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Endomyocardial Fibrosis: an Update After 70 Years

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Abstract

Purpose of Review This review aims at highlighting the need to better understand the pathogenesis and natural history of endomyocardial fibrosis when set against its changing endemicity and disease burden, improvements in diagnosis, and new options for clinical management.

Recent Findings Progress in imaging diagnostic techniques and availability of new targets for drug and surgical treatment of heart failure are contributing to earlier diagnosis and may lead to improvement in patient survival.

Summary Endomyocardial fibrosis was first described in Uganda by Davies more than 70 years ago (1948). Despite its poor prognosis, the etiology of this neglected tropical restrictive cardiomyopathy still remains enigmatic nowadays. Our review reflects on the journey of scientific discovery and construction of the current guiding concepts on this mysterious and fascinating condition, bringing to light the contemporary knowledge acquired over these years. Here we describe novel tools for diagnosis, give an overview of the improvement in clinical management, and finally, suggest research themes that can help improve patient outcomes focusing (whenever possible) on novel players coming into action.

Keywords Endomyocardial fibrosis · Inflammation · Neglected cardiovascular disease

Introduction

Endomyocardial fibrosis (EMF) is the most common restrictive cardiomyopathy worldwide, yet its geographical clustering and strong relationship with poverty has bottlenecked much needed progress. Even today, there is a gap in our understanding of the etiology, pathogenesis, and natural history of this devastating disease condition. EMF is an important cause of cardiomyopathy in the young. Although it has been described in several parts of the world, more than half of the EMF cases are reported in sub-Saharan African countries [1–5], and less commonly in South Asia and Latin America [1]. Given that access to quality medical services is typically restricted, especially in sub-Saharan Africa, the global burden of EMF is much under-reported and many patients unfortunately remain oblivious to this condition.

Indeed, EMF is one of the most neglected cardiovascular diseases considering that it causes severe disability and is responsible for a considerable proportion of premature deaths in endemic countries. Since its etiopathogenesis remains

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unknown and no biomarkers for early diagnosis are available, patients are usually diagnosed by specialists in tertiary or referral hospitals, only when showing overt signs of advanced disease and severe structural and hemodynamic complications. At these advanced stages, treatment is often ineffective and mainly directed towards control of complications such as chronic heart failure, arrhythmia, thromboembolism, and pulmonary hypertension. The case-fatality rate is high with death occurring suddenly, or after several years of chronic and progressive heart failure.

Upon post-mortem samples, Arthur Williams in 1938 reported for the first time large endocardial patches of fibrosis in two hearts in Uganda [6]; some years later, the same findings were described by Bedford, 1946 [7], but only in 1948 Jack Davies coined EMF as a distinct pathological entity by correlating the pathology features with clinical signs [8], thus allowing the diagnosis of EMF in life. Even with modern advances in non-invasive imagery, the access to these technologies in endemic areas has been vastly restricted, and there has been confusion in precise clinical staging and classic EMF descriptions.

Ever-changing designations used to describe EMF, namely tropical endomyocardial disease, endocarditis parietalis fibroplastica, endocardial fibrosis, constrictive endocarditis, endocardial fibroelastosis, and Davies disease, did not facilitate identification of patients and the scientific progress. The expression "Heart of Africa" was also used to designate this entity. However, the term "*Endomyocardial Fibrosis*" is the most appropriate terminology which best describes the cardiac abnormalities found and has been adopted worldwide. In 1965, the World Health Organization classified EMF as a restrictive cardiomyopathy of unclear etiology, but signposted certain infectious diseases or environmental risk factors [9].

Trends in Epidemiology

After its initial description in Uganda [8], EMF cases were reported in Kenya [10], Brazil [11], India [12], Venezuela [13], South Africa [14], and Zambia [15]. Case series from different parts of the world followed in Uganda, India, Mozambique, Ivory Coast, Nigeria [16], Brazil [17], and Venezuela [18] mainly describing its unique features. However, a complete picture of its autochthonous occurrence is not clearly defined as a clinico-epidemiological study and has yet to be undertaken in the endemic communities themselves. Note that nearly all of these are in underserved areas with limited access to adequate diagnostic tools alongside low capacity for health-related research. Reports of sporadic cases in Europe are increasing mainly related to migration and have been found in Spain [19], China [20], Turkey [21], UK [22], Switzerland [23], and Italy [24].

Though reportedly declining in India [25], EMF reports have been increasing in Africa due to availability of echocardiography, namely from Tanzania [26], Egypt [27], Congo [28], South Africa [29], Ethiopia [30], Zimbabwe [31], Senegal [32], Sudan [33], Ghana [34, 35], and Malawi [36, 37]. In this continent, EMF is an important cause of admission for acute heart failure [38] and has been consistently found in hospital series reporting on patients with heart failure, with proportions varying from 0.5% in all ages in Sudan [39] to as high as 6.4% in Nigerian children [40].

For reasons that are not yet understood but are no doubt important epidemiological clues, in most countries, there is a clustering of EMF cases in restricted geographical areas. In Mozambique, 2/3 of all cases assisted in a referral hospital were originally from coastal districts and their surroundings; these remote areas had an estimated cumulative incidence sevenfold higher (at 6.9/100,000) than others that were more accessible to health facilities and from where more patients would be expected [41]. More recently, Gupta and colleagues compared the incidence of EMF and its complications in two areas with major socioeconomic differences in India [42••]. More biventricular disease and atrial fibrillation was found in Trivandrum than those in Alleppey with 64.9% vs 14.3%; $p < 0.0.001$ and 44.2% vs 16.3%; $p < 0.001$, respectively, which might explain the lower 6-year survival rate in the former population (61% in the Trivandrum population vs 91.5% in patients from Alleppey). Nutritional factors were considered to play a role in this difference since Alleppey patients had higher exposure to fish, or similar ingested items, compared with the Trivandrum population, suggesting that the former could be more protected against magnesium deficiency and excessive cerium absorption, thus having a lower risk of EMF [42••].

The only community-based study available was performed in Mozambique [43]. It was found that 1 in each 5 people had EMF (prevalence of 19.8%), which is a clear indication for the need of future community-led studies to quantify this incipient disease burden. An important outcome of this large-scale community research was the improvement in echocardiographic assessment of EMF patients at early stages, as well as the possibility of standardized characterization of structural and hemodynamic abnormalities, contributing to a comprehensive classification and tailored management.

Exploring Etiology, Pathogenesis, and Natural History

Various potential etiological factors or triggers have been suggested, which may act in isolation or in combination [44–67]. Although a unified hypothesis for the etiology of EMF does not exist, it has been suggested that factors such as poverty, dietary, environmental, and infections may combine in a

susceptible individual to give rise to an inflammatory process that leads to endomyocardial damage and scar formation (Table 1). However, none of the hypotheses studied—including geochemical actors, infectious agents, dietary factors, hypersensitivity, autoimmunity, hypereosinophilia, genetic susceptibility, and ethnicity—can explain independently the occurrence of EMF worldwide. This suggests the need for combination of several independent causal pathways, some of which may be dominant in certain areas yet are only partial or even inconsequential in others. Little progress has been made in EMF etiopathogenesis in recent years, but some hints have implicated the role of eosinophils, chronic inflammation, infections, and genetic predisposition.

Seminal studies exploring the immune response in EMF have shown that severe blood eosinophilia, as mainly triggered by infection, is a common finding in EMF patients and it seems to be a major determinant of clinical signs. Eosinophilia from 10 to 30% of the total words white blood count counts, presenting sometimes over several months or even years, is a frequent finding in EMF and its magnitude seems to be inversely related to the duration of the illness [44]. On the other hand, cardiovascular disease is a leading cause of morbidity and mortality in hypereosinophilic syndromes [67]. The cross talk between eosinophils, mast cells, and cardiac fibroblasts is probably a key pathogenic factor in defective cardiac remodeling [1], but this has only been sparsely investigated in the context of EMF mostly because clinical settings and research infrastructures are remote from endemic rural regions. In 1983, data from UK (11 patients), India (47 patients), and Brazil (8 patients) were compared to assess features of endomyocardial disease in temperate and tropical regions, thus contributing to define the differential diagnosis between the hypereosinophilic syndrome and EMF [68]. Half of the UK patients were in early necrotic stage of the disease and all had biventricular involvement, while patients from tropical countries did not present in early necrotic stage, had isolated left or right disease, were younger, and originated from poor, malnourished communities with heavy parasite loads, especially filariasis in India.

It was suggested that the nature of the underlying disease and the rate of progression of endomyocardial lesions were

Table 1 Potential etiological factors or triggers and their proposed mechanism (with authors and year of study)

Etiological hypothesis	Author, year of Publication	Proposed mechanism
Hypereosinophilia due to parasitic infections Helminths, schistosomiasis, microfilaria loa-loa, or filariasis	Andy 1998; Rashwan et al. 1995; Beck and Schrire 1972; Ive 1967; Barbosa et al. 1998 Victor et al. 1996 Berenguer et al. 2003 [44–47, 50–52]	Acute eosinophilic endocardial injury leading to hypereosinophilia and endocardial lesion similar to that found in hypereosinophilic syndrome.
Other infectious agents [64] Plasmodium species Schistosoma Microfilaria Helminths Toxoplasma Coxsackie B virus	Beck and Schrire 1972; Brockington et al. 1967; Shaper et al. 1968; Ludlam and Somers 1966; Eling et al. 1988; Ijaola and Falase 1990; Kurtzhals et al. 1998; Shanks et al. 1992 [46, 48, 49, 53–56]	No mechanism has been consistently associated with EMF.
Autoimmunity Anti-heart antibodies (IgG, IgM, and IgA)	Vijayaraghavan and Sadanandan 1984; Shaper et al. 1968; Van der Geld et al. 1966; Jayesimi et al. 1984; Connor et al. 1968; Kartha et al. 1984; Davies 1990; [25, 49, 57, 58, 60–62]	Pathological studies failed to confirm the existence of large numbers of immunologically competent cells at the endomyocardial junction and antiheart antibodies (IgG, IgM and IgA).
Geochemical factors Drying staple foods Vitamin D–induced calcinosis Deficiency of magnesium High levels of cerium	Valiathan et al. 1993 [63]	Drying food in the sun would increase the levels of vitamin D in plants, leading to increase levels of calcium in people eating these plants. Vitamin D–induced calcinosis would cause cellular hyperplasia and excessive production of collagen and elastin in the endomyocardium. Deficiency of magnesium promotes the absorption of cerium and enhances its toxicity forming the basis for the initial injury of the heart.
Dietary factors Vitamin E deficiency Cassava roots dried in sunlight Plantains and bananas with high levels of serotonin	Jayesimi et al. 1978; Ferrans 1985; Ball 1954 [58, 65, 66]	Vitamin E deficiency produces cardiac enlargement and fibrosis in malnourished animals due to auto-oxidation of unsaturated lipids with deposition of ceroid bodies in the tissues, leading to endocardial fibrosis when the heart is affected. Roots of Cassava rich in vitamin D through sunlight. Plantains and bananas containing high levels of serotonin (5-hydroxytryptamine) because excess of serotonin in the blood stream produces cardiac lesion.

major determinants of the clinical features, with eosinophil granule toxins producing a rapidly progressive disease in temperate climate's hypereosinophilic syndrome, whereas slower progression would be seen in the tropical climates as these patients would have less marked eosinophilia in response to parasitic infections [69]. Blood hypereosinophilia was a common finding in people from endemic areas of EMF in Nigeria [69, 70] and is also commonly found in endemic areas in Mozambique, probably related to multiple parasitic infestations such as gastrointestinal helminthiasis, bladder and hepatosplenic schistosomiasis, and lymphatic filariasis, which are highly prevalent [71–73]. Indeed, early studies failed to show an increased prevalence of these infections in EMF patients when compared with the general population [60, 74–76].

Further research is needed to clarify the role of eosinophils and their vast arsenal of granule products (e.g., serotonin-mediating vasoconstriction and platelet aggregation) and inflammatory cytokines (e.g., TGF-β, fibroblast growth factor) in EMF pathophysiology. Likewise, investigation of the participation of (i) the eotaxin (chemokine) eosinophilic migration drive; (ii) cytokines that promote eosinophil proliferation, survival, and priming (e.g., IL-5); and (iii) the direct interaction of eosinophils with immune and other cells (e.g., mast cells, macrophages, fibroblasts) in the proximity is also needed, since these players may represent excellent putative biomarkers and/or therapeutic targets for altering the natural history of EMF. Despite the high prevalence of blood hypereosinophilia in EMF, tissue eosinophilia is rare in the established disease. Interestingly, the natural history of EMF seems to include recurrent flare-ups of inflammation [1] and the possibility of hypereosinophilia being an independent risk factor for EMF not attributable to parasitism has been postulated [77].

Owing to much altered hepato-portal-cardio circulation, associations between late-stage hepatosplenic schistosomiasis and EMF have been suggested but not proven. In addition, several case reports of EMF association with intestinal [78] and urinary [35, 79] schistosomiasis have been published. The biological plausibility for these associations is sound, particularly so since many EMF cases present with hepatosplenic disease, abdominal ascites (without peripheral edema), patient cachexia, alongside other characteristics ascribable to chronic intestinal schistosomiasis. It is also worthy of note that accurate diagnosis of late-stage intestinal schistosomiasis necessitates tissue biopsy for schistosome eggs and or ultrasonography for Symmer's pipestem fibrosis which is topotypical of hepato-splenic schistosomiasis. Both options have been either unavailable or overlooked in the diagnostic triage of EMF cases.

Notably, EMF cases cluster within both families and ethnic groups, suggesting either a role for a genetic factor in host susceptibility or common environmental triggers by share living locations or ongoing activities. The role of human leukocyte antigen (HLA) system was explored on a study in 71 patients with severe EMF and 137 geographically matched unaffected controls from Uganda and Mozambique [80]. EMF patients were more likely than controls to have the HLA-B*58 allele in Mozambique ($p = 0.03$) and the HLA-A*02:02 in Uganda ($p = 0.005$).

Autoimmunity is present in a large subset of patients with established EMF; autoimmune markers may provide adjunct tools for diagnosis and staging of EMF, potentially contributing to improve the management of EMF patients, by identifying those in whom immunosuppression is of potential benefit.

EMF is, therefore, an interstitial and inflammatory disease with typical distribution in the heart. This disease affects all layers of the ventricular and atrial walls, but fibrotic changes, chronic inflammatory infiltrates, and neovascularization are more prominent at sub-endocardium and inner myocardium. Deposition of fibrous tissue in the endomyocardium leads to severe restrictive physiology and atrioventricular valve regurgitation, a combination that is responsible for its very poor prognosis [1].

Progress in Diagnosis and Follow-up: the Missing Inflammation Biomarkers and Fairly Suitable Imaging Techniques

Over the last 70 years, diagnostic imaging for EMF has evolved greatly with the introduction of more affordable technologies and associated instrumentations. Ventricular endocardial fibrosis with organized thrombus is the hallmark of advanced right-sided disease, a situation that poses diagnostic and therapeutic challenges due to risk of thromboembolism associated with cardiac catheterization and complex management issues intra- and post-operatively [81, 82]. Sub-clinical EMF can currently be detected by echocardiography, and a scoring system has been proposed for early detection, based on the severity and distribution of cardiac lesions [43].

Little progress has been made in understanding the triggers of inflammation in EMF and, thus, early-stage diagnostic biomarkers are an unmet clinical need. Patients with recent onset EMF have increased levels of IL-6, a pro-inflammatory cytokine that is also increased in exercise-induced muscle damage [83], endothelial cell activation, and increased fibrinolysis, strongly suggesting that inflammation, endothelial injury, and pro-coagulant changes play an important role in the early stages of this condition [84]. The results suggest that an insult to the endocardium may be involved in the pathogenesis of EMF and that biomarkers could potentially be used for early detection and follow up of patients. It remains to be elucidated whether drugs against IL-6, like tocilizumab that has been approved for rheumatoid arthritis [85], also improves the outcome of EMF, although this strategy may be limited in low-income EMF endemic areas. High eosinophil counts

are usually present in patients with active disease, which can be defined by a state of inflammatory markers, increased thrombotic risk, and sometimes, active infection, such as schistosomiasis, filariasis, or any other unknown trigger. However, no clear definition of such active state and its significance is currently available.

The finding, that features detected by echocardiography are highly concordant with those found during surgical procedures and autopsies [86], reinforces this non-invasive imaging technique as the diagnostic tool of choice for diagnosis and management of EMF in endemic underserved areas of Africa. Therefore, EMF diagnosis and follow-up have been now possible in the majority of patients from endemic areas using this non-invasive diagnostic tool, which has a favorable cost/benefit ratio. Echocardiography confirms the diagnosis of EMF, describes the anatomical distribution of fibrotic lesions, assesses the severity of endocardial thickening, and identifies complications such as thrombus, valve dysfunction, and pulmonary hypertension (Fig. 1). Moreover, echocardiography features correlate well with microscopic abnormalities [86], consisting of fibrotic thickening of the endocardium and variable amount of inflammation, depending on the stage of the disease (Fig. 2). The non-invasive nature of echocardiography and the almost absence of consumable materials are also putative advantages of this method in low-income endemic regions, provided that long-term portable power accumulators are included in the setting.

The usual assumptions made when assessing systolic and diastolic ventricular function are not useful for a considerable number of EMF patients with moderate, severe, and advanced disease. Tissue Doppler imaging has a great potential for research on early stages of EMF, since it could potentially uncover early regional myocardial changes which, in addition to new markers of diastolic dysfunction (like NT-proBNP), would improve the pre-clinical diagnosis of EMF. The proposal of criteria for standardization of the diagnosis and classification of EMF [43] is useful for better understanding of the pathogenesis and pathophysiology and to allow comparison between series in different endemic areas. However, these criteria and scoring system need validation on follow-up studies—which are currently being undertaken—as well as testing in different geographical contexts.

Cardiac magnetic resonance (CMR) and other imaging techniques such as tridimensional ultrasound [87] may be used to add substantial information regarding the region of involvement as well as the various characteristics of the right atrial thrombus. CMR imaging with late gadolinium enhancement demonstrates the primary and secondary structural and functional abnormalities, namely myocardial edema, apical thrombus, and sub-endocardial delayed enhancement in the involved ventricles [88]. It seems ideally suited to diagnose this condition and monitor response to medical and/or surgical therapy [89].

The differential diagnosis of EMF includes rheumatic heart disease, tuberculosis, schistosomiasis, Ebstein malformation, tuberculous peritonitis, tuberculous pericarditis, and hypertrophic cardiomyopathy. While bacterial endocarditis is rare in EMF patients, one case with calcification and bacterial endocarditis has been recently described [90].

Current Management Options

Currently, there is no effective medical therapy for EMF or confident public health intervention to prevent it. Early diagnostic biomarkers are also an unmet clinical need preventing

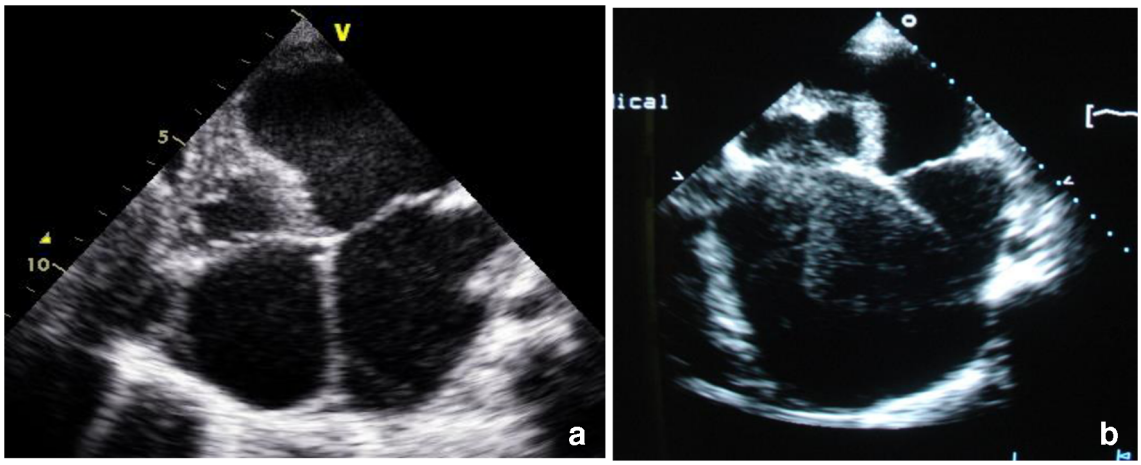

Fig. 1 Echocardiography performed using portable battery-powered devices provides most of the needed information for diagnosis and management of endomyocardial fibrosis. These two images show different stages of right-sided endomyocardial fibrosis from obliteration and mild retraction (**a**) to severe heart distortion caused by compression of left cavities by the tense right ventricle and aneurysmal right atrium, as well as retraction of the right ventricle (**b**). Images of spontaneous contrast can be seen across the tricuspid valve as well as an image suggestive of thrombus in the right atrium

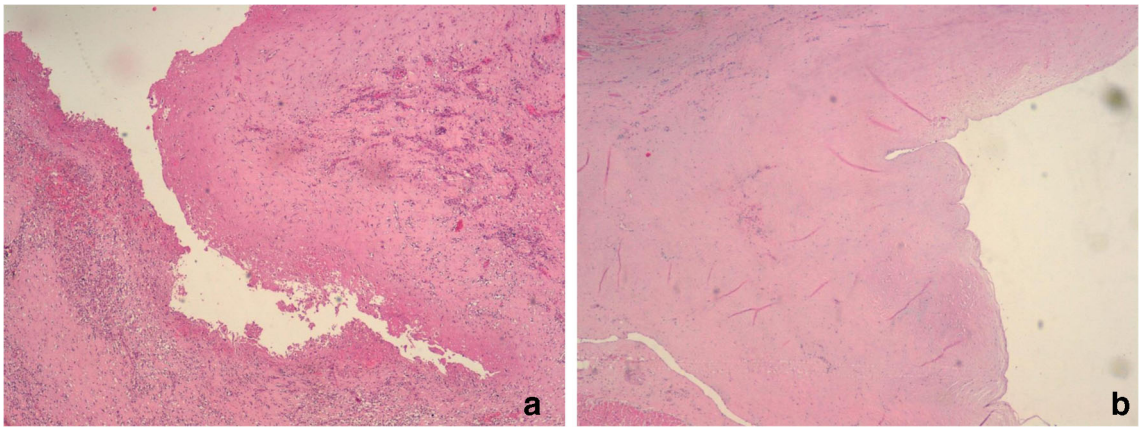

Fig. 2 Marked neovascularization, inflammatory infiltrates, and loss of definition of the endomyocardial transition due to fibrinoid deposition (at the area of thrombus dislodgment) are shown in a specimen from an excisional biopsy from a left ventricle with severe endomyocardial fibrosis in the thrombotic stage with marked peripheral hypereosinophilia (**a**). This specimen is from the right ventricle of a patient who died from severe right endomyocardial fibrosis with chronic heart failure, which shows marked endocardial thickening, hyalinization, and little cellularity, noting the intact endothelial line (**b**)

medical intervention with disease-modifying medications. A subset of patients present markers of inflammation, increased thrombolysis, and autoimmunity and may potentially benefit from the use of anti-inflammatory drugs, immunomodulators, and anticoagulants. The diagnostic and severity score system [43] represents the first attempt at standardization of echocardiographic examination of EMF and offers an essential management-driven tool for selection to surgery, as well as planning of tailored strategies for surgery.

While medical treatment may act initially, surgery is indicated whenever there are signs of a restrictive syndrome or a moderate to severe mitral incompetence; the only definitive contra-indication at the present time is the presence of recurrent ascites with hepatic fibrosis. Surgical treatment improves the prognosis—as demonstrated by the comparative study conducted in Abidjan between 30 operated patients and 31 non-operated patients in 1984 [91]—with isolated left-sided forms being the most favorable. New approaches and innovative-tailored surgical techniques improve early- and medium-term results of surgery, but long-term follow-up is needed to assess the rate of recurrence and survival free of major events.

Medical Therapy

The drugs used for the management of mild-to-moderate EMF cases include diuretics, renin-angiotensin system blockers, digoxin, β-blockers, anticoagulants, and corticosteroids. Intensive medical therapy improves the general status and partially corrects heart failure in most patients, but some die due to refractory heart failure and acute pulmonary thromboembolism. Resistance to medical therapy can be partially explained by the high prevalence of ascites and intestinal wall congestion, which prevents correct absorption of drugs through the gut. However, financial constraints, drug side effects, and/or cultural beliefs also play a role in determining lack of effectiveness of drug therapy. The availability of new targets for drug treatment of heart failure along with early diagnostic procedures has probably contributed to the improvement in the mean survival of patients with EMF [42••], which was 2 years after the onset of symptoms in the late seventies [92].

Interventions

Effusions in EMF are usually resistant to diuretic treatment and need periodical drainage, often as an emergency procedure (pericardiocentesis, paracentesis, or thoracocentesis). The results of the Spitz-Holter shunt—draining the ascites into the femoral vein—were disastrous and, thus, management of ascites relies on frequent evacuation of fluid by paracentesis. When associated with reinforced diet, this approach did not aggravate albumin depletion and was associated to noticeable improvement in response to oral medications. Over a period of 10 months, EMF patients un Uganda were recruited and randomized to receive 1 mg/kg per day of prednisolone (16) or placebo (19) and were followed for a maximum of 8 weeks [93••]. The primary outcome was re-accumulation of ascites and safety was assessed by self-reported side effects, physical exam, and laboratory assessment. Short-term prednisolone use was safe but did not prevent re-accumulation of ascites.

Surgery

EMF surgery is technically challenging [94] and unavailable in most endemic areas [95]. The technique of choice was initially extensive endocardial resection and atrioventricular

valve replacement with appreciable postoperative improvement and 10-year survival of approximately 70% [96]. Cardiac transplantation has been used only sporadically. Early open-heart surgery including partial endocardectomy, conservative valvular procedures, and other technical modifications [82, 97–100] reduced the occurrence of postoperative complete heart block and complications of valve prosthesis and thus improved outcomes. Nowadays, reparative operations target the specific components of the disease, which include (i) the fibrous plaques interfering with regional ventricular function; (ii) the small ventricular volume due to ventricular obliteration; (iii) immobilization of the papillary muscles from auriculo-ventricular valves; (iv) chordal abnormalities; (v) fusion of the leaflets to the ventricular wall; (vi) dilatation of the tricuspid and mitral annulus; and (vii) massive atrial dilatation. Whenever possible, structural and functional abnormalities are partially corrected through fibrous tissue resection for reopening of the ventricular trabecular portion, atrioventricular valvar repair with mobilization of the fused leaflets [82], extensive atrial reduction [99], and partial or total caval-pulmonary artery anastomosis [82, 100].

EMF's survival on the most recent publications is 37% at 10 years [42••]. Longer survival and arrest in disease progression may occur in patients with early-diagnosed mild disease and improved socioeconomic status; biventricular involvement (moderate-severe), right ventricular fibrosis, and the presence of tricuspid and mitral regurgitation are associated with greater mortality rates [17].

Conclusions and Perspectives

While the possibility of a global decline in EMF must be considered, changes in its incidence or prevalence cannot be fully supported by evidence, due to lack of epidemiological research on the subject. In recent years, we have witnessed the gain of new knowledge in several fields that are relevant to understanding EMF, namely endothelial cell biology, inflammation, hemostasis, regulation of collagen synthesis, remodeling, and mechanisms of fibrosis. However, this has not been paralleled by improvement in knowledge of EMF, at least in part, because it looks like the underlying causes of this disease are multifactorial and the way concurrent factors mutually influence each other vary dramatically among individuals. More recently, calcium metabolism and hemostasis have also been studied in EMF patients. Yet, no unifying theory about the pathogenesis of EMF has been produced so far, mostly because there is a lack of input from basic scientists interested in unraveling the underlying molecular mechanisms of this neglected disease, which disproportionally affects rural populations in low-income countries. Prospective case-control studies may help to define the relevance of avoidable environmental factors in the pathogenesis of EMF, namely parasites, viruses, diets, and allergens.

The subjects who are affected, identified, and extensively phenotyped offer unique opportunities for studying the natural history and the rate of progression of EMF using transthoracic echocardiography, but this needs to be supported by biomarkers yet to be identified and the use of new imaging techniques, which are still expensive and not readily available in most endemic areas. Thus, research on immune, molecular, and/or genetic mechanisms underlying the pathophysiology of EMF is deeply needed to prompt discovery of biomarkers and novel drug targets, thus supporting interventions that can improve outcomes and alter EMF's natural history.

Compliance with Ethical Standards

Conflict of Interest Ana Mocumbi, J. Russell Stothard, Paulo Correia-de-Sá, and Magdi Yacoub declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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