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MMED THESIS ON THE DIAGNOSTIC VALUE OF PERICARDIAL ASPIRATION AT GROOTE SCHUUR HOSPITAL

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University of Cape Town

THE DIAGNOSTIC VALUE OF PERICARDIAL ASPIRATION AT GROOTE SCHUUR HOSPITAL

SUMMARY

In this MMed thesis I have reviewed retrospectively the pericardial aspirations performed between 1 July 1987 and 12th October 1989 at Groote Schuur Hospital, Cape Town. Documenting the reasons for aspiration, the complications of pericardiocentesis, and how cytologic, bacteriologic and biochemical examination of the aspirate influenced the clinicians' management of the 52 patients reviewed. The relatively low mortality of less than 2% is noted, in a procedure carried out for the relief of cardiac tamponade in 57% of the patients.

A significant relationship between an ADA level higher than 51 international units per litre and a positive culture of mycobacterium tuberculosis from pericardial aspiration is demonstrated. The relatively low successful culture of mycobacterium tuberculosis (32% of the 29 patients clinically assessed as having tuberculous pericarditis) is noted, and recommendations to improve the yield from culture are made.

INTRODUCTION

The clinical and pathologic features of acute pericardial disease have been known for many years(46). By contrast, the approach to the aetiologic diagnosis in several pericardial syndromes is not well established. The most frequently disquieting dilemma for the clinical cardiologist is the patient with acute pericardial disease without an apparent cause (primary acute pericardial disease). Most patients have self-limited clinical features and do not constitute a major problem of management, despite an unrecognised cause in most cases; however, in many patients the illness is not self-limited, and in many of such patients even an extensive workup is likely to result in negative aetiologic conclusions. The possibility of life-threatening treatable disease makes aetiologic diagnosis a very important issue. In particular, tuberculous pericarditis is sometimes a very difficult diagnosis, and its early identification is necessary for successful treatment. The indications for pericardiocentesis and open pericardial drainage with biopsy are controversial. Dispute has mainly been based on the risk and therapeutic value with closed needle pericardiocentesis compared with surgical drainage, with less emphasis on the diagnostic capabilities of both procedures. General agreement as to the safest and most sensitive approach to the aetiologic diagnosis of acute pericardial disease is not found in published reports; in fact, attempts to analyse this common clinical problem are surprisingly scarce.

Pericardial disease presents a broad spectrum ranging from asymptomatic involvement in patients with rheumatoid arthritis through the disabling condition of constrictive pericarditis to the potentially fatal syndrome of cardiac tamponade. Pericardial friction rub in the course of acute myocardial infarction is common and rarely is the precursor of cardiac tamponade even in the presence of anticoagulation. The aetiology of the relapsing pericarditis remains obscure, and these conditions continue to pose difficult therapeutic problems. As yet, there is no definitive answer to the cause of pericarditis in patients undergoing dialysis for chronic renal disease, and the controversial issue regarding whether these patients should be treated medically or surgically remains unsettled. Pericarditis is associated with systemic lupus erythematosis (SLE), and usually occurs during flare-ups of disease activity, and is the most common cardiovascular manifestation of the disease(26). Pericarditis is detected clinically in approximately 20-40% of these patients during the course of their disease. Echocardiographic abnormalities can be detected in a high percentage of these patients, but the clinical significance of this is unclear. The prevalence of pericarditis in autopsy patients ranges from 43%-100% and averages 62%, where as the prevalence of myocarditis in autopsy series is approximately 40%(27). The inflammatory process may cause fibrinous or effusive pericarditis with the rare occurrence of pathognomonic haematoxyline bodies in the visceral pericardium. Pericardial fluid may be serous or grossly haemorrhagic with a high protein

content, low glucose content, and white cell count below 1000 per cubic millimeter (composed primarily of polymorphonuclear leukocytes). Low pericardial fluid complement levels relative to normal serum values have been reported. Cardiac tamponade occurs in less than 10% of patients with SLE and clinically recognized pericarditis, while the development of constrictive pericarditis has been reported but is extremely rare. Pericarditis due to SLE may be accompanied by other cardiac lesions, including verrucous endocarditis, inflammation and necrosis involving the conduction system, and coronary artery vasculitis.

In industrialised nations, the incidence of tuberculous pericarditis has decreased within the past three decades as a result of effective chemotherapy and public health surveillance. In a series of 231 consecutive patients who were evaluated prospectively using a rigorous protocol which included pericardiocentesis and biopsy, tuberculosis was diagnosed in only 4 per cent of patients and in 7 per cent of the subset who developed cardiac tamponade(47). The incidence of tuberculous pericarditis among patients with pulmonary tuberculosis ranges from about 1 to 8 per cent(48). The disease continues to be important in immunosuppressed patients and among the underprivileged, including South and West African blacks, the black poor of the United States, and Asian and African immigrants (49-51). For example, in Transkei tuberculous pericarditis is claimed to be the second most common cause of "heart failure" after rheumatic heart disease(21). Pericardial involvement usually develops by retrograde spread from peritracheal,

peribronchial or mediastinal lymph nodes or by haematogenous spread from the primary tuberculous infection. Less commonly, the pericardium is involved by breakdown and contiguous spread from a tuberculous lesion in the lung or by haematogenous spread from distant secondary skeletal or genitourinary infections (53,54). Pericarditis can also be caused by atypical mycobacteria(55), which has been reported in association with the acquired immunodeficiency syndrome(56). Viable acid-fast bacilli, fibrin deposits and granuloma formation are followed by the development of a pericardial effusion; usually haemorrhagic, but may be serous. Polymorphonuclear leukocytes are said to be present early in the development of the effusion, but later at the time of clinical presentation they are replaced by monocytes, lymphocytes and plasma cells. The rate of accumulation of fluid is variable. If the effusion develops slowly even large effusions may be well tolerated. Rapid accumulation of even relatively small effusions may cause haemodynamic compromise and tamponade(53). With absorption of the effusion, the pericardium thickens and a thick fibrous exudate is deposited on the parietal pericardium. The pathology is very variable and may range from a serous effusion, with a few strands of fibrin, to the more common haemorrhagic effusion. At this stage, viable acid-fast bacilli may no longer be present, but caseation may develop and penetrate the myocardium. Finally, fibrous pericarditis develops as the granulomatous reaction is replaced by fibrous tissue and collagen. These changes are followed by the accumulation of cholesterol crystals and the development of pericardial

calcification; encasing the heart in a fibro-calcific reaction which impedes diastolic filling, causing the classical clinical syndrome of constrictive pericarditis(57).

The presence of effusions in body cavities can be a confusing clinical problem in differential diagnosis. The examination of pleural and peritoneal fluids by cytologic methods has already proved to be of decisive value in the diagnosis of malignant, as well as non-malignant disease(4). Surveys of the possibilities and limitations of pericardial fluid cytology have been limited, probably because pericardial fluids constitute less than one percent of the serous fluids examined in a cytology laboratory. The purpose of this thesis is to show that the cytologic, bacteriologic and biochemical examination of pericardial fluids may play a significant role in the differential diagnosis of pericardial effusions.

At autopsy, 5-10% of patients with cancer may be found to have malignant pericardial disease(5). While the pericardial disease may remain subclinical in some patients, in many severe functional impairment or acute, life-threatening symptoms will develop. The latter are usually associated with pericardial tamponade and present an oncologic emergency requiring pericardiocentesis(6). Further therapeutic options then include pericardiectomy, local radiation therapy or chemotherapy depending upon prior treatment. New systemic treatment programmes will be indicated if the pericardial involvement represents relapse of previously treated disease. The diagnosis

of cancer related pericardial disease can be difficult especially when unsuspected or clinically occult. Antemortem diagnosis has improved in recent years because of increased awareness of pericardial complications and improved non-invasive cardiac diagnostic techniques. Of importance, approximately 50% of patients with symptomatic pericardial disease and underlying cancer may have non-malignant pericardial disease(7) including radiation pericarditis, idiopathic pericarditis, drug induced pericarditis, infection, hypothyroidism and auto-immune disorders. Because specific treatment depends on the cause, the aetiologic factor or factors must be established, with as little morbidity and as much certainty as possible.

Pericardiocentesis, a method successfully used since 1840, is dramatic and life-saving when performed to relieve cardiac tamponade. However, serious complications, including death, can occur. Some physicians believe that pericardiocentesis should not be performed routinely unless cardiac tamponade is present(1). They recommend direct surgical drainage of the pericardial sac(2), but unfortunately this procedure can also result in significant complications(3). This study was carried out to assess the risk of pericardiocentesis at Groote Schuur Hospital, Cape Town, with particular emphasis on identifying factors that could lead to improved selection of patients and minimize the hazards. I have reviewed retrospectively all the pericardial aspirations performed between 1 July 1987 through to 12 October 1989 in the catheter laboratory at Groote Schuur Hospital, Cape Town. I have attempted to review the reasons for

the aspirations, the complications of pericardiocentesis and how the data generated from these studies influenced the clinical management of the patient.

ANATOMY AND FUNCTIONS OF THE PERICARDIUM

The pericardium forms a strong flask-shaped sac with short tube-like extensions that enclose the origins of the aorta and its junction with the aortic arch, the pulmonary artery where it branches, the proximal pulmonary veins, and the vena cava. Fibrous tissue of the pericardium actually blends with adventitia of the great arteries to form strong attachments. In addition, the pericardium has firm ligamentous attachments anteriorly to the sternum and xiphoid process, posteriorly to the vertebral column, and inferiorly to the diaphragm.

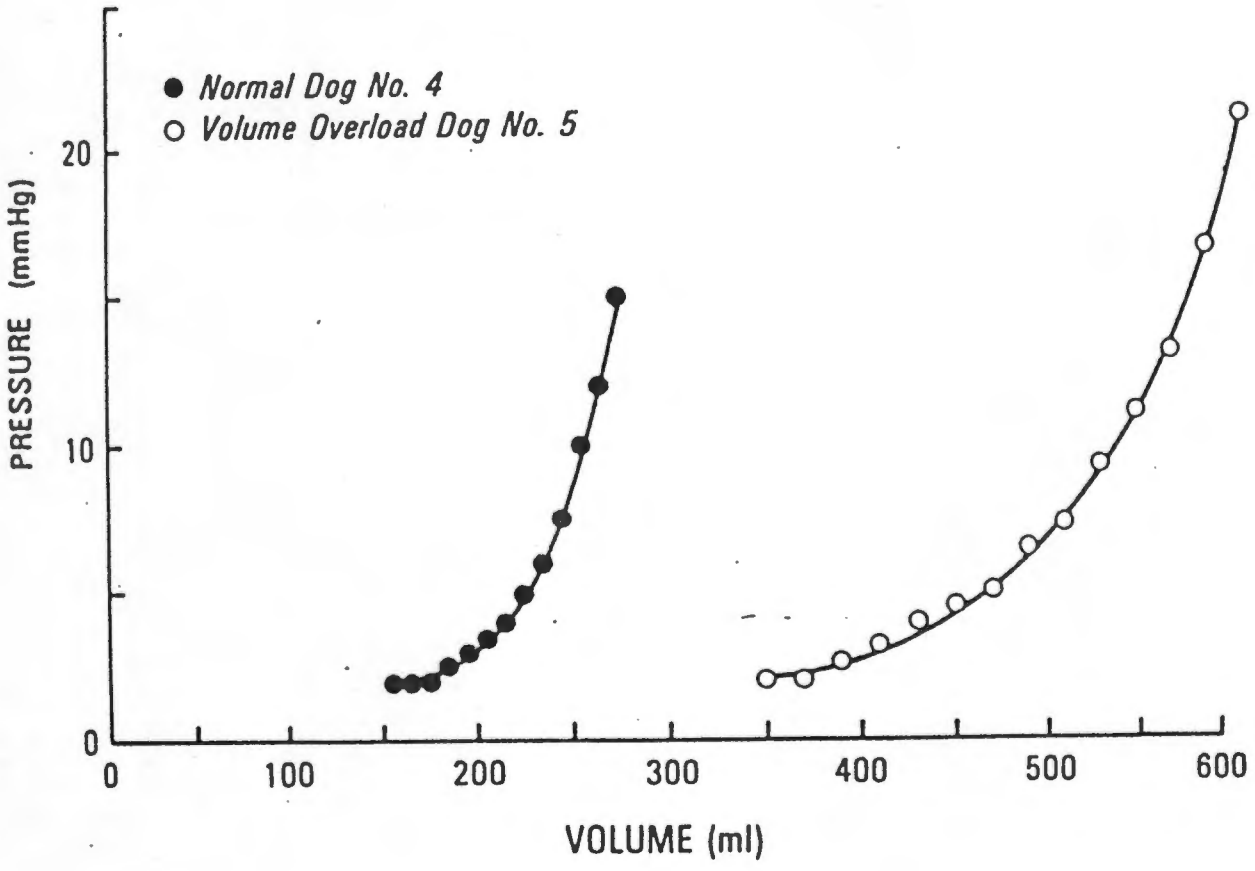
The human pericardium receives its arterial blood supply from small branches of the aorta and internal mammary and muscular phrenic arteries. The pericardium is innervated by the vagus, left recurrent laryngeal nerve and oesophageal plexus and also has a rich sympathetic innervation from the stellate and first dorsal ganglia and the cardiac, aortic and diaphragmatic plexuses. The phrenic nerves course over the pericardium en route to the diaphragm. The afferent nerves responsible for pain perception appear to be transmitted via the phrenic nerve, entering the spinal cord at C4-C5. Recent studies suggest that peripheral sensory fibres which enter the dorsal root ganglia at C8-T2 supply both the brachial plexus and the pericardium; this

provides a possible morphological explanation for referred pericardial pain.

The pericardium is composed of a fibrous outer layer and an inner serous membrane that has a single layer of microcilial cells. The inner serous layer is intimately attached to the surface of the heart and epicardial fat to form the visceral pericardium, and this inner serous membrane reflects back upon itself to line the outer fibrous layer to form the parietal pericardium. The serous visceral pericardium is attached to the parietal pericardium by delicate connective tissue with elastin fibres. The parietal pericardium is composed of collagen fibres interlaced with extensive elastic fibres which are wavy during childhood and become progressively more straight with age, suggesting that pericardia in the young are more compliant than those in the elderly. Electron microscopy of the pericardium reveals that exuberant microvili and long single cilia project from the serous mesothelium composing the visceral pericardium and the inner lining of the parietal pericardium, and increase markedly the surface area available for fluid transport. The human pericardium normally contains up to 50ml of clear fluid sufficient to be detected echocardiographically. The visceral pericardium is believed to be the source of normal pericardial fluid and of excessive fluid in diseased states. Normal pericardial fluid appears to be an ultrafiltrate of plasma, since electrolytes are present in pericardial fluid in concentrations compatible with such an ultrafiltrate; protein concentrations are about one third of those of the plasma and albumin is present in

a higher ratio in pericardial fluid, reflecting a lower molecular weight. Pericardial fluid also contains phospholipids, which serve as a lubricant to reduce friction between the surfaces of the parietal pericardium and the visceral pericardium. Current data suggests that drainage of the pericardial space occurs both via the thoracic duct, via the parietal pericardium, and by the right lymphatic duct via the right pleural space.

The pericardium's ligamentous attachments help to fix the heart anatomically and prevent excessive motion with changes in body position. The pericardium, also reducing friction between the heart and surrounding organs, provides a barrier against the extension of infection and malignancy from contiguous organs to the heart itself. The role of the pericardium in the regulation of the circulation is controversial, since congenital absence of the pericardium is not associated with adverse disturbances of cardiac function. However, observations in both dogs and man indicate that the pericardium may play a role in: 1) the distribution of hydrostatic forces on the heart; 2) the prevention of acute cardiac dilatation; and 3) diastolic coupling of the two ventricles. The relationship between pressure within the pericardium and total intrapericardial volume, which is the sum of the volume of the heart itself and the reserve volume of the surrounding pericardial sac, appears as a steep curve when plotted on a graph shown on page 13.



Pericardial pressure-volume curves from a normal dog(left) and from a dog with chronic volume overload(right). Note the normal pressure-volume curve(left) is initially flat but becomes extremely steep as total volume within the pericardium increases. In response to chronic cardiac dilatation, the pericardium enlarges in size and mass such that the pericardium can accommodate a large volume at low pressure(right) curve.

Thus, once the pericardium is filled, intrapericardial pressure rises sharply as volume is increased. Normally, the pericardial sac is filled with a thin film of fluid distributed throughout the pericardial space in such a way that the pericardial reserve volume is not exceeded. This permits respiratory and postural changes in cardiac volume and total intrapericardial volume to occur without significant changes in intrapericardial pressure. When measured with a fluid-filled or micromanometer-tipped catheter, pericardial pressure is nearly equal to intrapleural pressure and varies from -5 to +5 cmH2O during the respiratory cycle. When the volume of the heart or other contents of the pericardial sac increase and exceed the elastic limits of the pericardium, during diastole the heart is shifted to the steep portion of the curve relating intrapericardial pressure and volume, resulting in marked increases in intrapericardial and intracardiac pressures. However, the difference between the two pressures i.e. the transmural pressure, usually declines. In the extreme case of cardiac tamponade, in which both intrapericardial and intracardiac pressures are markedly increased, the transmural pressure distending the ventricles may fall precipitously, resulting in decreased ventricular diastolic volumes and preload. Taken together, these findings indicate that changes in intrapericardial pressure modestly modulate the regulation of stroke volume by ventricular preload, i.e. the Frank-Starling mechanism and exert a substantial influence only at higher ventricular and pericardial pressures.

The relatively non-distensible pericardium may help to limit acute distention of the heart. Recent studies in dogs suggest that the pericardium may restrain left ventricular filling, so that the ventricular volume is greater at any given ventricular pressure with the pericardium removed than with the pericardium intact(8). In addition, acute changes in intracardiac and total intrapericardial volume result in an upward shift of the left ventricular pressure volume relationship, which is in part mediated by the restraining effect of the pericardium.

The pericardium also contributes to the diastolic coupling between the two ventricles, i.e. to ventricular interdependence. The distention of one ventricle alters the distensibility of the other, even in the absence of the pericardium. This effect appears to be mediated in part by the interventricular septum, which tends to bulge into the left ventricle, causing a change in the shape of the left ventricle when the right ventricle is distended. In the absence of the pericardium, large increases in right ventricular volume and pressure are required to cause an appreciable increase in left ventricular filling pressure. In contrast the presence of an intact pericardium markedly attenuates the coupling between ventricular diastolic pressures(9). When right ventricular volume and pressure are increased with the pericardium intact, right and left ventricular filling pressures are closely correlated and left ventricular volume is smaller than in the absence of the pericardium, when cardiac distensibility is primarily related to properties of the myocardium. This effect of the pericardium on diastolic

ventricular interaction is present at normal filling pressures and becomes of increasing importance at high right ventricular filling pressures.

PERICARDIAL EFFUSION

Pericardial effusion may develop as a response to injury of the parietal pericardium with all causes of acute pericarditis. It may be clinically silent, but if the accumulation of fluid causes intrapericardial pressure to increase, resulting in cardiac compression, the symptoms of cardiac tamponade develop. The development of increased intrapericardial pressure secondary to a pericardial effusion depends on several factors: 1) the absolute volume of the effusion, 2) the rate of fluid accumulation and 3) the physical characteristics of the pericardium. The pericardial space in humans normally contains between 15 and 50ml of fluid, and if additional fluid accumulates slowly, the pericardium stretches; the pericardial sac can accommodate up to 1-2 litres without elevation of intrapericardial pressure. However, the normal unstretched pericardial sac can accommodate the rapid addition of only 80-200ml of fluid and still remain on the flat portion of the curve relating intrapericardial pressure and volume (See previous graph, page 13). If additional fluid is added rapidly to a volume exceeding about 150-200ml, a mild increase of intrapericardial pressure occurs. Intrapericardial pressure may also increase remarkably after the accumulation of a small amount of fluid if the pericardium is excessively stiff because of fibrosis or tumour infiltration. Chronic pericardial effusions persisting for more than six months may occur in any

form of pericardial disease. Often they are surprisingly well tolerated, with no symptoms of cardiac compression, and are discovered when a routine chest radiograph discloses an unexpectedly large cardiac silhouette. Chronic pericardial effusions are particularly likely to be found in patients with previous idiopathic or viral pericarditis, uraemic pericarditis, and pericarditis secondary to myxoedema or neoplasm. The management of chronic pericardial effusion depends in part on the cause. Stable and apparently idiopathic effusions in asymptomatic patients usually require no specific treatment except for avoidance of anticoagulants.

CARDIAC TAMPONADE

Cardiac tamponade is characterised by: 1) an elevation of intracardiac pressures, 2) progressive limitation of ventricular diastolic filling and 3) a reduction of stroke volume. When the addition of fluid into the pericardial space causes intrapericardial pressure to rise to the level of the right atrial and right ventricular diastolic pressures, the transmural pressure distending these chambers declines to close to zero and cardiac tamponade occurs. The rise of right atrial and intrapericardial pressures is less marked in the presence of hypovolaemia; therefore, cardiac tamponade may be masked when hypovolaemia is present. Further accumulation of intrapericardial fluid causes both intrapericardial and right ventricular diastolic pressures to rise together to the level of the left ventricular diastolic pressure, and subsequently all three pressures rise together associated with the fall in

systemic arterial pressure. If the left ventricular diastolic pressure is markedly elevated owing to pre-existing left ventricular disease, cardiac tamponade occurs when right atrial and right ventricular diastolic and pericardial pressures equalize but at a lower level than the left ventricular diastolic pressure(10). Equalization of intrapericardial ventricular filling pressures results in markedly diminished transmural distending pressures and diastolic volumes of both ventricles and a fall in stroke volume. The reduction in stroke volume is initially compensated for by reflex increases in adrenergic tone; both tachycardia and increase in the ejection fraction initially help to maintain forward cardiac output. With severe cardiac tamponade, as cardiac output declines, compensatory mechanisms are no longer sufficient to maintain a systemic arterial pressure, and perfusion of vital organs becomes impaired; reduced coronary perfusion causes selective hypoperfusion of the subendocardium. The addition of myocardial ischaemia during cardiac tamponade could further compromise left ventricular stroke volume.

Cardiac tamponade also alters the dynamics of systemic venous return and cardiac filling. Normally, systemic venous return occurs during ventricular ejection coincident with the systolic x descent of the venous pressure pulse, and a second surge occurs during the right atrial emptying with the opening of the tricuspid valve in diastole, corresponding to the y descent. In cardiac tamponade, the heart is compressed throughout the cardiac cycle. During ejection, intracardiac volume decreases resulting

in a fall in both intrapericardial and right atrial pressures, manifested as the x descent which is followed by a surge of systemic venous return into the right atrium. However, in diastole, the total volume within the pericardial space remains elevated despite opening of the tricuspid valve. Intrapericardial pressure remains elevated and is equal to, or exceeds, early diastolic right atrial pressure so that the transmural distending pressure is close to zero. As a result, this usual surge of systemic venous return during early diastole is abolished, right atrial emptying is impeded, and the right atrium is compressed or partially collapsed during diastole. These events are graphically reflected in the right atrial or systemic venous waveform in cardiac tamponade, in that the systolic x descent is prominent while the diastolic y descent is usually absent or attenuated.

Haemodynamic deterioration during cardiac tamponade is dependent critically on atrial compression during diastole with the secondary impairment of cardiac filling(11). Fowler and Gabel studied regional cardiac tamponade in dogs and showed that in isolated tamponade the right or left ventricular systolic pressure change is inconsequential and that a substantial fall in cardiac output and aortic pressure only occurs when the atria are also compressed. Echocardiographic studies of patients with cardiac tamponade indicate that right atrial diastolic collapse is uniformly present while left atrial and right ventricular diastolic collapse is variable. For example, right ventricular

collapse may be absent in pericardial tamponade in the presence of severe right ventricular hypertrophy(12).

During the development of tamponade, collapse of the right atrium and right ventricle initially occurs only in early diastole in association with delayed diastolic filling of the right ventricle and a modest fall in cardiac output without hypotension or overt haemodynamic deterioration. Pandiastolic right atrial and ventricular collapse indicates that pericardial pressure equals or exceeds right atrial and ventricular pressures throughout diastole so that the ventricles may fill only during atrial systole. This stage is accompanied by a severe reduction in ventricular volumes, a failure of compensatory mechanisms and hypotension(42,43). In this setting, pulsus alternans may occur due to a big variation in right ventricular output and left ventricular filling(42). During hypovolaemia with low right heart pressures, right ventricular collapse occurs at low intrapericardial pressures while volume expansion delays the development of right ventricular diastolic collapse and haemodynamic deterioration until the higher intrapericardial pressure is achieved(13). Sing et al have obtained simultaneous haemodynamic and two dimensional echocardiographic measurements in patients undergoing pericardiocentesis, and have shown that haemodynamic improvement first occurs at the point of disappearance of right ventricular diastolic collapse which is followed by a further improvement in cardiac output and the subsequent disappearance of right atrial collapse during continued pericardiocentesis.

Inspiration and the transmission of negative intrathoracic pressure to the pericardial space alter further the dynamics of right and left ventricular filling and are responsible for pulsus paradoxus, the inspiratory fall of aortic systolic pressure greater than 10 mmHg. The finding of the weakening of the arterial pulse during inspiration was described by Kussmaul in 1873 as the apparent paradox of the disappearance of the pulse during inspiration despite persistence of the heart-beat. It should be emphasised that pulsus paradoxus is an exaggeration of the normal inspiratory decline of left ventricular stroke volume by about 7 per cent and of systemic arterial pressure by 3 per cent(44). Inspiration is normally accompanied by an increase in diastolic dimension of the right ventricle, a small increase in left ventricular dimension, and increased velocity of flow from the vena cava into the right atrium(45). Pulsus paradoxus in cardiac tamponade appears to result from an exaggeration of these normal findings.

The clinical manifestations of the aforementioned changes in haemodynamics will depend on the size of the effusion as well as the degree of compression. Patients with pericardial effusions not causing cardiac compression may have no symptoms apart from a vague sensation of a dull ache in the chest. Large effusions may compress adjacent structures causing cough due to bronchial or tracheal compression, dyspnoea due to compression of lung parenchyma and hoarseness if the recurrent laryngeal nerve is compressed. A small effusion without cardiac compression may produce no abnormal physical signs apart from a pericardial

friction rub. When a large pericardial effusion is present cardiac dullness may be increased and be detected to the right of the sternum, the apex beat may be impalpable and the heart sounds soft and muffled. A large effusion compressing the left lower lobe bronchus may cause signs of consolidation at the left base (Ewart's sign). A friction rub may be heard even in the presence of a large effusion. Abnormalities of pulse, blood pressure and jugular venous pressure do not occur when the intrapericardial pressure is not raised. While tuberculous pericarditis may cause effusions which do not produce cardiac compression, it is more common for there to be at least some degree of compression which may be severe causing tamponade.

As the clinical syndrome of cardiac tamponade develops the physical findings will depend on the degree of elevation of pericardial pressure and the length of time the abnormality has been present. In extreme cases with severe compression patients are very ill and complain of dyspnoea; peripheral oedema, hepatomegaly and ascites will be present if the condition is long-standing. In addition to the signs of pericardial effusion outlined above, abnormalities of the pulse and venous pressure will be detected. The jugular venous pressure is elevated with a characteristic waveform which consists of a prominent systolic x descent and absent diastolic y descent. The peripheral arterial pulses may be rapid and of small volume. Pulsus paradoxus is characteristic and is critical in making a diagnosis; and is detected as an inspiratory decrease in amplitude of the palpated pulse. This is best sought in a large pulse such as the femoral;

complete disappearance of the palpated pulse during inspiration or total paradox occurs during severe tamponade. The magnitude of paradoxus can be estimated by sphygmomanometory.

The electrocardiographic abnormalities seen in acute cardiac tamponade include those of acute pericarditis and pericardial effusion per se. The development of electrical alternans is a more specific indicator of pericardial tamponade and reflects pendular swinging of the heart within the pericardial space(59). This may not be the only mechanism, because two-dimensional echocardiographic findings suggest that electrical alternans may be related to a beat-to-beat alteration of right and left ventricular filling(60). Electrical alternans may also occur in constrictive pericarditis, in tension pneumothorax, after myocardial infarction, and with severe cardiac muscle dysfunction. However, the appearance of electrical alternans in a patient with a known pericardial effusion is highly suggestive of cardiac tamponade(61). Electrical alternans of the QRS complex may occur in a 2:1 or 3:1 pattern. Alternans is usually limited to the QRS complex, but alternans of the P wave, QRS complex, and T wave may rarely occur and appears to be limited to extreme cardiac tamponade(62), often in association with neoplastic or tuberculous effusion. Both the abnormal heart motion within the pericardial sac, and electrical alternans disappear when pericardial fluid is aspirated.

The clinical features of constrictive pericarditis depend on how long the process has been present, and how severe it is, and

whether or not there is an active inflammatory process. Patients with only modest elevations of systemic venous and right atrial pressures will also have only modest elevation of the left ventricular end-diastolic pressure. Under these circumstances the predominant symptoms will be those secondary to hepatomegaly and ascites. If both left and right heart filling pressures are significantly elevated then symptoms of pulmonary venous congestion including dyspnoea on exertion and orthopnoea will be present.

Examination will confirm evidence of systemic venous congestion with elevation of the jugular venous pressure, peripheral oedema, ascites and hepatomegaly. The severity of hepatomegaly and ascites may be out of proportion to the degree of peripheral oedema and such patients are sometimes misdiagnosed as suffering from hepatic cirrhosis. The jugular venous pressure is however always elevated. The waveform is characteristic with rapid x and y descents. In very severe cases of pericardial constriction the neck veins may appear to be non-pulsatile and the abnormality may only be detected once the patient is in the upright position.

In patients with severe constrictive pericarditis palpation of the praecordium usually reveals a palpable third heart sound, diastolic lift or pericardial knock. This usually occurs about 120 mSecs after the aortic component of the second heart sound and corresponds in timing to the sudden cessation of ventricular filling and the early diastolic plateau of the diastolic ventricular volume curve; becoming prominent during inspiration.

The auscultatory signs are subtle. An early diastolic sound, commonly described as an early third heart sound, will be heard along the left sternal border in rigid constrictive pericarditis. This coincides with the diastolic lift, is accentuated by inspiration, and the stethoscope will often be observed to move coincident with this sound. A second sign, first described at Groote Schuur Hospital(58), is a highly characteristic, sudden, wide splitting of the second heart sound heard at the onset of inspiration. It is due to sudden, inspiratory reduction of left ventricular stroke volume, hence marked shortening of left ventricular systole with premature closure of the aortic second sound. This sound is often present in the absence of an early third heart sound.

ECHOCARDIOGRAM

In patients with an elevated jugular venous pressure and the possibility of cardiac tamponade, echocardiography is extremely useful and should be performed prior to consideration of pericardiocentesis, although in an emergency the clinician may be forced to perform an aspiration on the basis of clinical findings alone. The echocardiogram helps to document the presence and magnitude of a pericardial effusion. It can also rapidly differentiate cardiac tamponade from other causes of systemic venous hypertension, including constrictive pericarditis, cardiac muscle dysfunction and right ventricular infarction. The appearance of dense echos in the pericardial space suggests the presence of material other than free fluid. Echocardiograms can often detect both massive extra cardiac haematoma and extrinsic

compression of the heart by tumour, which can cause cardiac compression with the physiology of cardiac constriction or cardiac tamponade.

The M-mode and two dimensional echocardiogram can provide additional clues that a pericardial effusion is associated with cardiac tamponade. These important features include a marked reduction in the E-F slope and excursion of the anterior mitral valve leaflet and early systolic notching of the anterior right ventricular wall. The presence of the pulsus paradoxus is associated with sudden leftward motion of the septum during inspiration and an exaggerated increase in right ventricular size with a reciprocal decrease in left ventricular size. When the inspiratory reduction in left ventricular filling is extreme the aortic valve may close prematurely or fail to open and mitral valve opening may be delayed until atrial systole.

Diastolic right atrial and right ventricular compression or collapse occur early during the development of cardiac tamponade. Left atrial diastolic collapse can also occur when pericardial fluid is present behind the left atrium. Right ventricular diastolic collapse appears to be more predictive of cardiac tamponade than pulsus paradoxus, particularly occurring during hypovolaemia, but it may be absent in the presence of right ventricular hypertrophy. These echocardiographic findings of a pericardial effusion, an inspiratory increase in right ventricular dimension, and right atrial and ventricular diastolic collapse strongly support the clinical diagnosis of cardiac

tamponade. However, these changes are not a hundred percent sensitive or specific, and experimental studies indicate that the single echocardiogram cannot always predict the presence or severity of cardiac tamponade, a diagnosis made ultimately on clinical grounds.

PERICARDIOCENTESIS

Haemodynamic support during preparation of the patient for pericardiocentesis or pericardiotomy should include the administration of intravenous fluid, blood, plasma or saline. The rationale for volume expansion is that it has been shown to delay the appearance of right ventricular diastolic collapse and haemodynamic deterioration(14). In experimental cardiac tamponade, administration of norepinephrine and isoprenaline has produced an increase in cardiac output. The vasodilators hydrallazine and nitroprusside have also been employed in experimental cardiac tamponade to bring about an increase in cardiac output secondary to the reduction of systemic vascular resistance(38). The administration of vasodilators in conjunction with volume expansion must be done with extreme caution in patients with cardiac tamponade because it may be hazardous in patients with borderline hypotension(39). Positive pressure ventilation should be avoided whenever possible, since it has been shown to depress cardiac output further in patients with cardiac tamponade(40).

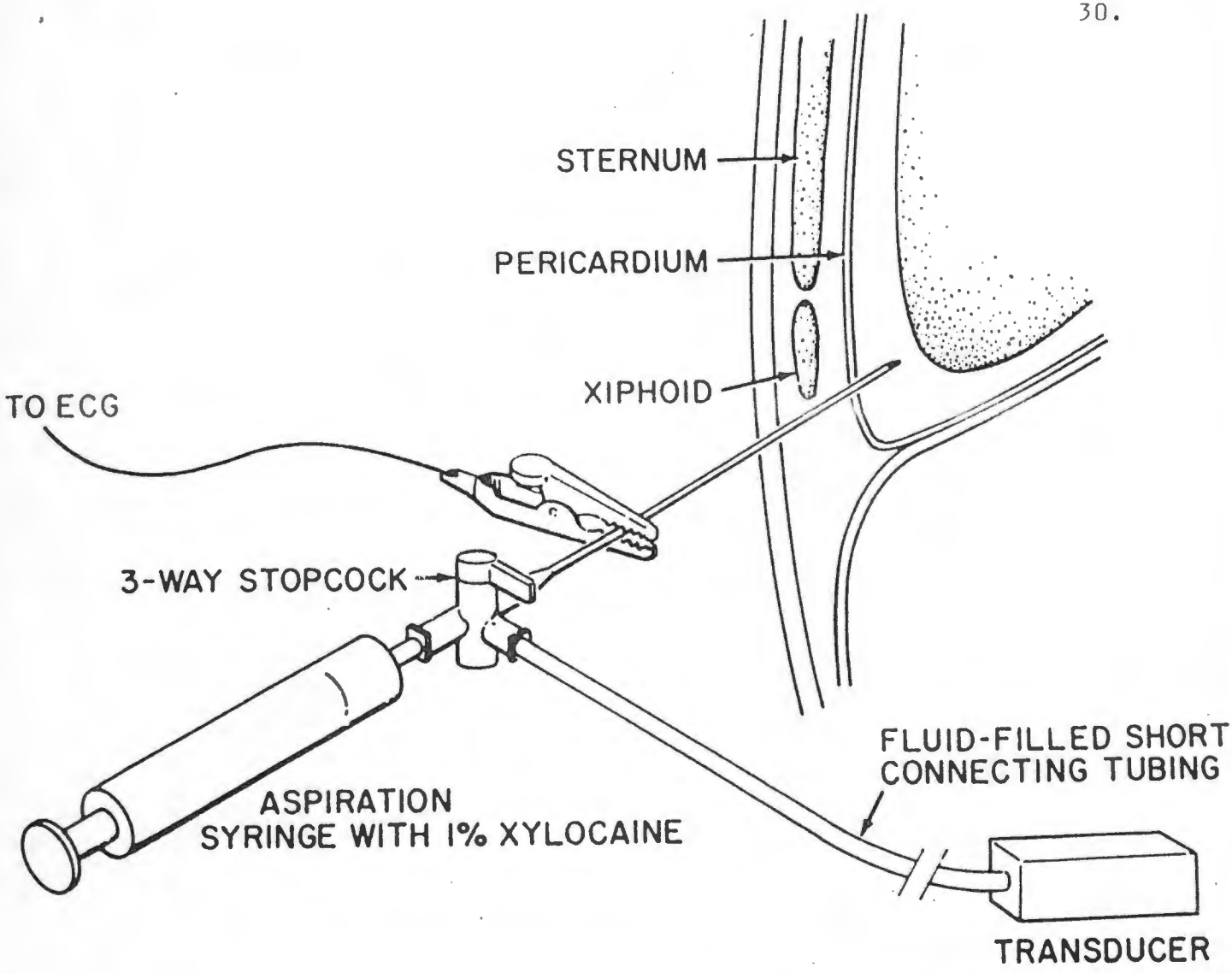
Pericardial fluid under pressure causing tamponade can be evacuated by: 1) percutaneous pericardiocentesis using a needle

or catheter, 2) pericardiotomy via a subxiphoid incision or 3) partial extensive surgical pericardiectomy. Considerable controversy exists regarding the exact indications for pericardiocentesis(15). The benefits of pericardiocentesis include the rapid relief of cardiac tamponade and the opportunity to obtain accurate haemodynamic measurements before and after pericardial aspiration. The major risk of percutaneous pericardiocentesis is laceration of the heart, coronary arteries or lung. Prior to the nineteen sixties, pericardiocentesis was usually performed blindly at the bedside using a sharp needle without haemodynamic or echocardiographic monitoring, and the risk of death or life-threatening complications appeared to be as high as twenty percent(41).

The technique has changed somewhat and the modern approach is exemplified by the Stanford experience in 123 patients(16). In the majority of patients pericardiocentesis was performed by a cardiologist in the cardiac catheterization laboratory using a subxiphoid approach under fluoroscopic guidance with haemodynamic and electrocardiographic monitoring. In this experience, 5 deaths occurred in association with pericardiocentesis; non-fatal haemopericardium developed in an additional 5 patients. Pericardiocentesis in this study was successful in obtaining pericardial fluid in 106 of 123 patients. Importantly, the probability of success in safely obtaining fluid was directly related to the size of the pericardial effusion, since fluid was obtained in 93% of patients with large effusions located both anteriorly and posteriorly echocardiographically but in only 58%

with a small posterior pericardial effusion. In 23 patients a specific aetiologic diagnosis was possible from the analysis of the pericardial fluid. Cardiac tamponade was successfully relieved by pericardiocentesis in 61%, while the remainder required subsequent surgical drainage owing to either failure to relieve tamponade or recurrence after a pericardiocentesis. Surgery was most frequently required in patients with acute traumatic haemopericardium.

At Groote Schuur Hospital the equipment used is similar to that shown in the diagram on page 30, except that we do not routinely connect up to a transducer to measure pressure in the pericardial space; and, in contrast to traditional bedside sharp-needle pericardiocentesis, we use a soft catheter for pericardial aspiration and thus eliminate the prolonged presence of a sharp needle in the pericardial sac, thereby minimising the risk of cardiac laceration. The procedure is best carried out with the patient's thorax and head tilted up, which enhances the pooling of the effusion anteriorly and inferiorly. We prefer the subxiphoid route, since it is extrapleural and avoids the coronary, pericardial and internal mammary arteries. A long 16-18 gauge pointed needle is attached via a stopcock to a hand-held syringe. The metal hub of the needle may be attached by a sterile connector to the V lead of an electrocardiographic machine, and the electrocardiogram should be continuously recorded.



Pericardiocentesis using the subxiphoid approach, which avoids the major epicardial vessels. A hollow needle, which is attached via a stopcock to an aspiration syringe and to a short length of connecting tubing to a transducer, is used to enter the pericardial space. When fluid is initially aspirated, the pressure waveform at the needle tip should be briefly examined to confirm that the needle tip is in the pericardial space. A floppy-tipped guidewire is then passed through the hollow needle, the needle is exchanged for a soft flexible catheter with end- and side-holes to facilitate safe and thorough drainage of the pericardial sac. (From Lorell, B. H., and Grossman, W.: Profiles in constrictive pericarditis, restrictive cardiomyopathy, and cardiac tamponade. In Grossman, W. [ed.]: Cardiac Catheterization and Angiography. Philadelphia, Lea and Febiger, 1986, p. 436.)

The needle is directed posteriorly until the tip passes posterior to the bony cage. The hub of the needle is then pressed toward the diaphragm and the needle is advanced with a 15-degree posterior tilt, either directly toward the patient's head or toward the right or left shoulder. The needle is smoothly and slowly advanced until the pericardial membrane is felt to "give" and pericardial fluid is aspirated or until ST-segment elevation and ventricular premature beats appear on the electrocardiogram, indicating that the needle has reached the epicardium. In the latter case, the needle is promptly and smoothly withdrawn while the operator attempts to aspirate pericardial fluid until the needle lies within the fluid-filled pericardial space and the ECG changes disappear. If fluid cannot be freely aspirated, the needle is slowly withdrawn out of the body, avoiding lateral motion; the needle is flushed and the procedure repeated.

Pericardiocentesis is now safer than it was a decade ago, and the procedure, when performed by an experienced operator, is associated with only approximately 0-5% risk of development of a life-threatening complication. The procedure is most likely to be successful and uncomplicated when performed in patients with clearcut echocardiographic evidence of a large effusion with an anterior clear space of 10mm or more. Cardiac tamponade associated with malignant pericardial effusion or prior radiation therapy can often be managed with pericardiocentesis alone or with a combination of pericardiocentesis, radiation therapy and local or systemic chemotherapy. This therapeutic approach may be

preferable in patients with advanced malignancy when it is desirable to avoid major surgery that is not definitive.

Pericardiocentesis is likely to be either complicated or unsuccessful in improving haemodynamics in patients with: 1) acute traumatic haemopericardium in which blood enters the pericardial space as rapidly as it can be aspirated; 2) a small pericardial effusion judged of less than 200ml in size; 3) absence of an anterior effusion on the basis of echocardiogram; 4) a loculated effusion; or 5) clot and fibrin as well as fluid in the mediastinal or pericardial space post-operatively. A very rare complication which may occur after the relief of cardiac tamponade is the development of sudden ventricular dilatation(17) and acute pulmonary oedema(18). The mechanism is probably a sudden increase in venous return following relief of pericardial compression in the presence of underlying ventricular dysfunction.

METHODS

Patients in whom pericardiocentesis was performed at Groote Schuur Hospital between 1 January 1987 and the 12 October 1989 were identified by a search of: 1) coded discharge summaries in the medical records department; 2) log books of the Cardiac Catheterization Laboratory; and 3) log books of the Cytology, Bacteriology and Chemical Pathology Laboratories. As a result 90 procedures in 85 patients were identified; a detailed search of medical records yielded adequate information on 52 of these patients. The patient group included 25 males and 27 females, with a median of 46 years ranging from 18-86. On the basis of race this group was divided into the following: 3 patients were white, 19 patients were coloured, and 30 patients were black.

The clinical presentation of each patient before pericardiocentesis was analysed to determine which clinical findings of pericardial disease were present before pericardiocentesis and whether the diagnosis had been pericardial effusion with or without cardiac tamponade. Because of the retrospective nature of the study, no attempt was made to quantitate the degree of cardiac compromise, the rapidity with which it developed or the extent to which constrictive pericarditis complicated cardiac tamponade. The specific clinical features assessed were the symptoms of chest pain and dyspnoea; the physical findings of pulsus paradoxus (greater than 10mmHg decrease in systolic pressure on inspiration), an elevated jugular venous pressure, and a pericardial friction rub; the electrocardiographic findings of arrhythmias, low voltage

(QRS complex less than or equal to 5mV in the limb leads or less than 10mV in the precordial leads) and total electrical alternans of the P, QRS and T waves; the chest radiographic findings suggestive of previous exposure to tuberculosis, and the echocardiographic finding of an echo-free space between the pericardium and the myocardium by the criteria of Feigenbaum(19).

It is a routine policy of the cardiac clinic that three specimens of aspirate are sent for analysis. 10ml of aspirate is sent in 50% alcohol to the Department of Cytology, 10ml is sent to the Department of Chemical Pathology for estimation of protein content, ADA and LDH levels. The third specimen is sent to the Department of Microbiology for gram stain and culture. Specimens for culture were inoculated on 4% blood agar, boiled blood agar, and McConkey agar, and were incubated at 37°rC in air enriched with 5% carbon dioxide. A Ziehl Nielsen stain was used for the detection of acid fast bacilli, and then culture was attempted on one of three different media: a fluid Kirschner culture, a Lowenstein-Jensen media, and on a Stonebrink media. These media were initially incubated for two weeks, then at weekly intervals, and from then on they were read for a total of eight weeks after their initial incubation.

Most of the procedures were carried out by senior registrars in a two year sub-speciality training programme in cardiology, under the supervision of full-time faculty members in cardiology. Either a subxiphoid or apical approach was used depending on the combination of the physical stature of the patient, the location

of the effusion on echocardiograph, taken in combination with the preference of the operator. All pericardiocenteses were performed in the cardiac catheterization laboratory with fluoroscopic and electrocardiographic monitoring. Air was not injected routinely into the pericardial space following removal of the fluid.

TABLE I

BREAKDOWN OF DIAGNOSES ON 52 ASPIRATIONS AT GROOTE SCHUUR HOSPITAL

GROUP	NUMBER OF PATIENTS
Clinical impression of TB pericarditis	
i) Culture positive	9
ii) Culture negative	20
Pericardial effusions associated with malignancy	11
Post cardiotomy syndrome	3
Iatrogenic cardiac tamponade	2
Others	7

TABLE II

FINDINGS IN CULTURE POSITIVE PERICARDIAL ASPIRATIONS

PATIENT NUMBER	AGE	RACE/SEX	RESIDENTIAL ADDRESS	CYTOLOGY SUGGESTED T.B.	MANTOUX	ADA	LDH	APPEARANCE OF ASPIRATE
1	25	BM	Khayelitsha	Yes	Positive	61	1000	Haemorrhagic
2	35	BM	Nyanga	Yes	Positive	43	650	Haemorrhagic
3	56	BF	Nyanga	-	Positive	-	-	Haemorrhagic
4	58	BF	Khayelitsha	Yes	-	90	893	Haemorrhagic
5	24	CM	(Fisherman)	No	-	64	1325	Straw-coloure
6	50	BM	Nyanga	No	Positive	66	6170	Haemorrhagic
7	30	BF	Transkei	-	-	88	1720	Straw-coloure
8	37	BF	Transkei	Yes	Positive	168	2490	Haemorrhagic
9	39	CF	Bonteheuwel	Yes	-	20	1670	Haemorrhagic

TABLE IIA

COMPARISON OF SYMPTOMS AT PRESENTATION IN PATIENTS WITH CULTURE-POSITIVE TB PERICARDITIS, WITH THOSE PATIENTS WITH PERICARDIAL EFFUSIONS ASSOCIATED WITH MALIGNANCY

	TB +ve (%)	MALIG (%)
Chest pain	50	33
Dyspnoea	100	88
Abdominal distension	33	0
Ankle swelling	55	0
Weight loss	33	22
Fever	55	0
Cough	78	66
Loss of appetite	22	88
TB contact	11	11

TABLE IIB

COMPARISON OF SIGNS ON PRESENTATION IN PATIENTS WITH CULTURE POSITIVE TB PERICARDITIS, WITH THOSE WITH PERICARDIAL EFFUSIONS ASSOCIATED WITH MALIGNANCY

	TB +ve(%)	MALIG (%)
Pyrexia	66	0
Oedema	55	11
Lymphadenopathy	22	11
Pulse > 120bpm	33	55
Pulsus paradoxus	88	88
Systolic bp < 100	22	55
Raised JVP	100	100
Impalpable apex	88	88
Friction rub	11	11
Hepatomegaly	77	88
Splenomegaly	0	0
Pleural effusion	55	55

TABLE III

CULTURE NEGATIVE PERICARDIAL EFFUSIONS THOUGHT TO BE CLINICALLY DUE TO M. TUBERCULOSIS

PATIENT NUMBER	AGE	RACE/SEX	RESIDENTIAL ADDRESS	CYTOLOGY SUGGESTED T.B.	MANTOUX	ADA	LDH	APPEARANCE OF ASPIRATE
10	46	BF	Khayelitsha	Yes	-	120	929	Haemorrhagic
11	49	BF	Guguletu	No	Negative	4	169	Straw-coloure
12	25	BF	Guguletu	Yes	Positive	46	-	Haemorrhagic
13	52	BM	Nyanga	Yes	Positive	58	563	Straw-coloure
14	40	BF	Guguletu	No	Positive	66	737	Haemorrhagic
15	18	BM	Nyanga	-	Positive	110	696	Haemorrhagic
16	48	BM	Nyanga	No	-	-	-	Haemorrhagic
17	69	BM	Nyanga	Yes	-	-	-	Haemorrhagic
18	19	BF	Transkei	No	-	18.9	-	Haemorrhagic
19	53	BF	Guguletu	-	-	-	-	Haemorrhagic
20	40	BM	Nyanga East	-	-	-	-	Haemorrhagic
21	38	BM	Langa	No	Positive	53	-	Haemorrhagic
22	56	BM	Cross Roads	No	-	10	110	Haemorrhagic
23	86	BF	Nyanga	No	Positive	80	443	Straw-coloure
24	48	BM	Nyanga	Yes	-	-	-	Haemorrhagic
25	57	CF	Athlone	No	Yes	18	2860	Haemorrhagic
26	39	CF	Kraaifontein	Yes	Yes	65	735	Haemorrhagic
27	34	BM	Cross Roads	Yes	-	76	657	Haemorrhagic
28	49	BM	Langa	No	-	54	652	Haemorrhagic
29	53	BM	Khayelitsha	Yes	-	31	22	Straw-colour

RESULTS

Table I (page 35) gives a breakdown of the diagnoses obtained on the 52 aspirations that have been reviewed. 57% of these aspirations presented with the clinical signs of tamponade. 29 of the patients subjected to pericardial aspiration were given the diagnosis of tuberculous pericarditis. Within this group 9 of the patients were found to be "culture positive", in that mycobacterium tuberculosis was subsequently grown on culture from the samples aspirated. In the group of "culture negative" patients, the clinicians looking after these patients had made a diagnosis of probable tuberculous pericarditis, had commenced their patients on antituberculous therapy, and claim to have demonstrated some clinical improvement in the patients condition prior to discharge. Of this latter group one patient subsequently produced a culture of mycobacterium tuberculosis from a culture taken of a lymph node biopsy.

Tables II (page 36) and III (page 39) subdivides the two groups of tuberculous pericarditis patients on the basis of whether their pericardial aspirates subsequently were "culture positive" or not. The mean age of presentation in Table II is 39.3 years, with 7 out of the 9 patients being black, with a predominance of females.

Tables IIA and IIB (pages 37 and 38) present the symptoms on presentation and clinical signs of this group of patients bacteriologically proven to have tuberculous pericarditis, and contrasts them with the patient group with no evidence of

tuberculous infection, but with effusions associated with a malignancy. There are no statistically significant differences between the two groups, due to small patient numbers, but it is of note that those patients with a malignancy-associated pericardial effusion presented with nó symptoms of abdominal distension, ankle swelling or fever. There are even fewer differences between the two groups on the basis of clinical signs; the signs of pericardial effusion with or without tamponade being common to both, with no signs appearing to be pertinent to the different aetiologies. There was a uniform absence of a recordable pyrexia in the malignancy-associated group.

It will be seen in Table II, page 36, that all the patients that had mantoux performed subsequently manifested strongly positive reactions (with induration, superficial blistering and a diameter greater than 10x10mm). 7 out of the 9 aspirates were haemorrhagic in appearance, and the ADA levels were all elevated with the exception of 1 patient, giving a mean value of 75 international units per litre(the normal range being 0-35 international units per litre), a median of 65, and one standard deviation of 43.89. Similarly, the LDH levels were also elevated with a mean value of 1990 international units per litre.

Table III, page 39, is a rather lengthy table that illustrates the spectrum of finding that the clinician has to deal with when presented with a high risk group for TB and a pericardial effusion. Once again the racial predominance of blacks is

clearly obvious, there being 11 black males and 7 black females comprising this group. 80% of the pericardial effusions were found to be haemorrhagic. The mean ADA level in this group was lower at 53.9 international units per litre (median 54 international units per litre; standard deviation of approximately 34.3). Concern must be expressed looking at the results of patients numbered 11 and 22 who present with such low ADA's:- a strikingly dissimilar trend compared to the other patients. Of interest patient 18, who was initially treated as a culture negative probable tuberculous pericarditis subsequently returned for further medical therapy and was found to have systemic lupus erythematosis with a proliferative glomerulonephritis.

Of the 29 patients subjected to aspiration in Tables II and III, it was alarming to discover that I could only find evidence of 10% returning to the outpatient department for any kind of follow-up by Groote Schuur Hospital. Hopefully some of these patients will have fallen under the care of the community TB clinics; but nevertheless these institutions are not designed for detailed supervision, and the patients require follow-up review by the medical team that commenced therapy.

Table IV, page 44, shows the data obtained on those pericardial effusions associated with underlying malignancy. It will be noticed that the racial predominance has now shifted to the coloured community, and carcinoma of the lung proved the most frequent malignancy to occur with a pericardial effusion, with

carcinoma of the oesophagus also being relatively common. The appearance of the aspirates was predominantly straw coloured, with two of the carcinomas of the lung and one carcinoma of the breast presenting with haemorrhagic effusions. Unfortunately the chemical pathological data is lacking in a majority of the cases, but the trend obviously is towards lower ADA (mean 21.61 international units per litre median 19, standard deviation of 14.6) and LDH levels.

Table V, page 45, lists three patients presenting with post-cardiotomy syndromes, all of which had straw coloured pericardial aspirates and occurred between 1 and 3 weeks after valve replacement surgery. The one ADA that was recorded was low at 19 international units per litre.

Table VI, page 46, lists some of the "other" aetiologies proposed to accompany the presenting pericardial effusions. Two patients with uraemic pericarditis are noted both presenting with haemorrhagic pericardial effusions. The clinical suspicion of phaeochromocytoma in patient 42 is still an unresolved problem, with further clinical investigations being carried out.

Table VII, page 47, refers to the two iatrogenic causes of cardiac tamponade that were noted during the collection time of this data. Both events occurred during cardiac catheterization, patient 50 being a complication of a misplaced transeptal puncture, whilst patient 51 developed rapid cardiac tamponade secondary to laceration of the left ventricle by the tip of a catheter being used for a balloon mitral valvuloplasty.

TABLE IV

PERICARDIAL EFFUSION ASSOCIATED WITH MALIGNANCY

PATIENT NUMBER	AGE	RACE/ SEX	TYPE OF MALIGNANCY	APPEARANCE	ADA	LDH	CYTOLOGY
31	39	BF	Leiomyosarcoma	Straw-coloured	-	-	Lymphocyte reaction ? tuberculosis
32	36	BM	Ca Oesophagus	Straw-coloured	-	-	Inflammatory smear
33	68	WM	Ca Lung	Haemorrhagic	14	-	-
34	33	CF	Ca Lung	Milky	-	-	-
35	47	CF	Ca Stomach	Straw-coloured	-	-	Atypia ? malignancy
36	60	CM	Ca Oesophagus	Straw-coloured	-	-	Degenerate mesothelial cells
37	28	CF	Bowel Lymphoma	Cloudy, Straw-coloured	45	690	Suspicious for malignancy
38	53	CM	Squamous cell Ca Lung	Haemorrhagic	24	978	Atypical cells with squamous features
39	50	CF	Ca Breast	Haemorrhagic	-	-	Malignant cells present ? adenocarcinoma
40	61	CM	Ca Oesophagus	Straw-coloured	6	47	Scattered mesothelial cells
41	55	CM	Ca Lung	Haemorrhagic	-	-	-

TABLE V

POST CARDIOTOMY SYNDROMES PRESENTING FOR PERICARDIOCENTESIS

PATIENT NUMBER	AGE	APPEARANCE	ADA	LDH	PROTEIN	PROCEDURE
42	25	Straw-coloured	-	-	-	Post aortic and mitral valve replacement
43	21	Straw-coloured	-	-	-	Post aortic valve replacement
44	24	Straw-coloured	19	794	55	Post mitral valve replacement

TABLE VI

SHOWING OTHER DIAGNOSES PROPOSED IN PERICARDIAL ASPIRATIONS

PATIENT NUMBER	AGE	RACE/SEX	CLINICAL DIAGNOSIS	APPEARANCE OF ASPIRATE
45	43	BF	? Phaeochromocytoma	Straw-coloured
46	49	CM	Uraemic pericarditis	Haemorrhagic
47	38	CF	Uraemic pericarditis	Haemorrhagic
48	27	CM	Bacterial endocarditis and congestive cardiac failure	Haemorrhagic
49	70	BF	E. Coli septicaemia	Straw-coloured
50	36	CF	Lupus pericarditis	Straw-coloured

TABLE VII

IATROGENIC CAUSES OF CARDIAC TAMPONADE REQUIRING PERICARDIOCENTESIS

PATIENT NUMBER	AGE	APPEARANCE	COMPLICATION
51	23	Haemorrhagic	Haemopericardium with tamponade, post transeptal puncture.
52	40	Haemorrhagic	Balloon mitral valvotomy with left ventricular rupture.

CYTOLOGY

It is the contention of the Department of Cytology that the morphology of lymphocytes stimulated by a tuberculous inflammatory response is different to that prompted by other inflammatory agents (personal communication from Dr G Learmonth, Department of Cytology, Groote Schuur Hospital). The cytology was thought to suggest tuberculosis in 5 out of 7, or 71% of the culture positive patients; and in 1 of the 8 patients presenting with a pericardial effusion associated with a malignancy i.e. a 12.5% false positive rate. The finding of abnormal cytology suggesting possible malignancy in 4 out of the 8 cytology smears in Table IV confirms the contribution that cytology may have to play in diagnostic pericardiocentesis, especially when it is combined with the finding of a low ADA level.

MICROBIOLOGY

The results of TB culture on 3 different media of pericardial aspirate yielded a positive culture in only 32% of the 29 patients clinically assessed to have tuberculous pericarditis. The routine culture on standard media was unhelpful except in the patient subsequently found to be HIV positive, who grew streptococcus salivarius; as well as mycobacterium tuberculosis on culture eight weeks later.

ADENOSINE DEAMINASE (ADA)

The record of an ADA level was obtained in 69% of pericardial aspirations. Performing an analysis of variance on the ADA levels from Table II (culture positive, page 36), Table III

(culture negative, but clinically presumed to have tuberculous pericarditis, page 39), and Tables IV and V, on pages 44 and 45 respectively (culture negative groups with no evidence of mycobacterium tuberculosis infection), one can see on page 50 that there is a statistically significant difference between the culture positive patients and those with no evidence for tuberculous infection(significance level of 0.0192); which can be expressed graphically on the box and whisker plots shown in Figure B, from the data recorded in Figure A; with the 95% confidence intervals for the "control" group being -8.9 to 48.25; whilst that of the "culture positive" group being from 50.24 to 99.75.

Figure A

TABLE OF MEANS OF ADA LEVELS FROM CULTURE POSITIVE(TBCULT), PRESUMED TUBERCULOUS(TBPRES), AND NON-TUBERCULOUS(CONTRL) PERICARDIAL EFFUSIONS

Level	Count	Average	Stnd. Error (internal)	Stnd. Error (pooled s)	95 Percent intervals	Confidence for mean
TBCULT	8	75.000000	15.520723	12.016798	50.245064	99.754936
TBPRES	14	57.135714	8.900349	9.083845	38.422742	75.848687
CONTRL	6	19.666667	5.696002	13.875803	-8.917871	48.251204
TOTAL	28	54.210714	6.423249	6.423249	40.978645	67.442784

ONE-WAY ANALYSIS OF VARIANCE

Range test: Conf. Int. Confidence level: 95

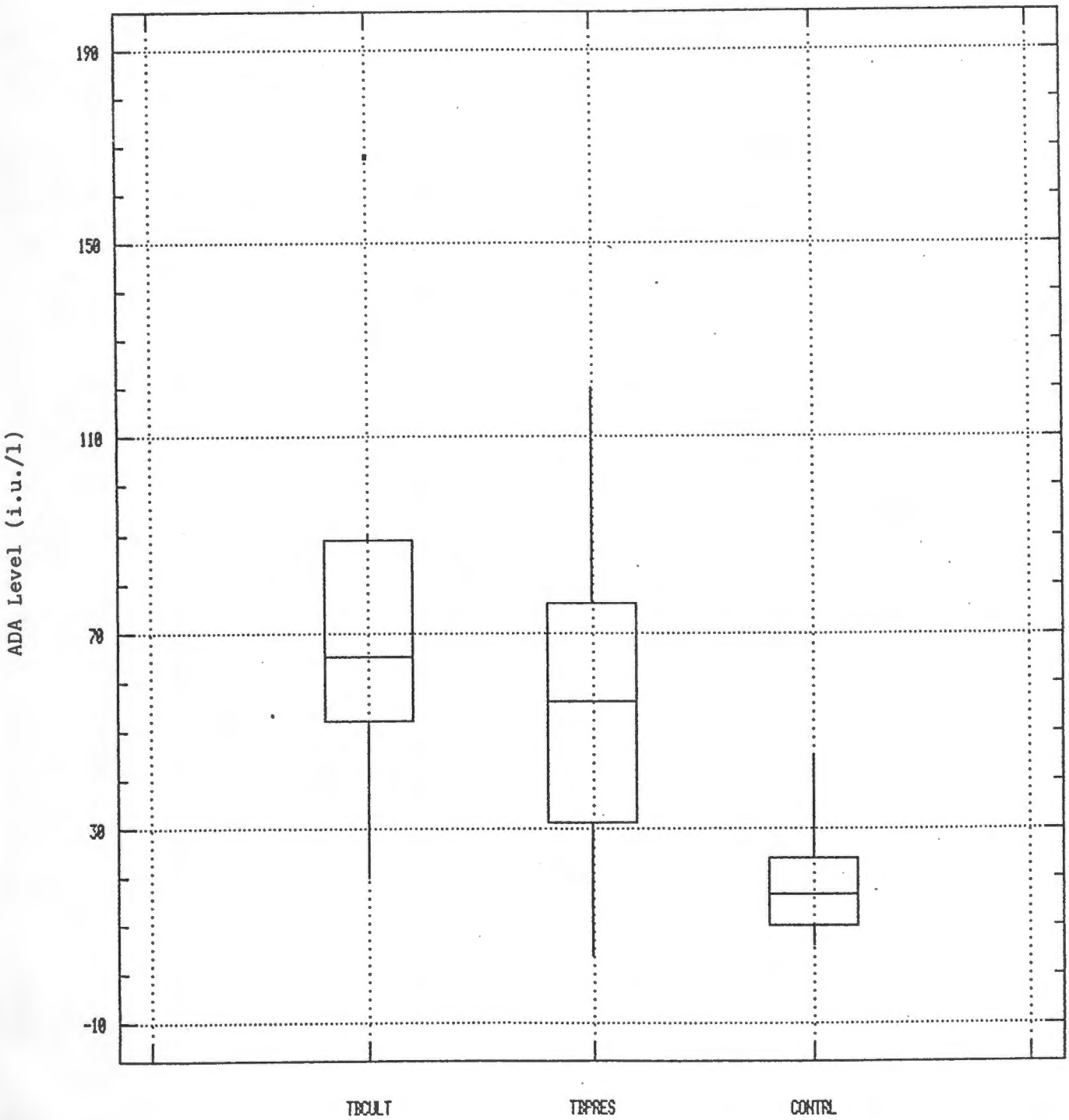
Analysis of variance

Source of variation	Sum of Squares	d.f.	Mean Square	F-Ratio	Sig. level
Between groups	10737.081	2	5368.5407	4.647	.0192
Within groups	28880.685	25	1155.2274		
Total (corrected)	39617.767	27			

0 missing value(s) have been excluded.

Figure B

BOX AND WHISKER PLOTS REPRESENTING AN ANALYSIS OF VARIANCE PERFORMED ON ADA LEVELS FROM TABLES II, III AND IV AND V COMBINED



DISCUSSION

Pericardiocentesis, a method successfully used since 1840, is dramatic and life-saving when performed to relieve cardiac tamponade. However, serious complications, including death can occur. In this study of the 52 aspirations performed there was only 1 death, which was not thought to be due to a direct complication of the procedure but involved a patient who whilst having his pericardium aspirated for cardiac tamponade, with concomitant severe pulmonary oedema, became markedly hypoxic and had a respiratory arrest. There was no evidence of ventricular laceration or air embolus at post-mortem. Some physicians believe that pericardiocentesis should not be performed routinely unless cardiac tamponade is present. They recommend direct surgical drainage of the pericardial sac, but unfortunately this procedure can also result in significant complications(20). These reservations are echoed by the Cardiac Clinic at Groote Schuur Hospital, and it is therefore with great disappointment that having set out to review 90 procedures performed on 85 patients between the 1 January 1987 and the 12 October 1989 I was only able to locate the data on 52 of these patients. In a country labouring under the problems of racial and language barriers, a researcher performing a data review retrospectively of medical records becomes heavily dependent upon the diligence of administrative, medical and nursing staff in providing the correct details of the patient to ensure that adequate medical records are kept. It is then of further interest to find that in 15 of the 52 patients that were reviewed (of which 5 were

performed for diagnostic purposes and 10 performed for relief of cardiac tamponade) that specimens appear to have either got lost or have been discarded prior to being sent to either the Departments of Chemical Pathology, Microbiology or Cytology. It must ultimately come down to the responsibility of the operator who has undertaken to perform a pericardiocentesis, that he or she ensures that the specimens are adequately analysed.

Pericardiocentesis is indicated to establish the cause of pericardial effusion and to relieve cardiac tamponade. Tamponade, which I have already defined in the introduction as an acute circulatory disturbance, characterised by pulsus paradoxus, raised jugular venous pressure and fall in cardiac output, requiring and relieved by pericardiocentesis, is a clinical diagnosis and was present in a relatively high percentage (57%) of the 52 patients reviewed in this study. Whilst partially reflecting the conservative approach to pericardiocentesis at this hospital, this also reflects the ill-health of these patients. It became apparent from patient review that a significant number of the black patients, whilst giving their residential addresses as Nyanga or Khayelitsha, had in fact only very recently arrived in Cape Town from Transkei, where the majority of their symptoms had gradually been developing. It was only when these symptoms became sufficiently severe to warrant medical attention that these patients then set about journeying from Transkei down to Cape Town for what they perceived as better medical attention. ie., the relatively high frequency of cardiac tamponade at the time of presentation must have been contributed

to by the prolonged length of time it had taken these patients to get to medical care.

77.7% of the culture positive tuberculous pericardial perfusions were found to be blood stained, often heavily. It is of course important for the operator to note that the fluid does not clot on standing and spreads rapidly on agar swab or paper towel, unlike blood which spreads more slowly(21).

Strang in his papers on tuberculous pericarditis in Transkei(21, 22), has remarked that culture of Mycobacterium tuberculosis from pericardial effusions can be improved considerably by the inoculation of a Kirschner culture at the bedside. In his Transkei study, this resulted in the culture of Mycobacterium tuberculosis from 59% of 189 pericardial effusions, a far higher figure than obtained in this study, when only 32% of the 29 patients clinically assessed to have tuberculous pericarditis were culture positive after eight weeks. It is unfortunate that at present a specimen taken at pericardiocentesis can take anything up to 24-hours (or longer at weekends) to get from the patient to the laboratory, where it can be plated out. Obviously, in those patients being subjected to pericardiocentesis for diagnostic purposes, this is usually an elective procedure performed during the course of the day when specimens can then be sent to the relevant laboratories in good time. The problem comes in managing those patients who present during "after-office hours" with features of acute tamponade and need a therapeutic pericardiocentesis performed as soon as

possible. It is the specimens from these patients that can suffer long delays before being analysed. It is also of interest that in his Transkei studies, Strang used a total inoculum volume of 70ml of pericardial fluid, whereas at present at Groote Schuur Hospital we use only 10ml. The suggestion therefore must follow that if we are to improve the diagnostic yield from patients with tuberculous pericardial effusions arrangements should be made whereby culture media should be on hand so that a direct inoculation can be performed at the time of aspiration; and that it would be a suggestion that a larger volume of aspirate is inoculated on to the culture media.

In view of the difficulty in diagnosing TB by conventional bacteriological and histopathological methods, and the high incidence of TB in South Africa, estimation of the ADA level in pleural, peritoneal and pericardial fluids has been undertaken in the investigation of possible tuberculosis(23). Adenosine deaminase activity is easy to measure, and may easily be done in the rural setting. ADA catalizes the conversion of adenosine to inosine, by the removal of ammonia. Activity is high in proliferating T lymphocytes, and increases with the degree of differentiation of certain subsets of T cells. ADA is also found in high concentration in maturing macrophages and monocytes. This raised activity of this enzyme is found in the blood, or any fluid where T lymphocytes, monocytes or macrophages are proliferating. The immune response to Mycobacterium tuberculosis is cell mediated, hence the cell types which release large amounts of ADA predominate. One may thus anticipate that ADA

activity may be raised in pericardial fluid in tuberculous pericarditis(24).

Martinez-Vazquez(25) looked at the ADA levels in three patients with culture positive tuberculous pericarditis and found these levels to be much higher compared to groups with neoplastic pericarditis or acute idiopathic pericarditis. It was Berman et al from the Department of Chemical Pathology at the University of Cape Town Medical School, that described tuberculous pleural effusions showing significantly higher levels of ADA activity compared with effusions due to other underlying lesions such as neoplasms, bacterial and viral infections and simple transudates (23). They proposed that levels of ADA above 30 international units per litre in effusions indicate probable tuberculosis. Subsequent studies have been done, and the same principles have been applied to pericardial effusions as well, suspected to be due to tuberculosis.

The above observations are borne out when one reviews table II, on page 36, with the culture positive patients showing significantly raised ADA levels in all cases except patient number 9. A similar trend is seen in Table III (page 39) where again the ADA levels are above the normal range, at a mean of 53.9 international units per litre. Performing an analysis of variance on the ADA levels one can see there is a statistically significant difference between the culture positive patients and those with no evidence for tuberculous infection (significance level of 0.0192); with the 95% confidence intervals for the

"control" group being -8.9 to 48.25; whist that of the "culture positive" group being from 50.24 to 99.75, indicating that an ADA level of 51 international units per litre or above has a highly significant likelihood of being associated with a tuberculous pericardial effusion, whilst an ADA level below 48 international units per litre is highly likely to be associated with a non-tuberculous cause for a pericardial effusion.

It is unfortunately a major short-coming of a tertiary care institution like Groote Schuur Hospital, which is up to 35km away from the accommodation of the majority of the patients listed, that follow-up was limited to a 10% rate of return to the Medical Out-Patient Department of the 29 patients listed in Tables II and III! It is therefore impossible to correlate the long-term outcome of these patients treated for tuberculosis with ADA levels obtained at pericardiocentesis. If a fuller appreciation of the natural history of this disease, and its response to therapy, is ever to be appreciated then ideally these patients should be followed up in a clinic with cardiological expertise and liaison facilities with the community.

Relatively low levels of ADA were obtained in patients numbered 11, 22, 25 and 18. It is of interest that this latter patient subsequently was diagnosed as having systemic lupus a and a proliferative glomerulonephritis.

The diagnosis of malignant pericardial disease is usually established when one or more of the following occur: 1) cytologic examination of pericardial fluid reveals malignancy; 2) autopsy

reveals pericardial tumour; 3) pericardiectomy reveals tumour; or 4) echocardiography, chest radiography or CT scan reveal tumour masses in the pericardium. Radiation pericarditis is usually established if there is a history of prior central thoracic irradiation of greater than 4000 rads. and either typical pathological changes or a history compatible with the diagnosis. In the 11 patients with pericardial effusion associated with malignancy, the suspicion of malignant pericardial disease, based on abnormal cytology with suspicion of malignant cells occurred in 4 of the 11 patients. 2 of the patients with carcinoma of the oesophagus, and 2 with carcinoma of the lung had received a course of radiotherapy and were thought to be suspicious of radiation pericarditis.

Pericardial metastases are found at post-mortem examination in 5-10% of patients with malignancy(28). Lung, breast and haematologic malignancies account for approximately 80% of reported cases(29). Primary pericardial malignancy is rare but the majority of reported cases have been mesotheliomas, with angiosarcomas and malignant fibrosarcomas rarely reported(30). Symptomatic pericardial disease due to malignancy may be suspected antemortem in about 20% of patients with malignant pericardial disease diagnosed at post-mortem examination. A high index of suspicion must be present since, when the condition is diagnosed, treatment may often lead to dramatic improvement although long-term survival remains poor. Non-malignant pericardial disease may be found in as many as 7% of cancer patients with post-mortem examination(31). In a prospective

study, Krikorian and Hancock (16), noted a 36% incidence of malignant pericarditis, with an 18% incidence of radiation and 44% incidence of "uncertain cause" in patients with malignancy and pericardial effusion. The data provided in this study would also suggest that a significant proportion of patients with pericardial disease and cancer may have a non-malignant or radiation related cause for the pericardial disease.

Table V, page 45, refers to the 3 patients, all of which have been subjected to prosthetic valve replacement who each presented with large pericardial effusions. Patients 43 and 44 also had coincident features of cardiac tamponade. It will be noted that the effusions were straw-coloured in all three cases and in the one case that an ADA level was measured and a level of 19 international units per litre was recorded.

Two of the patients in Table VI, page 39, presented with the clinical syndrome of uraemic pericarditis. Pericardial involvement in patients with chronic renal disease has been known since Bright described nephritis. Until recently, a pericardial friction rub and pain in patients with chronic renal disease were regarded as an interesting clinical phenomena displayed by patients approaching the terminus of their disease. With the advent of dialysis and renal transplantation programmes, and the radical change in their outlook of patients with chronic renal disease, any manifestation which may aggravate the patient's condition or prove a threat to life has now become important and merits treatment. The pericardium may become diseased in

patients undergoing chronic haemodialysis, less commonly in patients undergoing peritoneal dialysis. The manifestations may be confined to fever, a pericardial friction rub, ECG changes and general malaise. Both patients in this study manifested all these characteristics. Pericardial effusions may occur and may progress to cardiac tamponade. All of these manifestations may occur during the course of regular dialysis when the blood urea nitrogen and creatinine levels are well controlled, and it is therefore not possible to ascribe them to "uraemia". More likely, there is no single aetiology. It is thought that some of the cases may be caused by an auto-immune mechanism related to the renal disease itself, or perhaps to the dialysate, blood or materials in the dialyser. Increased susceptibility to infection is a well known manifestation of chronic renal disease. Immunoglobulins and complement have been found to be bound to the pericardium in some of these cases. Tuberculosis is an important cause of pericardial disease, and since patients with chronic renal disease have an increased susceptibility to tuberculous infection it is not surprising that some of the patients who develop pericardial disease in the course of haemodialysis are found to have tuberculous pericarditis. These observations emphasize the importance of not assuming that these patients have "uraemic pericarditis". Pericardial disease developing during haemodialysis merits diagnostic study.

The acquired immunodeficiency syndrome (AIDS) is associated with a variety of cardiac disorders, but cardiac disease has not played a major role in the clinical course of most immuno-

deficiency virus(HIV)-infected patients(32). Anderson et al evaluated 71 consecutive autopsies on patients who died from AIDS and noted that 52% showed evidence of myocarditis; gross cardiac findings included: isolated right ventricular dilatation(17%), biventricular dilatation(9%) and/or pericardial effusion(21%). In another clinical study, Monsuez et al(33) reported cardiac abnormalities in 29% (12 of 42) of patients with AIDS and in 9% (4 of 43) of patients with AIDS related complex; the most common abnormality was pericardial tamponade (11 patients). In a very recent review on the impact of HIV infection on tuberculosis in Zambia, Elliott et al(63) noted a particularly high prevalence of HIV in association with pleural and pericardial disease, in comparison with pulmonary disease, with 16 out of 19 (84%) patients with tuberculous disease being HIV positive.

In this study of patients in Cape Town I could only find reference to a single request for HIV screening in all the patients with pericardial effusions, on whom I could trace folders: this patient proved to be HIV positive patient; a fisherman and ex-prisoner of age 24 years who presented with cough, fever, weight loss and denied any homosexual encounters or intravenous drug abuse, who complained of pericarditic chest pain and shortness of breath and was found to have features of cardiac tamponade. Pericardiocentesis revealed a straw-coloured effusion which showed an ADA level of 64 and a LDH level of 1325. The routine culture of the aspirate grew a streptococcus salivarius and the TB cultures subsequently grew Mycobacterium tuberculosis. He was subsequently subjected to a pericardial biopsy which

confirmed the presence of granuloma on histological review. Acquired immuno-deficiency syndrome is a disease associated with defective cell mediated ammunity. Mycobacterium avium intracellulare has frequently been described and forms part of the Centres for Disease Control diagnostic criteria for AIDS(34). Sunderam(35) et al have found however that tuberculosis, often extra-pulmonary, with severe or unusual manifestations, occurs more frequently than mycrobacterium avium intracellulare disease in patients with AIDS. They found that culture documented tuberculosis was found in 21% of their total group of AIDS cases; a prevalence nearly one and a half times more than that of mycrobacterium avium intracellulare disease. It is possible that AIDS selects and magnifies diseases that are endemic to a particular locality, similarly to tuberculosis reported in Haitians with AIDS(36), and histoplasmosis in patients with AIDS from Indiana(37). The aggressive behaviour of tuberculosis in many AIDS cases suggest that AIDS may make usually pathogenic tuberculosis organisms behave in an even more virulent manner, somewhat like an opportunistic pathogen behaves in a compromised host. Sunderam(35) describes how extra pulmonary and disseminated tuberculosis was much more prevalent in comparison with their patients with tuberculosis who did not have AIDS. 72% of their tuberculosis and AIDS group had extra pulmonary tuberculosis as their major manifestation. Applying this to the South African context, and bearing in mind that only 1 of the 52 patients reviewed in this study was tested for the HIV virus, the question must be raised as to the incidence of HIV infection in

patients presenting with extra-pulmonary tuberculosis, and the suggestion must be proposed that patients presenting in future with a pericardial effusion should be screened for the AIDS virus.

CONCLUSIONS

In summary a retrospective study of the diagnostic value of pericardiocentesis at Groote Schuur Hospital has highlighted problems of data collection and keeping of medical records, as well as inadequate outpatient follow-up, relating to an invasive procedure that has associated morbidity and mortality. The complication rate of pericardiocentesis at this institution is relatively low with one death occurring out of the 52 patients that were studied.

With the diagnostic difficulties that occur with pericardial disease it is of considerable importance that if a patient is to be subjected to pericardiocentesis, for either diagnostic purposes or for the relief of cardiac tamponade, every effort should be made to perform the following: a mantoux, collect blood for HIV status, assess parameters of viral infection and perform a collagen screen; as well as collect specimens for ADA estimation, cytological evaluation, microbiological staining and especially tuberculous culture. It is further suggested that a larger inoculum should be used for the TB culture of 50-70mls of aspirate, and that this should be plated out at the time of pericardiocentesis either by the operator involved with the case, or by an attending microbiology technologist. An emphasis must be made to the supervising clinician that the sooner the specimens are put up for culture and are delivered to the relevant laboratory, the better the quality of the evaluation to be undertaken.

An ADA level of greater than 51 international units per litre is highly significant in its association with a tuberculous pericardial effusion; whilst an ADA level less than 48 international units per litre in association with pericardial cytology indicating no inflammatory response is strongly correlated with a non-tuberculous cause for effusion. The usefulness of combined ADA levels, mantoux test, HIV and collagen screens and cytological evaluation, in investigating a possible diagnosis of tuberculous pericarditis in the intervening period between the aspiration and the results of the six week culture requires further evaluation, preferably in the form of a prospective study that must establish a means of adequate follow-up, whereby the clinical outcome of culture-positive and culture-negative patients can be studied. It will only then be possible to appraise the specificity and sensitivity of these investigations, and appreciate the merits of the treatment regimes performed.

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