

## Cardiovascular Topics

# The management of tuberculous pericardial effusion: experience in 233 consecutive patients

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### Summary

**Aim:** We report on the 30-day and one-year outcome of consecutive effusive pericarditis patients, including those with tuberculous pericarditis, over a six-year-period.

**Methods and Results:** Patients with large pericardial effusions requiring pericardiocentesis were included in the study after having given written informed consent. Clinical and radiological evaluations were followed by echo-guided pericardiocentesis, and extended daily intermittent drainage via an indwelling pigtail catheter. A standard short-course anti-tuberculous regimen was initiated. A total of 233 patients was included. One hundred and sixty-two patients had pericardial tuberculosis (TB), including 118 (73%) with microbiological and/or histological evidence of TB and 44 (27%) diagnosed on clinical and supportive laboratory data. Over the six-year period, two patients developed fibrous constrictive pericarditis after receiving adjuvant corticosteroid therapy. The 30-day mortality (8.0%) was statistically higher for HIV-positive patients (corresponding mortality 9.9%) than for HIV-negative patients (6.2%;  $p = 0.04$ ). The one-year all-cause mortality was 17.3%. It was also higher for HIV-positive (22.2%) than for HIV-negative patients (12.3%;  $p = 0.03$ ). Cardiac mortality was equal for HIV-positive and -negative patients.

**Conclusion:** Tuberculous pericardial effusions responded well to closed pericardiocentesis and a six-month treatment of antituberculous chemotherapy. The former was effective and safe irrespective of HIV status.

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Tuberculous pericarditis is a life-threatening form of extrapulmonary tuberculosis (TB), which presents either as pericardial effusion or as constrictive pericarditis.<sup>1,2</sup> Treatment involves effective drainage of the pericardial space, followed by anti-tuberculous therapy. The latter has reduced TB mortality from 85%<sup>3</sup> to 17–40%.<sup>4–6</sup> However, the use of adjuvant corticosteroids for the prevention of constriction and TB-related death remains controversial.<sup>7–11</sup> If constriction develops, pericardiectomy is usually indicated.<sup>12</sup>

Standard management for pericardial effusion includes pericardiocentesis, ideally under guidance with echocardiography or fluoroscopy.<sup>2,13–16</sup> The most serious complications of pericardiocentesis include laceration and perforation of the myocardium and the coronary vessels, air embolism, pneumothorax, arrhythmias (usually vasovagal bradycardia) and puncture of the peritoneal cavity or abdominal viscera.<sup>17</sup>

We previously reported on our experience of pericardiocentesis with extended intermittent pericardial drainage in 170 patients, including 116 patients who presented with tuberculous pericardial effusion.<sup>18</sup> Contrary to the perception that HIV-positive patients would suffer more infective complications, none was encountered in any of the 54 HIV-infected patients studied.<sup>18</sup> We are now reporting on the thirty-day and one-year outcomes of 233 patients who presented with large pericardial effusions, focusing on the 162 patients who presented with pericardial TB.

### Methods

Patients presenting to Tygerberg Academic Hospital, Western Cape, South Africa with large pericardial effusions from February 1995 to June 2001 were enrolled in the study, which was approved by the ethics committee of Stellenbosch University and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent and received counseling for HIV antibody testing.

Baseline demographic, clinical, echocardiographic and electrocardiographic data were obtained. Histological/microbiological tuberculous pericarditis was diagnosed by one or more of the following criteria: (1) isolation of *Mycobacterium tuberculosis* from the pericardial fluid and/

or biopsy specimen; and/or (2) demonstration of granulomatous inflammation on histopathological examination of the pericardial biopsy sample. Clinical tuberculous pericarditis was diagnosed by one or more of the following criteria: (1) presence of a lymphocytic pericardial exudate together with measured ADA level  $\geq 40$  U/l; (2) presence of a lymphocytic pericardial exudate with compatible clinical features and a good response to anti-tuberculous chemotherapy; and/or (3) presence of a lymphocytic pericardial exudate with a positive sputum ZN stain and/or TB culture.

The pericardial effusion was drained by echocardiographically guided aspiration via an indwelling pigtail catheter for complete pericardial drainage, which was removed when the daily aspirate was less than 100 ml, when it became blocked, or when there was evidence of localised skin infection. Patients were examined twice daily for fever, change in haemodynamic status and clinical evidence of localised skin and/or pericardial infection. A standard short-course anti-tuberculous regimen was initiated according to South African National Tuberculosis Control Programme guidelines.<sup>19</sup> All HIV-positive patients received daily oral cotrimoxazole, but not antiretroviral therapy.

Patients were assessed one month after discharge and thereafter at three-monthly intervals for a minimum period of one year. Therapeutic response was assessed with regard to improvement or worsening of admission clinical features, evidence of infection at the puncture site and/or the pericardial space, and evidence of persisting effusion or pericardial constriction. Echocardiography was performed at baseline, at first follow-up, and thereafter as clinically indicated. Cardiac tamponade was diagnosed when the following were noted: inversion of  $\geq 30\%$  of the right atrial wall during late diastole/early systole and/or inward motion of the right ventricular wall in early diastole that persisted after mitral valve opening.<sup>20</sup>

**Statistics**

Interval (continuous) variables were expressed as means (standard deviation, SD). Statistical analysis of continuous variables was done with the Mann-Whitney *U*-test. Non-parametric data were expressed as median (range) and analysed with the Kruskal-Wallis one-way ANOVA tests and chi-square testing to establish statistical significance ( $p < 0.05$  statistically significant). Bonferroni (all pair-wise multiple-comparison ( $z$ -values  $> 2.394$ ) and Kruskal-Wallis multiple-comparison  $z$ -value tests ( $z$ -values  $> 1.960$ ) were used to establish statistically significant differences between groups. All statistical analyses were done using Statistica version 6.0.

**Results**

Of 233 patients treated by echo-guided pericardiocentesis, 162 patients (100 males and 62 females) had pericardial TB. ‘Definite’ TB was diagnosed in 118 patients and 44 were diagnosed with ‘probable’ TB. Eleven patients were on anti-tuberculous treatment at the time of pericardiocentesis and are included in this review. Eighty-four patients were HIV positive, including 81 with tuberculous pericarditis, two with

pericardial sepsis, and one patient with uraemic pericarditis.

The mean (SD) age at presentation differed significantly between HIV-positive and -negative patients with pericardial TB [31.9 (8.4) years vs 39.7 (15.9) years; ( $p < 0.05$ )]. The mean (SD) CD4<sup>+</sup> lymphocyte count for HIV-positive patients was 215 (202) cells/ $\mu$ l. Echocardiographic evidence of tamponade was found in 197 cases (87%). Chest wall puncture site was elected in 204 of the 233 patients (88%) and the subcostal approach in the remaining 29 patients (12%). The median (range) volume of pericardial fluid drained at initial pericardiocentesis was 791 (80–2 770) ml. The majority of pericardial effusions had a haemorrhagic macroscopic appearance (66.1%), 25% of effusions were straw-coloured and 3% resembled pus. A pigtail catheter was left *in situ* for intermittent daily drainage.

The pericardiocentesis-related complications are summarised in Table 1. The most common minor complication ( $n = 42$ ) was local pain at the site of catheter insertion. In four (2.4%) patients, local skin infection necessitated removal of the catheter; three of them were HIV positive and had CD4<sup>+</sup> lymphocyte counts below 200 cells/ $\mu$ l. No patient developed a pneumothorax during catheter insertion, but one developed a pneumothorax during catheter removal, which was managed by intercostal underwater tube drainage. No death was attributable to the pericardiocentesis procedure.

TB treatment was well tolerated and the six-month course was adequate regardless of HIV status. Three patients presented with liver toxicity, resulting in brief interruption and successful staggered reintroduction of treatment. HIV-positive patients also received daily oral cotrimoxazole. Nine patients with complicated pericardial effusions (namely recurrent pericardial effusions, loculated pericardial effusions and/or constrictive pericarditis) received oral prednisone according to published guidelines.<sup>7,21,22</sup> Non-tuberculous effusions were treated according to underlying cause. Septic pericarditis was treated with broad-spectrum antibiotics until the causative organism was identified by culture.

**TABLE 1. DESCRIPTION OF THE COMPLICATIONS IN 233 PERICARDIOCENTESES**

	TB/HIV+ (n = 81)	TB/HIV- (n = 81)	Non-TB (n = 71)
<i>Minor complications</i>			
Local pain	15 (19%)	12 (15%)	15 (21%)
Catheter removed inadvertently	2	3	2
Repeat pericardiocentesis	3	4	1
Catheter blockage	3	3	2
Leakage at skin insertion	3	4	2
Local skin infection	3	1	0
Local bleeding	1	1	0
Disconnection of system	1	2	1
<i>Major complications</i>			
Tamponade post-tap (non-fatal)	0	1	1
Intrapericardial sepsis	1	1	0
Thrombus left ventricle	0	1	0
Pneumothorax	0	1	0

**TABLE 2. THERAPEUTIC INDICATIONS FOR PERICARDIAL SURGERY**

	<i>Tuberculous pericarditis (n = 11)</i>	<i>Non-tuberculous pericarditis (n = 6)</i>
Recurrent effusion	3	1
Effusive constriction	4	2
Loculated effusion	1	2
Daily drainage > 100 ml	2	0
Obstructed tube	1	1
Fibrous constriction*	1	0

\*One patient had pericardial fenestration and total pericardiectomy was performed after two months of anti-tuberculous therapy.

Two patients with septic pericarditis underwent pericardial fenestration.

Thirty-six patients underwent pericardial surgery. Of these, 19 had diagnostic pericardial biopsies and 17 underwent therapeutic pericardial fenestration. One patient had a total pericardiectomy after developing fibrous constrictive pericarditis. The indications for the therapeutic biopsies are summarised in Table 2. Two tuberculous pericarditis patients died postoperatively while awaiting theatre. Both of them had echocardiographic evidence of poor left ventricular function; one was HIV positive. One patient underwent total pericardiectomy for constrictive pericarditis performed after two months of anti-tuberculous therapy; he was well at the one-year follow-up.

The 30-day all-cause mortality was higher in patients with non-tuberculous pericardial disease than in those with pericardial TB (20 vs 8.0%;  $p < 0.01$ ). The causes of death in the pericardial TB patients are presented in Table 3. The causes of the one-year mortality observed in pericardial TB patients are summarised in Table 4. The one-year all-cause

**TABLE 4. CAUSES OF ONE-YEAR MORTALITY IN TUBERCULOUS PERICARDITIS PATIENTS**

	n	<i>HIV negative (n = 10)</i>	<i>HIV positive (n = 18)</i>
Disseminated TB	3	1	2
Effusive constriction/ tamponade	6	3	3
Fibrotic pulmonary disease	3	3	
Systemic non-tuberculous infection	9	1	8
Underlying cardiomyopathy	2	1	1
Gastrointestinal haemorrhage	1		1
Underlying muscular dystrophy	1		1
Unknown	3	1	2

**TABLE 5. MORTALITY ACCORDING TO DIAGNOSTIC GROUPS**

	<i>30-day mortality (%)</i>	<i>One-year mortality (%)</i>
Tuberculosis (n = 162)	13 (8)	28 (17)
Malignancy (n = 22)	5 (23)	20 (91)
Uraemic (n = 12)	3 (33)	5 (42)
Septic (n = 5)	3 (60)	4 (80)
Other (n = 32)	3 (9)	13 (41)
Total	27 (11.6)	70 (30.0)

mortality was significantly higher ( $p < 0.001$ ) in patients who presented with non-tuberculous pericardial effusions than in the tuberculous pericarditis patients (60.0 vs 17.3%). In the tuberculous pericarditis group it was higher for HIV-

**TABLE 3. CAUSES OF 30-DAY MORTALITY IN PATIENTS WITH PERICARDIAL TB**

<i>Time period</i>	<i>Age (years)</i>	<i>HIV status</i>	<i>Cause of death</i>
< 24 hours	25	+	Drug abuse, pneumonia, septicaemia and respiratory failure (day 1)
24 hours to 7 days	31	+	Underlying muscular dystrophy, cardiac arrest (day 2)
	54	-	Disseminated TB, sudden deterioration in spite of daily pericardial drainage (day 4)
	40	+	Loculated pericardial effusion with tamponade and constrictive features, died pre-operatively due to massive gastrointestinal haemorrhage (day 4)
	36	+	Unexpected sudden cardiac arrest, echo showed no constriction or loculated effusion (day 4)
	28	+	Cerebral toxoplasmosis, status epilepticus, septicaemia, uraemia, progressive deterioration, no pericardial cause noted on repeat echo (day 5)
	43	-	Disseminated TB, sudden hypotensive episode followed by cardiac arrest (day 5)
7-30 days	29	+	CD4 <sup>+</sup> lymphocyte count 9 cells/ $\mu$ l, severe pain in left flank, delirious, diarrhoea, septicaemia (day 9)
	30	-	Chronic pulmonary fibrosis, cavitation, smear-positive pulmonary TB, cardio-respiratory failure (day 10)
	35	+	Underlying cardiomyopathy, removal of obstructed catheter on day 2. Cardiac arrest nine days later (day 11)
	53	-	Large residual effusion with tamponade and features of constriction - died due to acute peri-operative cardiac insufficiency (day 16)
	47	+	CD4 <sup>+</sup> lymphocyte count 43 cells/ $\mu$ l, severe diarrhoea, vomiting, tender abdomen, dysentery, septicaemia (day 17)
	53	-	Post-TB bronchiectasis, cor pulmonale, reactivation of TB, cardio-respiratory failure (day 20)

positive (22.2%) than for HIV-negative patients (12.3%;  $p = 0.04$ ). The 30-day and one-year all-cause mortality data are summarised according to diagnostic groups in Table 5.

Three pericardial TB patients (two HIV positive) died during the first 60 days after pericardiocentesis as a result of disseminated TB; one had interrupted anti-tuberculous therapy. HIV-related non-tuberculous infectious complications that resulted in death included *Pneumocystis carinii* pneumonia ( $n = 2$ ), cerebral toxoplasmosis with status epilepticus ( $n = 1$ ), cryptococcal meningitis ( $n = 1$ ), abdominal sepsis ( $n = 1$ ) and septicaemia ( $n = 3$ ). Low CD4<sup>+</sup> lymphocyte counts were associated with increased mortality risk. Seventy-five per cent of patients who died during the first year of follow-up had an admission CD4<sup>+</sup> lymphocyte count below 200 cells/ $\mu$ l, whereas admission CD4<sup>+</sup> lymphocyte counts below 200 cells/ $\mu$ l were observed in only 45% of 'one-year survivors'. The corresponding mean (SD) CD4<sup>+</sup> lymphocyte count for survivors was 237.2 (212.4) cells/ $\mu$ l compared to 155.1 (188.6) cells/ $\mu$ l for non-survivors ( $p < 0.01$ ).

## Discussion

Large pericardial effusions are usually the manifestation of underlying disease. The 60% mortality of the non-tuberculous group reflects the seriousness of the conditions that resulted in patients requiring therapeutic pericardiocentesis. Although the prognosis was significantly better for tuberculous pericardial disease, effective management is nevertheless of utmost importance. Without specific treatment, the reported average survival was 3.7 months and only 20% of patients were alive at six months.<sup>5</sup>

To initiate the most appropriate therapy, it is important to use sensitive and accurate diagnostic tools. We used the measurement of adenosine deaminase activity (ADA) and pericardial fluid differential leukocyte counts as rapid and hesitant diagnostic tools,<sup>20,24</sup> but in addition, aimed for microbiological confirmation. Our approach included the injection of a 7-ml aliquot of pericardial fluid into a BACTEC™ medium at the bedside immediately after completion of the pericardiocentesis procedure and the use of an automated radiometric BACTEC™ MGIT™ 960 system (Becton Dickinson and Co, Hood, USA). In addition, we also cultured sputum, blood, and when available pleural or peritoneal fluid. This aggressive approach resulted in a microbiological yield of 72.8%, and was equally effective in HIV-positive and -negative patients, in contrast to pericardial histopathology, which is significantly influenced by HIV co-infection.<sup>25</sup>

In our experience, the majority of patients who present to the echocardiography department with suspected pericardial TB are critically ill and have large pericardial effusions; 90% of those enrolled in this study had echocardiographic evidence of tamponade. On average, more than 800 ml of fluid were drained at the initial drainage procedure. The community-based epidemiology and clinical presentation of pericardial TB may differ significantly from our observations in hospitalised patients in a tertiary referral centre. However, in our experience, echo-guided pericardiocentesis with extended intermittent drainage resulted in effective relief of cardiac tamponade, and over the six-year period, an

almost complete absence of fibrous constrictive pericarditis.

Six patients (2.6%) had major complications related to pericardiocentesis. We observed a very low incidence of recurrence and only 19 patients were referred for therapeutic pericardial surgery, indicating a pericardiocentesis success rate of 92%. Procedural success rates are high in most series, generally more than 90%, whereas complication rates are approximately 4%.<sup>13,26,27</sup> In our study, pericardiocentesis was equally safe and effective in tuberculous pericardial effusions as in non-tuberculous pericardial effusions and our results were similar to those of other series reported from settings where only the minority of patients had pericardial TB.<sup>15,16</sup>

Patients were referred for pericardial surgery whenever pericardiocentesis failed to adequately drain loculated effusions or if echocardiography was suggestive of effusive-constrictive pericarditis. Besides the 19 diagnostic biopsies, pericardial fenestration was performed on 17 patients for therapeutic indications. The post-operative 30-day mortality for these 36 individuals was 5.6%, compared to 30-day mortality for surgical drainage of malignant pericardial effusions of 19.4%.<sup>28</sup> More specifically, complete pericardiectomy, partial pericardiectomy and subxiphoid or anterior transthoracic window were associated with 30-day mortality rates of 37.5, 23.8 and 8.6%, respectively.<sup>14</sup>

In the present series, two patients died while awaiting surgery. One had a massive upper gastrointestinal haemorrhage, while the other, a critically ill HIV-positive patient, died from tamponade, which could not be adequately relieved by catheter drainage, and underlying left ventricular dysfunction. Most patients can be adequately treated by pericardiocentesis. The technique is safe even in very sick and unstable patients and does not usually need to be performed in theatre. In selected stable patients, it can even be performed on an outpatient basis.<sup>29</sup> It is possible that in other settings a larger proportion of HIV-infected patients is affected by left ventricular systolic dysfunction, which may be associated with a higher mortality.

Effusive-constrictive pericarditis preceded fibrous constriction in the two patients who developed this complication. One refused surgery, but fortunately improved over a period of two years and therefore had transient constrictive pericarditis, which is a rare but important entity, since pericardiectomy is not indicated for these patients.<sup>30</sup> This patient's favourable outcome was possibly related to the installation of intrapericardial triamcinolone. The other patient was successfully treated by total pericardiectomy and was well at the one-year follow-up.

In effusive-constrictive pericarditis, pericardiocentesis usually fails to alleviate the features of haemodynamic compromise, and subtotal or complete pericardiectomy is not possible because the pericardium cannot be stripped from the epicardium. In our experience, patients with effusive-constrictive pericarditis required surgical fenestration to drain the fibrinous material from the pericardial space and to break down pericardial adhesions. This did not, however, address the main problem, namely the presence of a stiffened epicardium, which caused the constriction and could not be removed at that stage of the disease because a skin had not yet formed that would allow surgical stripping. Once

the fibrous skin becomes echocardiographically evident, total pericardiectomy should be performed in symptomatic patients before pericardial calcifications have formed or the onset of cardiac cachexia.<sup>12,22</sup>

An unfortunate proportion of deaths is attributable to disseminated TB<sup>3,31</sup> and despite the availability of anti-tuberculous chemotherapy, the mortality of disseminated TB is as high as 20 to 30%.<sup>32,33</sup> The HIV epidemic has considerably altered the frequency and descriptive epidemiology of disseminated TB,<sup>34,35</sup> which occurs more frequently and may be more difficult to diagnose in HIV-positive individuals.<sup>35,36</sup> Due to the multi-system involvement in disseminated TB, the clinical manifestations are protean. Presenting symptoms are dominated by systemic effects: fever, weight loss, anorexia and weakness.<sup>32,33,37-39</sup> Approximately 25% of patients with tuberculous pericarditis have evidence of other organ involvement at the time pericarditis is diagnosed, particularly pleuritis and lymphadenitis.<sup>3,31</sup>

The degree of immunodeficiency and risk for disseminated TB and other serious opportunistic infections and death correlates with CD4<sup>+</sup> lymphocyte cell counts.<sup>35,40</sup> In our study, 75% of HIV-positive patients who died during the first year of follow-up had admission CD4<sup>+</sup> lymphocyte counts less than 200 cells/ $\mu$ l compared to only 45% of the HIV-positive one-year survivors, and the majority of deaths were caused by opportunistic infections, septicaemia and disseminated TB.

The cornerstone of the treatment of HIV infection is highly active antiretroviral therapy (HAART), which has been shown to reduce the mortality and morbidity of people living with advanced HIV disease.<sup>41,42</sup> The goal of HAART is maximal and durable viral suppression to enable preservation and restoration of the immune system.<sup>40</sup> During the course of our study, HAART was not available at our hospital.

The recently improved accessibility of HAART will hopefully result in improved prognosis of HIV-infected TB patients, but may not do so because there are potential complex drug interactions, overlapping adverse reactions, potential non-adherence due to the pill burden, and drug malabsorption.<sup>40</sup> Despite these potential problems, HAART substantially reduces newly acquired immunodeficiency syndrome (AIDS) events and death in co-infected patients.<sup>44,45</sup> Paradoxical deterioration due to the immune reconstitution inflammatory syndrome has been reported to occur in 11 to 36% of patients with TB who start HAART.<sup>46,47</sup> Secondary preventive therapy with isoniazid reduces TB recurrence in HIV-infected patients and the absolute impact seems to be greatest among individuals with low CD4<sup>+</sup> lymphocyte cell counts.<sup>48</sup>

## Conclusion

Before the advent of anti-tuberculous chemotherapy, tuberculous pericarditis was often rapidly fatal, with a mortality rate of 80 to 85%.<sup>3,5</sup> Our series of 162 consecutive patients with tuberculous pericarditis demonstrated that the use of echo-guided pericardiocentesis with extended intermittent drainage and early initiation of anti-tuberculous therapy is associated with an extremely low risk for constriction and

cardiac death. This drainage technique is safe and effective irrespective of the patient's HIV status. The one-year all-cause mortality was higher in HIV-positive than in HIV-negative patients. The majority of deaths were caused by non-cardiac disease. CD4<sup>+</sup> lymphocyte counts below 200 cells/ $\mu$ l predicted a poor prognosis. It is possible that in other settings a larger proportion of HIV-infected patients is affected by left ventricular systolic dysfunction, which may be associated with a higher mortality.

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