The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.

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As the candidate's supervisor I have approved this thesis for submission.

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Executive Summary

Constrictive Pericarditis (CP) is an uncommon condition which is a known treatable cause of heart failure. It is a condition that affects people from both developed and developing countries. In developed countries the aetiology of CP has undergone a paradigm shift away from infectious causes such as tuberculosis to acquired causes such as previous cardiac surgery and mediastinal radiotherapy for cancer. In the developing world by far the commonest cause remains tuberculosis. All aspects of CP have been widely studies in developed countries however there is limited data and studies on the condition from developing countries and more specifically African countries where tuberculosis is endemic.

In South Africa the HIV/AIDS pandemic in association with persistent widespread poverty and poor socio-economic conditions has ensured that the incidence of tuberculosis infection remains exceedingly high. There have been numerous studies done evaluating the incidence, pathophysiology and treatment of tuberculous pericarditis in the HIV era. There however very limited data available describing CP in a South African setting.

The objectives of this single centre study are to contrast the clinical profiles; surgical outcomes and short term follow up of patients diagnosed with CP at Inkosi Albert Luthuli Hospital. Through this study we hope to gain insight into the effects of HIV on patients with CP and determine whether it has any influence on the natural history and outcomes when compared to HIV uninfected individuals.

It is hoped that information gained from this study will serve to further assist medical professionals in their understanding of CP and aim to improve both our management of patients with this debilitating condition and ultimately there life expectancy. In addition it is hoped that that study might serve as a catalyst for larger prospective studies in this field. Results missing (abstract) i.e aim, method, conclusion

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Part 1: The Review of Literature

1. INTRODUCTION

Constrictive pericarditis (CP) is a chronic debilitating condition which causes restricted heart filling and results in heart failure causing significant morbidity and mortality(1, 2). Importantly it remains one of the few treatable causes of heart failure and pericardectomy can be curative in the majority of patients (2, 3). Despite a noticeable paradigm shift in aetiology in developed countries where previous cardiac surgery and radiation therapy have become predominant causes, in South Africa and many other developing countries tuberculous pericarditis remains the main cause (1, 4-6). This is largely due to co-existing HIV epidemic which has continues to fuel a resurgence in all forms of tuberculosis. The impact of HIV on the clinical profile and surgical outcomes of patients undergoing pericardiectomy has not been well studied. Whilst medical therapy is warranted in a selective group of patients with transient constrictive pericarditis, the definitive treatment for CP is surgical pericardiectomy for which the mortality rates remain high between 5- 15% (4, 5, 7-10).

2. PERICARDIAL ANATOMY AND PATHOPHYSIOLOGY OF CONSTRICTION

The pericardium is a fibrous, fluid-filled sac that surrounds the heart and the origin of the great vessels. It consists of two layers, the visceral pericardium which is adherent to the epicardial surface of the heart, and the parietal pericardium which is a 2mm thick fibrous layer surrounding the heart. Pericardial fluid is secreted into the pericardial cavity providing lubrication between the two layers of pericardium. The pericardium can exert a found profound hemodynamic effect on the heart especially in situations where it becomes diseased (1,2). There are a variety of diseases that can involve the pericardium and these can result in a number of different clinical presentations

including: acute pericarditis, chronic pericarditis, pericardial effusion with or without tamponade and constrictive pericarditis (2).

In CP the thickened, fibrotic and at times calcified pericardium results in restricted diastolic filling of the heart (1). The restriction to filling results in elevation and equalization of filling pressures in all heart chambers including the inferior and superior vena cava and the pulmonary veins. The resultant high atrial pressures result in abnormal early and rapid filling of the both ventricles. As a result of early ventricular filling (occurring during early to mid-diastole) as well as the limitation imposed on ventricular expansion by the thickened pericardium, ventricular filling ceases in early diastole when the ventricles reach their volume limit as determined by the thickened pericardium.(1,3,11,12) This means that ventricular filling is almost entirely limited to early diastole. The main consequences of this restricted diastolic filling are twofold: firstly impaired right heart filling results in systemic venous congestion producing signs of hepatomegally, ascites, peripheral oedema and at times anasarca and even cardiac cirrhosis. Secondly, impaired diastolic filling results in a reduced stroke volume and cardiac output which produce dyspnoea, muscle loss and cachexia.

An important breakthrough in the understanding of the pathophysiological effects of CP was discovered in 1989 by Hatle et al who described the effects of dissociation of intrathoracic and intracardiac pressures as well as the influence of enhanced ventricular interaction.(1) Dissociation of intrathoracic and intracardiac pressure produces inspiratory variation in diastolic filling pressure across the mitral valve (1). On inspiration the decrease in intrathoracic pressure is not transmitted to the left heart chambers therefore producing a lower pulmonary venous to left atrial pressure gradient. This results in a decrease in the transmitral blood flow and underfilling of the left ventricle (1-3, 12). Enhanced ventricular interaction is also a direct result of the restriction to diastolic filling imposed by a thickened rigid pericardium (1-3,12). During inspiration underfilling of the left-sided chambers is accompanied by reciprocal increased right ventricular filling and leftward displacement

of the interventricular septum (1). The opposite occurs during expiration with decrease in right ventricular filling and increased left ventricular filling resulting in rightward displacement of the interventricular septum. These respiratory related changes in ventricular filling can be seen on echocardiography help distinguish CP from restrictive cardiomyopathy (1).

Ventricular ejection fraction in not normally affected in CP, however in cases where there has been longstanding chronic constriction, fibrosis and calcification may extend beyond the pericardium to the epicardial tissue(3). In these cases fibrosis and scarring of the myocardium occurs, and in patients with longstanding chronic pericardial constriction, it can result in myocardial atrophy which can have a direct effect on myocardial contraction (12). If the fibrosis and calcification is severe enough myocardial involvement may result in impaired myocardial contractility which can predispose to poorer outcomes following pericardiectomy. (12) This was highlighted by Seferovic et al who reported a series where pericardiectomy was withheld from patients who had documented myocardial fibrosis and atrophy which resulted in a decrease in mortality from 40% to 5% (12).

3. EPIDEMIOLOGY

Constrictive pericarditis is a rare condition which is frequently misdiagnosed and in resource limited settings potentially not diagnosed at all (12). These observations may have a significant on the true epidemiology of the condition and is likely to have resulted in significant under reporting of cases which are frequently mistaken for other causes of heart failure. Pericardial constriction may develop after an initial episode of acute or subacute pericarditis of any aetiology and has been found to occur more commonly in males when compared to females with a ratio 2.04:1 (3). There are limited studies correlating the risk of progression from acute pericarditis to chronic CP. In a prospective study by Imazio et al. 500 consecutive patients with acute pericarditis were evaluated to determine

the incidence of progression to developing CP. (13) They determined the following incidence rates for various different aetiologies of acute pericarditis (Table 1):

Table 1: Comparative incidence rates as characterised by aetiology

Aetiology	Cases/ 1000 person-years
Idiopathic/viral pericarditis	0.76
Connective tissue disease/pericardial injury syndrome	4.40
Neoplastic pericarditis	6.33
Tuberculous pericarditis	31.65
Purulent pericarditis.	52.74

(13)

In addition to the above findings it was noted that of the initial cohort, only 9 (1.8%) patients progressed on to develop chronic CP with a further 75(15%) developing transient CP which resolved over three months(13). Due to the small number of patients who develop CP it was not possible to determine statistically significant predictors of progression but patients who developed CP were noted to have had: a fever >38oC, incessant course, large pericardial effusion, nonviral non/non idiopathic aetiology, cardiac tamponade and failure to response to non-steroidal drugs after a week of treatment (13).

4. AETIOLOGY OF CONSTRICTIVE PERICARDITIS

Over the last two decades there has been a significant shift in the epidemiology of CP in the developed world. (Table 2) There has been a documented declining incidence of infectious aetiologies such as tuberculous constriction, with iatrogenic causes such as previous cardiac surgery

and mediastinal radiation becoming the commonest causes of constriction. (4, 5, 8). In South Africa however; along with other developing countries in Sub-Saharan Africa, India and Asia; tuberculous pericarditis remains the leading cause of CP (6). It has been estimated that between 17%-60% of patients diagnosed with tuberculous pericarditis progress to develop chronic constriction (14-16). Over recent years there has been a significant focus of attention on tuberculous pericarditis with numerous studies undertaken profiling the disease and attempting to explain and understand the pathogenesis of the development of constriction from acute tuberculous pericarditis (16, 19, 22-24).

Table 2: Aetiology of constrictive pericarditis in major series

Investigator	**Country**	**Study period**	**n**	**Causes**
Bertog et al(5)	USA	1977- 2000	163	Idiopathic/Viral 46%, Post surgery 37%, mediastinal irradiation 9%, tuberculosis 3.6%
Ling et al(4)	USA	1985-1995	135	Cardiac surgery 18%, Pericarditis 16%, Mediastinal irradiation 13%, Infectious 2.9%
Szabo et al(10)	Germany	1985-2012	89	Idiopathic 55%, Cardiac Surgery 23.6%, Tuberculosis 5.6%, medistinal radiation 5.6%
George et al(17)	USA	1995-2000	98	Idiopathic 44%, Post cardiac surgery 30%, Post radiation 17%, Infectious 1%, Tumour 3%
Chowdry et al(7)	India	1985-2004	395	Tuberculosis 88.9%, Previous cardiac surgery 2.36%, Malignancy 1.05%
Mutayaba et al(6)	RSA	1990-2012	121	Tuberculosis 90%, Idiopathic 5%, Miscellaneous 4%
Zhu et al(9)	China	1990-2012	165	Idiopathic 64%, Tuberculosis 23%, Previous cardiac surgery 11%, Infection 1%
Gopaldas et al (8)	USA	1998-2008	3851	No causes given

4.1 Tuberculous Pericarditis

In Sub-Saharan Africa the ongoing HIV/AIDS epidemic has resulted in a resurgence in pulmonary tuberculosis and its extra- pulmonary manifestations including tuberculous pericarditis (3). The incidence of TB pericarditis has been reported to be between 80,000 – 160,000 cases per year (18). In 2011 the WHO declared half a million active TB cases in South Africa. Amongst these individuals, 60% (300,000) had co-infection with HIV. In 2012, HSRC reported that 6.4 million South Africans were living with HIV (12.2%). These figures highlight the large burden that these conditions are placing on the health system in South Africa. It is therefore not surprising that tuberculous pericarditis is the commonest cause of pericarditis in Sub-Saharan Africa (14). Reuter et al identified tuberculous pericarditis as the aetiology of 69.5% of patients diagnosed with a pericardial effusion in a single series cohort between 1995 and 2001 (19). Of the patients with a confirmed tuberculous aetiology, only 2 out of 162 patients (1.23%) progressed to develop CP. (19)

The pathogenesis of tuberculous pericarditis has been well described (14, 20, 21). TB bacilli typically infiltrate the pericardium via one of three routes: inoculate of the lungs with retrograde lymphatic spread, contiguous local spread from a lung focus or haematogenous dissemination from a distant infectious site (20, 21). Tuberculous pericarditis has been shown to progress through four different pathological stages: a dry stage with predominate fibrinous exudates; an effusive stage with predominate lymphocytic exudates; resorptive stage with organisation, thickening and fibrosis and finally a constrictive phase (20).

Once the bacteria have infiltrated the pericardium, it is the intensity of the host's immune response that defines the accompanying clinical progression and the severity of the disease process (20).

In South Africa TB pericarditis has to be considered as the most likely cause in any patient diagnosed with a pericardial effusion. The reality is though that in resource limited settings where the vast

majority of patients with pericardial effusion present, the diagnosis can be challenging to prove. The gold standard remains direct identification of acid fast bacilli (AFB) in either pericardial tissue or fluid culture or from adjacent alternate sites via sputum or lymph node examination (20). The sensitivities and specificities of AFB culture from pericardial fluid have been reported to be between 0-75% depending on the culture medium used (20). Sputum positive cultures have been documented to be between 10 & 55% (16, 20). Recently, rapid mycobacterium tuberculosis PCR tests have become available with reported sensitivities being 80% and 15% for tissue specimens and fluid specimens respectively (21).

The introduction of antituberculous chemotherapy resulted in a dramatic improvement in the treatment of tuberculous pericarditis with a marked improvement in survival (14, 20). Prior to the introduction of antituberculous chemotherapy mortality of tuberculous pericarditis was in the region of 80-85% (19). Since the introduction of standard short course therapy mortality from tuberculous pericarditis has dropped to 17%-40%, and failure to treat patients with effusive CP results in approximately 90% of cases that survive progressing to develop CP (21).

The use of adjunctive corticosteroid therapy to treat tuberculous pericarditis has been controversial (21). In 2014 Mayosi et al published the first large prospective cohort of 1400 patients diagnosed with tuberculous pericarditis in which he showed that adjunctive therapy with prednisolone reduced the incidence of constrictive pericarditis and hospitalization (22). Despite the standardization of treatment regimens for tuberculosis across the world, in Sub Saharan Africa and especially in South Africa we are still faced with large numbers of patients diagnosed with tuberculous pericarditis progression to develop constriction. The precise characteristics of what causes patients with tuberculous pericarditis to progress and develop constriction remains poorly understood. Clearly there is differing immune responses to the TB bacillus and those individuals who have persistent and

aggressive inflammation with large effusions have been reported to have an increased likelihood of progressing to develop chronic constrictive pericarditis (13).

5. IMPACT OF HIV ON TUBERCULOUS PERICARDITIS & PROGRESSION TO CONSTRICTION

Ntsekhe et al have reported on the profound effect that HIV infection has had on the natural history of tuberculous pericarditis (14). Tuberculous pericarditis has been shown in previous studies to account for more than 85% of pericardial effusions in HIV positive individuals (19). In the setting of co-infection with HIV, tuberculosis produces a more disseminated infection with multiorgan involvement resulting in higher morbidity and mortality (14). Additionally, it has been reported to be associated with a higher incidence of myocardial involvement leading directly to impaired myocardial contractility (25). The actual effect of HIV on the incidence of constrictive pericarditis, however, still remains undetermined (3, 6). Ntsekhe et al conducted a prospective observational study in 2008 which proposed that HIV infection is associated with a reduced incidence of the development of constrictive pericarditis (26) In this study a total of 185 patients with suspected tuberculous pericarditis were enrolled and commenced on anti-tuberculous therapy. Of the 185 patients none of the 33 HIV seropositive patients developed constrictive pericarditis whereas 8 (24%) of the seronegative patients did (26). The reason for the observed protective effect of HIV infection on developing constriction has been attributed to CD4 helper cell depletion which are known mediators of fibrogenesis thereby producing less pericardial fibrosis and thickening as well as fewer granulomas (26). More recently Mutyaba et al analysed a series of 121 patients undergoing pericardiectomy for CP at Groote Schuur hospital in Cape Town and found that only 11(14%) of the patients were HIV positive and that HIV infected patients had no significant differences in their clinical profile and early outcomes compared with the HIV negative patients in that series. (6)

6. DIAGNOSIS

As a result of pericardial restriction the predominant symptoms in CP are related to fluid overload and decreased cardiac output. Typical congestive symptoms are peripheral oedema, elevated central venous pressure, hepatomegaly, pleural effusions and ascites. Hepatomegaly is often associated with venous pulsations and invariably accompanied by ascites and leg oedema. Exertional dyspnoea, fatigue, palpitations, weakness and exercise intolerance are a consequence of the low cardiac output. In the end stage cachexia, muscle wasting and anasarca are often present. Congestive signs, however, are not specific to constriction and constitute the heart failure syndrome for which there is a variety of causes. It is often difficult to differentiate CP from restrictive cardiomyopathy or other entities responsible for predominantly right-sided heart failure (1, 2, 27, 28). This dilemma necessitates the use of imaging modalities to aid in the diagnosis of CP. Despite advances in imaging modalities and haemodynamic monitoring, CP remains a diagnostic challenge in the modern era of medicine, and should be considered in any patient presenting with unexplained systemic venous congestion.

With the availability of two dimensional / Doppler echocardiography, distinguishing constrictive pericarditis from other causes of right heart failure has become considerably easier. Currently the basis of confirming or establishing a diagnosis of CP rests in carefully assessing cardiac function by means of two dimensional echocardiography supported with CT or MRI imaging in a patient presenting with clinical features typical of constrictive pericarditis. In most cases it is possible to make a diagnosis purely using non-invasive techniques; however in a few instances the diagnosis still necessitates full heart catheterization (1, 11).

The jugular venous pressure is almost always elevated in constrictive pericarditis with a noticeable deep y descent (2, 11). Other important signs to elicit on cardiac clinical examination which may point to CP include:

i) Kussmals sign is due to an increase systemic venous pressure on inspiration and is due to the loss of normal increased right sided venous return on inspiration.

ii) Pulsus paradoxus It occurs in approximately one third of patients and originates because of lack of transmission of the decreased intrathoracic pressure to the left heart chambers (11).

iii) Pericardial knock, a diastolic sound (early S3) brought about by the rapid halt to ventricular filling in early diastole, may also be difficult to discern from a third heart sound due to other causes of heart failure (28).

There are no specific diagnostic electrocardiographic (ECG) features that are considered diagnostic of constrictive pericarditis, although low voltages, nonspecific t wave changes, left atrial enlargement and atrial fibrillation have been frequently documented (2, 3, 28, 29). Typical radiological features in constrictive pericarditis include bilateral pleural effusions with a shaggy heart border and, in some instances, pericardial calcification. Calcification of the pericardium has been reported to be present in approximately 25% of patients with constrictive pericarditis and is frequently associated with atrial fibrillation (4). It is most easily seen on lateral radiograph and is most commonly located over the right ventricular and diaphragmatic surfaces of the heart (2). Although the cardiovascular examination provides a physician with many diagnostic clues to suggest CP, it cannot reliably exclude other conditions such as restrictive cardiomyopathy needs supportive investigation such as imaging with echocardiography, computer tomography scanning, magnetic resonance imaging scanning or at times heart catheterization.

6.1 Echocardiography

Two dimensional Doppler echocardiography serves as the single best initial investigation of patients with suspected constrictive pericarditis (30). Over recent years there have been considerable

advances in echocardiographic techniques with the development of pulsed tissue Doppler, colour Doppler tissue imaging and speckle- tracking imaging. Echocardiographic parameters that support constriction Sayed et al (3) include:

(1) increased pericardial thickness

(2) abnormal ventricular septal motion on m mode;

(3) dilatation and absent or diminished collapse of the IVC and hepatic veins;

(4) restrictive mitral and tricuspid inflow velocities, typically with respiratory variation

(5) preserved or increased medial mitral annulus early diastolic (e´) velocity M Mode

6.2 Cardiac Computed Tomography

Computed Tomography (CT) of the heart is a valuable imaging modality in diagnosing constrictive pericarditis. It can identify pericardial thickening (>4mm) and calcification (2). In addition it can show evidence of IVC dilation and pick up abnormal ventricular contouring as well as abnormal septal motion (3). It is important to note that constrictive pericarditis can still be present in the absence of pericardial thickening or calcification. Ling et al. documented the absence of both pericardial thickening as well as calcification in approximately 20% of patients with surgically proven constrictive pericarditis (4).

6.3 Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging (MRI) is of value when echocardiographic imaging is uncertain. It has been shown to be especially useful in identifying the following:

i) Ongoing pericardial inflammation

ii) Enhanced ventricular interdependence with respiratory variation in ventricular septal motion changes

iii) Blood flow velocities from atrioventricular valves

iv) Alterations in ventricular filling with respiration (3)

6.4 Cardiac catheterization

Despite advances in imaging techniques the distinction between CP and restrictive cardiomyopathy frequently presents a diagnostic dilemma to the clinician (2, 3). Both can have very similar clinical presentations and clinical findings and invariably requires the use of a combination of Doppler echocardiography, Cardiac CT or Cardiac MRI and on occasion cardiac catheterization to distinguish the two conditions and make the correct diagnosis. Clinically both conditions can present with systemic venous congestion and elevated jugular venous pressures. Typically a pericardial knock occurs in constrictive pericarditis and an S3 in restrictive cardiomyopathy but often they can be confused for one another. ECG and CXR are often non-specific and unhelpful and it is mainly on echocardiography where one can identify several distinguishing features which can make the correct diagnosis. The typical cardiac catheterization findings in patients with constrictive pericarditis include

i) Increased intra-atrial pressure

ii) Prominent x and y descents

iii) Equalization of end diastolic filling pressures in heart chambers

iv) Dip and plateau / Square root sign of ventricular pressure

v) Opposing changes in left and right ventricular filling and systolic pressure with respiration (1-3)

7. MANAGEMENT OF CONSTRICTIVE PERICARDITIS

7.1 Medical Therapy

A small percentage of patients have been documented to develop transient constrictive pericarditis (21). Strang et al, in a case series from South Africa, described that approximately 15-20 % of patients diagnosed with tuberculous CP who were commenced on antituberculous therapy showed evidence of resolution of constriction and improvement of symptoms (15). In the overwhelming majority cases constrictive pericarditis is a chronic progressive condition that does not respond to medical therapy and requires surgical management in the form of a pericardiectomy to definitively treat the condition (5, 10, 24, 31). Medical management of symptoms fluid overload and oedema with salt restriction and diuretics but pericardiectomy is ultimately required.

7.2 Surgical Therapy

Pericardiectomy involves radical excision of as much parietal pericardium as possible to allow for unrestricted atrial and ventricular contraction. The extent to which the pericardium can be excused is dependent on the amount of thickening, fibrosis and often calcification present and at times the fibrosis and calcification can extend and invade the myocardium as well (13). Total pericardectomy is defined as wide excision of the pericardium extending from anterior surface to the phrenic nerves posteriorly, superiorly to include the great vessels and the intracardiac portion of the superior vena cava and right atrial junction and inferiorly to the diaphragmatic surface to include the right atria – Inferior vena caval junction. Any excision less than this is termed sub-total pericardectomy.

8. OUTCOMES

8.1 Immediate Outcome

Pericardiectomy for constrictive pericarditis has a high perioperative mortality of between 5- 15% (4-6, 8, 9, 27, 29). There have been many studies over the years contrasting the clinical profiles and outcomes of patients undergoing pericardectomy for constrictive pericarditis. In reality despite advances in surgical technique and perioperative care the morbidity and mortality of patients undergoing pericardectomy remains high (Table 3).

Table 3: Perioperative mortality and determinants of mortality after pericardiectomy for constrictive pericarditis in a selection of large studies

Investigator	Country	Study Period	n	Perioperative Mortality	Predictors of mortality
Bertog et al	USA	1977- 2000	163	6.1 %	_
Ling et al	USA	1985-1995	135	6%	_
Szabo et al	Germany	1985-2012	89	7%	_
George et al	USA	1995-2000	98	7.1%	Cardiopulmonary bypass
Chowdry et al	India	1985-2004	395	7.6%	_
Mutayab et al	RSA	1990-2012	121	14%	Serum sodium, NHYA class IV
Zhu et al	China	1990-2012	165	5.4%	NYHA class

The profile of patients in South Africa with tuberculous pericarditis on the background of HIV infection makes our patient profile very different to those of developed countries where most of the outcome studies have been conducted. In South Africa there have been limited studies done on outcomes in patients following pericardiectomy (6, 33). In 1982 Fennel et at reported a 3%

perioperative mortality in 109 patients who underwent pericardiectomy; 97% of patients made a good post operative recovery with resolution of physical signs of constriction(33). HIV infection was not reported in this series.

More recently Mutuyaba et al reported a series of 121 patients in the Western Cape undergoing pericardiectomy for constrictive pericarditis where 91% of patients had probable or proven tuberculous pericarditis and 11.6% were HIV positive (16). Perioperative mortality rate was 14% ; preoperative serum sodium levels and NYHA class IV dyspnoea were identified as independent risk factors of early mortality (6). With specific reference to HIV infected patients in the cohort no significant difference was found both in clinical profile and outcomes compared to HIV negative patients (6).

8.1.2 Long Term Outcome

In South Africa to date there have been no studies done documenting the long term follow up of patients with constrictive pericarditis. Good long term outcomes have been confirmed in other studies done primarily in developed countries. Bertsog et al reported five year death rates for patients post pericardiectomy for CP of 19% before 1990 and 21% thereafter (5). In India Chowdry et al documented long term survival in a cohort of 395 patients with 338(85%) undergoing total pericardiectomy (Group 1) and 57(14.4%) undergoing partial pericardectomy (Group 2) as being 83.8 % at 17.9 years for group 1 and 73.9% for group 2 (7). In addition preoperative high right atrial pressure, hyperbilirubinemia, renal dysfunction, atrial fibrillation, pericardial calcification, thoracotomy approach, and partial pericardiectomy we identified as predictors of mortality (7).

9. RATIONALE FOR THIS STUDY

Constrictive pericarditis is one of the few treatable causes of heart failure as surgical pericardectomy is curative in most patients. In South Africa tuberculous pericarditis the commonest cause of CP and

is associated with a high degree of morbidity and mortality. Although the effect of HIV infection on the clinical outcomes and management of patients with tuberculous pericarditis has been well studied there is little data on the profile of constrictive pericarditis in HIV infected subjects. Recent studies have suggested that HIV alters the natural history of tuberculous pericarditis with fewer patients progressing to develop constriction. Our study aims to compare the clinical profile and surgical outcomes of patient with confirmed constrictive pericarditis in HIV infected and non-infected individuals. We hope to assess whether HIV infection, in an era where patients have had access to antiretroviral therapy, has had any significant impact of the clinical course of patients with constrictive pericarditis undergoing pericardiectomy and where it has had any effect on outcomes and mortality.

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Part 2: Final Study Protocol

Protocol:

Name: Graham Laurence

Student number: 993230264

Degree: MMed (Cardiology)

Supervisor: Prof DP Naidoo

Title of Study:

The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.

Aim of Study:

1. To evaluate the effect that HIV/AIDS has on the clinical profile of patients with constrictive pericarditis and
2. To evaluate outcomes in those patients undergoing pericardiectomy.

Specific Objectives (SO):

1. Assessment of clinical profile including:
    - Demographic data (age, gender, ethnicity, residential address)
    - Co morbid conditions (Diabetes Mellitus, Hypertension, Hypothyroidism
    - HIV status
    - Previous opportunistic infections (Tuberculosis, Pneumocystisis Carinii Pneumonia, Cryptococcus, Syphilis)

- Clinical Presentation (New York heart association class of dyspnoea)
- Physical examination (Peripheral oedema ,ascites ,pleural effusion, elevated jugular venous pressure, pericardial knock, pulsus paradoxus
- Biochemistry (Haemoglobin, potassium, sodium, urea, creatinine, liver function tests, CRP, ESR, BNP, CD4 count, HIV viral load, Hepatitis B surface antigen)
- Results of imaging (Chest X ray, Chest computerized tomography)

2. Echocardiographic findings:
    - Features of constriction (pericardial thickness, abnormal ventricular septal wall motion, evidence of IVC collapse, mitral valve inflow velocity evidence)
    - Assessment of left ventricular and right ventricular function).
3. Description of clinical outcomes:
    - medical management (diuretic usage)
    - surgical pericardectomy,
    - short term follow up post-surgery (symptoms, Doppler echocardiogram results)

Introduction:

Constrictive Pericarditis (CP) is a debilitating condition arising from chronic inflammation of the pericardium causing thickening and fibrosis resulting in impaired diastolic filling of the heart with reduced ventricular function. [1, 2] Importantly it remains one of the few treatable causes of heart failure. [4, 5]

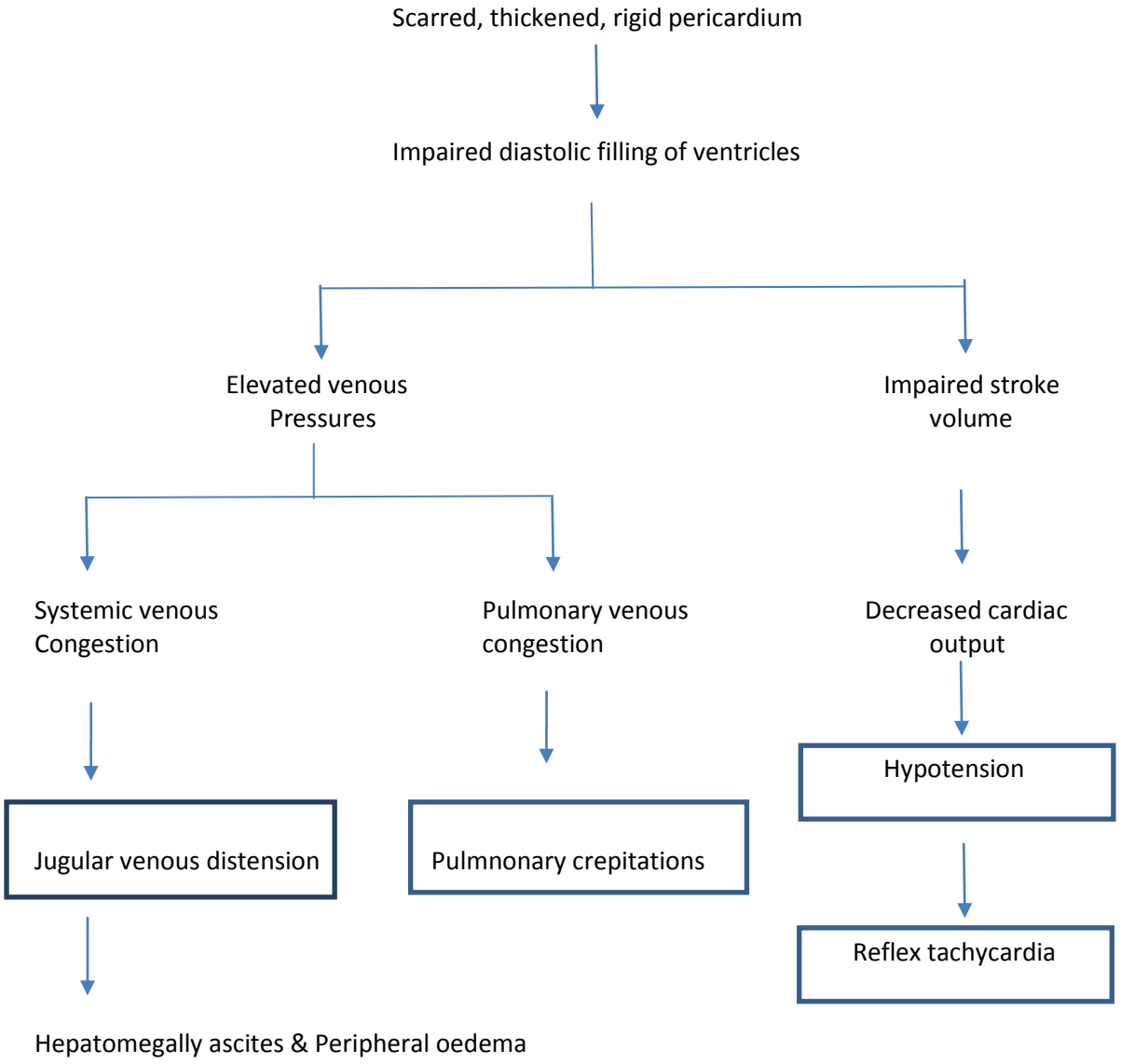
CP can develop following any pericardial disease process. [5] In developed countries the commonest aetiologies in the modern era of medicine are idiopathic causes, cardiac surgery and mediastinal radiation therapy. In developing and underdeveloped nations, where the human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) pandemic is highly prevalent, tuberculosis remains the major cause of CP [1-4, 14, 15]

In most cases of CP, diagnosis is established with non-invasive testing. Computerised tomography (CT) scanning and echocardiography provide imaging modalities that confirm constriction in most cases. However, in spite of these advancements of the modern era of medicine, CP still poses a diagnostic challenge to the clinician. It remains largely undiagnosed due to difficulty in differentiating it other causes of right heart failure and from restrictive cardiomyopathy (RCMO). In those patients in whom a diagnosis is confidently established, options for management are restricted to a few. Medical therapy to treat the right heart failure may be offered, but the definitive management is surgery with pericardiectomy. [1-5, 14-17] The challenge faced here by the attending physician lies in the selection of patients for surgery with regard to the risk – benefits ratios to the patient. Pericardiectomy carries a high mortality rate of 5 - 12% but unfortunately is also currently the only curative treatment in the majority of cases. [1, 3, 5, 14 -16]

Anatomy and Pathophysiology:

The pericardium is a fibrous, fluid filled sac surrounding the heart and the roots of the great vessels providing structural support, protection from infection and lubrication for heart movement. These functions allow it to have a significant haemodynamic impact on the heart. [5] The pericardium is not an essential structure and the heart can function normally in its absence either congenitally or from surgical resection. However, in clinical settings when the pericardium becomes diseased, cardiac function is disrupted. This may present clinically as acute or chronic recurrent pericarditis, pericardial effusion, and in severe cases, cardiac tamponade, and pericardial constriction. All of these manifestations of pericarditis can be challenging to manage and possibly life-threatening in some cases. [5]

The pathophysiological hallmark of CP is restriction to diastolic filling of the heart secondary to a thickened, fibrotic pericardium. This results in elevation and equilibration of filling pressures in all chambers of the heart and the systemic and pulmonary veins. As a result of the equalisation, almost all ventricular filling occurs in early diastole, limiting end diastolic volumes, and producing decreased left and right ventricular stroke volumes. This decrease in stroke volume causes decreased cardiac output and increased pre-load. The consequence of this can be appreciated as systemic venous congestion. This reflects clinically with signs of hepatic congestion, peripheral oedema, ascites and sometimes anasarca, and cardiac cirrhosis [10]



Impairment of ventricular filling causes a decrease in cardiac output, leading to fatigue, muscle wasting, and weight loss. In “pure” constriction, contractile function is preserved, until the very late stages when the constriction extends beyond the pericardium to the epicardial tissue. The myocardium is occasionally involved in the chronic inflammatory process and may become fibrosed. This leads to true contractile dysfunction which, at times, can be quite severe and is a prediction of a poor response to pericardiectomy.

Epidemiology:

Until the advent of HIV infection and its predisposition to tuberculosis CP was an uncommon condition. Approximately 9% of patients with acute pericarditis from any cause progress to develop constrictive physiology. The true frequency is dependent on the incidence of the specific causes of pericarditis. The risk of constrictive pericarditis following a first episode of acute pericarditis has been estimated in a previous study to be in the region of 1.8% [18]

In developed countries, viral causes, surgery and radiation remain the main causes of pericarditis, leading to CP. In developing countries that are plagued with a high prevalence of HIV and poor socio-economic situations, the commonest cause of pericarditis is tuberculosis (TB). The HIV statistics released by the WHO in 2011 declare half a million active TB cases in South Africa. Amongst these individuals, 60% (300,000) had co-infection with HIV. [9] In 2012, HSRC reported that 6.4 million South Africans were living with HIV (12.2%). [8] These statistics are clear indications the impact of the HIV pandemic on modern third world medicine. Its impact on the number of individuals infected with TB, and more particularly, TB pericarditis, is enormous. It is therefore not surprising that TB remains the commonest cause of pericarditis in the third world environment. CP is a serious

complication on TB pericarditis, documented to be present in between 30-60% of cases despite appropriate treatment with antituberculous chemotherapy. [6]

Furthermore, there is little data on the effect that HIV/ AIDS has on the clinical characteristics of CP, the progression of acute effusive tuberculous pericarditis to CP and the outcomes after pericardiectomy.[4] Studies done on tuberculous pericarditis have suggested that early initiation of anti- tuberculous chemotherapy combined with pericardiocentesis have had a significant impact in limiting the progression to developing CP. [11] To this effect, results from the 'The Investigation of the Management of Pericarditis in Africa (IMPI Africa) Registry' showed that HIV associated TB pericarditis is a more aggressive disease with a greater degree of myocardial involvement and high mortality rate of approximately 40%. [7, 8] In addition it has been shown that HIV has a significant effect on the natural history of tuberculous pericarditis with fewer HIV co-infected patients progressing to develop CP but having significantly higher mortality when compared to non HIV infected counterparts. [8, 12]

Causes of Constrictive Pericarditis:

Infectious	Tuberculous, Bacterial, Viral (commonly coxsackie and echo viruses), Fungal
Trauma	
Inflammatory	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Scleroderma, Sarcoidosis
Neoplastic	Breast and lung cancer, mesothelioma, melanoma
Radiation	Post mediastinal radiation therapy
End Stage Renal Disease	Uraemia
Idiopathic	

Diagnosis:

CP still presents a diagnostic challenge in the 21st Century. In South Africa it usually requires a combination of suggestive clinical signs and symptoms in patients who may or may not have been treated for pulmonary or extra-pulmonary TB. It presents as the heart failure syndrome but diagnosis of constriction requires clinical skill in searching for the signs of constriction.

I. Symptoms and signs suggestive of CP:

Fluid Overload	Peripheral oedema, elevated central venous pressure, hepatomegally, pleural effusions, ascites and anasarca
Decreased Cardiac Output	Exertional dyspnoea, fatigue, palpitations, weakness and exercise intolerance

Congestive signs are unfortunately not specific to constriction and constitute the heart failure syndrome for which there is a variety of causes. This dilemma necessitates the use of imaging modalities to aid in the diagnosis of CP. Despite advances in imaging modalities and haemodyamic monitoring, CP remains a diagnostic challenge in the modern era of medicine, and should be considered in any patient presenting with unexplained systemic venous congestion [17]. A comprehensive set of differential diagnoses must also be considered. The differential diagnoses must include:

(1) acute dilatation of the heart

(2) pulmonary embolism

(3) right ventricular infarction

(4) pleural effusion

(5) chronic obstructive lung diseases and;

(6) restrictive cardiomyopathy

The definitive diagnosis of CP is made incorporating a combination of clinical, radiological, echocardiographic, and haemodyamic parameters.

Pericardial calcification is a highly useful suggestive marker for CP and can be seen on chest radiograph, being best appreciated on lateral view. It is, however, only seen in approximately 25% of cases but, when present, it strongly suggests constriction. [5]

Echocardiography is the first choice of initial imaging and haemodyamic assessment tool available for use in both developed and developing countries: two-dimensional transthoracic echocardiographic findings include:

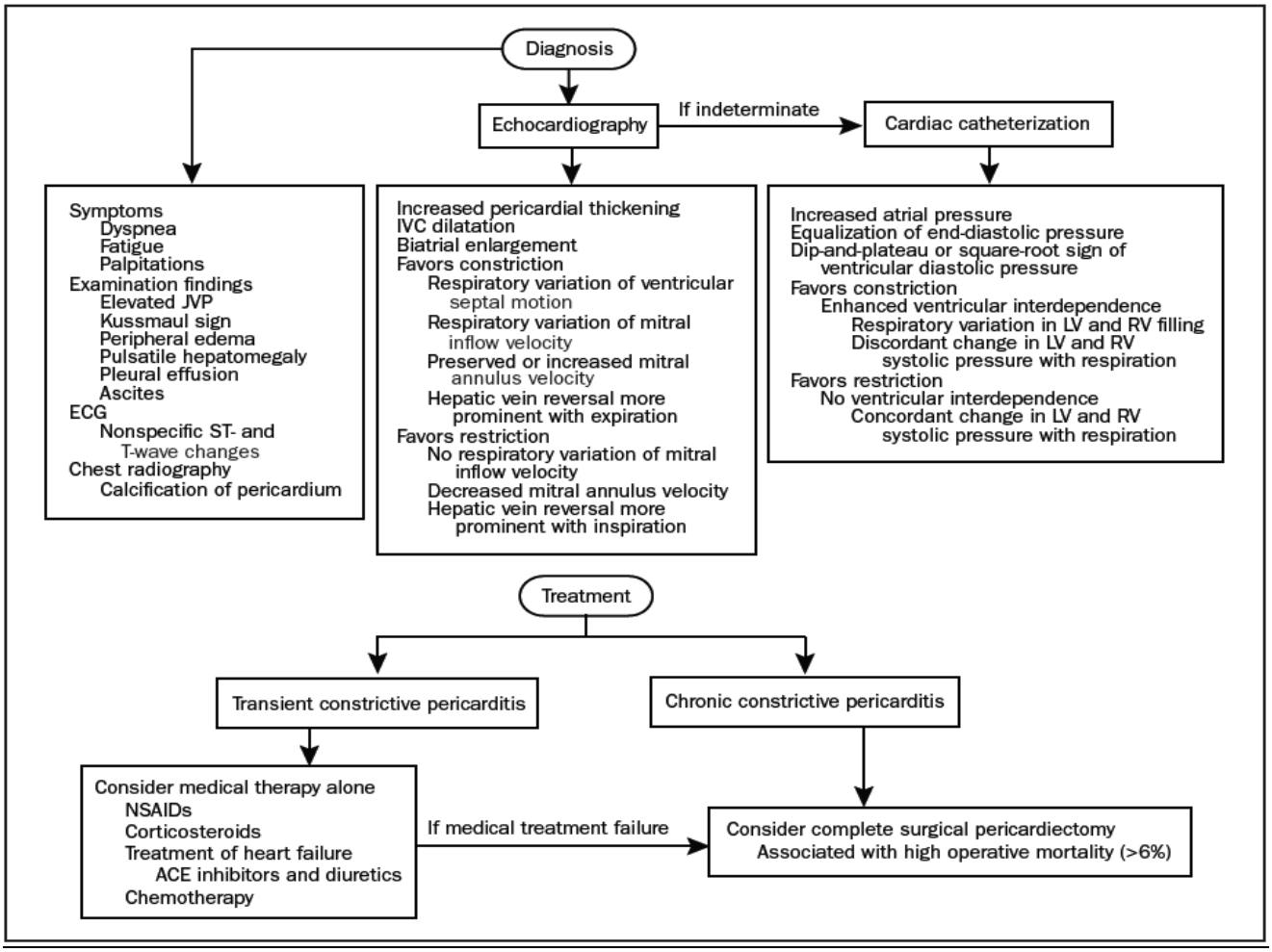
(1) increased pericardial thickness

(2) abnormal ventricular septal motion;

(3) dilatation and absent or diminished collapse of the IVC and hepatic veins;

(4) restrictive mitral and tricuspid inflow velocities, typically (but not always) with respiratory variation

(5) preserved or increased medial mitral annulus early diastolic (e´) velocity



Flow Diagram 1: Summary of diagnostic approach for constrictive Pericarditis **[5]**

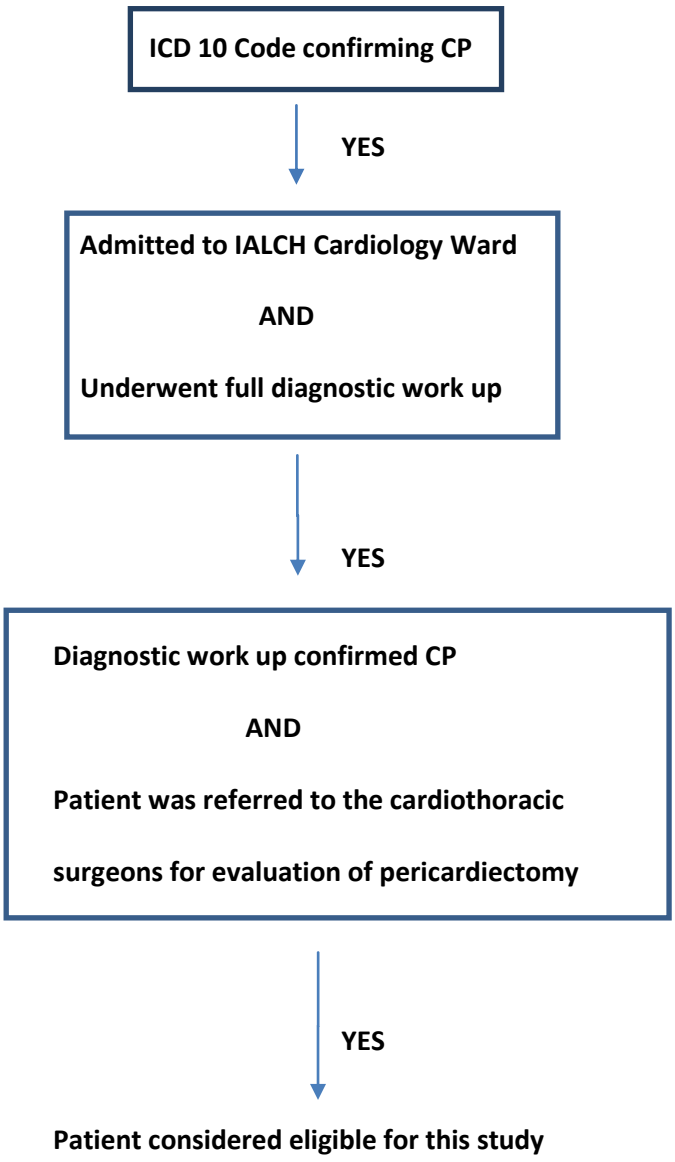
Treatment:

Constrictive pericarditis is a progressive disease but has a variable course. There have been no large randomized control trials profiling the natural history of this condition. Treatment options are generally limited. With the exception of patients with transient constriction following acute pericarditis, surgical pericardiectomy is the only definitive treatment for chronic constriction.[1-5] Patients with major comorbidities or severe debilitation are often at too high risk to undergo pericardiectomy and in this subgroup of patients mortality remains high. However, if not contra-indicated, surgery should not be delayed once the diagnosis is made. Medical management with diuretics and salt restriction is useful for relief of fluid overload and oedema, but patients ultimately

require surgical pericardiectomy. Results from large variety of international studies have consistently reported perioperative mortality rates of 5% to 15%. [2, 4, 5] Early mortality results primarily from low cardiac output, often in debilitated patients with prolonged cardiopulmonary bypass and difficult dissections.

The highest mortality occurs in patients with Class III or IV symptoms, supporting the recommendation of early pericardiectomy.

Study Design



Patients who had a complete work up done at Grey's hospital in Pietermaritzburg with CP confirmed on echocardiography and CT chest, and who had been referred to the Cardiothoracic surgeons at IALCH for pericardiectomy were also considered eligible for the study.

Patients will be selected for this study by using ICD 10 codes to identify patients who diagnosed with constrictive pericarditis during their visits to Inkosi Albert Luthuli Hospital (IALCH). The sample group will be further screened to assess which patients had both been admitted to the Cardiology Ward at IALCH and undergone a full diagnostic work up including: clinical assessment, blood testing echocardiography and chest computerized tomography. Those patients who had a full in-patient diagnostic work up confirming the diagnosis of constrictive pericarditis and who were referred to the cardiothoracic surgeons for evaluation of pericardiectomy will be considered eligible for the study. Patients who have had a complete work up done at Grey's hospital in Pietermaritzburg, with CP confirmed on echocardiography and CT chest, and who had been referred to the cardiothoracic surgeons at IALCH for pericardiectomy, will also be eligible for inclusion in the study.

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Study Population

- All patients referred to IALCH for evaluation of constrictive pericarditis will been screened for selection into the study. The sample population of patients with confirmed CP will be extracted. IALCH Department of Cardiology's capture area is Kwazulu natal (KZN) and part of the Eastern Cape. This will be the target population from which the sample population will be collected. In addition, those patients falling under the Grey's Hospital drainage area will also be included in target population.

Inclusion Criteria

- All patients with confirmed CP based on clinical echocardiographic and radiological investigations during in-patient work up done at IALCH Cardiology unit or Greys Hospital will be included.
- Only patients who had consented and undergone HIV testing or whose HIV status is known prior to admissions will be included.

Exclusion Criteria

- Patients who did not undergo in-patient evaluation for CP using diagnostic modalities of echocardiography, CT imaging will be excluded.
- Patients whose HIV status is unknown will be excluded.
- Patients who were admitted for inpatient evaluation of CP in the Department of Cardiology in whom a diagnosis of CP was not formally established will be excluded.

Sample size

- The population sample will include all patients who meet the criteria for inclusion during 2003 to 2013. Approximately 70 patients are expected.

Data Collection Methods and Tools

Data collection will be done using Speedminer Database which is a record collection of medical data captured including every entry (in-patient and out-patient, investigations, doctors' notes, paramedical notes and referrals) for every patient that has been to IALCH. All patients are given a 'Kwa-Zulu (KZ) number'. Using Speedminer Database, all patients that were seen from 2003 to 2013 as in-patients and out-patients at Cardiology are isolated by their KZ numbers. The patients are then sorted manually by KZ number on the Medicom Clinician Access (CA) Live System and each file read and reviewed for constrictive pericarditis with exclusion and inclusion criteria followed.

Data Analysis Technique

This is a retrospective analysis of patients admitted to the Cardiology unit at IALCH who have been diagnosed with constrictive pericarditis. Patients will be stratified into two groups: those with HIV and those without HIV, based on HIV Elisa testing. Categorical variables will be analysed by chi squared test. Continuous variables will be assessed by rank sum test. Multivariate analysis will be performed to determine the factors contributing to the development of constriction and the severity of clinical features in both groups.

Statistical Analysis

Group sample sizes of 37 in group one and 37 in group two achieve 80% power to detect a minimum absolute difference between the group proportions of 0.27 or 27%. The proportion in group one (the treatment group) is assumed to be 0.11 under the null hypothesis and 0.38 under the alternative hypothesis. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05.

Study Location

The study location is IALCH which is where the investigations take place echocardiography and CT scanning. The study source is the entire area that is referred to IALCH Cardiology for investigation further management, i.e. KwaZulu-Natal and part of the Eastern Cape.

Study Period

This is a retrospective study over 10 years, from July 2003 to December 2013. All patients that have been referred for investigated for constrictive pericarditis 2003 to 2013 at IALCH will be selected for. To ensure reliability of data, only patients who were admitted to the Cardiology Unit at IACLH or referred from Grey's Hospital with a proven diagnosis of CP will be considered eligible.

Limitations to the Study

1. The study is limited to the patients referred to IALCH hospital.
2. The study sample will be skewed towards African subjects because these are the majority of patients with constrictive pericarditis. The result, therefore, may not be applicable to non-African subjects.
3. The sample sizes are small therefore limiting the statistical significance of the results.
4. Long term follow up of patients remains problematic as the majority of patients are from distant rural areas where transport and communication difficulties limit their attendance at regular follow up clinics

Ethical Considerations

1. Scientific Validity

   This study is valid as it will contribute to the knowledge of the influence of HIV/AIDS on the clinical profile of CP and surgical outcomes following pericardiectomy. Currently, there is limited data from African countries on this subject.

2. Social Value

   The risk factors and the financial cost incurred in performing investigations: echocardiography and computer tomography, as well as the need for surgical treatment with pericardiectomy, warrant the need to identify those patients that do indeed have constrictive pericarditis. The social value of this would be to prevent exposing patients to these investigations and potential surgical procedures when they may likely be unnecessary and to offer it to them when there is a likely need.

3. Risk Benefit Ratio

   The benefits of the study are that:

- The influence of HIV/AIDS on the clinical profile of CP and surgical outcomes following pericardiectomy will be better understood
- Patients who need the investigations more may receive it
- Patients who do not need the investigations may not be exposed to them

The risks of the study are that:

- The results may lead to a patient needing the investigation not being offered it
- The results may lead to a patient not needing the investigation being offered it

4. Confidentiality

   This is a retrospective chart review study in which patients selected are anonymous. They are identified by their KZ numbers only.

5. Informed Consent

   This is a retrospective study. The investigations performed were done before the study was designed (2003 up until 2013). Patients were informed by their consulting doctors of the procedures and investigations to be performed and written informed consent obtained prior to the investigations being performed as part of the routine hospital protocol for management of patients.

6. Standards of Care

   The patients that form part of the study have been offered the highest standards of care which is a standard offered to all patients that are attended to at IALCH Cardiology. They are further offered further intervention that is the most beneficial and necessary for improvement of their quality of life and prolongation of life, based on the outcomes of investigations.

7. Conflict of Interest

   There is no conflict of interest.

8. Fair Selection of Patients

The patients are selected according to presentation. There are no demographic criteria or background criteria that preclude a patient from the study.

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ARTICLE for submission to the cardiovascular J Africa

The effects of HIV/AIDS on the clinical profile and outcomes post pericardiectomy of patients with constrictive pericarditis. A retrospective review.

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Abstract

Objective: The clinical profile and surgical outcomes of patients with constrictive pericarditis were compared in HIV positive and HIV negative individuals in Durban, KwaZulu-Natal.

Methods: This study was a retrospective analysis of all patients diagnosed with constrictive pericarditis at Inkosi Albert Luthuli Central Hospital over a ten year period (2004- 2014).

Results: Of 83 patients with constrictive pericarditis 32 (38.1%) were HIV positive with a mean CD4 count of 294 (SD+/- 127) cells/uL. Proven tuberculosis was found in 22(26.5%) subjects and 58(69.9%) had probable tuberculosis. Except for pericardial calcification which was more common in HIV negative subjects (n=15; 29.4 vs n=2; 6.3%; p=0.011), the clinical profile was otherwise similar in both groups. Fourteen patients died preoperatively (16.9%) and three patients perioperatively (5.8%). On multivariable analysis, age (OR 1.17; CI 1.03-1.34; p=0.02), serum albumin (OR 0.63; CI 0.43-0.92; p=0.016), gamma GT (OR 0.97; CI 0.94-0.1.0; p=0.034) and PA pressure (OR 1.49; CI 1.07-2.08; p=0.018) emerged as independent predictors of preoperative mortality. Pericardiectomy was performed in 52(63.8%) of whom 20(39.6%) were HIV positive. There were three early perioperative deaths (HIV-ve(2), HIV+ve(1)). Perioperative complications occurred more frequently in HIV positive patients (9 (45%) vs 6(17.6%) p=0.030).

Conclusions: The clinical profile of constrictive pericarditis is similar in both HIV negative and positive subjects. Without surgery tuberculous constrictive pericarditis was associated with a high preoperative mortality rate. In virally suppressed subjects pericardiectomy was not associated with an increased early perioperative mortality.

Key words: Constrictive pericarditis, HIV, pericardiectomy

Abbreviations and Acronyms

AIDS = acquired immunodeficiency syndrome

HIV = human immunodeficiency virus

NYHA = New York Heart Association

Introduction

Constrictive pericarditis remains an uncommon yet treatable cause of heart failure. [1, 2] The hallmark of constrictive pericarditis is impaired ventricular diastolic filling caused by a thickened, fibrosed pericardium resulting in decreased stroke volume and varying degrees of systemic venous congestion. [2-5] The natural history of this disorder remains unknown. [6] Whilst medical therapy has been used to successfully treat patients with constriction in its early stages, surgical pericardiectomy remains the only treatment for chronic constrictive pericarditis. [7, 8] Surgical mortality remains high and has been reported to be between 5 -14% in multiple large series. [1, 2, 6, 9-15] Over the past two decades there has been a changing spectrum of constrictive pericarditis in the developed world with a declining incidence of infective aetiologies, in particular tuberculosis. [1, 3] In Sub-Saharan Africa, tuberculosis remains the dominant cause; about 30-60% of patients diagnosed with tuberculous pericarditis progress to constriction despite appropriate anti-tuberculous therapy and adjunctive corticosteroids. [16] The co-existing HIV/AIDS epidemic has contributed to the resurgence of tuberculosis, and its various manifestations, including constrictive pericarditis in Africa. [2] The effect of HIV on the incidence, natural history and surgical outcomes of patients with constrictive pericarditis has not been adequately documented. [2] Recent data suggest that coexisting HIV infection may modify the clinical manifestations and natural history of tuberculous pericarditis and resultant constriction. [17, 18] Our study was designed to evaluate the clinical profile and surgical outcomes of HIV positive and negative patients with constrictive pericarditis.

METHODS

This study is a retrospective chart review of all patients referred to Inkosi Albert Luthuli Central hospital in Durban Kwazulu-Natal for evaluation and management of suspected constrictive pericarditis during the period 2004-2014. Patients eligible for inclusion in the study constituted those in whom the diagnosis of constrictive pericarditis was confirmed using a combination of clinical

symptoms and signs associated with typical echocardiographic and computer tomography (CT) scan findings. Clinical supporting features included peripheral oedema, ascites, pleural effusions, hepatomegaly, elevated jugular venous pressure and pericardial knock. Typical echocardiographic features of constriction were a thickened echogenic pericardium accompanied by paradoxical interventricular septal motion, and dilated non-compressible hepatic veins and inferior vena cava. Thoracic CT scans were used to confirm pericardial thickening, calcification, and demonstrate lymph node enlargement. Tuberculosis (TB) as the cause for constrictive pericarditis was inferred from a history of a previous diagnosis of tuberculosis, (pulmonary or extrapulmonary), or previous treatment for tuberculosis. Proven tuberculosis was defined by isolation of the organism or typical histological findings. Patients in whom the diagnosis of constrictive pericarditis was incorrect were excluded from the study population. Informed consent for HIV testing was obtained from all patients with suspected constriction who were referred to Inkosi Albert Luthuli hospital with a view to surgical pericardiectomy. Relevant data (demographics, HIV status, clinical symptoms and signs and symptoms, laboratory, echocardiographic, radiological, operative data and follow up findings were extracted.

In the subset that underwent pericardiectomy, constrictive pericarditis was confirmed intraoperatively by identifying constrictive features with pericardial thickening and fibrosis. Surgery was performed by median sternotomy without cardiopulmonary bypass in all but one patient. At operation the entire ventricular epicardium, apex and diaphragmatic surface of the heart was freed. The pericardium was removed anteriorly extending laterally to the phrenic nerves and the posterior pericardium was left in situ after being freed from the epicardium. Any resection less than this was deemed a partial pericardiectomy. Immediate perioperative mortality was defined as any death occurring during the index hospitalization.

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE 324/15)

Statistical Analysis

Data were analysed using Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Continuous variables were summarized using mean and standard deviation or median and interquartile range. Difference in means of continuous predictors by HIV status (i.e. two groups) were assessed using the student t-test. If the data were not normal then the Wilcoxon rank-sum test was used instead. If the data were not normally distributed then the Kruskal-Wallis equality-of-populations rank test was employed instead. Association between HIV status (2 and 3 group classification) and categorised explanatory variables/risk factors were assessed using a Pearson chi-square ($\chi 2$) test. If any cell count in the cross tabulation contained fewer than 5 expected observations then the Fishers exact test were used. Multivariate logistic regression were employed to estimate the strength of association (odds ratios) between the explanatory predictors and HIV status. A p-value of <0.05 was considered statistically significant.

RESULTS

Preoperative clinical profile

A total of 86 patients were eligible for inclusion during the study period (Fig 1). Three patients were excluded, (incorrect diagnosis n=2, HIV status unknown n=1) leaving 83 (43 male, 40 female) for analysis. The mean age of the total sample was 37.98 ± 12.91 yr (range 19-69). Of these patients, 32 (38.6%) were HIV positive, of whom 21 (65.6%) were on antiretroviral therapy and nineteen (59%) patients were virally suppressed (viral load < 1000copies/ml). In addition, a further 3 patients who were not on antiretroviral therapy had viral loads < 1000copies/ml. In total 8/32 (25.0%) patients

had a CD4 count of less than 200. The baseline characteristics stratified by HIV status are summarized in *Table 1.*

The aetiology of constriction was tuberculosis in 80/83 (96.3%) of patients. Constriction was deemed to have followed viral pericarditis in two patients and the third patient developed constriction following repeated radioablation procedures for tachyarrhythmias. Tuberculosis was proven in 22 (26.5%) patients and was considered the probable aetiology in a further 58 (69.5%) patients. Although proven tuberculosis was identified more frequently in HIV positive patients (40%) compared to HIV negative patients (17.6%), this finding was not statistically significant.

The mean body weight of HIV positive patients was 5 kg less those who were HIV negative (62.77 ± 12.01 vs 67.69 ± 13.05; p=0.09) but this finding was also not statistically significant. Moderate dyspnoea (NYHA class II) was present in almost two thirds (63.9%) of the patients and severe symptoms were present in 32.5% of patients. Similarly, two thirds (n= 57; 68.7%) of patients had ascites. There was no difference in the clinical characteristics between HIV positive and HIV negative patients except for peripheral oedema which was significantly more frequent in HIV negative patients (86.2% vs 65.6%; p=0.026). Atrial fibrillation was documented in five patients (all HIV negative), four of whom had extensive pericardial calcification on chest radiography.

All patients (n=83) had chest radiographs (CXR) and echocardiograms and 77 patients (94%) had thoracic CT scans. A total of 17 patients (20.5%) had pericardial calcification on CXR and one additional patient had pericardial calcification identified on CT scan only. Extensive pericardial calcification was more common in HIV negative compared to HIV positive patients (n=15; 29.4 vs

n=2; 6.3%; p=0.011) on the chest radiograph. Mediastinal lymphadenopathy was identified in 47 (61%) of patients and there was no difference between HIV positive and negative patients (p=0.642)

On echocardiography effusive constrictive pericarditis was found in seven (8.4%) patients of whom four were HIV negative and three HIV positive (p=ns). There was no significant difference in the ejection fraction (51.88% ± 7.5 vs 52.69% ± 4.96; p=0.593), and pulmonary arterial pressure (33.88mmHg ±8.86 vs 34.96mmHg ±7.76; p=0.571 between HIV negative and HIV positive patients respectively.

Laboratory data showed no significant differences in haemoglobin, white cell count, urea, creatinine and albumin levels between HIV negative and HIV positive patients. Of note, alkaline phosphatase (146.0 ± 67.7 vs 201.0 ± 108.8; p = 0.005), and gamma glutamyl transferase (172.96+104.76 vs 370+300 p=<0.001) levels were significantly elevated in HIV positive patients.

Preoperative mortality

Of the initial study cohort of 83 patients with constrictive pericarditis, 31 (37.3%) patients did not undergo pericardiectomy. Of these 31 subjects, four died in hospital shortly after admission (all HIV negative) from low cardiac output and the remaining 27 offered surgery did not return for operation. Survival status of those lost to follow up was established telephonically as well as checking the national registry of deaths. In this way it was established that a further ten had demised out of hospital (HIV positive n=4) yielding a total preoperative mortality of 16.7% (14/83)

(95% CI: 9.5-26.6 %). Bivariate logistic regression analysis identified seven predictors of preoperative mortality (*Table 2).* These were age (OR, 1.11; 95% CI, 1.04-1.18; p = <0.001), haemoglobin (OR, 0.67; CI, 0.45-0.99; p=0.031), albumin (OR, 0.90; CI, (0.82-0.99; p=0.019), aspartate aminotransferase (OR, 0.91;CI 0.85-0.98; p=0.003)and pulmonary artery pressure (OR, 1.13; CI, 1.05-1.22; p= <0.001). HIV status had no influence on the preoperative mortality (p=0.693). On multivariable analysis, age (OR 1.17; CI 1.03-1.34; p=0.02), serum albumin (OR 0.63; CI 0.43-0.92; p=0.016), gamma GT (OR 0.97; CI 0.94-0.1.0; p=0.034) and PA pressure (OR 1.49; CI 1.07-2.08; p=0.018) emerged as independent predictors of preoperative mortality.

Operative outcome of patients undergoing pericardiectomy

A total of 52 patients (62.7%) underwent pericardiectomy, which included 32 HIV negative patients (61.54%) and 20 HIV positive patients (38.5%). Of the twenty HIV positive patients, 15 (75%) were on antiretroviral therapy with successful viral load suppression (<1000 copies/ml). Pericardial biopsy specimens taken at the time of surgery showed histological evidence of tuberculosis in the form of granulomas and/or acid fast bacilli in 12/49(24.5%) of patients.

Complete pericardiectomy was achieved in 38 (73.1%) and there was no significant difference between HIV positive and negative patients (26; 81.3% vs 12; 60%; p= 0.093). There were three in-hospital perioperative deaths yielding a perioperative mortality rate of 5.7% (95% CI 9.5-26.7%). One patient (HIV positive) died of intraoperative haemorrhage in theatre and two (HIV negative) who were both severely symptomatic preoperatively (NYHA IV) with impaired ejection fraction, died in ICU as a result of a low cardiac output state. There was no significant difference in the length of ICU stay between HIV negative and HIV positive patients (4.28 ± 2.74 vs 5.11 ± 2.84 days; p=0.321).

Intraoperative complications included accidental myocardial wall or major vessel injury in ten (19.2%) patients, of whom one patient sustained massive haemorrhage and died intraoperatively and one patient developed ventricular fibrillation. There were two early perioperative deaths of patients while admitted to the ICU. Postoperative complications occurred in 7 patients (9.6%), 3 of whom had also suffered intraoperative complications. These postoperative complications were: sternal wound sepsis (1), re-intubation for respiratory failure and tachyarrhythmia (1), thoracotomy for postoperative haemorrhage(1), postoperative renal impairment(1) and low output cardiac failure(3). In total perioperative (intra- and post-operative) complications occurred significantly more frequently in HIV positive patients (HIV positive, 9; 45% vs HIV negative, 6; 17.6%; p=0.030). The higher complication rate in HIV positive patients could not be explained by left ventricular function since the left ventricular function was similarly preserved in both groups (HIV negative, 53.33% ± 6.7 vs HIV positive, 53.93 ± 6.79; p=0.783). In total there were 3 perioperative in-hospital deaths (intraoperative haemorrhage (n=1) and postoperative low output cardiac failure (n=2)).

Of the 49 patients who were discharged (3 died in hospital) after undergoing pericardiectomy, 41(26 HIV positive) returned for the six week postoperative follow up at our hospital. Six patients were followed up at their referral hospital and 2 were lost to follow up. Most patients improved their NYHA class by one or two levels (p<0.001)(Fig 1). The majority of patients had improved from NYHA class II to class I (n = 21, 50%) and NYHA class III to class I (n = 10, 23.8%). Eight patients showed no improvement in functional class. There was no significant difference in symptoms of dyspnoea (p=1.000) or ejection fraction (p= 0.785) between HIV positive and HIV negative patients.

DISCUSSION

This study shows a relatively high prevalence rate of HIV infection 32/83 (38.6%) amongst patients with constrictive pericarditis. HIV infection did not appear to influence early postoperative mortality. The HIV prevalence in our study is higher than 14/96 (14.6%) that reported by Mutyaba et al [2] in a recent South African study but less than 12/19 (63%) reported by Abubaker and colleagues [17] in a Nigerian study. Our findings contrast with Gopaldas et al [18] in the USA who found ten HIV positive patients with constrictive pericarditis out of a sample size of 3847 undergoing pericardiectomy. In keeping with other studies from developing countries [2, 11, 12, 19-21] tuberculosis 80 (96.4%) was identified as the main aetiology of constrictive pericarditis in our study and highlights the impact of the HIV/AIDS epidemic in refuelling a resurgence of tuberculosis infections. [(24, 25)] Similar to other series, [(2, 15)] proven tuberculosis (pericardial histology, culture of AFB from sputum, lymph nodes) was documented in 22(26.5%) of patients.

The natural history of tuberculous pericarditis has been previously described, including treatment options to prevent progression to constriction [16, 28, 30-32]. In contrast to Reuter's findings in TB pericarditis [26] we found histological evidence of definite tuberculosis in only nine operative pericardial biopsy specimens and could not determine from these small numbers whether histological evidence of tuberculosis is more common in HIV positive subjects.

Similar to Mutyaba et al [(2)], we have shown few differences in the clinical profile between HIV positive and HIV negative patients. Higher levels of alkaline phosphatase and gamma glutamyl transferase among HIV positive patients might have been due to hepatic tuberculosis or more likely to more severe hepatic congestion in these subjects. Of note there was no difference in the preoperative and follow up ejection fraction between HIV positive and HIV negative patients. This finding differs from studies in patients with tuberculous pericarditis co-infected with HIV who have

been found to have a higher prevalence of myopericarditis.[27,28] Although only three patients died, preservation of ejection fraction might explain why we found no significant differences in perioperative mortality observed between HIV positive and negative patients. It is also likely that antiretroviral therapy in our patients may have helped to preserve left ventricular function by preventing the development of opportunistic infection or HIV associated myocardial dysfunction.

Pericardial calcification was identified on chest radiography in 17(20,5%) of our study patients, which is similar to that reported in a recent series by Mutyaba et al [2] but much higher than the 5% reported by Strang et al in the pre HIV era. [19] Equivalent rates of pericardial calcification in HIV positive and HIV negative patients (21.4% vs 20.7%; p = 0.953) have been described in Mutyaba et al study[2]. In contrast, we found that pericardial calcification was an uncommon finding in HIV positive patients compared with HIV negative patients (6.3% vs 29.4%; p=0.011). Furthermore none of the eight patients with CD4 counts < 200 developed pericardial calcification. We attributed the higher prevalence of pericardial calcification amongst HIV negative patients to longer survival in these patients with prolonged duration of inflammation and progression to calcification; alternatively it could be explained by the suppression of CD4 helper by the HIV virus leading to less fibrogenesis and calcification in these subjects. [26]

Among the 31 subjects who did not undergo surgery, 15 patients were still alive at follow-up (survival status unknown in 2) and 5 reported improvement in their symptoms. Given that these patients had been diagnosed with tuberculous constriction and received antituberculous therapy it highlights what has been described previously by Strang et al [29]: a significant number of patients diagnosed with tuberculous constrictive pericarditis may undergo resolution of their symptoms on anti-tuberculous therapy. The high preoperative mortality rate of 16.78% emphasizes the importance of pericardiectomy in ensuring a successful outcome in subjects who do not respond to

antituberculous therapy. Our analysis of the preoperative outcome showed that HIV status had no influence on the preoperative mortality in constrictive pericarditis. Of the 14 deaths 4 were HIV positive. On bivariate analysis, older age, unsuppressed viral load, lower serum haemoglobin and albumin levels were shown to predict preoperative mortality. On multivariate analysis age, serum albumin, gamma GT and pulmonary artery pressure emerged as independent predictors of mortality.

Operative Outcomes. On analysis of patients undergoing pericardiectomy, we found that complete pericardiectomy was less likely to be achieved in HIV positive (n= 9, 50%) as compared to negative patients (n=37, 71%). Also perioperative complications appeared to be more common in HIV positive patients undergoing pericardiectomy. Whether this could be due to more inflammation with anatomical distortion making surgery more difficult is not clear. An important finding in our study is that we found no difference in the short term peri-operative outcome between HIV positive and HIV negative patients. Our perioperative mortality rate of 5.7% is consistent with that reported in the majority of series worldwide.[6, 9, 11-14, 18] Of two South African based studies, our in hospital perioperative mortality rate of 5.7% was higher that of Fennel et al [12] (4/109; 3.7%) in the pre-HIV era but less that the 14% 30 day perioperative mortality found by Mutyaba et al [2] in their series.

At the six week follow up visit, most patients in our series showed significant improvement in NYHA class (p = <0.001). (Table 5), with improvement in at least one functional class to NYHA I (78.6%) and NYHA II (21%). This finding is consistent with reported by Mutyaba et al [2] and Tetty et al. [20] Furthermore, ejection fraction was preserved in both HIV positive and negative subjects.

STUDY LIMITATIONS

Our study has limitations related to its retrospective design, including a number of patients lost to follow up whilst awaiting surgical pericardiectomy. Despite this we were able to obtain survival status in in most patients preoperatively and were able to show that number of subjects demised while awaiting surgery. Furthermore long term patient follow up was often not possible. Based on the available patient records we could only accurately comment on in-patient perioperative mortality and early six week follow up of postoperative patients.

CONCLUSION

This finding has important clinical implications: It shows that constrictive pericarditis is associated with a high preoperative mortality and emphasizes the benefits of surgery in patients who do not respond to antituberculous therapy. It also shows that whilst HIV infection is associated with a higher in hospital complication rate, early peri-operative mortality is unaffected in subjects who are on antiretroviral treatment and are virologically supressed.

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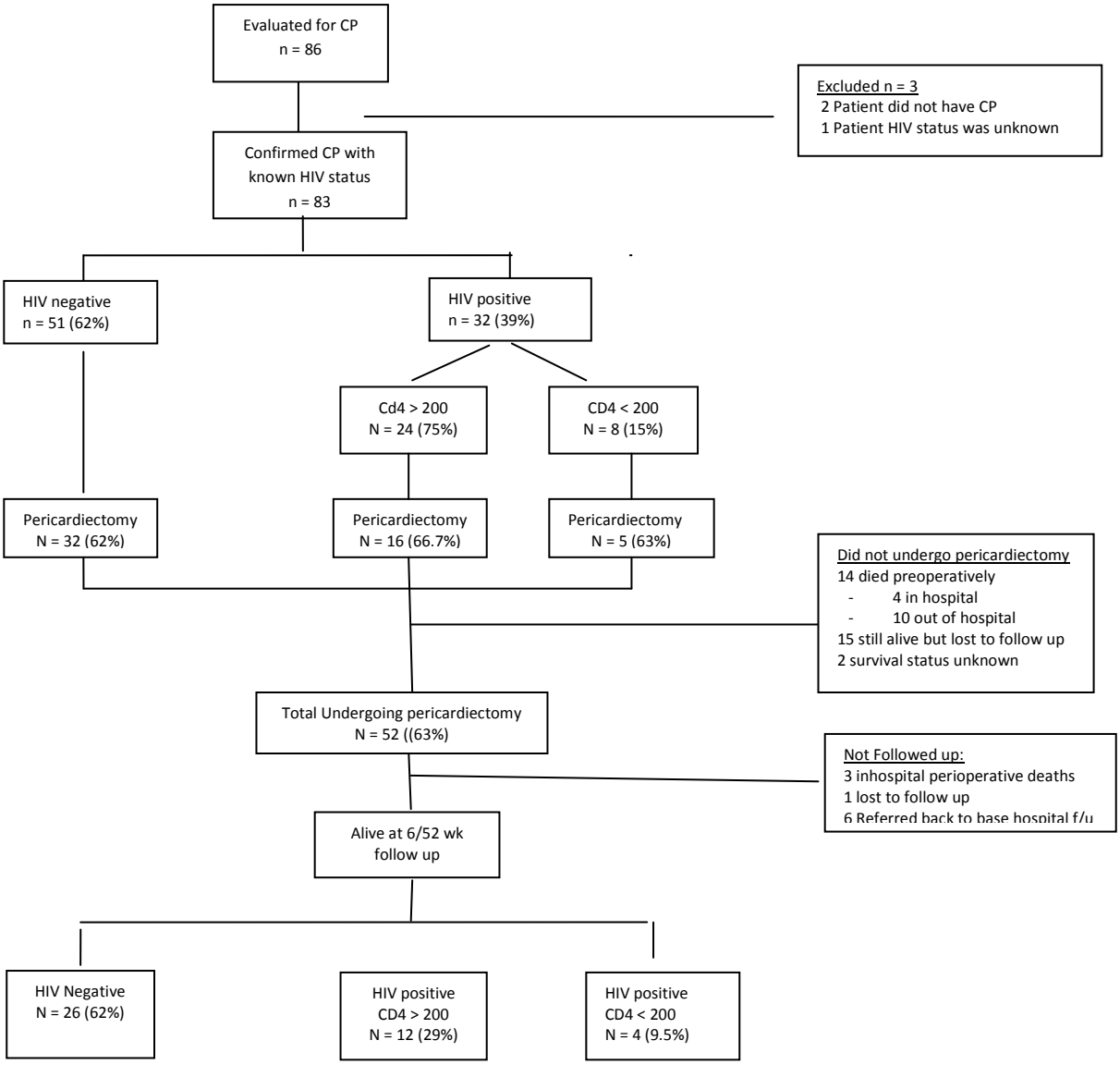

Figure 1: Early outcome of patients with constrictive pericarditis

TABLE 1: Baseline characteristics of study patients stratfied by HIV status

Characteristic	All (n = 83)	HIV negative (n = 51)	HIV Positive (n =32)	*P* valve
Age (y)	37.98 ± 12.91	38.82 ± 14.56	36.63 ± 14.56	.454
Weight	65.75 ± 12.81	67.69 ± 13.05	62.77 ± 12.01	.091
Gender				.245
Male	43(51.8)	29(56.9)	14(43.75)	
Female	40(48.2)	22(43.1)	18(56.35)	
Cause of constrictive pericarditis				.140
Probable tuberculosis	58(69.9)	39(76.5)	19(59.4)	
Proven tuberculosis	22(26.5)	9(17.6)	13(40.6)	
Other	3(3.6)	3(5.9)	0	
NYHA functional class				.841
I	3(3.6)	2(3.9)	1(3.1)	
II	53(63.9)	33(64.7)	20(62.5)	
III	22(26.5)	12(23.5)	10(31.3)	
IV	5(6.0)	4(7.8)	1(3.1)	
Examination				
SBP (mm HG)	110.83 ± 11.85	110.78 ± 11.67	110.91 ± 12.32	.964
DBP (mm HG)	70.57 ± 10.63	71.43 ± 9.86	69.19 ± 11.78	.352
Pulse rate (beats/min)	88.76 ± 14.72	86.35 ± 14.74	92.59 ± 14.05	.060
Jugular venous pressure	77(92.8)	48(94.1)	29(90.6)	.358
Pericardial knock	43(51.8)	24(47.1)	19(59.4)	.274
Hepatomegally	76(91.6)	46(90.2)	30(93.8)	.767
Ascites	57(68.7)	35(68.3)	22(68.8)	.991
Oedema	65(78.3)	44(86.2)	21(65.6)	.026
Chest x-ray				
Pericardial calcification	17(20.5)	15(29.4)	2(6.3)	.011
Pleural effusion	67(80.7)	43(84.3)	24(75.0)	.295
Echocardiography				
Ejection fraction (%)	52.19 ± 6.61	51.88 ± 7.50	52.69 ± 4.96	.593
End diastolic dimension (mm)	47.95 ±7.93	47.4 ±7.92	48.81 ± 8.01	.435
Left atrial size (mm)	43.85 ±8.57	44.86 ± 9.5	42.28 ± 6.70	.185
Septal bounce	81(97.6)	49(96.1)	32(100.0)	.257
Pulmonary Artery Pressure (mmHg)	34.31 ± 8.41	33.88 ± 8.86	34.96 ± 7.76	.571
Dilated IVC and hepatic veins	73(97.3)	45(100.0)	28(93.3)	.157
CT chest and mediastinum [k]				
Pleural effusion	58(75.3)	37(80.4)	21(67.7)	.282
Pericardial thickening	73(94.8)	45(97.8)	28(90.3)	.297
Pericardial calcification	18(23.4)	15(32.6)	3(9.7)	.032
Lymphadenopthy	47(61.0)	27(58.7)	20(64.5)	.642
Laboratory results: mean +-SD				
Haemaglobin g/dL	12.78 ± 1.75	12.91 ± 1.76	12.58 ± 1.74	.418
White cell count (10^9/L)	5.15 ± 1.47	5.25 ± 1.48	4.99 ± 1.46	.444
Platelets (10^9/L)	251.86 ± 84.37	244.20 ± 79.82	264.06 ± 91. 11	.299
Sodium (mmol/l)	136.96 ± 3.33	137.27 ± 3.50	136.47 ± 3.03	.286
Urea (mmol/l)	6.58 ±2.57	6.40 ± 2.79	6.86 ± 2.20	.429
Creatinine (µmol/l)	81.70 ± 20.51	81.76 ± 20.05	81.59 ± 21.55	.971
Albumin (g/l)	37.60 ± 6.33	38.04 ± 5.99	36.91 ± 6.89	.431
Aspartate aminotransferase (U/L)	39.35 ± 13.59	37.22 ± 10.51	42.28 ± 16.69	.110
Alanine aminotransferase (U/L)	25.21 ± 16.94	20.71 ± 10.70	32 ± 22.09	.002
Alkaline phosphatase (U/L)	167.40 ± 89.50	146.02 ± 67.70	201 ± 108.82	.005
Gamma glutamyl transferase U/L)	249.16 ± 224.09	172.96 ± 104.76	370 ± 300.59	<.001

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. *NYHA* , New York Heart Association; *IVC* , Inferior vena cava; CT, Computer Tomography. [k] CT scanning was not undertaken in 6 subjects (5 HIV negative and 1 HIV positive subject). No results for dilated IVC and hepatic veins for 8 subjects (6 HIV negative and 2 HIV positive).

Table 2: Bivariate logistic regression model of factos associated with preoperative mortality

Characteristics	Alive n = 69	Preoperative death n = 14	Odds ratio (95% CI)	P value
Age: mean+-sd	35.4+-11.7	50.7+-11.0	1.11 (1.04-1.18)	<0.001
Gender				
Female	33(47.8)	7(50.0)	0.92 (0.29-2.89)	.882
Male	36(52.2)	7(50.0)		
HIV Positive				.693
CD4 > 200	21(30.4)	3(21.4)	0.59(0.15-2.36)	
CD4 < 200	7(10.1)	1(7.1)	0.59(0.65-5.32)	
NYHA Class	69(100)	14(100)	1.50 (0.65-3.48)	.351
Haemaglobin g/dL	12.96 ± 1.70	11.91 ± 1.78	0.67 (0.45-0.99)	.031
White cell count (10 ?/L)	5.17 ± 1.45	4.99 ± 1.58	0.91 (0.61-1.37)	.660
Platelets (10 ?/L)	257 ± 89.01	224.64 ± 49.96	0.99 (0.99-1.00)	.160
Sodium (mmol/l)	137 ± 3.33	136 ± 3.28	0.91 (0.77-1.07)	.243
Urea (mmol/l)	6.37 ± 2.17	7.6 ± 3.96	1.17 (0.96-1.42)	.131
Creatinine (µmol/l)	80.37 ± 20.87	88.21 ± 17.94	1.02 (0.99-1.04)	.192
Albumin (g/l)	38.35 ± 6.29	33. 93 ± 5.37	0.90 (0.82-0.99)	.019
Aspartate aminotransferase (U/L)	41.16 ± 13.71	31.36 ± 9.97	0.91 (0.85-0.98)	.003
Alanine aminotransferase (U/L)	25.87 ± 16.88	22 ± 17.52	0.98 (0.94- 1.03)	.403
Alkaline phosphatase (U/L)	175.94 ± 93.06	125.29 ± 54.11	0.99 (0.98-1.00)	.061
Gamma glutamyl transferase U/L)	269.39 ± 235.30	149.43 ± 119.43	1.00 (0.99-1.00)	.071
Ejection fraction (%)	51.97 ± 6.75	53.29 ± 6.06	1.03 (0.94-1.13)	.491
Pulmonary artery pressure (mmHg)	32.80 ± 6.88	43 ± 11.19	1.13 (1.05-1.22)	<0.001

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. NYHA, New York Heart Association. CI, confidence interval.

TABLE 3: Operative characteristics of study patients stratified by HIV status

Characteristic	All (n = 52)	HIV Negative (n = 32)	HIV positive (n = 20)	P value
Pericardiectomy				.093
Total	38(73.1)	26(81.3)	12(60.0)	
Sub-total	9(17.3)	2(6.3)	7(35.0)	
Not known	5(9.6)	4(12.5)	1(5.0)	
Inotrope usage [P]	48(94.1)	31 (96.9)	17(85.0)	.547
Days in ICU	4.59 ± 2.84	4.28 ± 2.74	5.11 ± 2.84	.321
Post operative Complications	15(28.9)	6(18.8)	9(45.0)	.030
Pericardial histology [t]				
Granulomas	9(18.4)	4(12.9)	5(27.8)	.259
Acid fast bacili	3(6.1)	1(3.2)	2(11.1)	.546
Calcification	12(24.4)	10(32.3)	2/18(11.1)	.168
Post operative Ejection fraction [u]	53.55 ± 6.65	53.33 ± 6.70	53.93 ± 6.79	.783
Post operative six week follow up[v]				.687
NYHA I	33(80.4)	20(76.9)	13(86.7)	
NYHA II	9(21.4)	6(23.1)	2(18.8)	
Ejection fraction [y]	53 ± 9.16	52.44 ± 11.50	53.83 ± 4.67	.785

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. *ICU*, Intensive care unit. *NYHA*, New York Heart Association. [P] Details of inotrope usage was not availabe for 1 subject. [t] 3 Subjects histology results were not found (1 HIV negative, 2 HIV positive).[u] 9 subjects did not have post operative measurement of ejection fraction (4 HIV negative subjects and 5 HIV positive subjects). [v] 41 patients attended six week follow up (26 HIV negative, 15 HIV positive). Follow up ejection patients (HIV neg 10, HIV positive 5).

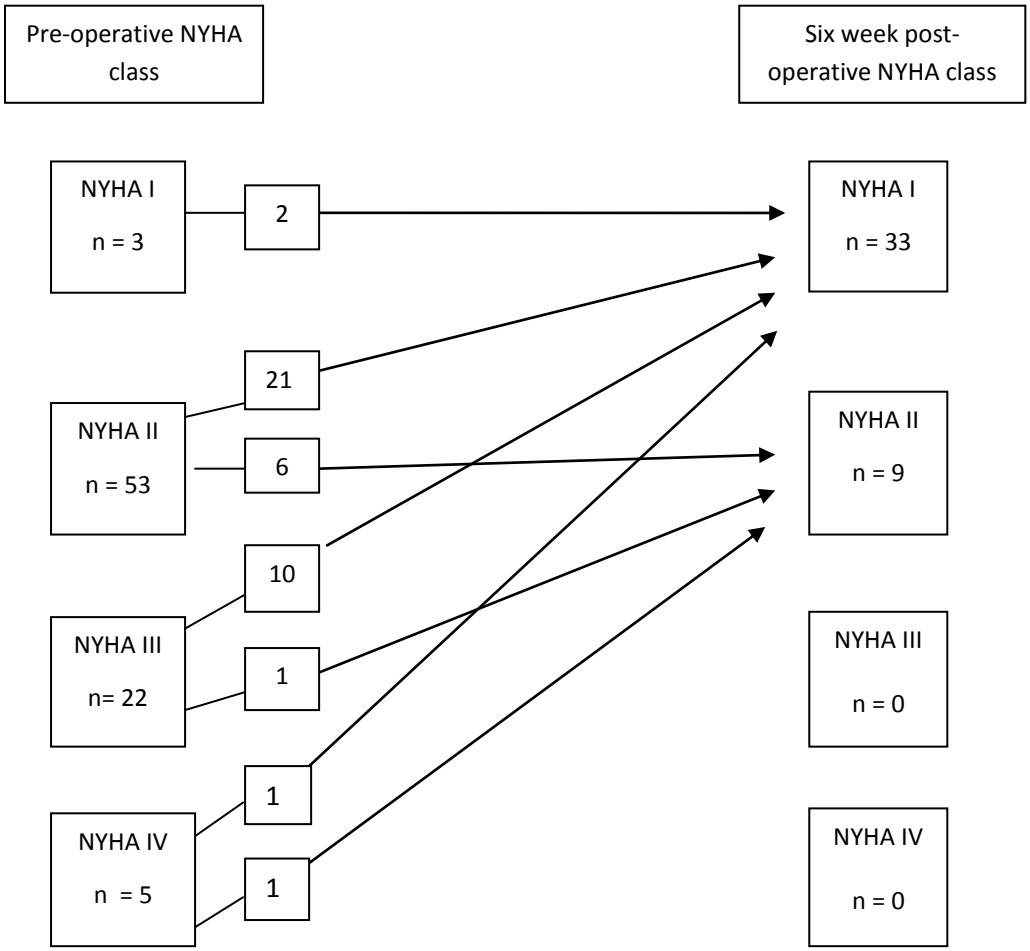

FIGURE 1. Comparison of preoperative and six week postoperative New York Heart Association functional status in 41 patients (P<.0001). NYHA, New York Heart Association. Most subjects improved by at least one functional class.

Appendix 1: The Guidelines for Authorship for the Journal selected for submission of the manuscript

INFORMATION FOR AUTHORS

The Cardiovascular Journal of Africa is pleased to consider original articles, reviews, discussions on topical issues, case studies, meeting reports and other contributions relevant to the understanding, treatment and care of vascular disease.

Original articles and reviews are sent for independent peer-review. Material is accepted for publication on the understanding that it has not been published elsewhere. Authors will be asked to confirm this in writing and transfer copyright to the Journal.

Authors submitting papers to CVJA should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more that once a year but in rare circumstances it may be twice.

Manuscript Processing Fee (effective 1 January 2016)

It has become necessary for the Cardiovascular Journal of Africa to charge a modest manuscripts processing fees for all articles submitted for publication.

- South African and African Authors: ZAR 1000
- International Authors: ZAR 2000

This is normal for most, if not all, journals. We so far have been able to survive without charging authors for submissions but can no longer do so. We regret that we have to implement this as from the 1st of January 2016. Payment will need to be made online and once payment has been received, the manuscript will be further processed for possible publication.

This payment is a processing fee and does not guarantee publication of the article. The processing fee is not refundable in the event of rejection as processing cost will have been incurred. **(Payment can be made online with a valid credit card)**

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The Cardiovascular Journal of Africa (CVJA), which incorporates the Cardiovascular Journal of South Africa, is particularly concerned with publication of scientific articles related to Cardiac and Vascular conditions and situations, concerning adults and children, in Sub Saharan Africa. But will accept articles from all parts of the world.

Basic Science publications related to clinical aspects either for elucidation, in-depth understanding or therapeutic approaches are accommodated. The Journal functions as official medium for other related societies which do not as yet have own Journals such as, Hypertension, Stroke, Nuclear Medicine and Magnetic Resonance in Cardiology, Paediatrics, Molecular and Cellular Cardiology, and Vascular disease in Diabetes and Obesity.

Index Medicus / PubMed Central / Medline and Sabinet lists the Journal for indexing and electronic citation. A printed version and an electronic version for citation and publication of abstracts are produced. The abstracts of articles published

appear on PubMed with a link out to Sabinet to give access to full text retrieval of published material. **In order to improve visibility for our authors, the CVJAfrica is now also able to index articles for PubMed Central.**

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All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by fax or mail (fax number +27 21 976 8129 or PO Box 1013, Durbanville, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format

Image Format	.tif
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Alpha Channels	None
Layers	Flattened

Alternative Image Format

Image Format	.jpg
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Compression Quality	Maximum

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

Reviews

Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a

separate box itemising two to five short principal statements. Acknowledgements, references, tables and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures and references as above.

Figures be sent to us in a high resolution JPEG format, but they MUST be sent separately from the Word document. If not in high resolution JPEG, then PowerPoint will do. Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by fax or mail (fax number 0866 644 202 or PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com** .

The status of progression of the peer-review system will be directly accessible by authors. The Editorial Manager system is particularly useful to authors and reviewers as there is a direct link to PubMed for viewing all related articles on the subject matter.

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Authors submitting papers to CVJA should also register as a reviewer as a quid pro quo for authors for reviewers reviewing your submission. If authors do not register as reviewers it may be taken in consideration when deciding on acceptance and rejection, and the time of publication. We do try not to call on a reviewer more that once a year but in rare circumstances it may be twice.

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The Cardiovascular Journal of Africa is launching an **online First Advance Online Publication (ePublication ahead of print)** with full text availability via Pubmed and this website which is accessible via Google and other search engines.

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ZAR 4000 for Authors outside of Africa
ZAR 1500 for African Authors (including South Africa)

Please note that the Online First option is only available once your article has been accepted for publication. Also note there will be no refunds, any payment made before an article is accepted / rejected will be forfeited.

Appendix 2: Ethical approvals

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

27 August 2015

Dr G Laurence (993230264)
Department of Cardiology
School of Clinical Medicine
Health Sciences
grahamlaur@yahoo.co.uk

Dear Dr Laurence

Protocol: The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.
Degree: MMed
BREC reference number: BE324/15

PROVISIONAL APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has considered your application received on 13 July 2015.

The study is given **PROVISIONAL APPROVAL** pending a response to the following:

1. Gatekeeper permission is required.

Only when full ethical approval is given, may the study begin. **Full ethics approval has not been given at this stage.**
PLEASE NOTE: Provisional approval is valid for 6 months only - should we not hear from you during this time - the study will be closed and reapplication will need to be made.
Your acceptance of this provisional approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.
BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

Yours sincerely
Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

cc supervisor: naidood@ukzn.ac.za

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
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Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

18 September 2015

Dr G Laurence
Department of Cardiology
IALCH

Dear Dr Laurence

Re: Approved Research: Ref No: BE324/15: The effects of HIV/AIDS on the clinical profile and outcomes post percardectomy of patients with constrictive pericarditis. A retrospective review.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

.....

Dr M Letebele
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management (HKRM)

330 Langalibalele street,
Private Bag X9051 PMB, 3200
Tel: 033 395 2805/3189/3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference: **HRKM24/16**
KZ_2016RP40_62

15 February 2016

Dear Dr G Laurence
(University of KwaZulu-Natal)

Subject: Approval of a Research Proposal

1. The research proposal titled **'The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 16/02/16.

Fighting Disease, Fighting Poverty, Giving Hope

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

17 February 2016

Dr G Laurence (993230264)
Department of Cardiology
School of Clinical Medicine
Health Sciences
grahamlaur@yahoo.co.uk

Protocol: The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.
Degree: MMed
BREC reference number: BE324/15

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 13 July 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 16 February 2016 to queries raised on 09 February 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval**.

This approval is valid for one year from **17 February 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **08 March 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: naidood@ukzn.ac.za
cc postgrad: jantjies@ukzn.ac.za

Patient Data Capture Sheet (MMed – Medicine)

Title: The effects of HIV/AIDS on the clinical profile and outcomes post pericardectomy of patients with constrictive pericarditis. A retrospective review.

Principal Investigator: Dr G Laurence

Supervisor: Prof DP Naidoo

Age	
Sex	
Referral region	
Cause of Constriction - Tuberculous - Idiopathic - Other	
Symptoms:	
- Duration	
- NYHA class (Preop)	
HIV status	
Co-Morbidities	
- Hypertension	
- Diabetes	
- Opportunistic infections (Syphilis, hepatitis)	
Examination Findings	
- Blood Pressure	
- Heart rate	
- Pulsus paradoxus	
- Early S3	
- Inspiratory splitting S2	
- Kussmauls sign	
- Ascities	
- Pleural effusion	
- Hepatomegally	
- Atrial fibrillation	
-	
Imaging	
- X ray: Pericardial calcification	
- CT chest: Pericardial thickening	

- Echocardiography: LV and RV function, septal wall motion abnormalities, IVC collapse, pericardial thickening	
Blood Results	
- Haemaglobin (g/dl)	
- Sodium	
- Urea	
- Creatinine	
- Albumin	
- AST/ALT	
- GGT/ ALP	
- CD4 count/ Viral load	
- Hepatits B Surface antigen	
- RPR	
Treatment	
- Pericardiectomy	
- Diuretic usage	
- ICU stay	
Follow up	
- Post op: NYHA status/ Ejection fraction	
- Duration of follow up	
Complications	