THE OCCURRENCE OF EFFUSIVE CONSTRICTIVE PERICARDITIS OF TUBERCULOSIS (TB) ORIGIN IN A COHORT OF PATIENTS WITH LARGE PERICARDIAL EFFUSIONS

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Submitted in partial fulfilment of the requirements for the degree of

MASTERS IN TECHNOLOGY (CLINICAL TECHNOLOGY)

In the

Department of Clinical Technology

Faculty of Health Sciences

Durban University of Technology

AUTHOR'S DECLARATION

This study represents original work by the author. It has not been submitted to any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Biomedical and Clinical Technology, Faculty of Health Sciences, Durban University of Technology under the supervision of Prof J.K. Adam (Head of the Clinical Technology programme) and the Department of Cardiology, Groote Schuur Hospital, Cape Town, South Africa under the supervision of Prof. M. Ntsekhe (Cardiology consultant and Head of Catheterization Laboratory).

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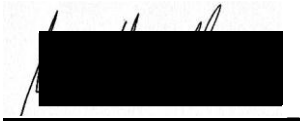
SIGNED: 

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DEDICATION

I dedicate this work to:

My family, especially my mother, for her constant love, guidance, prayers and encouragement.

ABSTRACT

INTRODUCTION

Effusive constrictive pericarditis (ECP) is a clinical syndrome characterized by concurrent pericardial effusion and pericardial constriction where constrictive haemodynamics are persistent after the pericardial effusion is removed. Although first observed in the 1960s, it was not until the publication of a 13 patient-case series by Hancock in 1971, and the prospective cohort publication by Sagrista-Sauleda in 2004, that more information about the aetiology, incidence, and prognosis of effusive-constrictive pericarditis became known (Sagrista-Sauleda, Angel, Sanchez, Permanyer-Miralda, and Soler-Soler 2004).

Hancock (1971) first recognized that some patients presenting with cardiac tamponade did not have resolution of their elevated right atrial pressure after removal of the pericardial fluid. In these patients, pericardiocentesis converted the haemodynamics from those typical of tamponade to those of constriction. Thus, the restriction of cardiac filling was not only due to the pericardial effusion but also resulted from pericardial constriction (predominantly the visceral pericardium). The hallmark of effusive-constrictive pericarditis is the persistence of elevated right atrial pressures after the intrapericardial pressure has been reduced to normal levels by the removal of the pericardial fluid.

AIMS AND OBJECTIVES

This study was carried out to determine the prevalence of ECP in a cohort of patients with large effusions of Tuberculosis origin. The primary objective was to measure pre and post- pericardiocentesis intrapericardial and right atrial cardiac pressures in all patients undergoing pericardiocentesis in order to determine the relative proportion of effusive constrictive pericarditis in these patients. The secondary objective was to determine if any echocardiographic features can help predict the presence of ECP by studying the three parameters two-week post-pericardiocentesis.

METHODOLOGY

Fifty consecutive patients with pericarditis presenting to Groote Schuur Hospital and surrounding hospitals referred for pericardiocentesis, who met the inclusion criteria were recruited to participate in the study. All patients had the right atrial and intrapericardial pressures simultaneously measured and recorded, before and after pericardiocentesis. The pressures were analyzed to determine the presence of ECP, which was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤12 mmHg after the intrapericardial pressure is lowered to below 2 mmHg.

Participants also had an echocardiogram done two weeks post pericardiocentesis. Three echocardiographic features of constriction were studied, to determine if they can predict the presence of ECP. The parameters studied were 1) Thickened pericardium, 2) Dilated inferior vena cava (IVC) and 3) Septal bounce.

RESULTS

This study showed a 34% (17 0f 50) prevalence of ECP in patients with TB pericarditis. It also showed a statistically difference in the right atrial and intrapericardial pressures pre and post pericardiocentesis, between patients with ECP and those without.

The echocardiographic parameters studied showed no difference between ECP and non ECP, and also did not predict the presence of ECP.

DISCUSSION

In the cohort of patients (*n*=50), the prevalence of ECP was found to be 34%. This is much higher than that observed in the Sagrista-Sauleda et al., (2004) study. They found a prevalence of 1.3% amongst patients with pericardial disease of any type and 6.95% amongst patients with clinical tamponade. The authors did state that they

expected the true prevalence to be higher than estimated as not all patients underwent catheterization.

Pre-pericardiocentesis pressures, both right atrial and intrapericardial, were found to be higher in patients with ECP than in those without. This is in keeping with published results, such as the study of Hancock (1971)

The echocardiographic parameters studied were two weeks post pericardiocentesis, because the diagnostic accuracy of echocardiogram has been shown to be very poor at the time of tamponade. The presence of these parameters (thickened pericardium, dilated IVC and septal bounce), did not predict the presence of ECP. This could be due to the fact that less than 50% of participants had an echocardiogram two weeks post pericardiocentesis.

CONCLUSION

The results of this study show that ECP is actually more common than thought in a population with TB pericarditis. This syndrome may be missed in most patients due to the fact that not all centres measure right atrial and intrapericardial pressures at the time of pericardiocentesis.

Echocardiography is not able to predict the presence of ECP. Other non-invasive imaging techniques such is computerized tomography (CT) and cardiac magnetic resonance imaging (CMRI) have shown good results in diagnoses of ECP.

The importance of early diagnosis of ECP lies in recognition that removal of pericardial fluid alone may not be enough; patients may need to have surgery. Given the high prevalence shown by the study, ideally all patients with pericardial effusion should have haemodynamic monitoring at the time of pericardiocentesis.

ACKNOWLEDGEMENTS

The author wishes to express her sincere gratitude to the following people for their assistance and encouragement during the preparation of this dissertation.

First and foremost, my thanks are due to God Almighty for his love and guidance.

Dr. M. Ntsekhe, my supervisor, for his expert advice, constructive criticism, his constant encouragement, guidance and patience during the research and preparation involved in this dissertation, I thank him for being my mentor and for the opportunity of working under his expert guidance.

Prof J.K. Adam, for her assistance and guidance throughout the project.

My family, especially my mother, for her support and prayers. You have been pillar of strength, inspiration and encouragement.

Mr. V. Mapolisa, for his assistance, support and encouragement

The patients and volunteers, who willingly and enthusiastically participated in this study. I thank them for their co-operation and patience.

My fellow clinical technologist, the C25 Cath Lab team, for their assistance.

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LIST OF ABBREVIATIONS

2D	Two dimensional
ADA	Adenosine deaminase
Cath Lab	Cardiac catheterization laboratory
CMRI	Cardiac Magnetic Resonance Imaging
CP	Constrictive pericarditis
CT	Computerized tomography
DPT	Disposable pressure transducer
ECG	Electrocardiogram
ECP	Effusive constrictive pericarditis
FA	Femoral artery
HIV	Human immunodeficiency virus
HR	Heart rate
IFN- γ	Interferon gamma
IMPI	Investigation of the Management of Pericarditis in Africa
IPP	Intrapericardial pressure
IVC	Inferior vena cava
LA	Left atrium
LV	Left ventricle
mmHg	Millimeters of mercury
NaCl	Sodium Chloride
NBP	Non-invasive blood pressure
PCR	Polymerase chain reaction
Pg/ml	Picogram per milliliter
RA	Right atrium
RAP	Right atrial pressure
RV	Right ventricle
RVOT	Right ventricular outflow tract
TB	Tuberculosis

U/L	Unit per litre
ZN	Ziehl Neelsen

CHAPTER ONE: INTRODUCTION

Effusive constrictive pericarditis (ECP) is a clinical syndrome characterized by the presence of both pericardial effusion and pericardial constriction, where the haemodynamic picture of constriction persists after the pericardial effusion is removed. Although first observed in the 1960s, it was not until the publication of a 13-patientcase series by Hancock in 1971, and the prospective cohort publication by Sagrista-Sauleda, Angel, Sanchez, Permaner-Miralda, and Soler-Soler, (2004), that more information about the aetiology, incidence, and prognosis of ECP became known (Sagrista-Sauleda, Angel, Sanchez, Permaner-Miralda, and Soler-Soler, 2004).

Hancock (1971) first recognized that in some patients presenting with cardiac tamponade, removal of the pericardial fluid did not lower the elevated right atrial pressure, but rather converted the haemodynamics from those typical of tamponade to those of constriction. This was because restriction of cardiac filling was not caused by pericardial effusion only but also resulted from constriction by the visceral pericardium. The hallmark of ECP is the persistence of elevated right atrial pressure after the intrapericardial pressure has been reduced to normal levels by the removal of the pericardial fluid (Sagrista-Sauleda et al., 2004).

Recognition of ECP is important, as it helps in determining whether or not visceral pericardiectomy is necessary. Removal of the pericardial fluid or creation of a pericardial window may be ineffective when visceral pericardial constriction is present, as visceral pericardiectomy is often required for optimal treatment.

However, not all cases of ECP progress to constriction. In some cases the constriction may be transient and may resolve. In these cases pericardiocentesis or medical treatment is used to manage the underlying condition, and pericardiectomy is not necessary (Bonnema, 2008).

The definitive diagnosis of ECP requires that the pericardiocentesis be performed in a catheterization laboratory, where recording of the right atrial and intrapericardial pressures can be done, before and after pericardiocentesis. However, this is not routinely done in most centres, which perhaps accounts for the lack of medical literature on the subject (Hancock, 2004).

The pre-pericardiocentesis haemodynamic pressure recordings in ECP are similar to those of tamponade and show elevated and equal (or nearly equal) intracardiac pressures i.e. the mean right atrial pressure, mean left atrial pressure, right ventricular end-diastolic pressure and left ventricular end-diastolic pressure are all equal. The transmural filling pressure (the difference between the intrapericardial pressure and right atrial pressure), which is the main determinant of cardiac filling, approaches zero and is usually less than 2 mmHg (Bonnema 2008). There is usually an inspiratory increase in right-heart filling pressures. A prominent *x*-descent and absent *y*-descent may also be noted. If pericardiocentesis is adequate, intrapericardial pressures should drop to near zero but in ECP this fails to restore cardiac haemodynamics to normal. This is because the persistent elevation and equalization of intracardiac diastolic pressures is caused by the visceral constrictive component of this syndrome. This constrictive physiology shows a biphasic pressure tracing in the right atrium, now with a prominent *y*-descent and dip-and-plateau right ventricular

pressure tracings, with absent or minimal respiratory variation. Persistent constriction after pericardiocentesis suggests a constrictive visceral pericardium and thus the diagnosis of ECP (Bonnema, 2008).

Echocardiography is important in the evaluation of patients suspected to have pericardial constriction (Little and Freeman, 2006). It usually demonstrates pericardial thickening. Restricted filling of both ventricles with a rapid deceleration of theearly diastolic mitral inflow velocity (E wave) and small or absent A wave can be seen on Doppler echocardiography. Substantial respiratory variation of the mitral inflow velocity (>25%), is also demonstrated (Oh, Hatle, Seward, Danielson, Schaff, Reeder and Tajik, 1994**).** In the setting of ECP echocardiography has some limitations. The thickening of the visceral pericardium may prevent right ventricular or right atrial free wall collapse, thus decreasing the accuracy of individual echocardiographic and Doppler flow patterns for the diagnosis of haemodynamic compromise. Thus, the diagnosis of ECP must be made haemodynamically by simultaneous measurement of the right atrial and intrapericardial pressures during a pericardiocentesis, (Oh et al., 1994).

According to Sagrista-Sauleda et al., (2004), in the presence of cardiac tamponade, the diagnostic accuracy of Doppler echocardiography is low. The diagnosis, therefore, requires intrapericardial pressure and right atrial pressure measurement before and after removal of pericardial fluid. Therefore, in this study the results of a two-week follow-up echocardiogram were used to determine the echocardiographic predictors of ECP.

The treatment of ECP can be difficult because pericardiocentesis does not relieve the impaired filling of the heart, and surgery to remove the fibrinous exudate coating the visceral pericardium is technically difficult. In patients with TB, treatment with anti-TB drugs should be used and serial echocardiography performed to detect the development of a pericardial skin that is amenable to surgical stripping (Mayosi, Burgess and Doubell, 2005); the value of corticosteroids in such patients is unknown (Mayosi, et al., 2005).

Although visceral pericardiectomy is much more difficult and dangerous than parietal pericardiectomy, it is necessary for a good clinical result in some cases of ECP (Hancock, 2004).

Mayosi et al. (2005), noted that ECP is a common presentation in Southern Africa. Sagrista-Sauleda et al. (2004), also state that ECP is an uncommon pericardial syndrome that may be missed in some patients presenting with tamponade. The causes of ECP are diverse and may be reversible (Sagrista-Sauleda et al., 2004). Because of the difficulty in establishing a definitive diagnosis, the prevalence of the syndrome in patients with TB pericardial effusions is unknown (Mayosi et al., 2005). Some authors have speculated that due to the inflammatory, exudative nature of TB effusions, ECP may be very common but under-recognized (Commerford and Strang, 1991) .

Ideally, all pericardial aspirations should be performed in the cardiac catheterization laboratory, as cardiac pressure measurement seems to be the only way to diagnose ECP, as non-invasive imaging studies may be helpful but are unreliable because of their inability to provide an accurate estimation of intrapericardial pressures.

Most of the prevalence studies undertaken have been performed in populations where TB is not common, thus information on TB pericarditis and the prevalence of ECP in patients with TB is very poor. This study, therefore, aims to show how common ECP is in a population of patients with TB pericarditis.

The primary objective of the study was to determine the prevalence of effusive constrictive pericarditis (ECP) in patients with large pericardial effusions of tuberculous origin. The secondary objective was to determine if any echocardiographic parameters at two weeks post pericardiocentesis can help predict the presence of ECP.

CHAPTER TWO: LITERATURE REVIEW

2.1 The normal pericardium

The pericardium is a double-walled fibroserous sac comprising two layers. These are the visceral pericardium, made of mesothelial cells, and the parietal pericardium, made of a fibrous layer. The parietal layer is fused to the internal surface of the fibrous epicardium, while the visceral pericardium is reflected on the heart, where it forms the external layer of the heart wall (Stouffer, 2008).

Measured pericardial pressure is normally sub-atmospheric, making it several millimetres of mercury lower than the pressure in the atria and ventricles during diastole. Owing to variations in cardiac volume, pericardial volume exceeds cardiac volume by 10–20%. This accounts for the pericardial reserve volume which allows physiological changes in cardiac volume to occur without restriction by the pericardium (Shabetai, 2004).

The pericardium has relatively inelastic properties, which limits acute dilatation and enhances interactions of cardiac chambers. The pericardium responds to long-standing stress by dilating, thus shifting the pericardial pressure volume to the right. This allows accumulating pericardial effusion to increase without compression of the cardiac chambers, and allows left ventricular remodelling to occur without pericardial constriction (Little and Freeman, 2006).

The normal pericardium appears as a hyperechoic, linear structure surrounding the heart. Increased echo-reflectivity occurs at the interface between cardiac tissue and the air-filled lungs (see arrows on Figure 1). Normal pericardial thickness is less than 3 mm (best assessed by transeosophageal echocardiography), but its appearance on transthoracic echocardiography is influenced by image quality and instrument settings (Solomon, 2007).

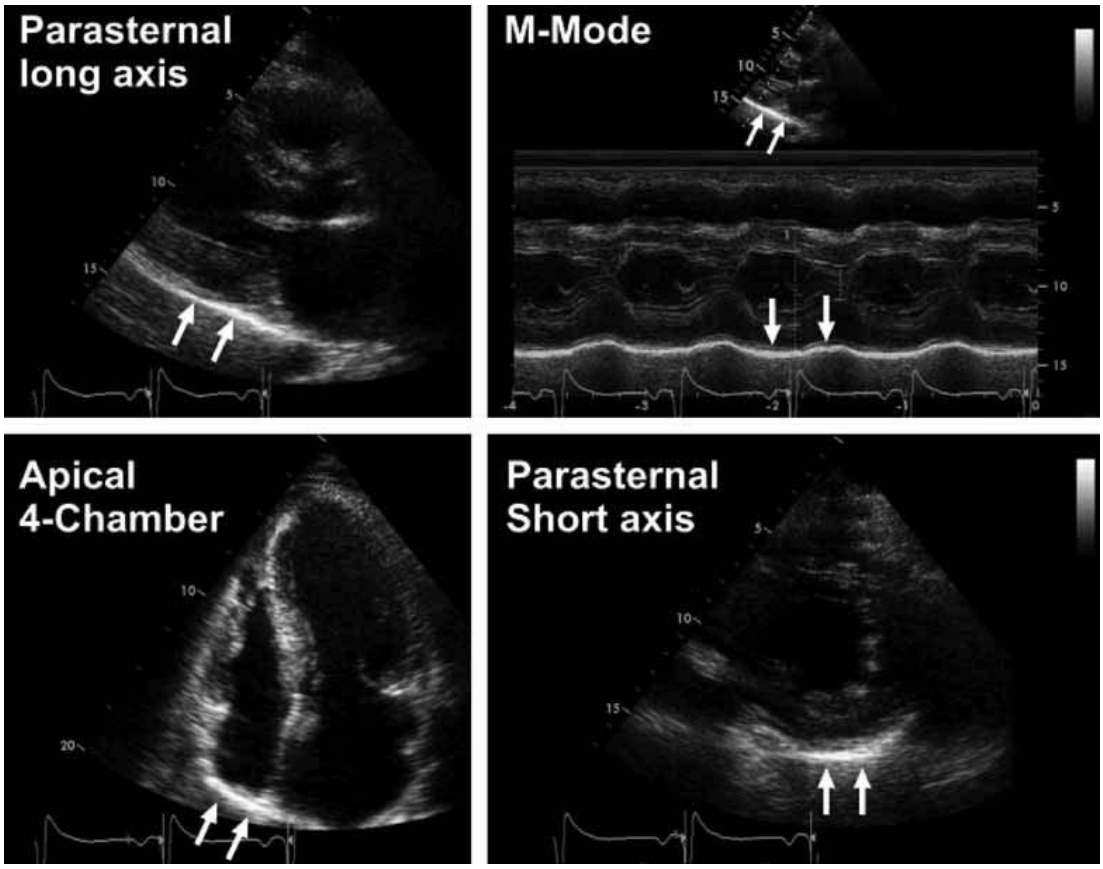


Figure 1.The normal pericardium *as shown by transthoracic echocardiogram* (Solomon, 2007).

2.1.1 Abnormal pericardial physiology

The pericardium limits acute cardiac cavity dilation during increased fluid accumulation. This is done by distributing forces across the heart, thus contributing to ventricular interdependency, whereby changes in pressure, volume, and function of one ventricle, influence function of the other (Strimel, 2009).

The pericardium plays a major role in cardiac changes during inspiration. During a normal inspiration the right atrium and ventricle fill, the pericardium limits dilatation of these chambers, causing bowing of both the atrial and ventricular septa to the left. This reduces left ventricular filling volume, resulting in a decrease in cardiac output. As the intrapericardial pressure increases, this effect becomes more pronounced,

leading to pulsus paradoxus, and development of pericardial tamponade. Acute inflammation of the pericardium with or without an associated pericardial effusion can occur as an isolated clinical problem or as a manifestation of systemic diseases. Tuberculous and bacterial infections are some of the causes of pericarditis (Little and Freeman, 2006).

Raised intrapericardial pressure can occur by three main mechanisms:
(1) increased fluid within the intrapericardial space;
(2) increased volume of the cardiac chambers; or
(3) increased stiffness of the pericardium.

This results in the following three potential adverse effects on the heart:
(1) a compressive effect which limits diastolic filling of the heart;
(2) increased diastolic filling pressures; and
(3) reduced stroke volume and cardiac output.

When this happens, compensatory mechanisms are activated, but if pericardial pressure increases rapidly, it can lead to death if not treated. The pericardium has a small capacitance reserve that will accommodate only small increases in cardiac chamber size and/or pericardial fluid volume of about 150–250 ml before significant increases in pericardial pressure occur (Ivens, Munt and Moss, 2007).

2.2 Tuberculous (TB) pericarditis

Tuberculous pericarditis is a very common pericardial disease in sub-Saharan Africa, and usually presents as pericardial effusion, constrictive pericarditis, or ECP. Tuberculosis is the cause of 50–70% of pericardial disease in sub-Saharan Africa, and it accounts for < 5% of pericardial disease in the developed world (Babik and Chamie, 2006). The prevalence of TB pericarditis in HIV-infected individuals with

pericardial disease is even higher, with TB accounting for 96-100% of cases in this group (Babik and Chamie, 2006).

In a study carried out in the Western Cape Province of South Africa, TB pericarditis accounted for 69.5% (162 of 233) of cases referred for diagnostic pericardiocentesis (Reuter, Burgess, Carsterns and Doubell, 2005). This was much higher than the 4-5% reported in developed countries. The HIV epidemic has resulted in the increased incidence of TB pericarditis in sub-Saharan Africa (Reuter et al., 2005). This is likely to be the same in other parts of the world where HIV is leading to the resurgence of TB. In the Western Cape, half of the patients presenting with large TB pericardial effusion are infected with HIV (Reuter et al., 2005).

2.2.1. Diagnosis of tuberculous pathogenesis

Pericardiocentesis is recommended in all patients with pericardial effusions, in whom TB is suspected (Mayosi et al., 2005). 10% of patients in a study conducted in South Africa presented with cardiac tamponade, which is regarded as an absolute indication for pericardiocentesis. The pericardial fluid in TB pericarditis is usually blood stained (Mayosi et al., 2005). However, malignant diseases may also cause a bloody pericardial effusion; thus confirmation of TB as the cause is important. TB caused by *Mycobacterium* remains the most common cause of pericarditis in Africa.

A definite diagnosis of TB pericarditis depends on the demonstration of tubercle bacilli in the pericardial fluid or histological section of the pericardium (Figure 2). The diagnosis should be confirmed by pericardiocentesis. Fluid should be sent for microscopy to identify acid-fast bacilli (AFB) and culture of tubercle bacilli (Mayosi et al., 2005). This can also be done by indirect methods such as pericardial fluid adenosine deaminase (ADA) levels as well as pericardial fluid interferon gamma (IFN-γ) levels.

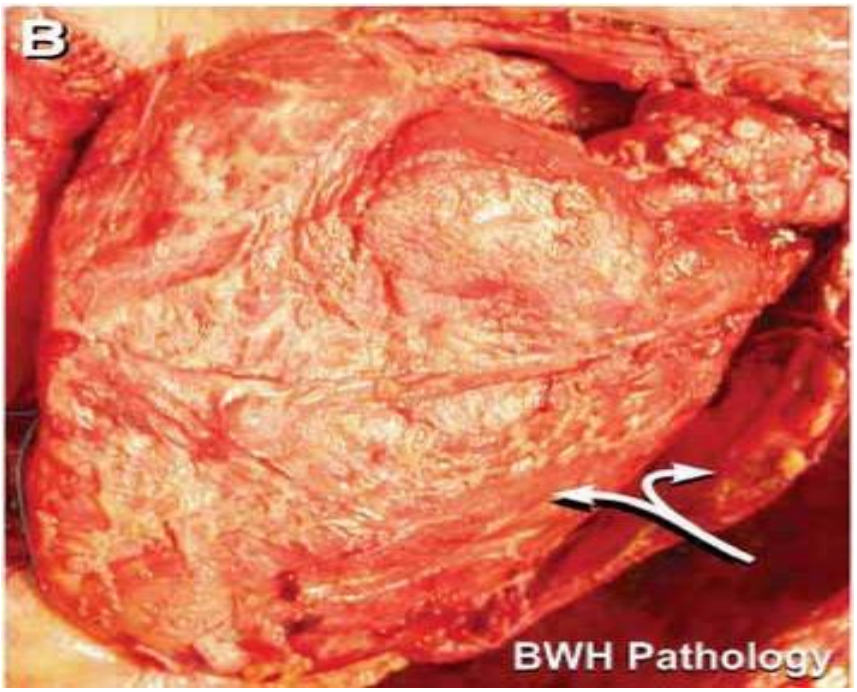


Figure 2.Acute bacterial pericarditis. *A deep red pericardium with fibrinoid deposits on both visceral and parietal layers, evidence of pericarditis* (Solomon, 2007).

2.2.2 Pericardial adenosine deaminase (ADA) activity level in diagnosis of TB pericarditis

In recent studies, the presence of elevated pericardial ADA levels has been shown to be suggestive of TB pericarditis (Mayosi et al., 2005). Different cut-off levels of pericardial ADA activity, ranging from 30-60 U/L, have been suggested as being indicative of TB pericarditis. The Western Cape study showed that pericardial ADA levels of 35 U/L, had a sensitivity and specificity of 90% and 74%, respectively, for the diagnosis of TB pericarditis. These results applied to both HIV-positive and HIV-negative patients. High ADA levels have been regarded as a strong prognostic indicator for the development of constrictive pericarditis in pericardial TB (Mayosi et al., 2005).

Reuter, Burgess, van Vuuren and Doubell (2006), also evaluated various levels of pericardial ADA. The best results were obtained at a cut-off level of 40 U/L, which

yielded a sensitivity and specificity of 90% and 74%, respectively. In their study, ADA levels were found to be higher in TB pericardial effusions compared to non-tuberculous effusions. The results were not affected by the HIV infection. Pericardial ADA level is very useful as it provides a rapid and accurate means of diagnosing TB pericarditis. Thus, in the present study, a minimum cut-off ADA level of 40 U/L was used to determine the presence of TB pericarditis.

2.2.3 Microbiological diagnosis of TB pericarditis

Rapid and accurate diagnosis is essential for effective treatment of TB pericarditis, but this is often difficult. Microbiological methods for diagnosing TB pericardial effusion include the Ziehl-Neelsen (ZN) acid-fast bacilli (AFB) stain and culture of *Myobacterium tuberculosis*. However, studies have shown that the ZN stained smears of pericardial fluid have poor sensitivity for detecting *Mycobacterium tuberculosis*, while culture is both slow and insensitive. If available, pericardial IFN-γ should be used as the diagnostic method of choice (Reuter et al., 2006).

In this study, the ZN stain was used to detect AFB in the pericardial fluid, so as to diagnose TB. This test was used because IFN-γ is more expensive and was not available for most patients.

2.2.4. Pericardial fluid interferon gamma (IFN-γ) concentration in diagnosis of TB pericarditis

In the study by Reuter et al., (2006), IFN-γ levels were significantly elevated in TB pericarditis compared to non-TB pericardial effusions and, importantly, concentrations never exceeded 50 pg/ml, in any of the non-tuberculous effusions. A cut-off of 50 pg/ml resulted in 92% sensitivity, 100% specificity and a diagnostic accuracy of 95%. These results were not influenced by HIV infection. Currently, the

use of IFN-γ is limited by both technical and financial resources. However, where available, it should be the diagnostic tool of choice.

The measurement of pericardial IFN-γ levels may offer another means of early diagnosis. In a study of patients with definite TB pericardial effusions, elevated levels measured by radio immuno assay in pericardial aspirate had a sensitivity of 92% and a high specificity of 100%, as a marker of TB (Mayosi et al., 2005). In a similar study of patients with diverse causes of pericardial effusion, a cut-off level of 200 pg/ml showed a sensitivity and specificity of 100% for the diagnosis of TB pericarditis (Burgess, Reuter, Carstens, Taljaard and Doubell, 2002). However, they also stated that the use of IFN levels is still limited in developing countries because of technical and financial resources.
Thus, in the present study IFN-γ cut off levels of 50 pg/ml were used, for positive diagnosis of TB.

2.3 The clinical forms of Tuberculous pericarditis

Tuberculous pericarditis presents clinically in three forms namely: pericardial effusion (section 2.3.1), constrictive pericarditis (section 2.3.3), and a combination of effusion and constriction, also known as ECP (section 2.3.4). The three clinical forms are discussed in detail below.

2.3.1. Pericardial effusion

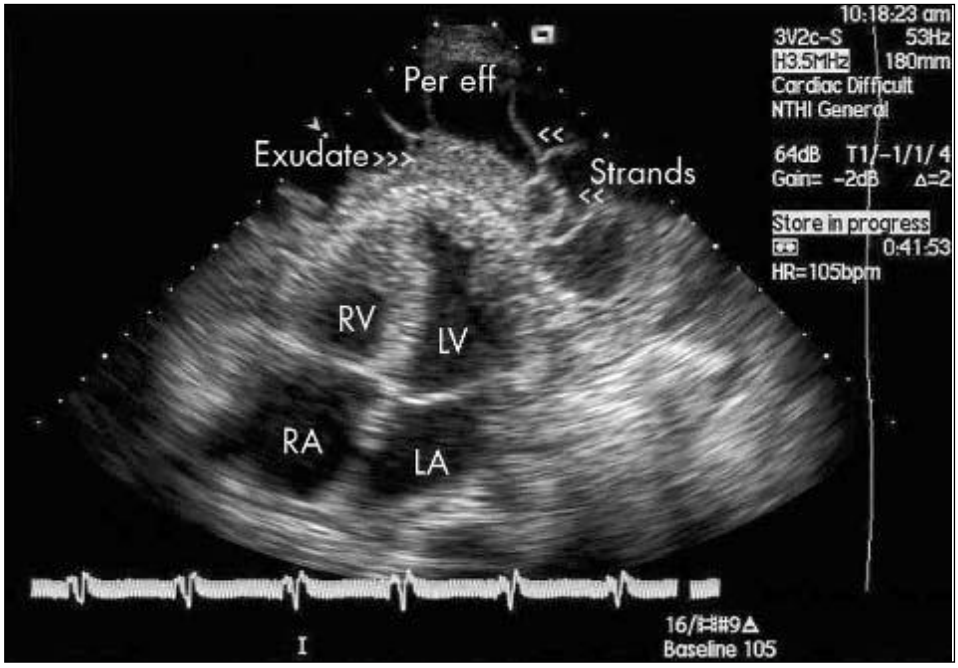
Pericardial effusion is defined as the presence of an increased amount of fluid in the pericardial space. The pericardial fluid can be serous, serosanguinous, pus, lymph or blood (Ivens, Munt and Moss, 2007). It could be caused by a different local or systemic disease or be due to idiopathic causes. The time it takes for fluid to accumulate influences the relationship between the size and adverse effects, thus resulting in either acute or chronic pericardial effusion. Large effusion usually occurs

over a long period of time, and may be initially asymptomatic, with symptoms such as dyspnoea and tamponade occurring at a later stage. Rapidly occurring effusions can lead to cardiac tamponade and death, if untreated. The rapid rise in pericardial pressure can be due to insufficient time for the non-compliant pericardium to stretch. Treatment includes both the removal of pericardial fluid and alleviation of underlying causes (Strimel, 2009).

2.3.1.1 Echocardiography in pericardial effusion

Echocardiography is the imaging modality of choice for the diagnosis of pericardial effusion (Strimel, 2009). Echocardiography is mostly useful in the evaluation of the effusion size, location and its haemodynamic effects. Pericardial effusion appears as an "echo-free" space between the visceral and parietal pericardium (Figure 3).

Pericardial effusions are described as small, moderate or large, depending on the "echo-free" space seen between the parietal and visceral layers on two-dimensional (2D) echocardiography (Strimel, 2009). Pericardial effusions are described as small if the "echo-free" space is less than 5 mm, and are usually located posteriorly. Moderate-sized effusions range from 5-10 mm and are usually circumferential. Large effusions are 10 mm or greater (Strimel, 2009). Excessive motion within the pericardial sac is characteristic of a large effusion. The presence of fluid adjacent to the right atrium is an early sign of pericardial effusion. Diastolic collapse of the right heart chambers occurs in severe cases, and is a sign of pericardial tamponade (Strimel, 2009).



LA: left atrium; LV: left ventricle; Per eff: pericardial effusion; RA: right atrium; RV: right ventricle.

Figure 3.Pericardial effusion. *Apical four-chamber view of a two-dimensional echocardiogram of a patient with TB pericardial effusion, showing multiple fibrin strands as linear or band-like structures crossing the pericardial space or protruding from the epicardium or parietal pericardium and exudates.* (George, Salama, Uthaman and Cherian, 2004).

2.3.2 Cardiac tamponade

Cardiac tamponade is defined as the accumulation of fluid in the pericardial space sufficient to raise the pressure surrounding the heart to the point where it impairs or alters cardiac filling. This raised pericardial effusion pressure compresses the heart, resulting in elevated venous pressures and impaired cardiac output causing shock. If untreated, cardiac tamponade can be fatal (Spodick, 2003). Pulsus paradoxus is the hallmark of cardiac tamponade, defined as a >10 mmHg drop in systolic arterial pressure during inspiration (Little and Freeman, 2006), (Figure 4).

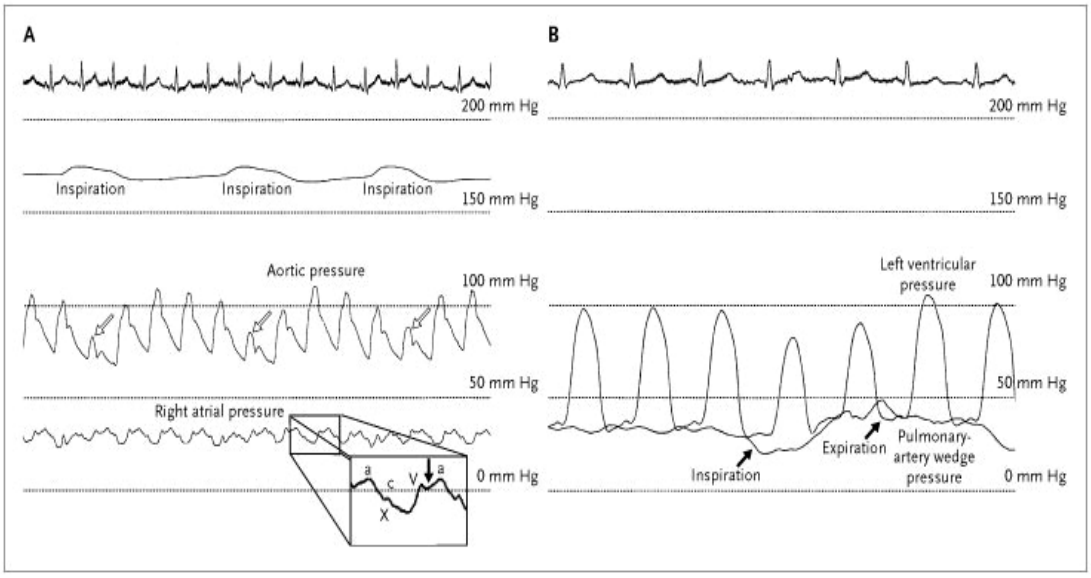


Figure 4. Pulsus paradoxus in cardiac tamponade. ***Panel A*** *shows the electrocardiogram, the respirogram, and the tracings of aortic pressure and right atrial pressure. There was an elevated right atrial pressure with an x-descent but blunting of the y-descent (solid arrow). On inspiration, there was a 30 mmHg decrease in aortic systolic pressure as well as a decrease in pulse pressure (open arrows) — findings that constitute pulsus paradoxus. The tracings of left ventricular pressure and pulmonary-artery wedge pressure* ***(Panel B)*** *show that the pulsus paradoxus is caused by under filling of the left ventricle during inspiration (due to a drop in the initial pressure gradient between the pulmonary-artery wedge pressure and the left ventricular diastolic pressure)* (Wu and Nishimura, 2003).

2.3.2.1 Haemodynamics of cardiac tamponade

The elevated pericardial pressure in cardiac tamponade impairs diastolic filling. Normal pericardial pressure is zero (Stouffer, 2008). Any increase can have haemodynamic consequences resulting in elevated intracardiac diastolic pressure (Stouffer, 2008). This impairs systemic and pulmonary venous return, leading to venous congestion and a decrease in cardiac output. This increase in pericardial pressure causes elevation and near equalization of the end diastolic pressures (right atrium, right ventricular diastolic, pulmonary artery diastolic and pulmonary wedge pressure). The right atrial pressures are elevated with a prominent *x*-descent and a blunt *y*-descent. In cardiac tamponade, compression of the heart occurs throughout

the cardiac cycle. This compression limits the fall in ventricular pressure during early diastole, causing a decrease in the amount of early diastolic filling, which results in a blunted *y*-descent seen in the atrial pressure tracing (Figure 5). Removal of pericardial fluid will result in a reduction of intrapericardial pressure, and the *y*-descent in the right atrial tracing becomes more apparent (Stouffer, 2008).

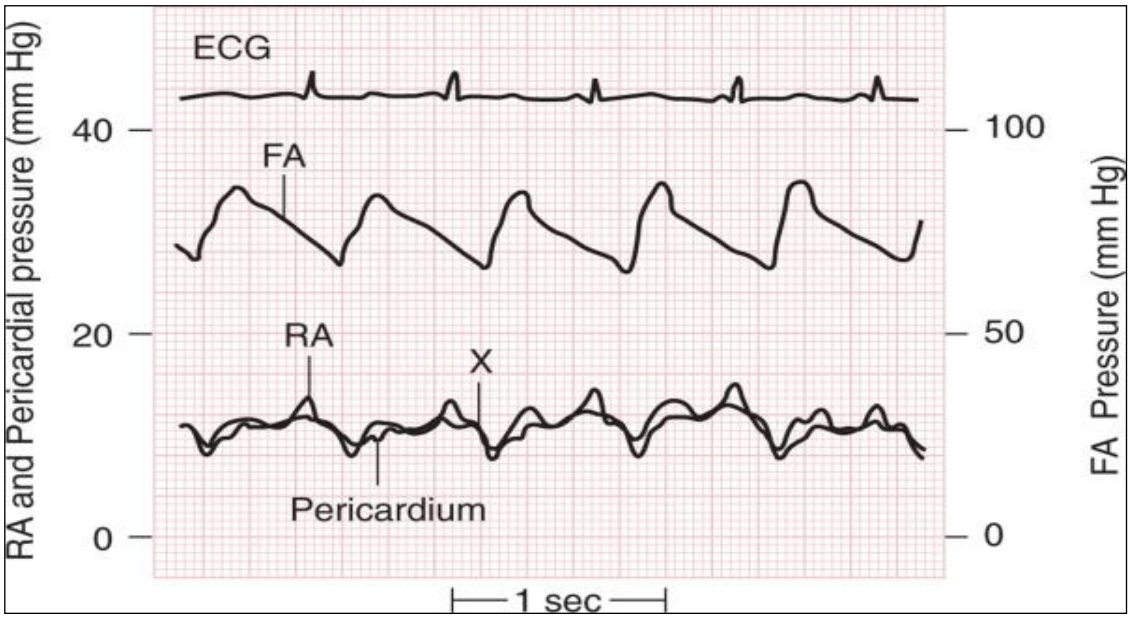
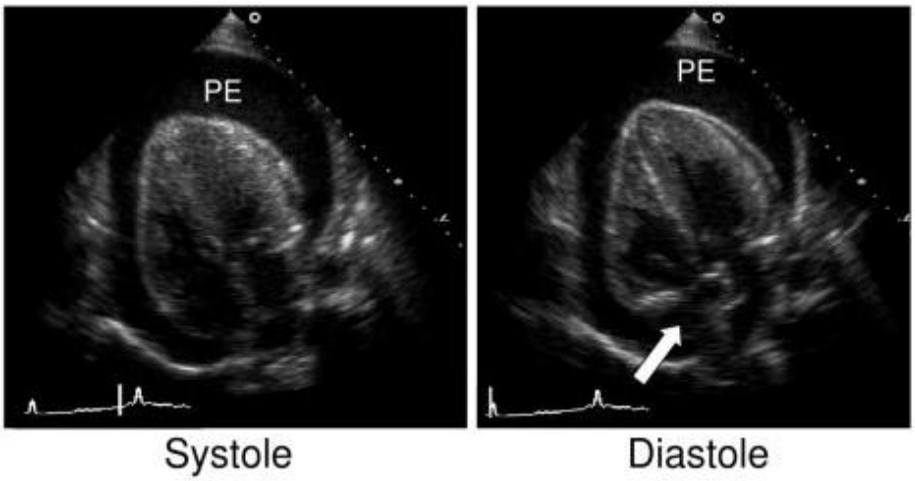


Figure 5. Simultaneous right atrial (RA), intrapericardial and femoral artery (FA) pressure recordings in a patient with cardiac tamponade. *There are elevated and equilibrated intrapericardial and right atrial pressures with a prominent x-descent and blunted y-descent suggestive of impaired right atrial emptying in early diastole. The arterial pulse pressure is narrowed* (Baim, 2006).

2.3.2.2 Echocardiography in cardiac tamponade

Echocardiography plays an important role in the evaluation of patients with cardiac tamponade and should be performed as early as possible. Echocardiography provides significant information regarding the size of the effusion, and its haemodynamic consequences (Solomon, 2007). During cardiac tamponade, diastolic collapse of the right atrial and ventricular wall occurs (Figure 6). This collapse is due to compression of the heart by the high pericardial effusion pressure. Right atrial

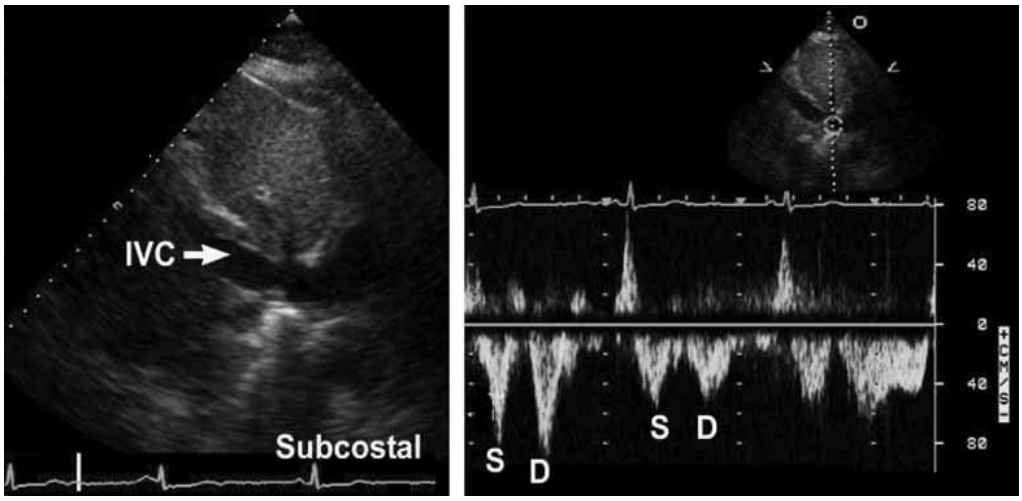
collapse is more sensitive for tamponade, while right ventricular collapse lasting for more than one third of diastole is a specific finding for cardiac tamponade (Hoit, 2002). Although echocardiography can provide important information, cardiac tamponade still remains a clinical diagnosis (Little and Freeman, 2006).



PE: Pericardial effusion

Figure 6.A two-dimensional echocardiogram in 4-chamber view from a patient with cardiac tamponade. *There is a large pericardial effusion apparent as an echo-free space around the heart. In diastole, there is collapse of the right atrium* (Solomon, 2007).

Doppler examination of right and left ventricular inflow patterns, using Doppler echocardiography, provides valuable information in the diagnoses of tamponade physiology. Right atrial collapse has a sensitivity of 90-100% for the diagnosis of cardiac tamponade, and right ventricular collapse has a lower sensitivity of approximately 60-88%, but has a very high specificity, between 90% and 100% (Solomon, 2007). Dilated inferior vena cava (IVC) without respiratory change or reduction of the IVC diameter during inspiration, on 2D echocardiography, indicates the elevated right atrial pressures and is a sensitive sign for cardiac tamponade (Figure 7). However, the specificity of this finding is only between 20% and 40%. The increase in respiratory variation of diastolic filling of the tricuspid or mitral valve inflow (i.e. >25%) is suggestive of tamponade physiology (Solomon, 2007).



S: systole; D: diastole.

Figure 7. Dilated inferior vena cava in a patient with cardiac tamponade. *Loss of normal respirophasic variation of the inferior vena cava diameter (<50% decrease during inspiration) is a reflection of significantly increased right atrial pressure* (Solomon, 2007).

2.3.3 Constrictive pericarditis

Constrictive pericarditis (CP) is defined as impedance to diastolic filling caused by a fibrotic pericardium (Schwefer, Aschenbach, Heidemann, Mey and Lapp, 2009). In CP the pericardium is thickened, fibrotic and non-compliant, resulting in impairment of right ventricular diastolic filling. In CP the myocardium is usually not affected, myocardial diastolic compliance is normal and early diastolic filling is unimpeded, but this is abruptly terminated when the myocardial reaches the stiff pericardium (Plappet and Sutton, 2006).

Constrictive pericarditis occurs in 30-60% of patients as a consequence of TB pericarditis, despite treatment with anti-TB drugs and corticosteroids (Mayosi et al., 2005). Tuberculosis is said to be the most frequent cause of CP in Africa and Asia. The clinical presentation of this syndrome varies significantly, ranging from asymptomatic to severe constriction. Thus, its diagnosis can often be missed in clinical examination (Mayosi et al., 2005).

The clinical presentation of CP is usually subtle and gradual, and the physical findings reflect the consequences of chronic elevation of the right heart pressures. These include jugular venous distension, hepatomegaly, ascites and peripheral oedema (Solomon, 2007).

2.3.3.1 Haemodynamics of constrictive pericarditis (CP)

The hallmark of CP is elevation and equalization of diastolic pressures (Little and Freeman, 2006), (Figure 8). Constrictive pericarditis is characterized by a thickened and stiff pericardium. This limits expansion of the cardiac chamber and restricts ventricular filling, leading to ventricular interdependency. As a result, the haemodynamics of the left and right heart chambers influence each other. The square root sign or the "dip-and-plateau waveform" on the ventricular pressure waveform is the main characteristic of CP. This is caused by the early rapid decrease of the ventricular pressure (producing a steep *y*-descent on right atrial pressure waveform tracings) and then the abrupt increases until systole. In the right atrial waveform, a prominent and rapid diastolic *y*-descent is followed by a steep A-wave and a blunted systolic *x*-descent because the atrium is attempting to eject blood into a right ventricle that is already filled to capacity (Figure 9), (Stouffer, 2008).

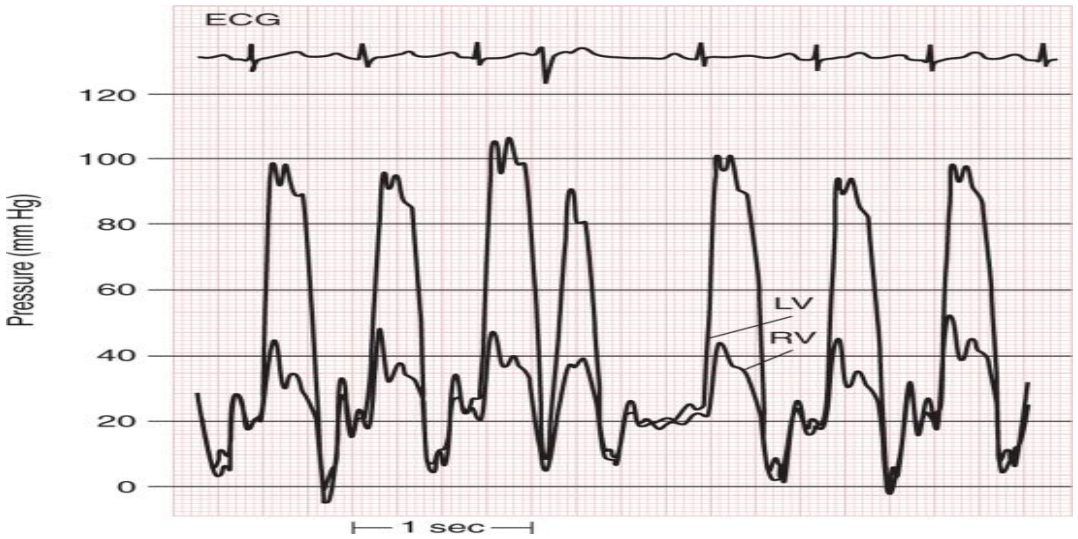
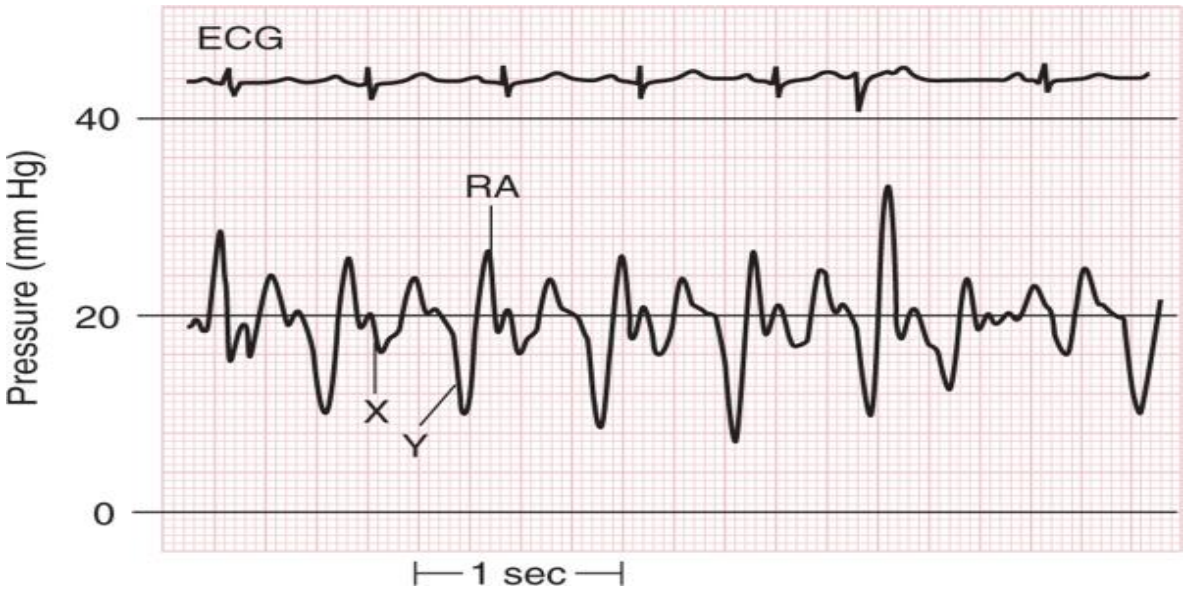


Figure 8. Simultaneous left ventricular (LV) and right ventricular (RV) pressure recordings in a patient with constrictive pericarditis. *There is equalization of LV and RV diastolic pressures and the "dip and plateau" most apparent with the prolonged diastole* (Baim, 2006).



RA: right atrial pressure; X: *x*-descent; Y: *y*-decent; ECG: electrocardiogram

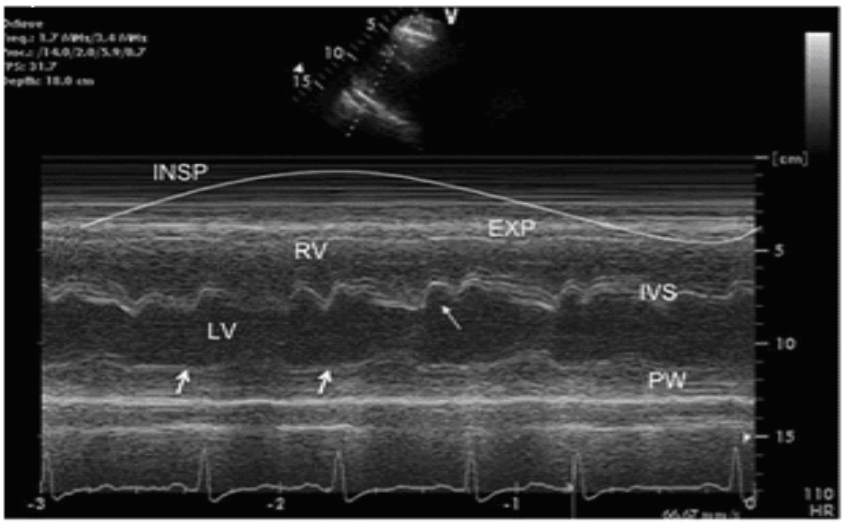
Figure 9. Right atrial (RA) pressure recording from a patient with constrictive pericarditis.*There is a prominent y-descent in the right atrial waveform, which indicates that the RA emptying is rapid and unimpeded in early diastole. The lowest point of the y-descent corresponds with the abrupt cessation of early diastolic ventricular filling. The prominent x- and y-descents give the RA waveform its characteristic M- or W-shaped appearance in constrictive pericarditis* (Baim, 2006).

2.3.3.2 Echocardiography in constrictive pericarditis (CP)

The diagnosis of CP requires a combination of both clinical and echocardiography findings. Echocardiography is not very specific for diagnosing CP. A combination of multiple features is used to make the diagnosis (Feigenbaum, Armstrong and Ryan, 2005).

Echocardiographic findings consistent with the diagnosis of CP include dilated IVC and hepatic veins due to elevated right atrial pressure. Ventricular chamber sizes and wall thicknesses are normal. The pericardium is thickened. Outward movement of the posterior left ventricular wall during mid- to late diastole is impaired, as a result of the limited filling caused by the stiffened pericardium (Figure 10). This pattern is also known as posterior wall "flattening" and is relatively sensitive as it is found in 85% of patients with CP, but nonspecific as it can also occur in normal individuals (Solomon, 2007). Other echocardiographic features in CP include paradoxical motion of the interventricular septum (septal "bounce"), (Solomon, 2007).

Pulsed Doppler signs include an accentuated A-wave of hepatic vein flow, an increased E velocity with a shortened deceleration time and a reduced A-wave velocity in trans-mitral diastolic inflow due to impaired late diastolic filling. There is also a marked respiratory variation in early diastolic right and left ventricular filling, with a more than 25% increase of trans tricuspid valve flow and more than 25% decrease of trans-mitral valve flow during inspiration (Figure 11A and B), (Solomon, 2007).



EXP: expiration; INSP: inspiration; IVS: interventricular septum; LV: left ventricle; PW: posterior wall; RV: right ventricle

Figure 10. M-mode recording, in the parasternal long-axis view in a patient with CP. *This shows a respiratory shift of the interventricular septum toward the left ventricle with inspiration and toward the right ventricle with expiration as a result of exaggerated ventricular interdependence. Small arrow denotes the early diastolic septal bounce, typically seen in CP. There is flattening of the posterior left ventricular wall during diastole (big arrows)* (Verhaert, Gabriel, Johnston, Lytle, Desai and Klein, 2010).

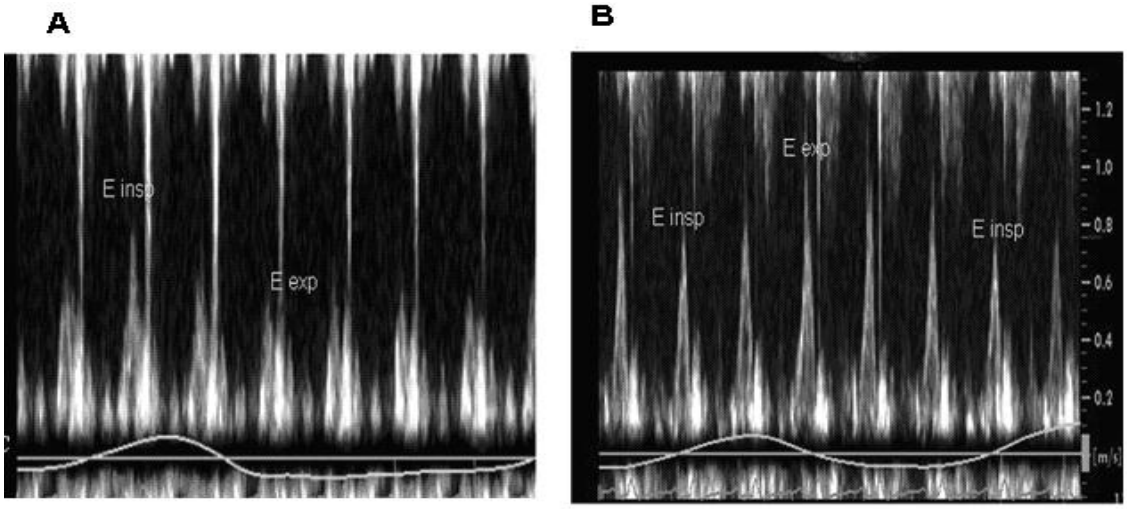


Figure 11.Pulsed wave Doppler respiratory variation in CP. (A) *Pulsed wave Doppler echocardiography of the mitral valve with marked (>25%) respiratorychanges of early mitral inflow velocity (*E). ***(B)*** *Tricuspid inflow velocity, showing the opposite changes. Tricuspid valve early diastolic velocity, increases with inspiration and decreases with expiration* (Verhaert et al., 2010).

2.3.4 Effusive constrictive pericarditis (ECP)

Effusive constrictive pericarditis (ECP) represents a combination of constriction and tamponade physiology. Mayosi et al., (2005), state that ECP is a common presentation in Africa. It is characterized by constriction of the heart by visceral pericardium in the presence of tense pericardial effusion. Patients with ECP usually present with pericardial effusion, and haemodynamic evidence of increased cardiac filling pressures. ECP diagnosis is made when there is evidence of elevated right atrial pressures, after the intrapericardial pressures have been normalized by pericardiocentesis.

Treatment of ECP is not easy as removal of the pericardial fluid on its own, in the presence of visceral pericardial constriction, is not sufficient. Visceral pericardiectomy is indicated in most cases. Medical management should be directed to the underlying cause; however, no trials have been done to guide therapy and the role of corticosteroid remains unknown (Mayosi et al., 2005).

2.3.4.1 The haemodynamics of effusive constrictive pericarditis (ECP)

The diagnosis of ECP is suspected clinically but definitively established by recording right heart and intrapericardial pressures before and after pericardiocentesis (Bonemma, 2008).

The hallmark of ECP is the persistent elevation of right atrial pressures, after pericardial fluid has been removed and the intrapericardial pressure lowered to near zero (Sagrista-Sauleda et al., 2004). The haemodynamic findings of ECP combine the findings of both cardiac tamponade and CP (Stouffer, 2008). The presence of constriction limits the expansion of cardiac chambers, causing equalization of diastolic pressures. Prior to pericardiocentesis, the haemodynamic findings of ECP resemble those of cardiac tamponade, with a preserved *x*-descent and small *y*-descent

on the right atrial pressure waveform. Pericardiocentesis changes the haemodynamic findings to those of constriction, with a return and exaggeration of the *y*-descent (Figure 13). An M- or W-shaped configuration can be seen on the atrial waveform. This is because the visceral pericardium, not the parietal, is constrictive. Owing to rapid filling in early diastole, the square root sign can be seen on the ventricular pressure waveform (Stouffer 2008).

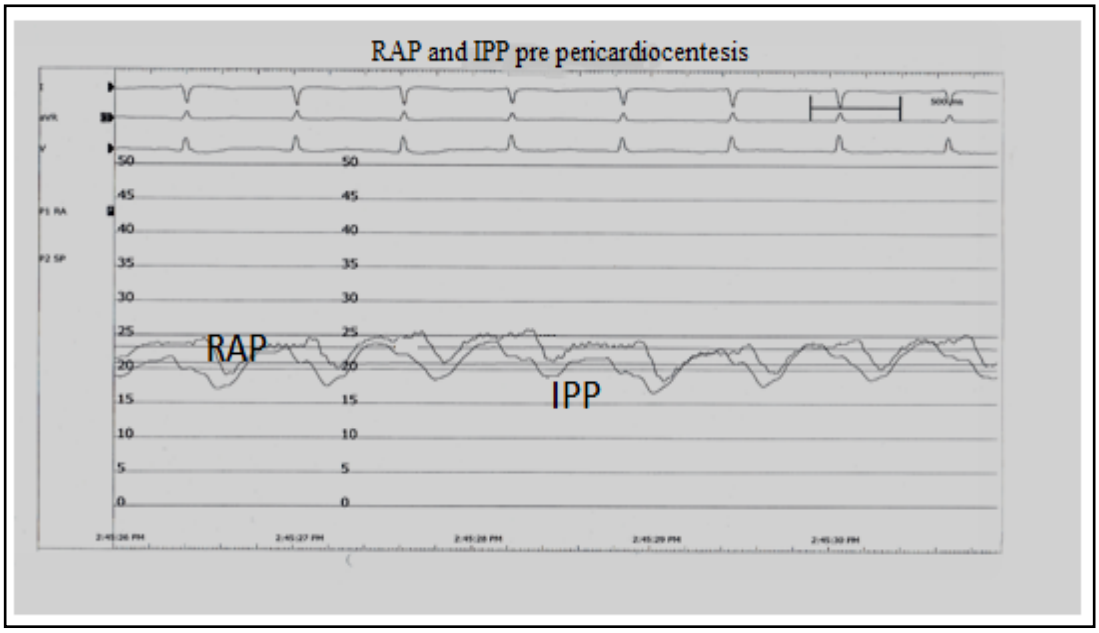


Figure 12. (a) Right atrial and intrapericardial pressure recording before pericardiocentesis in a patient with ECP, *the mean right atrial (RAP) and intrapericardial (IPP) pressures before pericardiocentesis respectively, 20 and 22 mmHg. (Image from a GSH patient, with permission from head of department).*

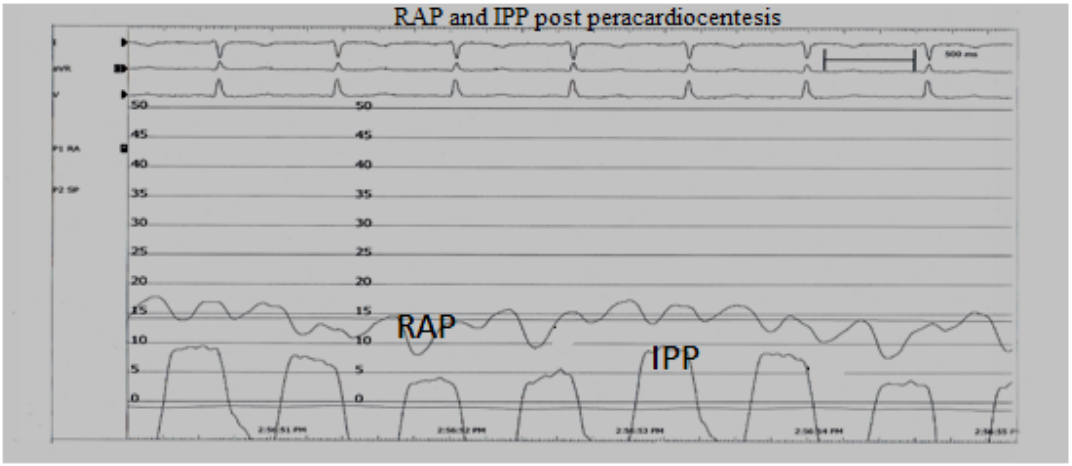
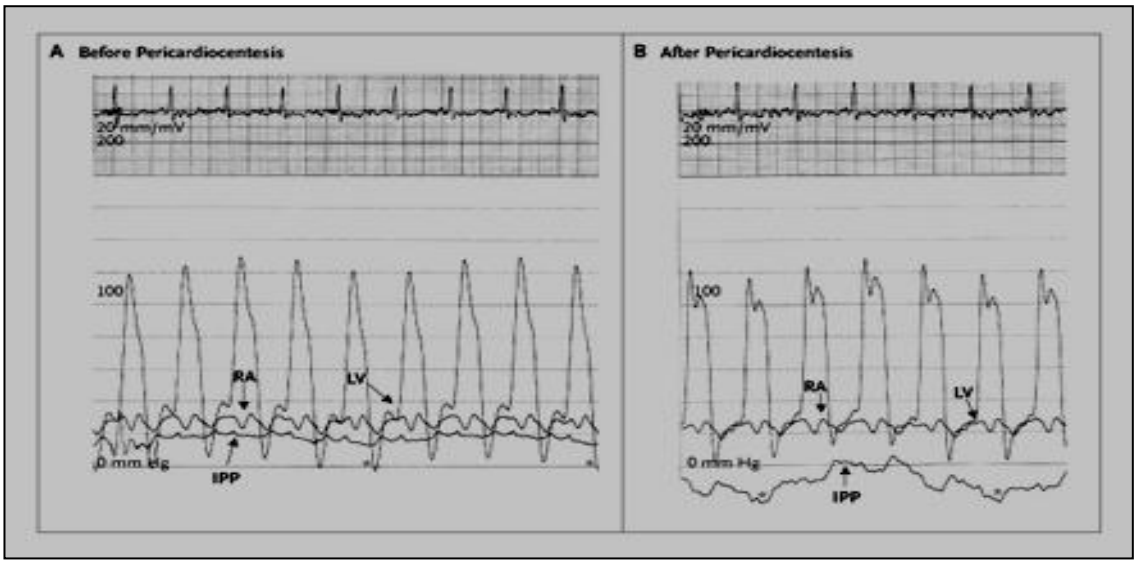


Figure 12. (b) Right atrial and intrapericardial pressure recording post pericardiocentesis in a patient with ECP, *the mean right atrial (RAP) and intrapericardial (IPP) pressures post pericardiocentesis respectively, 14 and -1 mmHg. (Image from a GSH patient, with permission from head of department).*



RA: right atrial pressure; LV: left ventricular pressure; IPP: intrapericardial pressure

Figure 13.Findings at catheterization during two spontaneous respiratory cycles before and after pericardiocentesis. *Before pericardiocentesis* ***(Panel A),*** *Intrapericardial pressure (IPP)is elevated (21 mmHg), as are the right atrial (RA) pressure (35 mmHg) and end-diastolic left ventricular (LV) pressure (35 mmHg). After pericardiocentesis* ***(Panel B****), the intrapericardial pressure drops below 0 mmHg, whereas the right atrial and left ventricular pressures are practically unchanged and a dip–plateau morphology of left intraventricular pressure is apparent* (Sagrista-Sauleda et al., 2004).

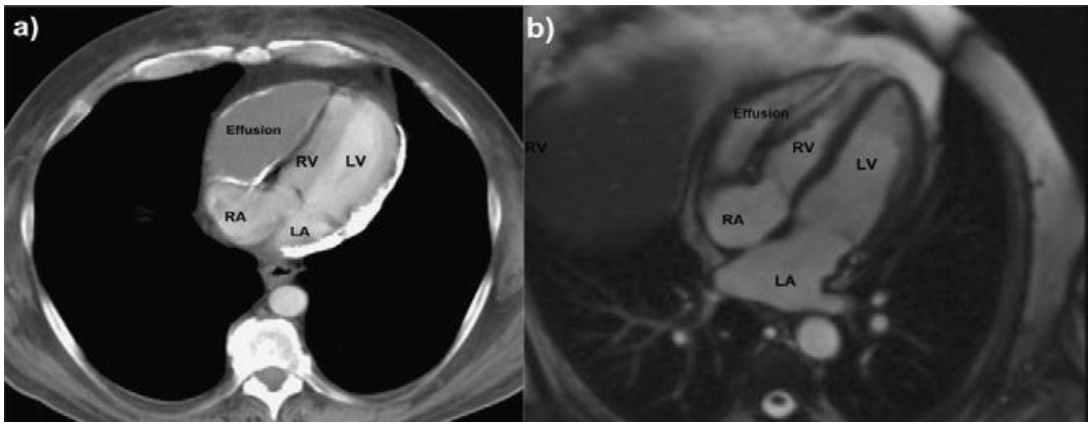
There are rare cases in which a loculated effusion may lead to constriction with regional tamponade of one or more cardiac chambers. Any form of chronic pericardial effusion can potentially organize into an ECP, even though the number of these cases is low (Hoit, 2002).

2.3.4.2 Echocardiography in ECP

Echocardiographic findings in ECP fall somewhere on a spectrum between the findings of a cardiac tamponade and CP, depending on whether the effusion has been drained and intrapericardial pressure has been normalized (Stouffer, 2008). These findings include a thick pericardium, abnormal ventricular septal motion, dilated IVC, and variation in ventricular size. There is a decrease in mitral flow velocity of greater than 25% with respiration, consistent with CP. Early diastolic collapse of the right atrium and right ventricle can also be seen. These features are also found in both CP and cardiac tamponade (Zagol, Minderman, Munirand D'Cruz, 2007).

2.3.4.3 Computed tomography (CT) and cardiac magnetic resonance imaging (CMR) in ECP

As previously stated, ECP is difficult to diagnose by echocardiography at the time of presentation with tamponade, and the diagnosis rests on performance of catheterization at the time of pericardiocentesis. However, this is not always feasible. Non-invasive imaging techniques, such as CT and CMR, are increasingly being used for the diagnosis of ECP (Figure 14).



RA: right atrium, RV: right ventricle, LA: left atrium; LV: left ventricle

Figure 14. Preoperative computed tomographyin ECP ***(a)*** *CT images using a steady-state free precession sequence* ***(b)*** *demonstrating ECP with a 2 cm anterior pericardial collection compressing the right ventricle and marked calcific thickening of the posterolateral pericardium surrounding the left ventricle* (Moorjani, Peebles, Tsang and Livesey, 2009).

Compared to echocardiography, CT and CMR are better at demonstrating the presence of abnormal pericardial thickening (Figure 15). Cardiac magnetic resonance imaging is also useful in further assessing the presence of constrictive physiology and providing prognostic information as to whether a pericardiectomy is required (Verhaert et al., 2010). The diagnostic performance of these imaging modalities for ECP compared to invasive haemodynamic assessment remains to be tested in appropriate diagnostic studies (Verhaert et al., 2010).

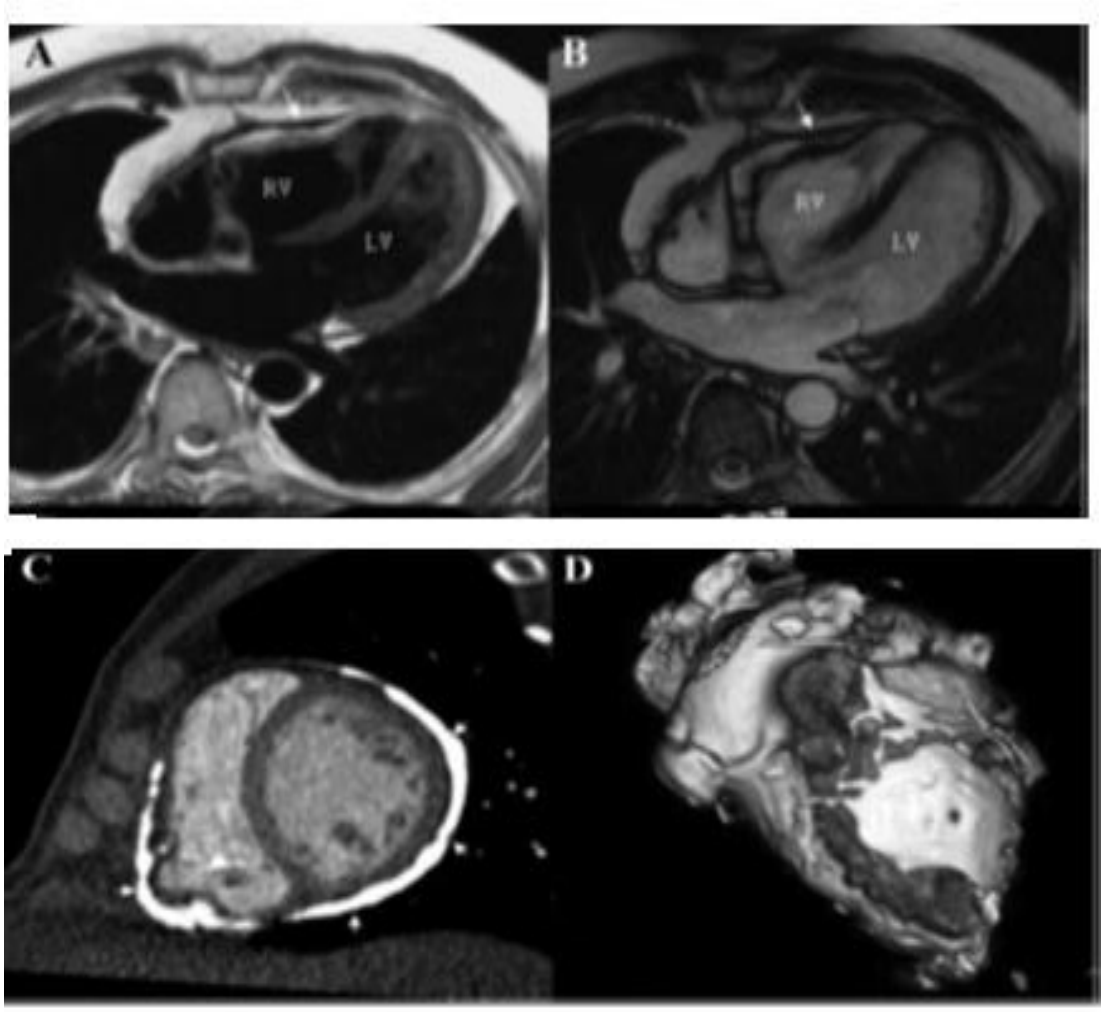


Figure 15.Classic anatomic findings of pericardial constriction by CMR. *Cardiac magnetic resonance findings of constriction demonstrated in black blood T2-weighted spin-echo **(A)** and steady-state free precession sequence cine sequence **(B)** in the horizontal long-axis view. Pericardial thickening (6 mm) is seen adjacent to the right atrium and ventricle (arrow), with characteristic tubular deformity of the right and left ventricles (RV/LV) and dilation of the right atrium. **(C)** CMR demonstrating the presence of circumferential pericardial calcification on a multiplanar reconstructed short-axis image (arrows). **(D)** Three-dimensional volume-rendered imaging showing the extent and anatomic distribution of pericardial calcium* (Verhaert et al., 2010).

Despite this, CMR has become the gold standard for the evaluation of pericardial disease because of its ability to provide accurate information on the pericardium, myocardial structure, function, inflammation and fibrosis (Russell et al., 2008).

CHAPTER THREE: MATERIALS AND METHODS

The primary aim of the study was to determine the prevalence of effusive constrictive pericarditis (ECP) in patients with large pericardial effusions of tuberculous origin.

There were 4 main objectives:

(1) to determine the proportion of patients with ECP in a cohort of consecutive patients with TB pericarditis, by measuring simultaneous right atrial and intra-pericardial pressure before and after pericardiocentesis.
(2) To describe the demographics and pericardial fluid characteriscs of patients with ECP.
(3) To compare the demographics and pericardial fluid characteristics of patients with ECP to those of patients without ECP.
(4) To look for a relationship between ECP and the presence of 3 specific echocardiographic features of pericardial constriction (thickened pericardium, dilated IVC and septal bounce), two weeks post pericardiocentesis.

3.1 Study design and population

This was a cross–sectional analysis of a prospective study of consecutive patients with large pericardial effusion of tuberculous aetiology, undergoing pericardiocentesis at Groote Schuur Hospital in Cape Town. The patient number recruited for the study (sample size) was calculated and verified by the head biostatistician from the University of Cape Town and was sufficient to show statistical significance.

Over the 3 years prior to the onset of the study an average of 53 patients referred to Groote Schuur Hospital with large pericardial effusions underwent either a diagnostic or therapeutic pericardiocentesis. Using a population size of 53, with an error margin of 5% and confidence level of 99%, the required sample size was calculated to be 50. For the primary objective (which was to estimate the prevalence of ECP in this population), given an expected (based on the literature) prevalence of 8%, a desired precision of 5% and a finite population size correction, the minimum number of patients required was 49.

Ethical approval was obtained from the Durban University of Technology Ethics Committee and permission was also obtained from the Higher Degree's Committee. The study was also carried out as a sub-study of the Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry (Mayosi et al., 2006).

Fifty consecutive patients with pericardial effusion presenting to Groote Schuur Hospital and surrounding hospitals referred for pericardiocentesis, who met the inclusion criteria, were recruited to participate in the study. Information about the study and consent forms were provided in the patient's language of preference (Appendix C, D, E and F). Patients were informed about the purpose and requirements of the study. Patients were informed that participation in the study was entirely voluntary and that they were entitled to withdraw at any point without affecting the medical treatment rendered to them. They were also informed that all information used in the study would remain confidential and that any data reported in scientific journals or published would not include information identifying them as a patient in the study.

All patients recruited into the study were under the care of a consultant cardiologist, who confirmed that patients required pericardiocentesis. The clinical evaluation of each patient included a complete medical history, physical examination, electrocardiography, chest radiography, echocardiography, and analysis of blood. This was followed by pericardiocentesis, and measurement of the pre- and post

intrapericardial (IPP) and right atrial pressures (RAP). Based on the results of the haemodynamic findings, patients were then classified and grouped as having ECP or not, depending on whether they met the definition of ECP.

3.2 Selection criteria

3.2.1 Inclusion criteria

1. Patients aged 18 years or above.
2. Large effusions >1cm anteriorly, confirmed on echocardiography.
3. Evidence of a tuberculous aetiology (patients on TB treatment or positive culture for TB or symptoms of TB) of the pericardial effusion.

3.2.2 Exclusion criteria

1. Pregnancy
2. Pus aspiration.
3. Patients with known cardiomyopathy or structural heart disease.
4. Patients under 18 years.
5. Lack of full haemodynamic information.

3.3 Definitions and criteria for diagnosis

3.3.1 Effusive constrictive pericarditis

ECP was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤12 mmHg after the intrapericardial pressure is lowered to 2 mmHg or below (Sagrista-Sauleda et al., 2004).

3.3.2 Tuberculous pericarditis (TB)

A “definite” diagnosis of TB pericarditis was based on the demonstration of tubercle bacilli in pericardial fluid or on a histological section of the pericardium. “Probable” TB pericarditis was based on the proof of TB elsewhere in a patient with otherwise unexplained pericarditis, a lymphocytic pericardial exudate with elevated adenosine deaminase levels, and/or appropriate response to a trial of antituberculosis chemotherapy (Mayosi et al., 2005).

3.4 Haemodynamic monitoring

3.4.1 Invasive pressure monitoring

For invasive pressure monitoring the Edwards LifeSciencesTruWave double disposable pressure transducer (DPT) sets, comprising of a compliant extension tubing (152 cm high pressure monitoring lines) were used (Figure 16). The tubing was connected to the catheters. The system was filled with fluid (0.9% NaCl saline heparinised with 1ml of 5000 unit heparin). A cable linked the Marquette MacLab amplifier monitor and this fluid-filled transducer set.

The system worked by pulsatile pressure at the tip of the catheter being transmitted through the connecting tubing (which was filled with fluid) to the diaphragm of the transducer. The movement of the transducer diaphragm (which was induced by pressure) was then converted into low-voltage electrical signals. These pressure signals were then amplified and converted by the amplifier and monitor into waveforms and digital value on an oscilloscope. An oscilloscope allowed the amplified pulse pressure wave to be viewed continuously as the events were occurring (Fawcett, 2006).

For this study the Prucka MacLab monitoring system was used (Figure 17). The amplifier takes a signal (1 mV) and reproduces it; so that it is displayed consistently

ten times that of the original signal. This ensures that a pressure reading of 100 mmHg appears as a waveform that is exactly twice that of a pressure reading of 50 mmHg.

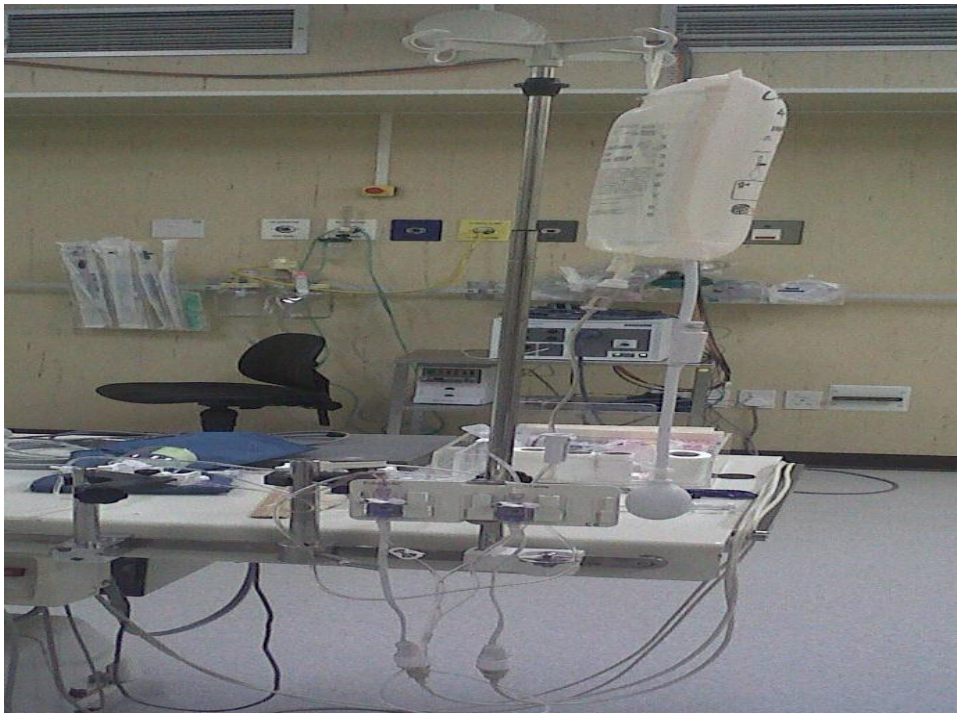


Figure 16. The Edwards LifeSciencesTruWave disposable pressure transducers, *mounted on a pole clamp back plate holder used for haemodynamic monitoring. (Image taken from Groote Schuur Cath Lab, with permission from head of department.)*

Figure 17.Prucka Mac-Lab® System for haemodynamic monitoring, *used in the cardiac cath lab at Groote Schuur Hospital. (Image taken from Groote Schuur Cath Lab, with permission from head of department.)*

In order for accurate pressure measurements to be displayed, the whole fluid-filled transducer system had to be unobstructed, zero referenced and levelled. The fluid-filled components of the system were connected to a flush device that was mounted on the transducer. An intravenous fluid bag (1 litre 0.9% NaCl mixed with 1ml of 5000 unit heparin) was put under pressure using an inflatable pressure bag. This was used to prime the transducer and to ensure that the system remained patent. The bag was pumped up to a pressure of 300 mmHg, to maintain patency of the system by delivering a counter pressure against the pulsatile pressure coming from the venous or arterial line of the patient.

3.4.1.1 Levelling

It is important to have the transducer at the correct level (Fawcett, 2006). The tip of the catheter inserted for pressure monitoring was approximately at mid-chest level of the patients just below the angle of the sternum. Examination using a fluoroscope showed that, with a patient in supine position, left ventricle and aorta were located

mid-way between the sternum and the top of the mattress on which the patient was lying (Fawcett, 2006).

With the patient lying in supine position on the cardiac catheterization laboratory (cath lab) table, a spirit level and ruler were used to measure the patient's mid-chest level. The transducers were then set according to the measurement, ensuring that they were also at the patient's mid-chest level, for accurate pressure measurements.

3.4.1.2 Zeroing

The transducer requires a zero reference point as a baseline for all other measurements. Pressure zeroing the transducer eliminates the effect that atmospheric and hydrostatic pressure have on pressure readings (Fawcett, 2006).

With the transducer placed at the patient's mid-chest level, and the pressure monitoring lines connected, the transducer and monitor display were zeroed. The stopcock was closed to the patient and opened to the atmosphere. The monitor was zeroed, and the monitored pressure reading displayed zero value, to confirm that the transducer had been zeroed to atmosphere. The stopcock was then closed to the atmosphere.

3.5 Pericardiocentesis and catheterization

The patient was brought to the cath lab, and placed in the supine position on the operating table. The investigator cleaned the patient's skin with an alcohol prep swab, thus preventing any grit, dust or sweat from affecting the readings of the electrodes. Electrocardiography (ECG) electrodes were placed on the patient and a five-lead channel electrocardiogram was connected for ECG monitoring. A blood pressure cuff and an oxygen saturation monitor were also connected. A new study was opened on the MacLab monitoring system. The patient's details were entered,

including the patient's name, hospital number and study number. Baseline electrocardiogram, heart rate, oxygen saturation levels and non-invasive blood pressure (NBP) were recorded.

The Edwards LifeSciencesTruWave disposable pressure transducers, mounted on a pole clamp back plate holder, were set up (Figure 16). A litre of heparinised saline was placed into a pressure bag pumped to 300 mmHg and connected to the transducers. The patient's mid-chest level was measured, and the transducers placed at the mid-chest level. The transducers were then flushed and primed with the heparinised saline. Both the monitor and transducers were then zeroed.

The doctor scrubbed and the patient was covered with sterile drapes. The patient was given lignocaine in the groin area as well as in the subxiphoid area. The femoral vein was then accessed. An incision was made in the subxiphoid area. 6 French sheaths were placed in both the femoral vein and subxiphoid area.

A 6 French multipurpose angiographic catheter was inserted into the femoral vein and placed in the right atrium. A 6 French pigtail angiographic catheter was also inserted into the subxiphoid area and placed within the intrapericardial space. All catheters were inserted under fluoroscopy.

Prior to the pericardiocentesis, the right atrial pressure and the intrapericardial pressure were measured using the Prucka Mac-Lab System for Haemodynamic Monitoring. The pressures were recorded at a scale of 20 mmHg or 50 mmHg, depending on how high the pressure was. A speed of 50 milliseconds was used during the recording so that the pressures could be clearly defined, the *x*-and *y*-descents could be seen clearly. Simultaneously a combined intrapericardial and right atrial pressure measurement was recorded prior to aspirations. All pressures recorded were printed.

A pericardiocentesis was done, with continuous haemodynamic monitoring. Some of the fluid aspirated was then transferred into the specimen bottles for laboratory analysis. The pressure measurements were repeated post pericardiocentesis. The

catheters were then removed. Heart rate and NBP were also recorded post aspiration. The pressure monitoring lines were removed and the transducers closed. The ECG electrodes, blood pressure cuff and saturation monitor were removed from the patient. The MacLab study was closed and the patient moved out of the cath lab.

The pressure tracings were analysed and the mean pressures recorded.

3.6 Laboratory analysis

3.6.1 Blood and pericardial fluid sample collection and analysis

Blood and pericardial fluid samples (5 ml) were collected during pericardiocentesis and sent to the National Health Laboratory Service (NHLS) for analysis. The laboratory is accredited by the South African National Accreditation System (SANAS)**.** A *Mycobacterium tuberculosis* culture was prepared. The ZN stain test was used to detect TB. Pericardial ADA activity level and IFN-γ concentration were measured on the pericardial fluid to support the diagnosis of TB (appendix E).

For this study, diagnosis of TB pericarditis was based on the demonstration of tubercle bacilli in pericardial fluid or on a histological section of the pericardium, as well as ADA activity levels ≥ 40 U/L and IFN-γ concentration levels of ≥50 pg/ml.

3.6.2 Tuberculosis diagnostic tests

3.6.2.1 The Ziehl-Neelsen (ZN) stain

The protocol for ZN staining at the Groote Schuur Hospital NHLS laboratory is provided below. A bacterial smear was heat fixed onto a microscope slide. The sample was dried by using steam. The heat kills the bacteria and attaches the sample to the slide so that it does not easily wash away.

The protocol for staining acid-fast organisms was as follows:

1. A strip of blotting paper was placed over the slide.
2. The covered slide was place over a screened water bath and then saturated with blotting paper containing the primary stain Ziehl'scarbol fuschion.
3. The slide was then allowed to sit over a water bath for 3 – 5 minutes, and the stain was re-applied if it began to dry out.
4. The blotting paper was removed and the slide rinsed until water ran clear.
5. The slide was flooded with decolourizer, acid alcohol, for 10 – 15 seconds and then rinsed.
6. The slide was flooded with counterstain, crystal violet, for one minute and then rinsed.
7. The slide was then gently blotted until dry and viewed under the microscope.

3.6.2.2 The diazyme pericardial adenosine deaminase assay

The protocol for the diazyme adenosine deaminase (ADA) assay kit used for the determination of ADA activity in pericardial fluid samples at the Groote Schuur Hospital NHLS laboratory is provided below (Table 1).

Sample specimen

Pericardial fluid was used for the ADA test.

Assay procedure

1. Parameter settings:

Method	: Kinetics	Temperature: 37 °C
Wavelength	: 550 nanometer	Reaction time: 10 min
Sample/Reagent	: 1: 54	

Water was used to blank (auto-zero) cuvette at 550 nm.

Table 1. ADA reagent table

Reagent 1 (R1) 50 mL	50 mMTris-HCltris(hydroxymethyl) aminomethane hydrochloride) pH 8.0. 0. 2 mM 4-AA (4-aminoantipyrine) 0.1 U/mL PNP (purine nucleoside phosphorylase) 0.2 U/mL XO (xanthine oxidase) 0.6 U/mL peroxidase Stabilizers
Reagent 2 (R2) 25 mL	50 mM Tris-HCl pH 4.0 10 mM adenosine 2 mM EHSPT (3-methylaniline)
ADA control 1.0 mL	Adenosine deaminase (bovine liver) and BSA

2. Assay:

1. Reagents R1 and R2 were pre-equilibrated to room temperature prior to the assay.

2. 180 microlitre (μL) of R1and 5 μL of plasma sample were mixed and incubated at 37^{o}C for 3 or 1.5 min.

3. 90 μL of R2 was added, and incubated for 5 min followed by monitoring the absorbance at 550 nm for 3 min with 1 min interval to obtain Δ A/min values.

4. The average rate of the absorbance change ΔA/min was calculated.

$$\Delta A/min = \frac{\Delta A_1 / min + \Delta A_2 /min + \Delta A_3/min}{3}$$

5. ADA activity (U/L) in the plasma sample was calculated by using the formula:

$$\text{ADA (U/L)} = \frac{\Delta A/\text{min. x Tv}}{\varepsilon \text{ x Sv x}} = \Delta A/\text{min x } 1708 \text{ L}$$

Where: ε: μmolar extinction coefficient of quinone dye ($\varepsilon = 32.2 \times 10^{-3}$ μM-1cm^{-1})

Tv: Total reaction volume (mL)

Sv: Sample volume (mL)

L: Cuvette light path length (1.0 cm)

ΔA/ min: absorbance change per minute

Using the above assay, an ADA activity of > 30 U/L is normally considered positive for TB. However an ADA of > 40 U/L was used for the study, as it had been shown to have a higher specificity and sensitivity (Reuter et al., 2006) .

3.6.2.3 The pericardial interferon gamma concentration test procedure

The protocol for IFN-γ test at the Groote Schuur Hospital NHLS laboratory is provided below.

An in-house IFN-γ specific enzyme-linked immunosorbent assay (ELISA) was carried out on the supernatants that were removed from the whole blood and pericardial fluid overnight.

1. The ELISA plate (Costar 3590, 96 well EIA/RIA plate, high binding) was coated with mouse anti-human IFN-γ monoclonal capture antibody (BD Bioscience 551221) at a final concentration of 2mg/ml in 0.1 Molar (M) carbonate coating buffer.
2. The plate was incubated at 4ºC overnight.
3. The plate was washed twice with PBS-Tween wash buffer (PBS/0.05% Tween-20) using an automated ELISA washer.
4. The plate was then blocked with PBS/10% FCS for 2 hours at room temperature before it was washed twice more.

5. The samples were added at 100 µl per well.
6. The standard was recombinant human IFN-γ (BD Bioscience 554617) with an initial concentration of 10 000 pg/ml.
7. This was serially diluted 1:3 with PBS-Tween/10% FCS to give standards with a concentration of 6666, 3333, 1111, 370, 123, 41 and 0 pg/ml.
8. The standards were added at 100 µl per well in duplicate wells.
9. The plate was incubated overnight at 4ºC in a plastic box to contain any spillages.
10. The next morning, the plate was washed 4 times before adding 100 µl of biotinylated mouse anti-human IFN-γ detection antibody (BD Bioscience 554550) at 1mg/ml in PBS-Tween/10% FCS.
11. The plate was incubated at room temperature for 45 minutes before it was washed 6 times. Avidin-Peroxidase (Sigma A3151) at 1mg/ml was diluted 1:1000 in PBS-Tween/10%FCS and 100 µl was added to each well.
12. The plate was placed in the dark at room temperature for 30 minutes before it was washed 8 times with PBS-Tween.
13. Freshly made OPD colour developer solution (1 citrate buffer tablet and 1 OPD tablet in dH_20) was added at 100 µl per well and incubated in the dark for approximately 5 minutes.
14. The reaction was stopped by adding 50 µl of 2M H_2SO_4 to each well.
15. The plate was read at an absorbance of 490 nm on a plate reader and the results were recorded.
16. The concentrations were calculated from a standard curve that was constructed from the standard concentrations.

3.7Echocardiography

In order to determine the echocardiographic predictors of ECP, patients had an echocardiogram study pre and post pericardiocentesis as well as 2 weeks post the aspiration. Two weeks post pericardiocentesis echocardiographic results were analyzed, to determine if any echocardiographic parameters can predict the presence

of ECP. The following echocardiography/ultrasound machines were used to record the echocardiogram: GE Vivid 3 with a 3S 1.7 MHz transducer or the portable Sonosite P17 with a 5.1 MHz transducer.

According to Oh et al. (1994), there are two-dimensional (2D) echocardiographic features which are suggestive of CP, namely: abnormal motion of the interventricular septum and a dilated IVC. These features should prompt serious consideration of CP diagnosis. Zagol et al. (2007), described five echocardiographic features that are essential for the diagnosis of CP, namely: a thick pericardium, septal bounce, dilated IVC, normal size and systolic ventricular function, as well as respiratory variation of the mitral inflow pattern.

In the present study, the first three echocardiographic features described by Zagol et al. (2007), were recorded and analyzed to determine if these echo variables correlated with ECP, namely: thick or bright pericardium (2D), septal bounce and a dilated IVC (2D).

3.8 Statistical methodology

Descriptive and accumulative statistics were calculated for all the recorded variables using the SPSS software. Differences between groups were tested using the Wilcoxon paired test, because of small sample size and lack of normalities within the variables analyzed. Univariate logistic regression models were used to test and establish statistical significance of independent co-variables analyzed. Independent variables were fitted to determine the association between patient variables and ECP. 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. All results were recorded as mean (SD) or mean ± SD unless otherwise stated.

CHAPTER FOUR: RESULTS

Fifty participants were enrolled in the study, the baseline demographic and pericardial fluid characteristics are summarized in Table 2.

Table 2: Sample characteristics for entire sample study group (*n*=50) except where otherwise noted

Characteristic	***n* (%) or mean ± SD**
Female	22 (44)
Age (years)	34.2 ± 9.2
HIV +ve	39 (78)
ADA > 40U/L	50 (100)
ZNS TB +ve	19 (38)
IFN- γ +ve (#)	23 (100)
ECP status +ve	17 (34)
Pressure (mmHg) findings before pericardiocentesis	
RAP	15.2 ± 6.7
IPP	13.7 ± 6.6
Pressure (mmHg) findings post pericardiocentesis	
RAP	8.9 ± 5.5
IPP	1.7 ± 2.9
Volume (ml) of fluid aspirated	1029 ± 415.8

***ADA**: adenosine deaminase; **IFN-γ**: interferon-gamma; **ZNS**: Ziehl-Neelsen stain; **RAP:** Right atrial pressure; **IPP**: intrapericardial pressure*. (# only 23 patients had the IFN- γ test)

Patients showed a significant decrease in both right atrial and intrapericardial pressures after pericardiocentesis, as shown in Table 2. In the entire study group the mean (SD) right atrial pressure was 15.2 (6.7) mmHg prior to pericardiocentesis being performed, decreasing to 8.9 (5.5) mmHg after pericardiocentesis ($p< 0.001$). The overall intra-pericardial pressure decreased from 13.7 (6.6) mmHg to 1.7 (2.9) mmHg, a decrease of 12.00 mmHg after pericardiocentesis ($p<0.001$).The mean ± SD pericardial fluid volume aspirated was 1029 ± 415.8ml.

The two week post pericardiocentesis echocardiographic features of constriction that were analysed are also shown in Table 3.

Table 3. Two week post pericardiocentesis echocardiography results

Echo results (*n* = 22)	
Thickened pericardium	19 (86)
Dilated IVC	5 (23)
Septal bounce	5 (23)

Of the 50 patients enrolled in the study only 22 had an echocardiogram study performed two weeks post pericardiocentesis. The two week post pericardiocentesis echocardiographic features of constriction that were analysed are shown in Table 3.

The prevalence of ECP in the study sample was (34%), binomial confidence interval calculated using normal approximation method, the confidence interval (CI) is 21-47%.

Demographics and diagnostic findings of ECP are shown and contrasted with those of patients without ECP, Table 4.

Table 4. Demographics and diagnostic findings in the ECP and non-ECP groups.

Characteristic	**ECP +ve*n (%)***	**ECP –ve*n (%)***	**P-value**
Sex - Male	8 (29)	20 (71)	0.84
Sex - Female	9 (41)	13 (59)	0.84
Age years mean (SD)	29 ± (34)	28 ± (31)	0.10
HIV +ve	11(28.2)	28 (71.8)	0.12
ADA > 40L/U	17 (34)	33 (66)	0.92
ZNS TB +ve	3 (15.8)	16 (84.2)	0.34
IFN-γ	7 (30.4)	16 (69.6)	0.68

Pressure and fluid volume results are compared between ECP and non-ECP participants in Table 5. Right atrial pressure pre and post-pericardiocentesis, were found to be different between ECP and non-ECP patients *p*-values < 0.001. Intrapericardial pressure post-pericardiocentesis was also found to be statistically significant between ECP and non-ECP patients with *p*-value of 0.04.

Table 5. Haemodynamic features of ECP as contrasted with those on non-ECP

Pressure results (mmHg)	**ECP +ve*mean (SD)***	**ECP –ve*mean (SD)***	**P-value**
RAP pre-pericardiocentesis	22.5 ± (5.1)	12.1± (4.2)	<0.001
IPP pre-pericardiocentesis	20.0 ± (5.4)	10.5 ± (4.4)	<0.001
RAP post-pericardiocentesis	15.2 ± (3.9)	5.6 ± (2.5)	<0.001
IPP post-pericardiocentesis	3.3 ± (3.4)	0.9 ± (2.1)	0.04
Volume of fluid aspirated (ml)	1025.9 ± (448.7)	131.5± (405.1)	0.74

The change in right atrial pressure and intrapericardial pressure pre and post pericardiocentesis was significantly different. In non-ECP patients, right atrial pressure had a mean decrease of 6.5 mmHg (p = 0.001), in ECP patients the decrease was 7.3 mmHg (p = 0.003). For intra-pericardial pressure, non-ECP patients had a mean decrease of 9.6 mmHg (p = 0.001) and ECP patients a mean decrease of 16.7 mmHg (p = 0.003) as shown in Table 6. The difference in pressures pre and post pericardiocentesis is also shown in Figure 18.

Table 6. Pressure changes in ECP +ve and ECP -ve

	RAP pre-pericardiocentesis	RAP post-pericardiocentesis	P-value
ECP +ve	22.5 ± (5.1)	15.2 ± (3.9)	0.003
ECP –ve	12.1± (4.2)	5.6 ± (2.5)	0.001
	IPP pre-pericardiocentesis	**IPP post-pericardiocentesis**	**P-value**
ECP +ve	20.0 ± (5.4)	3.3 ± (3.4)	0.003
ECP -ve	10.5 ± (4.4)	0.9 ± (2.1)	0.001

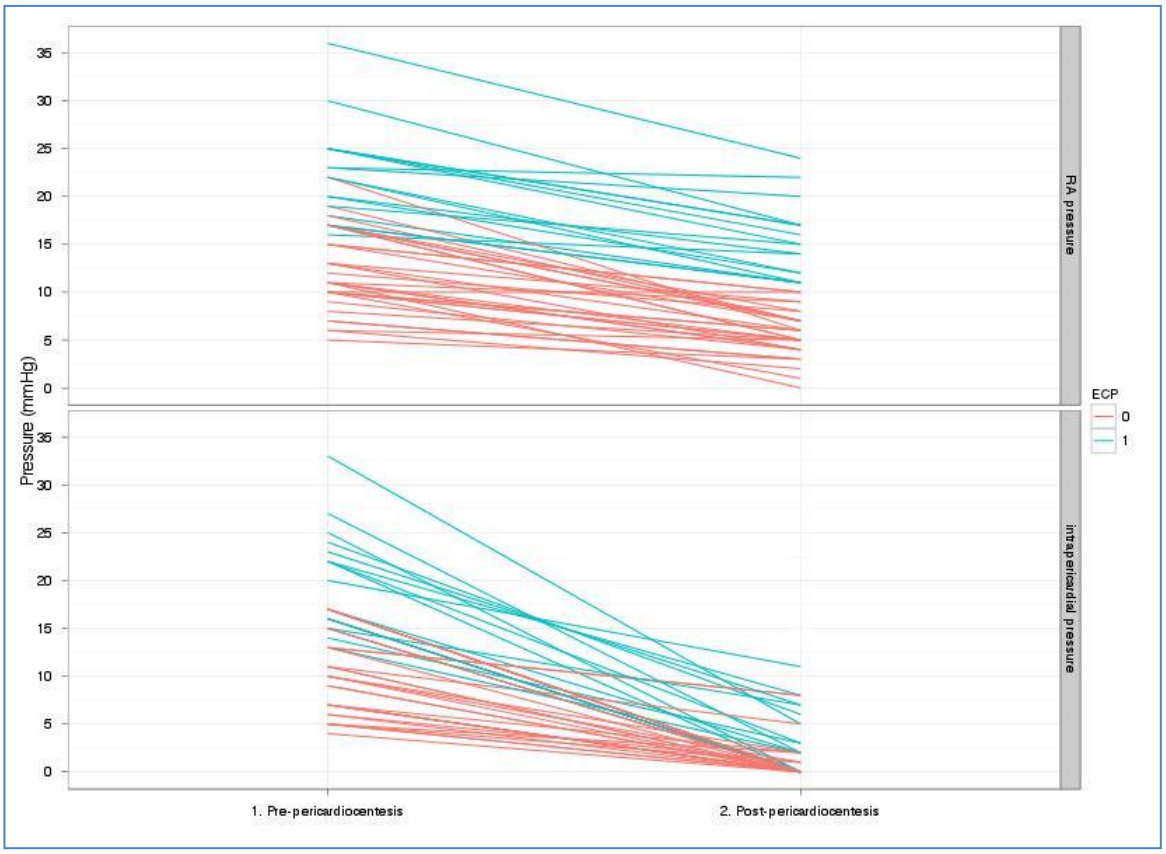


Figure 18. Change in RA pressure (top panel) and intra-pericardial pressure (bottom panel) pre and post pericardiocentesis. ECP patents in blue, non-ECP patients in red.

The two week post pericardiocentesis echocardiographic results of ECP as compared to those of non-ECP are shown in Table 7 below. The results showed that the difference was not statistically significant between the 2 groups in all 3 echocardiographic features of constriction compared.

Table 7. Two week post pericardiocentesis echocardiographic results.

Echo results	ECP +ve n (%)	ECP -ve n (%)	P-value
Thickened pericardium(n=19)	7 (36.8)	12(63, 2)	0.78
Dilated IVC(n=5)	3 (60)	2 (40)	0.62
Septal bounce(n=5)	3 (60)	2 (40)	0.62

Of 19 participants who had a thickened pericardium on echocardiography two weeks post pericardiocentesis, only 7 (36.8%), had ECP. 5 participants had both dilated IVC and septal bounce, and only 3 had ECP. The difference between the 2 groups was not significant, with p values of 0.78, 0.62 and 0.62 respectively.

Table 8. Univariate regression results*

Variable	**Coeff. Estimate**	**Std. Err**	***p*-value**
Gender (male)	-0.549	0.603	0.36
Age	0.061	0.039	0.07
HIV +ve	-1.3610	0.728	0.06
ADA #	0.00046	0.00475	0.92
Vol fluid drained	-3.674	7.257	0.96
IFN- γ CFF #	-0.00017	0.00016	0.295
Thickened pericardium #	-18.11	2284.10	0.99
Dilated IVC #	0.762	1.037	0.46
Septal bounce #	0.762	1.037	0.46
TB +ve	-1.5404	0.7278	0.034

*****ECP status (cases coded as 1) was modelled outcome against a single explanatory variable. Variables with # indicate a significantly smaller subsample in the regression model because of missing values.

Univariate regression results showed no association between HIV+ve patients and the presence of ECP. There was a positive association between TB culture positive and ECP. The regression results demonstrated that TB+ve patients were more likely to have ECP, *p*-value 0.034.

CHAPTER FIVE: DISCUSSION

There are not many studies which have been conducted to determine the prevalence and characteristics of tuberculous ECP using the gold standard haemodynamic methods. The studies previously done, such as the study by Hancock and Sagrista-Sauleda, did not focus on TB pericardial effusion. The results of this study are important because they provide novel accurate information on the prevalence of TB-associated ECP, the demographic, pericardial fluid and haemodynamic characteristics, and the potential diagnostic role of echocardiography at two weeks post pericardiocentesis. These results suggest that ECP is a common manifestation of TB pericarditis with unique haemodynamic features characterized by a high initial right atrial pressure. Furthermore, there were no significant pericardial characteristics that distinguished it definitively from non-ECP, and the two-week echocardiograph was not particularly helpful.

ECP is a very important condition that needs to be recognized, diagnosed and investigated further to increase knowledge about the condition. This is because ECP progresses to non-effusive chronic CP in less than a year in a significant proportion of patients, and CP is an important cause of heart failure (Hancock 1971). Early diagnosis of ECP may result in a decision for early pericardiectomy, preventing this progression to pericardial fibrosis and constriction (Hancock, 1971).

There is a paucity of literature about this mixed form of effusive and constrictive pericarditis, which is characterized by constriction of the heart by the visceral pericardium in the presence of tense effusion in a free pericardial space (Hancock, 1971). Confirmation of the diagnosis of the syndrome is technically challenging and time consuming. It requires the demonstration of persistent constrictive haemodynamics after evacuation of pericardial fluid and relief of tamponade by invasive haemodynamic recordings of the pressure in the right atrium and the intrapericardial space before and after the removal of fluid (Hancock, 2004). Part of the problem has been that such a procedure is not routinely performed in most hospitals, which may result in difficulty in diagnosis, leading to patients being

missed (Bonemma, 2008). This is especially true in the developing world where TB pericarditis is common and TB is the main cause of CP and a frequent cause of heart failure (Mayosi et al., 2005).

Hyung, Jong-Min, Tae, Sang-Hyun, In-Hyun, Duk-Hyun, and Jae-Kwan (2010), stated that TB pericarditis is arguably the leading cause of pericarditis in the world. However, recent studies on the diagnosis and management of pericardial disease have paid scant attention to TB (Mayosi et al., 2005). According to Babik and Chamie (2006), TB pericarditis is the most common pericardial disease in sub-Saharan Africa, with TB accounting for 50 – 70% cases of pericardial disease. However, TB only accounts for <5% of cases of pericardial disease in the developed world.

It is the author's belief, after a thorough review of the literature on ECP, that prior to this present study, the prevalence of ECP in patients with definite TB pericardial effusions was not known and had not been investigated. Reports on pericarditis caused by TB have been relatively infrequent in studies from the United States and Europe (Hancock, 2004).

In the cohort of patients (n=50), the prevalence of ECP was found to be 34%. This is much higher than that observed in the Sagrista-Sauleda et al., (2004) study. They found a prevalence of 1.3% amongst patients with pericardial disease of any type and 6.95% amongst the subgroup of patients with clinical tamponade. Unlike our study, which was limited by the relatively small sample size, these estimates were from samples of 1184 and 218 respectively. The authors did state that they expected the true prevalence to be higher than estimated as not all patients underwent catheterization. In an article by Bonnema (2008), it is stated that most cases of ECP in developing countries are often due to infectious causes such as TB. Ntsekhe, Wiysonge, Gumedze, Maartens, Commerford,Volmink and Mayosi (2008) found evidence that it is likely that ECP prevalence in patients with TB pericarditis may be much higher than in other forms of pericarditis, which have formed the basis of most studies previously done on ECP. The high prevalence of ECP in TB pericarditis

patients found in this study accurately reflects the true prevalence of ECP in TB pericarditis patients.

Pre-pericardiocentesis pressures, both right atrial and intrapericardial, were found to be higher in patients with ECP than in those without. This is in keeping with published results, such as the study of Hancock (1971).

The three echocardiographic features of constriction, studied two weeks post pericardiocentesis, could not predict the presence of ECP. They also did not show any statistical difference in both groups. However, the low number of patients studied should also be considered when interpreting these results..

In the present study, there was no significant difference in ECP prevalence between males and females, which was similar to the reports in literature. The age of the participants ranged from 29 to 44 years, with a mean of 34 years. This was lower than in the report by Sagrista-Sauleda et al., (2004), in which the mean age was 46 years.

There was no association between HIV infection and presence of ECP in the study sample. This could be because HIV infection is associated with a lower incidence of pericardial constrictions in patients with TB pericarditis, as suggested by Ntsekhe et al., (2008). There was no significant difference in HIV+ve patients between patients with and without ECP.

Again, there was no statistically significant difference in ECP prevalence between TB+ve and TB-ve patients, looking at the results of all three tests performed to confirm TB+ve. The regression results demonstrated that TB culture +ve patients are more likely to have ECP.

The overall results of this study showed that, in settings where the prevalence of TB pericarditis is high, ECP was more common than expected. These findings are important because they suggest that more of an effort should be made to look for and diagnose ECP in high TB pericarditis settings where a higher prevalence of ECP is likely to be found. These findings should encourage most centres to perform right

atrial pressure and intrapericardial pressure measurement at time of pericardiocentesis.

Echocardiographic parameters in this study did not identify predictors of ECP. However, a larger study may be able to establish echocardiographic predictors of ECP. There are currently no published diagnostic criteria for ECP using echo (Ntsekhe et al., (2008); thus a big study may assist to establish them.

Determination of echocardiographic parameters that can predict the presence of ECP will ensure that patients' diagnosis is not missed and appropriate treatment can be prescribed. Knowing that the patient has ECP helps the physician to decide on the appropriate treatment for the patient, which can vary from consecutive medical therapy to a pericardiectomy by means of thoracotomy.

Study limitations

Despite the attempt to enrol consecutive patients, this was not always possible. Full haemodynamic data could not always be collected for a number of reasons, including the following: (a) not all patients had pressure measurements during pericardiocentesis because of staff constraints; (b) the researcher was not able to be present during all examinations; (c) some of the patients did not have a full echocardiogram study as they were admitted as an emergency, while some did not have a full echocardiogram post pericardiocentesis because they had to be transferred to their referring hospital immediately after the procedure. This inability to enrol consecutive patients may have introduced some selection bias. The sample size was fairly small and hence limited the power to detect small differences in groups.

CHAPTER SIX: CONCLUSION

To the best of my knowledge this study represents the first attempt to determine the prevalence of tuberculous ECP by systematically using the gold standard method of direct measurements of the right atrial and intra-pericardial pressures before and after pericardiocentesis, in a prospective cohort of patients with confirmed tuberculosis. Additional questions were addressed in this study included: (a) what are the demographic and pericardial fluid characteristics of patients with ECP, and are they different from patients without? (b) what is the role of echocardiography in establishing the diagnosis in the early post pericardiocentesis period?

From the results of this study several important conclusions can be drawn. First and foremost is that TB-related ECP is a relatively common presentation of patients with large TB pericardial effusions. 35% of patients had confirmed ECP, much higher than reported in previous reports. The second conclusion was that there are no major differences in demographic and pericardial fluid characteristics between those patients with ECP and those without ECP, and therefore no simple variables which predict the presence of this condition. The third and final conclusion was that the three commonly used echocardiographic variables used to assess patients for the presence of constrictive physiology, correlated poorly with a haemodynamically confirmed diagnosis of ECP.

Until this study, prevalence of tuberculous ECP in patients was unknown, as there has never been a formal study to address this question. The issue is important because the available evidence suggest that patients who present with this condition are at a significant risk of progressing to chronic constrictive pericarditis, and several authors recommend prophylactic pericardiectomy when the condition is recognised. The largest study to determine the prevalence of the condition was conducted predominantly in idiopathic pericarditis, which is associated with a very low incident

of future chronic constrictive pericarditis. Tuberculosis on the other hand is associated with a relatively high incidence of chronic constrictive pericarditis, and for this reason the hypothesis of the study was that ECP would be relatively common.

Not all patients presenting with large tuberculous pericardial effusions are likely to undergo a detailed haemodynamic assessment as was performed in this study. For this reason it was important to determine if there were major demographic and pericardial fluid characteristic differences between patients with and those without ECP. No significant differences in a number of variables were demonstrated.

Finally, echocardiography is widely available but its diagnostic accuracy for this condition in the pre-pericardiocentesis period is known to be poor. What remained unknown prior to this study is the diagnostic utility of echocardiography for ECP in the post pericardiocentesis period. This study suggests that three simple variables correlated poorly with the diagnosis. In view of the potential importance of TB ECP and its impact on the natural history and long-term outcomes of TB pericarditis, the finding of this study that the condition is common, opens the field for further research to understand the mechanisms or disease, pursue non-invasive therapeutic options and to try and establish a simple non-invasive widely available method of establishing the diagnosis.

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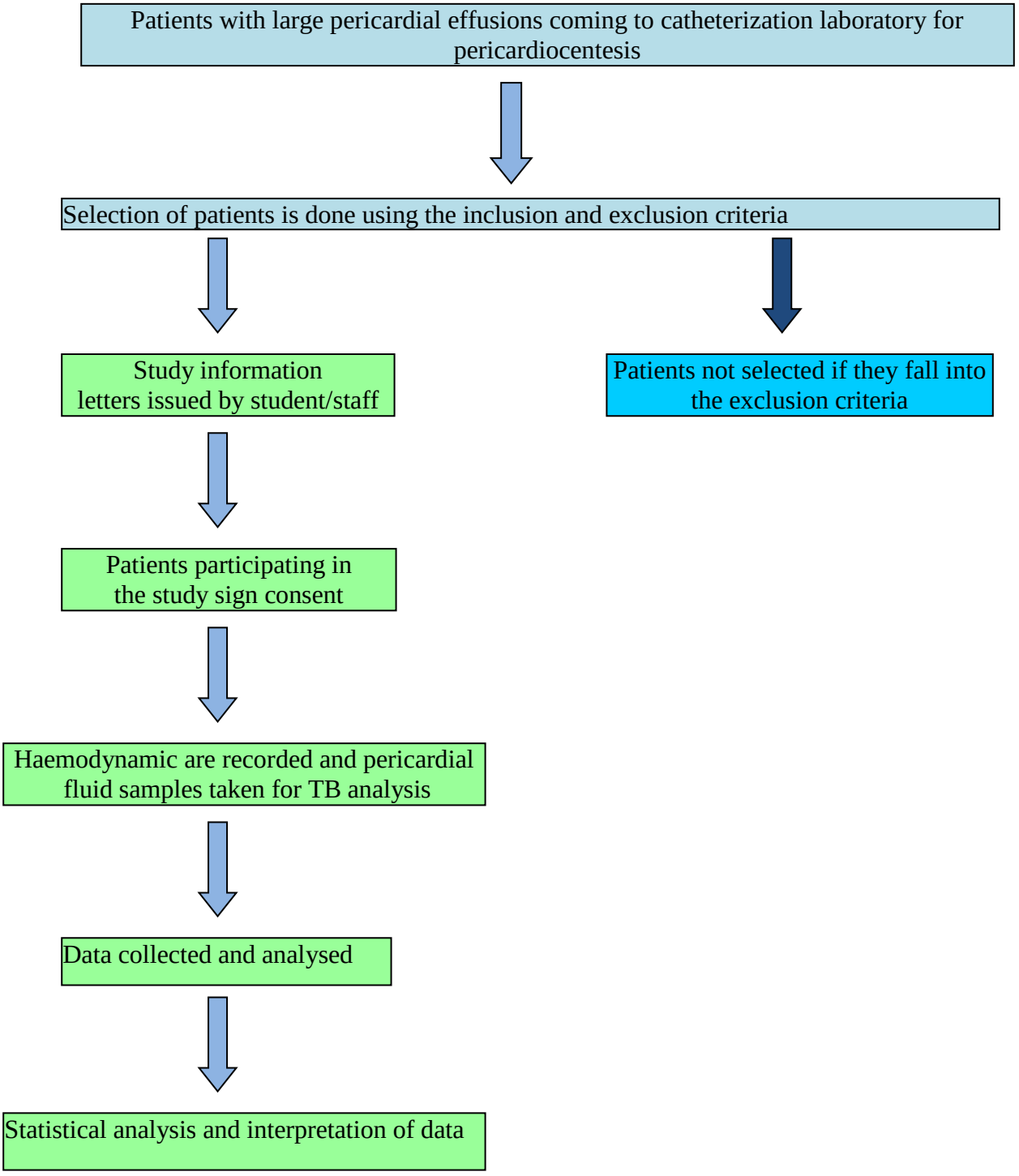
APPENDICES

APPENDIX A

FLOW CHART- SUMMARISING THE RESEARCH PROCESS



APPENDIX B

Information Letter and Consent

Title of the Research Study:

The occurrence of ECP (ECP) of Tuberculosis (TB) origin in a cohort of patients with large pericardial effusions.

Principal Investigator:

Miss A.L. Motete, student in Master's Degree: Clinical Technology (Cardiology) at Durban University of Technology.

Brief Introduction and Purpose of the Study:

ECP is a disease of the heart caused by accumulation of fluid within the layer covering the heart (pericardium), resulting in the heart constricting and unable to pump well even after the fluid has been removed. This study aims to determine the prevalence of this disease and how helpful an echocardiogram (heart sonar) is, in diagnosing this disease.

Outline of the Procedures:

People with large pericardial effusions will be invited to participate in the study. You will be transferred to the Cardiac Clinic, Groote Schuur Hospital, Cape Town. When you arrive, a cardiac doctor will take your medical history, examine you and arrange for you to have a chest X-ray; and electrocardiogram, an echocardiogram (which is "heart scan" method of examining the heart using sound waves) as well as blood tests.

You will be required to sign consent for the pericardiocentesis (draining of fluid around the heart muscle) as well as consent for the study.

You will then be taken to the cardiac catheterization laboratory where a pericardiocentesis (draining of fluid around the heart) as well as right atrial and intrapericardial pressure measurement will be done simultaneously. During the pericardiocentesis a catheter (a small pipe) is inserted through the upper edge of your abdominal wall into the heart sac and the fluid inside is drained. Intra-pericardial pressure will also be measured using the same catheter. A second catheter will be inserted in your femoral to the heart to measure the right atrial pressure.

A sample pericardial fluid and blood collected during the test will be sent to the laboratory for analyses, to determine if you have TB.

You will be sent to the cardiac ward where an echocardiogram will be done within 24 hours of the pericardiocentesis to assess the results.

You will be watched in hospital for half a day afterwards to make sure everything is alright. No extra visits will be required.

Risks or Discomforts to the Subject:

There will be no risk to the participants, as all the tests being conducted as part of this study are recommended in all patients with pericardial effusion and represent the best international standard of care.

Benefits:

The new information gained from the study will help to improve diagnosis and treatment of patients with ECP. This diagnosis is believed to be missed or under diagnosed, and therefore, it is believed that patients do not receive relevant adequate treatment.

Reason/s why the Subject May Be Withdrawn from the Study:

The subject may be withdrawn from the study if unable to obtain cardiac pressures during the pericardiocentesis.

Remuneration:

There will be no remuneration given to the participant.

Costs of the Study:

The participant will be liable for the normal costs for the routine medical procedures needed; no extra costs will be added for the research.

Confidentiality:

Participants will be identified by a code and not by name. Their details will be kept confidential in a subject file, which will be stored in a locked office in the Department of Cardiology, Groote Schuur Hospital.

Research-related Injury:

There will not be any research- related injuries.

Persons to Contact in the Event of Any Problems or Queries:

Miss Lerato Motete	Prof Jamila Adam	Dr. Mpiko Ntsekhe
Principal Investigator	Supervisor	Supervisor
021 4044094	031 373 5291	021 4046090

Statement of Agreement to Participate in the Research Study:

I_____ subject's full name,

ID number_____ have read this document in its entirety and understand its contents. Where I have had any questions or queries, these have been explained to me by _____ to my satisfaction. Furthermore, I fully understand that I may withdraw from this study at any stage without any adverse consequences and my future health care will not be compromised. I, therefore, voluntarily agree to participate in this study.

Subject's name: _____Subject's signature: _____Date: _____

Researcher's name: **_____Researcher's signature**: **_____ Date: _____**

Witness name: **_____Witness signature: _____Date:_____**

APPENDIX C (Information letter and consent in IsiXhosa)

Incwadi yokuchaza nesivumelwano

Isihloko socwaningo

Ukuvama kwesifo se-ECP, kubantu abasoleka ngokuba nesifo sephepha.

Umncwaningi

U Nks. A.L. Motete, umfundi we-Master's Degree: Clinical Technology (Cardiology) e- Durban University of Technology.

Incazelonenjongoyocwaningo.

Isifo i-ECP sisifo esibangwa ukwanda kwamanzi ajikelaza inhliziyo, esenza ukuba inhliziyo icinane yaye ingakwazi ukubetha kakuhle. Olucwaningo lujonge ukuhlola ukuba sande kangakanini esisifo kubantu abanesifo sephapha, kanye nokujonga ukuba inceda kangakanani i-echorcardiograme ukufumani esisifo.

Uvavanyo lwentliziyo:

Simema abantu abanesifo samanzi ajikeleza intliziyo esibangw asisifo sephepha ukuba bathabathe inxaxheba koluphando. Uzakuthi uthunyelwe kwicandelo lesifo sentliziyo kwisibhedlela saseGroote Schuur, eKapa. Ekufikeni kwakho ugqirha uzakukujonga imbali yokugulakwakho, akuxilonge, alungisele ukubaujongwe ukubethakwentliziyo, ukusebenzakwentliziyo kunye novavanyo lwegazi.

Uzakutshikitsha isivumelwano sokutsalwa kwamanzi entlizini, uvavanyo kanye nokuba ingxenye yophando.

Uzakuyiswa egumbini labucala elilungiselwe ukuvavanywa nokutsalwa kwamanzi kwintliziyo. Kuyakuthi kutsalwe amanzi akwintliziyo. Inaliti iyawufakwa kudonga olungasentliziyweni kanye nasemlenzeni, kutsalwei ncindi namanzi akwintliziyo, ukuphand angakumbi. Kuzakuthi kujongwe nokubetha kwentliziyo.

Emva kokuba sekwenziwe konke okhu, uzakuya egumbini lwentliziyo, apho uzakwenziwa uvavanyo lokukhangela ukusebenz akwentliziyo (i-echocardiogram). Emvakwakho uzakukhululwa ukuba uye ekhaya. Loluphando aluding iukuba ubuyele esibhedlela uzokwenz aolunye uvavanyo,

Ubungozi

Ukuba yingxenye yoluphando akuzukufaka impilo yakho engozi, ngokuba konke ukuhlolwa okuzokwenziwa kuyingxenye yokwelashwa kwesisifo ngokomgangatho kazwelonke.

Umvuzo:

Ulwazi olutsha esizakulifumana lwawukwenza sizame ukuphucula unyango lwesisifo.

Isizathu sokuba ungakhutshwa koluphando:

Isiguli singakhutshwa koluphando uma ezinye inchukatsh angesifo zingafumaneki.

Ukubhatalwa:

Akukho mvuzo wemali ofumanekayo ngokuba ingxenye yoluphando.

Imali ozakuyibhatala ngoluphando

Awuzubhatalaanto koluphando

Imfihlakalo:

Yonk eincukacha neziphumo ziyawugcinwa ngokufihlekileyo kwisibhedlela iGroote Schuur eKapa. Igama lomguli alizikusetshenziswa.

Ukonzakala okumayelan anophando:

Uphando alukubeki encupheni yokonzakala nangaluphi uhlobo

Abantu ongabathinta mayelana nemibuzo okanye ingxaki ngoluphando:

Nksz Lerato Motete	Prof Jamila Adam	Dr. Mpiko Ntsekhe
Umphandi	Umhloli	Umhloli
021 4044094	031 373 5291	021 40406090

Isivumelwano sokuthabatha inxaxheba koluphando:

(Mna_____(igama lakho ngokugcwele)

(inombolo yomazisi (ID)_____ndifundile futhi ndiyaqonda lencukacha yoluphando. Apho ndinemibuzo, ndiyendafumana incazelo egculisayo ku_____ ngaphezukokho ndiyaqonda ukuba ndingayeka ukuba ingxenye yophando ngaphandle kokuphazamiseka konyangolwami.

Ndiyavuma ukuba yingxenye yoluphando.

.

Igamalomguli: _____Tyikitya: _____Usuku: _____

Iingqina: _____Tyikitya: _____Usuku: _____

Umphandi: _____Tyikitya: _____Usuku:_____

APPENDIX D (information letter and consent in Afrikaans)

Inligting Brief en toestemming

Titel van die Studie

Die voorkoms van oordrewe konstriktiewe perikarditis van tuberkulose (TB) oorsprong in 'n groep van pasiënte met 'n groot perikardiale effusies.

Hoofnavorser

Mej AL Motete, student in Meestersgraad Kliniese Tegnologie (Cardiology) by Durban Universiteit van Tegnologie.

Kort inleiding en doel van die studie

Oordrewe konstriktiewe perikarditis is 'n siekte van die hart wat veroorsaak word deur opeenhoping van vloeistof in die laag van die hart (perikardium), wat die hart beklem en dus in hie staat is om goed te pomp nie , selfs nadat die vloeistof verwyder is. Die doel studie van hierdied is om die voorkoms van die siekte en die nuttigheid van 'n echocardiogram (hart sonar) in die diagnose van die siekte te bepaal.

Gee 'n oorsig van die prosedures

Mense met groot perikardiale effusies sal genooi word om deel te neem aan die studie. Jy sal geheem word na die Hart-Clinic, Groote Schuur Hospitaal, Kaapstad. Wanneer jy daar aankom, sal 'n hart dokter jou mediese geskiedenis neem, en jou en daar saldat jy ‘n reël vir jou 'n borskas X-straalkry. ‘n elektrokardiogram, 'n ekocardiogram kry as okk bloedtoeste.

U sal verwag word om toestemming te teken vir die perikardiosentesis (dreinering van vloeistof rondom die hart spiere) asook toestemming vir die studie. U sal dan geneem word na die hartkateters laboratorium, waar 'n perikardiosentesis (dreinering

van vloeistof rondom die hart) sowel as regteratriale en intrapericardial druk meeting gelyktydig gedoen sal word. Tydens die pericardiocentesis 'n kateter ('n klein pyp) is ingevoegword, deur die boonste rand van die abdominale wand, na tot binne in die hartsak en die vloeistof binne gedreineer word. Intra-perikardiale druk sal ook gemeet word deur dieselfde kateter. 'N Tweede kateter sal plaas word u in femorale veen na die hart toe waar die reg atriale druk gemeet.

'N monster perikardiale vloeistof en bloed wat ingesamel is tydens die toets sal gestuur word na die laboratorium vir ontleding, om te bepaal of u TB het.
U sal gestuur word aan die hart saal waar 'n ekocardiogram binne 24 uur van die perikardiosentesis gedoen sal word die resultate te beoordeel.
U sal gekyk word in die hospitaal vir 'n halwe dag na die prosedure om seker te maak alles is in orde. Geen ekstra besoeke sal van u verwag word nie.

Risiko's of ongemak aan die onderwerp

Daar sal geen risiko vir die deelnemers wees nie , die toetse wat gedsen word is deel van hierdie studie gedoen word aanbeveel in alle pasiënte met perikardiale effusie en verteenwoordig die beste internasionale standaard van sorg.

Voordele

Die nuwe inligting wat uit die studie sal help om die diagnose en behandeling van pasiënte met oordrewe konstriktiewe perikarditis te verbeter. Hierdie diagnose daar ward geglo gemis of word verkeerd gediagnoseer word, en daarom word geglo dat pasiënte nie ontvang nie relevant voldoende behandeling.

Rede waarom die deelnemer onttrek kan word uit die studie

Die deelnemer nag onttrek word uit die studie, indien daar die druk te kry tydens die volgende verkry word gedurende die perikardiosentesis nie.

Vergoeding

Daar sal geen vergoeding gegee word aan die deelnemer nie.

Koste van die Studie

Die deelnemer sal verantwoordelik wees vir die normale koste vir die roetine mediese prosedures wat nodig is, geen ekstra koste sal bygevoeg word vir die navorsing nie.

Vertroulikheid

Deelnemers sal geïdentifiseer word deur 'n kode en nie by die naam. Hulle besonderhede sal vertroulik gehou word in 'n vak lêer, wat in 'n geslote kantoor in die Departement van Kardiologie, Groote Schuur Hospitaal gestoor sal word.

Navorsing-verwante besering daar geen navorsing-verwante beserings wees nie.

Persone te kontak in die geval van enige probleme of navrae

Mej Lerato Motete	Prof Jamila Adam	Dr Mpiko Ntsekhe
Hoofnavorser	Oorsiener	Oorsiener
021 4044094	031 373 5291	021 4046090

Verklaring van die ooreenkoms om deel te neem in die Studie

Ek_____ (volle naam),

ID nomer _____ het hierdie dokument in sy geheel en die inhoud daarvan verstaan. Waar ek enige vrae gehad hierdie aan my verduidelik deur _____ tot my tevredenheid. Ek verstaan ook dat ek kan ontrek van hierdie studie op enige stadium sonder enige nadelige gevolge en my toekoms gesondheidsorg sal nie benadeel word. Ek het dus vrywillig in gestem om deel te neem in hierdie studie.

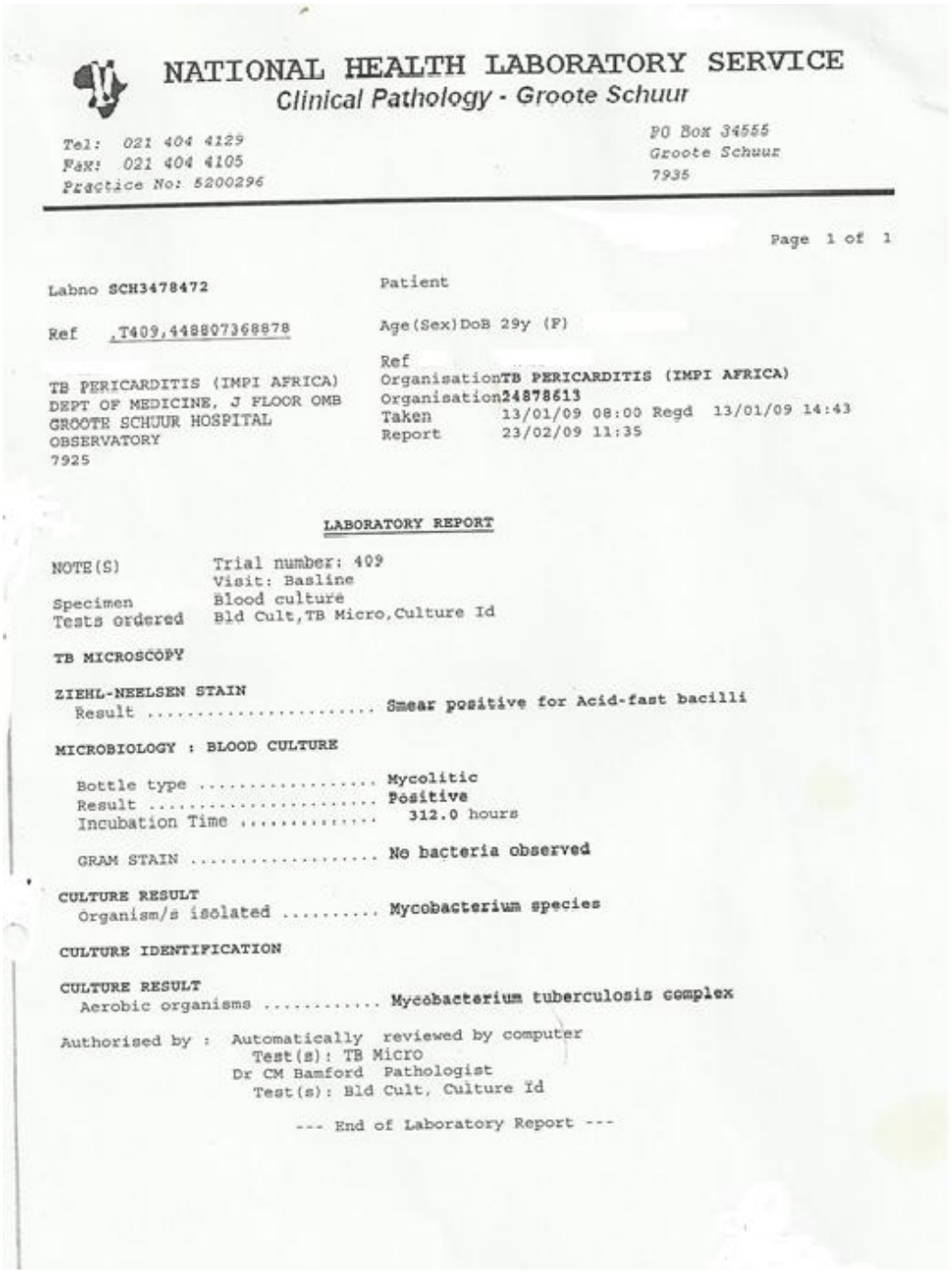
Onderwerp se naam_____ handtekening _____ Datum _____

Navorser se naam _____ handtekening _____ Datum _____

Getuie naam _____ handtekening _____ Datum _____

APPENDIX E

Laboratory analyses sample



NATIONAL HEALTH LABORATORY SERVICE
Clinical Pathology - Groote Schuur

Tel: 021 404 4129
Fax: 021 404 4105
Practice No: 5200296

PO Box 34555
Groote Schuur
7935

Page 1 of 1

Labno SCH3478472

Ref ,T409,448807368878

TB PERICARDITIS (IMPI AFRICA)
DEPT OF MEDICINE, J FLOOR OMB
GROOTE SCHUUR HOSPITAL
OBSERVATORY
7925

Patient

Age(Sex)DoB 29y (F)

Ref
Organisation TB PERICARDITIS (IMPI AFRICA)
Organisation 24878613
Taken 13/01/09 08:00 Regd 13/01/09 14:43
Report 23/02/09 11:35

LABORATORY REPORT

NOTE(S) Trial number: 409
Visit: Basline
Specimen Blood culture
Tests ordered Bld Cult,TB Micro,Culture Id

TB MICROSCOPY

ZIEHL-NEELSEN STAIN
Result ..... Smear positive for Acid-fast bacilli

MICROBIOLOGY : BLOOD CULTURE

Bottle type ..... Mycolitic
Result ..... Positive
Incubation Time ..... 312.0 hours

GRAM STAIN ..... No bacteria observed

CULTURE RESULT
Organism/s isolated ..... Mycobacterium species

CULTURE IDENTIFICATION

CULTURE RESULT
Aerobic organisms ..... Mycobacterium tuberculosis complex

Authorised by : Automatically reviewed by computer
Test(s): TB Micro
Dr CM Bamford Pathologist
Test(s): Bld Cult, Culture Id

--- End of Laboratory Report ---

Pericardial Fluid ADA results

NATIONAL HEALTH LABORATORY SERVICE

GSH Ward Enquiries Server

Tel: 021 404 4129
Fax: 021 404 4105
Practice No: 5200296

PO Box 34555
Groote Schuur
7935

Labno SCH3286499

Patient

Ref ,ACI1454

Address 16 PINTAIL CRESCENT
ZEEKOEIVLEI
GRASSY PARK,7941

C26 Coronary Care ICU
GROOTE SCHUUR HOSPITAL
OBSERVATORY
CAPE TOWN
7925

Age(Sex)DoB 32y (F) 22/04/1976

Ref Dr

Ward-Hosp C26 Coronary Care ICU
GROOTE SCHUUR HOSPITAL

Ward-Hosp 19836212

Taken 02/10/08 (*) Regd 02/10/08 17:19
(*)=Collection time not stated

Report 10/03/09 09:24 1st 07/10/08 10:25

LABORATORY REPORT

NOTE(S) Time of collection not stated
Specimens Fluid
PERICARDIAL
Tests ordered WCC,RCC,F Cells,Interpret,Fluid,f - ADA

CHEMISTRY TESTS		Flags	Ref Ranges
F-Adenosine Deaminase	55.0 U/l		

INTERPRETATION
Ascitic fluid :ADA activity >30 U/l is suggestive of TB
Pleural/Pericardial Fluid:ADA activity >30 U/l with a predominance of lymphocytes suggests TB or malignancy, while ADA activity of >30 U/l with a predominance of neutrophils suggests an infective origin