THE INITIATIVE TO INVESTIGATE THE MANAGEMENT OF PERICARDITIS IN AFRICA (IMPI) REGISTRY: A SUBSTUDY ON THE CAUSES OF CONSTRICTIVE PERICARDITIS AND PREDICTORS OF MORTALITY IN PATIENTS WITH CONSTRICTIVE PERICARDITIS REQUIRING PERICARDIECTOMY AT GROOTE SCHUUR HOSPITAL (THE CONSTRICTIVE PERICARDITIS SUBSTUDY)

by

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Figures and Tables:

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List of abbreviations:

-GSH: Groote Schuur Hospital

-UCT: University of Cape Town

-NYHA: New York Heart Association. A schema for classifying severity of symptoms of heart disease depending on degree of shortness of breath

-HIV/AIDS: Human Immuno-deficiency Virus / Acquired Immune Deficiency Syndrome

-CART: Combination Anti-Retroviral Therapy

-CP: Constrictive pericarditis

-TB: Tuberculosis

-HR: Hazard ratio

-95% CI: 95% confidence interval

-CT scan: Computed Tomography scan

-MRI scan: Magnetic Resonance Imaging scan

-RV: Right ventricle

-LV: Left ventricle

-TR: Tricuspid regurgitation

-CVP: Central Venous Pressure

Abstract

Background: Causes of constrictive pericarditis and predictors of peri-operative outcome following pericardiectomy are not clearly elucidated, especially in Africa, where disease characteristics differ from developed countries. Furthermore, the impact of HIV/AIDS on pericardial constriction and outcomes following surgery is unknown. We set out to investigate the causes of constrictive pericarditis, the outcomes after pericardiectomy and the predictors of mortality in Cape Town, South Africa during a 22-year period of high HIV/AIDS prevalence.

Methods: A retrospective review of records of all patients who underwent pericardiectomy for constrictive pericarditis at Groote Schuur Hospital from 1 January 1990 to 31 December 2012 was performed.

Results: Of 121 patients, thirty six (29.8%) had proven tuberculosis, 74 (61.2%) presumed tuberculosis, six (5%) idiopathic, and 5 (4%) miscellaneous causes of constrictive pericarditis. Seventeen patients (14%) died peri-operatively with low cardiac output syndrome the main cause of mortality. In multivariable analysis, serum sodium (HR=0.88, 95%CI 0.80-0.97 p=0.009) and pre-operative New York Heart Association (NYHA) class IV (HR=3.42, 95%CI 1.29-9.08, p=0.014; compared with combined class I-III) were independent predictors of early mortality. There were 14 (11.6%) HIV positive patients with a mean CD4 cell count of 284 ± 133 cells/µl. No early deaths occurred in the HIV positive patients.

Conclusion: Tuberculosis is the main cause of constrictive pericarditis in South Africa. Despite its efficacy at relieving symptoms of heart failure, pericardiectomy is associated with a high peri-operative mortality rate which was not influenced by HIV status. NYHA IV functional class and hyponatraemia predict early mortality after pericardiectomy.

(249 words)

CHAPTER 1: LITERATURE REVIEW

Constrictive pericarditis is a curable cause of heart failure that occurs as a result of fibrous thickening of the pericardial sac that surrounds the heart. Renowned Spanish physician Avenzoar (1113 – 1162) described serofibrinous pericarditis in the middle ages. (1) In 1669, Richard Lower[1], the pre-eminent physician in the court of Charles II of England noted 'dyspnoea and intermittent pulse in a patient with constrictive pericarditis.'(2) The pericardial knock of constrictive pericarditis was first described in 1842 by Dominic Corrigan[2](3) while pulsus paradoxus, common in constrictive pericarditis was first described by Adolf Kussmaul[3] in 1873. (4) In 1929, Edward Doles Churchill performed the first pericardiectomy for adhesive pericarditis in the USA. (5)

The visceral and parietal layers compose the normal pericardium. The visceral layer is a single sheet of ciliated mesothelial cells that line the entire outer surface of the cardiac chambers and the origins of the great vessels. This monolayer reflects outwards onto a thin fibrous sheet that completely surrounds the heart and origins of the great vessels to form the parietal pericardium. The pericardial space is created by this reflection and normally contains 15-50ml of clear serous fluid. The parietal pericardium is tethered to the diaphragm, the sternum and the vertebrae by ligaments that confer stability to the heart and great vessels during the cardiac cycle. Together, the pericardial bi-layer and space (with its constituent fluid) function to prevent excessive dilatation of the myocardium during diastole (thus preserving ventricular contractility by preventing excessive stretch in diastole), evenly distribute physical forces over the underlying cardiac chambers and act as a barrier to the contiguous spread of pathology from the extra-pericardial space to the heart. The limitation of cardiac dilatation afforded by the pericardium gives rise to the phenomenon of ventricular interdependence – overfilling of one ventricle reduces the filling of the other ventricle when the maximal filling volume allowed by

[1] Richard Lower (1631-1691): English physician. Also named the Circle of Willis (after his mentor) and perfomed the first human blood transfusion in 1667.
[2] Sir Dominic John Corrigan (1802 – 1880): Irish physician. Also described Corrigan's sign and Corrigan's pulse of aortic valve insufficiency
[3] Adolf Kussmaul (1822-1902): Noted German physician and clinician. Apprenticed under Rudolf Virchow. Notable for many eponyms in modern medicine including Kussmaul's breathing, Kussmaul's sign and Kussmaul-Maier disease (Polyarteritis nodosa)

the compliance of the parietal pericardium is reached (usually 15-20% in excess of the normal filling volume). (6) Exaggerated ventricular interdependence is seen in many disease states of the pericardium including constrictive pericarditis.

In constrictive pericarditis, hypertrophied, fibrotic, adherent and at times calcified visceral and parietal pericardium have reduced compliance thus preventing adequate filling of the ventricles in diastole, with systolic function usually preserved. Fibrosis in constrictive pericarditis occurs over a long time as a result of recurrent or chronic inflammation of the pericardium due to various causes. Some of these causes are shown in Table 1. Figure 1 demonstrates pericardial adhesion and thickening in a heart recovered at autopsy from a patient with tuberculous constrictive pericarditis while figure 2 is the microscopic appearance of the same heart illustrating the hypertrophy and fibrosis of the visceral pericardium. Figure 3 illustrates extension of fibrosis into the myocardium in the same patient; this may occur in cases of longstanding constrictive pericarditis. In a minority of patients with constrictive pericarditis (20%), the pericardium is not thickened i.e. < 3mm. (7-9)

Causes of constrictive pericarditis
1. Unknown antecedents
2. Post idiopathic pericarditis
3. Infections -Bacterial: Streptococcus pneumonia, Staphylococcus aureus, Tuberculosis -Fungi: histoplasmosis, coccidioidomycosis -Viral: Coxsackie B
4. Connective Tissue Diseases: Rheumatoid Arthritis, Systemic Lupus Erythematosus
5. Maligancy: Primary mesothelioma, metastatic disease from lung, breast, lymphoma, melanoma
6. Post-trauma
7. Post cardiac surgery
8. Post radiation therapy
9. Drug therapy: methysergide
10. Rare causes: Sarcoidosis, post-myocardial infarction, Rheumatic heart disease

Table 1: Causes of constrictive pericarditis (adapted from Fowler NO. Constrictive Pericarditis: its history and current status (5)

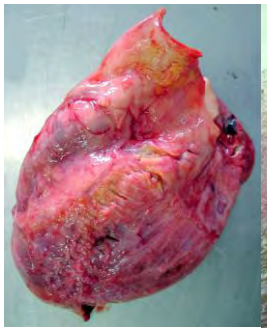

Fig 1: Postmortem specimen of a heart with tuberculous constrictive pericarditis demonstrating thickening and fibrosis of the visceral pericardium

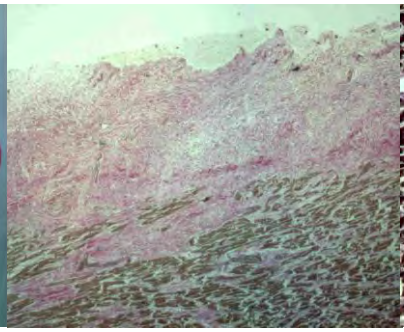

Fig 2: Microscopic appearance of the heart in Fig. 1 showing a hypertrophied and fibrotic pericardium overlying the myocardium

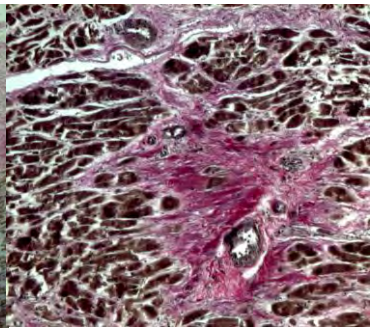

Fig 3: Microscopic appearance of the heart in Fig. 1 showing the fibrotic process extending into the myocardium as can occur in longstanding constrictive pericarditis.

When the heart is constricted, the rigid pericardium does not transmit negative (inspiratory) intrathoracic pressure to the cardiac chambers. This negative pressure is, however, transmitted to the (unconstricted) pulmonary veins causing a diminution in transfer of pulmonary venous blood to the left heart with reduced trans-mitral flow and thus underfilling the left ventricle. (1) This negative pressure simultaneously causes increased venous return to the right heart causing increased trans-tricuspid flow and right ventricular volume in diastole. This volume increase is accompanied by elevation in diastolic right ventricular pressure and subsequent shift of the interventricular septum to the left (to accommodate the volume increase) in deference to ventricular free wall which is constricted by a rigid pericardium. This further reduces left ventricular filling and subsequent stroke volume and illustrates the exaggerated ventricular interdependence for which constrictive pericarditis is known. (6,8) The opposite occurs during expiration.

Patients with pericardial constriction present mainly with longstanding signs and symptoms of predominantly right heart failure as pericardial constriction causes systemic congestion out of proportion to pulmonary congestion. (8) The symptoms include abdominal and lower limb swelling and effort intolerance developing insidiously over months to years. Table 2 highlights common signs in patients with pericardial constriction. The Vogelpoel-Beck sign* is of particular interest as it is eponymously named after two physicians who practiced at Groote Schuur Hospital

in the past century; it describes the transient sudden splitting of the second heart sound at the onset of inspiration as the aortic valve closes earlier than expected due to the underfilling of the left ventricle. (10) It commonly accompanies a significant pulsus paradoxus as the same mechanism underlies both signs. Severe constriction can present as cardiac cirrhosis with jaundice and protein-losing enteropathy. (11)

Physical signs in constrictive pericarditis

Physical sign	**Frequency of observation**
Sinus tachycardia	47 (70%; persistent atrial fibrillation in 2)
Significant pulsus paradoxus	32 (48%)
Raised jugular venous pulse	67 (100%)
Apex palpable	39 (58%)
Pericardial knock	14 (21%)
Increased cardiac dullness	17 (25%)
Heart sounds soft	51 (76%)
Third heart sound	30 (45%)
Vogelpoel-Beck sign*	24 (36%)
Hepatomegaly	67 (100%)
Ascites	60 (89%)
Oedema	63 (94%)

Table 2: Physical signs noted by a single observer in 67 patients with constrictive pericarditis (Adapted from Strang JI. Tuberculous Pericarditis in Transkei(12)

A definitive diagnosis of pericardial constriction depends on the presence of pericardial thickening and demonstration of changes in cardiac haemodynamics arising from reduced pericardial complicance. The electrocardiogram (ECG) commonly demonstrates small QRS complexes, sinus tachycardia and widespread T-wave flattening or inversion. (8,13) In pure constrictive pericarditis, the chest x-ray reveals a normal sized heart with evidence of pulmonary congestion or pleural effusions and sometimes, pericardial calcification. On echocardiography, a thickened pericardium is represented by an echo-bright pericardium. Echocardiography with doppler measurement is used to demonstrate haemodynamic changes that are suggestive of pericardial constriction. These

include exaggerated septal wall shift towards the left ventricle with inspiration, dilatation and diminished collapse of the inferior venacava and hepatic veins with inspiration, rapid early diastolic (e wave) deceleration and blunted late diastolic (a wave) velocities on trans-mitral and trans-tricuspid inflow doppler measurement with respiratory variation. (7,8,14) Tissue doppler imaging especially of mitral annular velocity and 2-dimensional speckle tracking to detect longitudinal and circumfrential myocardial deformation are echocardiographic techniques that are especially of use in differentiating pericardial constriction from restrictive cardiomyopathy. (1) Pericardial thickening (> 3mm thick), calcification and abnormal septal motion can be demonstrated by Computed Tomography (CT) scanning. (8) Cardiac Magnetic Resonance Imaging (MRI) can also demonstrate pericardial thickening, calcification and abnormal septal motion. The presence of pericardial adhesions which can be seen on tagged cine MRI images is a very reliable sign of pericardial constriction. (8) MRI can further demonstrate the presence of myocardial inflammation, fibrosis and atrophy which may be useful in prognostication and clinical decision making regarding management. (13)

Cardiac catheterisation is used to demonstrate the haemodynamic features of pericardial constriction especially when the diagnosis is in doubt. The typical findings include elevated atrial pressures, elevated right and left end-diastolic ventricular pressures with equalisation of the end-diastolic pressures of all four chambers (within 5mmHg of each other) and the dip-and-plateau configuration of the ventricular diastolic pressures. (8) The most specific haemodynamic feature of constrictive pericarditis is the demonstration of enhanced ventricular interdependence manifesting as an increase in the amplitude of the right ventricular (RV) pressure tracing with a concomitant decrease in the amplitude of the left ventricular (LV) pressure tracing with inspiration – the systolic area index. (7,15) This change in systolic area with respiration distinguishes pericardial constriction from restrictive cardiomyopathy and is demonstrated in Figure 4. (7,15)

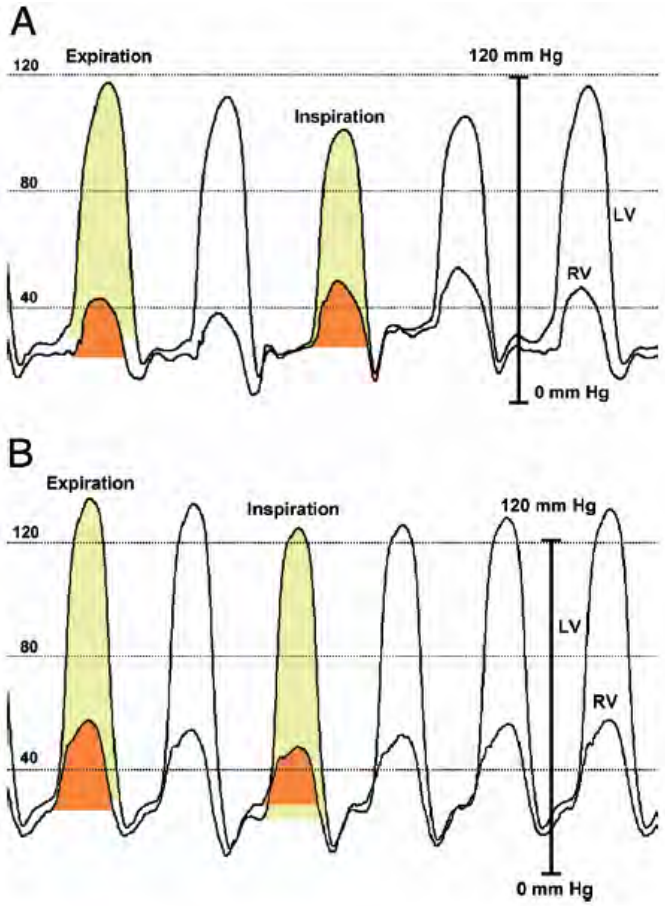

Figure 4: In constrictive pericarditis (A), inspiration causes less filling of the LV, and the amplitude of LV pressure tracing decreases (yellow shaded area) as compared with expiration. The RV pressure tracing increases with inspiration (orange shaded area). This discordant pressure change between the LV and RV occurs in constrictive pericarditis.
In restrictive cardiomyopathy (B) the changes in LV and RV systolic pressures with respiration are concordant. During inspiration the amplitude of the RV pressure tracing decreases (orange shaded area) as compared with expiration. The amplitude of the LV pressure tracing (yellow shaded area) is unchanged during inspiration and expiration. There is early rapid filling, elevation and end-equalization of the LV and RV pressures in both cases (dip-and-plateau configuration)
(Adapted from Talreja et al. Constrictive Pericarditis in the Modern Era. Novel Criteria for Diagnosis in the Cardiac Catheterization Laboratory. (15)

Management of pericardial constriction with diuretics achieves symptomatic relief but does not address the underlying problem. Persistent symptoms despite adequate diuresis usually necessitates pericardiectomy – surgical excision of the diseased pericardium. (9,14) Pericardiectomy is a major procedure that involves thoracotomy with or without cardiopulmonary bypass and carries a 30-day mortality of up to 10%. (9) Pericardiectomy cures most patients of their symptom but up to 30% of patients may still report symptoms of pericardial constriction years after undergoing pericardiectomy due to a combination of disease and surgical-related factors. (7)

A review of the literature on constrictive pericarditis and pericardiectomy was conducted with a view to understanding the different experiences of clinicians

involved in the management of patients with pericardial constriction worldwide and comparing this to local practice. A literature search of Pubmed and Medline using the keywords 'constrictive pericarditis', 'pericardiectomy' and 'HIV/AIDS' was carried out. Among others, the aims were to explore the causes of constrictive pericarditis around the world, to determine the mortality following pericardiectomy for constrictive pericarditis and understand the factors influencing mortality, to explore the effect of Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS) on the clinical profile of constrictive pericarditis and outcomes after pericardiectomy and to compare clinical and haemodynamic parameters before and after pericardiectomy. Original reports, review articles, professional society guidelines and case reports relevant to achieving the aims set out were collated and reviewed.

Causes of Constrictive Pericarditis

The aetiology of pericardial constriction displays a dual pattern – infective causes predominate in the developing world while non-infective causes prevail in the developed world. Tuberculosis infection is the predominant cause in the developing world. Tuberculosis accounted for 65% of cases in patients undergoing pericardiectomy for constrictive pericarditis in one study in China (16) with similar studies in Ghana, India, South Korea and Turkey revealing a prevalence rate of 63.6%, 61%, 42.4% and 38% respectively. (17-20) Fennell estimated that tuberculosis was the cause of constriction in all 109 patients that underwent pericardiectomy at a single centre in South Africa. (21) Other bacterial infections that account for constrictive pericarditis in the developing world include *Staphylococcus aureus* and *Haemophilus influenza.* (22) In contrast, tuberculosis accounts for less than 5% of cases of pericardial constriction in the developed world. (23-25)

The aetiology of pericardial constriction in the majority of patients in developed countries is unknown with 33 – 45% of patients undergoing pericardiectomy having no readily identifiable cause. (23-26) It is assumed that a significant portion of these cases is due to prior viral pericarditis. (25) Other causes identified include connective tissue diseases, prior cardiac surgery, prior mediastinal irradiation and uraemia.(27) While still the predominant cause, idiopathic causes are on the decline in recent years (24) while chest irradiation and prior cardiac surgery are becoming increasingly identified as causes in the developed world. (23-25) By contrast, the HIV/AIDS epidemic means that tuberculosis continues to be the leading cause of pericardial constriction in the developing world.

Pericardiectomy: Mortality and its determinants

Pericardiectomy offers the prospect of curing chronic constrictive pericarditis and is advocated when symptoms persist despite optimal medical therapy. (9) The removal of the diseased pericardium is done via a midline sternotomy or left anterolateral thoracotomy. Left anterolateral thoracotomy allows the surgeon greater access to the ventricular pericardium without extensive mobilisation of the heart while midline sternotomy allows easier access to the aorta and right atrium in case cardiopulmonary bypass is required. Primary installation of cardiopulmonary bypass is not recommended due to the risk of bleeding with systemic heparinisation. (9) Complete resection of the diseased pericardium should be attempted as far as is possible as this has been proven to have better haemodynamic and mortality outcomes than incomplete pericardiectomy. (9,28,29) Failure to completely resect the pericardium is usually due to intra-operative haemodynamic instability or advanced disease with myocardial involvement and extensive pericardial calcification.

The reported peri-operative mortality following pericardiectomy for pericardial constriction ranges between 6 – 12% in most large series. (9) Table 3 shows the

reported peri-operative mortality (in-hospital + 30-day mortality rates) in a selection of studies spanning different regions and time periods. It is of note that perioperative mortality in the past two decades has declined slightly but remains high in most centres at 6-10%. The causes of early mortality following pericardiectomy are ventricular arrhythmias, respiratory failure, sepsis, low-output cardiac failure and post-operative renal failure, with the latter two accounting for most deaths. (16,23,24,30) Mortality due to low-output cardiac failure is mainly due to pre-surgically unrecognised presence of myocardial atrophy or fibrosis (see figure 3) (9) One year survival following pericardiectomy was reported at 93.7% in one single centre study from China(16) while 1-year, 5-year, and 10-year survival rates were 82.5%, 64.3%, and 49.2%, respectively from a single centre in the United States of America. (27) These survival statistics mirror what is commonly reported in other studies. (24,26,30)

Author*	Country of study	Time period	Number of cases	Peri-operative mortality (%)
Bashi V, et al	India	1954 - 1985	118	16
Bertog SC, et al	USA	1977 - 2000	163	6.1
Cinar B, et al	Turkey	1990 - 2005	70	8.6
Tokuda Y, et al	Japan	2008 - 2012	346	10
George TJ, et al	USA	1995 - 2010	98	7.1
Ling LH, et al	USA	1985 - 1995	135	6
McCaughan, et al	USA	1936 - 1982	231	14
Ghavidel, et al	Iran	1994 - 2006	45	4.4
Tettey M, et al	Ghana	2000 - 2005	11	0
Chen RF, et al	Taiwan	1990 - 2003	23	8.7
Szabo C, et al	Germany	1988 - 2012	89	7
Lin Y, et al	China	2005 - 2010	51	3.9
Bozbuga N, et al	Turkey	1985 - 2002	36	6
Ariyoshi T, et al	Japan	2000 - 2011	16	12.5
Fennel (1982)	South Africa	?	109	3.6
Arsan, et al	Turkey	1983 - 1993	105	10.5
Tirilomis, et al	Germany	1970 - 1990	71	5.6

Table 3: Peri-operative mortality after pericardiectomy for constrictive pericarditis in a selection of studies. (*see references)

Numerous factors are reported to predict mortality following pericardiectomy. While a few are repeatedly found by different authors to be predictors of mortality, the majority of factors identified do not reproduce their mortality effect when looked at in other settings. Aetiology of constrictive pericarditis is the only factor that has good reproducibility as a predictor of long-term mortality in different settings with pre-operative functional status (New York Heart Association, NYHA*), left ventricular ejection fraction, renal dysfunction and the need for cardiopulmonary bypass at time of surgery being less reproducible but regularly reported predictors of mortality. Advanced age (30), longer duration of symptoms (31), higher Child-Pugh Score (32), hypoalbuminaemia (27), hyponatraemia (23), higher pulmonary artery pressures (23), higher right atrial pressures (33), increased early mitral valve inflow velocity (19), hyperbilirubinaemia (33) and ascites (29) are infrequently reported to predict mortality after pericardiectomy for constrictive pericarditis. Pericardial calcification has not been shown to predict mortality. (23)

In numerous studies, the aetiology of constrictive pericarditis has been shown to be a predictor of long term mortality with post-irradiation disease having the worst prognosis while idiopathic constrictive pericarditis has the best prognosis. George, et al found prior irradiation to be an independent predictor of 10 year mortality (HR 3.19, 95% CI 1.19 – 8.55, p=0.02) with 5-year survival differing by aetiology of constriction (idiopathic, post-surgery and post-radiation 5-year survivals of 79.8%, 55.9%, and 11.0%, respectively; $p < 0.001$) (27) Numerous other authors have found a similar pattern with poor long-term outcome in patients with post-irradiation compared to those with idiopathic causes for pericardial constriction. (23,24,26) The study by Szabo, et al found that all 5 patients with irradiation-induced disease had died within 5 years of surgery. (26) Tuberculous, uraemic and post-infarction constrictive pericarditis have survival statistics comparable to idiopathic pericardial constriction. (26,30) The higher mortality in patients with post-irradiation pericardial constriction is likely due to the deleterious effect of radiation on intra-thoracic organs.

Poor pre-operative functional class as measured by the NYHA classification has also been frequently found to determine mortality. NYHA Class 4 (dyspnoea at rest) was found to predict peri-operative mortality and major morbidity (OR 3.85, 95% CI 1.77–8.35, p<0.0001) in a nationwide Japanese study (34) and was found to be a predictor of poor survival at 10 and 15 years after pericardiectomy in studies conducted in Germany and the USA respectively. (24,26) It also negatively predicted both peri-operative and late mortality in 71 patients that underwent pericardiectomy in Germany. (33) The higher mortality related to a poor pre-operative functional class has led to many clinicians and professional society guidelines advocating pericardiectomy early in the course of constrictive pericarditis. (9)

Left ventricular dysfunction manifested by a reduced ejection fraction or other measures of cardiac dysfunction has also been shown to be a predictor of mortality following pericardiectomy. Ha and colleagues undertook pre-operative cardiac catheterisation in 40 patients with pericardial constriction and found that those with abnormal left ventricular contractility and relaxation properties had longer in-hospital stay post pericardiectomy, higher peri-operative mortality and higher mortality two years after pericardiectomy compared to those in whom these indices were normal. (35) Reduced left ventricular ejection fraction was found to negatively predict long term survival in a retrospective study involving 163 patients over a 24-year period. (23) Other authors have, however, found that left ventricular ejection fraction as assessed at echocardiography could not predict surgical outcome (19,36) The study by Kang et al looked at multiple parameters on echocardiography in 85 patients and found that only higher early diastolic mitral valve inflow velocity could independently predict mortality following pericardiectomy. (19)

Pre-operative abnormal renal function (high serum creatinine) has also repeatedly been shown to be an independent predictor of mortality following pericardiectomy. Pre-operative renal failure was found to predict peri-operative mortality (OR 2.62, 95% CI 1.22–5.64, p=0.014) in a nationwide Japanese study (34) while a single

centre study in China found that it predicted a higher 1-year mortality after pericardiectomy. (16) Bertog and colleagues found that worse renal function predicted poor long-term survival in their single centre study. (23)

Also frequently reported to predict mortality is the need for cardiopulmonary bypass at surgery. George, et al showed that the use of cardiopulmonary bypass conferred a higher likelihood of death at 30 days post-surgery (HR 21.2, 95% CI 1.81–248.44, p=0.02) (27) while another study reported 2.46 higher odds of death at 30 days. (34) Not surprisingly, cardiopulmonary bypass predicts higher peri-operative mortality as most practitioners use it only in situations of intra-operative haemodynamic instability such as occurs with massive bleeding or severe myocardial dysfunction.

HIV/AIDS, constrictive pericarditis and pericardiectomy

HIV/AIDS and related opportunistic infections form a significant burden of disease in the developing world. (37) Tuberculosis is the predominant opportunistic infection in patients with HIV/AIDS. (37) Effusive tuberculous pericarditis is the commonest cardiovascular manifestation of tuberculosis in HIV-seropositive individuals (38) and dual infection is associated with a 6-month mortality rate greater than twice that of tuberculous pericarditis alone - 40% vs. 17%, p=0.001. (39) The majority of pericardial effusions in HIV-seropositive individuals were found to be tuberculous in origin in South Africa and Tanzania. (40,41) Constrictive pericarditis is one of the most serious sequelae of effusive tuberculous pericarditis and is reported to occur in 17-60% of patients with effusive disease. (42) However, HIV-seropositive patients with effusive tuberculous pericarditis rarely progress to constrictive pericarditis. (38,43,44) In a randomised control trial of steroids vs. placebo in the treatment of effusive tuberculous pericarditis in HIV-seropositive patients, constriction was an infrequent outcome in the trial population and no deaths due to constrictive pericarditis occurred. (45) It is understood that the reduced incidence of progression to pericardial constriction is due to the immunosuppressive effect of

HIV that renders the patient unable to mount an immune response to the tuberculoproteins in the pericardium. (29,38,44,45-47) Given the high 6-month mortality associated with co-infection with HIV and tuberculous pericarditis and the fact that fibrosis is a delayed element of the pericardial immune response, it is conceivable that death occurs before clinical pericardial constriction can occur. This observation has also been alluded to by other authors. (42,45) No studies have looked at the effect of CD4 cell count or the use of Combination Anti-Retroviral Therapy (CART) on the progression to constrictive pericarditis in patients with effusive tuberculous pericarditis.

As a result of the infrequency of development of tuberculous constrictive pericarditis in HIV-seropositive individuals, there are no published studies that have looked at pericardiectomy and its outcomes in such patients. It is expected that with the recent increase in access to CART in the management of HIV, more patients with effusive tuberculous pericarditis will go on to develop pericardial constriction due to the reduction in immunosuppression associated with the use of CART in HIV.

Pre- and post pericardiectomy clinical and haemodynamic features

All pre- and post pericardiectomy comparative studies have shown improvements in the clinical and selected haemodynamic profiles of the patients surveyed. Complete normalisation of cardiac haemodynamics is reported in 60% of patients. (9) A widely reported measure of fluid status, the central venous pressure (CVP), has been shown to decrease early on after pericardiectomy thus implying a reduction in the volume status of the patients. A significant drop in mean CVP (pre 15.3±3.7mmHg; post 8.8±3.1 mmHg, $p<0.001$) was reported in one series with 16 patients (48) while a nearly 50% drop in CVP was reported in another series with 89 patients. (26) Kang and colleagues showed a non-significant CVP drop in their series (19) whereas Bozbuga and colleagues showed a significant drop in CVP after pericardiectomy (pre 14±4.2mmHg; post 7.4±2.1mmHg, $p<0.004$) (30) Post-operative reduction in CVP has not been shown to predict outcome after pericardiectomy.

Pre and post-pericardiectomy comparisons of echocardiographic features have also been undertaken with varying results. The left ventricular ejection fraction (LVEF), a widely reported echocardiographic feature, has not been shown to change much after surgery. (19,49) Senni and colleagues conducted extensive echocardiographic examinations before and after pericardiectomy and found that diastolic filling characteristics remained abnormal in a substantial number of patient and that this correlated well with symptoms of residual constriction. (49) In a cohort of 28 patients with echocardiographic tricuspid regurgitation (TR) and constrictive pericarditis undergoing pericardiectomy (but not tricuspid valve surgery), TR was found to have remained the same in 50% of patients, worsened in 29% and improved in 22% of the patients. (50) The study reported no impact on survival in the cohort that had undergone tricuspid valve surgery (for TR) concomitantly with pericardiectomy. Thirty patients with tuberculous constrictive pericarditis that underwent catheterisation before and after pericardiectomy showed a significant reduction in right ventricular end-diastolic pressure (pre 12.7±4.4mmHg; post 7.2±2.7mmHg, p=0.015), a non-significant reduction in left ventricular end-diastolic pressure (pre 11.5±3.0mmHg; post 8.8±2.2mmHg, p=0.08) and a non-significant reduction in the pulmonary artery pressure (pre 20.0±4.4mmHg; post 16.7±3.1mmHg, p=0.1) (30)

The most often reported measure of efficacy of pericardiectomy is the NYHA functional class before and after surgery. Virtually all studies report improvements in NYHA class after pericardiectomy. These improvements are noted both in the short term and even after up to 15 years of follow up in survivors. (18,21,24,26,30,48,51) In general, most patients are in NYHA class 2 (dyspnoea with moderate exertion) or class 3 (dyspnoea with mild exertion) prior to pericardiectomy and report an improvement of atleast one or two classes. A few patients remain in the same functional class while even fewer report a worsening of functional class. A worsening of functional class after pericardiectomy is usually associated with the presence of co-morbid disease such as coronary artery disease,

valvular heart disease or cardiomyopathy. Figure 5 is a typical representation of NYHA class changes that take place with pericardiectomy and is adapted from a study by Ling and colleagues. (24)

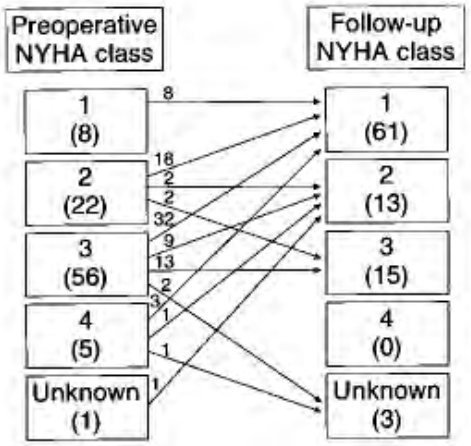

Figure 5. Change in NYHA functional class in 93 late survivors, showing marked symptomatic improvement in most patients after pericardiectomy. NYHA class was indeterminate in 1 patient before surgery and unknown in 3 patients at latest follow-up.

In summary, constrictive pericarditis is curable cause of chronic heart failure whose pathophysiological, haemodynamic and clinical features are well known. The aetiology of constrictive pericarditis varies by region with tuberculosis being the most predominant cause in the developing world. Pericardiectomy offers a chance to cure the syndrome and has been studied extensively in the developed world. The peri-operative mortality associated with pericardiectomy varies but can be as high as 10% and multiple factors that seem to predict mortality have been identified, mainly from studies in the developed world. There is no consensus on which factors irrefutably predict outcome after pericardiectomy and results of studies carried out in the developed world are not necessarily applicable to the developing world due to the different nature of disease characteristics and resource availability.

In addition, the HIV/AIDS pandemic that currently afflicts the developing world changes many aspects of the disease and its management and calls for research from the developing world to answer specific pertinent questions that arise as a result of the unique nature of the disease in this setting. Besides a study in 1982, there has not been any further examination of pericardiectomy for constrictive pericarditis in South Africa. Of particular concern is the need to define the causes of constrictive pericarditis and the mortality following pericardiectomy for constrictive pericarditis in our setting. It is also important to ascertain which factors can be used to predict mortality following pericardiectomy in our setting in order to aid decision making and management of constrictive pericarditis given the limited resources at our disposal. The impact of HIV/AIDS on the clinical profile and outcomes after pericardiectomy also needs to be studied.

A retrospective study of patients that have undergone pericardiectomy for constrictive pericarditis at Groote Schuur Hospital will be undertaken to try and answer some of the questions that remain unanswered in the management of constrictive pericarditis in South Africa. It will be the first opportunity in a long time to study this often forgotten condition and generate local data that will guide management going forward. It will also allow us to gauge how we compare to the developed world when it comes to the clinical profile and management of constrictive pericarditis.

(3991 words)

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CHAPTER 2: JOURNAL READY MANUSCRIPT

Constrictive Pericarditis Requiring Pericardiectomy at Groote Schuur Hospital in Cape Town, South Africa: Causes and Peri-operative Outcomes in the HIV Era (1990 – 2012)

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Abstract

Background: Causes of constrictive pericarditis and predictors of peri-operative outcome following pericardiectomy are not clearly elucidated, especially in Africa, where disease characteristics differ from developed countries. Furthermore, the impact of HIV/AIDS on pericardial constriction and outcomes following surgery is unknown. We set out to investigate the causes of constrictive pericarditis, the outcomes after pericardiectomy and the predictors of mortality in Cape Town, South Africa during a 22-year period of high HIV/AIDS prevalence.

Methods: A retrospective review of records of all patients who underwent pericardiectomy for constrictive pericarditis at Groote Schuur Hospital from 1 January 1990 to 31 December 2012 was performed.

Results: Of 121 patients, thirty six (29.8%) had proven tuberculosis, 74 (61.2%) presumed tuberculosis, six (5%) idiopathic, and 5 (4%) miscellaneous causes of constrictive pericarditis. Seventeen patients (14%) died peri-operatively with low cardiac output syndrome the main cause of mortality. In multivariable analysis, serum sodium (HR=0.88, 95%CI 0.80-0.97 p=0.009) and pre-operative New York Heart Association (NYHA) class IV (HR=3.42, 95%CI 1.29-9.08, p=0.014; compared with combined class I-III) were independent predictors of early mortality. There were 14 (11.6%) HIV positive patients with a mean CD4 cell count of 284 ± 133 cells/µl. No early deaths occurred in the HIV positive patients.

Conclusion: Tuberculosis is the main cause of constrictive pericarditis in South Africa. Despite its efficacy at relieving symptoms of heart failure, pericardiectomy is associated with a high peri-operative mortality rate which was not influenced by HIV status. NYHA IV functional class and hyponatraemia predict early mortality after pericardiectomy.

(249 words)

Ultramini abstract

Not much is known about pericardiectomy for constrictive pericarditis in the developing world. This study is the largest on the subject emanating from Africa in the HIV/AIDS era. It highlights the importance of early referral for pericardiectomy in constrictive pericarditis and the safety of surgery in those infected with HIV/AIDS.

(50 words)

Constrictive pericarditis (CP) is a treatable cause of heart failure. Fibrosed, non-compliant parietal and visceral pericardium impede ventricular filling in diastole thereby reducing stroke volume and giving rise to systemic venous congestion. (1) Causes of pericardial fibrosis are varied (2) with studies showing that infective causes are prevalent in the developing world. (3-5) Pericardiectomy is the standard method of relieving pericardial constriction. (6) Outcomes after pericardiectomy and predictors of mortality have been studied extensively in the developed world (7-9) but only a few small studies have examined the causes and outcome of patients with constrictive pericarditis requiring pericardiectomy in Africa. (5, 10) Due to differences in disease patterns and resource availability, the findings of studies conducted in the developed world may not be an accurate reflection of the experience of constrictive pericarditis requiring pericardiectomy in Africa.

Over the past 20 years, South Africa has seen an increase in the prevalence of pulmonary and extra-pulmonary tuberculosis (TB) largely driven by increases in the incidence and prevalence of human immunodeficiency virus/Acquired Immune Deficiency Syndrome (HIV/AIDS). (11) The effect of the increase in HIV/AIDS on the clinical characteristics of constrictive pericarditis and outcomes after pericardiectomy is not known.

We conducted a study to examine the causes, determinants of 30-day mortality, functional outcomes and the impact of HIV/AIDS on the clinical profile and outcomes after pericardiectomy at Groote Schuur Hospital in Cape Town, South Africa.

METHODS

A retrospective review of records of all patients that underwent pericardiectomy for constrictive pericarditis at the Chris Barnard Division of Cardiothoracic Surgery of Groote Schuur Hospital was undertaken. Patients that underwent pericardiectomy between 1 January 1990 and 31 December 2012 were eligible for the study. Patient records were reviewed and data of interest (demographic information, clinical signs

and symptoms, haemodynamic and laboratory data, operative techniques and outcomes) were entered into a standardised data capture sheet. Patients whose records could not be found were excluded from the study. The diagnosis of constrictive pericarditis was based on typical clinical and echocardiographic findings with confirmation of pericardial fibrosis and constriction intra-operatively (6). Commonly encountered clinical features included peripheral oedema with hepatomegaly and ascites, pulsus paradoxus and pleural effusions while echocardiography typically revealed pericardial thickening, paradoxical septal motion, dilated inferior venacavae and typical respiratory variation in doppler flow across the mitral/tricuspid valves. Cardiac catheterisation and/or computed tomography (CT) scanning were done in cases of diagnostic uncertainty to confirm pericardial thickening and constriction. All patients had surgery via median sternotomy with particular care being taken to free up the entire ventricular epicardium, apex and diaphragmatic surface of the heart. Once freed, the pericardium was removed anteriorly extending laterally close to the phrenic nerves with the posterior pericardium left in-situ after being freed from the epicardium (total pericardiectomy). Any resection less than this was considered partial pericardiectomy. Cardiopulmonary bypass was used at the discretion of the surgeon or when haemodynamic instability prevented adequate exposure of the adherent pericardium. Presumed tuberculosis as a cause for constrictive pericarditis was defined as the presence of a history of pulmonary tuberculosis or the initiation of empiric anti-tuberculous therapy by the attending physician, prior to pericardiectomy. Proven tuberculosis was defined as the presence of *Mycobacterium tuberculosis* in pericardial tissue/fluid or sputum by microscopy or culture. The presence of caseous pericardial tissue at surgery was also considered confirmatory of tuberculosis. Peri-operative mortality was defined as death from any cause occurring during the index hospitalisation or within 30 days of surgery even if the patient had been discharged from hospital. The study was approved by the University of Cape Town Human Research Ethics Committee. (HREC REF 558/2012)

STATISTICAL ANALYSIS

Categorical data were compared using the χ^2 test and continuous data were compared using the t test. The Kaplan-Meier method was used to calculate probabilities of death events, and the log-rank test was used to compare these probabilities by group. Cox proportional hazards regression models were fitted to determine risk factors associated with mortality. In this analysis, and due to small numbers, NYHA class I-III were combined and modelled as baseline risk vs NHYA class IV. Variables found to be significantly associated with the outcome were included in the final model. The proportionality assumption of the Cox models was tested using –ln[–ln (survival)] curves and regression of scaled Schoenfeld residuals on functions of time. All tests were two-sided, and a p-value <0.05 was considered significant. Statistical analysis was conducted using SPSS software (Version 20).

RESULTS

A total of 128 patients underwent pericardiectomy for constrictive pericarditis during this period; seven were excluded from the study because of missing records. Of the 121 patients in the study, 79 (65.3%) were male and the mean age was 41.3 ± 16.1 years (range 14 – 74). There were two cases of recurrent constriction requiring re-pericardiectomy 2 months after initial surgery. Total pericardiectomy was possible in 105 patients (88.2%) with 14 (11.8%) undergoing partial pericardiectomy. Five (4.1%) patients underwent concomitant mitral valve repair, one patient underwent concomitant aortic valve replacement with coronary artery bypass grafting. Baseline characteristics stratified by mortality status are summarised in Table I.

One hundred and ten (90.9%) patients had constrictive pericarditis due to either proven or presumed tuberculosis; 36 (29.8%) had proven tuberculosis while 74 (61.2%) had presumed tuberculosis. Six (4.9%) patients had idiopathic constrictive pericarditis while other causes each accounted for 1 patient (Figure 1). The patient with radiation-induced constrictive pericarditis had undergone chest irradiation for Hodgkin's lymphoma 20 years previously while the patient with Kaposi sarcoma was

HIV negative. Table II highlights causes of constrictive pericarditis reported in similar studies worldwide (3,4,7-9,12-17). Sixty three (52.1%) patients underwent diagnostic cardiac catheterisation with only one case of coronary artery disease documented at coronary angiography. All 63 patients had elevation and equalisation of diastolic pressures with the dip-and-plateau configuration typical of constrictive pericarditis. 18 patients (14.9%) underwent cardiac CT scanning. Intra-operative complications included 27 (22.3%) cases of inadvertent myocardial wall or major vessel injury with bleeding, tachyarrhythmias requiring cardioversion (n=6, 5%) and phrenic nerve injury (n=2, 1.7%). Low output cardiac failure was the commonest post-operative complication (n=80; 66.1%) with sternal wound sepsis (n=9, 7.4%), other site sepsis (n=9, 7.4%), acute kidney injury (n=9, 7.4%), re-thoracotomy for bleeding (n=4, 3.3%), re-thoracotomy for placement of ventricular-assistive devices (n=2, 1.7%), respiratory complications (n=6, 5%), neuropsychiatric complications (n=5, 4.1%), and tachyarrhythmias (n=3, 2.5%) accounting for other post-operative complications. There was no intra-operative mortality. Seventeen (14%) patients died post-operatively while still in hospital, one of whom had undergone concomitant mitral valve repair. Nine (52.9%) of these patients were in NYHA class IV prior to surgery. Low output cardiac failure was directly or indirectly responsible for death in 11 patients while acute kidney injury was implicated in the deaths of 6 patients. Post-operative sepsis was implicated in 4 deaths and post-operative bleeding, rapid atrial fibrillation and respiratory failure were each implicated in 1 death. One patient's death was sudden and unexplained while the cause of death in two patients was not apparent from their records. Figure II shows the overall Kaplan-Meier survival plot for the study population. The 30-day survival rate in this study was 86%. Completeness of pericardiectomy did not have any effect on peri-operative mortality (Hazard ratio (HR) =1.74, 95% CI 0.61 – 4.97, p=0.077). The period during which pericardiectomy was undertaken did not affect peri-operative mortality (1990 – 2000 mortality: 8/46 (17%); 2001 – 2012 mortality 9/75(12%); p=0.41). There was no difference in mortality between patients with proven compared to those with presumed TB pericarditis (p=0.632).

In univariable Cox proportional hazards regression analysis, variables significantly associated with peri-operative mortality were pre-operative New York Heart Association (NYHA) class (class IV HR =4.99, 95% CI 1.92-13.03, p=0.001, compared to combined class I-III), pre-operative total daily dose of diuretic (furosemide) (HR=1.003, 95% CI 1.001-1.006, p=0.019), pre-operative serum creatinine (HR=1.09, 95% CI 1.01-0.03, p=0.002) and pre-operative serum sodium (HR= 0.86, 95% CI 0.80 – 0.93, p<0.0001). In multivariable analysis, serum sodium (HR=0.88, 95% CI 0.80-0.97, p=0.009) and pre-operative NYHA class (class IV HR=3.42, 95% CI 1.29-9.08, p=0.014 compared to combined class I-III) were independent predictors of early mortality (Table III).

Fourteen of 96 patients (14.6%) tested were found to be HIV positive on serology while the HIV status of 25 of the 121 study patients (20.6%) was unknown. Most of the patients with an unknown HIV status underwent pericardiectomy in the early 1990s before the advent of routine pre-operative HIV testing. The baseline characteristics of the HIV positive and HIV negative patients are compared in Table IV (online supplement). Women were over-represented in the HIV positive group (8 female (57.1%) vs. 6 male (42.9%); p=0.024) while haemoglobin (mean = 13.2 ± 1.7 g/dl vs. 12.1 ± 2.0 g/dl, p=0.031) and serum creatinine (mean = 86 ± 25 µmol/l vs. 68 ± 9 µmol/l, p=0.012) were found to be significantly lower in the HIV positive cases compared with the HIV negative cases. No HIV positive patients underwent surgery on cardiopulmonary bypass. The average CD4 count at time of surgery was 284 ± 133 cells/µl (range = 50-435 cells/µl). Nine of the 14 (64.3%) patients were taking combination anti-retroviral therapy (CART) at the time of surgery. No peri-operative deaths occurred in the HIV positive group.

Pre-operative and 30-day post-operative NYHA functional status was available for 73 (60.3%) of the 121 patients. (Figure III, online supplement) Most showed improvement in functional status (p<0.0001) with the majority changing from NYHA class II to class I (n=25, 34.2%) and NYHA class III to class I (n=21, 28.8%). Seven (9.6%) patients remained in the same functional class while two (2.7%) patients had deterioration in their functional status at 30 days post pericardiectomy. Prior to

surgery, the majority of the patients had NYHA class III symptoms (n=35, 47.9%) with a majority reporting class I symptoms 30 days after surgery. (n=50, 68.5%)

DISCUSSION

We have studied the aetiology of constrictive pericarditis and early outcomes after pericardiectomy in 121 patients over a 22 year period in a single centre from Sub-Saharan Africa. To the best of our knowledge, this is the first large study of the aetiology and predictors of peri-operative outcome of constrictive pericarditis in the HIV/AIDS era in Africa. Our results have some variation from those reported in recent similar series covering the same subject. (7-9,14,17,18) Although our findings are relevant to practitioners in South Africa and other developing countries, the globalization of health implies practitioners in North America and Europe are likely to treat increasing numbers of immigrants and refugees with tuberculosis and its sequelae such as constrictive pericarditis. (19)

One hundred and ten (90.9%) of the patients in our study had either proven or presumed tuberculosis as a cause for constrictive pericarditis. This is higher than reported in other series from China, Ghana, India, South Korea and Turkey where TB remains a major cause of constrictive pericarditis. (Table II) Tuberculosis accounted for 65% of cases in patients undergoing pericardiectomy for constrictive pericarditis in a study from China (14) with studies in Ghana, India, South Korea and Turkey revealing a prevalence rate of 63.6%, 61%, 42.4% and 38% respectively. (3-5,13) Only 36 (32.7%) of the 110 patients had a proven diagnosis of tuberculous constrictive pericarditis. This difference highlights the diagnostic difficulty faced by clinicians in resource limited settings where TB is endemic – without recourse to advanced diagnostic techniques to determine the aetiology of constrictive pericarditis, the clinician, armed only with knowledge of the background high prevalence of TB, is forced to treat empirically for TB in order to avoid the technical difficulty and associated morbidity/mortality that comes with performing pericardiectomy on patients with active/untreated tuberculous pericarditis. (10) This common scenario is a likely contributor to the large number of cases of TB constrictive pericarditis seen in our series and may mean that TB is over-reported as

a cause for constrictive pericarditis in South Africa. Fennell, in an earlier South African study, alluded to similar difficulties and a similar course of action in managing constrictive pericarditis. (10) He surmised that all 109 patients in his cohort had TB constrictive pericarditis. (10) Despite the possibility that TB pericarditis as a cause for constrictive pericarditis may be over-reported in this study, there is little doubt that TB remains the leading cause of effusive and subsequent constrictive pericarditis in South Africa. A local study found TB to account for 69.5% of large pericardial effusions in this region of South Africa. (20) The use of imaging studies such as CT scan or magnetic resonance imaging (MRI) may help to reduce diagnostic uncertainty in situations where active pericarditis / myopericarditis (as might occur in active TB pericarditis) needs to be excluded. (21) It is also worth noting the rarity with which mediastinal irradiation, autoimmune diseases and other causes of constrictive pericarditis commonly reported in developed countries are seen in our setting (Table II) (7,8,17) Only one patient underwent pericardiectomy for radiation-induced constrictive pericarditis in 22 years at our centre compared to 17 patients in 10 years in the study by Ling and colleagues. (7)

Our study has found a higher peri-operative mortality than that reported in similar series worldwide. We have reported a 30-day mortality rate of 14% whereas others have reported mortality rates in the range of 6 – 10%. (7,12,16,17) The only recent study to show similar peri-operative mortality is that of Ariyoshi and colleagues which had 12.5% mortality but only among 16 patients (22), while McCaughan et al reported a peri-operative mortality rate of 14% in a cohort of 231 patients from 1932 to 1986. (15) Bashi and colleagues reported a 16% peri-operative mortality rate in 118 patients who underwent surgery between 1954 and 1985. (3) Mortality in our study was not influenced by the decade during which pericardiectomy took place. Unlike Chowdhury and colleagues who found partial pericardiectomy to predict peri-operative mortality, we found no difference in outcome in those that had total vs partial pericardiectomy using a similar surgical technique to that utilised by Chowdhury and colleagues. (23) Kang, et al who described total and partial pericardiectomy as we have also found no difference in outcome. (13)

We have found pre-operative NYHA class to be independently associated with peri-operative mortality in our population. Compared with pre-operative combined NYHA I, II and III functional status, patients with pre-operative NYHA IV symptoms had higher risk of peri-operative death. Other authors have found a similar statistically significant association between pre-operative NYHA IV status and early mortality - Tokuda and others found 3.85 higher odds of early death ($p<0.0001$) (16) while Tirilomis and colleagues reported increased risk of death with pre-operative NYHA class IV symptoms ($p<0.01$) (24) Pre-operative NYHA class IV signifies more severe disease with a greater degree of cardiac dysfunction that is more likely to result in peri-operative morbidity and mortality. In studies that have looked at long term outcomes after pericardiectomy, pre-operative NYHA class IV has also been found to be a predictor of mortality. (7,17)

We have also found pre-operative serum sodium to be inversely associated with 30-day mortality i.e. lower serum sodium is associated with increased early mortality. Bertog, et al also reported that low serum sodium was associated with a higher overall mortality in their cohort of 163 patients. (8) A low serum sodium is a reflection of severe fluid overload in gross heart failure (dilutional hyponatraemia) or the use of higher doses of diuretic (as occurred in our study) in patients with severe fluid overload. Alternatively, hyponatraemia reflects generalised electrolyte imbalance as a marker of severe illness such as would occur in syndrome of inappropriate anti-diuretic hormone (SIADH) or sick cell syndrome. (25) Although not so in our study, other factors found to be associated with 30-day mortality include left ventricular dysfunction (26), use of cardiopulmonary bypass (9,16) and pre-operative renal failure. (16)

Low output cardiac failure was found to be a major contributor to mortality in our setting having occurred in 11 of 17 (64.7%) deaths. It was also found to be the predominant cause of peri-operative death by other authors. (7,8,14,27) Low-output cardiac failure is mainly due to the presence of myocardial atrophy and/or fibrosis especially in cases of long-standing constriction. (6) Despite the use of inotropes, intra-aortic balloon pump and fluid resuscitation, a significant number of deaths associated with low output cardiac failure still occurred in our study.

Fourteen (11.6%) patients in our study had serological evidence of HIV infection. To the best of our knowledge, this is the first study to document the prevalence, clinical characteristics and outcomes in HIV positive patients undergoing pericardiectomy for constrictive pericarditis. A recent nationwide study in the United States of America had less than 10 HIV positive patients out of a population of 3847 undergoing pericardiectomy. (28) The low frequency of HIV in our cohort may reflect the apparent protective effect of HIV infection on progression to constrictive pericarditis. (12,29-32) All HIV positive patients in our study had TB pericarditis as the cause of constrictive pericarditis (6 proven tuberculosis, 8 presumed tuberculosis) The average CD4 count was 284 cells/µl indicating some degree of immunological integrity thereby increasing the likelihood of progression to pericardial constriction. A CD4 count of 284 cells/µl is higher than what we commonly see in other cases of extra-pulmonary TB and may be a result of the use of CART which, at 64.3%, is higher than what was seen in the background population during the bulk of the period of study. (33)

The only significant differences between the HIV positive and negative populations are in gender (more female HIV positive patients), a lower (but still largely normal) haemoglobin in the HIV positive group and a lower creatinine which may reflect the reduced body habitus usually associated with HIV infection – these differences did not affect outcome between the two groups. There were no early deaths in the HIV positive population. The high prevalence of TB in our study and the pre-HIV era study by Fennell (10) suggests that the advent of HIV/AIDS has not affected the causality pattern of constrictive pericarditis in South Africa. Fennell reported in-hospital mortality of 3%, whereas we found 30-day mortality of 14%. The outcome results of our study and those of Fennell are not comparable because of differences in the methods of the two studies. This study has shown that when TB constrictive pericarditis does occur in HIV positive patients, the clinical characteristics and peri-operative outcome are comparable to what is seen in HIV negative patients.

Despite higher than commonly reported peri-operative mortality, we have shown that most survivors experienced marked improvement in their effort tolerance as measured by the NYHA classification. The majority of our patients on whom data

was available at both time points improved from NYHA class II and III pre-operatively to class I effort tolerance at 30-days post surgery ($p<0.0001$). Ling et al reported similar improvements in a cohort of 93 late survivors after pericardiectomy. (7)

In summary, our study has shown that although effective at relieving symptoms of constrictive pericarditis, pericardiectomy in Cape Town is associated with a high peri-operative mortality of 14%, mainly related to low output cardiac failure. Pre-operative NYHA class IV and hyponatraemia have been shown to predict peri-operative mortality. As expected, the prevalence of TB constrictive pericarditis is very high although the possibility exists that TB is over-reported as a cause for constrictive pericarditis. We have also shown that there are no major differences in the clinical profile and early outcomes in patients with HIV infection that undergo pericardiectomy for constrictive pericarditis, compared to their HIV negative counterparts. Our study illustrates the need for early recourse to pericardiectomy before symptoms deteriorate to NYHA class IV or severe fluid overload – delay may result in myocardial atrophy as a result of chronic myocardial constriction and leads to worse outcomes. It also highlights the need to search for ways of reducing early mortality through improved management of post-pericardiectomy low cardiac output syndrome and the need for better diagnostic techniques in constrictive pericarditis in our setting.

LIMITATIONS

Our study was limited by the small number of missing patient records and missing data from available patient records due to the retrospective design of the study. Despite these limitations, the study has identified the prognostic role of low serum sodium and NYHA functional class IV as predictors of outcome. Furthermore, the study has a small number of HIV infected patients and can therefore not provide definitive information on the impact of HIV infection in patients with constrictive pericarditis requiring pericardiectomy. Finally, the follow-up period included the first 30-days following surgery. Longer-term studies of outcome are required.

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Characteristic	All, n=121	Alive, n=104	Died, n=17	p-value
	n (%)	n (%)	n (%)	
Mean age, yrs	41.3 ± 16.1	40.2 ± 16.1	47.6 ± 14.7	0.08
Gender				0.546
Male	79(65.3)	69(66.3)	10(58.8)	
Cause of constrictive pericarditis				0.679
Tuberculosis	110(90.9)	95(91.3)	15(88.2)	
Other	11(9.1)	9(8.7)	2(11.8)	
Pre-op NYHA^{+}				0.001
I	3(2.5)	2(1.9)	1(5.9)	
II	38(31.4)	36(34.6)	2(11.8)	
III	57(47.1)	52(50.0)	5(29.4)	
IV	23(19)	14(13.5)	9(52.9)	
Mean symptom duration, months	12.5 ± 22.4	5.3 ± 4.4	13.7 ± 23.9	0.154
HIV Status				0.274
HIV +ve	14(11.6)	14(13.5)	0(0.0)	
HIV-ve	82(67.8)	69(66.3)	13(76.5)	
HIV unknown	25(20.6)	21(20.2)	4(23.5)	
Hypertension	12(9.9)	9(8.7)	3(17.6)	0.25
Diabetes mellitus	3(2.5)	3(2.9)	0(0.0)	0.478
Mean total daily diuretic dose*, mg	119 ± 101	109 ± 71	174 ± 192	0.014
Mean weight, kg	65 ± 12	64.8 ± 12.2	66.1 ± 10.7	0.715
Mean systolic BP$^{¤}$, mmHg	111 ± 15	112 ± 15	108 ± 13	0.262
Mean diastolic BP, mmHg	70 ± 11	71 ± 11	68 ± 11	0.288
Mean pulse rate, beats per minute	89 ± 16	88 ± 16	95 ± 14	0.091
Pulsus paradoxus	77(63.6)	68(65.4)	9(52.9)	0.323
Ascites	92(76)	77(74)	15(88.2)	0.204
S3 Knock	64(52.9)	57(54.8)	7(41.2)	0.297
Pleural effusion	96(79.3)	83(79.8)	13(76.5)	0.753

Hepatomegaly	108(89.3)	95(91.3)	13(76.5)	0.066
Pericardial calcification[¥]	28(23.1)	25(24.0)	3(17.6)	0.562
Atrial fibrillation	10(8.3)	7(6.7)	3(17.6)	0.13
Low QRS amplitude	77(63.6)	63(60.6)	14(82.4)	0.084
Mean LVEF[§], %	57 ± 11	57 ± 11	58 ± 14	0.704
Mean haemoglobin, g/dl	13.1 ± 1.7	13.1 ± 1.7	13.0 ± 1.5	0.759
Mean serum sodium, mmol/l	137 ± 5	138 ± 4	133 ± 7	<0.0001
Mean serum creatinine, µmol/l	83 ± 23	81 ± 18	99 ± 38	0.002
Total pericardiectomy¢	105(88.2)	93(90.3)	12(75)	0.077
On cardio-pulmonary bypass	20(16.5)	15(14.4)	5(29.4)	0.123
Post-operative inotropes	80(66.1)	63(60.6)	17(100)	0.001
Mean post-op ICU stay, days	3.4 ± 2.3	3.4 ± 1.8	3.5 ± 4.4	0.96

Table I: Baseline characteristics of study patients categorised by mortality status. Continuous variables are shown as mean with standard deviation in brackets while categorical variables are shown as the absolute value with percentage of the total in brackets

± standard deviation; [+] New York Heart Association functional class; * diuretic used was furosemide; [¤] blood pressure; [¥] on CXR or at cardiac catheterisation; [§] Left ventricular ejection fraction, as measured on echocardiogram or at cardiac catheterization; [¢] anterior pericardium excised between phrenic nerves and posterior pericardium freed. Completeness of pericardiectomy could not be ascertained on one patient in each sub-group of patients.

Author	Country of study	Time period	Number of cases	Aetiology of constrictive pericarditis	Peri-operative mortality(%)	Predictors of peri-operative mortality
Bashi, et al (3)	India	1954 – 1985	118	Tuberculosis (61%)	16	Pre-operative NYHA III and IV
Bertog, et al (8)	USA	1977 – 2000	163	Idiopathic (46%), prior cardiac surgery (37%), post-radiation (9%), miscellaneous (8%)	6.1	_
Cinar, et al (12)	Turkey	1990 – 2005	70	Tuberculosis (100%)	8.6	Ascites, duration of symptoms
Tokuda, et al (16)	Japan	2008 – 2012	346	_	10	*Moderate-severe chronic lung disease, renal failure, pre-operative NYHA IV, prior cardiac surgery, cardio-pulmonary bypass

George, et al (9)	USA	1995 – 2010	98	Idiopathic (45%), prior cardiac surgery (31%), post-radiation (17%), tumour (3%), infection (1%), haemopericardium (1%), asbestos (1%)	7.1	Cardio-pulmonary bypass
Ling, et al (7)	USA	1985 – 1995	135	Idiopathic (33%), prior cardiac surgery (18%), pericarditis (16%), post-radiation (13%), connective tissue diseases (7%), infection (3%), miscellaneous (10%)	6	_
McCaughan, et al (15)	USA	1936 – 1982	231	Idiopathic (73%), pericarditis (10%), infection (6%), post-radiation (5%), prior cardiac surgery (2%), connective tissue disease (2%), miscellaneous (2%)	14	Pre-operative NYHA IV

Szabo, et al (17)	Germany	1988 – 2012	89	Idiopathic (55%), prior cardiac surgery (23.6%), post-radiation (5.6%), tuberculosis (5.6%), uraemia (4.5%), inflammatory (3.5%), post-infarction(2.2%)	7	_
Lin, et al (14)	China	2005 – 2010	51	Tuberculosis (65%), idiopathic (25%), prior cardiac surgery (6%), connective tissue disease (2%), post-trauma (2%)	3.9	_
Arsan, et al (4)	Turkey	1983 – 1993	105	Tuberculosis (38%), malignancy (15%), uraemia (11.4%), connective tissue disease (10.5%)	10.5	_
Kang, et al (13)	South Korea	1996 – 2010	85	Idiopathic (57.6%), tuberculosis (42.4%)	1.2	_

Table II: Causes of constrictive pericarditis, peri-operative mortality and determinants of mortality after pericardiectomy for constrictive pericarditis in a selection of large studies (3,4,7-9,12-17). *Predictors of peri-operative mortality or major morbidity.

Factor	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	p-value	Hazard Ratio (95%CI)	p-value
Serum sodium	0.86(0.80-0.93)	<0.0001	0.88(0.80-0.97)	0.009
Serum creatinine	1.09(1.01-1.03)	0.002	1.01(0.99-1.03)	0.089
Total daily dose (furosemide)	1.003(1.00-1.006)	0.02	1.00(0.99-1.01)	0.312
NYHA		0.001		0.014
Class I-III	1		1	
Class IV	4.99(1.92-13.03)		3.42(1.29-9.08)	

Table III: Univariate and multivariate Cox proportional hazards regression models of factors associated with mortality

Characteristic	HIV –ve, n=82 n (%)	HIV +ve*, n=14 n (%)	p-value
Mean age, yrs	40.2 ± 16.1	32.1 ± 7.2	0.068
Gender			0.024
Male	60(73.2)	6(42.9)	
Cause of constrictive pericarditis			0.256
TB	75(91.5)	14(100)	
Other	7(8.5)	0(0.0)	
Pre-op NYHA			0.724
I	2(2.4)	0(0.0)	
II	25(31.7)	4(28.6)	
III	36(43.9)	8(57.1)	
IV	18(22.0)	2(14.3)	
Mean symptom duration, months	12.6 ± 25.1	5.8 ± 5.1	0.316
Hypertension	8(9.8)	0(0.0)	0.222
Diabetes Mellitus	2(2.4)	0.(0.0)	0.555
Mean total daily diuretic dose, mg	124 ± 115	126 ± 75	0.953
Mean weight, kg	64.5 ± 12.7	64.6 ± 10.4	0.976
Mean systolic BP, mmHg	111 ± 15	109 ± 12	0.629
Mean diastolic BP, mmHg	70 ± 12	74 ± 9	0.154
Mean pulse, bpm	89 ± 16	96 ± 16	0.121
Pulsus paradoxus	53(64.6)	7(50)	0.296
Ascites	65(79.3)	11(78.6)	0.953
Diastolic knock	38(46.3)	8(57.1)	0.455
Pleural effusion	63(76.8)	13(92.9)	0.172

Hepatomegaly	71(86.6)	13(92.9)	0.512
Pericardial calcification	17(20.7)	3(21.4)	0.953
Atrial fibrillation	7(8.5)	0(0.0)	0.256
Low QRS amplitude	52(63.4)	10(71.4)	0.562
Mean LVEF, %	56 ± 11	60 ± 13	0.241
Mean haemoglobin, g/dl	13.2 ± 1.7	12.1 ± 2.0	0.031
Mean serum sodium, mmol/l	136 ± 5	137 ± 2	0.721
Mean serum creatinine, µmol/l	86 ± 25	68 ± 9	0.012
Total pericardiectomy	71(88.8)	13(92.9)	0.646
On cardio-pulmonary bypass	17(20.7)	0(0.0)	0.06
Post-operative inotropes	56(68.3)	8(57.1)	0.413
Mean post-op ICU stay, days	3.6 ± 2.6	3.2 ± 1.0	0.564

*Mean CD4 count 284±133 cells/µl

Table IV: Baseline characteristics of the 96 study patients with known HIV status. Continuous variables are shown as mean with standard deviation while categorical variables are shown as the absolute value with percentage of the total in brackets. *(online supplement)*

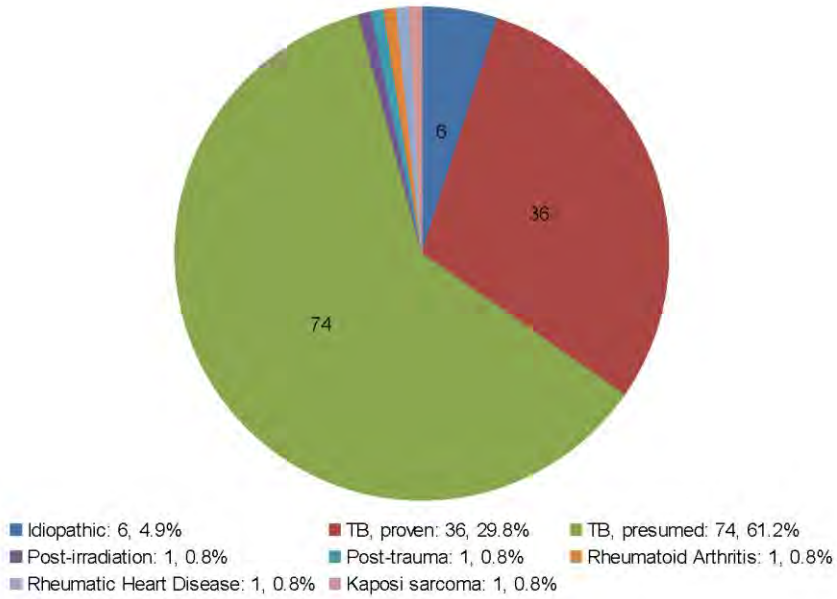

Figure I: Causes of constrictive pericarditis in 121 patients who underwent pericardiectomy (1990 – 2012)

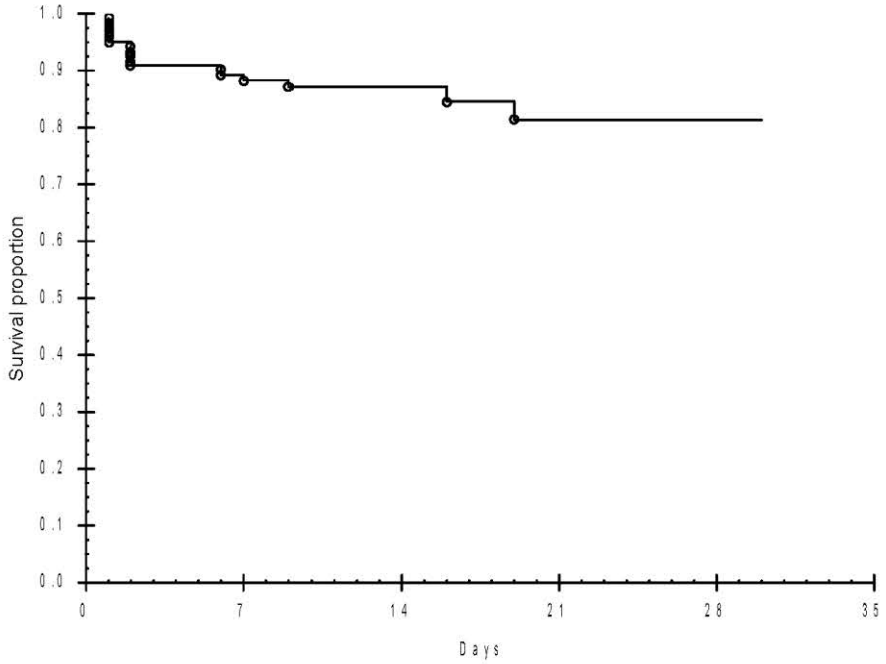

Figure II: Kaplan-Meier 30-day survival plot. 17/121 patients (14%) died within 30 days of pericardiectomy.

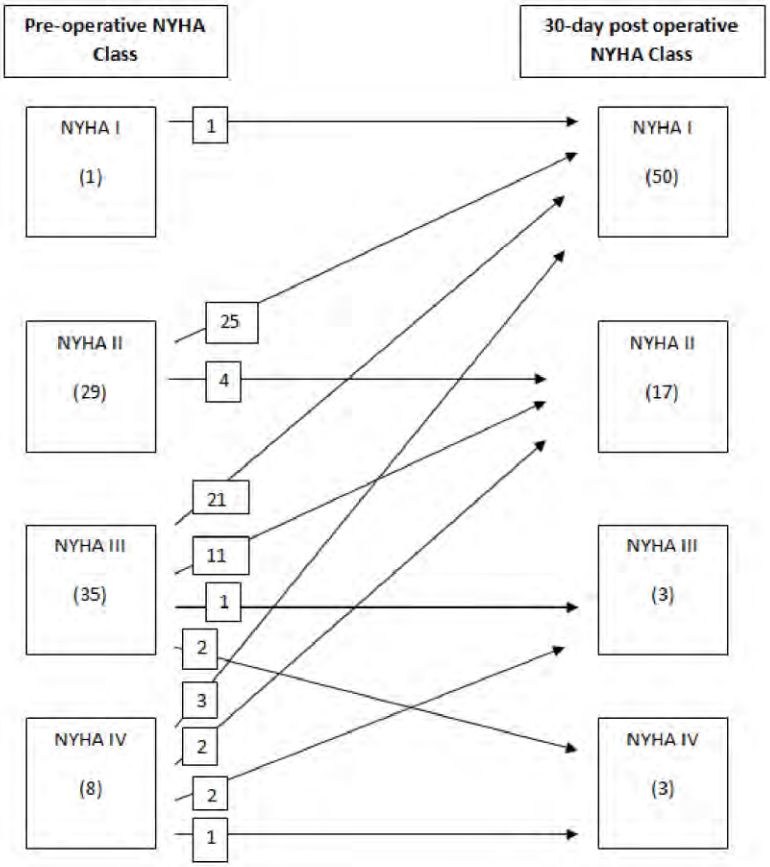

Figure III: Comparison of pre- and 30-day post operative NYHA functional status in 73 patients ($p<0.0001$) *(online supplement)*

Appendix 1: Journal of Thoracic and Cardiovascular Surgery - Instructions to Authors

Article Preparation

Manuscripts must be written so that a reasonably well-informed member of the thoracic surgical community can understand them. The primary goal of the Journal is the dissemination of information and education. Arcane content must be explained and considered understandable by the editorial staff. Articles are chosen based on their probability of achieving this goal. Authors are encouraged to follow the principles of clear scientific writing, such as those described by Gopen and Swan, as well as Blackstone.

All manuscripts must adhere to the length requirements outlined below.

Note: **To allow all manuscripts to be judged fairly, manuscripts exceeding length limitations are returned for shortening prior to review.**

Original Research Article: The *Journal* publishes original research in surgery and translational physiology as it relates to acquired and congenital cardiovascular disease, cardiothoracic transplantation, and general thoracic surgery. Meritorious work from closely related specialties, such as anesthesiology, molecular biology, pathology, pulmonary medicine, cardiology, and perfusion, is encouraged and will receive appropriate consideration if the linkage to our specialty is clear.

Original research articles are grouped in the *Journal* according to one of the following categories: Acquired Cardiovascular Disease; Congenital Heart Disease; General Thoracic Surgery; Evolving Technology/Basic Science; Perioperative Management; Cardiothoracic Transplantation; Cardiothoracic Surgical Education and Training. Authors are asked to self-categorize their articles during the submission process.

Note: **Submission to the *Journal* constitutes an author declaration that the manuscript is a single-journal submission and has not been submitted to another journal simultaneously.**

Length Requirements: **Original research articles may not exceed 7 printed pages, including title and abstract.** The following guidelines offer the best approximation of appropriate article length. Submitted articles that do not meet these guidelines will be returned to the corresponding author for appropriate revision, prior to review.

- Title page, 250-word structured abstract, and a 50-word ultramini abstract
- A manuscript that contains no more than 3500 words in the body of the text, excluding abstracts and references

- A maximum combination of 5 figures and/or tables. Additional figures or tables may be submitted for online-only inclusion. A reference in the printed text will direct readers to the additional online content
- No more than 35 references
- A limit of 7 authors; exceptions are made for multi-center trials and can be requested for other situations, provided all authors meet the listed requirements

Appendix 2: Data collection sheet

IMPI Trial Sub-Study: Pericardiectomy for Constrictive Pericarditis (1990 – 2012)

Initials		Name		Surname		ID num											
Folder no		DOB		Age		Gender	M	F	Priority	Elec	Urg	Emerg					
DO Surgery		Cause of CP	TB (p)	TB (s)	Idiopathic	Other											
Leg swelling	Y	N	Abd swelling	Y	N	Pre-op NYHA	I	II	III	IV	Other						
Duration (m)		Prev TB	Y	N	TB presently	Y	N	Duration of Rx		HIV +ve	Y	N	U	CD4			
HAART	Y	N	Hypt	Y	N	DM	Y	N	IHD	Y	N	Other					
Diuretic	Lasix	Dose		N	O	ACE-I	Y	N	Other		Weight (kg)						
Height (cm)		BMI		sBP		dBP		Pulse		Pulsus	Y	N	JVP	R	N		
Oedema	Y	N	Ascites	Y	N	Jaundice	Y	N	S3 Knock	Y	N	Creps	Y	N	Pleural eff	Y	N
Hepar	Y	N	Other sign		Cardiomegally	Y	N	Peric Ca2+	Y	N							
AF	Y	N	ECG V-rate		QRS Ampl	L	N	TWI	Y	N	Other ECG						
Peric thick	Y	N	Size (mm)		Peric eff	Y	N	Size(mm)		IVC Dilated	Y	N					
RV Press		Septal bounce	Y	N	TR	Y	N	LVEF		Other							
Catheter	Y	N	LVEDP		RVEDP		Other										
CT Chest	Y	N	Findings														
MRI heart	Y	N	Findings														
Hb		WCC		Creat		Na		K+		TBili		Alb		AST			
ALT		ALP		GGT		INR		AFB Status	Pos	Neg	Unknown						
Histo result																	
Approach	M/sternotomy	Other		Completion	Total	Partial	CPB	Y	N								
Other procedure	N	Y		Intra op compl													
	Other op notes																
ICU Duration		Ventilated	Y	N	Ionotropes	Y	N	Vasopressin	Y	N	IABP	Y	N				
ICU D/C date		D/C Home Date		Post op complications													
NYHA at 30d		Diuretic	Lasix	Dose		N	Other		Oedema	Y	N	JVP	R	N			
Echo	Y	N	Findings														
NYHA at 6m		Diuretic	Lasix	Dose		N	Other		Oedema	Y	N	JVP	R	N			
Echo	Y	N	Findings														
NYHA at 12m		Diuretic	Lasix	Dose		N	Other		Oedema	Y	N	JVP	R	N			
Echo	Y	N	Findings														

Other notes:

Appendix 3: Faculty of Health Sciences (UCT) ethics approval

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411
email: sumayah.ariefdien@uct.ac.za

12 November 2012

HREC REF: 558/2012

Dr Arthur Mutyaba,
Medicine
OMB

Dear Dr Mutyaba,

PROJECT TITLE: THE INITIATIVE TO INVESTIGATE THE MANAGEMENT OF PERICARDITIS IN AFRICA (IMPI) REGISTRY: A SUBSTUDY ON THE CAUSES AND PREDICTORS OF MORALITY IN PATIENTS WITH CONSTRICTIVE PERICARDITIS REQUIRING PERICARDIECTOMY AT GROOTE SCHUUR HOSPITAL (THE CONSTRICTIVE PE

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 15 November 2013

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 4: Groote Schuur Hospital letter of authorisation

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bhavna Patel
E-mail : Bhavna.Patel@westerncape.gov.za

Dr Arthur Mutyaba
Department of Medicine
J47 – Old Main Building

E-mail: akaggwe@yahoo.com ; Bongani.Mayosi@uct.ac.za & Johan.Brink@uct.ac.za

Dear Dr Mutyaba

RESEARCH: The Initiative to Investigate the Management of Pericarditis in Africa (IMPI) Registry: A Sub-study on the Causes and Predictors of Mortality in Patients with Constrictive Pericarditis Requiring Pericardiectomy at Groote Schuur Hospital (The Constrictive PE)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

a) Your research may not interfere with normal patient care
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible. Please contact Mr Noel Weeder on ext. 4066 or 4058 in this regard.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Confidentiality must be maintained at all times.

I would like to wish you every success with the project.

Yours sincerely

DR BHAVNA PATEL
SENIOR MANAGER: MEDICAL SERVICES
Date: 5th December 2012

c.c. Dr B. Eick
Dr B. Jacobs
Dr A. Krajewski

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