Clinical course of endomyocardial fibrosis

PRABHA N GUPTA, MARTHANDAVARMA S VALIATHAN,
KUMARALINGAM G BALAKRISHNAN, CHANDRASEKHARAN C KARTHA,
MRINAL K GHOSH*

*From the Indian Council of Medical Research Centre for Research in Cardiomyopathies, Sree Chitra Tirunal Institute for Medical Sciences and Technology and *Quality Assurance Division, Vikram Sarabhai Space Centre, Trivandrum, India*

SUMMARY The survival pattern, morbidity, and clinical course of 145 patients with endomyocardial fibrosis who were followed up between November 1975 and June 1987 were studied. The diagnosis was confirmed in all cases by cardiac angiography, or echocardiography, or necropsy. Percentage survival at the end of one and 9.5 years was 76.11 and 26.35 respectively.

History, physical examination, electrocardiography, and cardiac catheterisation were studied at the first presentation. The determinants of early mortality were studied by univariate Kaplan-Meier estimates compared by the log rank test and Cox proportional hazards multiple regression analysis. Significant univariate predictors of early mortality were QRS axis above $+90^\circ$, intraventricular conduction delay (QRS duration >0.12 s), duration of symptoms before presentation, New York Heart Association functional classes III and IV, presence of embolic episodes, right atrial mean pressures >20 mm Hg, right ventricular end diastolic pressure >20 mm Hg, and aortic oxygen saturation $<85\%$. The significant multivariate predictors of mortality were cyanosis, New York Heart Association functional class at first presentation, and right atrial mean pressure >20 mm Hg.

The bleak prognosis of endomyocardial fibrosis did not substantially improve despite advances in the medical management of congestive cardiac failure during the period of the study.

Endomyocardial fibrosis has been extensively characterised in terms of clinical,¹ radiological,² and echocardiographic features,³ and its surgical management standardised in recent years.^{4,5} There have, however, been few studies on its clinical course.⁶ We report on the clinical course of endomyocardial fibrosis in the south western state of Kerala in India, where the disease is prevalent.

Patients and methods

One hundred and forty five patients in whom the diagnosis was confirmed by cardiac angiography (121), echocardiography (2), or necropsy (17) or both angiography and necropsy (5) and who were followed from November 1975 to June 1987 form the basis of this report. Forty six patients who were treated by endocardiotomy and valve replacement during the

same period were excluded because they were the subject of a detailed report.⁴

CLINICAL FEATURES

Table 1 lists the clinical features of patients in the present series. The mean (SD) age of the patients at first presentation was 26.3 (14.1) years for women ($n = 70$) and 21.1 (11.9) years for men ($n = 75$); 33.1% were under 15. Thirty one (21%) patients had had symptoms for less than 2 years before presentation to the hospital. Seventy two (49.7%) were in New York Heart Association functional classes III and IV at first presentation. The proportion of patients with right and left heart failure was the same at first presentation (37.9%). Apart from atrial fibrillation, arrhythmias were uncommon in these patients. Ventricular extrasystoles were seen in five (3.4%). Sixteen (11.03%) of the patients were anaemic (haemoglobin <100 g/l). The large proportion of patients belonging to the New York Heart Association classes III and IV (49.7), with ascites (40.0%), peripheral oedema (24.8%), cardiothoracic ratio $>60\%$ (57.2%), and other features show how

Requests for reprints to Dr Marthandavarma S Valiathan, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.

Accepted for publication 10 August 1989

Table 1 Clinical profile of 145 patients with endomyocardial fibrosis at first presentation

Variable	Percentage
Febrile illness at onset	9.7
Atypical or anginal chest pain	13.1
Duration of symptoms < 24 months	21.4
Swelling of the lower limbs	24.8
New York Heart Association classes III and IV	49.7
Below the age of 15 years	33.1
Right heart failure at first presentation	37.9
Left heart failure at first presentation	37.9
Cyanosis	15.9
Ascites	40.0
Clubbing of digits	11.0
No murmurs at first presentation	26.2
Cardiothoracic ratio > 0.6	57.2
Haemoglobin < 100 g/l	11.0
Absolute eosinophil count > 2000/ μ l	11.7
Atrial fibrillation	32.4
Ventricular extrasystoles	3.4
Junctional rhythm, or heart block	3.4
Right axis deviation (> + 90°)	31.7
Intraventricular conduction delay (QRS > 0.12 s)	21.4

severe and advanced the disease was when the patients sought medical attention. The distribution of eosinophil counts in the patients varied as follows: 0–500/ μ l, 54 (37.2%); 501–1000/ μ l, 30 (20.7%); 1001–1500/ μ l, 25 (17.2); 1501–2000/ μ l, 19 (13.1). Eosinophilia of > 2000/ μ l was seen in 17 patients (11.7%).

ECHOCARDIOGRAPHY

Echocardiographic data were available in 86 patients. The mean (SD) left ventricular internal dimensions in diastole and systole were 4.17 (1.19) cm and 2.9 (1.07) cm respectively. Pericardial effusion was present in 35 (40.7%), intracavitary thrombi in 11 (12.8%), and myocardial calcification in 16 (18.6%) patients.

CARDIAC CATHETERISATION

Right and left heart catheterisation was performed in 126 patients and the cardiac output and index calculated by the Fick method. Diagnosis of endomyocardial fibrosis was established in these patients on the basis of angiographic features.⁷ Table

2 summarises the data from cardiac catheterisation and angiography.

FOLLOW UP

All patients were regularly followed every 6 months by prior appointment. Patients were also referred by the local physician or came on their own because of symptoms. Patients who did not attend were sent at least three postal reminders. Information on deaths at home was available from the relatives of 21 patients. Nineteen patients were lost to follow up during the first year. Repeat angiograms were performed in twelve patients during the follow up period.

STATISTICAL ANALYSIS

All patient variables for those surviving one year and those who died were compared by a *t* test for quantitative data and a χ^2 test for qualitative data. The significant variables in this analysis were chosen for the log rank test. Nineteen clinical variables and seven haemodynamic ones (from cardiac catheterisation) were analysed for their impact on survival by the log rank test.⁸

Cox proportional hazards multiple regression analysis⁹ was also applied to the variables studied by the log rank test. We used a BIOSTAT program.

Cox proportional hazards regression analysis of the seven haemodynamic variables was also carried out in patients with predominant involvement of the right ventricle and of the left ventricle.

Programs were written in CDC Cyber Fortran IV language. The linearity assumption was validated by the analysis of variance technique, and the significance of the predictor variables was studied by the F test.

Results

During the follow up of 334 patient years, 25 embolic episodes of the territories of the iliofemoral (6), pulmonary (10), carotid (8), and mesenteric arteries (1) developed in 24 patients. Three of the patients presenting without murmurs developed regurgitant

Table 2 Data (mean (SD)) from cardiac catheterisation in 126 patients with endomyocardial fibrosis

Predominant involvement	Total number	Involvement of contralateral ventricle	Mean RA pressure	Mean RVEDP	Mean LVEDP	PA mean pressure
RV	66	56	18.04 (6.70)	18.30 (6.20)	15.19 (6.30)	24.15 (14.20)
LV	45	33	11.40 (7.50)	15.44 (9.40)	23.27 (8.30)	38.34 (18.01)
BV	15	15	14.10 (8.44)	19.16 (10.16)	24.53 (6.50)	33.46 (12.60)

RV, right ventricular endomyocardial fibrosis; LV, left ventricular endomyocardial fibrosis; BV, biventricular endomyocardial fibrosis; RA, right atrial, LVEDP, left ventricular end diastolic pressure; RVEDP, right ventricular end diastolic pressure; PA mean, pulmonary artery mean pressure.

Table 3 Cause of death in 66 patients with endomyocardial fibrosis who died during follow up of 11 years 7 months

	No	Percentage
Congestive cardiac failure	16	24.2
Severe right ventricular failure, hepatic coma	9	13.6
Embolic phenomena	11	16.7
Terminal arrhythmias	6	9.0
Unknown causes (death at home informed by letter)	21	31.8
Others*	3	4.5

*Meningitis (1), Drug allergy (1), chronic obstructive airway disease (1).

murmurs after a year of follow up. Eleven developed ascites, four atrial fibrillation, and four evidence of ventricular hypertrophy on the electrocardiogram at varying intervals after the first presentation.

Of our series of 145 patients, 66 died during the follow up period of 334 patient years. Table 3 shows the causes of death. Of the 66 deaths, 32 occurred during the first year of follow up (25.4%). The survival rate was 76.1% at the end of one year, 68.0% at 2 years, 35.6% at 5 years, and 26.4% after 9.5 years (figure).

NECROPSY

Necropsies were performed in 22 patients who died in the hospital.¹⁰ Eighteen had obliteration of both ventricular cavities. The trabecular portion and papillary muscles were seen to be particularly vulnerable to fibrotic changes. The causes of death in this group were congestive cardiac failure, bronchopneumonia, or embolic episodes. Cavity obliteration

Survival curve (Kaplan-Meier) of 145 patients with endomyocardial fibrosis. Numbers are individuals at risk.

of the right ventricle alone was seen in three patients. In one, the left ventricle alone was affected. In two who were diagnosed to have pure left ventricular endomyocardial fibrosis at angiography, necropsy showed obliteration of the apex and some involvement of the trabecular portion of the right ventricle.

UNIVARIATE ANALYSIS

The factors significantly affecting survival were considerable anaemia (haemoglobin < 100 g/l), development of embolic episodes, QRS axis more than +90°, delayed intraventricular conduction (QRS duration > 0.12 s), New York Heart Association classes III and IV, a short symptomatic history before admission to hospital, the presence of cyanosis, and left and/or right ventricular failure at first

Table 4 Selected clinical variables that were significant in univariate analysis in 145 patients with endomyocardial fibrosis

Prognostic factor	No	Percentage survival			p value*
		At 1 year	At 2 years	At 5 years	
Duration of symptoms before presentation:					
< 24 months	31	38.14	None	None	
> 24 months	114	83.68	77.32	40.46	< 0.01
Cyanosis:					
Absent	122	80.83	71.46	36.93	
Present	23	46.99	39.16	31.32	< 0.01
Haemoglobin:					
< 100 g/l	16	36.45	27.34	13.67	
> 100 g/l	129	80.45	73.27	40.14	< 0.01
QRS axis:					
< +90°	99	82.56	77.36	47.78	
> +90°	46	61.77	48.03	8.89	< 0.01
Intraventricular conduction delay QRS duration(s):					
< 0.12	114	80.14	72.34	42.92	
> 0.12	31	60.5	51.5	19.20	< 0.01
New York Heart Association class:					
I and II	73	82.7	75.59	47.09	
III and IV	72	65.34	59.55	23.42	< 0.01
Embolic phenomenon:					
Absent	120	80.99	74.7	38.56	
Present	25	45.72	28.58	19.05	< 0.01

*Log rank test of Kaplan-Meier estimates.

Table 5 Univariate analysis of 126 catheterised patients with endomyocardial fibrosis (mortality determinants by log rank test of Kaplan-Meier estimates)

Variable	No	% survival at 1 year	% survival at 2 years	% survival at 5 years	p
RA mean pressure:					
< 20 mm Hg	93	83.7	68.7	42.5	< 0.01
> 20 mm Hg	33	57.2	36.4	19.4	
RVEDP:					
< 20 mm Hg	90	87.7	72.1	39.7	< 0.01
> 20 mm Hg	36	48.0	31.5	15.7	
LVEDP:					
< 15 mm Hg	56	79.2	61.6	39.8	NS
> 15 mm Hg	70	74.1	59.5	27.4	
Aortic oximetry:					
< 85%	14	60.6	43.3	10.8	< 0.01
> 85%	112	78.1	62.6	43.5	

RA, Right atrial; RVEDP, right ventricular end diastolic pressure; LVEDP, left ventricular end diastolic pressure.

presentation (table 4). The analysis showed that age, sex, and predominantly right or left ventricular endomyocardial involvement had no effect on survival.

The haemodynamic data showed that right atrial mean pressures > 20 mm Hg, right ventricular end diastolic pressure > 20 mm Hg, and aortic oxygen saturation of < 85% were associated with significantly shorter survival (table 5). The value of left ventricular end diastolic pressure, pulmonary artery mean pressure, aortic mean pressure, and pulmonary artery oxygen saturation had no significant effect on survival.

MULTIVARIATE ANALYSIS

The most important multivariate predictors of survival were cyanosis, New York Heart Association class at first presentation, and right atrial mean pressures above 20 mm Hg (table 6). Because separate analysis of the predominant involvement of the right and left ventricular endomyocardial fibrosis did not yield any significant information, the results of analysis of pooled data are presented.

PROGRESSION OF ENDOMYOCARDIAL FIBROSIS

Twelve patients had repeat cardiac catheterisation over a period of 2–3 years. Of these, eight had angiographic progression of the disease. Three showed advancement of the disease in the same ventricle and five had new involvement of the previously uninvolved ventricle during the repeat

study. Three patients with left ventricular disease developed partial right ventricular obliteration within 12, 24, and 28 months respectively. Two of them also developed tricuspid regurgitation. Left ventricular apical obliteration developed within 12 months in two patients with right ventricular disease; mitral regurgitation also developed in one.

Discussion

Previous reports on the clinical course of endomyocardial fibrosis were generally based on the study of smaller numbers of patients.⁶ The main objective of the present study was to follow the natural history of patients with endomyocardial fibrosis after their first presentation to the hospital. Our present data suggest that the disease has a less unfavourable course than what was previously reported by D'Arbela *et al* who noted that 43.5% of their patients died in the first year of follow up with the death of a majority of patients taking place in 3–4 years.¹¹ Parry and Abrahams followed patients with endomyocardial fibrosis and found their clinical course to be varied and marked by rapid deterioration, chronicity, or acute on chronic manifestations.⁶ We have noted similar patterns of survival in the present study. The early deaths among patients presenting with a clinical history of less than two years which proved to be a significant univariate predictor of mortality suggested a more severe and rapidly fatal form of endomyocardial fibrosis distinct from the chronic form of the disease. It is also possible that the first two years after the onset of symptoms represented the acute phase of the disease and patients who survived this stormy period might progress to a chronic "burnt-out" phase with longer survival. The grave prognosis of the acute phase is corroborated by the series of D'Arbela and colleagues who reported that 43.5% of their patients died during the first year.

Table 6 Cox proportional hazards multivariate analysis of clinical and haemodynamic determinants of mortality

Variable	p value
Cyanosis—present or absent	0.003
Right atrial mean pressure > < 20 mm Hg	0.002
NYHA class I and II v III and IV	0.008

NYHA, New York Heart Association.

We found cyanosis to be a significant multivariate determinant of survival. The restriction of ventricular compliance and the high right ventricular end diastolic pressure, which stretches open the foramen ovale and causes a right to left shunt, explains the prognostic significance of cyanosis.

Among the significant electrocardiographic criteria for survival, a QRS axis of more than $+90^\circ$ is likely to be caused by dilatation of the right ventricular outflow tract with delayed activation of that region or right ventricular preponderance secondary to severe pulmonary hypertension. Right ventricular failure at first presentation as shown by raised right ventricular end diastolic pressure was also shown to influence survival adversely.

In common with other reports on endomyocardial fibrosis from Kerala¹² we found no significant eosinophilia in the present series. Statistical analysis did not show eosinophilia to be a significant determinant of survival.

Surprisingly left ventricular end diastolic pressure and pulmonary artery mean pressure were not found to be significant determinants of early mortality when analysed separately even in predominantly left ventricular endomyocardial fibrosis. We speculate that this paradoxical finding may be due to the early stage of the disease, when patients with left ventricular endomyocardial fibrosis tend to seek medical attention with distressing symptoms like dyspnoea. In contrast, patients with right ventricular endomyocardial fibrosis approach hospitals at a late stage with advanced features of the disease such as obliteration of the right ventricular inflow and frank right ventricular failure. It seems that raised left ventricular end diastolic pressure and pulmonary artery mean pressure are subsumed by the early phase of the disease when the functional reserve of the left ventricle is substantially unimpaired.

Echocardiography has several limitations in quantifying the morphological changes in endomyocardial fibrosis and seems to be a weak tool in the prediction of survival. For example, an irregularly shaped chamber may give inaccurate measurements of left ventricular dimensions at the chordal level because the apical portion of the ventricle alone may be involved by fibrosis in the initial stage of the disease.

Several factors were shown to influence significantly the course of patients with endomyocardial fibrosis in the present series but predominant involvement of a particular ventricle was not one of them. This is probably because endomyocardial fibrosis is essentially a biventricular disease—both angiography and necropsy show fewer cases with one affected ventricle. Furthermore, the angiographic progression of the disease towards the involvement of the previously unaffected ventricle in five cases also points to the biventricular nature of the disease.

Even though the grave prognosis of endomyocardial fibrosis has long been known, we attempted to identify the determinants of survival on the basis of clinical, haemodynamic, necropsy, and follow up data in 145 patients in the south western state of Kerala in India. In an earlier report from this institution, two year survival among 46 patients who underwent endocardiotomy and valve replacement was 67% and 29 patients showed a significant improvement in their functional class.⁴ The survival rate at 5 years and 8 months was 60.8%. It seems that the outcome in surgically treated patients is better than their medically treated counterparts who are reported in the present study.

PNG thanks the Indian Council of Medical Research for financial support. We thank the Institute for the use of facilities in the study and the Vikram Sarabhai Space Centre for the use of the computer.

References

- 1 Valiathan MS, Balakrishnan KG, Kartha CC. A profile of endomyocardial fibrosis. *Indian J Pediatr* 1987;54:229-36.
- 2 Sasidharan K, Kartha CC, Balakrishnan KG, Valiathan MS. Early angiographic features of right ventricular endomyocardial fibrosis. *Cardiology* 1983;70:127-31.
- 3 Vijayaraghavan G, Davies J, Sadanandan S, Spry CJF, Gibson DG, Goodwin JF. Echocardiographic features of tropical endomyocardial disease in South India. *Br Heart J* 1983;50:450-9.
- 4 Valiathan MS, Balakrishnan KG, Sankarkumar R, Kartha CC. Surgical treatment of endomyocardial fibrosis. *Ann Thorac Surg* 1987;43:68-73.
- 5 Balakrishnan KG, Venkitachalam CG, Pillai VRK, Subramanyan R, Valiathan MS. Post-operative evaluation of endomyocardial fibrosis. *Cardiology* 1986;73:73-84.
- 6 Parry EH, Abrahams DG. The natural history of endomyocardial fibrosis. *Q J Med* 1965;34:383-408.
- 7 Sasidharan K, Balakrishnan KG, Venkitachalam CG, Sapru RP. Radiological features of endomyocardial fibrosis. In: Sapru RP, ed. *Endomyocardial fibrosis in India*. New Delhi: ICMR, 1983:90-103.
- 8 Mathews DE, Farewell V. *Using and understanding medical statistics*. New York: Karger, 1985:67-87.
- 9 Kalbfleisch JD, Prentice RI. *The statistical analysis of failure time data*. New York: Wiley, 1980:70-117.
- 10 Kartha CC, Sandhyamani S. An autopsy study of tropical endomyocardial fibrosis in Kerala. *Indian J Med Res* 1985;82:439-46.
- 11 D'Arbela PG, Mutazindwa T, Patel AK, Somers K. Survival after first presentation with endomyocardial fibrosis. *Br Heart J* 1972;34:403-7.
- 12 Sapru RP, Balakrishnan KG, Iyer KS, Shanmugham J, Asok PP, Sehgal S. Haematological, biochemical, immunological and electrophysiological studies in endomyocardial fibrosis. In: Sapru RP, ed. *Endomyocardial fibrosis in India*. New Delhi: ICMR, 1983:175-82.