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Review article

Endomyocardial fibrosis: A form of endemic restrictive cardiomyopathy

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ABSTRACT

Endomyocardial fibrosis is a form of endemic restrictive cardiomyopathy that affects mainly children and adolescents, and is geographically restricted to some poor areas of Africa, Latin America and Asia. It is a condition with high morbidity and mortality, for which no effective therapy is available. Although several hypotheses have been proposed as triggers or causal factors for the disease, none are able to explain the occurrence of the disease worldwide.

In endemic areas of Africa endomyocardial fibrosis is as common a cause of heart failure as rheumatic heart disease, accounting for up to 20% of cases of heart failure and imposes a considerable burden to the communities and the health systems. However, due to lack of resources for research in these areas, the exact epidemiology, etiology and pathogenesis remain unknown, and the natural history is incompletely understood.

We here review the main aspects of epidemiology, natural history, clinical picture and management of endomyocardial fibrosis, proposing new ways to increase research into this challenging and neglected cardiovascular disease.

Keywords: endomyocardial fibrosis, restrictive cardiomyopathy, endemic disease

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INTRODUCTION

Depending on the part of the world one lives in, restrictive cardiomyopathy is either one of the rarest forms of myocardial disease (usually seen in the elderly) or is endemic and affects mainly children and adolescents (being secondary to endomyocardial fibrosis) [1].

Endomyocardial fibrosis (EMF) is the most common form of restrictive cardiomyopathy [2], largely due to its considerable prevalence in some highly-populated areas of sub-Saharan Africa [3]; it occurs mainly in the tropical environments of developing countries where it affects mostly children of low-income communities [2,4]. In endemic areas of Africa, EMF is a main cause of heart failure, comparable to rheumatic heart disease (RHD) [2], accounting for up to 20% of all cases [5]. The exact epidemiology of the disease is unknown, its etiology and pathogenesis remain unclear and the natural history is not completely understood. Therefore, no effective therapy is currently available for EMF.

Possible etiological factors

No single proposed factor can explain the occurrence of EMF worldwide. The factors most frequently implicated in the etiopathogenesis of EMF are ethnicity [6], poverty [7], cassava [8–10], serotonin [11], malnutrition [12], magnesium deficiency [13], cerium and vitamin D, infections (viral and parasitic), autoimmunity, eosinophilia [14], toxic agents (plant toxins) and heredity [15].

Since there have been reports of sporadic cases of EMF in foreign people from temperate areas after short stays in endemic regions [16,17], and in view of climatic restrictions of the disease, the role of infectious agents appears plausible. *Plasmodium* species [18,19], *Schistosoma* [20], *Microfilaria* [21,22], *Helminths* [23–25], *Coxsackie B* virus, Arboviruses and *Toxoplasma gondhi* [26,27] have all been considered as possible causes or triggers for disease.

While the importance of genetic predisposition is less studied, it is supported by the finding of familial cases of EMF in clinical series [28,29] and demonstration of familial clustering of cases in a community-based study in Mozambique [30]. Both environmental and genetic factors may play a role in determining familial EMF.

Research in African populations has shown evidence of higher prevalence of anti-heart antibodies in EMF patients when compared to those with rheumatic heart disease, dilated cardiomyopathy and healthy controls [31,32]; it is not clear whether these autoantibodies are the cause or the result of EMF. In a subset of EMF patients from Mozambique who had their serum tested for the presence of anti-myocardial proteins [33], strong immunoglobulin G (IgG) reactivity against myocardial proteins was found. These patients also had an increase in immunoglobulin M (IgM) reactivity when compared to healthy controls, corroborating previous findings from India [34,35].

Epidemiology

The major determinants of EMF seem to be age, gender, ethnicity, social deprivation and eosinophilia. More than half of all EMF cases are diagnosed during the first decade of life [2,30] and a second peak incidence occurs in women of childbearing age [7]. Adult preponderance has been found in young women from Uganda, but in Mozambique, males were more commonly affected, while in other studies, both sexes were equally affected [15,30,36–38].

There is regional variation in the incidence of EMF [6,15,39]. Countries with large series of patients include Uganda, Côte d'Ivoire, Nigeria, Mozambique, India and Brazil. In Uganda there was preponderance of the condition in immigrants from the neighboring countries of Rwanda and Burundi [7], while in Mozambique a striking incidence rate was found in an ethnic group from a rural coastal area [39]. Although reported sporadically in people from high socio-economic levels after short visits to endemic areas [16,17], EMF affects mainly poor people living in resource-deprived areas.

Hypereosinophilia is a usual finding in patients with EMF seeking medical attention, reaching 10–30% of white blood cell counts over several months or even years [40]. Diseases such as Loeffler's eosinophilic parietal endocarditis and eosinophilic collagen vascular disease, which are associated with severe chronic eosinophilia, are known to cause endomyocardial damage [41]. As a result, many authors consider EMF to be the tropical variant of the hypereosinophilic syndrome encountered in temperate climates as it is associated with the overproduction of IL-5 and causes fibrotic lesions identical to those seen with EMF [42].

In Uganda, eosinophilia does not affect patients with EMF any more than the population at large [43], nor has eosinophilia been recognized in the thrombotic and fibrotic endocardial lesions studied in biopsy [44] and necropsy specimens [36,45]. Studies from Nigeria [46] also failed to show any difference between the mean eosinophil counts in patients with EMF and controls from the general population. Degranulated eosinophils were absent in blood and bone marrow aspirates from patients, and the mean concentrations of eosinophil granule basic proteins were not different in the two groups. Unfortunately, only one study looked at hypereosinophilia in patients with recent history of disease [23] showing highly significant inverse relationships between hypereosinophilia and the duration of symptoms in EMF patients.

Natural history

The disease appears to start as a febrile episode that is associated with facial swelling, body itching, hypereosinophilia and thromboembolism [23]. Ventricular thrombosis affects mainly the apices and the recess behind the posterior leaflet of the mitral valve [36]. Endocardial fibrosis, thought to result from organization of thrombi, reduces ventricular cavity size and impedes adequate filling, leading to restrictive physiology; it also affects the papillary muscles, chordae and/or leaflets causing valve distortion that results in severe atrioventricular regurgitation.

The natural history of EMF is not completely understood because patients usually present late to medical attention. Particularly in right predominant cases, the most common form of the disease [47], patients remain asymptomatic for long periods [48]. At presentation most patients have complications such as heart failure, arrhythmias or thromboembolism. Signs of chronic disease are the consequence of sustained low cardiac output and include finger and toe clubbing, growth retardation, testicular atrophy, failure to develop male secondary sexual characteristics and cachexia [49,50].

Pathology

The pathological hallmark of established EMF is focal or diffuse endocardial thickening. The macroscopic appearance and the sites of involvement in the ventricle are distinctive and there seems to be no primary involvement of extra-cardiac organs. Microscopically there is deposition of dense fibrous tissue in the sub-endocardium with superimposed thrombosis and calcification in advanced stages [51,52].

Knowledge is mostly based on autopsies done on patients who have died from complications of long-standing heart failure or rapidly progressive acute EMF [31,36,45] due to lack of cardiac catheterization and open-heart surgery facilities in most endemic areas. More recently, histological findings *in vivo* have documented endomyocardial biopsies obtained through cardiac catheterization [53,54] or surgery [55,56].

Macroscopical appearance

In advanced right ventricular EMF, an aneurysmal right atrium determines cardiomegaly and the characteristic right border notch or retraction. The pericardial sac may present adhesions between the parietal and visceral layers. Thrombosis and fibrosis are characteristically prominent in ventricular apices and at the posterior wall of the left ventricle, behind the posterior leaflet of the mitral valve [36]. The scar tissue may be massive, causing apical obliteration, as well as fixation, and obliteration of the papillary muscles and chordae tendineae. The left ventricular apex is frequently scarred and thrombosed, but never contracted. The semilunar valves and the great vessels are usually not involved.

Microscopy

The hallmark of EMF is endocardial thickening due to acellular fibro-collagen tissue deposition underneath the endothelial layer of the endocardium (Fig. 1). A marked degree of myocardial loss is rare, although subendocardial myocytolytic lesions are seen [45]. Mild inflammatory infiltrates, predominantly with lymphocytes, are frequent but intense eosinophilic infiltrates and small vessel disease are unusual [52,53].

There is consensus that the cardinal feature of EMF is abnormal stimulation of cardiac fibroblasts, leading to enhanced collagen synthesis. Myocytolisis is a minor component and could be caused by entrapment by fibrosis and toxicity by the same factors which produce the interstitial injury.

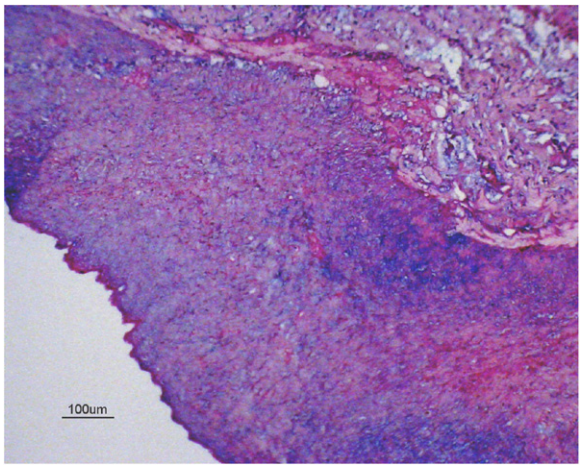

Figure 1. Severe irregular endocardial thickening is shown in photomicrography of a ventricle affected by advanced endomyocardial fibrosis (10X Alcian Blue).

Clinical picture and pathophysiology

The clinical picture of EMF depends on the ventricle affected, the duration of disease and the presence of signs of activity. Cachexia, malnutrition and hypoalbuminemia are characteristic of advanced disease. Despite their low age, patients have chronic and severe disease associated with malnutrition, stunned growth, signs of long-standing heart failure, atrial fibrillation and presence of endocardial calcification, confirming the malignant nature of this condition. Clinical feminization occurs in male patients with chronic disease [57].

Right ventricular EMF is the most common form of presentation either in isolation or as part of biventricular disease. It presents with chronic systemic venous hypertension that leads to exophthalmos, elevated jugular pressure, gross hepatomegaly and congestive splenomegaly; chronic thromboembolism may lead to pulmonary hypertension [58,59]. In left ventricular EMF, a soft and short systolic murmur confined to early systole is usually found. This is associated with a delayed opening snap and a loud pulmonary component of the second sound [2], indicating increased pulmonary pressures. In bilateral disease there are a combination of signs from left and right EMF.

Several distinctive features cannot be explained solely by low cardiac output and retrograde congestion [60], including central cyanosis, giant ascitis in the absence of pedal edema, hyperpigmentation of lips and gums, proptosis and parotid swelling. Ascitis is not fully explained by congestion since the fluid is an exudate with predominance of lymphocytes and high protein content; it is thought to be due to peritoneal inflammation and reduced reabsorption of peritoneal fluid caused by fibrosis. Fibrosis is also present in skeletal muscle suggesting a generalized fibrous process that would explain the remarkable skeletal muscle atrophy present in some patients [61]. Arterial oxygen desaturation occurs in advanced right EMF even in the absence of atrial septal defect or patent foramen ovale [62].

Atrial enlargement, one of the most important pathophysiological adaptation mechanisms that maintains cardiac output, is associated with impairment in exercise capacity [63]. The presence of pericardial effusion further impairs the diastolic function (which has already been compromised by endocardial thickening) and also decreases the capacity for exercise.

Progression to generalized edema and hypoalbuminemia can occur in advanced disease with hepatic dysfunction, and is precipitated by repeated drainages of ascitis fluid for symptomatic relief.

Complementary exams

Hypereosinophilia is a common finding usually found without any evidence of infection or parasitism, occurring in over a quarter of patients seen in hospitals [7,23].

In advanced stages of the disease, the electrocardiogram shows low-voltage QRS complexes, non-specific ST-T wave changes, conduction disturbances and atrial arrhythmias [65]. In right EMF there is a tall and broad right atrial wave, dominant R wave or “qR” pattern in the leads V3R or V1, and delayed right ventricular conduction [47]. Conduction defects occur in approximately half of the patients [64].

The chest X-ray of right EMF shows cardiomegaly due to severe right atrial enlargement, a bulge over the left heart border due to dilatation of the infundibulum and hypoperfused lungs [2]. In left EMF, the main pulmonary artery is prominent, there is an exaggeration of the blood vessels in the lung fields and left atrial enlargement [47]. Cardiomegaly can be exaggerated by pericardial effusion, and pleural effusion is also a common finding (Fig. 2).

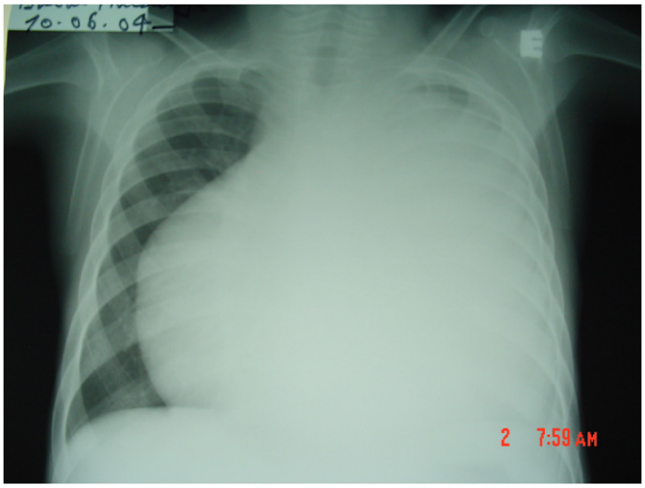

Figure 2. Chest radiography of a child with advanced right EMF showing cardiomegaly with right atrial dilatation and abundant left pleural effusion.

Due to the presence of advanced heart failure, ascitis and cachexia cardiopulmonary exercise testing is of limited clinical application in patients with EMF. Therefore, the left atrial dimension has been proposed to estimate the functional capacity [63].

Echocardiography is the gold standard technique for diagnosis of EMF as it accurately assesses the pathological abnormalities of chronic disease [52], revealing dense endocardial echocardiograms along different parts of the mural and valvar endocardium, atrioventricular valve dysfunction and restrictive filling pattern [66]. A typical feature of EMF is the obliteration of the trabecular portion of the right ventricle [67,68], which is suggested by filling defects, and is best seen by four-chamber view [69]. In advanced cases, there is shrinkage of the cavity creating an apical notch, free tricuspid regurgitation, slow flow through the right cavities with spontaneous contrast, right atrial thrombi and considerable pericardial effusion [70] (Fig. 3). Regarding left EMF, the ventricular apex can be obliterated, resulting in a round shape of the ventricle, restricted movement of the fibrotic apex of the left ventricle and a compensatory contractile mechanism causing an exaggerated and distinctive motion of the basal portion of the left ventricle [71]. On M-mode, the septal and posterior wall can assume an M-shaped movement on the basal portion of the ventricle, a finding relatively common in isolated or predominant left EMF [71]. The fusion of the posterior mitral leaflet to the wall causes severe eccentric mitral regurgitation and results in severe atrial enlargement (Fig. 4).

The transmitral velocity flow, the duration of the deceleration time and the isovolumic relaxation time reveal the presence of a left ventricular restrictive filling pattern. There is a brisk, early diastolic filling with poor filling in the remainder of diastole, absence of respiratory changes and presence of a normal pericardium enabling distinction from constrictive pericarditis. The transtricuspid flow is also very much impaired in advanced disease due to equalization of pressure in the right cavities.

Tomography may be used to characterize calcification suspected at the X-ray and echocardiography stages [72]. Magnetic resonance imaging (MRI) is the best imaging technique, adding precision to the diagnosis by delineating hypoperfused areas corresponding to fibrosis, confirming the existence of thrombus or calcifications, and providing functional information [73–75]. It has also been shown to be useful in establishing the prognosis through quantification of fibrous tissue deposition patterns [76], but is not readily available in most endemic areas of Africa. Cardiac catheterization and endomyocardial biopsy are seldom used.

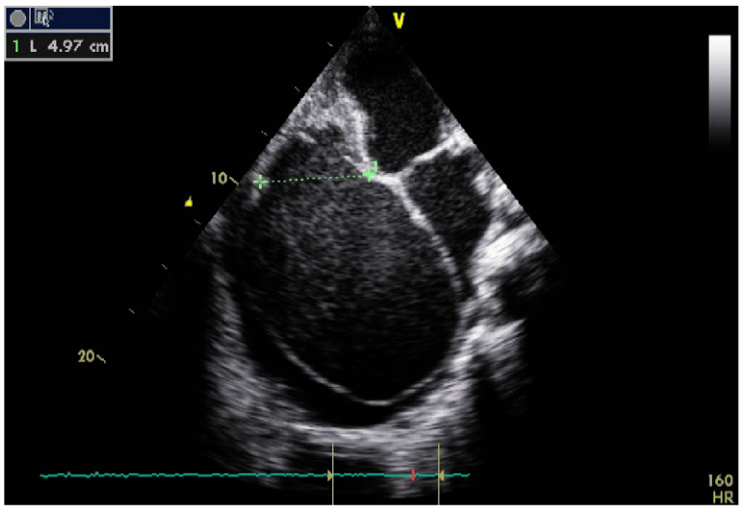

Figure 3. Echocardiographic features of predominant right endomyocardial fibrosis are shown in this picture, namely obliteration of the right ventricle with reduction of cavity volume, tricuspid annulus dilatation, aneurismal right atrium with spontaneous contrast. There is compression of the left cavities, thickening of the mitral leaflets and pericardial effusion.

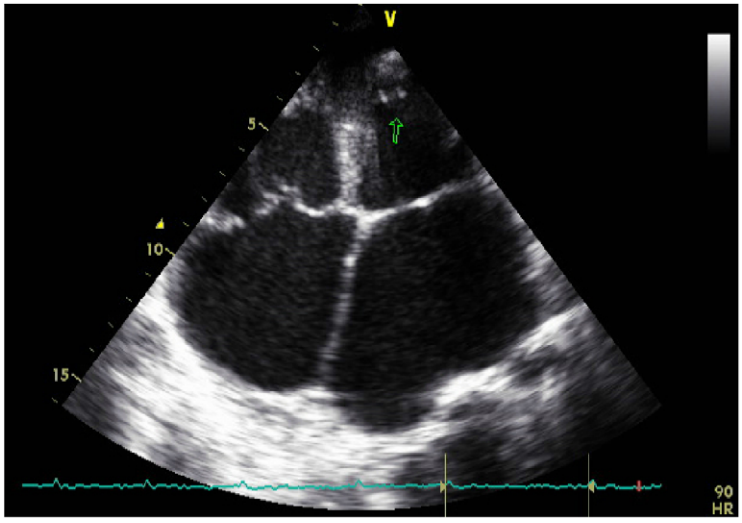

Figure 4. The main echocardiographic signs of bilateral endomyocardial fibrosis are seen in this photograph: small ventricles with large atria, filling defect in the apices suggesting thrombus on the left ventricle (arrow).

Differential diagnosis

In areas endemic for EMF, distinction should be made from RHD, dilated cardiomyopathy, tuberculous pericarditis and constructive pericarditis, hence the need for echocardiography [2,77]. Past history of rheumatic fever, evidence of mitral stenosis or involvement of the aortic valve favors RHD, but pure mitral insufficiency may be particularly difficult to differentiate from left EMF when fibrosis and endocardial thickening affects predominantly the valve tissue. Of notice is the concurrence of RHD and EMF in some patients [31,78]. Dilated cardiomyopathy is a diagnosis by exclusion of other possible causes of cardiac failure [79]. Finally, right EMF may mimic Ebstein malformation [80].

Management

The medical management of EMF consists of ameliorating acute disease, as well as preventing and treating heart failure, arrhythmias and thromboembolism. In poor settings, where the disease is endemic, this is usually achieved with the use of corticosteroids, diuretics, vasodilators, digitalis,

beta-blockers and anticoagulants. Patients with advanced disease need large doses of drugs and frequent admissions to hospital for invasive procedures to alleviate effusions and control arrhythmias.

The use of oral corticosteroids in patients with EMF and hypereosinophilia is not supported by clinical trials or longitudinal studies on the effects of this therapy. Indeed, several reports show that they have no or little influence on the natural course of EMF [2,40,49] and Rutakingirwa et al. [7] suggest that eosinophilia is a putative cause of EMF, independent of parasitism. Therefore, the use of corticosteroids must be balanced with its known disadvantages and risks in populations with high prevalence of infectious diseases, particularly tuberculosis.

Although it is logical to think that recurrent pericardial effusions can benefit from pericardiopleural windows or pericardioperitoneal shunts, this remains to be shown in prospective studies. Surgical procedures for the control of tense ascitis have had no success [81] and therefore management of ascitis relies on frequent evacuation of fluid by paracentesis; sometimes intravenous replacement of albumin at the time of the procedure is used to compensate protein loss [2].

Surgery increases survival and quality of life, when compared to medical therapy [82,83], but must be performed before irreversible cardiac and hepatic damage occurs. The surgical treatment of EMF is based on the following important facts: severe disease is fatal if untreated; the severe hemodynamic derangement caused by restriction of the diastolic filling and atrioventricular regurgitation can be corrected; in a considerable number of cases endocardectomy is feasible through a relatively well preserved cleavage plan releasing an unaffected and somehow healthy myocardium. Low rates of recurrence have been reported [84] although the real numbers remain uncertain [85,86].

Surgical procedures tailored to structural abnormalities have been used with promising results [87,88] but, due to a lack of human and material resources for open-heart surgery in most endemic areas, experience has been growing slowly. Relative contra-indications for surgery in poor-settings are large long-standing ascitis, extreme cachexia, chronic pulmonary thromboembolism, extensive endocardial fibrosis or calcification, impaired myocardial function and extreme shortening of leaflets with valve replacement being anticipated.

Right heart lesions are approached through right atriotomy; this allows wide access to the right ventricular cavity through a usually markedly dilated tricuspid annulus. Combination of sharp and blunt dissection through a cleavage plan is used to excise the thick fibrous endocardial lining, separating it from the myocardium (Fig. 5) while ensuring conservation of the tricuspid valve chordae and papillary muscles, and avoiding the conduction tissue [87]. Recreating the cavity inside the trabecular part is achieved by separating the fused *trabeculae*. Tricuspid valve repair is always needed and right atrial reduction and thrombectomy may be performed (Fig. 6).

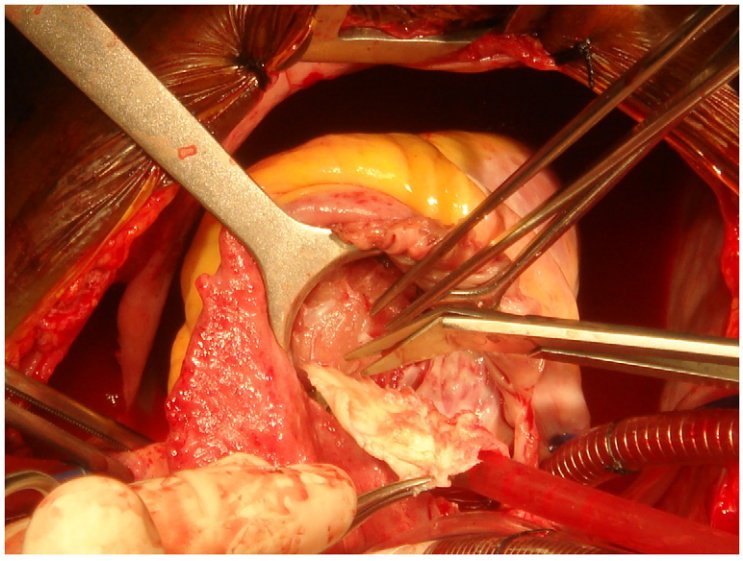

Figure 5. Intraoperative image of the surgical procedure to excise the thickened endocardium. Myocardium with healthy appearance is seen underneath the excised endocardium.

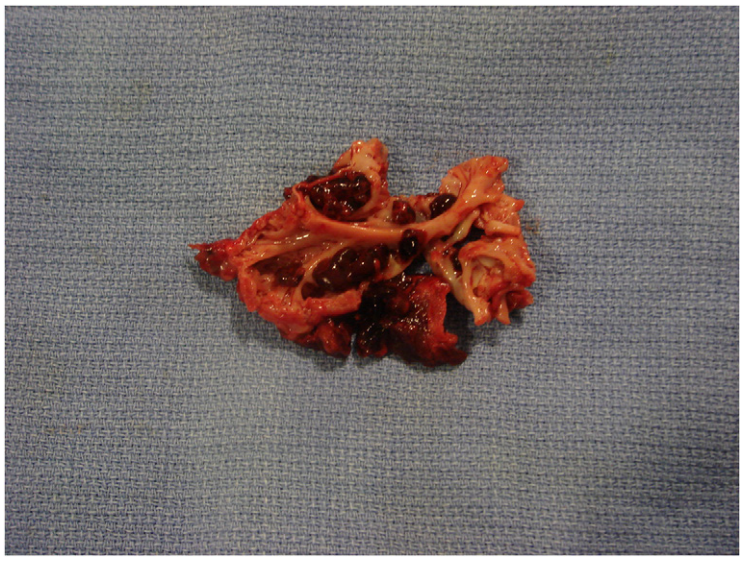

Figure 6. Excised right atrial appendage of a patient with right EMF, aneurysmal right atrium and thrombi attached to its wall.

With left EMF, the mitral annulus and inflow part of the left ventricle are exposed through atriotomy. This allows the assessment of distribution and extent of valve lesions in most patients but ventriculotomy may be required for complete evaluation of apical lesions [88]. Surgery consists of conservative endocardectomy and mitral valve repair or replacement.

Patients with right EMF may benefit from cavopulmonary anastomosis and 1.5 ventricle repair [89–91]. Marked clinical and hemodynamic improvement usually occurs after this procedure, allowing for the completion of open-heart surgery for endocardectomy some months later. The Glenn procedure is mandatory in patients with a small right ventricular cavity after endocardectomy [89–91].

Immediate post-operative complications include; severe low cardiac output syndrome, pericardial tamponade and complete atrioventricular block. Hospital mortality rates were initially reported at 18–29% [84–86,92] due to low cardiac output state and complete atrioventricular block following extensive endocardial resection. Late mortality was also high and mainly related to complications of valve prosthesis, documented valve thrombosis and uncontrolled bleeding. The results of surgery have been improving with the use of valve repair and new techniques for myocardial protection.

Prognosis

EMF carries high morbidity and mortality. The mean survival of EMF patients after diagnosis was approximately two years [2]. Death results from chronic heart failure, arrhythmia and thromboembolism. Surgery can correct some structural and functional abnormalities but it has been associated with uncertain, long-term outcomes. Recurrences and appearance of EMF lesions on the contralateral ventricle after surgery have been reported in proportions varying from 6–18.8% [93]. Cardiac transplantation has been used in one patient [94].

Survival has improved with advances in therapy for heart failure and arrhythmias, as well as in prevention of thromboembolism. Patients with right-sided disease present better tolerance to exercise and may remain relatively asymptomatic for several years, despite severe disease associated with cardiomegaly and intermittent pericardial effusion [48,95]. Their lack of disability and relative longevity seems to be associated with the capacity to increase cardiac output and slightly decrease the right atrial pressure.

The rates of infective endocarditis are very low in EMF patients despite the higher number of invasive procedures to which they are submitted. This might be related to the absence of inflammatory changes in the outer regions of the thickened endocardium, which does not favor the development of vegetations.

RESEARCH CHALLENGES AND NEW OPPORTUNITIES

Cardiovascular diseases in Africa can differ greatly across certain groups of populations, especially due to variations in exposure to known risk factors, unhealthy lifestyles, access to healthcare, genetic factors and environmental conditions—the latter including traditional customs. The dominant factors limiting research in areas endemic for EMF are; lack of trained human resources, absence of suitable infrastructure and financial constraints. Initial efforts to unveil the etiology and mechanisms of EMF in Africa came from Uganda through pathological and clinical studies performed before availability of echocardiography in the continent. The possibility of using portable battery-powered machines for echocardiograms in remote communities unveiled important aspects of the natural history and pathophysiology of EMF [30,33,87], and may foster research into the epidemiology and mechanisms of the disease [95].

North-South collaboration projects to empower tertiary healthcare facilities in Africa have made contributions to tackle clinical and research challenges in Mozambique and Uganda. The role of surgery in improving knowledge must not be overlooked but, in view of the burden of EMF management in underserved areas of the globe, concerted efforts from local scientists, communities, insurance companies and governments are needed to insure long-term sustainability of these initiatives. A shift from descriptive studies to basic research is needed, including testing of interventions and understanding of mechanisms, in order to identify new therapeutic targets that may improve prognosis.

COMPETING INTERESTS

The author of this review has no competing interests.

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