Epidemiology and Etiology of Cardiomyopathy in Africa

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Background—Cardiomyopathy, an often irreversible form of heart muscle disease that is associated with a dismal outcome, is endemic in Africa. The primary objective of this review was to summarize the current state of knowledge on the epidemiology and etiology of cardiomyopathy in people living in Africa and to identify new avenues for research.

Methods and Results—We searched MEDLINE (January 1, 1966, through February 12, 2005) and reference lists of articles for relevant references. Unlike other parts of the world in which cardiomyopathy is rare, dilated cardiomyopathy is a major cause of heart failure throughout Africa. Similarly, peripartum cardiomyopathy is ubiquitous on the continent, with an incidence ranging from 1 in 100 to 1 in 1000 deliveries. There is an apparent marked regional variation in the pathogenesis of dilated cardiomyopathy and peripartum cardiomyopathy, underlining the heterogeneity of causative factors in these conditions. By contrast, endomyocardial fibrosis is restricted to the tropical regions of East, Central, and West Africa. Although the pathogenesis of endomyocardial fibrosis is not fully understood, it seems that the conditioning factors are geography and diet, the triggering factor may be an as yet unidentified infective agent, and the perpetuating factor is eosinophilia. Although epidemiological studies are lacking, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy seem to have characteristics similar to those of other populations elsewhere in the world.

Conclusions—There is a need for large-scale epidemiological studies of the incidence, prevalence, determinants, and outcome of cardiomyopathy in Africa to inform strategies for the treatment and prevention of heart muscle disease on the continent. (Circulation. 2005;112:000-000.)

Key Words: Africa • cardiomyopathy • heart failure • infection • alcohol

Overall mortality in the developed world shows the preeminence of cardiovascular and neoplastic conditions. By contrast, infective and parasitic conditions remain the dominant causes of death and disability in Africa. Although the causes of heart failure vary within and between African countries, the pathogenesis remains largely nonischemic, with hypertension, rheumatic heart disease, and cardiomyopathy being the major causes of cardiovascular disease, whereas tuberculous pericarditis and pulmonary heart disease account for the remainder.

The cardiomyopathies pose the greatest challenge of all the cardiovascular diseases in Africa because of their greater prevalence in societies still plagued by diseases of famine and pestilence; the difficulty in diagnosis, which often requires specialized cardiological investigations that are lacking in resource-poor environments; the lack of access to effective interventions, such as heart transplantation; and the high mortality associated with these often irreversible disorders of heart muscle.

Since the first reports of heart failure of unknown cause in Africa appeared approximately 60 years ago, it has been recognized that the entity of “cryptogenic heart disease” in Africa represented more than one syndrome, although terms such as “cardiopathy,” “primary parietal endomyocarditis,” “primary mural endocardial disease,” and “cardiomyopathy” were initially used to embrace all forms of idiopathic heart disease. The cardiomyopathies are now defined as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathies.

The primary objective of this article was to summarize the literature on what is known about unique features of the epidemiology and etiology of the cardiomyopathies in Africa. These aspects of the disease, which are of vital importance for the treatment and control of the disease, have received scant attention in the international literature. We also identify areas in which knowledge is deficient and directions in which research efforts should be directed with particular reference to Africa. The pathological conditions, clinical features, and treatment of the cardiomyopathies, which have been reviewed elsewhere and apply universally, are not discussed in this review.

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We performed a MEDLINE search with the terms "cardiomyopathy, dilated cardiomyopathy, endomyocardial fibrosis, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia/cardiomyopathy" from January 1, 1966, through February 12, 2005, and consulted reference lists of the relevant articles and reviews on the subject. Only studies conducted in Africa and published in English were retrieved, and articles with important insights about the epidemiology and/or etiology of cardiomyopathy in Africa are cited.

**Dilated Cardiomyopathy in Africa**

**Epidemiology**

Idiopathic DCM is a clinical syndrome of heart failure that is associated with impaired systolic function and left ventricular dilatation in the absence of an identifiable cause. DCM vies with rheumatic heart disease and hypertension as one of the leading causes of heart failure in Africa.1

In South Africa and Uganda, DCM accounts for 10% to 17% of all cardiac conditions encountered at autopsy4,7,8 and in many parts of Africa, for 17% to 48% of patients who are hospitalized for heart failure.9–11 Whereas the incidence and prevalence of DCM in the United States and elsewhere is reported to be 4 to 8 per 100 000 person-years and 36.5 per 100 000 individuals, respectively,6 there are no population-based data on the burden of DCM in Africa.

DCM occurs at any age, but it is common in the third and fourth decades of life, and men are affected twice as commonly as women. Two thirds of patients with DCM, especially those who are more than 55 years of age, have persistently low arterial pressure, ventricular arrhythmias, and/or atrioventricular valve incompetence and die within 5 years of their first symptom.12,13

**Etiology**

Although the causes for DCM are largely unknown, it is generally accepted that the disease probably represents a final common expression of myocardial damage that could be provoked by multiple insults, including hemodynamic, infective, immunologic, toxic, nutritional, and genetic factors.6 The causative factors that have been examined in Africans include (1) “burnt-out” untreated hypertension, (2) infection and myocarditis, (3) autoimmune mechanisms, (4) iron overload and other metabolic factors, (5) genetic factors, (6) alcohol and nutritional deficiency, and (7) pregnancy.

The problem of distinguishing burnt-out hypertensive heart disease from DCM at first clinical presentation occurs for several reasons.14,15 First, the initial presentation of DCM may be accompanied by blood pressure readings in the hypertensive range in up to 8% of cases.15 Conversely, patients with hypertensive heart disease and severe systolic dysfunction may present initially with the blood pressure in the normal range, with hypertension declaring itself after a period of treatment; their presenting blood pressure is low because of their markedly reduced cardiac output.16 Second, the end-organ effects of hypertension, such as renal involvement and aortic dilatation, may not be apparent clinically.15 Although some have suggested that hypertensive heart disease of sufficient severity to produce congestive cardiac failure is invariably associated with advanced stages of retinopathy, whereas fundi are normal in cases of DCM,16 others have observed that retinopathy, the readily identifiable “fingerprint” of hypertension, is uncommon in Africans in the absence of uremia.15 Hypertension as the cause of heart failure may be recognized in retrospect on the basis of a rise in blood pressure to hypertensive levels after institution of therapy for heart failure.

The investigation of the role of infection and myocarditis in the pathogenesis of DCM in Africans has revealed striking regional variation. In Nigeria, infection with *Toxoplasma gondii* and coxsackievirus B is thought to play a major role in the pathogenesis of DCM on the basis of serological findings in case-control studies, but this assertion has not been substantiated by histological studies.17,18 By contrast, in Kenya, where half of the patients with DCM are reported to have histological signs of a previous myocarditis, no serological evidence of a previous or recent coxsackievirus B infection or any other common viral infections has been found, leading to the proposal that the myocarditis was a result of an inappropriate immunologic reaction to myocardial muscle.19 In South Africa, no pathological findings supportive of a previous viral myocarditis, persistent slow virus infection, or autoimmune process have been observed.20 Studies from Cameroon have demonstrated evidence for *trypanosomiasis* on immunofluorescence test in 27.5% of patients with DCM, compared with 1.9% of normal control subjects, suggesting that some cases of cardiomyopathy may be caused by untreated subclinical attacks of African trypanosomiasis, which produce immune complexes that damage the cardiac tissue in which the parasite is lodged.21 In African patients with DCM in the presence of a positive HIV test, preliminary data suggest that unlike Western series, in which viral myocarditis may be an important cause, nonviral causes of myocarditis, such as toxoplasmosis and mycobacteria, may be dominant.22

There are several lines of evidence that support the role of excessive immune activation in the pathogenesis of DCM in parts of Africa. In keeping with other autoimmune diseases, an imbalance between helper and suppressor T cells has been demonstrated in Kenyan patients with DCM, who demonstrate higher T-cell helper/suppressor ratio in case patients compared with normal subjects.23 The proliferating T cells could possibly induce effector cytotoxic T cells and B-lymphocyte clones producing anti-heart antibodies. These abnormalities may be linked to the high prevalence of endemic infections, such as malaria, trypanosomiasis, and viral infections.19,21,23

There is emerging clinical trial evidence from South Africa that supports the immune activation hypothesis of heart failure in African patients with DCM. Studies in patients with DCM and peripartum cardiomyopathy (PCM) showed significantly increased plasma levels of the inflammatory cytokine tumor necrosis factor (TNF)-α and a plasma marker of apoptosis, Fas/Apo-1.24–27 This observation has led to randomized studies of the effectiveness of the immunomodulating agent pentoxifylline in patients with heart failure caused by cardiomyopathy.24,27–29 Pentoxifylline reduces the synthesis of TNF-α by blocking transcriptional activation, and the drug has been shown to inhibit apoptosis in different human
cell types in vitro and in vivo. Treatment with pentoxifylline lowered the TNF-α and Fas/Apo-1 plasma levels in treated patients compared with control subjects. This effect was associated with an improvement in effort tolerance, left ventricular function, and a trend toward a lower mortality in patients on standard heart failure therapy. Pentoxifylline seems to have the same beneficial effects in patients with heart failure caused by nonischemic and ischemic DCM, suggesting that the immune activation that is seen in DCM may be a marker of heart failure and not a specific causative factor in DCM. Inflammation and immune activation is likely to contribute to only a fraction of patients with DCM, and targeting treatment with an immunomodulating action to that subgroup may be important. Elevated plasma levels of C-reactive protein identified those patients who responded to pentoxifylline. However, it remains speculative whether immunomodulation contributes to a larger extent to the pathogenesis in heart failure in Africans than in other populations.

A recent systematic review has highlighted the limitations of the available evidence for the effectiveness of pentoxifylline in the treatment of heart failure. The existing trials are small in size (with a total of 144 randomized participants) and do not provide reliable and robust estimates of the effect of pentoxifylline on important outcomes, such as mortality. The promising results that have been obtained with pentoxifylline in the treatment of heart failure caused by cardiomyopathy need to be tested in large multicenter randomized trials with the power to determine mortality benefits.

Iron excess because of consumption of iron-containing beer, previously referred to as Bantu hemosiderosis, may be an important and potentially reversible causative factor in some parts of Africa. The poor correlation of cardiac and hepatic iron deposits with heart disease may have led to the underrecognition of dietary iron overload as an important factor in the pathogenesis of DCM. High levels of serum ferritin have been documented in a small study of cases of DCM compared with patients with heart failure resulting from other causes, with 50% of cases having ferritin levels >500 ng/mL. The potentially significant role of dietary iron overload in the pathogenesis of DCM requires further investigation.

Although no studies have been conducted to assess the degree of familial aggregation of DCM in Africans, several association studies suggest that genes may play a role in the susceptibility to DCM in this population. An association with HLA-DR1 and DRw10 antigens has been reported in South African patients, implying that genetically determined immune-response factors play a role in the pathogenesis of some individuals with DCM. A common mitochondrial DNA polymorphism (T16189C) has also been found to be a genetic risk factor for DCM in a South African cohort, with a population-attributable risk of 6%. These genetic associations have been replicated in other populations, suggesting that they are likely to represent genuine genetic risk factors for DCM worldwide. Mutation screening studies in patients with idiopathic and familial DCM have identified a family with early-onset DCM caused by a known mutation in the troponin T gene (Arg141Trp), but they failed to reveal mutation in the cardiac and skeletal actin genes.

Role of Alcohol and Thiamine Deficiency

The association between chronic alcohol use and DCM is well established. A cultural feature in African society is communal drinking, which makes it difficult to assess the degree of alcohol use according to an individual’s daily consumption. A communal drinking score based on a qualitative impression of how much alcohol was drunk, level of consciousness, behavior; gait; frequency of drinking days in a week (scored on a scale of 0 to 7); and duration of drinking in years identifies the morbid chronic medical diseases associated with alcohol use in “communal” drinkers, including DCM. Some local alcoholic beverages, such as palm wine, may be rich in vitamin B, which provides an avenue for research into the type of alcohol and DCM in Africa.

Alcohol is a contributory factor in up to 45% of patients with DCM in Africa. The transketolase response to thiamine pyrophosphate suggested thiamine deficiency in 25% to 30%, and vitamin B1 deficiency was present in 20% of alcoholics with DCM. Although severe biochemical thiamine deficiency is present in 4% of alcoholic patients with heart failure, only 1% to 2% present with beriberi heart disease.

Beriberi is a reversible form of myocardial failure precipitated by thiamine deficiency. The cardiovascular presentation of beriberi may be classified into 2 variants: first, classic beriberi with hyperkinetic circulation and predominantly right-sided myocardial failure responsive to thiamine therapy (“high-output beriberi”); and second, the acute pernicious form, or shoshin beriberi, presenting as a fulminant illness with cardiovascular collapse, myocardial failure, and severe lactic acidosis (“low-output beriberi”). Unless prompt treatment with thiamine is instituted, the mortality rate is very high. In South Africa, high-output and low-output beriberi are equally prevalent in alcoholic patients.

Peripartum Cardiomyopathy

The syndrome of cardiac failure in the puerperium was first described in modern times in the 1930s in New Orleans. Subsequent reports from the United States, South Africa, Jamaica, Latin America, and West Africa have revealed that the condition is common in developing countries, particularly among women of African descent, and is uncommon in industrialized countries. Furthermore, in developed countries, PCM often has a more malignant course, with histological evidence of myocarditis, which may demand treatment with immunosuppressive drugs and, in some cases in which drugs fail, cardiac transplantation.
The cause of PCM is unknown. Several pathogenetic factors have been suggested, including poor socioeconomic status, unrecognized hypertension in pregnancy, excessive dietary salt intake, selenium deficiency, high parity, advanced maternal age, twin pregnancy, prolonged lactation, and viral myocarditis.51 PCM seems to be more common in women of African descent than in other races.46,54,55 It is not clear, however, whether this putative racial association is real or merely reflects the increased frequency of PCM in women of lower socioeconomic status.55 Although multiparous women who are older than 30 years of age are recognized to be at increased risk for PCM, it is important to note that 18% to 20% of cases may be young primigravid patients.48,56

The highest incidence of PCM in the world is reported from the Zaria province of Nigeria.51 This high number of cases is attributed to traditional practices that include eating kanwa, a dry lake salt, while lying on a heated mud bed in a humid room and frequent hot baths for 40 days after delivery in an attempt to stimulate breast milk production. Excessive vasodilatation, hypervolemia with edema, and possibly hypotension are the postulated mechanism leading to PCM in this group.50,51,54

Although PCM shares many features with other forms of nonischemic DCM, an important distinction is that women with PCM have a higher rate of spontaneous recovery of ventricular function. However, in a single-center prospective study of 100 South African patients with PCM, 15% died, and only 23% normalized their left ventricular function despite optimal medical therapy.56 Elevation of C-reactive protein at baseline, which may be present in up to 45% of cases, correlates with larger left ventricular dimensions and lower ejection fraction.57

**Endomyocardial Fibrosis in Africa**

Endomyocardial fibrosis (EMF) is a form of restrictive cardiomyopathy in which dense fibrous tissue in the endocardium restricts ventricular diastole and distorts the papillary muscles of the atrioventricular valves. EMF occurs primarily in tropical and subtropical areas worldwide. In Africa, the disease was first described in 1946,3 and it was subsequently reported in Uganda, Kenya, Tanzania, Mozambique, Gabon, Congo, Cameroon, Sudan, Nigeria, Coté d’Ivoire, and Ghana.58 It is uncommon in Northern and Southern Africa.59 EMF in Africa is more commonly right sided or bilateral, and rarely left sided (Figures 1 and 2).

EMF is said to be the most common form of heart disease in Ugandan hospitals, where it accounts for nearly 20% of cases referred to an echocardiography service.60 The only epidemiological survey performed in Africa, to the best of our knowledge, was based on an echocardiographic diagnosis of EMF in the Inharrime district of Mozambique. In a sample of 948 inhabitants from an endemic area and aged between 4 and 45 years old, a prevalence of 8.9% was reported, suggesting that EMF was a major form of heart disease in the region (B. Ferreira, PhD, unpublished data, 2001).

In addition to geography, several factors have been associated with the pathogenesis of EMF in Africa, including (1) ethnicity, (2) poverty, (3) diet, (4) age and sex, (5) eosinophilia, and (6) infection. In Uganda, the disease is more common among immigrants from neighboring Rwanda and Burundi who have settled in specific geographic districts of the country.61 Apart from a report of a Rwandese family in whom EMF was associated with an unusually high incidence of hyperimmune malarial splenomegaly,62 the role of familial and genetic factors has not been studied systematically in this condition. EMF predominates in children and young adults, with a peak incidence at the ages of 11 and 15 in both sexes;
women show a second peak between 26 and 30 years.13 A female preponderance (F:M ratio = 2:1) has been found in Uganda but not in Nigeria, where some workers have found no sex difference, whereas others have found a male preponderance of 2:1.58

EMF is said to be a disease of poor people with low educational attainment who walk barefoot and consume cassava as the sole staple diet and minimal amounts of meat and fish.61 However, EMF is still being described in foreigners who have lived in tropical Africa,59 suggesting that the disease cannot be explained solely on the basis of social deprivation. The hypothesis that “prolonged ingestion of tuber (cassava/tapioca) crops associated with extreme deprivation of protein causes EMF” has been tested in an animal model.63 A controlled experiment showed that monkeys fed an uncooked cassava diet compared with those on an uncooked banana diet developed heart failure and histological changes that are similar to those in the human disease. This study shows that the disease can be induced experimentally in the monkey, thereby providing some support for the high-cassava/low-protein diet hypothesis.

Eosinophilia has also been proposed as a major risk factor for EMF in both East and West Africa.51,64,65 The level of eosinophilia has been found to be inversely related to the duration of illness, leading to the notion that patients who do not have eosinophilia are at a late stage of EMF.65 In fact, the few cases diagnosed in the acute thrombotic phase, which is the first clinical phase before the development of the scar, show hyper eosinophilia with degranulation and vacuolation of the eosinophils. This has led to the suggestion that Loeffler’s endocarditis, which is occasionally seen in non-tropical countries, and EMF represent the extremes of the same disease.60 Eosinophils contain major basic protein, cationic protein, protein X, and other substances that are released during degranulation and that are toxic to the endocardium and myocardium, resulting in mural thrombosis and fibrosis.69

The localization of endemic EMF primarily to low-lying tropical rain forest zones and its predominant occurrence among rural dwellers and farmers suggest a vector-borne pathogenic agent.65 Many different parasites have been suggested as the responsible triggers for the eosinophilia. Microfilaria have been proposed by some as the most likely cause of hyper eosinophilia in Nigerian patients,65 but this observation has not been confirmed by other investigators.67 EMF is prevalent in Africa where malaria is also prevalent. Although no causal relationship has been established, endocardial thrombi that formed in mice infected with Plasmodium falciparum and a rebound eosinophilia reported after malarial infection in Thailand suggest that malaria may perhaps have a role in EMF.13 In Egypt, where EMF may be associated with periportal fibrosis, a link with schistosomiasis has been suggested.68 No role has been found for coxsackieviruses B, arboviruses, and T gondii.69

The clinical features of EMF depend on the stage of disease and the anatomical involvement of the heart. Thirty percent to 50% of children and adolescents report an initial illness with fever, chills, night sweats, facial swelling, and urticaria.13 This illness may disappear, or it may lead to rapidly developing cardiac failure and early death, or it may evolve into established and apparently inactive EMF with predominantly right ventricular or left ventricular disease.13 Ascites with little or no peripheral edema is the characteristic clinical feature regardless of which ventricle is involved.60 Unlike congestive right heart failure, the ascites is an exudate in 75% of cases and is associated with peritoneal fibrosis. An exudative pericardial effusion of variable degree is a common presentation. These observations suggest that EMF is a systemic inflammatory disease, which has been called the “EMF syndrome.”70 Prognosis is poor in this condition, and death usually occurs within 2 years of diagnosis. Remission is unusual, and the response to conservative treatment for heart failure is poor.13

Other Cardiomyopathies in Africa

Hypertrophic Cardiomyopathy
HCM, a condition that is characterized by unexplained cardiac hypertrophy, was said to be a rare disease in black Africans in the pre-echocardiography era.71 Subsequent echocardiographic studies have, however, dispelled this myth.72,73 In Ghana, HCM is the third most common form of cardiomyopathy, after DCM and EMF,11 and in Ethiopia, HCM accounts for 34% of all cardiomyopathies diagnosed at echocardiography.74 HCM is recognized as an autosomal dominant disorder that is caused by mutations in at least 10 different genes that code for sarcomeric proteins.75 The majority of HCM-causing mutations have arisen independently in most families studied, suggesting that the majority occurred relatively recently as new mutations. This finding predicts that HCM is likely to be evenly distributed among different populations worldwide.76 Experience elsewhere in the world has revealed numerous mutations in the sarcomeric protein genes, such that many families have a “private” mutation. In South Africa, however, there are 3 recurring (or founder) mutations that have been found in 45% of genotyped patients of European and mixed ancestry.77 Consequently, South African patients with HCM referred for molecular diagnosis are initially screened for the 3 founder mutations (ie, β-MHC Arg403Trp, β-MHC Ala797Thr, and cTNT Arg92Trp), and more extensive screening is performed only in their absence.75

Arrhythmogenic Right Ventricular Cardiomyopathy
ARVC is characterized macroscopically by dilatation and reduced systolic function of the right ventricle and microscopically by myocardial cell loss with partial or total replacement of the right ventricular muscle by adipose and fibrous tissue. To the best of our knowledge, ARVC was first described in Africa in 2000,76 approximately 40 years after the first case was described.78 Mokhobo and Mntla80 have subsequently reported a series of 8 patients with isolated right ventricular cardiomyopathy who presented with symptoms of heart failure and apparently no arrhythmias; no special imaging, electrophysiological, or histological tests were performed to identify features of ARVC in these patients.
The dearth of reports on ARVC in Africa is probably related to the lack of sophisticated cardiac electrophysiology facilities and expertise required for the diagnosis of the disease. Initial information from the ARVC Registry of South Africa suggests that ARVC occurs in all segments of the population and that its clinical features, frequency of familial disease, and outcome are similar to experience that has been gathered elsewhere in the world.

Conclusions and Future Challenges

DCM is a major cause of heart failure in Africa. Similarly, PCM is ubiquitous on the continent. There is an apparent marked regional variation in the pathogenesis of DCM and PCM, underlining the heterogeneity of pathogenetic factors in these conditions. By contrast, EMF is restricted to the tropical regions of East, Central, and West Africa. Although the pathogenesis of EMF is not fully understood, it seems that the conditioning factors are geography and diet, the triggering factor may be an as yet unidentified infective agent, and the perpetuating factor is eosinophilia. Although epidemiological studies are lacking, HCM and ARVC seem to have characteristics similar to those of other populations elsewhere in the world.

Reliable information about the incidence, prevalence, determinants, and outcome of cardiomyopathy in Africans is lacking. The epidemiological information is essential to the development of health policies for the diagnosis, treatment, prevention, and control of this condition, which is endemic on the continent. Large, well-designed epidemiological studies are needed to elucidate not only the modifiable risk factors for cardiomyopathy, which would help in the design of preventive programs, but also the genetic and molecular epidemiology of cardiomyopathy on the continent.

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Disclosures

None.

References


39. Sliwa et al Cardiomyopathy in Africa


45. Sliwa et al Cardiomyopathy in Africa


51. Sliwa et al Cardiomyopathy in Africa


AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

AQ1—“Journal style favors “cause,” “origin,” “pathogenesis,” etc., when discussing the cause of a disease or condition. The official definition of etiology is “the study of causes.””

AQ2—“From the Department of…” Authors’ affiliations correct as shown here?

AQ3—I have cited Reference 17 here because it does not seem to be otherwise cited in your original text. If this is incorrect, please cite where more appropriate, but keep references in numerical order.

AQ4—Please confirm that “Disclosures: None” is accurate for all authors.