The medical treatment of endomyocardial fibrosis in 2009

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ABSTRACT

Objectives To study the natural history of medically treated patients with endomyocardial fibrosis (EMF) and to see whether the usage of common drugs affected survival.
Design A real-world all-comers analysis with follow-up.
Setting A teaching hospital.
Analysis Cox proportional hazards multiple regression and Kaplan–Meier curves for survival with both univariate and multivariate analysis.
Results The mean age of this population was 40.5±5 years at first symptom. The mortality was also less than previous reports at 10.38%. The dominant type of EMF was dominant left ventricular EMF in 49, right ventricular EMF in 52 and biventricular EMF in 53. On univariate analysis by Kaplan–Meier curves and log-rank test patients on warfarin had a better survival (at 5, 10 and 15 years—97.3, 87.54% and 87.54%, respectively) compared with no warfarin at 5, 10 and 15 years (91.37%, 88.9% and 66.68%), log rank test NS. On multivariate analysis when sex, the presence of complications, use of ACE inhibitors, use of aldactone, use of digoxin, frusemide and warfarin and age (age at entering the study) were entered into the analysis, the following results were obtained—men had a shorter time to death. Furthermore, when patients taking aldactone and those not taking aldactone were examined it was found that those on aldactone had a higher mortality and shorter time to death.
Conclusion On analysis of the usage of warfarin, those not on it had a shorter time to death; likewise did older patients.

Endomyocardial fibrosis (EMF) is a disease of unknown aetiology found in Kerala, India,[1] Uganda[2 3] and other tropical countries.

Various studies of populations of EMF have been described with poor long-term prognosis. We have observed short survival as well as long survival in EMF, but only a few studies have discussed the medical or surgical treatment of EMF.[4–7]

In this study we re-examined the determinants of survival, the change in the demographic nature (age of disease presentation) and the presence of associated diseases such as diabetes mellitus, systemic hypertension and coronary artery disease that were not reported by us in previous studies.

PATIENTS AND METHODS

The study covered the period March 1997 to 31 March 2009, during which time 160 patients with EMF were registered as inpatients or outpatients. Of these six were lost to follow-up. The remaining 154 patients were followed up and formed the basis for this report. In all patients the functional status, complications and status either dead or alive were determined either by telephone, letter or direct interview. All stable patients were followed up every 6 months. Unstable patients were followed up monthly and medications were started as and when the patients were symptomatic. For example, if the patient had cardiac failure, diuretics were started. If the patient had a left atrial or right atrail thrombus oral anticoagulants, mostly warfarin were started (or if there was any embolic phenomenon). If the patient had atrial fibrillation generally digoxin was used to control the ventricular rate and if the patient had significant mitral regurgitation the patient was started on ACE inhibitors, usually enalapril due to the lower cost. All patients had investigations as and when needed and records were kept. All patients had ECG, radiograms and echocardiograms performed using System 5 and Vived 7 echoDoppler machines, although these data was not used in the analysis.

In all patients the following variables were analysed—age at first presentation, age, sex, type of EMF, New York Heart Association (NYHA) class, type of rhythm (sinus, atrial fibrillation or others), blood urea, haemoglobin, total count, differential count and erythrocyte sedimentation rate, and the presence of complications such as congestive cardiac failure (CCF), cerebrovascular accident (CVA), etc. The total follow-up in months was also analysed. Furthermore, the use of drugs was noted. The presence of associated conditions such as diabetes mellitus, systemic hypertension, etc. were noted. The drugs specially noted were ACE inhibitors, aldactone, digoxin, frusemide, warfarin and metalazone.

Statistical analyses

The discrete variables were analysed by χ^2 test and the continuous variables by a Student's t test. On univariate analysis significance was assumed at the $p<0.05$ level. Survival was analysed by Kaplan–Meier curves by a computer program from RCC TVM. Univariate analysis of survival with and without various variables was analysed by log-rank test. Significance was assumed at the $p<0.05$ level. Significant variables were entered into a Cox proportional hazards multiple regression. Furthermore, our series was compared with three other series of EMF patients when similar data were available.

RESULTS

The mean age of patients in this group (2009) series was older (53.15±14.5 years, n=154). This was

Table 1 Mean age of EMF patients

Author		Mean age, years
Present study	154	53.15±14.5
Balakrishnan *et al*[8]	206	25.3±13.5
Gupta *et al*[1]	145	26.3±14.1 female
Present study vs Balakrishnan *et al*[8] t=19, p<0.001		21.1±11.9 male

EMF, endomyocardial fibrosis.

older than the series of Gupta *et al*[1] and Balakrishnan *et al*[8] (see table 1, present study versus Balakrishnan *et al*[8]—p<0.001). The age of the first presentation in this series appeared to be older than in other series. The minimum age at first symptom was 12 years and the maximum was 76 years. The mean age at first symptom was 40.0±5.3 years (table 1).

The NYHA class at presentation was NYHA class I 35 (23.06%), class II 52 (34.26%) and class III 65 (42.76%). No patient presented in class IV. This series of patients seemed to be less sick than in previous studies. In the study of Gupta *et al*,[1] 49.7% appeared to be in classes 3 and 4. In the series of Balakrishnan *et al*,[8] 39.3% were in classes 3 and 4.

The following complications developed on follow-up: CCF, 71 (46.10%); CVA, eight (5.19%); left ventricular failure, six (3.8%); supraventricular tachycardia, three (1.94%); syncope, one (0.64%); ventricular tachycardia, one (0.64%) and subdural haematoma, one (0.64%).

During follow-up 16 patients died (10.38%) and 138 patients survived. This points to a lower mortality in this series. The mortality of EMF patients seems to have reduced over the years. The survival in this series seems higher than in previous series. The mortality in the current series was 16/154 (10.38%), which was significantly less when compared with Gupta *et al*[1] 66/145 (45.51%) χ^2=48, p<0.001, or even when compared with Balakrishnan *et al*[8] 74/206 (35.92%) χ^2=30, p<0.001.

The common presenting symptoms were: dyspnoea on exertion, 51 (32%); CCF, 39 (25%); palpitation, 32 (20.39%); chest pain, 23 (15.13%); incidental, 5 (3.2%); CVA, two (1.5%); pulmonary oedema, one (0.64%); ascitis, one (0.64%).

Compared with previous studies the pattern of EMF remained almost the same: left ventricular EMF, 49/154; right ventricular EMF, 52/154 and biventricular EMF, 53/154 (table 2) (percentages were 31.18%, 33.76% and 34.41%). This is not much different from the series of Balakrishnan *et al*.[8] In the series of Gupta *et al*[1] the same figures were 45/126 (35.71%), 66/126 (52.38%) and 15/126 (11.9%), respectively.

The higher incidence of biventricular EMF in the series of Balakrishnan *et al*[8] may be because it is a referral hospital (tertiary) and therefore patients with a later stage of the disease may be presenting there.

Table 2 Types of EMF at presentation

Type of EMF	Author	Presence of CHF	%
(A) Type of EMF			
LV EMF	Present study	15/49	30.60%
RV EMF	Present study	35/52	63%
BV EMF	Present study	24/53	47%

Author	LV		RV		BV	
(B) Types of EMF—various series						
Present study	49/154	31.18%	52/154	33.76%	53/154	34.41%
Balakrishnan *et al*[8]	14/206	6.7%	51/206	24.75%	141/206	68.4%
Gupta *et al*[1]	45/126	35.71%	66/126	52.38%	15/126	11.9%

BV, biventricular; CHF, cognitive heart failure; EMF, endomyocardial fibrosis; LV, left ventricular; RV, right ventricular.

The electrocardiograms of the patients were reviewed and the incidence of supraventricular arrhythmias was noted and compared with historical controls. The incidence of atrial fibrillation was 60% in the series of Nair.[9] This was more than in the other series. Later series had almost the same incidence of atrial fibriallation (Balakrishnan *et al*,[8] 33%, present study 44% (68/154) and Gupta *et al*,[1] 32%).

Echocardiographic observations

The details are in table 3. The present study had a higher incidence of myocardial calcification. This probably reflects the older age at presentation of this series 1 versus 2 (χ^2=18, p<0.01).

Compared with the series of Gupta *et al*,[1] the present series had significantly fewer intracardiac thrombi. This may be because of the usage of more oral anticoagulants—1 versus 2 (χ^2=3.9, p<0.05), 2 versus 3 (χ^2=16.22). Compared with the earlier series of D'Arbela *et al*[2] the present series had fewer intracardiac thrombi—2 versus 3 (χ^2=16.22, p<0.01).

Analysis of pericardial effusion—1 versus 2 (χ^2=21, p<0.001), 2 versus 3 (χ^2=50, p<0.001). The present series had less pericardial effusion (5.19% vs 24.13%) compared with the series of Gupta *et al*.[1]

As can be seen, the incidence of embolism is significantly less in the current series compared with the series of Gupta *et al*.[1]

It was believed that this might be due to the increased use of medical treatment in this cohort. These drugs were started empirically as symptomatic treatment, such as anticoagulation in patients with atrial fibrillation or right atrial thrombus, or ACE inhibitors in patients with severe CCF, pedal oedema and ascitis, but this seems to have contributed to the prolonged survival in these patients. Therefore, it was believed that sharing these data would help other patients with EMF. Furthermore, we have personally seen two patients who had massive RA thrombi, which after approximately 5 years of follow-up on later echocardiogram had right atrial dilatation but no thrombus.

Drugs and survival in EMF

The details of drug treatment in this study are given in table 4. Thirteen out of 88 (14.7%) patients on digoxin died as did three out of 66 (4.5%) not on digoxin. This probably reflects that digoxin was started in the more sick patients and was a marker of sicker patients. It is unlikely to have contributed directly to cardiac mortality. The use of aldactone was also associated with poor survival. This was statistically significant. This again shows that drugs were given to the sicker section of patients who then died sooner.

Treatment with ACE inhibitors

Ten out of 69 patients on ACE inhibitors died (14.4%) and six out of 85 (7%) patients not on ACE inhibitors died. There was no effect on survival by simple χ^2.

In the overall population ACE inhibitors could not prolong survival. In fact, those on ACE inhibitors died earlier, but on subgroup analysis, the 5-year survival of left ventricular EMF on ACE inhibitors was 86.67%, 10-year survival was 75.83% and 15-year survival was 75.83%. This is still better than previously reported studies. The similar figures for right ventricular EMF are 81.20%, 73.08% and 73.08%, respectively. For biventricular EMF the values are 96.15% at 5 years, 96.15% at 10 years and 96.15% at 15 years (no finding reached statistical significance). So it is possible that biventricular EMF once symptomatic benefits from ACE inhibitors.

There were 26 patients with biventricular EMF on ACE inhibitors. Of these, one patient died (3.8%). This was not

Table 3 Echocardiographic observations in the present series, other series and the incidence of embolism

(A) Echocardiographic findings in this series			
Pericardial effusions			8 (5.19%)
Myocardial calcification			48 (31.16)
Right atrial thrombus			3 (2%)
Thrombus in the inferior vena cava and hepatic vein and deep vein thrombosis			1 (0.64%)
Series	**Pericardial effusion**	**Intracavitary thrombus**	**Myocardial calcification**
(B) Comparison of ECHO findings in EMF			
Gupta *et al*[1]	35/145 (24.13%)	11/145 (7.58%)	16/145 (11.03%)
Present study	8/154 (5.19%)	4/154 (2.5%)	48/154 (31.16%)
D'Arbela *et al*[2]	10/16 (62.5%)	4/16 (25%)	5/16 (31.25%)
(C) Embolism in EMF			
Present study		5.78%	8/154
D'Arbela *et al*[2]		12.5%	2/16
Balakrishnan *et al*[8]		14.5%	11/206
Gupta *et al*[1]		19.5%	25/145
Gupta *et al*[1] vs present study χ^2=4.5, p<0.05			

Analysis of pericardial effusion—1 versus 2 (χ^2=21, p<0.001) 2 versus 3 (χ^2=50, p<0.001).
Analysis of intracardiac thrombi—2 versus 3 (χ^2=16.22, p<0.01).
EMF, endomyocardial fibrosis.

significantly different from biventricular EMG patients who did not receive ACE inhibitors (2/28, 7.1%, χ^2 NS) (log-rank test NS).

Lifestyle diseases and EMF

As our population is older we are probably the first series to report on lifestyle diseases. Eleven patients had systemic hypertension (7.2%), three patients had non-insulin-dependent diabetes mellitus (1.92%), one patient had insulin-dependent diabetes mellitus (0.64%) and two patients had rheumatic heart disease (1.29%). In 20 patients coronary angiograms were performed (13 men and seven women). None had any significant disease. In the study of Kinare *et al*[10] the incidence of rheumatic heart disease was one per 21 (4.76%).

Table 4 Drugs and survival in EMF

Drug treatment in EMF	Percentage	Survival with With At 5 years %	No No drug %
(A) The following numbers of patients were treated with various drugs			
Warfarin	42/154 (27.27%)	97.62	91.37
ACE inhibitors	69/154 (44.80%)	88.13	97.2
Aldactone	24/154 (15.58%)	79.15	95.72
Diuretics (furosemide)	91/154 (59.09%)	88.62	100
Digoxin	88/154 (57.14%)	89.35	98.48

		Dead	Alive	Log rank
(B) The univariate analysis of survival and drugs is given below				
Warfarin treatment		3	39	NS
	18.75%			
Not on warfarin		13/16	115	
	81.25			
Aldactone (spironolactone antagonist)	Yes	6	16	p<0.0022
	37.5%			
	No	10	122	
	62.5%			
Diuretic	Yes	15	76	p<0.0176
	No	1	62	
Digoxin	Yes	13	75	0.1657
	87.5%			
	No	3	63	Simple χ^2 p<0.05
	12.5%			

	Dead	Alive	Total	Log rank
ACE inhibitors	10 (14.4%)	59	69	NS
No ACE inhibitors	6 (7%)	79	85	
Total	16	138		χ^2 NS

EMF, endomyocardial fibrosis.

Multivariate analysis

On multivariate analysis very interesting findings were observed. When sex, the presence of complications, use of ACE inhibitors, use of aldactone, use of digoxin, frusemide and warfarin and age (age at entering the study) were entered into the analysis the following results were obtained.

Comparing survival in men and women, men had a shorter time to death (p<0.08, RR 3.33, 95% CI 0.87 to 12.79). Furthermore, when patients taking aldactone and those not taking aldactone were examined it was found that those on aldactone had a higher mortality and shorter time to death (p<0.01, RR 0.17, 95% CI 0.05 to 0.59).

On analysis of the usage of warfarin: p<0.02, RR 4.4, 95% CI 1.23 to 17.20. Those not on warfarin had a shorter time to death. Age: older patients had a shorter time to death (p<0.08, RR 1.08, 95% CI 0.27 to 4.24).

DISCUSSION

It appears that EMF is a disease that initially is asymptomatic and once it becomes symptomatic has a rapid downhill course. In biventricular EMF prolonged ACE inhibitor treatment improves survival, but aldactone and digoxin do not improve overall survival.

In biventricular EMF ACE inhibitors probably prevent the progression of mitral regurgitation and help survival, but not significantly in left ventricular EMF even though left ventricular EMF has mitral regurgitation. This is probably because left ventricular EMF patients also have significant pulmonary arterial hypertension. This group of pulmonary arterial hypertension patients does not do well on ACE inhibitors.

As can be observed the number of right ventricular and biventricular EMF patients on ACE inhibitors is almost the same, but 21.4% of the right ventricular EMF patients died compared with 3.8% of patients in the biventricular group. It

has been observed that in left ventricular EMF due to prolonged back pressure to the lungs pulmonary venous hypertension is followed by pulmonary arterial hypertension. In right ventricular EMF although Tricuspid Regurgitation occurs this is a low pressure Tricuspid Regurgitation with no elevation in pulmonary artery pressures.

In biventricular EMF which ventricle would dominate the haemodynamic picture is difficult to predict or generalise. In a previous study of 126 catheterised patients, it was observed by Gupta *et al*[1] that the mean pulmonary artery pressure in left ventricular EMF was 38.34±18.01 mm Hg, compared with 33.46±12.60 mm Hg in biventricular EMF. In this study the mean pulmonary artery pressures in right ventricular EMF were only 24.1±14.15 mm Hg.

In this series there is no surgical patient. Many of the patients were asymptomatic but once symptomatic they were started on empirical treatment at the wish of the treating physician. As can be seen, there was definitely a trend towards better survival in those who received warfarin. Furthermore, ACE inhibitors given to biventricular EMF patients definitely appeared to promote longer survive (15 years survival with warfarin—87% vs 66.6% without warfarin).

This present series is older than the previous series. In a setting of newer drugs that have been proved to prolong survival such as ACE inhibitors and aldactone (spironolactone antagonist) the long-term prospects of EMF have improved. The general Kerala population also shows the same demographic trend, with the average life expectancy being 70 years. In this population the age of the average EMF patient was also increasing, but new cases were being diagnosed. This population had more lifestyle diseases such as hypertension or diabetes mellitus. However, reports from the neighbouring centre have not reported the association of lifestyle diseases.

In recent years there has been a refinement in the type of echoDoppler machines available. Therefore, this might have been the reason for the visualisation of more calcified myocardiums in recent years.

Other authors have commented on the older age at presentation of EMF. Tharakan and Bohora[11] studied EMF patients presenting to a tertiary referral centre. In the period of 1991–2001 the average age of the patients was 33 years compared with the previous study of Gupta *et al*[1] from the same institute. At the same time they had not mentioned the incidence of coincident systemic hypertension. They also mentioned the referral for coronary artery disease. They have summarised the medical treatment of EMF and commented on the improved survival compared with older series (mortality <10%).

Medical treatment although empirical has historically at least improved survival. The patient numbers of new cases are not sufficient to conduct a ramdomised trial. Furthermore, the ethics committee may not sanction withholding medications from sick EMF patients.

An interstitial cellularity has been noticed in EMF. It is fanciful to postulate that this was reduced by ACE inhibitors in some of our patients and that the fewer number of deaths in the biventricular EMF group was due to this.

It is also possible that the haemodynamics of biventricular EMF protect the patient from early death. The left ventricular involvement in isolated left ventricular EMF causes the development of pulmonary hypertension. In all diseases the presence of pulmonary hypertension is an adverse prognostic factor. Furthermore, in right ventricular EMF the elevated right ventricular pressures and poor right ventricular function caused death similar to what occurs in Ebstein's anomaly; the right ventricle just fails to pump blood to the lungs. So in both right ventricular and left ventricular EMF late administration of either aldactone or ACE inhibitors did not help survival.

This is a small beginning in the medical treatment of a puzzling disorder.

Competing interests None.

Ethics approval The study received ethics approval from the institutional ethics committee of the Medical College Hospital, Trivandrum, India.

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