Current perspective on endomyocardial fibrosis

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Endomyocardial fibrosis (EMF) is an obliterative cardiomyopathy of uncertain etiology, with fibrotic deposits on the endocardial surface of the apices and inflow of either or both ventricles. The clinical presentation depends largely on the extent of diastolic ventricular filling abnormality and atrio-ventricular valve incompetence, subsequent to involvement of chordo-papillary mechanism by the fibrotic process. Its prevalence is typically seen in the tropical regions and clinical diagnosis is facilitated by the availability of 2D echo Doppler evaluation. Over the past three decades, there has been a significant down trend in both the prevalence and severity in the presentation of EMF. It is postulated that the less severely involved cases are presenting later in the course of natural history of the disease, as evidenced by the higher age group and the less severe clinical symptomatology of patients. Surgical intervention is limited to severely symptomatic patients, as the fibrotic process rarely progresses over time, though the resultant hemodynamic alteration can progress over time, resulting in clinical deterioration.

Keywords: Apices and inflow, current perspective, endomyocardial fibrosis, ventricles.

Introduction

ENDOMYOCARDIAL fibrosis (EMF) is an obliterative cardiomyopathy characterized by fibrotic thickening and obliteration of the right (RVEMF), left (LVEMF) or both ventricles (BVEMF) with a predilection to selectively involve the ventricular apices and inflow region and sparing the outflow tract. The disease process is limited to the endocardium, and where the fibrotic process involves the endocardium extensively, it results in decreased diastolic chamber compliance, impeding ventricular diastolic filling. When the fibrotic process involves the papillary muscles and the sub-valvular mechanism, valve immobility results in atrio-ventricular (AV) valve incompetence. The fibrotic process does not involve the valve leaflets, the atria, or the great vessels and extra cardiac involvement is not known.

EMF was originally described by Bedford and Konstam[1] in 1946 in African soldiers, and by Davies[2] in 1948 in Uganda. The disease is widely prevalent in Brazil, South America; Uganda, Nigeria and Ivory Coast, Africa and in southern India, especially Kerala[3–8]. It is noteworthy that all these regions fall in the tropical belt. The clinical data from Kerala had RVEMF as the commonest presentation[3–9]. Several other regions have also reported EMF in smaller numbers[10–13]. The autopsy-proven cases had similar incidence of RV, LV and biventricular involvement[9–11]. With 2D echo and angiographic studies, BVEMF and LVEMF are being more frequently recognized; so also are milder forms of RVEMF.

Controversies in aetio-pathogenesis of EMF

The morphological features of EMF have been well characterized by several elegant pathological studies from autopsy specimens[10–12,14]. The fibrous tissue is rich in collagen and the separation of this layer from the underlying myocardium is indistinguishable with fibrous tracts extending into the myocardium. This fibrous tissue lacks cellular infiltrates. It leads to effacement of the trabeculae of the ventricles imparting a smooth, glistening appearance. Grossly, the RV appears shrunken in size from the exterior, but the LV morphology is not altered when seen from the exterior.

The etiology of EMF is an enigma and several hypotheses have been proposed, but none of them has been validated[15,16]. Chronic beri beri[17], loa-loa infection[18], toxoplasma gondi infection[19], filariasis-induced occlusion of cardiac lymphatics[20], anaemia and helminthic infection[21], hypersensitivity to streptococcal infections and rheumatic heart disease association[22] have been postulated, but not convincingly validated. As has been seen in carcinoid heart disease, which produces endocardial thickening with high levels of serotonin, the possibility of excessive consumption of plantains with high serotonin content causing EMF was also postulated[23–25]. Vitamin D-induced calcinosis triggering a fibroplastic response in the heart, with excessive collagen production, in those who may derive an overdose of vitamin D through roots of cassava, has also been postulated as a pathogenic mechanism underlying EMF in the tropics[26]. EMF as a cardiac manifestation of eosinophilia and EMF being a final stage where hyper-eosinophilia has been muted,

were also suggested[27–30], but the manifestations of EMF could not be explained fully[19] as no deposition of eosinophil proteins on cardiac tissue was ever reported. A geochemical hypothesis of EMF was considered, with the levels of cerium and thorium shown to be significantly higher in endocardial samples[31–33]. Cerium in the presence of magnesium deficiency, in experimental studies on rats, has been shown to enhance collagen production and produce sub-endocardial fibrosis[34–39]. However, in spite of so many postulates, none of them, has been accepted as the sole cause of the disease and a combination of more than one etiology, genetic predilection and otherwise undiscovered agent as a cause is still open for research.

Changing clinical presentation

The extent of obliterative endocardial involvement and AV valve incompetence affecting either or both ventricles will determine the clinical symptomatology.

A comparative analysis of 295 cases[40] seen from 1976 to 1990 and 123 cases seen from 1991 to 2001 at Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Thiruvananthapuram revealed certain important demographic variations. The average age of the newly diagnosed cases in 1991–2001 was 33 years, compared to 25 years in the 1976–90 series. Only 3% of the patients were below 10 years and 12% between 11 and 20 years, while 28% of the patients were below 15 years in the 1976–90 series. The number of newly diagnosed cases decreased from 20 per year in 1976–90 to 10 cases per year in 1991–2001.

To further clarify this issue, we analysed the newly diagnosed cases from 2001 to 2007 at SCTIMST. There were 54 newly diagnosed cases of EMF during this period (7–8 new cases every year). Majority of these were above 30 years of age and only 23% were below 30 years (6% were below 20 years and none below 10 years). There were two patients above the age of 60 years. Proportion of patients with RVEMF, LVEMF or BVEMF was not significantly different. There were two deaths (4% mortality during average follow-up of 36 months) and both of them presented as end-stage heart failure. The remaining patients have been clinically stable over an average follow up of 36 months. Newly diagnosed cases of EMF were older and less symptomatic. In a substantial number of patients, EMF was diagnosed incidentally when patients presented with nonspecific symptoms and were detected to have abnormal ECG or echocardiographic features.

The reason for the demographic variation is likely to be due to an absolute decrease in the incidence of the disease as evidenced by marked reduction in the number of newly diagnosed cases. The higher age at presentation compared to the 1980 data can be explained by clinical presentation of milder forms of the disease later in the course of natural history of EMF, so that patients presented in fourth and fifth decades of life.

The clinical features at presentation varies depending on the extent of involvement and the ventricle involved. Isolated RVEMF, with obliterative changes and no tricuspid incompetence, is mildly symptomatic, and the only abnormal clinical finding may be a giant or prominent 'a' wave in the jugular venous pulse (JVP). At the other extreme, patients with isolated RVEMF with severe tricuspid regurgitation (TR) present with features of chronic right heart failure with markedly elevated JVP and expansile large 'v' waves, pulsatile liver, hepatomegaly, ascites, oedema, cyanosis, cachexia and malnutrition. They may also have pericardial effusion, marked cardiomegaly, RV third heart sound, and inconspicuous systolic murmur of TR. The severity of TR rather than the presence of RV diastolic dysfunction is the more important determining factor for the clinical outcome of patients with RVEMF. An occasional patient with severe RVEMF can have cyanosis due to right-to-left atrial shunting through a patent and stretched fossa ovalis defect. Isolated LVEMF, in the absence of AV valve incompetence, is often minimally symptomatic. Hemodynamic study may reveal a prominent 'a' wave in the PA wedge pressure, and LV end diastolic pressure may be elevated. We have a few patients who have presented with severe pulmonary venous and pulmonary arterial hypertension entirely due to LV diastolic compliance failure, in the absence of mitral incompetence, but this is distinctly rare. Features of pulmonary arterial hypertension will depend on the presence of pulmonary venous hypertension resulting from mitral incompetence as well as diastolic LV dysfunction. Biventricular involvement is seen in at least 50% of patients and clinical presentation depends upon the severity of mitral incompetence, tricuspid incompetence and diastolic dysfunction due to obliterative changes in both the ventricles. These patients are hemodynamically more compromised and deteriorate rapidly, and have a poor prognosis.

Patients may present with atrial arrhythmias, more commonly atrial fibrillation (AF), or embolic stroke. Atrial thrombus, commonly seen in the right atrium, is due to stagnating blood in the large right atrium, especially in the presence of AF. Pericardial effusion is seen in a significant number of patients with RVEMF, and correlates with the severity of the systemic venous congestion. However, it generally does not result in cardiac tamponade and rarely requires pericardiocentesis.

Not uncommonly EMF is detected incidentally in patients with rheumatic or other heart diseases. When we analysed 54 patients diagnosed as EMF from 2001 to 2007, 30% of them were referred for symptoms of atypical chest pain and palpitation with an abnormal ECG (ST-T changes) or an abnormal 2D echo finding, and were primarily referred to exclude coronary artery disease or apical hypertrophic cardiomyopathy. One of the patients with RVEMF had RV outflow (RVOF) obstruction and had successful RV endocardectomy and RVOF recon-

struction, without the need for tricuspid valve surgery. Another patient had symptomatic RVOF ventricular tachycardia (VT), which was treated by radio frequency ablation. RVOF VT was presumed not to be related to the underlying RVEMF.

Natural history

Patients with EMF, generally present in the late fibrotic stage of the illness. Whether an acute inflammatory or thrombotic stage of the disease exists and the fibrotic stage is a sequel, is open to speculation. As we have not seen a patient through the active or acute inflammatory or thrombotic stage going onto the fibrotic stage (end stage), we can only discuss the natural history of the fibrotic stage when the patient presents to the physician. The functional class at presentation usually determines the short-term outcome. Patients in New York Heart Association (NYHA) classes III and IV with severe systemic venous congestion, ascites and oedema or pulmonary venous congestion, pulmonary venous hypertension with pulmonary oedema or pulmonary arterial hypertension, fare poorly over short term and have mortality as high as 30% at 1 year and 50% at 2 years. However, asymptomatic patients or mildly symptomatic patients remain stable, without progression of symptoms for several years. It has not been possible to demonstrate progression of the obliterative changes over a short term, and hence generally symptomatic worsening is due to valvular incompetence, which is often progressive (valve incompetence begets valve incompetence).

Natural history study reported from SCTIMST, of 206 patients seen from 1975 to 1991 revealed a survival of 82, 53 and 37% at 1, 5 and 10 years respectively. Some of the factors influencing mortality were LV involvement with LV failure, pulmonary arterial hypertension, right atrial mean pressure more than 20 mm Hg, and NYHA class III and IV. This study excluded 89 patients who were subjected to surgery during the same period. Of the 206 patients, 179 had angiography and hemodynamic study, 20 were diagnosed by echocardiography and seven were diagnosed at autopsy. Fifty-one patients had RVEMF, 14 had LVEMF and 141 had BVEMF. Twenty-eight per cent of patients were below the age of 15 years.

During this period, 89 patients had surgery (mean age 25 years), of which 60% were females. Ninety-five per cent patients were in NYHA class III and IV, with an operative mortality of 29% and late mortality of 12%. Among the 43 patients available for follow-up, 50% were in class I and 40% in class II. Surgical intervention included MV replacement and/or TV replacement along with LV and/or RV endocardiectomy depending on ventricular involvement and AV valve incompetence. Iso-

lated LV endocardiectomy or bi-directional Glenn (BDG) shunt was not done during this period.

Progression of EMF

Though patients presenting with EMF often have clinical and hemodynamic deterioration during follow-up, progression of fibrotic cavity obliteration has not been documented over time. Few patients who had repeat angiographic studies, did not suggest progression of the cavity obliteration. It is likely that the patient presents in the chronic fibrotic stage of the disease due to hemodynamic derangement, both diastolic dysfunction and AV valve incompetence, leading to clinical deterioration. Also, follow-up angiographic studies few years after surgery for EMF did not show progression of the fibrotic cavity obliteration nor new fibrotic changes in the non-affected ventricle.

Treatment

Medical treatment options are decongestive therapy, antiarrhythmic treatment for AF and oral anticoagulation for AF and pulmonary or systemic embolism. Ninety per cent of the patients were receiving digoxin and diuretics on follow-up. A handful of patients with RVEMF had repeated hospitalizations for abdominal paracentesis, to relieve tense ascites. Pericardiocentesis for cardiac tamponade or large effusion was seldom needed, despite large pericardial effusions being common in severe RVEMF.

In 1971, Dubost et al.[41] had introduced surgical treatment of EMF by endocardial decoritication and AV valve replacement. A plane of cleavage can be easily developed and all of the yellow–white thickened endocardium removed. Surgical options are LV endocardiectomy, AV valve repair or replacement and exclusion of fibrotic RV in a pure RVEMF by a BDG connection[42]. Prosthetic valve can be mechanical or bio-prosthetic. Though several patients had mitral and tricuspid valve replacement during 1980–91 for BVEMF, this is now rarely offered because of the poor long-term outcome for mechanical prosthetic valves, especially placed in the tricuspid position. Patients with BVEMF, with mild RV involvement are offered MV replacement and LV endocardiectomy. However, BDG shunt is offered only to patients with isolated RVEMF, with no pulmonary hypertension, mitral incompetence or diastolic dysfunction. Any grade of LVEMF is considered a contraindication for BDG shunt. Surgical treatment has always been contemplated for NYHA class III and IV EMF patients at our institute in the past. Presently a careful 2D echo Doppler examination can detect surgical candidates of EMF with a fair amount of certainty. However, we continue to subject these patients to hemodynamic and angiographic study when surgical

intervention is planned, either BDG surgery for isolated RVEMF or MV replacement for isolated LVEMF.

The rationale for surgery has been the following.

- Poor prognosis in the long term with medical treatment in class III and IV patients (surgery offers 5 year survival of 65–75%; 10 year survival[10] of 60–70% and actuarial 17 year survival[14] of 55%).
- Hemodynamic derangement is due to restriction and AV valve incompetence (correctable by endocardiectomy and AV valve repair or replacement).
- Rarity of myocardial involvement by fibrosis.
- Rarity of recurrence of same fibrotic process after endocardiectomy.

Analysis of 89 operated cases in the eighties in our institute[14] showed 1 month mortality as high as 30% and an additional 12% late mortality. Commonest cause of death was low cardiac output. Late complications were mostly related to prosthetic valve dysfunction, essentially due to problems of prosthesis in tricuspid position and poor compliance to optimal anticoagulation. There is a high incidence of thrombosis of the mechanical valve. Only seven patients (6%) were offered surgical procedures among our last 121 patients (1991–2000) which included LV endocardiectomy and MVR in three, LV endocardiectomy alone in one, biventricular endocardiectomy in one, BDG shunt with partial endocardiectomy and RVOT patch with De Vega annuloplasty in one, and BDG alone in one. All patients had symptomatically improved at the time of the last follow-up.

De Oliveria et al.[43] had suggested that resection of endocardial fibrous tissue early in the clinical course can be done with preservation of AV valves for better results and mortality of less than 5%. Mitral valve repair alone by freeing leaflets and papillary muscle from the fibrous tissue and annuloplasty has been contemplated in LVEMF, with endocardiectomy limited to the area of papillary muscles[44].

Surgical treatment for advanced RVEMF can be best summarized by the following surgical operation notes from our institute: A 40-yr-old female patient with isolated severe RVEMF, severe CHF and atrial fibrillation, was operated on 26 February 2007 with DeVega's TV annuloplasty, RA reduction surgery, RV endocardiectomy to restore papillary muscle and chordal function, and BDG shunt. At surgery, RA was large and papery thin, RV shrunken with RV apex to annular distance reduced to 4 cm, moderate pericardial effusion and dilated SVC and IVC. TV leaflets were normal, but all the papillary muscles were embedded in thick fibrous tissue resulting in non-coapting leaflets and gross TV incompetence. RVOF was dilated, but the RV inflow was completely replaced by fibrous tissue. RV endocardiectomy was done to release the papillary muscles and chordae. TV annuloplasty, RA reduction surgery and BDG

shunt was done. The patient regained sinus rhythm, remained in NYHA class I and was discharged home on the 10th post-operative day.

Is there a time decline?

There is both a decrease in incidence as well as decrease in severity of symptoms at presentation of patients with EMF over the past three decades.

In 1980, Sapru et al.[9] reported clinical profile of 64 consecutive patients with EMF seen during 1975–80 and diagnosed by hemodynamic and angiographic study.

Seventy per cent of the patients were below 30 years of age (11% below 10 years, 40% between 11 and 20 years) and 64% were in NYHA classes II and III, and 34% in NYHA class IV.

In contrast, among the 54 patients of EMF seen between 2001 and 2007, only two patients were in class IV and 80% were in NYHA class I or class II. There were no patients below 10 years of age, 6% were below 20 years and 17% between 20 and 30 years (23% below 30 years of age). There were two deaths (4% mortality), both of them presented as end-stage heart failure. The rest of them have been clinically stable over an average follow-up of 36 months. We continue to get a steady number of newly diagnosed cases of EMF, though they are older and less symptomatic.

The demographic studies reveal a trend towards higher age at presentation, with a marked decrease in patients presenting below 20 years of age, a relatively benign course in over 80–90% of patients with stable symptoms over several years of follow-up, and a mortality of 4% during an average follow-up period of 36 months. Mortality was limited to patients presenting with end-stage heart failure. All these findings may be explained by the reduced incidence of the disease, a less severe form of the disease and later presentation of the milder forms of the disease. Today we do not see the adolescent with cachexia, elevated JVP, severe ascites, oedema, and stunted growth with underlying EMF, a common clinical scenario two decades ago.

However, data from a tertiary-care centre taken in isolation may not reflect the true incidence and prevalence of the disease, as only the more symptomatic patients get preferentially referred.

Some important observations need mention:

1. The age group of EMF at presentation has dramatically changed, from a disease predominantly of the young in their teens during 1976–90, to disease presenting in the fourth to sixth decade of life presently.
2. There are no cases in the age group less than 10 years in the past seven years, and only 8% are below 20 years of age.

3. The number of patients with EMF, presenting in NYHA classes III and IV, has decreased and prognosis has improved, with a mortality of less than 10% over 3 year follow-up.
4. A significant percentage of patients are referred for abnormal ECG or echocardiographic abnormalities, and on further evaluation, diagnosed as EMF, and these patients are often only mildly symptomatic.

It may be inferred that new cases of EMF are decreasing and patients with milder form of the disease are presenting later in the course of natural history of the disease, accounting for the later age at presentation as well as mild symptoms at presentation.

Conclusion

Endomyocardial fibrosis continues to be reported though in a much older population and is often mildly symptomatic or asymptomatic and carries a good prognosis, especially in assymptomatic patients. Progression of the fibrotic process, surprisingly, has not been consistently documented, and hence it appears to be the burnt-out stage of the disease. In the fifth and sixth decade, patients are often evaluated for chest pain and ECG and echocardiographic evaluation leads to the diagnosis of EMF, though we have two patients with EMF aged above 50 years with associated coronary artery disease.

EMF remains an enigma, but cannot be written-off as part of history as cases will continue to be reported from other parts of the country, though the number of severely symptomatic patients is on the decline in Kerala.

Worldwide prevalence of this predominantly tropical disease also needs to be closely monitored and with population movement across continents, an occasional case of EMF may be found anywhere in the world. As etiology of the disease remains speculative, eradication by preventive measures is presently not feasible.

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