Contemporary Reviews in Cardiovascular Medicine

Tropical Endomyocardial Fibrosis
Natural History, Challenges, and Perspectives

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Abstract—Tropical endomyocardial fibrosis (EMF) is a neglected disease of poverty that afflicts rural populations in tropical low-income countries, with some certain high-prevalence areas. Tropical EMF is characterized by the deposition of fibrous tissue in the endomyocardium, leading to restrictive physiology. Since the first descriptions in Uganda in 1948, high-frequency areas for EMF have included Africa, Asia, and South America. Although there is no clear consensus on a unified hypothesis, it seems likely that dietary, environmental, and infectious factors may combine in a susceptible individual to give rise to an inflammatory process leading to endomyocardial damage and scar formation. The natural history of EMF includes an active phase with recurrent flare-ups of inflammation evolving to a chronic phase leading to restrictive heart failure. In the chronic phase, biventricular involvement is the most common presentation, followed by isolated right-sided heart disease. Marked ascites out of proportion to peripheral edema usually develops as a typical feature of EMF. EMF carries a very poor prognosis. In addition to medical management of heart failure, early open heart surgery (endocardectomy and valve repair/replacement) appears to improve outcomes to some extent; however, surgery is technically challenging and not available in most endemic areas. Increased awareness among health workers and policy makers is the need of the hour for the unhindered development of efficient preventive and therapeutic strategies.

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Key Words: endomyocardial fibrosis ■ epidemiology ■ health services accessibility ■ heart failure ■ mortality

Tropical endomyocardial fibrosis (EMF) remains a mysterious and challenging cardiovascular disease. The condition is characterized by the deposition of fibrous tissue in the endomyocardium, leading to restrictive physiology. EMF affects mainly the poorest populations and is likely to be the leading cause of restrictive cardiomyopathy in the developing world.1-3

The phenotypic expression is variable, according to the stage at which it is diagnosed, usually leading to heart failure and premature death in children and adolescents.2 EMF has remained poorly understood since its first description in 1948,4,5 Investment in research has been extremely limited, with EMF appearing neither on the public health agenda of countries where it is endemic nor among the scientists from developed countries.1 The mechanisms of EMF thus remain largely unknown, thereby precluding the development of effective prevention and therapeutic strategies. The pathogenesis might combine genetic and environmental factors, which could explain the distribution of the disease in specific geographic hot spots worldwide.3

Untreated EMF carries a very poor prognosis, and there is no specific management so far. Early surgery appears to improve outcomes to some extent;6,7,8 however, surgery is technically challenging and not available in most endemic areas. The wider use of echocardiography in the developing world and recent innovations in molecular biology and other innovative technologies (if properly applied) have the potential to further our understanding of this disease, thereby opening new pathways for early diagnosis and treatment.3,11,12

Epidemiology
Since the first descriptions by Davies9 in Uganda in 1948, high-frequency areas for EMF have included Africa, Asia, and South America.7,13 In sub-Saharan Africa, EMF has been predominantly clustered in Uganda, along the low-lying coastal belt of Mozambique, and in some part of West Africa, but

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sporadic cases have also been reported in Congo and Malawi, among others.\(^{14-24}\) India has witnessed a striking burden of EMF along the coastal area and rain forest of Kerala State,\(^{25-27}\) and in China, a high prevalence has been found in the province of Guangxi.\(^{28}\) In South America, EMF has been reported mainly in Brazil and Colombia.\(^{29,30}\) A community-based study carried out with systematic echocardiography to capture also subclinical disease, documented a striking burden of EMF, with an estimated prevalence rate up to almost 20%.\(^{31-33}\) Of the general population in a rural community in Mozambique (100 km north of Maputo). A recent decline observed in India and some regions of Nigeria contrasts with the persistent high trends in other areas, underlining the potential influence of socioeconomic and environmental factors on the disease.\(^{34-38}\)

EMF affects predominantly impoverished young adults of lower socioeconomic status, with a bimodal distribution peaking at 10 and 30 years of age.\(^{31,39}\) Data on sex distribution are mixed. In women, ages of childbearing age present a 2-fold higher prevalence compared with men.\(^{40}\) By contrast, other studies have not observed a specific sex difference in adults,\(^{41,42}\) and a male preponderance has been reported in Mozambique\(^{43}\) and Nigeria.\(^{44,45}\)

The long-term outcome from medical treatment in advanced stages is very poor,\(^{46}\) with 75% mortality at 2 years.\(^{47}\) Overall, EMF accounts for ≈20% of hospitalizations for heart failure in Nigeria, Equatorial Guinea, and Uganda,\(^{6,44-46}\) where the disease represents the second leading cause of pediatric admission for acquired heart disease, after rheumatic heart disease.\(^{46}\)

### Origin and Pathogenesis

The pathogenesis of EMF remains unclear, and there is a need for more systematic research and the use of contemporary technologies to test older, classic hypotheses, which have varied across studies. Poverty, malnutrition, parasitic infestation, genetics, and cluster ethnicity have all been proposed as causes/cofactors. The various theories advanced for the etiopathogenesis of EMF are revisited below.

**Eosinophilia, Infectious Disease, and Autoimmunity**

Similarities with the Loffler syndrome\(^{47,48}\) and the prevalence of parasites in the endemic countries\(^{26,27}\) led to consider eosinophilia and infections as potential primary triggers.\(^{49-53}\) An excessive immune response to the trigger (Figure 1) has been suggested to be the link between certain parasitic infections and EMF.\(^{54-59}\) This has been demonstrated, for example, by increased circulating levels of IgE\(^{53,60,61}\) and the occurrence of hyperimmune malaria-related splenomegaly among Rwandan immigrants affected by EMF.\(^{62}\) Immunological investigations have revealed the presence of autoantibodies (IgG and IgM) directed against myocardial proteins.\(^{58,63}\) However, the peculiar fact that eosinophils are limited only to the early stages of EMF,\(^{53}\) the inconsistent geographical matching with important parasitic infections (eg, schistosomiasis and filariasis in Southeast Asia),\(^{64-66}\) and the lack of difference in parasitic loads between EMF patients compared with control subjects all argue against a straightforward parasitic-related immunological mechanism.\(^{57,66}\) The disease afflicts individuals in rural settings, which are also endemic for malaria, but again, geographic distributions of EMF and malaria have not matched in a coherent fashion to allow causal links to be drawn.\(^{50,69-79}\) Furthermore, malaria has never been described as being associated with myocardial or endocardial damage.\(^{80}\)

The concept of molecular mimicry, similar to rheumatic heart disease,\(^{72,75}\) has also been proposed as a mechanism but without compelling evidence.\(^{74}\)

### Environmental Factors, Dietary Factors, and Toxins

Although several environmental/toxic factors such as magnesium deficiency, cerium toxicity, the cyanogenic glycosides, high vitamin D, serotonin toxicity,\(^{58,59,62,81-96}\) and, more recently, the potential effect of certain herbal preparations,\(^{97}\) have been advocated in the pathogenesis, no confirmatory evidence firmly establishes these hypotheses. It has been speculated that, in genetically predisposed people, poor diet per se may lead to a dysfunction in the regulatory and functional mechanisms of eosinophils, which, as in eosinophilic leukemia, may cause necrosis, thrombosis, and finally fibrosis.\(^{67}\) This is supported by the fact that long-standing dietary imbalance with low-protein intake is generally seen along with EMF.\(^{12}\)

One of the more popular diet-related hypotheses has proposed an important role for cassava, which is almost universally consumed in certain areas of Africa and other developing areas. Cassava (Manihot esculenta Crantz), a tuber, is an important dietary staple for >500 million people in developing countries\(^{98}\) because it is cheaper than other carbohydrate sources, especially rice and maize. Cassava contains a toxic cyanogenic glycoside called linamarin that can liberate hydrogen cyanide in the gut during digestion. In the absence of proper processing/cooking methods, toxic levels of the glycoside may persist in the tuber during consumption. Normally, cyanide is detoxified in the body by conversion to thiocyanate via the sulfur-containing enzyme rhodanase. A low-protein diet, especially if deficient in sulfur-containing amino acids, may decrease the detoxification capacity and thus increase vulnerability to the toxic effects of cyanide.\(^{99}\) This can be compounded by excessive consumption of cassava as the sole source of dietary energy and protein. Tissue hypoxia and lipid peroxidation occurring from sublethal doses of cyanide might alter myocardial cell biology, as can be seen with neuronal toxicity.\(^{100}\) In animal models, the development of intracellular vacuoles, endocardial thickening, and interstitial fibrosis has been demonstrated with cassava intake, and this process was seen to be independent of eosinophilia or parasitic infestation. Furthermore, the fact that improved socioeconomic status and a significant drop in cassava intake paralleled a decline in EMF rates in Kerala, India, adds some credence to a role for cassava. However, certain inconsistencies remain such as the mismatch between the distribution of EMF and malnutrition in Africa and the occurrence of the disease among subjects from nontropical areas who have spent only a short time in endemic areas.\(^{57,69,94}\)

It bears mention that malnutrition may also contribute to the pathogenesis of EMF by increasing susceptibility to parasitic infections.\(^{14}\) Finally, the higher prevalence of right-sided
heart disease suggests a role for potentially toxic factors removed by the lung.33

**Genetic Susceptibility**

Genetic susceptibility has also been proposed as a potential explanation for the high prevalence of EMF in specific areas.3,15,27,101 Instances of familial occurrence3,62,95 and rare cases among very young children102–105 suggest the existence of a genetic predisposition, although exposure to environmental factors during the antenatal period may explain some early-life cases.105

Ethnic clustering of cases3,62,95,96 has also suggested the role of genetics; however, this has been recently challenged by other data. For instance, in Uganda, EMF is more common among immigrants from neighboring Rwanda and Burundi,13 but it also occurs in whites who have lived in endemic regions57,76,93,94 or in immigrants coming from areas where the disease is anecdotal. Thus, the role of genetic predisposition in EMF is unclear at present and needs further study.

**Summary of Etiopathogenesis**

Although there is no clear consensus on a unified hypothesis, it seems likely that dietary, environmental, and infectious factors may combine in a susceptible individual to give rise to an inflammatory process leading to endomyocardial damage and scar formation (Table 1). There is an urgent need to better understand the underpinnings of this disease to develop effective interventions.

**Natural History and Presentation**

Contrasting with the still obscure pathogenesis, the natural history of EMF has been well documented (Figure 1) and includes an active phase with recurrent flare-ups of inflammation evolving to a chronic phase leading to restrictive heart failure.
Active Form: Inflammation

EMF usually starts with a febrile illness associated with pancarditis and eosinophilia, dyspnea, itching, and periorbital swelling. There is no specific biological marker for EMF, with eosinophilia at diagnosis varying widely between absent and 70%. Higher rates are reported in the early stages, and peculiarly, the circulating eosinophils are often morphologically abnormal. Acute inflammation of the heart results in myocardial edema, eosinophilic infiltration, subendocardial myofiber necrosis, and vasculitis. The ECG is nonspecific and may show low-voltage QRS, ST–T–wave changes, conduction disturbances, and atrial or ventricular arrhythmias. On echocardiography, homogeneous infiltrates fill in layers of the cardiac walls, and pericardial effusion is common. Mural thrombi may also occur along the endocardial surfaces of the apical and valvular pockets; at this stage, thromboembolic events are frequent. Subsequently, as the inflammatory process declines and eosinophils become undetectable, both interstitial fibrosis and myocyte hypertrophy develop and may lead to myocardial ischemia and cicatricial fibrosis (chronic phase: Figure 2B). The clinical distinction of the active phase of EMF from acute rheumatic fever in these endemic areas can be challenging. An unknown number of cases evolve rapidly to heart failure and death, whereas other individuals pass through a subacute “burnout” phase without sequelae.

Transient Progressive Form: Toward the Chronic Phase

Similar to rheumatic heart disease, the recurrence of active episodes may facilitate the evolution to the chronic phase of EMF. With such an evolution, systemic inflammation becomes rare, and markers of inflammatory activity such as hypoalbuminemia and liver or kidney dysfunction are rarely observed. As chronic heart failure develops, edema and ascites become manifest. One distinguishing feature is that the ascitic fluid in patients with EMF is mostly exudative with a pleocytosis of white blood cells, mostly lymphocytes. Radiological signs are usually nonspecific, showing varying degrees of cardiomegaly, and only exceptionally reveal the typical linear endocardial calcifications. On echocardiography, as the myocardium returns to normal thickness, the affected areas unevenly evolve into endocardial scars (Figure 2B and 2C), and a restrictive syndrome occurs with chamber distortion and dilated atria (Figure 2D). Typically, the fibrotic process stops abruptly just before the ventricular outflow tract. The occurrence of endomyocardial calcification spots is usually a marker of burnt-out disease resulting from intermittent flare-ups of inflammation alternating with quiescent phases.

To date, the factors responsible for the evolution of the disease and the basis for fast-progression versus slow-progression phenotype (that remain asymptomatic for a long period of time) remain poorly understood.

Chronic Form

In the chronic phase, biventricular involvement is the most common presentation (up to 55%), followed by isolated right-sided heart involvement and, in rare cases, isolated left-sided heart disease. When right ventricular restriction predominates, the long-standing systemic venous hypertension...
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Marked ascites out of proportion to peripheral edema (Figure 3) usually develops as a typical feature of both right- and left-sided heart EMF. Abundant ascites with lymphocytic exudates and peritoneal fibrosis but without pedal edema had led researchers to propose an EMF systemic syndrome with peritoneal inflammation. Decreased reabsorption of proteins and liver disease with exudative enteropathy may also occur in the most severe cases. In addition to nonspecific signs of chronic heart failure, including digital clubbing, growth retardation, testicular atrophy, failure to develop male secondary sexual characteristics, and cachexia, more specific features of EMF include hypertrophy of the parotid gland, periorbital edema, and proptosis.

Atrial fibrillation occurs in >30% of cases. Right bundle-branch block are common, but EMF patients only rarely require a pacemaker. In advanced EMF with severe pulmonary hypertension (usually resulting from recurrent pulmonary embolism), ECG patterns include right ventricular hypertrophy and rightward frontal plane QRS axis deviation. The patient may die of progressive heart failure or experience sudden death caused by pulmonary thromboembolism or ventricular arrhythmias.

Pronounced cardiomegaly, biatrial dilatation, pulmonary infundibular dilatation, and postcapillary pulmonary hypertension are all typical radiological markers of biventricular EMF (Figure 4). Pleural and pericardial effusions are very common regardless of the laterality of the affected chambers. Because echocardiography is almost always adequate for the diagnosis of EMF, invasive hemodynamic study with pressure assessment is no longer routinely used. When performed, the classic “dip and plateau” pattern (or square root sign) in the
right ventricular pressure tracing, low cardiac output, and pulmonary arterial hypertension can be seen. Ventriculography highlights the “shrunken” anatomy, valvular regurgitation, and atrial remodeling.\(^{128,129}\)

### Pathology

At pathological examination, the ventricles look small with grossly dilated atria, and on histopathology, endocardial thickening is considered the hallmark for identifying patients with EMF, a feature of advanced disease.\(^{34}\) Endocardial thickening usually corresponds microscopically to an increased number and abnormal stimulation of cardiac fibroblasts in the subendocardium, leading to enhanced collagen synthesis (Figure 6). Mild to moderate inflammatory infiltrates composed mainly of lymphocytes are prevalent along the interface between the endocardium and the myocardium. Myocardial lesions such as inflammatory infiltrates, interstitial fibrosis, and scars are prominent in areas adjacent to subendocardial fibrosis and altered vessels, suggesting that they likely occur in response to ischemic injury caused by microvascular changes.\(^{34}\) Cardiac tissue eosinophilia is rare in advanced disease. There is a lack of vessels in the outer endocardium, in clear contrast to rheumatic heart disease.

### Morphological Assessment/Diagnosis

Echocardiography has become the mainstay of diagnosis,\(^{3,20}\) which allows optimal delineation of the morphology and noninvasive hemodynamics.\(^{130,131}\) Before 2008, the criteria described for diagnosing EMF applied only to the disease in its advanced stages.\(^{132,133}\) Major and minor criteria and a severity scoring system have since been proposed in an effort to capture several aspects of the natural history and phenotypes\(^{3}\) (Table 2). According to this classification, EMF is diagnosed when there are 2 major criteria or 1 major criterion with 2 minor criteria.\(^{3}\) Because some features seem to occur before severe chamber/valve distortion, the criteria have also been proposed for use in early diagnosis but have yet to be validated through follow-up studies.

Echocardiographically, in chronic forms, a restrictive syndrome with shrunken ventricles, severely dilated atria (Figure 2D), and major valve dysfunction is seen as a result of the global fibrosis. In advanced right-sided EMF, the cardiac apex becomes severely retracted, and the trabecular chamber is almost virtually obliterated, leading to dilatation of the outflow tract.\(^{134}\) Obliterative fibrosis of the posterior tricuspid pocket results in severe tricuspid regurgitation. The echocardiographic features for diagnosing right EMF also include right atrial enlargement (Figure 2E), restrictive inflow pattern, dilated inferior vena cava, and pericardial effusion.\(^{128}\) In very advanced cases, fibrosis may extend to the myocardium and atria.\(^{135}\) In biventricular EMF, progressive entrapment of the posterior mitral leaflet results in severe regurgitation (with a high-pitched regurgitation murmur) without ventricular remodeling as the left ventricle becomes small and stiff.\(^{11,128,132,136-138}\) The left atrium is markedly dilated, the mitral inflow pattern is restrictive, and pulmonary hypertension is common.\(^{128}\) In endemic countries, different forms of EMF may be misdiagnosed\(^{12}\) as dilated cardiomyopathy, constrictive pericarditis, or other restrictive cardiomyopathies such as amyloidosis, hemochromatosis, and sarcoidosis.\(^{139}\) An extremely enlarged right atrial chamber in EMF may also mimic Ebstein anomaly.\(^{140}\) Mild left EMF may also be difficult to distinguish from rheumatic heart disease affecting the mitral valve.

Although not available in most countries where EMF is common, cardiac magnetic resonance imaging provides additional value for the diagnosis of EMF, including the potential assessment of early disease.\(^{141}\) Cardiac magnetic resonance imaging outlines the degree of chamber distortion and the extent of thrombosis\(^{11,12,142-144}\) (Figure 5). Perfusion studies accurately map the hypoperfused myocardial areas and avascular structures, whereas late-gadolinium-enhancement images correlate with fibrosis.\(^{145}\) Cardiac magnetic resonance imaging would be an ideal tool for monitoring the response to treatment and for defining anatomic details before surgery.\(^{146}\) Computed tomography scans are more readily available but rarely used and may show the endocardial calcifications or the

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**Figure 3. Clinical profile of tropical endomyocardial fibrosis.**

Typical clinical appearance of the disease showing striking ascites, regardless of which ventricle is involved, contrasting with little or no peripheral edema. Usually, when these patients have edema of the lower extremities, they have also an exudative enteropathy with a low serum protein content.
intracavitary thrombi. On occasion, F-18 fluorodeoxyglucose positron emission tomography scan may be useful to rule out sarcoidosis as a differential diagnosis.

**Current Management Strategies**

Medical management consists of symptomatic treatment of heart failure (e.g., diuretics, angiotensin-converting enzyme inhibitors) offered in combination with aspirin or anticoagulation in view of the potential for intracardiac thrombi. Paracentesis offers short-term relief only, because ascites often reaccumulates rapidly. By analogy with Loeffler syndrome, corticosteroids and immunosuppressive drugs may be helpful in the early stages, but there are no randomized, clinical trials to support their routine use.

Open heart surgery increases survival compared with medical treatment. Access to heart surgery, however, is severely limited in many endemic areas. Where expertise exists, EMF may be successfully treated with surgical endocardectomy and valve repair/replacement.

The use of cavopulmonary connections may be helpful in pure right-sided EMF with a small right ventricular cavity. Mitral and tricuspid valve replacement, frequently performed in the 1980s, is used less frequently now because of poor long-term outcomes from mechanical prostheses, especially in the tricuspid position. Although the early postoperative mortality may be up to 20% and variable rates of recurrence after surgery have been reported, timely surgical treatment still appears to be the only option to substantially improve outcomes at present. Patients with end-stage EMF may not be suitable for surgery, including those with clinical signs of advanced disease such as gross and long-standing ascites, chronic pulmonary thromboembolism, extensive endocardial fibrosis, right ventricular hypoplasia, or extreme cachexia. In the resource-poor
settings where this disease predominates, instances of heart transplantation are at best anecdotal.159,160

**Challenges and Perspectives**

EMF still causes significant morbidity among impoverished people in specific geographical pockets. Nevertheless, specific data on the burden of EMF are scant, and robust epidemiological population-based studies are urgently needed. Considering the high prevalence observed in some rural communities (up to 20%),3 we might expect that, even considering the highly heterogeneous distribution of the disease, EMF is likely to afflict hundreds of thousands of people in sub-Saharan rural Africa. This first view appears in contrast with a recent overview by Damasceno and colleagues24: in The Sub-Saharan African Survey (THESUS-HF) study, which included >1000 patients with acute heart failure from 9 African countries, including Mozambique, Nigeria, Cameroon, and Uganda, only 1.3% of all patients presented with EMF. It is noteworthy that this and other similar studies commenting on EMF prevalence in sub-Saharan Africa have focused on clinically overt heart failure. But, in order to assess true prevalence and to aim for meaningful prevention and early management strategies, it is important to account for subclinical disease. Furthermore, these studies have been carried out at hospital settings or in urban areas (such as in the THESUS-HF survey)24 and thus may not be truly reflective of overall prevalence in the general population. As a disease of the poorest population often found in remote rural areas, EMF may not be adequately captured by the aforementioned clinical studies. These potential sources of selection bias may explain the apparent discrepancy in prevalence figures. Providing accurate disease estimates will increase awareness among both health workers and policy makers and encourage them to tackle the disease. Further validation of the echocardiographic criteria defined recently3 will help strengthen epidemiological surveillance by providing a standardized tool for early diagnosis. Prospective cohorts with subclinical EMF detected by echocardiography would clarify the prognosis and either support or refute the need for systematic screening.

Secondly, there is a crucial need to further our understanding of the pathogenesis. Malnutrition and high cassava intake seem to act as independent cofactors in the pathogenesis of the disease regardless of other triggers such as infections and genetics, but this remains to be convincingly demonstrated. There is an urgent requirement for well-conducted case-control studies to identify predisposing factors. If EMF is an acquired condition, identification of a single factor or a combination of environmental/toxin-related factors could lead to effective eradication of the disease. Multicenter investigations into environmental and nutritional factors should be promoted to identify common backgrounds across different high-prevalence areas. Robust international collaborations are needed to achieve statistical power and to overcome inaccuracies caused by hidden bias.

Input from basic science researchers and geneticists, in combination with that from epidemiologists and clinicians, will help carry out well-directed studies in hospitals and in the community to address the issue of genetic susceptibility.203 Insights from molecular research addressing potential molecular mimicry and autoimmune pathways and characterization of autoantibodies and their targets should shed light on the mechanisms involved. Investigations involving genomics and proteomics are likely to clarify the final common pathways leading to endocardial damage. For instance, markers such as C-reactive protein or inflammatory cytokines such as tumor necrosis factor-α might play a central role in

**Figure 6.** Surgical view and pathology features of tropical endomyocardial fibrosis. Surgical view of an endocardial resection from the ventricular cavity (**left**). Histological section (**right**) showing a thick fibrous shell removed surgically by endocardectomy. There are several calcific nodules among the fibrous tissue and inflammatory infiltrates at the border zone with the myocardium (Masson trichrome stain).
episodic inflammatory flare-ups\textsuperscript{161} and be targeted for therapy. Inhibition of the protein FIP1L1-PDGFR\textalpha, a constitutively activated tyrosine kinase found in idiopathic hypereosinophilic syndromes, by imatinib is a potential example of such a therapeutic target,\textsuperscript{162} especially for patients with early EMF and prominent eosinophilia. These therapies, however, need to be proven and cost-effective to be viable in low-resource settings.

Until a specific treatment to halt the fibrotic process or a specific environmental factor triggering the pathogenesis is identified, cardiac surgery appears to be the only treatment option for advanced cases. The long-term efficiency of such a strategy, however, is unknown. Large numbers of surgical candidates may not be deemed fit for surgery when presenting late; therefore, early identification is key. In addition, access to cardiac surgery is extremely limited in low-income nations.\textsuperscript{46,163,164} Ultimately, improvement in living standards and access to care must be emphasized to prevent morbidity and mortality related to EMF, a still largely neglected disease.

**Conclusions**

Tropical EMF is a neglected disease of poverty that afflicts rural populations in tropical low-income countries, with some certain high-prevalence areas. EMF remains one of the most mysterious and poorly understood cardiovascular diseases, and increased awareness among health workers and policy makers is the need of the hour for the unhindered development of efficient preventive and therapeutic strategies. A better understanding of the disease, standardized training, and high-volume surgical expertise are needed in the attempt to improve outcomes from this devastating disease.

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**Disclosures**

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**References**


