Rheumatic heart disease and endomyocardial fibrosis: Distinguishing the etiology of mitral regurgitation in low-resourced areas

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ABSTRACT

Rheumatic heart disease (RHD) and endomyocardial fibrosis (EMF) are 2 neglected cardiovascular diseases that disproportionately affect young populations, living in poverty. RHD characteristically occurs in low- and middle-income countries, as well as in some disadvantaged populations within high-income countries, such as the Aboriginal peoples of Australia. In contrast, EMF is primarily a tropical cardiomyopathy, with both high-prevalence countries and high-prevalence regions within affected countries.

The etiology, pathogenesis, echocardiographic findings, interventions and prognosis are quite distinct. While RHD is unarguably the most preventable of all cardiac diseases, resulting from untreated or undertreated group A streptococcal infections, EMF's etiology remains unclear. It has been related to infections, dietary factors and toxic agents, and currently there are no specific drugs to treat EMF.

The distinction of mitral lesions due to RHD from left-sided EMF, can be difficult in endemic areas for both diseases, especially in the context of lack of resources for diagnosis. However, the correct distinction is highly important since medical management, surgical and interventional options and prognosis are considerably different. Here we describe the features that allow this distinction in African settings where both diseases occur, paying particular emphasis to echocardiography.

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INTRODUCTION

Rheumatic heart disease (RHD) and endomyocardial fibrosis (EMF) continue to exert a high burden among young populations living in conditions of poverty. RHD is common in almost all low- and middle-income countries, and in some disadvantaged populations within high-income countries, such as the Aboriginal peoples of Australia. In contrast, EMF is primarily a tropical cardiomyopathy, with both high-prevalence countries and high-prevalence regions within affected countries.

While it has been postulated that RHD and EMF are 2 distinct expressions of the same pathological process,[(1)] this is not widely believed. In fact, the etiology, pathogenesis, echocardiographic findings, interventions, and prognosis are quite distinct. RHD is unarguably the most preventable of all cardiac diseases, resulting from untreated or undertreated group A streptococcal infections, classically streptococcal pharyngitis, which trigger the immunological reaction acute rheumatic fever, leading to acute and chronic cardiac damage. After ARF/RHD is established, penicillin prophylaxis is a powerful modifier of disease course, with good adherence leading to stabilisation and sometimes regression of disease when initiated early.[(2)] In contrast, attempts to relate EMF to infections, dietary factors and toxic agents have failed to unveil the exact etiology and pathogenesis, and currently there are no specific drugs to treat EMF. Surgery is technically very demanding, and improvement in knowledge has been slow.

Despite these differences, it can be challenging to distinguish RHD from left-sided EMF in a clinical context, in particular when faced with mitral regurgitation in a low-resource setting. Making this distinction correctly is of high value, as the medical management, surgical and interventional options, and prognosis are considerably different.

Acute EMF vs. acute RHD

Acute mitral regurgitation can be viewed as part of the acute phase of both RHD (acute rheumatic fever, ARF) and EMF. As both are clinical diagnoses, lacking a confirmatory test, additional diagnostic work-up is needed. Of the 2, the clinical presentation of acute rheumatic fever is most clearly defined, and outlined in the Jones Criteria.[(3)] Indeed, in almost all cases, the diagnosis of ARF requires evidence of a recent streptococcal infection, as the link between untreated or undertreated group A streptococcus (GAS) and ARF is well established. Importantly, the

newest revision of the Jones Criteria[3] allows for echocardiographic evidence of carditis as a major criterion (as opposed to previous iterations allowing only auscultation), and provides less stringent diagnostic requirements for areas considered to be at moderate to high risk, meant to improve the diagnostic sensitivity.

In the setting of ARF, carditis occurs in more than 50% of patients, and is predominantly characterised by mitral valvulitis.[4] Less often, the aortic valve is also involved with resulting aortic regurgitation.[5-7] Rheumatic nodules, or a beaded appearance of the mitral leaflet that resolves as inflammation subsides, distinguish the mitral valve in ARF from other etiologies, but are found in only 25 - 50% of patients with acute carditis.[8,9] The mechanism of mitral regurgitation during the first episode of ARF is most commonly annular dilation resulting from a dilated left ventricle, followed by excessive motion of the anterior mitral leaflet caused by chordal elongation (inflammation), and in severe cases, chordal rupture. In recurrent ARF, the mechanisms are more complex, involving restricted leaflet mobility secondary to previous scarring, annular dilation, and leaflet prolapse.[9]

In contrast to ARF, the acute phase of EMF is poorly understood and incompletely described. There is no clear consensus on EMF's etiology, with various infectious, nutritional and environmental factors implicated, but not proven. It has been challenging to identify patients in the acute phase of disease and the majority of those affected are diagnosed in the late stage. Most consistently, acute EMF has been characterised by generalised allergic/immunological features including fever, abdominal distension, facial or periorbital swelling, body itching, urticaria, and neurological features, and associated with hypereosinophilia and myopericarditis.[10] A study in a rural endemic area of Mozambique found a prevalence of established EMF at 19.8% in the general population; only 22% of participants with echocardiographic features of EMF recalled fever or other complaints consistent with acute EMF.[11]

Common to both chronic disease states, is the belief that an acute phase exists for the majority of patients and that repeated insults (GAS exposure for RHD, unclear for EMF) contribute to the chronic cardiac manifestations. Historically, it was believed that RHD could not exist without a clear history of ARF, however echocardiographic screening studies showing a high prevalence of RHD absent history of ARF,[12,13] and the striking discrepancy between ARF and RHD burden in low-income countries is calling this into question. What is more likely is that while some patients exhibit a clear inflammatory state prior to development of chronic disease, some also suffer a sub-clinical course, presenting only when cardiac manifestations bring them to clinical attention.

PATHOLOGY

The pathological features of the mitral valve in both RHD and EMF are distinct and diagnostic, though rarely available in low-resource settings until post-mortem exam. Aschoff's bodies, granulomatous inflammatory nodules, are the histological hallmark of acute rheumatic carditis. In chronic RHD, the mitral valve is fibrotic and firm, typically with thickening of both leaflets seen most prominently at the tips.[14] Additionally, in advanced RHD there is thickening of the mitral valve chordal apparatus, with shortening and fusion of the chordae, as well as commissural fusion. This pathology results in immobility of the posterior mitral leaflet and pseudo-prolapse, also known as excessive motion of the anterior mitral leaflet.[15] This is notably different than classical mitral valve prolapse involving the mid-portion of the leaflet body, occurring when the tip of the leaflet extends beyond the closure plane during ventricular systole, resulting in non-cooptation and mitral regurgitation. Severe mitral annular calcification is rare[16] and the ventricular myocardium is grossly normal.

EMF is marked by focal or diffuse areas of endocardial thickening, characterised by a white, smooth, and shiny endocardial surface. The mitral valve leaflets invariably shows diffused irregular thickening, with fibrotic nodules and thickened chordae. The posterior leaflet, its chordae and the posterior papillary muscle are partially, or totally, fused to the posterior wall.[17,18] The anterior papillary muscle may be fused to the wall, with variable restriction of its mobility contributing significantly to mitral regurgitation and an additional component of mitral stenosis. Thrombosis and fibrosis are characteristically prominent in the ventricular apex and the posterior wall of the ventricle behind the posterior leaflet of the mitral valve. The left ventricular apex is frequently scarred and thrombosed, with varying degrees of obliteration, but without retraction of the apex. The semilunar valves are never involved.[17,18]

CLINICAL AND LABORATORY FEATURES

Though ARF is marked by evidence of group A strep infection and elevated inflammatory markers (ESR, CRP), chronic RHD has no distinguishing laboratory features. The biological profile of chronic EMF is also typically unremarkable, though high eosinophil counts are found in a variable proportion of cases.[19] Because patients with LEMF do not present the exuberant clinical features of chronic right EMF – such as finger clubbing, growth retardation, testicular atrophy, failure of the development of secondary sexual characters or cachexia - and are usually in a better general status, suspicion of LEMF may arise from the combination of a typically soft and short systolic murmur associated with a delayed opening snap. This is in contrast to cardiac auscultation in RHD, which frequently reveals a high-pitched, blowing and holosystolic apical murmur radiating to the axilla.

Electrocardiography

There are no specific electrical findings that distinguish chronic left-sided EMF from chronic RHD. The electrocardiogram in both cases reflects the severity of mitral regurgitation and the presence and degree of mitral stenosis with variable left ventricular and left atrial enlargement as well as a signs of right ventricular hypertrophy and strain when significant pulmonary hypertension is present. The exception to this is acute rheumatic

fever, classically marked by tachycardia and PR prolongation (a minor criterion for carditis in the Jones criteria). Wenckebach phenomenon and complete heart block are relatively rare.[20]

Echocardiography

Echocardiography is an essential tool in the diagnosis and management of RHD and EMF. Structural and hemodynamic abnormalities are important to classify valve lesions in acute and chronic phases, as well as to track progression of valve abnormalities and help determine the time for surgical intervention.

In rheumatic fever with carditis echocardiography identifies and quantifies valve abnormalities, ventricular dysfunction and pericardial effusion.[8,21] Acute rheumatic valvulitis is characterised by annular dilatation, elongation of the chordae to the anterior leaflet, nodular thickening of valve leaflets and postero-laterally directed mitral regurgitation jet.[8,9,21] Chordal thickening in the context of acute carditis suggests recurrence of acute rheumatic fever in patients with established rheumatic heart valve disease.[22] Mild mitral regurgitation present during the acute phase usually resolves weeks to months after, while patients with moderate-to-severe carditis have persistent mitral regurgitation. In most cases, the left ventricle is dilated with preserved or increased fractional shortening; however, a variable degree of ventricular dysfunction may occur in very advanced cases in African patients.

Isolated mitral regurgitation is the most common abnormality found in chronic RHD[9,21,23] and the most common morphological abnormalities are (a) valve and/or chordal thickening (Figure 1a); (b) restrictive leaflet motion due to chordal thickening, shortening or fusion, commissural fusion and leaflet calcification or thickening (Figure 1b); and (c) chordal elongation, rupture or prolapse (Figure 1b).[24-27] The posterior mitral leaflet is usually shortened and immobile resulting in non-coaptation of the leaflets.[28] Rarely there may be calcification of the subvalvar apparatus.[16]

Unique echocardiographic features of mitral regurgitation due to LEMF are large endocardial plaques, obliteration of ventricular apices or mitral valve recess, ventricular and atrial thrombi, ventricular cavity volume reduction, enlarged atrium, restricted mobility of the atrioventricular valve leaflets, fusion of the papillary muscles to the wall and abnormalities of the ventricular regional wall motion.[29-33] There is usually diffuse atrioventricular valve leaflet thickening and abnormal movement of the interventricular septum and/or posterior LV wall.[11] On the left side, the ventricular apex is never retracted; it becomes thicker leading to considerable reduction of the longitudinal diameter of the ventricle, resulting in a spherical ventricular shape. These features are shown in Figure 2a. Moderate pericardial effusion and endocardial calcification may be occasionally found.[34-36] Both the restriction to ventricular filling and the atrioventricular valve regurgitation result in an increase in atrial pressure, that leads to aneurysmal left atrium (Figure 2b).

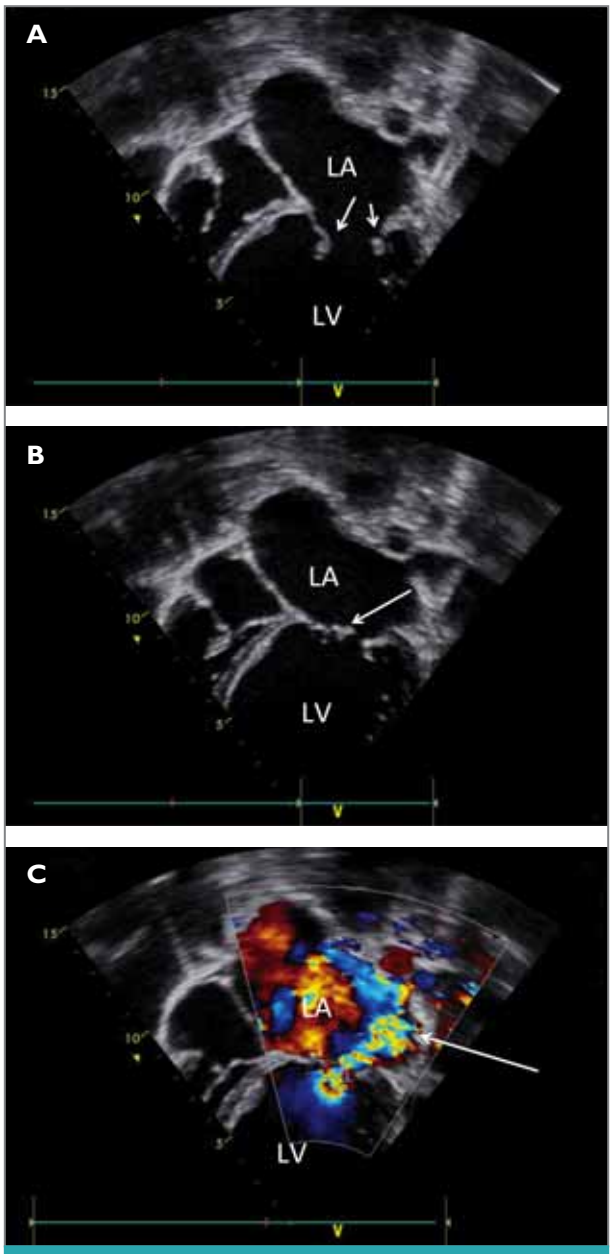

Figure 1A: 2D echocardiogram in apical 4-chamber view in a patient with advanced rheumatic heart disease. The left atrium (LA) is severely dilated, and the mitral valve leaflets demonstrate the characteristic "rolled appearance" at the leaflet tips as well as poor leaflet excursion during diastole secondary to shortening of the mitral valve chords and mitral commissural fusion.

Figure 1B: 2D echocardiogram in apical 4-chamber view in the patient with advanced rheumatic heart disease – now during ventricular systole. The white arrow shows the classical "excessive motion of the anterior mitral leaflet" that results most commonly in advanced RHD from poor mobility of the posterior mitral leaflet. Additionally, there is an obvious coaptation defect leading to the severe mitral regurgitation seen in Figure 1c.

Figure 1C: Colour Doppler 2D echocardiogram in apical 4-chamber view in the patient with advanced rheumatic heart disease – during ventricular systole. The white arrow shows the severe mitral regurgitation resulting from mitral leaflet non-coaptation.

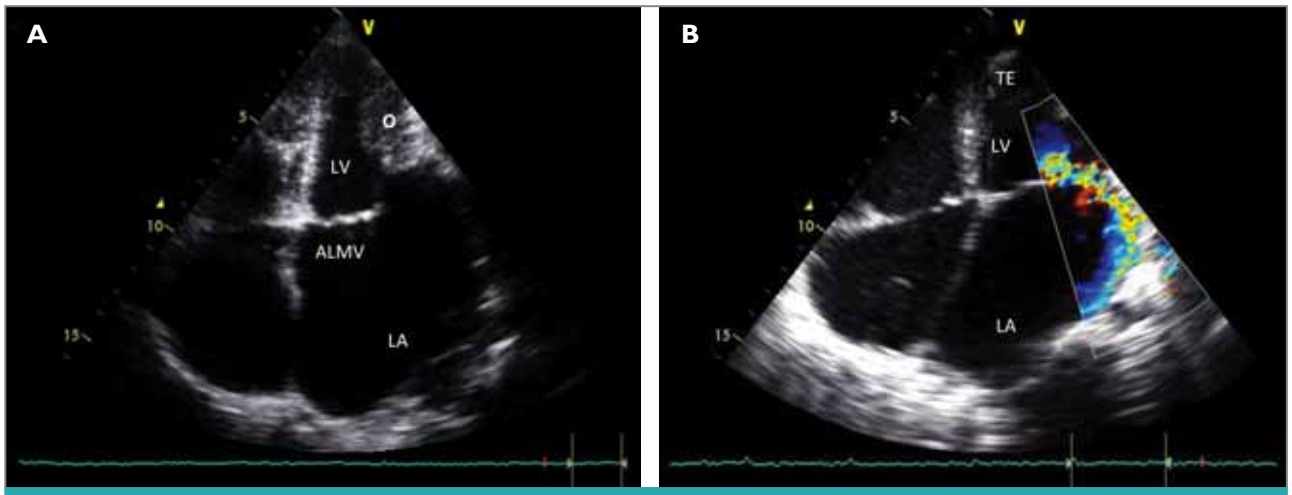

FIGURE 2A: 2D echocardiogram in apical 4-chamber view in a patient with predominant left Endomyocardial Fibrosis. The left ventricle (LV) is small. The anterior leaflet of the mitral valve (ALMV) is diffusely thick; the posterior leaflet cannot be seen due to its engulfment in the obliteration of the posterior mitral recess (O). This fusion of the posterior leaflet to the wall is the basis for non-coaptation and severe mitral regurgitation. The left atrium (LA) is aneurysmal while the left ventricle does not present dilatation.
FIGURE 2B: Colour Doppler 2D echocardiogram in apical 4-chamber view in the same patient seen in Figure 2A showing severe mitral regurgitation and the aneurysmal left atrium (LA). Also notice the spherical shape of the small left ventricle (LV), with thickened endocardium in the apex (TE).

The restricted movement of the fibrotic left ventricular apex and its obliteration are accompanied by compensatory contractile mechanism that results in exaggerated and distinctive motion of the basal portion of the left ventricle, the so-called Merlon sign.[33,37] On M-mode the interventricular septum motion assuming an M-shaped movement, as a result of rapid anterior movement in early diastole.[38]

In early stages of EMF spontaneous contrast and ventricular thrombi may be observed in a normally contracting left ventricle.[33] Ventricular obliteration – consisting in partial or complete exclusion of a portion of the ventricle from the circulation – affects both the apex and the recesses of the posterior mitral valve leaflet excluding these parts from the ventricular cavity.[33]

The most important echocardiographic features that assist in the differential diagnosis of Left-predominant Endomyocardial Fibrosis and Rheumatic Mitral Regurgitation. (Table 1)

Other imaging techniques

Imaging techniques such as axial tomography, magnetic resonance imaging and hemodynamic studies with ventriculography may complement anatomic and functional information in EMF. Computed Tomography, although seldom used in endemic areas, may help in depicting morphologic features of EMF, by allowing direct visualisation as well as mapping of fibrosis in the endocardium and within the myocardial wall. The presence of a linear calcification distal to the pericardium (along the inner border of the myocardium) suggests EMF at conventional and spiral computed tomography.[39] Magnetic Resonance Imaging has many advantages for diagnosing LEMF as it confirms the existence of thrombus or calcifications, and allows an exact delineation of hypoperfused areas that correspond to fibrosis. Advanced imaging is not routinely recommended or useful in the evaluation of patients with RHD, though 3-dimentional echocardiography has some incremental benefit for surgical planning for mitral valve repair.

INVASIVE DIAGNOSIS

While cardiac catheterisation can confirm hemodynamic abnormalities in EMF patients, it is not routinely recommended as it can be misleading in localised or mild forms of the disease and technically challenging and dangerous in advanced disease. Endomyocardial biopsy is difficult in areas of dense endocardial fibrosis and may give false negative results.

Left-sided EMF is characterised by elevated left ventricular end-diastolic pressure with dip-plateau pattern. Pulmonary hypertension is variably damped by the presence of the right ventricular disease. The left ventricular angiogram shows a spherical left ventricle, due to apical obliteration, with varying degree of mitral regurgitation.

Cardiac catheterisation is not recommended for routine evaluation of patients with RHD, unless the severity and reactivity of pulmonary hypertension is in question. However, interventional catheterisation, in the form of mitral balloon valvuloplasy, forms a central pillar of treatment for RHD patients with mitral stenosis, with an echocardiographic Wilcon's score of ≤8 predicting a favourable outcome with percutaneous valvuloplasty and that >8 favouring a surgical approach.[40]

TABLE 1: Distinguishing features to differentiate patients with rheumatic mitral regurgitation from those with left-dominant endomyocardial fibrosis.

	Rheumatic Heart Disease	Endomyocardial Fibrosis
Acute Phase	Acute Rheumatic Fever, Evidence of recent GAS infection, PR prolongation on ECG	Generalised Allergic/ Immune features: facial/ periorbital swelling, itching, urticaria, abdominal distension
Pathology	ARF: Ashoff bodies Chronic RHD: fibrotic, thickened MV, posterior leaflet immobility, chordal thickening and commissural fusion, normal endocardium	Focal or diffuse areas of endocardial thickening (white, smooth, shiny endocardial plaques), posterior mitral leaflet fused to LV free wall +/- anterior mitral leaflet fused to septal wall, thrombosis/fibrosis of LV apex with LV apical obliteration at later stages
Clinical	High-pitched, blowing, holosystolic apical murmur, radiating to the axilla	Soft, short systolic murmur with a delayed opening snap
Laboratory	ARF: evidence of GAS and elevated inflammatory markers Chronic RHD: None	Variable presentation with eosinophilia
ECG	ARF: tachycardia, prolonged PR Chronic RHD: No specific features	EMF: No specific features
Echocardiography	Morphological (thickened MV,"elbow deformity", restricted posterior mitral leaflet, chordal thickening) and Functional MV disease (MR +/- MS), with concurrent AV involvement (typically AI) in ≈ 20% patients, normal endocardium, typically with normal LV function in all but the most severe cases	Bright endocardial plaques; Plastered posterior mitral leaflet, sometimes completely adherent to the wall; Spherical left ventricle due to reduced longitudinal dimension; Obliterated left ventricular apex or posterior papillary muscle recess; LV apical thrombus; Endocardial calcification of the apex of the left ventricle; Spontaneous contrast or intra-cavitary thrombi; M-movement of interventricular septum and/or posterior wall; LA dilation out of proportion to MR (aneurysmal LA) and sometimes with pericardial effusion

AI = aortic valve, AV = aortic valve, ARF = acute rheumatic fever, ECG = electrocardiogram, GAS = group A streptococcus, LA = left atrium, LV = left ventricle, MR = mitral regurgitation, MV = mitral valve, PR = PR interval.

SURGICAL MANAGEMENT

RHD surgery is indicated when patients are symptomatic, have impairment of left ventricular function and/or severe pulmonary arterial hypertension. Because patients with advanced RHD are younger in Africa, surgical management is done trying to avoid the hazards of lifelong anticoagulation associated with prosthetic valves, hence the use of mitral repair. Frequently, the decision regarding the type of valve surgery includes not only clinical-echocardiographic criteria but also the assessment of the capacity to adequately follow-up and comply with anti-coagulation, usually related to economic constrains and, sometimes, cultural believes. Mitral valve repair should probably be the first choice to maximise survival and reduce morbidity associated with valve replacement in young patients and for those living in remote areas, even accepting a risk of reoperation.

Surgery for EMF requires a high level of technical expertise and experience. Though high risk, surgery increases survival and improves quality of life when compared to medical therapy[32] and is indicated in patients in NYHA classes III and IV who have structural lesions suitable for correction. Endocardectomy is the mainstay of surgical treatment for EMF, allowing relief of diastolic dysfunction through the removal of the fibrotic endocardium. In most cases, a clearly delineated cleavage plane allows for the removal of the stiff endocardium, revealing healthy myocardial tissue. Corrective surgery, using subtotal ventricular endocardial resection to avoid atrioventricular block, atrioventricular valve repair to treat mitral and tricuspid incompetence,[41] and new techniques of myocardial protection has reduced peri-operative mortality and morbidity.

PROGNOSIS

In low-resource settings, the tendency of both RHD and EMF to be diagnosed in the advanced stage, the lack of cardiology expertise, limited resources for medical management, and severely restricted or non-existant interventional and surgical options, results in poor outcomes for patients with both diseases. A recent multinational registry for RHD (REMEDY), containing clincial data and outcomes for patients with a new diagnosis of RHD, showed a 2-year case fatality rate of 16.9% with median age of death only 28.7 years.[42] When ideal medical and interventional therapy is availible, outcomes for RHD are much improved, with the majority of mortality related to compliance with secondary prophylaxis (lifetime for those requiring surgery), and complications of anticoagulation in those with mechanical mitral valves. Outcomes for patients with EMF, regardless of access to high-quality medical care, are substantially worse, though improving with strategies aimed at controlling heart failure symptoms, avoiding or treating arrythmias, and a push towards earlier surgical intervention.[41] Currently, endo-cardial resection with atrioventricular valve replacement has a reported 70% 10-year survival.[43]

Conflict of interest: none declared.

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