ORIGINAL ARTICLE

A Population Study of Endomyocardial Fibrosis in a Rural Area of Mozambique

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ABSTRACT

BACKGROUND

Endomyocardial fibrosis is the most common restrictive cardiomyopathy worldwide. It has no specific treatment and carries a poor prognosis, since most patients present with advanced heart failure. On the basis of clinical series, regional variations in distribution have been reported within several countries in Africa, Asia, and South America, but large-scale data are lacking on the epidemiologic features and early stages of the disease.

METHODS

We used transthoracic echocardiography to determine the prevalence of endomyocardial fibrosis in a rural area of Mozambique. We screened a random sample of 1063 subjects of all age groups selected by clustering. Major and minor diagnostic criteria were defined, and a severity score was developed and applied. Cases were classified according to the distribution and severity of the lesions in the heart.

RESULTS

The estimated overall prevalence of endomyocardial fibrosis was 19.8%, or 211 of 1063 subjects (95% confidence interval [CI], 17.4 to 22.2). The prevalence was highest among persons 10 to 19 years of age (28.1%, or 73 of 260 subjects [95% CI, 22.6 to 33.6]) and was higher among male than among female subjects (23.0% vs. 17.5%, P=0.03). The most common form was biventricular endomyocardial fibrosis (a prevalence of 55.5%, or 117 of 211 subjects [95% CI, 48.8 to 62.2]), followed by right-sided endomyocardial fibrosis (a prevalence of 28.0%, or 59 of 211 subjects [95% CI, 21.9 to 34.1]). Most affected subjects had mild-to-moderate structural and functional echocardiographic abnormalities. Only 48 persons with endomyocardial fibrosis (22.7%) were symptomatic. The frequency of familial occurrence was high.

CONCLUSIONS

Endomyocardial fibrosis is common in a rural area of Mozambique. By using echocardiography, we were able to detect early, asymptomatic stages of the disease. These findings may aid in the study of the pathogenesis of the disease and in the development of new management strategies.

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Endomyocardial fibrosis is a neglected tropical disease that affects an estimated 10 million people worldwide.[1] The disease is the most common cause of restrictive cardiomyopathy, with impaired filling of one or both ventricles caused by deposition of fibrous tissue on endocardial surfaces. This results in right heart failure, left heart failure, or both. The heart failure is associated with atrioventricular-valve regurgitation. Endomyocardial fibrosis is a major cause of illness and death in areas where it is endemic, and in its severest form carries a very poor prognosis, with an estimated survival of 2 years after diagnosis. The cause and pathogenesis of the disease are poorly understood; several theories are being considered.[2] Currently, there is no specific drug therapy, and surgical treatment of advanced cases carries a poor prognosis and is rarely performed. Most studies of endomyocardial fibrosis have been done in Uganda,[3,4] Nigeria,[5] the Ivory Coast,[6] south India,[7-9] and Brazil[10] in regions situated within 15 degrees of the equator. However, cases have been reported in countries outside the tropics, including industrialized countries.[11-18] Regional variations in the distribution of endomyocardial fibrosis have been noted in countries where the disease is endemic.[19,20]

A study of autopsies performed between 1975 and 1977[21] described the first five recognized cases of endomyocardial fibrosis from Mozambique, showing that the condition was not so rare as previously thought. Subsequently, clinical cases were reported,[22] and an analysis of referrals to a cardiovascular unit in the capital, Maputo, over a 10-year period showed that a large proportion of patients came from Inharrime, a rural coastal district in the south of Mozambique.[23] A prevalence study carried out in this district, with cardiac auscultation as the screening method, confirmed endomyocardial fibrosis as a public health problem, with a prevalence reaching 8.9% among persons 5 to 45 years of age.[24] Most of the literature on endomyocardial fibrosis describes clinical series of patients in advanced stages of the disease, and large-scale epidemiologic studies are lacking.[25]

We designed a study using systematic sampling of the community coupled with detailed echocardiographic examination in randomly selected subjects. The aims were to determine the prevalence of endomyocardial fibrosis in Inharrime, Mozambique, and to describe its severity and mode of presentation in the community.

METHODS

STUDY AREA

Inharrime is a coastal district of Mozambique (Fig. 1) with an area of 2744 km^2 and a population of approximately 76,500; all parts of the district are located at least 400 km from any major referral center for cardiovascular diseases. The district is divided into five zones called *localidades*, which are in turn divided into 59 smaller areas called *povoados*. Most of the people are agricultural workers with a very low income. Less than 1% of households have access to electricity and piped water.

SAMPLE-SIZE CALCULATION

The sample size was calculated by an adaptation of the two-stage cluster-sampling approach.[26] For practical and logistic reasons, we opted for a cluster size of 30 subjects. The number of clusters was calculated by the formula $C = p \times (1 - p) \times D \div s^2 \times b$, where C is the number of clusters, p is the expected prevalence of the condition (7%; the prevalence in a previous study[24] was lower), D is the study design effect (1.58, with a rate of homogeneity of 0.02),[26] s is the required standard error of the estimated prevalence (1%), and b is the cluster size.[26] We thus arrived at a sample size of 33 clusters, corresponding to a minimum of 990 subjects.

SAMPLE SELECTION

The sample was selected at two stages, first at the povoado level and second at the household level. Since there were no data on the population size of individual povoados, we could not use probability-proportional-to-size sampling. We therefore selected 33 villages by simple random sampling. Community leaders from the selected villages were asked to create a list of all households in each povoado. We then used random sampling to select the first household to be studied in each povoado. Second-stage clustering was performed after the investigators had visited the index household.

A household was defined as a group of people living together for more than 3 months and sharing food on a daily basis. The investigators obtained written informed consent from the head of the household when they arrived at the index household. An identification card was issued to the family and each member was assigned a unique identification number. The exact location of the house was registered with the use of a

global positioning system (Garmin eTrex Legend) for follow-up visits.

The households surrounding the index household within the limits of the village were noted. A number was assigned to each, and the next household to be visited was chosen by simple random selection. This procedure was repeated for the next household until at least 30 subjects had been enrolled. The Mozambican National Bioethics Committee approved the research protocol.

DATA COLLECTION

Demographic data were obtained from every member of each selected family with the use of a questionnaire. A cardiologist then performed detailed transthoracic echocardiography on each family member with the use of a hand-carried, battery-operated echocardiographic system (Vivid *i*, General Electric) with M-mode, two-dimensional, and Doppler (pulsed, continuous, and color) imaging. The following were obtained: apical two-, four-, and five-chamber views; parasternal long-axis and short-axis views at the level of the papillary muscles and the aortic valve; subcostal views; and suprasternal views (parallel to the aortic arch). Electronic records of relevant data were kept.

DIAGNOSIS AND CLASSIFICATION OF ENDOMYOCARDIAL FIBROSIS

We defined major and minor criteria for the diagnosis of endomyocardial fibrosis on the basis of features of advanced disease and pathologic features of early stages described in postmortem studies.[1] Endomyocardial fibrosis was diagnosed in the presence of two major criteria or one major criterion associated with two minor criteria (Table 1). Diagnoses were accepted after agreement of two independent, experienced cardiologists. Endomyocardial fibrosis was classified as biventricular, right-sided, or left-sided according to whether the structural lesions involved both ventricles without predominance of one side, only or predominantly the right ventricle, or only or predominantly the left ventricle, respectively. We also developed a severity-scoring system based on the type and degree of the structural and functional changes (Table 1). Possible scores ranged from 0 to 35; cases with scores of 8 or less were classified as mild, those with scores of 8 to 15 as moderate, and those with scores of 15 or more as severe. A detailed clinical examination was performed in all subjects with endomyocardial fibrosis.

Figure 1. Mozambique.

STATISTICAL ANALYSIS

Frequencies are given as absolute numbers and percentages; continuous data are reported as means ±SE. We used the chi-square test to compare percentages between groups and logistic regression to test for trends in percentages of continuous variables. Association between continuous variables was expressed by the Pearson correlation coefficient, with a t-test for zero correlation. Variation within families was examined by mixed-model analysis of variance. Prevalence data are presented as means with 95% confidence intervals. Analyses were performed with Minitab Release 13 and SAS Release 8.02 software.

RESULTS

STUDY POPULATION

We selected 217 households to be visited. The family was absent in 3 households, and the remaining 214 households had a total of 1249 members. The mean family size was 5.8±0.2 (range, 1 to 19); the mean age was 22.6±0.6 years; 682 (54.6%; 95% confidence interval [CI], 51.8 to 57.4) were female; and all but 4 were black. One hundred eighty-six eligible subjects (14.9%) were not examined: 99 were adult men who were away

Table 1. Criteria for Diagnosis and Assessment of the Severity of Endomyocardial Fibrosis.*

Criterion	Score
Major criteria	
Endomyocardial plaques >2 mm in thickness	2
Thin (≤1 mm) endomyocardial patches affecting more than one ventricular wall	3
Obliteration of the right ventricular or left ventricular apex	4
Thrombi or spontaneous contrast without severe ventricular dysfunction	4
Retraction of the right ventricular apex (right ventricular apical notch)	4
Atrioventricular-valve dysfunction due to adhesion of the valvular apparatus to the ventricular wall	1–4†
Minor criteria	
Thin endomyocardial patches localized to one ventricular wall	1
Restrictive flow pattern across mitral or tricuspid valves	2
Pulmonary-valve diastolic opening	2
Diffuse thickening of the anterior mitral leaflet	1
Enlarged atrium with normal-size ventricle	2
M-movement of the interventricular septum and flat posterior wall‡	1
Enhanced density of the moderator or other intraventricular bands	1

* A definite diagnosis of endomyocardial fibrosis was made in the presence of two major criteria or one major criterion associated with two minor criteria. A total score of less than 8 indicates mild endomyocardial fibrosis, 8 to 15 moderate disease, and more than 15 severe disease.
† The score is assigned according to the severity of atrioventricular regurgitation.
‡ M-movement of the interventricular septum refers to a pattern of movement observed on M-mode echocardiography that is thought to be due to obliteration or restriction of the left ventricular apex combined with mitral regurgitation.

from home working as miners in neighboring South Africa; 79 were not at home (the families said that disease was not the reason for their absence); and 6 had traveled to hospitals outside the community in search of treatment (no clear diagnosis of cardiac disease was suggested by the history given by the family). Echocardiography was not performed in two subjects who had uncontrolled and aggressive behavior. No other subjects declined to freely participate.

PREVALENCE, TYPE, AND SEVERITY OF ENDOMYOCARDIAL FIBROSIS

We performed 1063 transthoracic echocardiographic procedures. The mean age of the screened subjects was 22.5±0.7 years, and 611 (57.5% [95% CI, 54.5 to 60.5]) were female. Two hundred eleven of the screened subjects (19.8% [95% CI, 17.4 to 22.2]) had endomyocardial fibrosis. The disease was biventricular in 117 subjects (55.5% [95% CI, 48.8 to 62.2]), right-sided in 59 (28.0% [95% CI, 21.9 to 34.1]), and left-sided in 35 (16.6% [95% CI, 11.6 to 21.6]). Of the 211 affected subjects, 163 (77.3%) had mild disease, 39 (18.5%) had moderate disease, and 9 (4.3%) had severe disease. Only 48 persons with endomyocardial fibrosis (22.7%) were symptomatic. Figure 2 shows echocardiograms illustrating different types and degrees of severity of endomyocardial fibrosis. The most frequent lesions in mild disease were apical obliteration of the right ventricle, diffuse thickening of the mitral valve, and mild mitral or tricuspid regurgitation.

The prevalence of endomyocardial fibrosis differed among age groups (P=0.001), but there was no systematic increase or decrease in prevalence with age (P=0.94 for all comparisons) (Fig. 3). The prevalence was highest among subjects 10 to 19 years of age (73 cases in 260 subjects, or 28.1% [95% CI, 22.6 to 33.6]). Left-sided endomyocardial fibrosis was more common than biventricular or right-sided endomyocardial fibrosis among subjects over 30 years of age (32.7% vs. 11.3%, P<0.001).

The prevalence of endomyocardial fibrosis was significantly higher among male than among female subjects (23.0% vs. 17.5%, P=0.03); the difference between the sexes was greatest in the group that was 20 to 29 years of age (Fig. 3). There were no significant differences between male and female subjects in the location of the principal lesions (P=0.29).

Of the 214 families studied, 99 had no cases of endomyocardial fibrosis, 63 had one case, and 52 had more than one case. There was no correlation between the percentage of persons with endomyocardial fibrosis in a family and the family size (r=0.095, P=0.17). However, the chance of a person's having the disease was higher when other members of the family had it. As compared with the overall prevalence of endomyocardial fibrosis (19.8% [95% CI, 17.4 to 22.2]), the prevalence was 24.0% (95% CI, 20.6 to 27.4) among persons who had one or more other family members with endomyocardial fibrosis, 28.3% (95% CI, 23.4 to 33.2) among those with two or more affected family members, and 38.8% (95% CI, 31.2 to 46.4) among those with three or more affected family members.

DISCUSSION

In this study we used echocardiographic screening to examine the prevalence, type, and severity

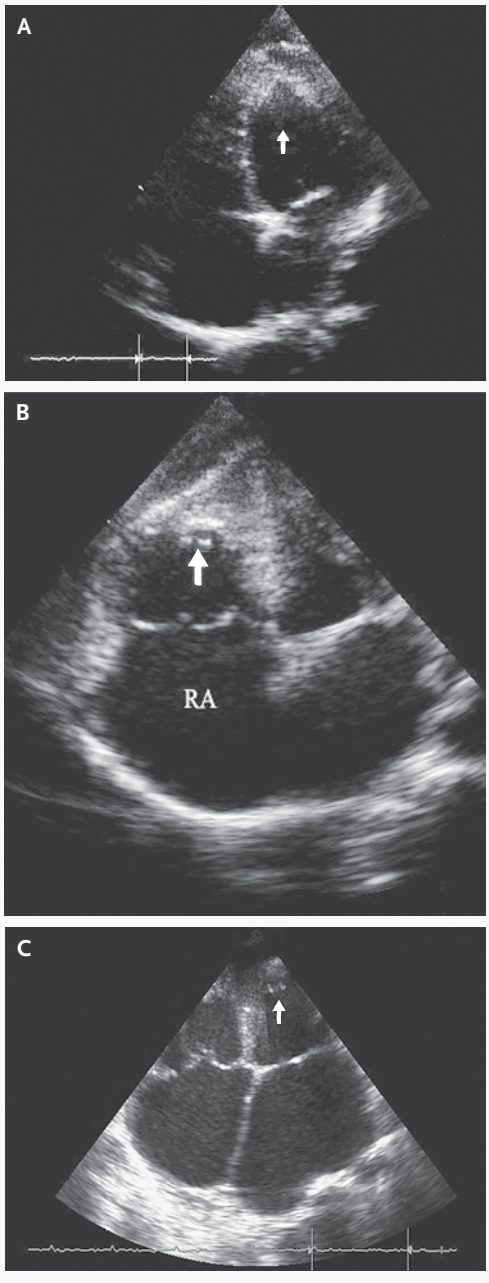

Figure 2. Echocardiograms Showing Types and Degrees of Severity of Endomyocardial Fibrosis.

Panel A shows mild left endomyocardial fibrosis with occupation of the left ventricular apex (arrow). The interventricular septum is dense, with a thickened anterior mitral leaflet. Panel B shows moderate right endomyocardial fibrosis, with obliteration of the trabecular part and fibrous floor of the right ventricular cavity (arrow). The right atrium (RA) is dilated. Panel C shows severe bilateral endomyocardial fibrosis, with obliteration of the left ventricular apex (arrow), thickened valves, and biatrial dilatation.

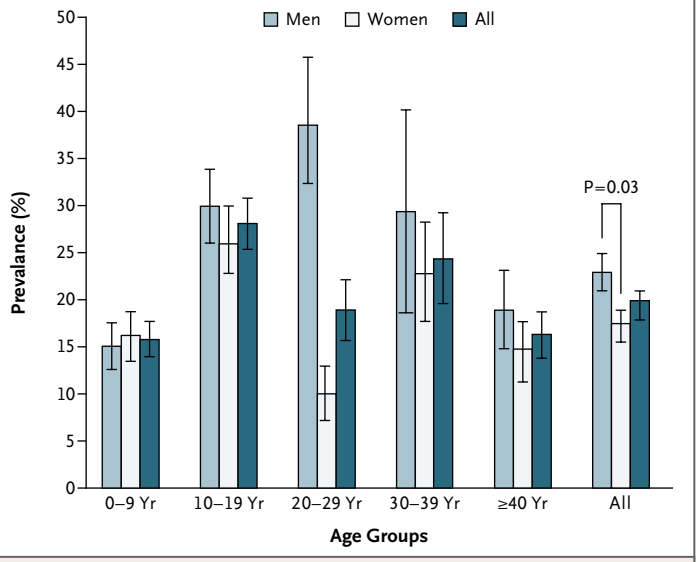

Figure 3. Prevalence of Endomyocardial Fibrosis According to Age Group and Sex.

I bars indicate standard errors.

of endomyocardial fibrosis in a community in Mozambique. Echocardiography is the standard technique for the diagnosis of this condition, but the criteria described in the literature apply only to the disease in the advanced stages.[27,28] We describe a set of criteria for the diagnosis and classification of endomyocardial fibrosis (Table 1) that we believe will be useful in staging the disease, studying its progression, and comparing the results of different epidemiologic studies.

The prevalence of endomyocardial fibrosis in the community we studied (19.8%) was higher than the 8.9% found in a previous survey in Inharrime that used cardiac auscultation followed by confirmation with the use of echocardiography.[24] The lack of association between clinical and echocardiographic findings in endomyocardial fibrosis has previously been reported[29] and may partly explain the late presentation of patients in hospital-based series.[2]

We identified several types of endomyocardial fibrosis by echocardiography, some of which represented early stages not previously described with the use of this diagnostic tool but corresponding to the findings from autopsy studies.[1] Mild endomyocardial fibrosis was common in all age groups in our study. In addition, we identified several specific features of endomyocardial fibrosis, including thrombus involving the mitral

subvalvular apparatus with mild regurgitation, obliteration of the right ventricular trabecular cavity, and obliteration of the recess between the posterior wall and the posterior papillary muscle. We are presently conducting echocardiographic follow-up of these subjects to clarify the natural history of the disease.

In our population, left-sided endomyocardial fibrosis was more frequent among adults over 30 years of age than among younger subjects. In clinical series, by contrast, the percentage of subjects with left-sided endomyocardial fibrosis is lower in persons over 30 years of age than in younger persons, perhaps because of early death from severe pulmonary hypertension and low cardiac output.[30]

The prevalence of endomyocardial fibrosis showed a bimodal age distribution, with the first peak occurring in the second decade of life and the second in the fourth decade (Fig. 3). This age distribution, which is also found in hospital-based studies,[20] may reflect the age of exposure to an infection, a cohort effect of exposure to an episodic environmental factor, or exposure to the same etiologic factors early in life with delayed manifestation of the disease in some subjects.

Endomyocardial fibrosis was more frequent in male than in female subjects. There were no differences between the sexes in the relative prevalence of different types of endomyocardial fibrosis (biventricular, left-sided, or right-sided).

Our study confirms the familial occurrence of endomyocardial fibrosis that was previously reported in clinical series,[9,31] which could be due to genetic or environmental factors or both. Future studies correlating the disease with specific genetic patterns and cohort studies looking at the role of environmental factors will help to clarify this issue.

The high prevalence of endomyocardial fibrosis in this community cannot be generalized to the country of Mozambique. Local variations in the distribution of this disease have been noted in other African countries.[19,20,31] Several factors, such as poor diet, low socioeconomic status, malnutrition, viral infection, parasitic disease, and genetic differences, may be implicated.[30,32] Our study, by using objective methods of diagnosing, classifying, and grading the severity and stage of the disease in a relatively large cohort of patients with mild as well as severe forms of the disease, can help in understanding the pathophysiology, progression, and therapeutic response of the disease.

One limitation of our study is that 14.9% of the initial sample was not available for echocardiographic evaluation. However, extensive questioning of family members and community leaders suggested that this group did not have advanced disease or other characteristics that would distinguish them from the sample studied.

This study showed a high prevalence of endomyocardial fibrosis in a rural community of Mozambique. Echocardiography, together with the use of a newly described grading system, detected and characterized early and asymptomatic stages of the disease. The prevalence was highest among persons 10 to 19 years of age and was higher among male than among female subjects. Further work is required to evaluate the mode, mechanisms, and rate of progression of endomyocardial fibrosis, as well as the role of genetic susceptibility in determining the types of the disease and its patterns of familial occurrence. The large population of subjects affected offers unique opportunities for studying the basic molecular mechanisms responsible for the disease; the results could help to develop strategies for prevention and treatment and could be valuable for understanding other forms of cardiomyopathy and diseases involving fibrosis.

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No potential conflict of interest relevant to this article was reported.

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