REFERENCES

1. Editorial (1977): S. Afr. med. J., **52**, 137.
2. Williams, R. L. and Allen, B. D. (1962): Aerospace Med., **33**, 545.
3. Lamb, L. E., Green, H. C., Combs, J. J. *et al.* (1960): *Ibid.*, **31**, 973.
4. Dermksian, G. and Lamb, L. E. (1958): J. Amer. med. Ass., **168**, 1623.
5. *Idem* (1958): *Ibid.*, **168**, 1200.
6. Jasper, H. H. (1958): Electroenceph. clin. Neurophysiol., **10**, 371.
7. Kiloh, L. G. and Osselton, J. W. (1966): *Clinical Electroencephalography*. London: Butterworths.
8. Cobb, W. A. *in* Hill, D. and Parr, G. eds (1963): *Electroencephalography*. London: Macdonald.
9. Hill, D. *in* Hill, D. and Parr, G., eds (1963): *Ibid.*

Primary Cardiac Amyloidosis

A Case Presentation

J. Z. PRZYBOJEWSKI, A. R. DANIELS, J. J. VAN DER WALT

SUMMARY

A young man with primary cardiac amyloidosis presented clinically as a case of 'restrictive' cardiomyopathy with an initial diagnosis of constrictive pericarditis, probably of tuberculous origin. Cardiac catheterization showed features compatible with restrictive cardiomyopathy or constrictive pericarditis but pericardial biopsy was negative. Percutaneous right ventricular endomyocardial biopsies established amyloid infiltration of the myocardium, but rectal, tongue and liver biopsies were all negative for amyloidosis. Bence-Jones protein was absent from the urine. Serum electrophoresis, immunophoresis, and bone marrow examination all failed to detect possible multiple myelomatosis as a cause of secondary amyloidosis. Respiratory function tests showed a restrictive picture, probably secondary to chronic congestive cardiac failure. Thus, this case is the second example of primary cardiac amyloidosis in the world literature which has been diagnosed by right ventricular endomyocardial biopsy. Phonocardiographic features of early aortic valve closure are reported for the first time in amyloid restrictive cardiomyopathy. Since tuberculous constrictive pericarditis is an important cause of cardiac disease in this country, with effective therapy, the authors stress more frequent use of endomyocardial biopsy as a safe diagnostic tool to exclude other similar disease states. The patient was offered the possibility of a cardiac transplantation in view of the localized nature of his disease, but refused. He now continues to respond unsatisfactorily to antifailure therapy with, presumably, a poor prognosis.

S. Afr. med. J., **57**, 774 (1980).

Cardiology Unit, Departments of Internal Medicine and Anatomical Pathology, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP

J. Z. PRZYBOJEWSKI, M.B. CH.B., F.C.P. (S.A.)

A. R. DANIELS, M.B. CH.B.

J. J. VAN DER WALT, M.MED. (PATH.), M.D.

Date received: 12 September 1979.

CASE PRESENTATION

A 25-year-old Coloured man was admitted to Tygerberg Hospital in September 1978 with a history of 3 years of dyspnoea on moderate exertion which had increased shortly before admission. There was no history of tuberculous contact.

On examination he was found to be generally well but there was mild ankle oedema. The pulse was regular at 85/min with a small volume. The blood pressure was 120/70 mmHg and there was a pulsus paradoxus of 10 mmHg. The jugular venous pressure was markedly elevated, with prominent 'a' and 'v' waves and rapid 'x' and 'y' descents. The cardiac apex was impalpable but there was a very prominent diastolic left parasternal heave. The first heart sound was normal, but the most striking feature was the abrupt and short-lived wide splitting of the second heart sound at the pulmonary area just at the onset of inspiration. There was a soft fourth sound at the apex but no third sound. A grade 2/6, blowing, pansystolic murmur could be heard in the mitral area; it radiated to the axilla, but did not increase in intensity with respiration and was thus in keeping with mitral insufficiency. There were no diastolic murmurs. All the peripheral pulses were normal. Further examination revealed a 4 cm, tender, non-pulsatile

hepatomegaly but no splenomegaly. The rest of the clinical examination was negative.

The electrocardiogram (Fig. 1) showed a sinus rhythm of 75/min with first-degree atrioventricular block (PR interval 0,22 s). The mean QRS axis was 87° and the QT interval was normal. Features of both left and right atrial hypertrophy could clearly be seen. There was also right ventricular hypertrophy with systolic overload. Possible left ventricular hypertrophy, as shown by voltage and secondary ST-T-wave changes, together with digitalis effect, was seen.

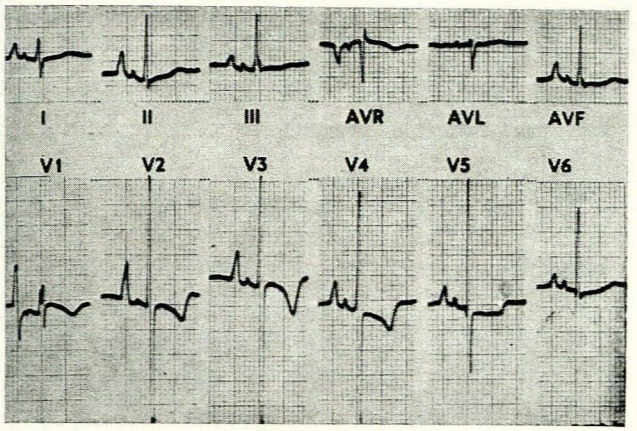

Fig. 1. Twelve-lead ECG showing bi-atrial hypertrophy and right ventricular systolic overload pattern. There is also evidence of digitalis effect and possible left ventricular hypertrophy. Tracing full-standardization.

The chest radiograph (Fig. 2) showed marked cardiomegaly with enlargement of both atria, the right and possibly the left ventricle, dilatation of the main pulmonary artery, and significant upper lobe pulmonary venous congestion. There was no pericardial or valvar calcification, but there were possible small calcified foci in the hilar areas.

Biochemical investigation showed slight elevation of hepatic enzymes and a mildly depressed serum albumin level in keeping with congestive cardiac failure.

Haematological investigations, including bone marrow (tuberculosis and myeloma) and trephine biopsy, were negative. The Mantoux reaction was strongly positive (20 mm).

At this stage the differential diagnosis was constrictive pericarditis (tuberculous), pericardial effusion with constriction, restrictive cardiomyopathy (unknown aetiology) and rheumatic mitral valve disease with underlying cardiomyopathy.

Treatment was started with digoxin and diuretics with slight improvement in the patient's dyspnoea following diuresis.

A red cell splenic scan showed two filling defects compatible with infarcts. Pericardial effusion was excluded by a radio-isotope scan which showed a large 'cold' area next to the left ventricular apex, which could be interpreted as a positive 'halo' or 'horseshoe' sign, being due to marked thickening of the myocardium.

Immunological investigations to exclude possible systemic disease were all negative. Serum electrophoresis and immunophoresis, as well as urinary immunophoresis, showed a normal pattern.

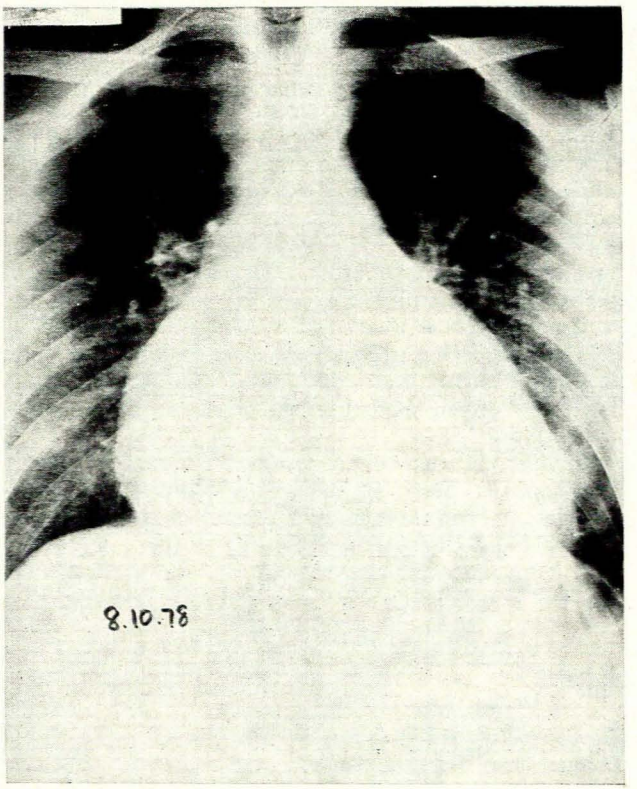

Fig. 2. Chest radiograph showing pancardiomegaly, dilatation of main pulmonary artery segment and marked upper lobe pulmonary venous congestion.

Echocardiographic studies followed in a further attempt at diagnosis. These were performed with a Picker Ultrasound 80 cardiac imager, as well as a KB Aerotech transducer (Model CT22DM), medium focused, with a 13 mm diameter and frequency of 2,25 MHz. The echocardiographic measurements, with their normal values, are given in Table I.

TABLE I. ECHOCARDIOGRAPHIC MEASUREMENTS

Measurements	Result	Normal range
Left atrial dimension (cm)	5,0	1,9 - 4,0
Left ventricular dimension (cm)	5,5	3,7 - 5,6
Right ventricular dimension (cm)	2,0	0,7 - 2,3
Interventricular septum thickness (IVS) (cm)	1,0	0,6 - 1,1
Left ventricular posterior wall thickness (LVPW) (cm)	1,0	0,6 - 1,1
IVS/LVPW ratio	1/1 or 1	<1,3
E-F slope (mm/s)	123	>35

As can be seen there is slight left atrial dilatation, in keeping with reduction of left ventricular compliance secondary to amyloid infiltration (diagnosis known in retrospect). However, it is interesting to note that neither the left nor the right ventricle is thickened, in spite of diastolic compliance being diminished and despite the results of the previous investigations. It is further intriguing to see a normal 'mitral valve slope' (E - F slope).[1] Also, the left ventricular free wall and interventricular septum are of normal dimensions despite the findings of Borer *et al.*[2] The echocardiogram (Fig. 3) shows qualitative 'flattening' of the left ventricular endocardial wall motion during diastole but it was impossible to calculate this characteristic quantitatively, as described by previous workers.[3] The pericardium was not thickened and there was no pericardial effusion. A striking finding was the presence of abnormal (paradoxical) interventricular septal wall motion, as is clearly seen in Fig. 3.

Thus, the echocardiogram demonstrated some features in keeping with a 'restrictive' cardiomyopathy, which have been interpreted as being characteristic of constrictive pericarditis.

Cardiac catheterization was then undertaken using the percutaneous Seldinger technique. The haemodynamic calculations and intracardiac pressures are indicated in Tables II and III respectively.

A left ventricular cine angiogram (Fig. 4) showed that the left ventricle appeared to contract normally, without any obvious distortion, increase in trabeculation or abnormally prominent papillary muscles. However, what can be clearly recognized is the thickening of the left ventricular free wall, as evidenced by the distance between the dye margin and the left anterior descending coronary artery. Moderately severe mitral insufficiency and a moderately dilated left atrium free of any filling defects were visualized, excluding a possible intra-atrial thrombus. The right atrial cine angiogram showed a significantly dilated right atrium, with subsequent filling of the right ventricle demonstrating thickened and coarse trabeculations, but without any obvious distortion.

TABLE II. HAEMODYNAMIC CALCULATIONS

Measurement	Result
Cardiac output (Fick) (l/min)	3,6
Cardiac index (Fick) (l/min/m^2)	2,4
Stroke volume (ml/beat)	46
Stroke work index (g/M/m^2)	34,8
Diastolic filling period (s/min)	30,8
Systolic ejection period (s/min)	10,8
LV dp/dt (mm/s)	1 851
Pulmonary vascular resistance (U)	2,8
Index (U/m^2)	2,9
Systemic vascular resistance (U)	24,8
Index (U/m^2)	37,1
Pulmonary/systemic resistance ratio (%)	11

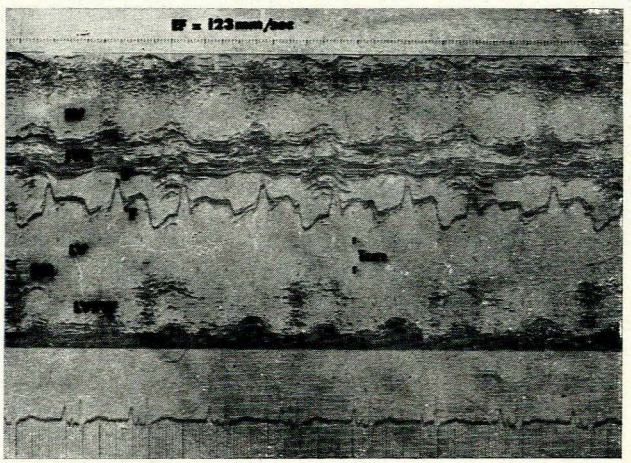

Fig. 3. Echocardiogram showing paradoxical septal wall motion with 'flattening' of the left ventricular endocardial wall motion during diastole. The 'mitral valve slope' (E-F) is normal. There is no pericardial effusion (RV = right ventricle; IVS = interventricular septum; LV = left ventricle; PM = papillary muscle; LVPW = left ventricular posterior wall).

After cardiac catheterization the differential diagnosis was narrowed down to either a constrictive pericarditis or a restrictive cardiomyopathy. The patient was then subjected to an open pericardial biopsy; the pericardium was normal and there was a small quantity of pale yellow pericardial fluid.

TABLE III. INTRACARDIAC PRESSURES

Catheter position	Pressure (mmHg)	Comment
Right atrium	'a' wave 18; 'x' descent 6; 'v' wave 15; 'y' descent 8; mean 11	Moderate right atrial hypertension with 'W' or 'M'-shaped configuration to contour
Right ventricle	64/0 - 15	Early 'diastolic dip'. Late 'diastolic plateau'. Elevated end-diastolic pressure
Main pulmonary artery	64/28; mean 32	No pulmonary valve stenosis. Moderately severe to severe pulmonary hypertension
Pulmonary capillary wedge (right)	'a' wave 33; 'x' descent 27; 'v' wave 31; 'y' descent 24; mean 25	Moderately elevated pressures. No mitral stenosis
Left ventricle	124/15 - 32	Elevated early and end-diastolic pressures. Mild early 'diastolic dip'
Ascending aorta	124/80; mean 100	Normal pressures. No aortic stenosis

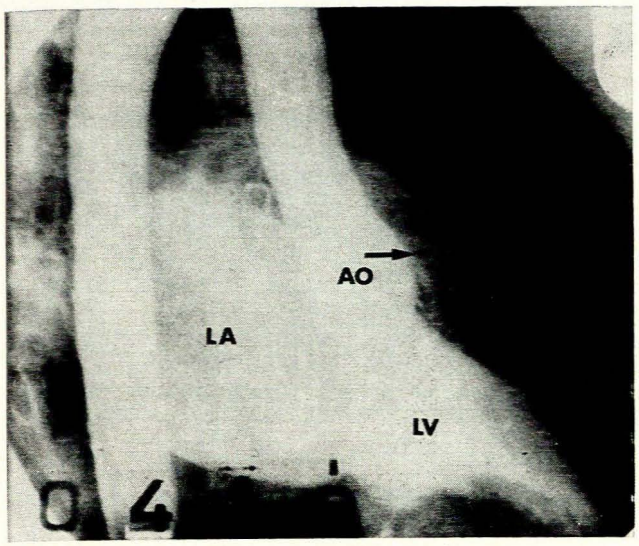

Fig. 4. Left ventricular cine angiogram (right anterior oblique projection). Thickened left ventricular (LV) myocardium is seen delineated by distance between left anterior descending coronary artery (arrowed) **and endocardium. Mitral insufficiency filling an enlarged left atrium (LA) is also seen (AO = aorta).**

Following this procedure, the patient started antituberculosis therapy (ethambutol 1 200 mg/d, streptomycin 1 g/d, isoniazid 400 mg/d, and pyridoxine 25 mg/d) pending the histology report. The patient was also maintained on anti-cardiac failure therapy. Surprisingly the pericardium was normal, so the antituberculosis drugs were discontinued and the patient was discharged. A final diagnosis of a restrictive cardiomyopathy of unknown aetiology was made.

The patient was readmitted 1 month later to the medical wards, with a history of sudden onset of a left hemiparesis and dysphasia. He was in atrial fibrillation but had not noticed any aggravation of his effort intolerance. The clinical diagnosis was that of an embolus which probably arose from the heart. It was decided not to convert the rhythm and he was given physiotherapy and antiplatelet drugs, as well as maintenance digoxin and diuretics. The patient recovered rapidly without evident neurological deficit and he was discharged 2 weeks after admission. One month after the second admission he was readmitted to the medical wards for the third time. On this occasion he gave a history of sudden onset of severe loin pain. A diagnosis of acute pyelonephritis was made and the patient was successfully treated with antibiotics. He was again discharged to be followed up at the Cardiac Clinic

At the Cardiac Clinic the patient was in atrial fibrillation with a satisfactory ventricular response. He continued to complain of dyspnoea on moderate exertion, but was otherwise asymptomatic. There were still signs of cardiac 'constriction' clinically and therefore diuretic therapy was increased.

Some 5 months after his third admission, the patient was readmitted for a fourth time, complaining of increasing dyspnoea despite medication. Clinically, there did not appear to be more severe cardiac constriction, but he was still in atrial fibrillation. The patient was then given heparin intravenously and, in view of his worsening symptoms, the atrial fibrillation was converted to sinus rhythm. Quinidine gluconate therapy was then started. Investigations to exclude a possible acute pulmonary embolism all proved to be negative. The patient was then mobilized and the anticoagulant discontinued. A repeat chest radiograph (Fig. 5) showed that the features of constriction were now far more impressive and the heart contour was deformed and reduced in size.

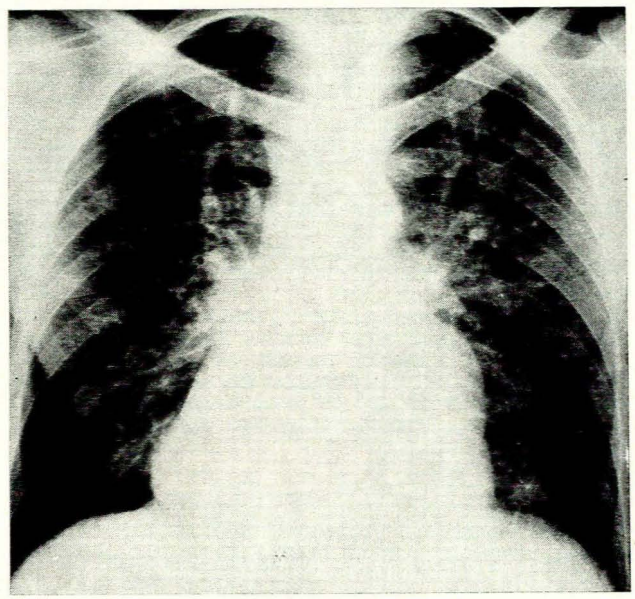

Fig. 5. Chest radiograph showing constriction with cardiac deformity.

A phonocardiogram (Fig. 6) was then recorded, with simultaneous tracings of the cardiac sounds, the external carotid pulse, and the ECG. Synchronous tracings were recorded at the mitral area, the fourth left intercostal space, and the pulmonary area. The interval of moderately exaggerated inspiration was signalled on the recording. The aortic component of the second heart sound was recognized by relating it to the dicrotic notch of the carotid pulse.[4] To improve the accuracy of the measurements, the R wave of the ECG and the peak vibrations of the cardiac sounds were employed to measure the R-A2 and R-P2 intervals.[5] All measurements were made to the nearest 0,01 second. The results of these measurements were as follows: R1-A2 0,34, R2-A2 0,34, R3-A2 0,28, R4-A2 0,34, R1-P2 0,38, R2-P2 0,38, R3-P2 0,38, R4-P2 0,38.

Because of the undetermined aetiology, it was decided to carry out a transvenous endomyocardial biopsy with an Olympus FB-2 Biotome from the right femoral vein by the method of Brooksby *et al.*[6] Five endomyocardial biopsy specimens were obtained from various areas of

the right ventricle and immediately placed in 2% glutaraldehyde solution. The procedure was completed without any complications. After fixing in 1% buffered osmium tetroxide, the specimens were embedded in Spurr's resin and cut on an LKB ultramicrotome. Sections were stained with lead and uranium and examined on a Zeiss EM 9 electron microscope at an accelerating voltage of 60 kV.

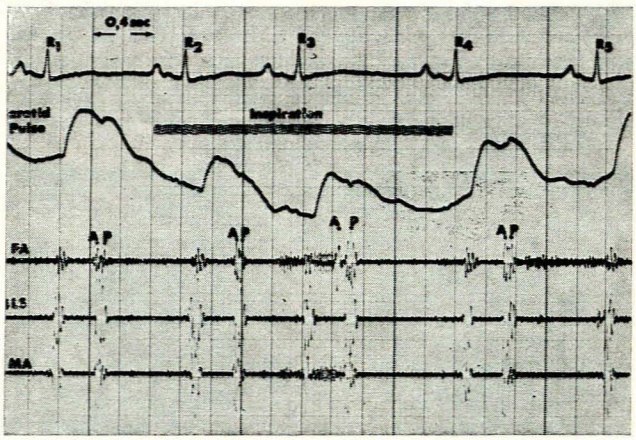

Fig. 6. Phonocardiogram showing inspiratory splitting of second heart sound after onset of inspiration, due to aortic component moving towards preceding QRS complex (refer text) (PA = pulmonary area; 4LS = 4th left intercostal space; MA = mitral area; P = pulmonic component; A = aortic component of second heart sound).

At low magnification (Fig. 7) the picture was that of highly disorganized myocardium due to severe patchy interstitial fibrosis. The 'fibrous' areas could be resolved to show an admixture of collagen and amyloid fibrils forming a tangled array (Figs 8 and 9). The amyloid fibrils varied little in width and had the characteristic periodic beaded appearance. Small deposits of amyloid could be seen between muscle cells where the latter appeared relatively normal, degenerate or hypertrophied, while extensive deposits of amyloid completely replaced muscle cells in places. In some areas the muscle cells showed masses of closely packed mitochondria, and some lipofuscin was noted. The muscle cells at times had a wavy outline with the amyloid extending up the basal lamina. Amyloid was never observed inside the muscle cells. The capillaries were not remarkable in any way. At times collagen and amyloid extended up to involve the capillary basement membranes; where extensive deposits of amyloid were present in the connective tissues, there appeared to be a reduction in the number of capillaries.

It was decided to carry out respiratory function tests as a possible aid to a diagnosis of amyloid involvement of the lungs. The patient displayed features of moderately severe restrictive pulmonary disease (Table IV). This was accepted as being in keeping with chronic congestive cardiac failure, and it was felt unnecessary to perform a lung biopsy. Routine follow-up with anti-failure therapy is being conducted at present. Unfortunately his response is poor. Cardiac transplantation has been offered but the patient has refused.

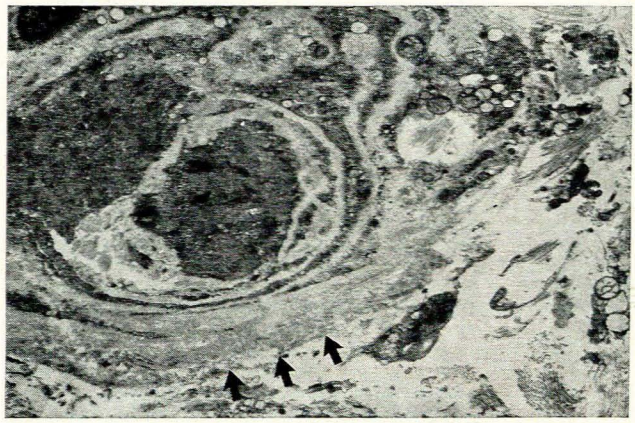

Fig. 7. Disorganization of myocardium due to interstitial amyloid deposits (arrows) **(magnification × 14 000).**

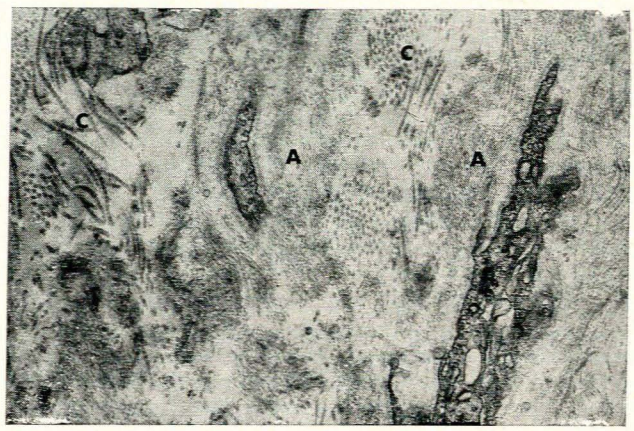

Fig. 8. Amyloid fibrils (A) in bundles and parallel array (C = collagen) (magnification × 32 000).

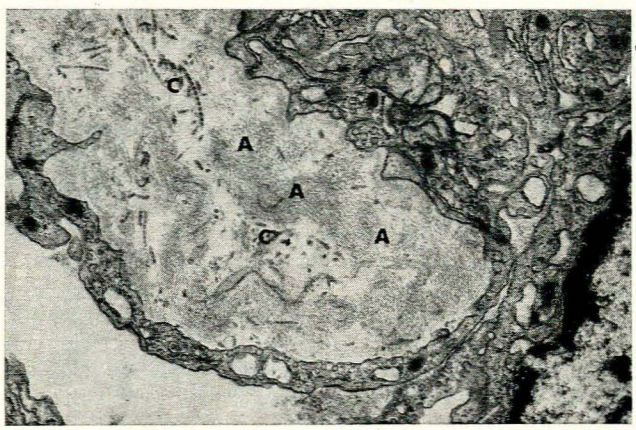

Fig. 9. Amyloid fibrils (A) and collagen (C) abutting against cell wall (magnification × 32 000).

TABLE IV. RESPIRATORY FUNCTION TESTS

Parameter	Predicted (ml)	Measured (ml)	% predicted
Vital capacity			
Inspired	**5 530**	**3,200**	**58**
Expired	**5 530**	**3 600**	**65**
Inspiratory capacity	**3 690**	**2 000**	**54**
Expiratory reserve volume	**1 840**	**1 200**	**65**
Functional residual capacity	**4 480**	**2 550**	**57**
Residual volume (RV)	**1 900**	**1 350**	**71**
Total lung capacity (TLC)	**7 550**	**4 550**	**60**
RV/TLC × 100	**<33%**	**30%**	
Forced expiratory volume in 1 s (FEV_1)	**4 200**	**2 900**	**69**
Area under flow-volume curve (AFV)	**30,5**	**15,2**	**49,8**
Single-breath nitrogen washout test	**2%**	**2%**	**100%**

DISCUSSION

Involvement of the heart in amyloidosis has intrigued investigators for many decades and there is continuing interest in primary involvement of this organ, considered to be rare. So-called 'senile cardiac amyloidosis' has been documented at autopsy in some 30 - 69% of patients older than 60 years.[7,8] However, in these instances, the cardiac amyloid deposits are generally scanty and do not appear harmful.[9,10] In contrast, those patients manifesting symptoms of congestive cardiac failure have far more extensive myocardial infiltration.[11] In one series[12] heart disease was noted in some 67% of patients. Of these, 90% with primary amyloidosis, 90% with myeloma-associated amyloidosis and 54% with secondary amyloidosis had cardiac involvement. Furthermore, chronic congestive cardiac failure was seen in 60% of those with primary, 40% of those with myeloma-associated and 36% of those with secondary amyloidosis. Unfortunately, the majority of cases are only diagnosed *post mortem*. Thus, facilities for antemortem diagnosis, such as strong clinical suspicion and awareness of the existence of the disease and, most significantly, endomyocardial biopsy of either ventricle, should be stressed.

The phonocardiographic features in this case are interesting. Reference to Fig 6 will indicate that soon after the beginning of inspiration the splitting of the second heart sound abruptly increased by 0,06 second (R3A2 - R2A2). This increased inspiratory splitting was not due to P2 moving away from the preceding R wave of the ECG, but was entirely due to A2 moving towards the R wave, that is shortening of the R3 - A2 interval. It will also be appreciated that the reduction in the carotid arterial pressure[13] coincided with this increase in splitting of the second heart sound, and that it returned to normal after return to the expiratory phase. Back *et al.*,[14] in a most elegant study, were the first to report this peculiarity of the second heart sound in patients with constrictive pericarditis, and attempted to elucidate the mechanism of pulsus paradoxus. Under normal circumstances inspiration causes increased splitting of the second heart sound, which can be as great as 0,1 second.[15] This was initially attributed to movement of P2 away from the aortic component,[15] but subsequent investigators[5,16-18] showed that some 18 - 50% of this increase in splitting during the inspiratory phase was also contributed to by movement of A2 toward the first heart sound.

Apart from premature closure of the aortic valve found in constrictive pericarditis,[14] it has also been described in left atrial myxoma[19] as well as in mitral insufficiency,[20,21] and has been stated to be due to a reduction of volume of blood ejected into the aorta in the latter two disease states. As far as the present authors are aware, the present patient is the first with restrictive cardiomyopathy demonstrating phonocardiographic features previously stated to be typical of constrictive pericarditis.[14] The haemodynamic mechanism can probably be explained by the relative non-compliant atria and ventricles, giving rise to the changed pressure-volume relationship, a feature previously described in acute cardiac tamponade,[22,23] such as occurs in severe constrictive pericarditis.

Since the clinical presentation and cardiac catheterization findings of constrictive pericarditis can be identical with those in restrictive myocardial disease of amyloidosis, it is worth while pointing out the salient echocardiographic differences. Voelkel *et al.*[3] demonstrated that left ventricular posterior wall (LVPW) 'flatness', as calculated by measuring the diastolic change in distance from the crystal artefact to the LVPW endocardium, was less than 1 mm in 11 of 12 patients with constrictive pericarditis. This was in keeping with previous reports[24-26] of qualitative 'flattening' of the left ventricular endocardial wall motion during diastole. Pericardial thickness has been found by some workers[25,26] to be increased in constrictive pericarditis, but Gibson *et al.*[27] found poor correlation with thickening at surgery. This is largely due to the fact that the pericardial thickness is a function of gain setting. Voelkel *et al.*[4] found this parameter to be of little help in separating patients with constrictive pericarditis from normal subjects.

The cardiac catheterization features are quite characteristic. As can be seen, the main negative deflection of the right atrial curve occurs somewhat prematurely during the isometric relaxation period of the right ventricle and is caused by the rapid egress of blood from atrium to ventricle at the moment the intraventricular pressure falls below the venous pressure. The right and left ventricular pressure tracings demonstrate the features of 'restriction' or 'constriction' in that there is an early 'diastolic dip' followed by a 'diastolic plateau' which culminated in elevated end-diastolic pressures. These features are more marked in the

right ventricular curves. The 'dip' and 'plateau' are due to rapid filling of the ventricle caused by both the high venous filling pressure and the reduced compliance or distensibility of the ventricle. The fact that the pulmonary capillary wedge pressure is raised, and that the left ventricular pressure curve configuration is abnormal, indicates that there is increased filling pressure of the left ventricle and that the infiltrative process is biventricular. A decrease in left ventricular contractility is reflected in the low stroke volume (approximately half normal). This is in turn reflected in the increased pulmonary vascular resistance. Another interesting feature is the relatively low peak left ventricular systolic pressure despite the markedly elevated end-diastolic pressure. This is further evidence of diminished left ventricular contractility.

The first published case of primary cardiac amyloidosis diagnosed by right ventricular endomyocardial biopsy was that of Hedner *et al.*[28] in 1975. This report was followed by that of Schroeder *et al.*[29] of 2 patients who presented with restrictive cardiomyopathy and in whom right ventricular endomyocardial biopsy revealed amyloidosis. However, both of these patients had secondary amyloidosis and one of them was turned down for cardiac transplantation because of this. Chew *et al.*[30] then went on to publish a case of restrictive cardiomyopathy ('stiff heart' syndrome), diagnosed by left ventricular endomyocardial biopsy, in a patient who had secondary amyloidosis associated with multiple myelomatosis. The most recent case of primary amyloidosis with cardiac involvement ('restrictive' cardiomyopathy), who presented with the nephrotic syndrome and in whom the diagnosis was made by left ventricular endomyocardial biopsy, was that of Chan and Ikram.[31] Thus, the present case is the second case of primary cardiac amyloidosis in the world literature which has been diagnosed by endomyocardial biopsy of the right ventricle.

In conclusion, the authors strongly recommend more frequent use of endomyocardial biopsy in early diagnosis of cardiac disease of uncertain aetiology. Serial biopsies could also contribute significantly to ascertain the progression or regression of endomyocardial disease, as well as determining the effects of various treatment regimens.

The authors wish to sincerely thank Miss H. Weymar of the Cardiac Clinic of this hospital for her diligent preparation of the manuscript and for the production of the photographs. Thanks are also due to Mr F. A. C. Tiedt for technical assistance with the electron microscopy and photography. Finally, we wish to thank Dr C. Vivier, Medical Superintendent of Tygerberg Hospital, for permission to publish.

REFERENCES

1. Zaky, A., Nasser, W. K. and Feigenbaum, H. (1969): Circulation, **37**, 789.
2. Borer, J. S., Henry, W. L. and Epstein, S. E. (1977): Amer. J. Cardiol., **39**, 184.
3. Voelkel, A. G., Pietro, D. A., Folland, E. D. *et al.* (1978): Circulation, **58**, 871.
4. Leatham, A. (1952): Brit. med. Bull., **8**, 333.
5. Shafter, H. A. (1960): Amer. J. Cardiol., **6**, 1013.
6. Brooksby, I. A. B., Swanton, R. H., Jenkins, B. S. *et al.* (1974): Brit. Heart J., **36**, 908.
7. Schwartz, P. and Kurucz, J. (1965): J. Amer. geriat. Soc., **13**, 718.
8. Wright, J. R., Calkins, E., Breen, W. J. *et al.* (1969): Medicine, **48**, 39.
9. Pomerance, A. (1965): Brit. Heart J., **27**, 711.
10. Lee, H. Y. and Kaufmann, W. (1957): Arch. Path., **64**, 494.
11. Buerger, L. and Braunstein, H. (1960): Amer. J. Med., **28**, 357.
12. Brandt, K., Cathcart, E. S. and Cohen, A. S. (1968): *Ibid.*, **44**, 955.
13. Schrire, V. and Gordon, H. (1957): Paper presented at the 41st South African Medical Congress, Durban.
14. Beck, W., Schrire, V. and Vogelpoel, L. (1962): Amer. Heart J., **64**, 765.
15. Leatham, A. (1958): Lancet, **2**, 607.
16. Boyer, S. H. and Chisholm, A. W. (1958): Circulation, **18**, 1010.
17. Castle, R. F. and Jones, K. L. (1961): *Ibid.*, **24**, 180.
18. Aygen, M. M. and Braunwald, E. (1962): *Ibid.*, **25**, 1962.
19. Kaufman, G., Rutishauser, W. and Hegglin, R. (1961): Amer. J. Cardiol., **8**, 350.
20. Perloff, J. K. and Harvey, W. P. (1958): Circulation, **18**, 998.
21. Brigden, W. and Leatham, A. (1953): Brit. Heart J., **15**, 55.
22. Isaacs, J. P., Berglund, E. and Sarnoff, S. J. (1954): Amer. Heart J., **48**, 66.
23. Isaacs, J. P., Carter, B. M. and Haller, J. A. (1952): Bull. Johns Hopk. Hosp., **90**, 259.
24. Feigenbaum, H. (1976): *Echocardiography*. Philadelphia: Lea & Febiger.
25. Popp, R. L. (1976): Circulation, **54**, 538.
26. Horowitz, M. S., Rosen, R. M., Harrison, D. C. *et al.* (1974): Circulation, **50**, suppl. 3, p. 87.
27. Gibson, T. C., Grossman, W., McLaurin, L. P. *et al.* (1974): *Ibid.*, **50**, suppl. 3, p. 86.
28. Hedner, R., Rausing, A., Steen, K. *et al.* (1975): Acta med. scand., **198**, 525.
29. Schroeder, J. S., Billingham, M. E. and Rider, A. K. (1975): Amer. J. Med., **59**, 269.
30. Chew, C., Ziady, G. M., Raphael, M. J. *et al.* (1975): Amer. J. Cardiol., **36**, 438.
31. Chan, W. and Ikram, H. (1977): Aust. N.Z.J. Med., **7**, 427.