Recent advances in the epidemiology, diagnosis and treatment of endomyocardial fibrosis in Africa

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ABSTRACT

Endomyocardial fibrosis (EMF) continues to be an important and disabling disease in many parts of Africa, although its prevalence has declined in some parts of the continent. Increased access to medical care in general and increased availability of echocardiography in some parts of the continent have led to recognition of the disease in areas in which the disease had not been previously reported, and this has given new insights into its natural history. However, the early manifestations of EMF continue to elude clinicians and researchers, and no progress has been made in defining its aetiology. Advances have, however, been made in establishing the epidemiology and improving clinical diagnosis and management, through modern medical therapy and improved surgical techniques. Research is still required to define clinical, biological and echocardiographic markers of early stages of EMF, so that advances in the knowledge of its pathogenesis and pathophysiology can be made. This will hopefully determine preventive measures and avoid the burden of this debilitating condition in this continent.

INTRODUCTION

Endomyocardial fibrosis (EMF) was first reported by Arthur Williams in 1938[1] in two hearts with large endocardial patches of fibrosis in Uganda. Similar reports also came from Nigeria in 1946 among Nigerian soldiers serving in World War II[2] and from patients seen in East Africa by Davies.[3] It was Davies who first described the disease as a distinct entity, correlating its pathological findings with its clinical features. Since then, EMF has been reported in other parts of Africa and further afield, such as India, Brazil and other parts of the world.[4]

EMF is characterised by thickening of the ventricular endocardium with dense and white fibrous tissue that often extends to the inner third of the myocardium, causing cavity obliteration and restriction of ventricular filling by blood.[5] The atrioventricular valves may become enmeshed by the scar tissue, which consequently binds down the posterior valve leaflet and leaves the valve perpetually open. Free regurgitation of blood occurs because of this, resulting in an enormously dilated atrium, cardiomegaly and congestive heart failure.

EPIDEMIOLOGY

The epidemiology of EMF in Africa remains incompletely understood. This is because early manifestations of the disease are not sufficiently characterised and definitive diagnosis is often made only when the disease has reached an advanced chronic stage when the causative factors are no longer easy to detect.

Geographical distribution

Countries where EMF was initially studied include Uganda, Nigeria and Ivory Coast.[5] Then the disease was described in Egypt, Ethiopia, Congo, Mozambique, Kenya, Sudan, Zimbabwe, South Africa, Ghana, Zambia, Senegal and Tanzania.[6]

The increasing availability of echocardiography in Africa has led to detection of the disease in new areas of the continent and at levels that were unsuspected. In Mozambique, portable battery-powered echocardiographic screening performed on a random sample of 1063 subjects of all age groups in an endemic district showed an overall prevalence of EMF of 19.8% (95% CI 17.4% to 22.2%). EMF was recently reported in Malawi, in children who presented with advanced stages of the disease.[7]

Trends in its incidence and prevalence have been difficult to define. In 2007, Ellis *et al*[8] confirmed that the prevalence of EMF in Uganda had not changed. However, in Nigeria, a decline in the prevalence of EMF has been shown.[9 10] The change is marked in the south-west of Nigeria, with a reduction from 10% in the 1960s and 1970s to 0.02% for medical cases and 0.04% for cardiac cases in the first decade of the 21st century.[9] The positive impact of improved healthcare delivery on the control of communicable diseases is thought to be responsible for these observed changes.

Age and gender distribution

While EMF is often seen in children and adolescents, it may also occur in both infants[11 12] and older people.[13] A second peak of incidence is found during the reproductive years in women.[14] While most hospital-based studies on EMF have failed to show a preponderance of one gender over the other,[4] one population study in Mozambique showed higher prevalence among males (23.0% vs 17.5%, p=0.03).[13]

AETIOLOGY AND PATHOGENESIS

The underlying cause and mechanisms of endocardial fibrosis remain unclear. Recent research has brought no major advance in our knowledge of the pathogenesis of EMF, and the role of factors such as poverty, infectious agents, inflammation, autoimmunity, and genetic, geochemical and dietary factors remains unclear.[4 14] While myocardial fibrosis has been linked to increased levels of transforming growth factor β1,[15] there have been no studies focusing on the underlying mechanisms of endocardial fibrosis in EMF.

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Infectious agents

No specific organism has been associated with EMF in a consistent manner. An association of EMF with cardiotropic viruses and *Mycoplasma pneumonia* in Brazil has been suggested.[16] In Africa, where many of the regions endemic for EMF are also highly endemic for malaria, this parasite was suggested to be a trigger for the disease. However, severe and complicated malaria is not associated with myocardial damage, when measured by the presence of troponin in serum and echocardiographic evidence of systolic dysfunction.[17] Schistosoma species have also been implicated in the pathogenesis of EMF, particularly because its occurrence is linked to hypereosinophilia,[18] but also because there are several reports of coexistence of the two conditions.[19 20]

Autoimmunity

The presence of antibodies against myocardial proteins has been demonstrated in a subset of patients from Mozambique with advanced EMF.[21] IgG reactivity to myocardial proteins was stronger and more common in patients with EMF than in healthy controls from the same population. Moreover, the degree of serum reactivity correlated with the severity and activity of the disease.

Hypereosinophilia

Despite the finding of hypereosinophilia in up to 30% of patients with EMF, the role of cardiovascular allergy in the pathogenesis of this condition remains controversial. Blood and tissue eosinophilia have not been consistently recognised in patients with thrombotic and fibrotic endocardial lesions studied using biopsy samples obtained during surgery.[22]

Genetics

There is no compelling evidence to support the contribution of inherited factors to the pathogenesis of EMF.[23] Familial occurrence of EMF, initially reported among clinical cases and later confirmed in the community,[13] as well as marked phenotypic variability in EMF expression may suggest an influence of host factors in determining the establishment and outcome. Hereditary factors are also suggested by the recent finding of EMF in an infant born in a non-endemic area, who had a father who came from an endemic region.[11]

Traditional medicines

The role of toxic herbal decoctions taken as medicines in causing EMF has been suggested in a recent publication from Uganda, but there is no convincing proof of this assertion.[24]

NATURAL HISTORY

The unknown triggers of EMF seem to lead to various outcomes: subclinical course, clinical progressive disease, or burnt out disease with no residual abnormality. When triggers cause considerable inflammation, there is progression to necrosis and/or thrombosis resulting in formation of endomyocardial scar. The successive stages of necrosis, thrombosis and fibrosis are described as sequential, but no study has performed serial clinical and/or echocardiographic evaluation or analysed serial endomyocardial biopsy specimens.

PATHOPHYSIOLOGY

EMF is a disease of poverty, which is probably the template that allows other triggers to cause cardiac inflammation responsible for the initial pancarditis. Poverty and the associated low protein intake lead to increased susceptibility to infections that may act as triggers. The role of the eosinophil in the pathogenesis of EMF is controversial. Whether the eosinophil actually induces myocardial necrosis and subsequent fibrosis or is attracted to the endocardial surface as a result of the initial insult is not clear.

Inflammation is present in all layers of the heart, and occurs in both early and late stages of the disease.[22] The underlying inflammatory process evolves to cause patchy endocardial fibrosis, which results in reduced compliance and, ultimately, restrictive physiology as the endomyocardial surface becomes more generally involved.

Endocardial fibrosis involves predominantly the ventricular apices and the atrioventricular valves; these valves are tethered by the papillary muscles leading to tricuspid and mitral regurgitation. Myocardial fibrosis increases the stiffness of the heart, resulting in the restrictive physiology; along with atrioventricular valvular regurgitation, ventricular stiffness results in atrial enlargement, which is linked to atrial arrhythmias.

Atrial fibrillation (AF) occurs in more than 30% of patients with EMF, followed by other rhythm or conduction abnormalities such as junctional rhythm, heart blocks and intraventricular conduction delay.[25] Fibrosis also reduces conduction velocity, impairs activation pattern, and may provide the substrate for arrhythmia.

The mechanism responsible for the pronounced lesions seen in the ventricular apices is not well understood, but may be related to the poor vascularisation of these parts of the cardiac chambers. Poor vascularisation in the apices may result in failure of cardiac cell repair, endomyocardial degeneration and fibrosis, which lead to thrombosis and thromboembolism. While the changes described above can potentially explain most of the symptoms in patients with EMF, several features that occur in this condition are not clearly explained. These include labial cyanosis, parotid hypertrophy, ascites and absence of pedal oedema.

The existence of large ascites with little or no oedema is a striking finding. The ascitic fluid contains more white blood cells and higher protein content than expected in heart failure. Some observations suggest peritoneal inflammation with increased sequestration of fluid and fibrosis, with decreased reabsorption as the main cause of the striking ascitis.[26]

DIAGNOSIS

The clinical diagnosis of EMF is difficult to determine in the absence of cardiac failure. Structural and functional information can be provided by ECG and imaging techniques, namely echocardiography, angiocardiography, CT and MRI.

Physical examination

Right ventricular EMF

The syndrome of right ventricular EMF is characterised by grossly raised systemic venous pressure, hepatic distension, jugular venous distension with positive Kussmaul's sign, and ascites, but peripheral oedema is often absent. The right ventricular outflow tract is often abnormally pulsatile causing a heave at the left upper parasternal area. Murmurs are typically absent, although other signs of tricuspid regurgitation are present. A third sound is usual; so also is pericardial effusion. Patients may also present with facial oedema and periorbital puffiness, proptosis, central cyanosis, finger and toe clubbing, tricuspid regurgitation, as well as pulsatile and enlarged liver.

Left ventricular EMF

In left ventricular EMF, there are signs of mitral regurgitation due to tethering of the posterior mitral leaflet, but the systolic murmur is typically soft, short and confined to early systole. A delayed opening snap is present, related to the abnormal movement of the anterior leaflet.

Bilateral EMF

EMF lesions are seldom restricted to one side of the heart. The majority of patients with EMF have bilateral EMF. Predominance of right-sided lesions is the most common form; by reducing pulmonary perfusion, right EMF lesions reduce the hazards of severe pulmonary hypertension caused by left-sided lesions allowing longer survival.

Acute EMF

Acute EMF is diagnosed when there is fever, hypereosinophilia, myopericarditis, abdominal distension, facial oedema, periorbital swelling, body itching, and urticarial and, occasionally, neurological features such as stroke. In contrast, signs such as finger and toe clubbing, growth retardation, testicular atrophy and failure of the development of male secondary sexual characters are features of chronicity.[27]

By the time patients present to hospital, the disease is usually at an advanced stage. Pericardial effusion is present in 40% of cases of childhood EMF, aggravating the restrictive cardiomyopathy. Many of the children present with exophthalmus, jaundice, peripheral cyanosis, finger clubbing, severe ascites and AF. Dissociation between clinical and echocardiographic findings is common, mainly in right forms of the disease.[28]

Biological profile

No specific laboratory test can diagnose EMF. Typically there is lack of evidence of infection, allergy, poisoning or any consistent association with parasitism and eosinophilia.[29] Hypereosinophilia is a common finding in over a quarter of the patients presenting to hospitals. Hypoproteinaemia is characteristic of very advanced disease. The ascitic fluid is typically an exudate with predominant lymphocytes; it contains more white blood cells and has higher protein content than the ascitic fluid of the patients with right heart failure without EMF, suggesting a role for inflammation in the pathogenesis of EMF.[5 30]

The results of studies of the coagulation and activation of the immune system in Mozambique have not been conclusive, but suggest a role for autoantibodies in pathogenesis.[21]

Electrocardiography

The ECG in established EMF reflects the structural abnormalities of the cardiac chambers and the conduction system, the subsequent haemodynamic changes, and the presence of pericardial effusion. The ECG often suggests atrial enlargement, reflecting increased pressure and volume overload. Patients with large pericardial effusion often have low-voltage QRS.

In right ventricular EMF, the abnormalities include peaked P waves in lead II and QR pattern with diminutive R wave in lead V1 (figure 1). Dominant R wave in lead V2 in the absence of QR pattern in V1 is found in some patients. In left ventricular EMF, left atrial abnormality in ECG parallels the diastolic dysfunction and degree of mitral incompetence; there is uniform ST segment depression and T wave inversion more evident in the lateral chest leads, similar to apical hypertrophic cardiomyopathy and non-ST elevation acute coronary syndromes. In patients with advanced left ventricular EMF and resultant pulmonary hypertension, there are features of RV hypertrophy and rightward frontal plane QRS axis deviation.

Atrial arrhythmias are common, and AF is the end stage in most patients with advanced EMF, occurring in advanced and uncorrected forms of both right and left ventricular EMF. It is noteworthy that patients with right ventricular EMF and AF rarely have fast ventricular response, in striking contrast with those with AF and left ventricular EMF. Ventricular tachycardia and sudden death attributable to malignant ventricular arrhythmia may occur.[31]

Electrophysiological studies of patients in sinus rhythm have shown lower AV Wenckebach heart rate on incremental atrial pacing. The atria have pockets of low-voltage splintered atrial activity. The injury potentials obtained from the RV endocardium have low voltages corresponding to areas of fibrotic endocardial involvement, but the pacing threshold at the fibrotic areas was, surprisingly, within normal range.[31] Complete heart block and sick sinus syndrome are rare in patients with EMF.

Less affected patients are often diagnosed when evaluated for non-specific symptoms and an abnormal ECG. The ECG is neither sensitive nor specific enough to rule in or rule out EMF, and meticulous echocardiographic examination is the investigation of choice to detect milder forms of EMF.[31]

Echocardiography

Echocardiography has been used as the lone technique for diagnosis and management of EMF in Africa, where it has become relatively available at referral hospitals. The diagnosis is made in the presence of dense endocardial echoes associated with a restrictive pattern and characteristic structural abnormalities. There is up to 82.8% agreement between transthoracic echocardiography and intraoperative findings in patients with severe EMF, confirming this non-invasive technique as the one of choice for diagnosis and surgical management of chronic EMF in endemic areas.[22]

M-mode, two-dimensional and Doppler examination are enough to make an accurate diagnosis of established EMF on echocardiography. The criteria often used for diagnosis of right ventricular EMF are apical obliteration (figures 2 and 3), reduction of the right ventricular cavity, cleavage plane between the fibrous tissue and myocardium, parietal thrombosis, dilatation of the right ventricular outflow tract, paradoxical movement of the interventricular septum, dilatation of the right atrium, a tricuspid valve that is adherent to the endocardium, tricuspid regurgitation, diastolic opening of the pulmonary valve, dilatation of the inferior vena cava, rapid deceleration of the E-wave with inexpressive A-wave on the Doppler, and pericardial effusion. For the diagnosis of left ventricular EMF, the most important features are the reduction in longitudinal diameter of the left ventricle which becomes spherical or oval, dilatation and hyperkinesis of the basal portion of the left ventricle (Merlon sign), restriction and disappearance of the posterior leaflet of the mitral valve, eccentric mitral regurgitation, and severe dilatation of the left atrium.[32]

Studies in rural communities have revealed some features of EMF before severe cavity and valve distortion occurs.[13] These criteria have been proposed for early diagnosis and assessment of the severity of EMF, but have yet to be validated through follow-up studies.

Chest x-ray

The chest x-ray in right ventricular EMF often shows right atrial enlargement and a bulge over the left heart border associated with dilatation of the right ventricular infundibulum; the lung

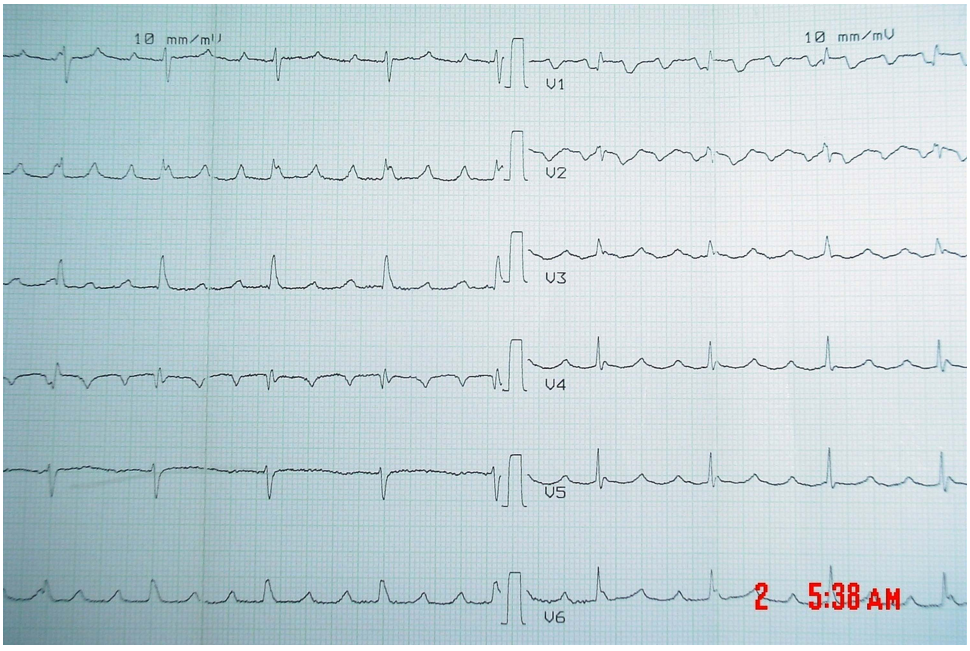

Figure 1 ECG showing some of the usual features in advanced right ventricular endomyocardial fibrosis such as peaked P waves, atrial arrhythmia and QR pattern in V1.

fields appear normal or hypoperfused. In left ventricular EMF, there is markedly prominent main pulmonary artery and changes suggestive of pulmonary hypertension are found in the lung fields, associated with left atrial enlargement. Rarely, endocardial calcification may be seen.

Computed tomography

Although rarely used, CT can accurately depict the morphological and dynamic features of EMF, through direct visualisation and mapping of fibrosis within the myocardial wall.[33] This can be of use in patients with severe heart distortion in areas without access to MRI. Calcification is seen as a linear calcification distal to the pericardium and along the inner border of the myocardium.

Magnetic resonance imaging

MRI is the gold standard technique for diagnosis of EMF, including diagnosis of early disease,[34 35] but is not widely used in Africa as it is unavailable in most endemic areas. First-step myocardial perfusion scans allow exact delimitation of hypoperfused areas that correspond to fibrosis, and confirm the existence of avascular structures (thrombus, calcification). Myocardial suppression scans, acquired after injection of gadolinium, help to delimit exactly the disease extension through delayed hyper-enhancement of the pathological areas, independent of actual thickening.[36] The detection of subendocardial fibrosis has good histopathological correlation, providing a comprehensive tool for non-invasive assessment of EMF.[37]

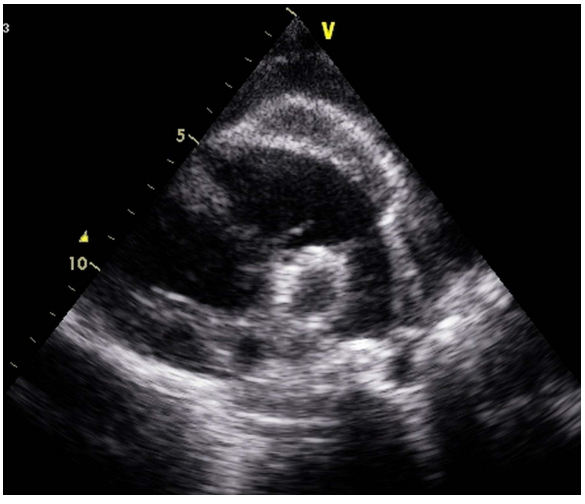

Figure 2 Echocardiography of a patient with right endomyocardial fibrosis found during a community study, showing obliteration of the ventricular cavity and ventricular cavity reduction.

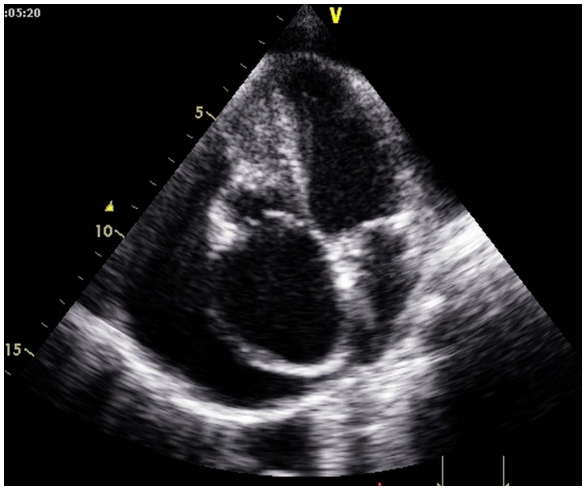

Figure 3 In this echocardiographic image, right atrial dilatation, right ventricular obliteration and marked reduction of the right cavity dimensions with the beginning of apical retraction are easily seen. There is also pericardial effusion.

MRI is ideal for monitoring the response to medical and surgical treatment, as it can demonstrate the presence, location and extent of structural and functional abnormalities, even in patients with contorted anatomy, informing the managing physician on the feasibility of cardiac surgery.[38] In endemic areas for both EMF and tuberculosis, it can help to distinguish between cardiomyopathy and constrictive pericarditis in difficult cases.

Cardiac catheterisation

Cardiac catheterisation and angiography are not used routinely for diagnosis because non-invasive techniques are adequate. However, they can be necessary to assess the haemodynamics in patients with severe heart distortion in whom an accurate echocardiographic evaluation cannot be made. At cardiac catheterisation in right ventricular EMF, there are equal pressures in the right atrium, right ventricle and pulmonary artery, both in form and amplitude. Angiograms show flattened right ventricular apex, smoothening of trabeculae, free tricuspid reflux, large right atrium with prominent superior vena cava and active infundibulum.[39 40] Left ventricular EMF has characteristically very high left ventricular end-diastolic pressure with dip-plateau pattern; a variable degree of pulmonary hypertension is found, usually damped by the presence of the important right ventricular disease. The angiography of the left ventricle shows obliteration of the apex with varying degrees of mitral regurgitation; contractility varies from normal to severely impaired depending on the sites and severity of endocardial fibrosis; amputation of the apex is suspected if the distance from coronary arteries to the contrast inside the ventricular cavity is increased.[39 40]

Endomyocardial biopsy enables a definitive pathological diagnosis to be made, but is not essential for diagnosis or management, and may be technically difficult.

PATHOLOGY

Comparison of findings of transthoracic echocardiography with those obtained from both intraoperative examination and evaluation of tissue obtained by excisional biopsy has confirmed endocardial thickening as the most prominent abnormality.[22] Indeed endocardial thickening is considered the only useful parameter for identifying patients with EMF on histopathology,[41] and is the most striking feature of advanced disease (figure 4).

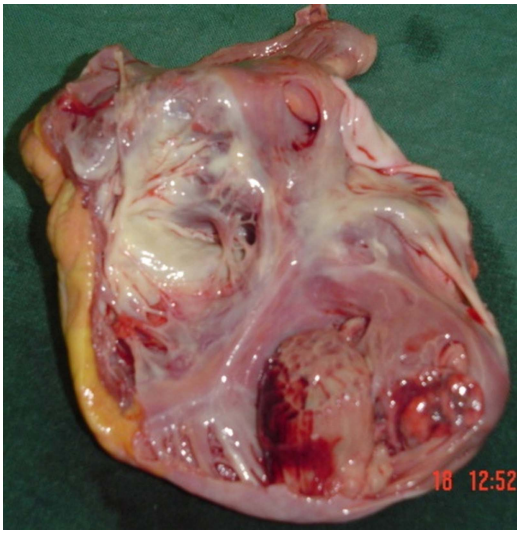

Figure 4 Post-mortem specimen of right endomyocardial fibrosis. Notice the large thrombus in the right atrium and extensive fibrosis of the right ventricle, with disappearance of its trabecular pattern.

Ventricular endocardial thickening usually involves the walls and atrioventricular valve apparatus in variable extension; it corresponds microscopically to increased number of fibroblasts in the subendocardium. The involvement of the inner myocardium seems to be an extension of the subendocardial changes rather than a fibroblast proliferation process, since there is no subendothelial vessel thickening and CD34 staining of vessels is negative.[22]

Mild to moderate inflammatory infiltrates composed mainly of lymphocytes are present on microscopic evaluation of most hearts, predominantly in the interface between the endocardium and the myocardium. Myocardial lesions such as inflammatory infiltrates, interstitial fibrosis and scars are more prominent in areas adjacent to subendocardial fibrosis and altered vessels, suggesting that they are a response to ischaemic injury caused by vascular changes. Cardiac tissue eosinophilia is rare in advanced disease.[22 42] There is a lack of vessels in the outer endocardium in clear contrast with rheumatic heart disease.

Differential diagnosis

In Africa, EMF must be differentiated from conditions such as rheumatic heart valve disease, dilated cardiomyopathy, constrictive pericarditis and tuberculous pericarditis. Endocardial fibroelastosis, Löeffler endocarditis, Ebstein's disease, neoplastic infiltration of the myocardium, amyloidosis, haemochromatosis, apical type of hypertrophic cardiomyopathy and myocardial sarcoidosis should also be considered depending on the clinical context.[31 40]

Differentiation between left EMF and rheumatic mitral disease may be challenging, in areas where the two conditions are highly prevalent. Mitral regurgitation with disproportionately high pulmonary pressure, absence of free border thickening in the mitral leaflets, attachment of the posterior mitral leaflet to the wall, involvement of the papillary muscles, and lack of left ventricular dilatation in the presence of severe mitral regurgitation, all favour the diagnosis of EMF.

EMF may be difficult to differentiate from constrictive pericarditis, but careful evaluation of the pericardium and endocardium on echocardiography allows the correct diagnosis to be made in most patients. EMF is diagnosed in the presence of normal pericardial thickness, severely dilated atria, large '*a*' waves, early diastolic dip and reversed diastolic pressure gradient across the pulmonary valve.

MANAGEMENT

In Africa, EMF is usually managed using medical therapy and invasive procedures for relief of pleural, pericardial and peritoneal effusions. Only a few hospitals are able to perform open heart surgery, and even fewer have the expertise to operate on patients with EMF.

In acute disease, oral corticoids are recommended for 7–10 days. However, the use of these drugs in Africa has to be balanced with the known risks of exacerbating common comorbidities such as tuberculosis, other bacterial infections, parasitic infestations and congestive heart failure.

Heart failure is controlled with diuretics, ACE inhibitors and β-blockers. Digitals are used to control heart rate in patients with atrial fibrillation or at imminent risk of losing sinus rhythm due to enlarged atria. In selected patients, oral anticoagulants are usually started for prevention of thromboembolism in atrial fibrillation and/or in the presence of ventricular or atrial thrombi.

Surgical treatment

Surgery is an option for patients with structural abnormalities that are amenable to correction. It is indicated in all patients with EMF in New York Heart Association class III and IV, as it increases survival and improves quality of life compared with medical therapy.[43 44]

The surgery is technically demanding, consisting of resecting the fibrous endocardium and correcting the atrioventricular valve abnormalities. It has been associated with high morbidity and mortality, mainly due to complications of valve replacement and extensive endocardial resection.

Innovative surgical approaches include partial resection, with preservation of the valve apparatus, atrioventricular valve repair and mobilisation of the trabeculae in right ventricular cavity obliteration, which reconstitutes the right ventricular cavity[45 46] (figure 5). The use of cavopulmonary anastomosis is helpful in cases of a small right ventricular cavity at the end of the resection procedure.[47 48] Atrial size reduction is an additional procedure used to lower the risk of thrombi formation and arrhythmia.[46] The results of these innovative procedures need long-term follow-up to ascertain their effect on survival.

PROGNOSIS

The overall prognosis of EMF is poor. The survival of patients with EMF after diagnosis is reported to be 2 years. The advent of new drugs for treatment of heart failure, antiarrhythmic compounds and use of echocardiographic-guided procedures for management of effusions may have contributed to the improvement in survival and quality of life of patients with EMF, but no data are available to support this statement. Moreover, recurrence after surgery has been documented.[49]

Death usually results from complications of chronic heart failure, but may be sudden resulting from acute thromboembolism and arrhythmia. Thromboembolism is associated with migration of thrombi from either the atria or the ventricles, and leads to acute or chronic pulmonary thromboembolism as well as to stroke or other forms of systemic emboli.

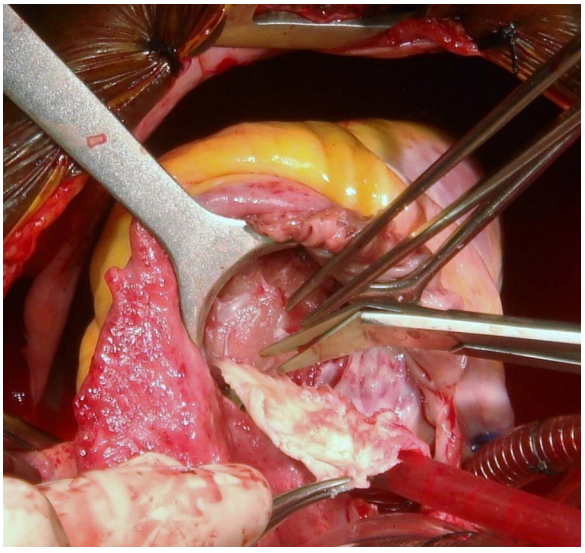

Figure 5 Intraoperative image of endocardial resection for treatment of right endomyocardial fibrosis, which releases the myocardium underneath the plaque of fibrous tissue and increases the size of the ventricular cavity.

CONCLUSIONS

EMF is a neglected disease of unknown aetiopathogenesis and unclear natural history, for which little improvement in knowledge of the basic mechanisms has occurred. A single community-based study using portable echocardiography in Africa has used new definitions of diagnostic criteria for early disease. Validation of these criteria is needed to allow studies into the epidemiology and natural history. Research into the mechanisms of the disease is the key to identifying new therapeutic targets and improving the outcome, and will allow the design of preventive measures to avoid the disease or progression to advanced forms. Areas of particular interest for research in Africa include evaluation of the role of infectious agents, toxic plants and allergy inducers.

The search for specific drugs aimed at preventing or controlling fibrosis must be combined with efforts to define and apply tailored surgical procedures, so that the devastating effects of this neglected disease can be avoided. Joint efforts in several endemic areas of Africa may be necessary to overcome the lack of expertise and financial constraints in the continent.

Contributors AOHM planned and wrote initial draft of the article and is responsible for its overall content. AOF contributed to the final content and editing of the manuscript.

Competing interests None.

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