**ENDOMYOCARDIAL FIBROSIS: AN UPDATE AFTER 70 YEARS**

Ana Mocumbi1,2, J. Russell Stothard3, Paulo Correia-de-Sá4,5, Magdi Yacoub6,7

1 Universidade Eduardo Mondlane, Faculdade de Medicina, Maputo, Mozambique

2 Instituto Nacional de Saúde, Marracuene, Mozambique

3 Liverpool School of Tropical Medicine, United Kingdom

4 Centro de Investigação Farmacológica e Inovação Medicamentosa. Portugal

5 Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), Universidade do Porto, Portugal.

6 Imperial College London, London, United Kingdom

7 Aswan Heart Centre, Egypt

**Corresponding author:**

**Ana Olga Mocumbi**

Vila de Marracuene

EN1, Parcela nr 3943

Maputo, Moçambique

[amocumbi@gmail.com](mailto:amocumbi@gmail.com)

**SUMMARY**

Endomyocardial fibrosis (EMF) was first described in Uganda by Davies more than seventy years ago (1948). Despite its poor prognosis, the etiology of this neglected tropical restrictive cardiomyopathy still remains enigmatic nowadays. Here, we highlight the need to better understand EMF when set against its changing endemicity and disease burden, improvements in diagnosis and new options for clinical management. 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 improving patient outcomes focusing (whenever possible) on novel players coming into action.

**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 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 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 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 fibroelastose 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 given its more obvious focus here. 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 sign-posted 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 clinico-epidemiological study 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], Turky [21], United Kingdom [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 7-fold higher (at 6.9/100,000) than others that were more accessible to health facilities and from where more patients would be expected [44]. More recently, Gupta and colleagues compared the incidence of EMF and its complications in two areas with major socioeconomic differences in India [45]. More biventricular disease and atrial fibrillation was found in Trivandrum than 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 six 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 to 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 [45].

The only community-based study available was performed in Mozambique [46]. 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 & NATURAL HISTORY**

Various potential etiological factors or triggers have been suggested, which may act in isolation or in combination **[47-70**]. 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)**. 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 WBC 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[47]. On the other hand, cardiovascular disease is a leading cause of morbidity and mortality in hypereosinophilic syndromes [70]. The cross-talk between eosinophils, mast cells and cardiac fibroblasts is probably a key pathogenic factor in defective cardiac remodelling [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 [71]. Half of 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 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 [72]. Blood hypereosinophilia was a common finding in people from endemic areas of EMF in Nigeria [72,73] 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 [74-76]. Indeed, early studies failed to show an increased prevalence of these infections in EMF patients when compared to the general population [63, 77-79].

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 eosinophils 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 [80].

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 [81] and urinary [35, 82] 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 oedema), 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 [83]. 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 immunosupression 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 subendocardium 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 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 [84,85]. 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.

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 [86], 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 [87]. 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 antibodies against IL-6, like tocilizumab that has been approved for rheumatoid arthritis [88], 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 [89], 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 has 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. Moreover, echocardiography features correlates well with microscopic abnormalities [89]. The noninvasive nature of echocardiography, and the absence of consumable materials are also putative advantages of this method in low-income endemic regions, providing that long-term portable power accumulators are included in the setting. [**Figure**]

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 [46] 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 [90] 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, subendocardial delayed enhancement in the involved ventricles [91]. It seems ideally suited to diagnose this condition and monitor response to medical and/or surgical therapy [92].

The differential diagnosis of EMF includes rheumatic heart disease, tuberculosis, schistosomiasis, Ebstein malformation, tuberculous peritonitis, tuberculous pericarditis, hypertrophic cardiomyopathy. While bacterial endocarditis is rare in EMF patients, one case with calcification and bacterial endocarditis has been recently described [93].

**CURRENT MANAGEMENT OPTIONS**

Currently, there is no effective medical therapy for EMF nor confident public health intervention to prevent it. Early diagnostic biomarkers are also an unmet clinical need preventing medical intervention with disease modifying medications. A subset 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 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 [94] – 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 dye 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 believes 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 [45], which was 2 years after the onset of symptoms in the late seventies [*95*].

**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 ascitis into the femoral vein - were disastrous and, thus, management of ascitis relies on frequent evacuation of fluid by paracenthesis. 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, participants 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. [96] 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 [41] and unavailable in most endemic areas. [97]. The technique of choice was initially extensive endocardial resection and atrioventricular valve replacement with appreciable postoperative improvement and 10 year survival of approximately 70% [98]. Cardiac transplantation has been used only sporadically. Early open-heart surgery including partial endocardectomy, conservative valvular procedures and other technical modifications [85, 99-102] reduced the occurrence of postoperative complete heart block, 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 [85], extensive atrial reduction [101] and partial or total caval-pulmonary artery anastomosis [85,102].

EMF’s survival on the most recent publications is 37% at ten years [45]. 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 affected identified and extensively phenotyped offers 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 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.

**REFERENCES**

1. Grimaldi A, Mocumbi AO, Freers J, Lachaud M, Mirabel M, Ferreira B, Narayanan K, Celermajer DS, Sidi D, Jouven X, Marijon E. Tropical Endomyocardial Fibrosis: Natural History, Challenges, and Perspectives. Circulation. 2016 Jun 14;133(24):2503-15.
2. Rwebembera J, Manyilirah W, Zhu ZW, Nabbaale J, Namuyonga J, Ssinabulya I, Lubega S, Lwabi P, Omagino J, Okello E. Prevalence and characteristics of primary left-sided valve disease in a cohort of 15,000 patients undergoing echocardiography studies in a tertiary hospital in Uganda. BMC Cardiovasc Disord. 2018 May 4;18(1):82.
3. Chelo D, Nguefack F, Mbassi Awa HD, Kingue S. Endomyocardial fibrosis in Sub Saharan Africa: The geographical origin, socioeconomic status, and dietary habits of cases reported in Yaounde, Cameroon. Ann Pediatr Cardiol. 2015 Sep-Dec;8(3):202-9.
4. Gallagher J, McDonald K, Ledwidge M, Watson CJ. Heart Failure in Sub-Saharan Africa. Card Fail Rev. 2018 May;4(1):21-24.
5. Glezeva N, Gallagher J, Ledwidge M, O'Donoghue J, McDonald K, Chipolombwe J, Watson C. Heart failure in sub-Saharan Africa: review of the aetiology of heart failure and the role of point-of-care biomarker diagnostics. Trop Med Int Health. 2015 May;20(5):581-588.
6. Williams AW. Heart disease in the native population of Uganda. Part I: Syphilitic heart disease. *East Afr Med J 1938*;15:279
7. Bedford DE, Konstam GLS. Heart failure of unknown aetiology in Africans. *Br Heart J* 1946;8:236
8. Davies JNP. Endocardial fibrosis in Africans. *East Afr Med J 1948*;25:10
9. Hutt MSR, Ikeme AC, Lucas AO et al. Cardiomyopathies. *Bull Wld Hlth Org* 1965;33:257-66
10. Turner PP, Manson-Bahr PEC. Endomyocardial fibrosis in Kenya and Tanganyika Africans. Br Heart J. 1960;22:305–10.
11. de Mattos A, Achutti A, Fagundes L, de Lima C, Faraco E. [Endomyocardial fibrosis. The 1st published case in Brazil]. Arq Bras Cardiol. 1963;16:67-76.
12. Mehrotra AN, Maheshwari HB, Khosla SN, Kumar S. Endomyocardial Fibrosis. A Report Of Two Cases In Brothers. J Assoc Physicians India. 1964;12:845-50.
13. Suárez JA, De Suárez C. Endomyocardial fibrosis of the right ventricle: an anatomy-pathologic study of the first Venezuelian case. Acta Cient Venez. 1967;18(4):98-105. Spanish. PubMed PMID: 5595206.
14. Rose AG, Uys CJ, Timme AH, Botha JB. Endomyocardial fibrosis at autopsy in Cape Town. S Afr Med J. 1974;48:1363–7.
15. Lowenthal MN. Endomyocardial fibrosis: familial and other cases from northern Zambia. Med J Zambia. 1978;12:2–7.
16. Bukhman G, Ziegler J & Parry E. Endomyocardial fibrosis: still a mystery after 60 years. *Plos Neglected Tropical Diseases* 2, doi:10.1371/journal.pntd.0000097 (2008).
17. Barretto AC, da Luz PL, de Oliveira SA, Stolf NA, Mady C, Bellotti G, Jatene AD, Pileggi F. Determinants of survival in endomyocardial fibrosis. Circulation. 1989;80 (3 Pt 1): I177-82.
18. Puigbo JJ, Combellas I, Acquatella H, Marsiglia I, Tortoledo F, Casal H, Suarez JA. Endomyocardial disease in South America--report on 23 cases in Venezuela. Postgrad Med J. 1983;59(689):162-9.
19. López Ramón M, García de la Calzada MD, Domínguez Cunchillos M, Salazar Mena J. Tropical endomyocardial fibrosis in Spain. An Pediatr (Barc). 2013;78(5):326-9.
20. Yin R. Endomyocardial fibrosis in China. Chin Med Sci J. 2000;15(1):55-60.
21. Cağli K, Uygur B, Ozlü F, Gölbaşi Z. [Endomyocardial disease: a case report]. Turk Kardiyol Dern Ars. 2009;37(2):136-40.
22. Laing HC, Sharratt GP, Johnson AM, Davies MJ, Monro JL. Endomyocardial fibrosis in a European woman and its successful surgical treatment. J Thorac Cardiovasc Surg. 1977;74(5):803-7. PubMed PMID: 916720.
23. Gyr K, Fernex M, Wick R, Burckhardt D. [African endomyocardial fibrosis. Report of a case seen in Basel]. Dtsch Med Wochenschr. 1970;95(40):2028-32.
24. Pavia M, Cugini A, Buffa J. Restrictive cardiomyopathy caused by endomyocardial fibrosis. Description of a case observed in Piedmont]. Minerva Cardioangiol. 1985;33(6):357-61.
25. Vijayaraghavan G, Sivasankaran S. Tropical endomyocardial fibrosis in India: a vanishing disease! Indian J Med Res. 2012;136(5):729-38.
26. Maro E, Janabi M. Echocardiographic profile of endomyocardial fibrosis in Tanzania, East Africa. Cent Afr J Med. 2004;50:91–4.
27. Antonio JH, Diniz MC, Miranda D, Soares HI, Melo E, Miranda D, et al. Endomyocardial fibrosis in Egypt: an illustrated review. Heart. 1997;77:391.
28. Kimbally-Kaky G, Ekoba J, Nkoua JL, Bouramoue C. Endomyocardial fibrosis: report of 22 Congolese cases. Ann Cardiol Angeiol (Paris). 2000;49:287–95.
29. Cilliers AM, Adams PE, Mocumbi AO. Early presentation of endomyocardial fibrosis in a 22-month-old child: a case report. *Cardiol Young*. 2011;21(1):101-3.
30. Abate S. Endomyocardial fibrosis in Ethiopia. Ethiop Med J. 1988;26:193–8.
31. Hakim JG, Matenga JA, Ternouth I. Endomyocardial fibrosis in Zimbabwe\_how rare is it? A report of two cases. Cent Afr J Med. 1996;42:262–5.
32. Sankale M, Quenum C, Diop B, Bao O, Koueke P. A further case of endomyocardial fibrosis in Dakar. Bull Soc Med Afr Noire Lang Fr. 1969;14:477–86.
33. Ali SK. Endomyocardial fibrosis: an under-diagnosed cause of cardiomyopathy in Sudanese children. J Trop Pediatr. 2009;55:343–6.
34. Amoah AG, Kallen C. Aetiology of heart failure as seen from a National Cardiac Referral Centre in Africa. Cardiology. 2000;93:11–18.
35. Assimeng J, Segbefia CI, Neequaye J. Endomyocardial fibrosis associated with Schistosoma haematobium. Ghana Med J 2014;48(4):225-7
36. Soliman EZ, Juma H. Cardiac disease patterns in northern Malawi: epidemiologic transition perspective. J Epidemiol. 2008;18:204–8.
37. Kennedy N, Miller P, Adamczick C, Molyneux E. Endomyocardial fibrosis: the first report from Malawi. Paediatr Int Child Health. 2012;32(2):86-8.
38. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med.* 2012;172(18):1386-94.
39. Khalil SI, Khalil S, Tigani SE, Saad HA. Endomyocardial fibrosis in Sudan: clinical and echocardiographic features. Cardiovasc J Afr. 2017;28(4):208-214.
40. Wilson SE, Chinyere UC, Queennette D. Childhood acquired heart disease in Nigeria: an echocardiographic study from three centres. Afr Health Sci. 2014;14(3):609-16.
41. Yangni-Angate KH, Meneas C, Diby F, Diomande M, Adoubi A, Tanauh Y. Cardiac surgery in Africa: a thirty-five year experience on open heart surgery in Cote d'Ivoire. Cardiovasc Diagn Ther. 2016;6(Suppl 1):S44-S63.
42. Nkoke C, Menanga A, Boombhi J, Chelo D, Kingue S. A new look at acquired heart diseases in a contemporary sub-Saharan African pediatric population: the case of Yaoundé, Cameroon. Cardiovasc Diagn Ther. 2015;5(6):428-34.
43. Sani UM, Ahmed H, Jiya NM. Pattern of acquired heart diseases among children seen in Sokoto, North‑Western Nigeria. Niger J Clin Pract. 2015;18(6):718-25.
44. Ferreira B, Matsika-Claquin MD, Hausse-Mocumbi AO, Sidi D, Paquet C. Geographic origin of endomyocardial fibrosis treated at the central hospital of Maputo (Mozambique) between 1987 and 1999. *Bull Soc Pathol Exot*. 2002;95(4):276-9.
45. Gupta PN, Kunju SM, Rajan B, Koshy AG, Vishwanathan S, George PS, Velappan P. Geographical variation in the clinical presentation of endomyocardial fibrosis in India? Indian Heart J. 2018;70(1):56-65.
46. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. *N Engl J Med*. 2008;359(1):43-9.
47. Andy JJ, Ogunowo PO, Akpan NA, Odigwe CO, Ekanem IA, Esin RA. Helminth associated hypereosinophilia and tropical endomyocardial fibrosis (EMF) in Nigeria. *Acta Tropica 1998*;69(2): 127-40
48. Rashwan MA, Ayman M, Ashour S, Hassanin MM & Abouzeina AA. Endomyocardial fibrosis in Egypt - an illustrated review. *British Heart Journal* 1995; 73, 284-289
49. Beck W, Schrire V. Endomyocardial fibrosis in Caucasians previously resident in tropical Africa. *Br Heart J 1972*. ;34:915-8.
50. Ive FA, Willis AJP, Ikeme AC, Brockington IF. EMF and filariasis. *Quart J Med 1967;* 36:495-516.
51. Brockington IF, Olsen EGJ, Goodwin JF. Endomyocardial Fibrosis in Europeans resident in Africa. *Lancet 1967*;289(7490):583-588.
52. Shaper AG, Hutt MSR, Coles RM. Necropsy Study of Endomyocardial Fibrosis and Rheumatic Heart Disease in Uganda 1950-1965. *Br Heart J 1968*;30:391-401.
53. Barbosa MM, Lamounier JA, Oliveira EC, Souza MV, Marques DS, Lambertucci JR. Short report: Endomyocardial Fibrosis and cardiomyopathy in an area endemic for schistosomiasis. *Am J Trop Med Hyg 1998*;58(1):26-7.
54. Victor EG, Lira V, Arruda A, Monteiro I, Lima R. Granulomas cardiacos a ovos de schistosoma e fibrose endomiocardica. Arq Bras Cardiol 1996;67(4):259-261
55. Berenguer A, Plancha E, Gil JM. Right ventricular endomyocardial fibrosis and microfilarial infection. *Int J Cardiol 2003*;87:287-9
56. Ludlam GB, Somers K. Incidence of toxoplasma antibodies in Ugandans with special reference to cardiomyopathy. *Trans R Soc Trop Med Hyg 1966*; 60(5):621-5
57. Eling WMC, Jerusalem CR, Heinen-Borries UJ, Hermsen CC, Run-van Breda JJ. Is malaria involved in the pathogenesis of tropical endomyocardial fibrosis? *Acta Leidensia 1988*;1:47-52
58. Kurtzhals JAL, Rimert CM, Tette E et al. Increased eosinophil activity in acute *Plasmodium falciparum* infection – association with cerebral malaria. *Clin Exp Immunol 1998*;112:303-307
59. Shanks GD, Wilairatanaporn C. Eosinophilic response to malaria. *Southeast Asian J Trop Med Public Health* 1992; 23(4): 795-7
60. [van der Geld H](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22van%20der%20Geld%20H%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_RVAbstractPlus), [Peetoom F](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Peetoom%20F%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_RVAbstractPlus), [Somers K](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Somers%20K%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_RVAbstractPlus), [Kanyerezi BR](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kanyerezi%20BR%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_RVAbstractPlus). Immunohistological and serological studies in endomyocardial fibrosis Lancet 1966; 2(7475):1210-3
61. Jaiyesimi F, Ojo CO and Falase AO. Vitamin E status in endomyocardial fibrosis and other forms of heart disease. *Nig Med J 1978*;8:5-7
62. Shaper AG, Kaplan MH, Mody NJ, McIntyre PA. Malarial Antibodies and Autoanti-bodies to Heart and other tissues in the immigrant and indigenous peoples of Uganda. *Lancet 1968*;291(7556):1342-7
63. Connor DH, Somers K, Hutt MSR, Manion WC, D’Arbela 9. PG. Endomyocardial fibrosis in Uganda (Davies’ disease). Part I: An epidemiologic, clinical, and pathologic study. *Am Heart J* 1967; *74* : 687-709.
64. Kartha CC, Valiathan MS, Eapen JT, Rathinam K, Kumary TV, Kutty VR. Enhancement of cerium levels and associated myocardial lesions in hypomagnesaemic rats fed on cerium-adulterated diet. In: Endomyocardial Fibrosis Valiathan MS, Somers K, Kartha CC (eds). Oxford University Press 1993, Dehli. pp 243-253
65. Davies H. Endomyocardial fibrosis and the tuberous diet. *Int J Cardiol 1990*;29:3-8
66. Valiathan MS, Shymkrishnan KG. Surgical treatment of endomyocardial fibrosis: Kerala experience. In: Endomyocardial Fibrosis Valiathan MS, Somers K, Kartha CC (eds). Oxford University Press 1993, Dehli. pp 220-227
67. Ijaola O, Falase AO. Distribution of antibodies against Coxsackie B viruses, arboviruses and toxoplasma gondii among patients with endomyocardial fibrosis (EMF) compared with normal subjects from EMF endemic and non-endemic zones of Nigeria. *Afr J Med med Sci 1990*;19:93-103.
68. Ferrans VJ, Van Vleet JF. Cardiac lesions of selenium-vitamin E deficiency in animals. *Heart Vessels Suppl 1985*:1294-7.
69. Ball JD, Williams AW, Davies JN. Endomyocardial fibrosis. 6. *Lancet* 1954; *266* : 1049-54
70. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. Immunol Allergy Clin North Am. 2007;27(3):457-75.
71. Davies J, Spry CJ, Vijayaraghavan G, De Souza JA. A comparison of the clinical and cardiological features of endomyocardial disease in temperate and tropical regions. Postgrad Med J. 1983;59(689):179-85.
72. Ijaola O and Falase AO. The aetiology of endomyocardial fibrosis (EMF): Eosinophilia and parasitic infestations in EMF patients and normal subjects from EMF endemic and non-endemic zones of Nigeria. *Tropical Cardiology 1988*;14(53):17-23.
73. Urhoghide GE, Falase AO. Degranulated eosinophils, eosinophil granule basic proteins and humoral factors in Nigerians with endomyocardial fibrosis. *Afr J Med med Sci 1987*;16:133-9.
74. Dgedge M, Novoa A, Macassa G *et al*. The burden of disease in Maputo City, Mozambique: registered and autopsied deaths in 1994. *Bull World Health Organ*;79(6): 546-552.
75. Gujral L, Vaz RG. (2000) Prevalence, risk behaviour and level of information on urinary schistosomiasis in primary school students from the Primeiro de Junho Helath District , Maputo, Mozambique. *Cad Saude Publica*; 16(1):43-50
76. Traquinho GA, Quinto L, Nalá RM, Vaz RG, Corachan M. (1998) Schistosomiasis in Northern Mozambique. *Trans R Soc Trop Med Hyg*;92(3):279-81
77. Brockington IF, Olsen EGJ. Loeffler endocarditis and Davies’endomyocardial fibrosis. *Am Heart J 1973*;85(3):308-22.
78. Carlisle R, Ogunba EO, McFarlane H, Onayemi OA, Oyeleya VO. (1972) Immunoglobulins and antibody to Loa loa in Nigerians with Endomyocardial Fibrosis and other heart diseases. *Br Heart J*;34:678-80.
79. Brockington IF Endomyocardial fibrosis, filariasis and eosinophilia. In: Cardiovascular disease in the tropics (Ed by AG Shaper, MSR Hutt and Z Fejfar) 1974; pp 42-45. British Medical Association, London.
80. Rutakingirwa M, Ziegler JL, Newton R, Freers J. Poverty and eosinophilia are risk factors endomyocardial fibrosis (EMF) in Uganda. *Trop Med Inter Health 1999*;4(3):229-35.
81. Bustinduy AL, Luzinda K, Mpoya S, Gothard P, Stone N, Wright S, Stothard JR. Endomyocardial fibrosis (EMF) in a Ugandan child with advanced hepatosplenic schistosomiasis: coincidence or connection? Am J Trop Med Hyg. 2014;91(4):798-800.
82. Mocumbi AO, Goncalves C, Damasceno A, Carrilho C. Active schistosomiasis, severe hypereosinophilia and rapid progression of chronic endomyocardial fibrosis. *Cardiovasc J Afr*. 2016;27(5):e4-e6.
83. Beaton A, Sable C, Brown J, Hoffman J, Mungoma M, Mondo C, Cereb N, Brown C, Susmmar M, Freers J, Ferreira MB, Yacoub M, Mocumbi AO. Genetic susceptibility to endomyocardial fibrosis. Glob Cardiol Sci Pract. 2014;2014(4):473-81.
84. Lachaud M, Lachaud C, Sidi D, Menete A, Jouven X, Marijon E, Ferreira B. [Tropical endomyocardial fibrosis: Perspectives]. Ann Cardiol Angeiol (Paris). 2018;67(2):74-81.
85. Mocumbi AO, Sidi D, Vouhe P, Yacoub M. An innovative technique for the relief of right ventricular trabecular cavity obliteration in endomyocardial fibrosis. J Thorac Cardiovasc Surg. 2007 Oct;134(4):1070-2. PubMed PMID: 17903544.
86. Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen TL, MacLean DA, Pedersen BK (March 1997). *Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage.* The Journal of Physiology. 499 ( Pt 3) (3): 833–41.
87. Thesis. Mocumbi A. Imperial College London. 2008

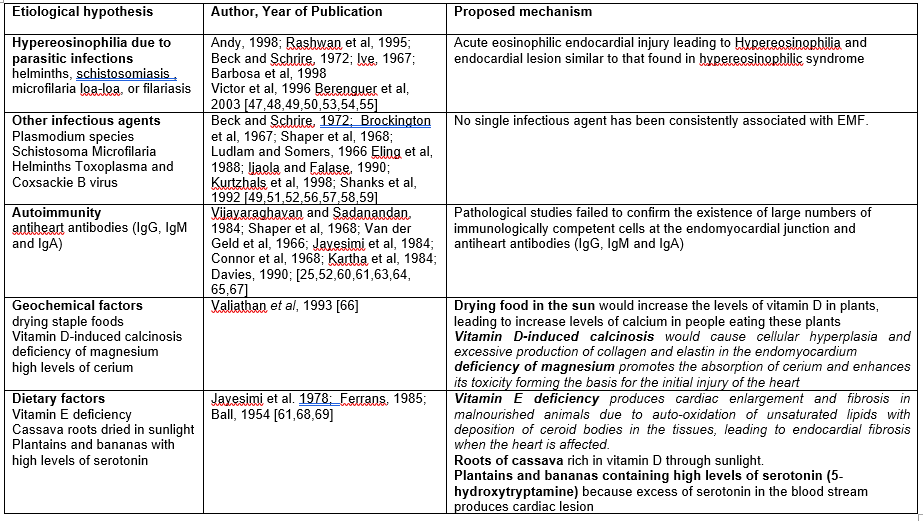
Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J, Kremer J. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Annals of the Rheumatic Diseases* 2008. 67 (11): 1516–23.

1. Mocumbi AO, Carrilho C, Sarathchandra P, Ferreira MB, Yacoub M, Burke M. Echocardiography accurately assesses the pathological abnormalities of chronic endomyocardial fibrosis. *Int J Cardiovasc Imaging*. 2011;27(7):955-64.
2. Kharwa Kharwar RB, Sethi R, Narain VS. Right-sided endomyocardial fibrosis with a right atrial thrombus: three-dimensional transthoracic echocardiographic evaluation. Echocardiography. 2013;30(10):E322-5.
3. Chaosuwannakit N, Makarawate P. Cardiac magnetic resonance imaging for the diagnosis of endomyocardial fibrosis. Southeast Asian J Trop Med Public Health. 2014;45(5):1142-8.
4. Smedema JP, Winckels SK, Snoep G, Vainer J, Bekkers SC, Crijns HJ. Tropical endomyocardial fibrosis (Davies' disease): case report demonstrating the role of magnetic resonance imaging. Int J Cardiovasc Imaging. 2004;20(6):517-22.
5. Aikawa T, Kamiya K, Mitsuhashi T, Anzai T. Endomyocardial fibrosis presenting as apical calcification and infective endocarditis. Eur Heart J. 2019;40(12):1016.
6. Bertrand E. [Endomyocardial fibrosis or fibroplastic endocarditis. Indications and results of surgical treatment]. Ann Cardiol Angeiol (Paris). 1984;33(1):35-41.
7. Somers K, Patel AK, D’Arbela PG. The Natural History of African Endomyocardial Fibrosis. Proceedings of the VIII World Congress of Cardiology Hayase S and Murao S (eds) Excerpta Medica 1978, Holland.
8. Nabunnya YB, Kayima J, Longenecker CT, Josephson RA, Freers J. The safety and efficacy of prednisolone in preventing reaccumulation of ascites among endomyocardial fibrosis patients in Uganda: a randomized clinical trial. BMC Res Notes. 2015;8:783. doi: 10.1186/s13104-015-1761-0.
9. Zilla P, Yacoub M, Zühlke L, Beyersdorf F, Sliwa K, Khubulava G et al. Global Unmet Needs in Cardiac Surgery. *Glob Heart*. 2018. pii: S2211-8160(18)30094-2.
10. Schneider U, Jenni R, Turina J, Turina M, Hess OM. Long-term follow up of patients with endomyocardial fibrosis: effects of surgery. Heart. 1998;79(4):362-7.
11. Nair U, Evans T, Oakley D. Surgical treatment of endomyocardial fibrosis with preservation of mitral valve. Heart 1980;43:357-359.
12. Metras D, Coulibaly AO, Ouattara K. The surgical treatment of endomyocardial fibrosis: results in 55 patients. Circulation. 1985;72(3 Pt 2):II274-9.
13. Mocumbi AO, Carrilho C, Burke MM, Wright G, Yacoub MH. Emergency surgical treatment of advanced endomyocardial fibrosis in Mozambique. *Nat Clin Pract Cardiovasc Med*. 2009;6(3):210-4.
14. Kumar N, Prabhakar G, Fawzy ME, al Halees Z, Duran CM. Total cavopulmonary connection for right ventricular endomyocardial fibrosis. Eur J Cardiothorac Surg. 1992;6(7):391-2.

LEGENDS

TABLE

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



FIGURE

(LEFT) Left ventricle with severe endomyocardial fibrosis complicated with large apical thrombus that dislodged suddenly and caused patient’s death; below see specimen from that ventricle with marked neovascularization, inflammatory infiltrates and loss of definition of the endomyocardial transition due to fibrinoid deposition (at the area of thrombus dislodgment).

(RIGHT) Severe right ventricle endomyocardial fibrosis with areas of thick endocardium near the subvalvar apparatus attachments. This corresponds (below) to areas of marked endocardial thickening, hyalinization and little cellularity; notice the intact endothelial line.

