarditis; and c) that effusive constrictive pericarditis itself may be a risk marker for subsequent chronic constrictive pericarditis (Hancock 1971), fibrin strands quantified by an appropriate method may predict effusive constrictive pericarditis.

Naturally occurring objects cannot be described using classic Euclidian mathematics (Mandelbrot 1983). This is because very few natural objects are a close approximation of classical geometrical shapes such as triangles, squares, or rhomboids of Euclid (Euclid' Elements, Book 1, circa 300 BCE). Instead objects, such as coastlines, leaves and the cardiovascular system have an intrinsic irregularity or roughness, that is determined by energy flow constraints (Mandelbrot 1983). A powerful tool for describing the complex

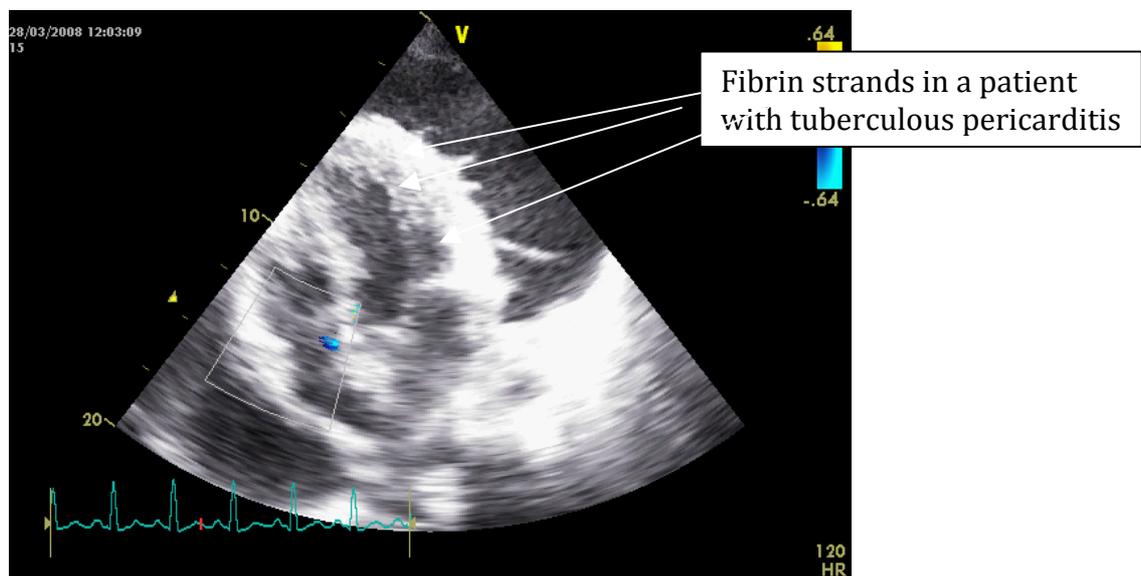
roughness of such naturally occurring objects is fractal geometry (Mandelbrot 1983). As Mandelbrot wrote, “a cloud is not a sphere, nor is a mountain a cone”(Mandelbrot 1983).

In classical Euclidian geometry, a point has zero dimensions, a line a dimension of one [i.e. it has only one side], a planar figure a dimension of two [e.g. a square] and a cube a dimension of three. However, describing and characterizing rough surfaces such as coastlines necessitates the use of a dimension between one and two. The higher that dimension, i.e. the closer it is to two the more rough the surface [in other words a wavy line may be so complex that it approaches a planar figure]. In this application, the roughness of surfaces and objects impart a dimension higher than the Euclidian dimension that by necessity includes fractions. The fractal dimension is a measure of the space-filling properties of an object; the closer the measure is to the classic Euclidean dimension in which the object is embedded, the greater its space-filling properties (Mandelbrot 1983; Maher and Harries 1997). For example, the surface of a crocodile’s tail with a hypothetical fractal dimension of 1.34 is more space-filling than a straight line, because its dimension is greater than one; but it does not completely fill the plane in which it is embedded because its dimension is less than two. Finally, fractal dimensions can be thought of as a summary of the numbers and sizes of the small and recurrent shapes that impart the roughness (Lopes and Betrouni 2009). The term fractal itself comes from the Latin *fractus*, which means “broken” or “fragmented”, i.e., rough. This innovative way of looking at and quantifying naturally occurring objects has often been coined “the geometry of nature”

Fibrin strands [Figure 10], defined here as pedunculated string or band-like echogenic material with a base attached to the pericardium and a body which floats within the pericardial fluid, impart a roughness to the pericardium. A close examination of this echogenic material makes the non-applicability of standard geometry to quantify fibrin strands self-evident and the appropriateness of fractal geometry appealing. Indeed it could be argued that because of their obvious “roughness” there are no other approaches that can be used to quantitate these strands.

Identifying that natural objects such as fibrin strands have a fractal structure or geometry has important implications. First it confirms that these objects cannot be quantified by standard Euclidean geometric tools such as length and area (Paumgartner, Losa et al. 1981). Second, it recognizes that the application of geometric analytic tools such as the use of fractal dimension is a more valid method of quantifying the objects (Cross and Cotton 1992).

Figure 10: Four-chamber echocardiograph demonstrating large pericardial effusion and fibrin strands



Finally, quantification of natural objects such as fibrin strands using fractal dimension is more likely to provide an objective mechanism of discriminating between different types or sizes of fibrin strand images in different types of pericarditis.

7.2 Study objectives

Using echocardiographs from patients with tuberculous pericarditis I set out to answer two questions.

First, I sought to determine whether band-like fibrin strands have a fractal geometry that meets the mathematical definition of a fractal structure that can be quantified by fractal dimension

Second, in the event that fibrin strands had a fractal geometry, I sought to determine whether quantification by fractal dimension allowed for the

discrimination between effusive constrictive pericarditis and pure effusive pericarditis in patients with large tuberculous effusion.

7.3 Methods

The study population, inclusion and exclusion criteria, and definitions of the pericardial syndromes and the overall conduct of the study have been described in the chapter 3 [3.4.1 and 3.4.2].

At presentation a limited echocardiogram was performed to confirm the presence of a large pericardial effusion, assess its hemodynamic sequelae, exclude significant underlying structural heart disease and determine the safest approach for pericardiocentesis. Images were stored as either cine loops or still images. The selection of images for the purpose of determining the fractal geometry of the fibrin strands was done retrospectively. For reproducibility and consistency two views were pre-selected for analysis; the sub-xyphisternal [sub-costal] view (Figure 9) and the four-chamber view (Figure 10). To be included in the analysis a minimum of two clearly identified fibrin strands had to be present and the quality of the images had to be of a standard to allow for accurate measurement. Fifteen patients with seventeen images of acceptable quality were available for inclusion in the study.

7.3.1 Echocardiographic image analysis

An important fractal geometric observation is that, when using a grid or ruler to estimate the length of naturally occurring fractal structures such as a coastline, as the size of the grid decreases the length of the rough coastline increases towards infinity (Mandelbrot 1967; Mandelbrot 1983). Using this principle, a box counting method in which the rate of change of the length of the coastline relative to the length of the grid, can be used to compute the fractal dimension (Mandelbrot 1967; Falconer 1990)

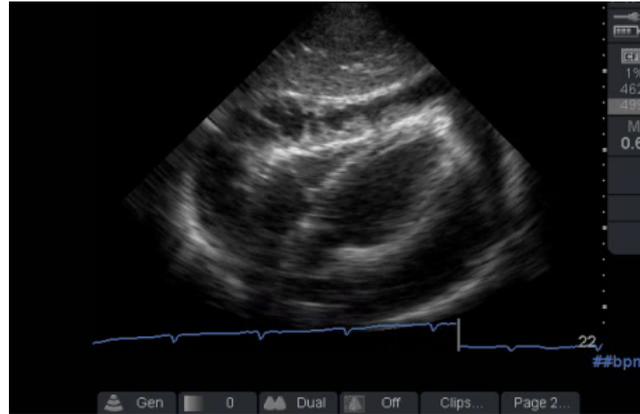


Figure 11: Sub-costal echocardiographic view of the pericardium

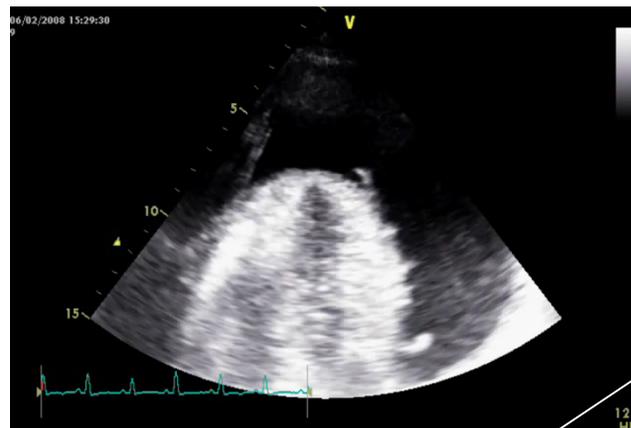


Figure 12: Four-chamber echocardiographic view of the pericardium

Each echo image was saved in a TIFF digital photo format following which they were replicated five times and exported as encapsulated postscripts into Microsoft (MS) PowerPoint. Five grids of cells [boxes] of side length $2s$, s , $s/2$, $s/4$, $s/8$ and $s/16$, where $s=7\text{mm}$, (or series $s/2^m$, where m is an integer) were created using Adobe Illustrator version CS4. Each grid was imported into MS PowerPoint and embedded within the 5 separate images so that there were 15 identical images with 5 embedded grids of descending cell size for each original image. I then manually counted the number of boxes N , inside which at least one point was covered by some component of the identified fibrin strands. Dr Tawanda Gumbo (Division of

Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA), who supervised this aspect of the project, recounted a random selection of images for quality control.

7.3.2 Mathematical analysis

The fractal dimension was measured using the box counting method (Mandelbrot 1983; Falconer 1990) and calculated as:

$$D_b = \lim_{s \rightarrow 0} \frac{\log N(s)}{\log (1/s)} \quad (\text{Mandelbrot 1983})$$

where D_b is the box-counting fractal dimension of the fibrin strand, s is the side length of the box and $N(s)$ is the smallest number of boxes of side length s to cover the outline of the object being measured. Because the limit zero cannot be applied to natural objects, the dimension was calculated by:

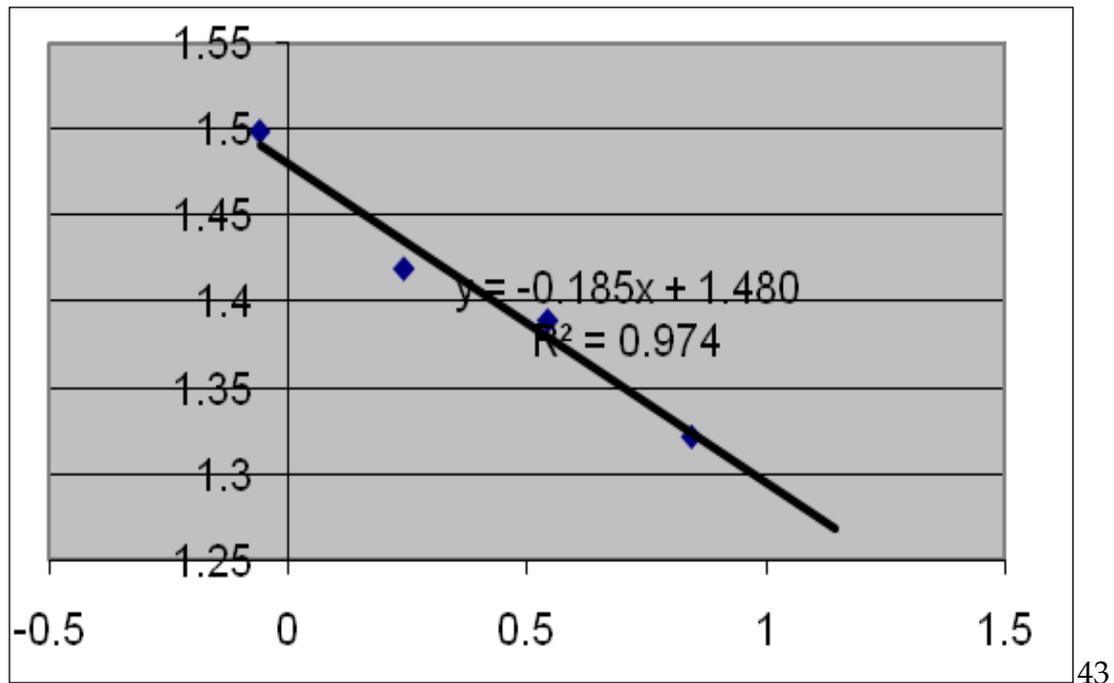
$$D_b = d \quad (\text{Mandelbrot 1983})$$

where d is the slope of the graph of logarithm $[\log] (N(s))$ against $\log (1/s)$. In this particular case, the dimension is similar to the Hausdorff-Besicovitch dimension in any metric space.

The fractal dimension was measured five times for each fibrin-strand-containing image. For some of the images, no additional information was gained by increasing the box size beyond 7mm^2 i.e., as s increased the log of s remained constant. As shown in Figure 11, log-log graphs of the side of the length of the square cells within each grid against the number of cells, were plotted. Linear regression of the log-log function was then used to calculate the slope. The dimension was calculated as "1+slope." The correlation coefficient $[R^2]$ for the linear regression was also calculated. A second method was used to check the validity of the method, for box sizes where $m \geq 1$ in the series $s/2^m$. In this method, the fractal dimension was calculated as $= [\log (\text{number of boxes for } s/2^{m+1} / \text{number of boxes for } s/2^m)] / \log 2$. An average was calculated for each successive pair of boxes. The Hausdorff-Besicovitch [fractal] dimension calculated based on each of these two methods had to be identical. The fractal dimensions of fibrin strands for patients with each of the two hemodynamically distinct groups of effusive pericarditis and effusive constrictive pericarditis were then compared using Student's t test. However, since the true distribution and variance assumptions of fractal dimensions of

strands are unknown, non-parametric tests were also employed for independent samples.

Figure 13: The log of the minimum number of cells on the y-axis and the log of the length of the cells with the grid. The slope of the line is determined by linear regression of the log-log function.



7.4 Results

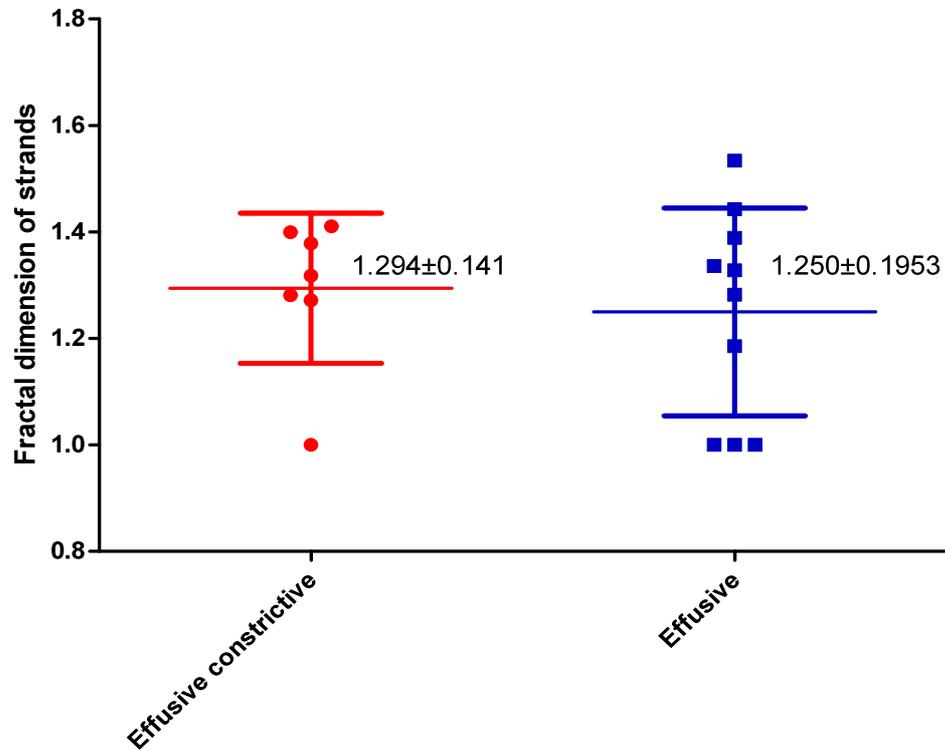
The measured fractal dimension exceeded the geometric dimension in all the images except with the largest grid. The correlation coefficient [R^2] for the fractal dimension was greater than 0.5 in all of the images and the majority had correlation coefficients greater than 0.9. The fractal dimensions and the correlation coefficients (R^2) are provided in Table 10.

Table 10

Patient study # Echo view	Fractal dimension	R ²
120 4 chamber		
70 Subcostal	1.248	.972
78 4 chamber	1.3269	.9484
87 4 chamber	1.3239	.804
87 Subcostal	1.121	.5411
123 Subcostal	1.534	.994
76 4 chamber	1.2028	.677
110 Subcostal	1.3416	.9911
95 4 chamber	1.2607	.784
88 4 chamber	1.711	.7067
112 Subcostal	1.1754	.877
96 4 chamber	1.1632	.5214
94 4 chamber	1.3081	.8596
101 Subcostal	1.2107	.8671
101 4 chamber	1.2716	.8966
114I Subcostal	1.2871	.8921
121 4 chamber	1.3995	.9907

Comparing patients with effusive and tuberculous effusive constrictive pericarditis, there was no significant difference between the fractal dimensions of the two hemodynamically distinct phenotypes using parametric tests [Figure 12]. Application of non-parametric tests also revealed no significant differences, so that the unpaired t-test with Welch's correction revealed a difference in fractal dimension of 0.044 ± 0.081 ($p=0.595$).

Figure 14: Comparison of fibrin strand fractal dimension stratified by pericarditis phenotype`



7.5 Discussion

Since the recognition that fibrinous pericarditis is associated with various echogenic abnormalities on two dimensional echocardiography (Martin, Bowden et al. 1980), there have been multiple attempts to describe, quantify and utilize these echo abnormalities diagnostically (Alio-Bosch, Candell-Riera et al. 1991; Liu, Li et al. 2001; George, Salama et al. 2004; Kim, Song et al. 2008) These attempts have been limited to conventional quantitative and descriptive methods only. To the best of my knowledge, fractal geometry and dimensions have never been used in cardiology or radiology to quantify echocardiography-derived intrapericardial echogenic abnormalities such as fibrin strands. However in the natural sciences, particularly anatomy, the usefulness of these tools in quantifying and describing dimensions is well established (Cross and Cotton 1992; Heymans,

Fisette et al. 2000). Examples include the use of fractal dimension in the description of neurons (Takeda, Ishikawa et al. 1992), motor nerve terminals (Reichenbach, Siegel et al. 1992; Tomas, Santafe et al. 1992) , colonies of bacteria (Obert, Pfeifer et al. 1990) and the patterns of the cerebral cortex (Cook, Free et al. 1995) to mention a select few.

The results of this study are important in that they have the potential to extend the use of fractal geometry and fractal dimensions to pericardial disease and specifically tuberculous pericarditis. We have demonstrated in this small study with a limited number of echo images from patients with this condition that fibrin strands, like many naturally occurring objects, are a fractal structure and are therefore quantifiable by fractal geometry and dimensions. Given that fibrin strands are not unique to a tuberculous etiology and are common in other causes of inflammatory or fibrinous pericarditis, it may be that the fibrin-strand fractal dimension can be used to identify the etiology of pericarditis [tuberculosis vs. purulent vs. malignant].

In this study we were however unable to demonstrate that the fibrin-strand fractal dimension could be used to distinguish effusive constrictive pericarditis from effusive pericarditis. There are a number of important limitations of this study. The first and most important limitation is the small number of quality images of the pericardium that were available to adequately compare cases of effusive and effusive constrictive pericarditis. Given the dynamic fluid nature of fibrin strands and the difficulty in capturing adequate pictures of them on still images, future studies addressing this issue will have to consider acquiring more images, with longer cine loops and should consider integrating many more views than the two used here. In addition serious consideration should be given to the use of software that produces consistently high-resolution images throughout the cardiac cycle.

7.6 Conclusions

These results demonstrate that the measured fractal dimension of fibrin strands exceeds the Euclidian geometrical dimension over the entire range of grid scales used. This fulfils the mathematical definition of a fractal structure (Mandelbrot 1983). It is therefore appropriate to conclude that fractal dimension is the most useful and reproducible tool to quantify this

naturally occurring echogenic material in patients with tuberculous pericardial effusion.

The use of the fibrin strand fractal dimension to compare differences between effusive constrictive pericarditis and effusive pericarditis did not yield a statistically significant difference. Whether this apparent lack of difference is real or a function of the small numbers in this study can only be answered in a larger study.

Chapter 8

Biomarkers in tuberculous effusive constrictive pericarditis

8.1 Introduction

Following significant injury or necrosis tissue undergoes a process of regeneration and repair that has been called tissue remodeling (Kumar, Abbas et al. 2005). The process may result in one of two outcomes: a] replacement of injured cells with cells of the same type leaving no lasting evidence of damage (i.e. complete healing); and b] replacement of injured cells by connective tissue leading to scarring (i.e. tissue fibrosis) (Mutsaers, Bishop et al. 1997; Wynn 2008). While often beneficial, this process can become pathological if it is prolonged, resulting in excess extracellular matrix deposition and replacement of normal tissue with fibrous tissue (Li, Chen et al. 2007). Although the mediators and mechanisms of tissue remodeling are the same in the body, there are however unique responses to injury in the different tissues and organs (Wynn 2007).

The pathways involved in tissue remodeling are numerous and involve a number of integrated responses to tissue injury that include factors essential for hemostasis, activation of the innate immune response and inflammation, cellular proliferation and fibrosis. Galectin-3 (Sharma, Pokharel et al. 2004; Henderson, Mackinnon et al. 2008), N-acetyl-Ser-Asp-Lys-Pro [AcSDKP](Liu, D'Ambrosio et al. 2009), transforming growth factor beta [TGF- β], and IL-10 (Wynn 2004; Meneghin and Hogaboam 2007), interferon gamma [IFN- γ], tumor necrosis factor alpha [TNF- α], interleukin [IL]-6, IL-1 β (Meneghin and Hogaboam 2007), are mediators that have been shown to influence inflammation, and the regulation of healing and fibrosis in response to tissue injury.

Constrictive pericarditis is characterized histologically, by a change in the normal pericardial architecture and composition to one characterized by fibrous thickening and a chronic lymphoplasmacytic infiltrate (Gimlette 1959; Oh, Shimizu et al. 2001). At the other end of the clinical spectrum, the pericardial histology of patients with large fibrinous exudative effusions typical of active tuberculous pericarditis is characterized by varying degrees of active granulomatous inflammation with or without necrosis (Mayosi,

Burgess et al. 2005; Reuter, Burgess et al. 2006). Approximately 25% of patients with tuberculous effusive pericarditis develop constrictive pericarditis within 6-12 months of diagnosis (Desai 1979; Bhan 1980). Presumably, the pericardium of the majority of patients with effusive tuberculous pericarditis heals while approximately 25% undergo pathological remodeling, the result of which is fibrous thickening and constrictive pericarditis. The triggers for and the predictors of the latter process are not known (Suwan and Potjalongsilp 1995).

Effusive constrictive pericarditis is characterized by both a compressive pericardial effusion and evidence of constrictive physiology. Whether the constrictive physiology is due to early fibrotic thickening and scarring of the pericardium or loss of compliance from edema, fibrin and changes of sub-acute inflammation typical of TB pericarditis is not clear (Sagrista-Sauleda, Angel et al. 2004; Reuter, Burgess et al. 2006). This may be important because, early fibrotic change may suggest a high risk of progression to chronic constrictive pericarditis whereas inflammatory change with minimum fibrosis may suggest the possibility that both resolution of pericardial inflammation and subsequent normal healing remain.

The nature of the immune response to tuberculosis within the pericardium remains to be fully elucidated. A single small study concluded that tuberculous pericarditis was driven by a cell-mediated delayed hypersensitivity response. The cytokines IFN- γ , TNF- α , IL-6 and IL-10 were found to be abundant while there were negligible amounts of IL-4 (Burgess, Reuter et al. 2002). Little is known about the relationship between the immune response, the state of pericardial remodeling and the specific pericardial syndromes. Establishing unique biomarker profiles for patients with TB pericarditis may be useful for a number of reasons. These include: a] to provide clues to the tuberculous etiology of the pericarditis; b] to provide important insights into the mediators and mechanisms of tissue injury, remodeling and fibrosis in pericardial disease; and c] to provide guidance to the development of new pharmacotherapeutic strategies to reduce inflammation induced immunopathology and prevent pericardial fibrosis.

In order to explore these questions further, I have compared the biomarker profile of effusive versus effusive constrictive pericarditis in

patients with tuberculous pericarditis who were enrolled in the *Initiative for the investigation and Management of Pericarditis* (IMPI) in Africa tuberculous pericarditis registry.

8.2 Hypotheses to be tested

1] Tuberculous effusive pericarditis and effusive constrictive pericarditis reflect different stages of pericardial remodeling in the pathway from effusion to pericardial constriction. Effusive constrictive pericarditis is likely to be characterized by higher levels of biomarkers involved in extracellular matrix deposition and fibrosis than those patients with effusive pericarditis because of the evidence of established constrictive physiology

2] Alternatively, the constrictive physiology that is characteristic of effusive constrictive pericarditis is due to loss of pericardial compliance related to increased visceral pericardial inflammation and injury compared to effusive pericarditis and not early fibrotic thickening. Tuberculous effusive constrictive pericarditis as compared to effusive pericarditis may be characterized by a biomarker profile consistent with excess mediators of excessive immunopathology and not increased extracellular matrix deposition and fibrosis.

The specific hypotheses that were tested are:

1. There may be significant differences in the following biomarkers involved in the regulation of extracellular matrix production and fibrosis in the pericardial fluid and peripheral blood of patients with effusive constrictive pericarditis versus effusive pericarditis: TGF- β , Galectin-3, AcSDKP and IL-10 .

2. There may be significant differences in the pro-inflammatory cytokines IFN- γ , TNF- α , IL-1 β , IL-6, as well as IL-17 and IL-22 in the pericardial fluid and peripheral blood of patients with effusive constrictive pericarditis versus effusive pericarditis.

8.3 Materials and methods

Between January 2006 and June 2008, patients who met the inclusion criteria and were enrolled in the prospective cohort had serum and pericardial fluid collected for cytokine and biomarker analysis by enzyme-linked immunosorbent assay (ELISA).

8.31 Processing of serum and pericardial fluid

Venous blood obtained via peripheral venipuncture was centrifuged at 3000 revolutions per minute (rpm) for 10 minutes, following which serum was removed and stored in 0.1% sodium azide at -80°C until the ELISA was performed.

Kerryn Matthews and I carried out the ELISA on the serum and cell free pericardial fluid samples for measurement of the following cytokines: IFN- γ , TNF- α , TGF- β , IL-1 β , IL-6, IL-10, IL-17 and IL-22. The assays were carried out on the cell free pericardial fluid only for galectin-3 and AcSDKP. Samples of pericardial fluid obtained from 26 patients with no known pericardial disease who were undergoing valve replacement and coronary bypass surgery were used as controls.

8.32 Galectin-3 specific ELISA and other assays

The principles of the ELISA procedure are outlined with the example of the galectin-3 assay below. The ELISAs for the other biomarkers and cytokines followed the same principles using specific ELISA kits with appropriate variations specific to the individual protocols.

Diluted cell free pericardial fluid samples from study subjects (cases and controls), and galectin-3 standard are added to microwell plates precoated with monoclonal antibodies to human galectin-3. Galectin-3 in the samples and standard should bind to the monoclonal antibodies. A biotin-conjugated anti-human galectin-3 antibody is then added to the plate to bind to any galectin-3 captured by the monoclonal antibodies. This is followed by a wash step with phosphate buffered saline with Tween 20 [PBST-20X], a wash buffer that removes any unbound galectin-3 and biotin-conjugated anti-galectin-3 from the plates. Streptavidin horseradish peroxidase [HRP], a highly sensitive detector conjugate that binds to antibodies in enzyme immunoassays, is then added to the plate where it binds to any unwashed antibody complexes. Following an incubation period in the microwells unbound streptavidin-HRP is washed out with PBST 20X and a substrate solution [tetramethylbenzidine], which is oxidized by the horseradish peroxidase, is added to the wells. This last step generates a colored product, whose color intensity is in proportion to the amount of galectin-3 present in the microwells. The reaction is finally terminated by the addition of phosphoric acid. The absorbance of

each microwell is then read at a primary wave length of 450nm using an ELISA reader.

Details of the specific ELISA kit used for measurement of each of the other biomarkers is summarized in Table 11.

Table11: ELISA kits

TNF- α specific ELISA	BD Biosciences, Human TNF ELISA Set, catalogue number 555212
IL-1 β specific ELISA	R&D Systems, DuoSet ELISA Development System catalog number DY201
IL-6 specific ELISA	eBioscience, catalogue number 88-7066
IL-17 specific ELISA	eBioscience, catalogue number 88-7371
IL-22 specific ELISA	Komabiotech, catalogue number K0131234
IL-10 specific ELISA	MABTECH, catalogue number 3430-1H
IFN- γ specific ELISA	BD Biosciences antibody pair 551221 and 554550
TGF- β specific ELISA	R&D Systems, catalogue number DY 240
Galectin-3 specific ELISA	BenderMed BMS 279/2CE
AcSDKP specific ELISA	SPIBIO-A05881

8.4 Statistical Analysis

The Shapiro-Wilks test was used to test if the cytokine levels were normally distributed. Differences between the two groups [effusive constrictive pericarditis versus effusive pericarditis] were tested using the Student *t* test, or Mann-Whitney test, where appropriate, for continuous variables, and the χ^2 test for categorical variables. Univariate logistic regression models were fitted to determine the association between the measured cytokine and effusive constrictive pericarditis. All tests were two sided and a p-value <0.05 was considered significant. Statistical analysis was performed using SPSS version 17.

8.5 Results

Thirty-six patients were found to have effusive constrictive pericarditis and 32 had effusive pericarditis. The baseline variables of all the participants stratified by pericardial phenotype are provided in Chapter 6 [Table 9 pages 79-81]. The group with tuberculous effusive constrictive pericarditis was significantly older, but did not differ with respect to gender, HIV status, median CD4 counts or proportion of participants who had a positive pericardial fluid tuberculosis culture.

8.51 GALECTIN-3.

The median level of galectin-3 measured in the cell free pericardial fluid of patients with tuberculous pericarditis was 11 ng/ml [IQR 7.55-15.60], which was similar to the 12 ng/ml [IQR 7.49-19.62] found in the normal control pericardial fluid ($p=0.19$). There was no significant difference in galectin-3 level between patients with effusive constrictive pericarditis and those with effusive pericarditis $p=0.88$ [Figure 15, Table 12]. Galectin-3 levels did not differ by HIV status.

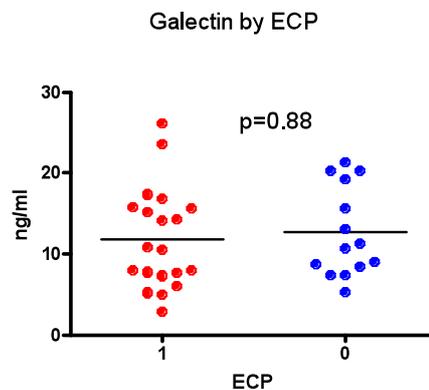


Figure 15: Scatterplot of Galectin-3 in ng/ml grouped by effusive constrictive pericarditis (ECP) present (1) and no effusive constrictive pericarditis (0)

8.52 AcSDKP

The levels of AcSDKP in participants with tuberculous pericarditis (156pg/ml [IQR 126.18-187.43]) was significantly lower than in the controls without pericardial disease (412pg/ml [IQR 146.71-717.92]), $p=0.03$ [Figure 16]. No significant difference in measured AcSDKP was noted between those with and without effusive constrictive pericarditis $p=0.49$ [Figure 17, Table 12]. There were no differences in the levels stratified by HIV status.

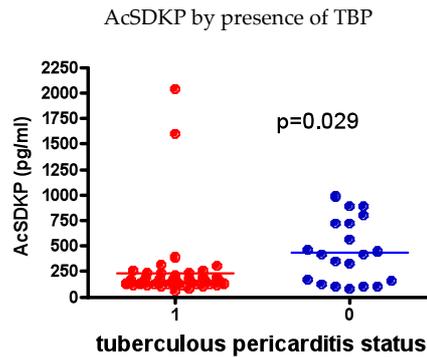


Figure 16: Scatterplot of AcSDKP [pg/ml] grouped by cases with tuberculous pericarditis (TBP) (1) and controls undergoing cardiac surgery without pericarditis (0)

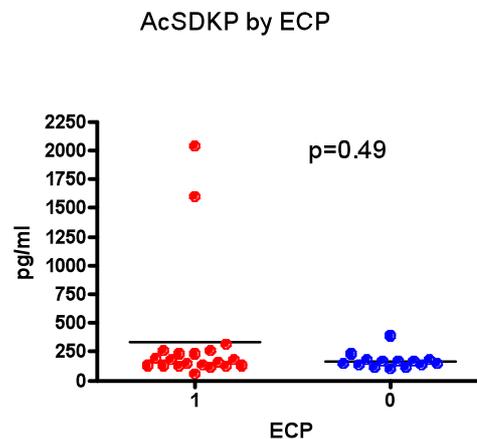
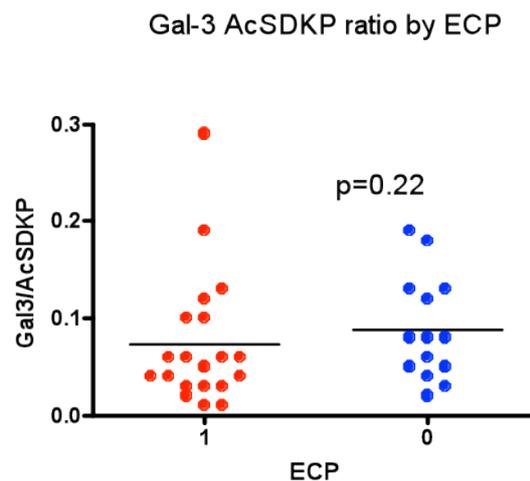


Figure 17: Scatterplot of AcSDKP [pg/ml] in tuberculous pericarditis patients with (1) and without (0) effusive constrictive pericarditis

8.53 Galectin-3/AcSDKP ratio

The median galectin-3/AcSDKP ratio for the all patients with tuberculous pericarditis was 0.06 [IQR 0.01-0.3] and 0.03 for controls [IQR 0.02-0.06]. The ratio in patients with effusive constrictive pericarditis was 0.06 compared to 0.08 in those with effusive pericarditis. This was not statistically significant [$p=0.22$] [Figure 18].

Figure 18: Scatterplot of Gal-3/AcSDKP ratios by those with (1) and without (2) Effusive constrictive pericarditis



8.54 Cell free pericardial fluid IL-1b, IL-6, IL-10, IL-17, IL-22, TNF, IFN- γ & TGF- β

IL-1 β , IL-6, IL-10, IL-17, IL-22, TNF, IFN- γ , and TGF- β levels were not detected in the cell free pericardial fluid samples of control patients [mean 0.0 pg/ μ l]. There were significantly higher cell free pericardial fluid levels of IL-10, IL-22, and IFN- γ in the patients with tuberculous effusive constrictive pericarditis relative to those with effusive pericarditis [Figures 19]. This difference was 6-fold in the case of IL-10 and 2-3 fold with IL-22 and IFN- γ respectively. Figure 20 presents the IFN- γ pericardial fluid levels stratified by those with (1) and without (0) ECP

Figure 19: Scatterplots of IL-10 and IL22 in pg/ml inpatients with (1) and without (0) effusive constrictive pericarditis

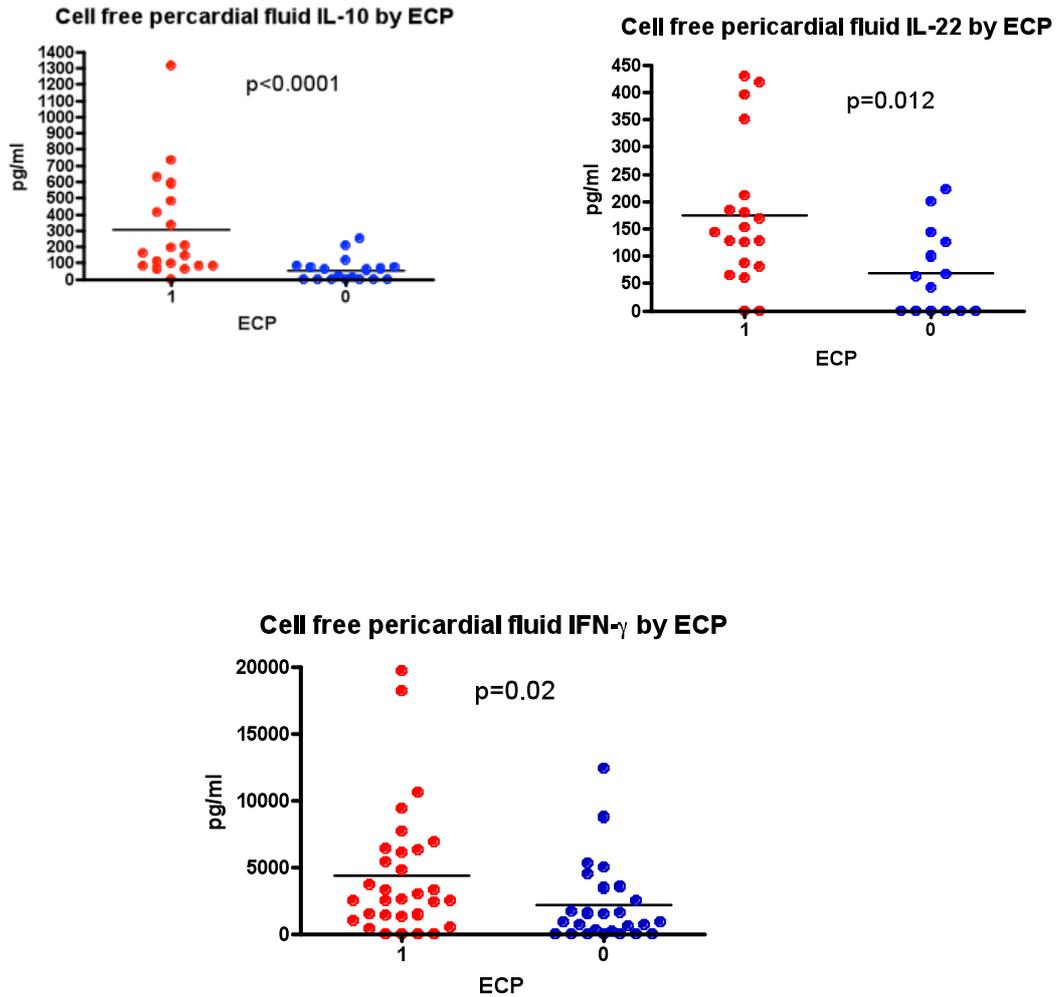


Figure 20: Scatterplot of pericardial IFN-gamma in patients with (1) and without (0) effusive constrictive pericarditis

No differences were noted in the measured amounts of pericardial IL-6, IL-17, IL-1 β or TNF- α . Table 12 summarizes all of the cell free pericardial fluid cytokine results.

Table 12: median pericardial fluid cytokine levels in patients with effusive and effusive constrictive pericarditis

Pericardial fluid cytokine (pg/ml median [IQR])			
	Effusive pericarditis	Effusive constrictive pericarditis	P value
IL-1β	10.0 [0.0-12.0]	9.0 [1.0-25.0]	0.62
IL-6	1885.3 [1302.5-4912.2]	1608.0 [1223.0-4246.0]	0.36
TGF-β	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.32
IL-17	0.0 [5.0-12.0]	0.0 [0.0-12.0]	0.58
IL-22	52.0 [0.0-118.0]	144.0 [83.0-198.0]	0.012
TNF-α	31 [0.0-82]	62 [0-123]	0.26
IL-10	39.0 [0.0-76.3]	158.0 [85.0-446.0]	<0.0001
Galactin-3	9750.0 [7400.0-18500.0]	12400.0 [7500.0-16200.0]	0.882
AcSDKP	153.7 [127.1-173.4]	162.1 [126.8-247.5]	0.234
IFN-γ	890.0 [51.0-3179.0]	2568.0 [1328.0-6210.0]	0.024

8.55 Serum IL-1b, IL-6, IL-10, IL-17, IL-22, TNF, IFN- γ & TGF- β

In the serum, IL-10 and TGF- β levels were significantly higher in patients with effusive constrictive pericarditis than those without [figure 21 and table 13].

Table 13: median serum cytokine levels in patients with and without ECP

Serum cytokine pg/ml median [IQR]	Effusive pericarditis	Effusive constrictive pericarditis	P value
IL-1β	7.2 [0.0-10.2]	7.0 [0.0-10.2]	1.000
IL-6	40.9 [0.0-87.7]	7.9 [0.0-56.4]	0.604
TGF-β	34.1 [0.0-136.1]	121.5 [24.0-299.0]	0.019
IL-17	0.0 [0.0-14.9]	0.0[0.0-13.1]	0.533
IL-22	0.0 [0.0-15.7]	0.0 [0.0-74.5]	0.066
TNF-α	0.0 [0.0-103.0]	0.0 [0.0-3.3]	0.118
IL-10	0.0 [0.0-250.0]	386.0 [0.0-849.3]	<0.0001
IFN-γ	0.0 [0.0-37.6]	0.0 [0.0-0.0]	0.095

raised TGF- β and IL-10 in peripheral blood. Of note is that this biomarker signature, which shows a mix of Th1, Th2 and other cytokines, may tell an important story about the immune response, and the state of the visceral pericardium in effusive constrictive pericarditis.

IFN- γ , one of the major inflammatory cytokines responsible for the control and resistance to infection with *MTb* (Flynn, Chan et al. 1993) was significantly higher in the pericardial fluid of patients with effusive constrictive pericarditis. These higher levels are consistent with a more vigorous inflammatory response, which is further corroborated by the higher levels of the pro-inflammatory cytokine IL-22. TNF- α levels were not significantly different in the two groups. However under conditions in which the immune response to *MTb* is characterized by evidence of a mixed inflammatory [IFN- γ ,] and regulatory [IL-10] response, there is evidence to suggest that TNF- α can contribute to enhanced tissue inflammation and injury. Furthermore this cytotoxic TNF- α activity is potentiated by IFN- γ (Hernandez-Pando and Rook 1994; Hernandez-Pando, Orozco et al. 1996). It is possible therefore that although the TNF- α levels were not significantly higher in the group with effusive constrictive pericarditis, in the presence of the mixed cytokine response, TNF- α contributed to significantly greater inflammation and injury.

IL-22 is a cytokine that is highly expressed in many different chronic inflammatory diseases (Zenewicz and Flavell 2008; Trifari, Kaplan et al. 2009; Wolk, Witte et al. 2010) but its exact role in *MTb* infection is under investigation (Scriba, Kalsdorf et al. 2008). Whether the higher levels of pericardial fluid level of IL-22 contribute to the excess inflammation or protect against immunopathology or both is unknown (Wolk, Witte et al. 2010). Finally IL-10 is a macrophage-derived cytokine that down regulates inflammation and plays an important role in the immune response to TB (Shaw, Thomas et al. 2000). In addition to its role in suppression of inflammation there is evidence to suggest that it is also a potent suppressor of fibrosis (Nelson, Lauwers et al. 2000; Mu, Ouyang et al. 2005). It is possible therefore that the markedly elevated levels of IL-10 in the patients with effusive constrictive pericarditis are involved in the suppression of an intense

inflammatory response, prevention of excessive immunopathology and suppression of maladaptive remodeling and fibrosis.

The second important finding from this work is that the biomarkers, Galectin-3, AcSDKP and TGF- β , which are all potent activators and regulators of myofibroblast activity, extracellular matrix production and fibrosis were not significantly different in patients with and without effusive constrictive pericarditis. Furthermore levels of IL-10, which is a potent inhibitor of fibrosis, were elevated in effusive constrictive pericarditis relative to effusive pericarditis.

Fibroblasts play an important role in tissue remodeling (Hinz, Phan et al. 2007). Following recruitment, activation and transformation of fibroblasts into myofibroblasts, these cells become the predominant source of the extracellular matrix that is laid down to replace injured tissue (Hinz 2007; Meneghin and Hogaboam 2007). In the setting of recurrent or persistent tissue injury and inflammation (such as in tuberculous pericarditis), continued activation of the tissue repair and replacement machinery may lead to maladaptive tissue remodeling, fibrosis and tissue scarring. Recent evidence suggests that crucial to the transformation of fibroblasts into myofibroblasts are both TGF- β (Peng, Carretero et al. 2010) and galectin-3, a ubiquitous animal lectin (Henderson, Mackinnon et al. 2006; Henderson and Sethi 2009). In experimental models of hepatic fibrosis, galectin-3 expression was shown to be upregulated relative to controls without fibrosis and disruption of the galectin-3 gene interfered with subsequent hepatic fibrosis following exposure to a noxious agent (Henderson, Mackinnon et al. 2006). A similar role of galectin-3 in fibrosis has also been shown in the heart (Sharma, Pokharel et al. 2004; Lok, Van Der Meer et al. 2010) and kidneys (Henderson, Mackinnon et al. 2008). The impact of both TGF- β and galectin-3 on myofibroblast activation and fibrosis is attenuated by AcSDKP (Cavasin, Liao et al. 2007; Liu, D'Ambrosio et al. 2009; Peng, Carretero et al. 2010) a ubiquitous mammalian tetra-peptide derived from thymosin β 4 (Rossdeutsch, Smart et al. 2008). An increase in the levels of AcSDKP counter-balances the effects of galectin-3 and TGF- β on fibroblasts and collagen deposition.

The third important finding of this study is that tuberculous pericarditis is associated with significantly lower levels of AcSDKP in pericardial fluid

than normal controls. This was independent of HIV status. Low levels of AcSDKP may represent: a] a novel mechanistic explanation for the high incidence of chronic constrictive pericarditis in TB pericarditis, and b] a novel biomarker for the diagnosis of a tuberculous etiology. AcSDKP is a thymosin β 4 derived tetrapeptide that down regulates inflammation and suppresses fibrosis. The anti-fibrotic effects of this compound are mediated at least in part by counter-balancing the impact of galectin-3 and TGF- β on fibroblasts and collagen deposition (Rossdeutsch, Smart et al. 2008). Interestingly the anti-fibrotic effect of angiotensin-converting enzyme inhibitors may be mediated via its effect on increasing the levels of AcSDKP (Rossdeutsch, Smart et al. 2008; Liu, D'Ambrosio et al. 2009).

Finally, there are some data to suggest that in patients with HIV there may be important differences in the immune response within the pericardium (Reuter, Burgess et al. 2006) and that these differences do have clinically important sequelae (Ntsekhe, Wiysonge et al. 2008). One possible reason why HIV status did not have an effect on the levels of the biomarkers is the ability of chemokines to be reproduced by multiple cells (Emery and Lane 1997; Mantovani 1999). Data from studies of pericardial tuberculosis show that even though CD4 cells are an important source of IFN- γ in response to *MTb* infection (Flynn, Chan et al. 1993), the levels of IFN- γ remain unaltered in the pericardial fluid of HIV-infected patients with CD4 depletion (Reuter, Burgess et al. 2006).

There were a number of limiting factors in this study: a] the small number of participants might have prevented the elucidation of important differences between the groups so possible differences may have been missed; b] I was only able to sample the participants once, while the process of remodeling is dynamic and important changes occur over time; c] categorizing the syndrome of effusive constrictive pericarditis as either present or absent ignores the continuous nature of the severity of tissue injury and the degree of tissue remodeling. Patients with effusive constrictive pericarditis complicated by heart failure may have a different biomarker profile to patients with a marginally elevated central venous pressure.

8.61 Implications for clinical practice and future research

These findings have far reaching implications for research into the diagnosis and treatment of effusive constrictive pericarditis and tuberculous pericarditis. The marked difference in the pericardial fluid and specifically serum levels of IL-10 in those with and without effusive constrictive pericarditis provides the possibility for the development of a diagnostic test for this unique pericardial syndrome. In addition the utility of low AcSDKP pericardial fluid levels as a diagnostic marker of tuberculous pericarditis needs to be tested in prospective studies of unselected patients with large pericardial effusions. Furthermore prospective studies would help to determine whether pericardial AcSDKP levels correlate with the development of constriction, and whether angiotensin converting enzyme inhibitors prevent the development of constrictive pericarditis. Finally if the results of this study suggesting that effusive constrictive pericarditis is the result primarily of inflammation and not fibrosis can be replicated and confirmed, it would provide a rational basis for the treatment of patients with the syndrome with anti-inflammatory agents to lead to more rapid resolution of the often debilitating constrictive physiology.

Chapter 9

Tuberculous effusive constrictive pericarditis: 6-month incidence rates of constrictive pericarditis and mortality compared to effusive tuberculous pericarditis

9.1 Introduction

“The natural history of effusive constrictive pericarditis appears to be the progression into non-effusive chronic constrictive pericarditis, usually in less than a year” (Hancock 1971). This conclusion from Hancock’s seminal publication on effusive constrictive pericarditis was important for two reasons. First, it supported the anecdotal observations about the natural progression of the syndrome (Gonin, Froment et al. 1951), and secondly, it had an important influence on the subsequent management of patients in whom the diagnosis was made. Faced with patients with effusive constrictive pericarditis, clinicians advised combined visceral and parietal pericardiectomy in the belief that all such patients would progress to chronic constrictive pericarditis within a year (Pillay, Sarpel et al. 1976; Rasaretnam and Chanmugam 1980). Our own experience of patients with tuberculous effusive constrictive pericarditis from the IMPI tuberculous pericarditis registry, suggested that a minority of such patients progressed to develop constrictive pericarditis (Ntsekhe, Wiysonge et al. 2008). A major limitation of this registry was that the diagnosis of effusive constrictive pericarditis was not confirmed hemodynamically or imaging in a large proportion of patients. Therefore a well-designed prospective study with follow-up would help clarify the issue.

A limited number of prospective studies involving patients with newly diagnosed effusive constrictive pericarditis have been published (Nugue, Millaire et al. 1996; Sagrista-Sauleda, Angel et al. 2004; Mayosi, Wiysonge et al. 2006; Reuter, Burgess et al. 2007). Only two studies with a total of 20 patients with the syndrome, provided pericardial disease related outcome data beyond 6 months of follow-up (Sagrista-Sauleda, Angel et al. 2004; Reuter, Burgess et al. 2007). Of the 20 patients, one fourth did not undergo early pericardiectomy [often because they did not consent] and all were alive and symptom free at follow-up.

Given the limited prospective data on outcome of patients with effusive constrictive pericarditis and the uncertainty about the optimal management of

such patients, we used the *Initiative for the Investigation and Management of Pericarditis* [IMPI] registry to conduct test two hypotheses:

1. Tuberculous effusive constrictive pericarditis is associated with a higher incidence of the composite outcome of symptomatic and asymptomatic constrictive pericarditis compared to effusive tuberculous pericarditis; and

2. Tuberculous effusive constrictive pericarditis is associated with a significantly higher six-month mortality rate than effusive pericarditis.

9.2 Methods

Details of the design and conduct of this prospective study including the follow-up schedule are provided in chapter 2 [2.4.1 and 2.4.2]. At 6 months following the diagnosis of tuberculous pericarditis, all patients underwent a clinical assessment that included echocardiographic evaluation. The variables used to assess patients for the diagnosis of symptomatic constrictive pericarditis and asymptomatic constrictive pericarditis are outlined in Table 14. Participants who were not available for follow-up evaluation were contacted telephonically for their vital status. Those who could not be contacted telephonically or through their next of kin were traced using information provided by the South African Department of Home Affairs and with the help of a professional tracing company.

9.21 Outcome ascertainment

The diagnosis of constrictive pericarditis is challenging even when patients are subjected to the 'gold standard' of invasive hemodynamic assessment (Wood 1961; Nishimura 2001; Talreja, Nishimura et al. 2008). However, where there is a high pretest probability and clinical likelihood of constrictive pericarditis, such as in a patient with previous tuberculous pericarditis or radiation exposure presenting with signs and symptoms of heart failure, ruling out alternative causes of heart disease is as important to establishing the diagnosis as ruling in the disease in patients where the pre-test probability is unknown (Nishimura 2001; Wang and Bashore 2004).

Table 14: List of variables used to establish a diagnosis of constrictive pericarditis

Symptoms (Ling, Oh et al. 1999)	
	Exertional dyspnea or fatigue
	Swelling of the legs
Clinical signs (Ling, Oh et al. 1999)	
	Peripheral edema, ascites or pleural effusion
	Jugular venous pressure ≥ 4 mmHg
	Pericardial knock
	Palpable pulsus paradoxus and/or measured pulsus paradoxus >10 mmHg
Echocardiographic findings (Maisch, Seferovic et al. 2004)	
	Pericardial thickness >5 mm
	Trans mitral/tricuspid flow variation with respiration $>25\%$
	Dilated inferior vena cava (IVC)
	Septal bounce

Participants [all of whom had moderate or large tuberculous pericardial effusion at study entry] met diagnostic criteria for symptomatic and asymptomatic constrictive pericarditis if the following criteria from Table 14 were met:

9.22 Symptomatic constrictive pericarditis

1. A minimum of one symptom plus two clinical findings where the left ventricular systolic function was preserved [shortening fraction $>24\%$], or
2. A minimum of one symptom plus three echocardiographic findings, or
3. A minimum of one symptom plus a raised jugular venous pressure >4 mmHg and one echocardiographic finding

9.23 Asymptomatic constrictive pericarditis

1. Any two clinical findings with preserved left ventricular systolic function [Shortening fraction >24%], or
2. Any one clinical finding plus two echocardiographic findings, or
3. Any three echocardiographic findings were present.

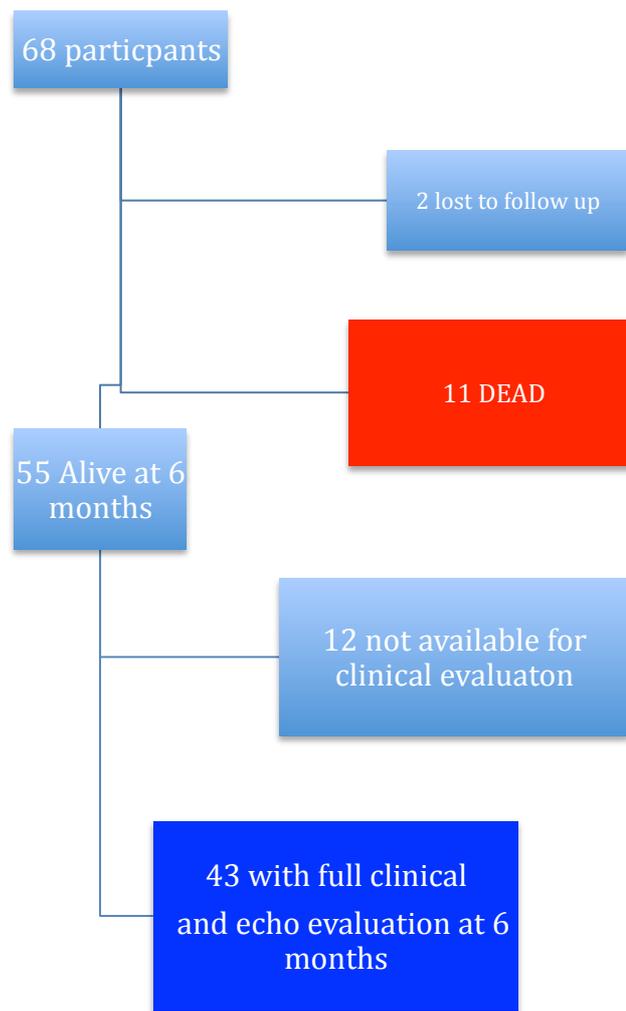
9.3 Statistical analysis

For the purpose of comparing outcomes between the two groups, categorical data were compared using Pearson χ^2 or, when appropriate, the Fisher exact test, and continuous variables using the Mann-Whitney test. Survival probabilities of patients in the two groups were calculated by the Kaplan-Meier product limited method and compared using the log-rank test. Survival was calculated as the time from date of enrolment into the study to the date of death, and censored at the date of that the participant was last known to be alive (date of last medical assessment) or the date the patient completed a 6-month follow-up. Cox proportional hazards regression models were fitted to determine factors associated with likelihood of death, which was expressed as a hazard ratio (HR), with 95% confidence interval (CI). In a separate analysis, logistic regression models were fitted to calculate the likelihood of developing the composite outcome of symptomatic or asymptomatic constrictive pericarditis at 6 months, which was expressed as a risk ratio with 95% confidence interval.

In both analyses, the following potential confounding factors were considered: age, gender, pericardial tamponade, the use of corticosteroids and HIV status (and in a sub-analysis of patients with HIV, CD4+ T cell count and use of anti-retroviral therapy). Data analysis was done with SPSS [version 7.0].

9.4 Results

As shown in Figure 22, the vital status was available for 66 of the 68 participants [97%] at 6 months; 2 patients with effusive constrictive pericarditis were lost to follow-up. Of the 55 participants known to be alive at 6 months, 43 [23 with effusive constrictive pericarditis and 20 with effusive pericarditis] were available for full clinical evaluation [11/68 patients were dead, 2 were lost to follow-up and 12 were not available]

Figure 22: Patient follow-up flow chart

9.41 Mortality

Eleven [16.7%] of the 66 patients with available vital statistics died during the first 6 months of treatment for tuberculous pericarditis. Table 15 provides the mortality rates stratified by baseline variable. The cause of death was not ascertained.

Table 15: Mortality by baseline variables

Variables	Dead	Alive	P value
TOTAL	11	57	
Age	33 [29-58]	31 [27-41]	0.227
Gender			0.523
Female	27.3%	38.6%	
Male	72.7%	61.4%	
HIV STATUS			0.14
HIV +	54.6%	77.2%	
HI V -	45.5%	22.8%	
CD4 <200	54.5%	57.9%	0.14
Oral steroids	45.5%	56.1%	0.372
Anti-retroviral therapy	0%	5.3%	0.58
Yes	0	3	
No	11	54	
Cardiac tamponade			0.99
Yes	54.5	54.4	
No	45.5	45.6	

Patients with effusive constrictive pericarditis had a 6-month mortality of 14.7% [5/34] compared to 18.8% [6/32] for patients with effusive pericarditis. By Cox regression analysis the hazard ratio [HR] for effusive constrictive pericarditis was 0.63 [95% CI 0.18-2.23; P=NS]. The Kaplan-Meier survival analysis stratified by the presence of effusive constrictive pericarditis is shown in Figure 23. There was no significant difference between the survival curves [p=0.44]. Table 16 shows the Cox regression analysis conducted to determine risk factors for death. None of the variables was statistically significant

Figure 23: Kaplan-Meier survival analysis for participants with and without effusive constrictive pericarditis.

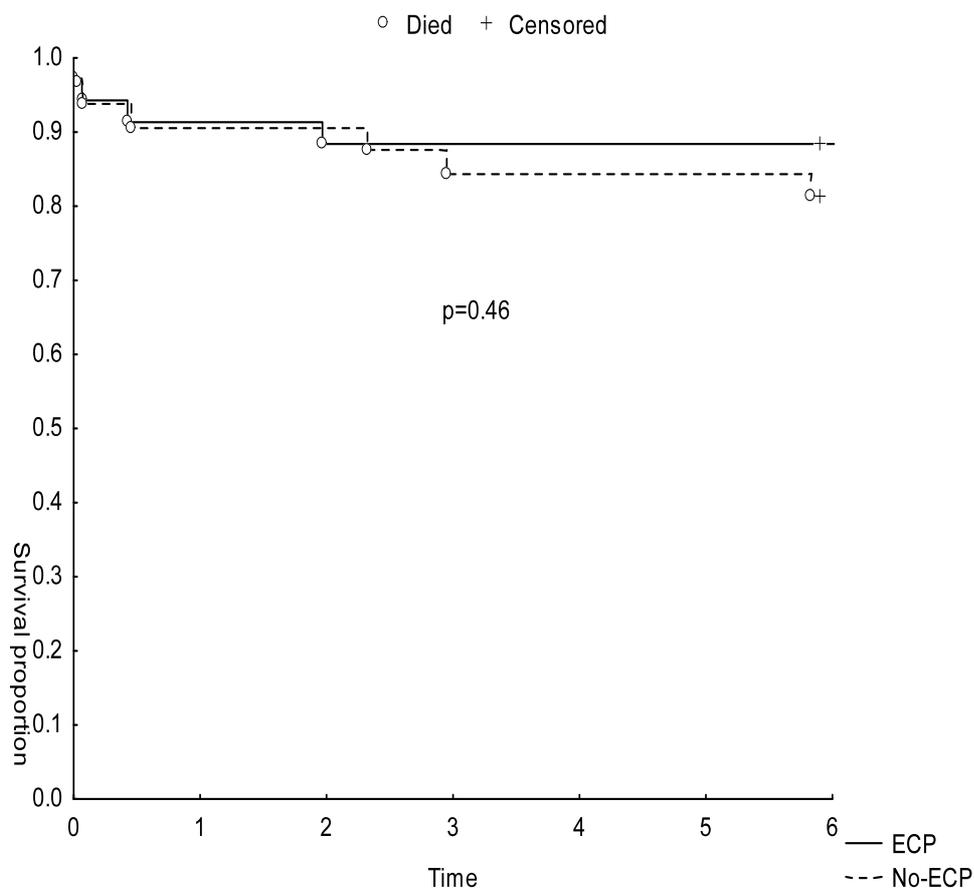


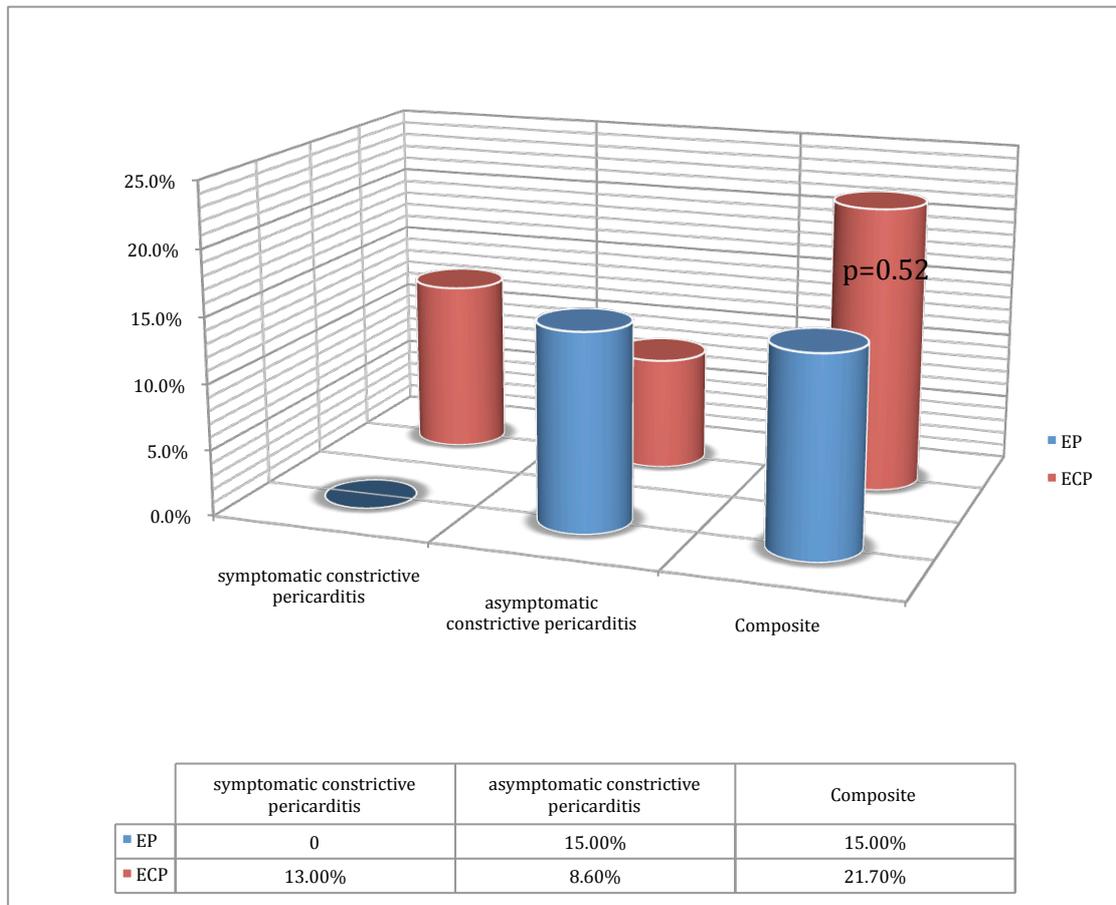
Table 16: Cox proportional hazard regression model for factors associated with death

Characteristic	Hazard ratio (95% CI)	P value
Age	1.02 [0.98-1.06]	0.30
Male gender	2.39 [0.51-11.24]	0.27
HIV+	0.31 [0.09-1.10]	0.85
CD4 <200	0.71 [0.20-2.44]	0.58
Tamponade	1.4 [0.40-4.96]	0.22
Steroids	0.76 [0.22-2.67]	0.68
ECP	0.63 [0.18-2.23]	0.47

9.42 Asymptomatic and symptomatic constrictive pericarditis

The composite outcome of symptomatic and asymptomatic constrictive pericarditis occurred in 18.6% of the 43 participants reviewed at 6 months. The incidence was 21.0% in those with effusive constrictive pericarditis compared to 15.0% in those with effusive pericarditis [p=0.52] [Figure 24]. None of the participants required pericardiectomy.

Figure 24: Six-month pericardial disease related outcomes for participants with and without effusive constrictive pericarditis.



In a logistic regression analysis, the risk ratio [RR] of developing the composite outcome at 6 months for those with effusive constrictive pericarditis was 1.67 [CI 0.36-7.8] p=0.52. None of the potential confounding variables showed significance for an association with the outcomes [Table 17].

Table 17: Logistic regression model of risk factors for the composite of clinical and subclinical constrictive pericarditis

Characteristic	Risk ratio (95% CI)	P value
Age	1.01 [0.96-1.06]	0.78
Male gender	1.27 [0.30-3.34]	0.74
HIV	1.03 [0.24-4.38]	0.48
Tamponade	.42 [.09-1.8]	0.22
ECP	1.67 [0.36-7.80]	0.52
Steroids	2.60 [0.58-11.5]	0.17

9.5 Discussion

There are two important conclusions to draw from this study, which compares the mortality rate and incidence of constrictive pericarditis in patients with and without tuberculous effusive constrictive pericarditis.

First, tuberculous effusive constrictive pericarditis is not associated with an increase in the risk of developing the composite any constrictive pericarditis despite there being a trend to an increase in symptomatic constrictive pericarditis alone; however, the study was underpowered to conclusively show small but important differences between the effusive constrictive and effusive groups. Despite the increased risk (RR 1.67 [CI 0.36-7.8]), the majority of survivors with effusive constrictive pericarditis do not progress to develop severe constrictive pericarditis; none of the participants with the syndrome required pericardiectomy and 79% had no evidence of constrictive physiology at 6 months. Why is there such a contrast in the incidence of constrictive pericarditis compared to the patients in the Hancock series who all needed pericardiectomy? The answer may lie in the fact that the participants in the Hancock series were selected from patients who had been symptomatic for long periods [often between one and two years] and all were referred for pericardiectomy because of a diagnosis of constrictive pericarditis (Hancock 1971). This is in contrast to the patients in this registry and other recent registries where patients were referred because of suspected pericardial tamponade (Sagrista-Sauleda, Angel et al. 2004). Given the thickened fibrotic visceral pericardium found on histology in most of the participants in that study, that their symptoms and constrictive physiology

failed to resolve after pericardiocentesis should perhaps not have come as such a surprise.

Our results suggest that a diagnosis of tuberculous effusive constrictive pericarditis is not, on its own, an indication to recommend visceral pericardiectomy for the prevention of subsequent constrictive pericarditis. In fact the majority of the patients had no evidence of constrictive pericarditis at follow-up. Individual patients with effusive constrictive pericarditis, who develop intractable heart failure or other intolerable symptoms, may clearly require surgery but the decision can be individualized.

The second important conclusion to emerge from this study is that the risk of death at 6 months was not increased in those with effusive constrictive pericarditis relative to those with effusive pericarditis. Previous prospective studies with outcome data on patients with effusive constrictive pericarditis have focused on the outcome of constrictive pericarditis and the need for pericardiectomy (Sagrasta-Sauleda, Angel et al. 2004; Reuter, Burgess et al. 2007) so this finding is unique and highly informative. The overall 6-month mortality rate of 13.6% in this study was lower than observed in the first phase of the IMPI registry where it was 26% and rose to 40% in those who were HIV-infected (Mayosi, Wiysonge et al. 2008). This was despite the fact that the majority [73.5%] of patients were HIV infected and an equally low proportion of participants [4.4%] were placed on anti-retroviral therapy in the first six months. There are however important differences between the two registries, which may have had a significant impact on the mortality rates. To begin with in this study all participants underwent full evacuation of the pericardial effusion by percutaneous pericardiocentesis as opposed to only 30% of patients in the original registry. This raises the question of whether routine drainage of infected exudative pericardial effusion may have a mortality and morbidity benefit compared to selective drainage. In light of the data from this study and similar data from earlier studies suggesting improved outcomes with complete drainage (Strang, Kakaza et al. 1988) a randomized control trial to test the two strategies would be important. Secondly, all patients in this study were enrolled with an established tuberculous etiology whereas this was not true in the original registry (Mayosi, Wiysonge et al. 2006). It is possible that in a cohort of patients with

unconfirmed tuberculous etiology, patients with alternative causes for their disease are likely to respond poorly to anti-tuberculous therapy.

There are several important limitations to this study. First, several types of bias were noted. The number of patients who were lost to clinical follow-up was very high (12 of 55 [21.8%] living participants). Differential loss to follow-up introduces significant bias into cohort study designs such as this one and does limit the validity of the results. In this study, the number of patients who were alive and not seen clinically was equally distributed amongst the two groups, and their baseline variables did not differ significantly, so it is unlikely that they would have altered the relative risk of a composite outcome significantly. We took a number of steps to reduce selection bias, which is almost always present in observational studies. Patients were clearly defined and stratified accordingly and an attempt was made for them to be enrolled consecutively.

A second limitation was the use of effusive constrictive pericarditis as a categorical phenotype; participants either met the criteria or they did not. However in reality the syndrome has a spectrum of severity, which may itself influence the likelihood for specific outcomes. It is not inconceivable that a patient with a residual right atrial pressure that is twice normal is more likely to have evidence of constrictive pericarditis at six months than a patient with a residual right atrial pressure one or two millimeters of mercury above normal even if they both have effusive constrictive pericarditis. This continuous aspect of the spectrum of severity could not be assessed with the limited number of patients and events. Although this was the largest prospective study of patients with proven effusive constrictive pericarditis to date, it was underpowered to detect small but significant differences.

9.51 Implication for practice and research

For clinicians who until now have been recommending prophylactic visceral pericardiectomy to patients diagnosed with tuberculous effusive constrictive pericarditis the results of this study suggest that they may have reason to pause and rethink the approach.

Many outstanding questions remain unanswered. Why is the overall mortality rate in tuberculous pericarditis so high? What is the mechanism of death? Neither tamponade at presentation nor effusive constrictive

pericarditis was associated with increased risk of mortality, but the absolute mortality rates of both remained high. Therefore relative differences in risk may have been small. Interestingly in this cohort of patients the mortality rate amongst those who were HIV-uninfected was higher than those who were co-infected. This may reflect the play of chance in a small study that is not powered to test the impact of pericardial disease on mortality.

What is the natural history of those patients with persistent pericardial disease at 6 months, manifest as either clinical or subclinical constrictive pericarditis? It is likely that although they did not require pericardiectomy in the short term, their lifetime risk of the operation must be significant relative to those who had no evidence of residual disease. Long-term follow-up of these patients will be important to provide answers to these questions.

Chapter 10

Conclusions

10.1 Principal findings

There are five principal findings from this series of studies. First, effusive constrictive tuberculous pericarditis is a common phenotypic expression of a specific pathophysiological response to tuberculosis within the pericardium. It is not a rare syndrome defined by the co-incidental sum of a few hemodynamic parts. Using the gold standard method of invasive determination of intra-cardiac and pericardial pressures before and after pericardiocentesis, we have demonstrated that this picture is present in 53% of patients with large tuberculous pericardial effusion. Secondly, this common tuberculous pericardial syndrome does not appear to have a significant impact on either mortality rates or the incidence of constrictive pericarditis in the first six-months.

Thirdly, the pericardial fluid and peripheral blood biomarker profile of patients with this syndrome is fundamentally different from those without the syndrome. The proposal is that this profile, suggests strongly that inflammation and immunopathology and not fibrosis may account for the constrictive physiology that is one of the defining features of effusive constrictive pericarditis. The elevated gamma interferon and IL-22 reflect the magnitude and severity of the inflammation and injury within the pericardium and while the elevated IL-10 and peripheral blood TGF- β reflect the attempt to respond to it. Significantly none of the selected markers of active fibrosis were elevated in the pericardium. This finding is consistent with the observation that effusive constrictive pericarditis may not necessarily increase the risk of developing constrictive pericarditis; inflammatory injury may resolve and heal whereas fibrotic scarring is unlikely to reverse.

The fourth important finding is that it is the height of the right atrial pressure and not the presence of pericardial tamponade that predicts effusive constrictive pericarditis. This confirms a hypothesis generated from the original Hancock case series, that the hemodynamic impact of a constricting pericardium and compressive fluid are additive and reflected in a higher right atrial pressure than compressive fluid alone. It also provides evidence against a long held belief that pericardial tamponade is a pre-requisite for the

syndrome. This finding may prove important in efforts to refine methods to establish a non-invasive diagnosis of effusive constrictive pericarditis.

The fifth and final finding is that tuberculosis associated band-like fibrin strands, identified by echocardiography, have a fractal as opposed to a euclidean geometric structure and can therefore be quantified using fractal analysis. Prior to this study, band like fibrin strands were a useful echocardiographic finding only because they suggested an inflammatory process was underway in the pericardium. The results of this experiment demonstrate that these strands can be accurately measured and quantified and the potential exists that such measurements have diagnostic significance. This is to the best of my knowledge the first time that fractal analysis has been applied to the description of echocardiographic abnormalities in pericardial disease.

10.2 Future directions

The major finding from this, the largest study to date of carefully phenotyped participants with TB effusive constrictive pericarditis, has confirmed that effusive constrictive disease is a common form of tuberculous pericarditis. With the evidence that the syndrome occurs frequently, and that it does not appear to increase the risk of constrictive pericarditis at 6 months, the one outstanding question is: should the diagnosis be considered and looked for in all patients presenting with tuberculous pericarditis? Until the long-term outcomes of our cohort are available or a larger prospective study powered to provide more definitive answers to the outstanding questions about outcomes is performed, the answer is yes. Close follow-up of these patients for up to six months after TB treatment has been completed would be prudent. Further research efforts in this area should focus on developing a simple method of establishing the diagnosis, and obtaining more information about long term outcomes in order to best inform guidelines and practice.

Three new potential strategies for investigating methods of diagnosis of effusive constrictive tuberculous pericarditis have arisen from this work. First, the potential for the syndrome's unique biomarker signature to be used as a diagnostic tool should be investigated further. The remarkably high level of IL-10 in pericardial fluid and serum make it candidate biomarker to aide in the diagnosis of effusive constrictive disease. In addition to providing

important insights on pericardial remodeling in response to tuberculosis, if future studies can demonstrate that it has an adequate sensitivity, specificity and overall diagnostic accuracy, the biomarker profile could prove to be a practical solution.

Second, the finding that a right atrial pressure greater than 15mmHg is specific for effusive constrictive tuberculous pericarditis holds significant promise. Given the improvements in the ability of echocardiography and ultrasound to estimate the height of the right atrial pressure, this is an area that has a lot of potential and may yield results that are implementable into practice within a short space of time.

Third, the novel finding that fractal geometry can be used to assess and analyze echocardiographs of fibrin strands has important implications for not just the diagnosis of tuberculous pericarditis but also other cardiac disease. The results of this proof of concept study could open the door for the use of “nature’s geometry” to provide another method of differentiating normal from pathological findings at imaging. Given the growing array of cardiac imaging modalities in clinical practice, use of the fractal architecture and dimension has the potential to add great value to the analysis and interpretation of cardiac pathology.

Finally, the discovery that TB pericarditis is associated with a significantly lower level of N-acetyl-Ser-Asp-Lys-Pro [AcSDKP] (an anti-fibrotic biomarker) in the pericardial fluid than in normal controls presents a biological rationale for the testing of angiotensin converting enzyme (ACE) inhibitors to prevent adverse pericardial remodeling in this disease. The anti-fibrotic effect of ACE inhibitors is mediated partly by increasing the levels of AcSDKP in tissues. This work has therefore set the scene for a potential role of ACE inhibitors in reducing adverse pericardial remodelling, morbidity and mortality in TB pericarditis.

Publications to arise from this work

- 1 Ntsekhe M, Syed F, Mayosi B, Russell J, Usim OE. The prevalence of effusive constrictive physiology and cardiac tamponade in patients with suspected tuberculous pericardial effusion. *European Society of Cardiology 2008; 29 (Abstract Supplement):434 (P2720)*. [Presented as a poster at the European Society of Cardiology Congress 2008, 30 August – 3 September, Munich, Germany]
- 2 Ntsekhe M, Syed FF, Russell J, Usim U, Mayosi BM. The prevalence and hemodynamic predictors of effusive constrictive physiology in stable patients with large exudative pericardial effusion. *Cardiovascular Journal of Africa 2008; 19:S27* [Presented at the South African Heart Association 9th Annual Congress, 2-5 November 2008, Wild Coast Sun, South Africa]
- 3 Ntsekhe M, Syed FS, Russell J, Usim P, Mayosi BM. The prevalence of effusive constrictive pericarditis in patients with confirmed tuberculous pericarditis. *Journal of the American College of Cardiology 2009;53 (Suppl A):A169* [Presented at the American College of Cardiology 58th Annual Scientific Session and i2 Summit, 29-31 March 2009, Orlando, Florida, USA]

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