Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 14, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.03.074

STATE-OF-THE-ART PAPER

Cardiovascular Disease in the Developing World

Prevalences, Patterns, and the Potential of Early Disease Detection

David S. Celermajer, MBBS, PHD,*† Clara K. Chow, MBBS, PHD,*‡§ Eloi Marijon, MD,‖ Nicholas M. Anstey, MBBS, PHD,¶# Kam S. Woo, MBBS, MD**

Sydney and Darwin, Australia; Paris, France; Hong Kong, China

Over the past decade or more, the prevalence of traditional risk factors for atherosclerotic cardiovascular diseases has been increasing in the major populous countries of the developing world, including China and India, with consequent increases in the rates of coronary and cerebrovascular events. Indeed, by 2020, cardiovascular diseases are predicted to be the major causes of morbidity and mortality in most developing nations around the world. Techniques for the early detection of arterial damage have provided important insights into disease patterns and pathogenesis and especially the effects of progressive urbanization on cardiovascular risk in these populations. Furthermore, certain other diseases affecting the cardiovascular system remain prevalent and important causes of cardiovascular morbidity and mortality in developing countries, including the cardiac effects of rheumatic heart disease and the vascular effects of malaria. Imaging and functional studies of early cardiovascular changes in those disease processes have also recently been published by various groups, allowing consideration of screening and early treatment opportunities. In this report, the authors review the prevalences and patterns of major cardiovascular diseases in the developing world, as well as potential opportunities provided by early disease detection. (J Am Coll Cardiol 2012;60:1207–16) © 2012 by the American College of Cardiology Foundation

Globally, cardiovascular diseases (CVDs), which include coronary heart disease (CHD), strokes, rheumatic heart disease (RHD), cardiomyopathy, and other heart diseases, represent the leading cause of death (1). In 2001, it was estimated that there were 16 million deaths from CVD, but somewhat surprisingly (given that the vast majority of studies concerning CVD are carried out in "developed" regions such as the United States and Western Europe), 13 million of these CVD deaths occurred in low-income and middle-income countries, compared with 3 million in high-income countries (1). Although CVDs have previously been characterized as affecting "rich" countries, age-specific rates of CVD have declined in these areas, while they are increasing rapidly in many middle-income and low-income countries. In low-income and middle-income countries, the proportion of all deaths due to CVD in 2001 was 28%, compared with 23% in 1990; the corresponding proportions in developed countries were 39% and 48% (1,2).

Although most CVDs in the world are due to atherosclerosis (CHD and ischemic strokes), other CVDs due to infection (e.g., RHD, Chagas' heart disease, cardiomyopathy from human immunodeficiency virus (HIV) infection, cerebrovascular complications of malaria) remain common in many regions of the developing world (Fig. 1). Early functional and structural changes of the vessels and/or heart (before the onset of symptoms and/or advanced disease) are now detectable in some of these diseases (particularly but not exclusively by ultrasound) (3,4), and recent studies of early detection using these modalities have been published and have provided insights into the early stages of these disease processes.

Particular challenges in addressing the increasing burden of CVD in developing countries include low budgets for health (including for screening, prevention, and treatment), as well as the education and skill mix of the health workforce.

From *The University of Sydney, Sydney, Australia; the †Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia; ‡The George Institute for Global Health, Sydney Australia; §Department of Cardiology, Westmead Hospital, Sydney, Australia; ‖Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, France; ¶Global Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, Australia; #Department of Infectious Diseases, Division of Medicine, Royal Darwin Hospital, Darwin, Australia; and the **School of Life Sciences, The Chinese University of Hong Kong, Hong Kong, China. Dr. Celermajer's work is supported by a National Health and Medical Research Council Program Grant. Dr. Chow's work in India was supported by a National Health and Medical Research Council (Australia)/National Heart Foundation (Australia) cofunded fellowship, and she is funded by a Sydney Medical School Foundation Chapman Fellowship. Dr. Anstey is supported by a National Health and Medical Research Council of Australia Practitioner Fellowship and Program Grant. Studies carried out with the Maputo Heart Institute were supported in part by the Magdi Yacoub Institute and Chain of Hope (United Kingdom), by Chaîne de l'Espoir (France), and by Cadeia de Esperança (Portugal). Aspects of our work in China were supported by the Dr. Leung Kit Wah Project Fund. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 31, 2012; revised manuscript received February 29, 2012, accepted March 6, 2012.

Abbreviations and Acronyms

ARF = acute rheumatic fever
CHD = coronary heart disease
CV = cardiovascular
CVD = cardiovascular disease
EMF = endomyocardial fibrosis
HIV = human immunodeficiency virus
IMT = intima-media thickness
NO = nitric oxide
RHD = rheumatic heart disease

The prevention of advanced disease is appealing in these settings, as many forms of CVD have long pre-symptomatic phases during which inexpensive treatment may improve outcomes (e.g., antibiotic prophylaxis in RHD, salt reduction in hypertension), or more expensive interventions might be best reserved for those with known pre-clinical disease (e.g., polypills for subjects at high vascular risk).

Recent developments in non-invasive or minimally invasive imaging and diagnostic methods for studying the heart and vessels, such as portable ultrasound, raise several interesting possibilities: local workforce training in diagnosis (and interventions), screening for common and potentially treatable subclinical diseases, targeted screening for high-risk patients, and locally relevant research endeavors.

CVD in developing countries: problems with documentation. Unfortunately, although the projections for CVD in developing countries are alarming, there is a paucity of high-quality data about CVD (or indeed even about risk factor levels) from many of these countries. The 2001 Global Burden of Disease Study reported no data available on causes of death by age and sex for 24.3% of the global population. Data were unavailable for 0.3% of the population in high-income countries but 89.8% of the population in sub-Saharan Africa, 48.1% in the Middle East and North Africa, 24.2% in South Asia, and 21.1% in East Asia and the Pacific (1). Robust national information about the prevalence of CVD is also unavailable in many countries (5); this lack of data is particularly pronounced for disadvantaged regions of these countries, such as rural areas or urban or semiurban poor areas.

Atherosclerotic Cardiovascular Disease

China. DISEASE BURDEN. China is the largest developing country in the world, with a land mass of 9.6 million km^2 and a population of more than 1.33 billion. Coronary disease in China is less prevalent, but stroke prevalence is much higher compared with most Western developed countries. In Beijing, the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Diseases age-adjusted annual CHD event rate was 81 per 100,000 men and 35 per 100,000 women in the early 1990s, compared with age-adjusted CHD mortality rates of 46 per 100,000 men and 26 per 100,000 women in the early 1980s (6). There was large variation in prevalence between rural and urban Chinese and between northern and southern Chinese (7), reflecting interactions of genetic susceptibility, environmental changes (usually secondary to urbanization), and increased affluence. With rapid economic transition and modernization, for example, the rate of CVD events (coronary events plus strokes) increased from 2.3% to 4.4% annually in the period from 1984 to 1999, for adults aged 35 to 74 years (8).

CHANGING PREVALENCE OF RISK FACTORS. Data from a USA-PRC Collaborative Study of Cardiovascular Epidemiology cohort of 9,903 participants followed for 17 years to 2000 identified that ischemic CHD and stroke in China were positively related to age, current smoking, systolic blood pressure, serum total cholesterol, diabetes mellitus, and body mass index in both Chinese men and women (9). The population-attributable risk for myocardial infarction for Chinese male current smokers in the INTERHEART

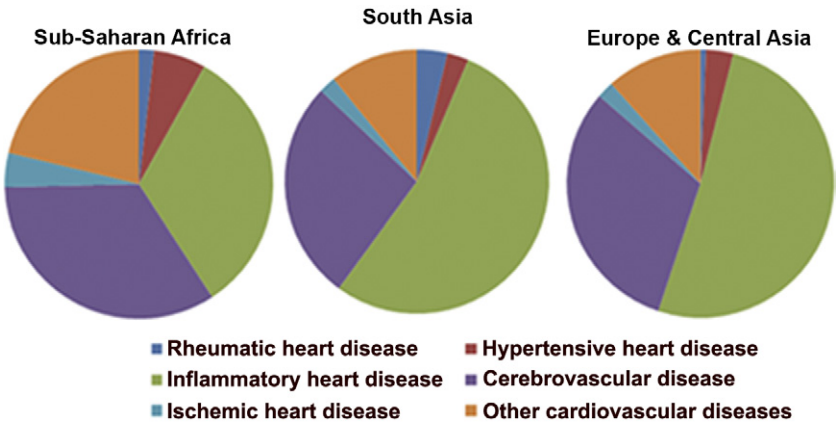

Figure 1 Causes of Cardiovascular Death in 2001, by Region

This figure was created from data from Mathers CD, et al. The burden of disease and mortality by condition: data, methods, and results for 2001. Global Burden of Disease and Risk Factors. New York, NY: Oxford University Press, 2006:45–240.

study was 43.6% (95% confidence interval: 38.9% to 48.4%) (10). Hypertension and smoking were identified as the most important risk factors for ischemic CVD (including stroke). Hypertension currently affects 25% of China's population, with higher prevalences in cities (25.1%) and urban areas (17.1%) than in rural areas (15.6%) (11). Chinese men account for 10% of adults in the world but smoke about 30% of the world's cigarettes. Passive smoking is also highly prevalent (53.5%) among nonsmokers (12).

The prevalences of overweight and hypercholesterolemia increased steadily by 137% and 88%, respectively, for men and by 95% and 65%, respectively, for women, over the past decade (13). Metabolic syndrome is present in 30.4% of Chinese patients with coronary disease (14). Metabolic syndrome plus overweight was present in 9.8% to 13.9% of men and 8.5% to 17.8% of women aged 35 to 74 years from 2000 to 2005, higher in northern than southern Chinese (15). This rate was even higher (age-adjusted rate 21.2%) in southern modernized Chinese in Hong Kong (16).

INSIGHTS FROM EARLY IMAGING STUDIES IN CHINA. In a series of community-based cardiovascular (CV) health surveys in mainland and overseas Chinese (the Chinese Atherosclerosis in Aged and Young studies), we have found Chinese adults to be less susceptible than whites to age-related endothelial dysfunction (an early surrogate marker of atherosclerosis) (17). Westernization or modernization of Chinese adults was associated with significantly greater carotid intima-media thickness (IMT), another validated marker of subclinical atherosclerosis (18). Young Chinese adults have less evidence of endothelial dysfunction than young white adults with similar direct or indirect exposure to cigarette smoke (passive smoking) (19). Westernized Chinese in Sydney and San Francisco, however, are more susceptible to the dose-related vascular effects of smoking (pack-years) and to the impact of low high-density lipoprotein cholesterol (19). Taken together, these data indicate a relative sparing of the damaging CV effects of risk factors in rural Chinese, which is lost with progressive urbanization.

The impact of lifestyle and occupational changes on atherogenesis has recently been studied in 475 subjects living in the Three Gorges territories of the Yangtze River from 2006 to 2008, where the Three Gorges Dam was built, leading to rapid changes in occupation and lifestyles for more than 1 million rural people who were suddenly displaced to the city. These adults, compared with farmers, developed greater waist-to-hip ratios, higher blood cholesterol and triglyceride levels, a 4 times higher prevalence of metabolic syndrome, and greater carotid IMT (20) over 2 to 4 years.

Overweight and obesity are particular problems in urban China. We have shown that mild to moderate overweight in children in Hong Kong is associated with arterial endothelial dysfunction and increased carotid IMT compared with lean children (21). Fortunately, dietary and exercise interventions significantly improve such obesity-related signs of vascular dysfunction in children (22). The adoption of healthy lifestyles at an early age seems a potentially beneficial strategy for atherosclerosis prevention in China in the 21st century.

India. DISEASE BURDEN. There are relatively few mortality studies from India. In 2006, the Global Burden of Disease Study reported detailed cause-of-death estimates for the South Asian region, based on 2001 data (1). CHD was reported to be the number 1 cause of death in South Asia, accounting for 13.6% of all deaths, and stroke was the fourth leading cause of death, accounting for 6.8% of all deaths (1). The largest and most recent study of directly collected data on adult (age ≥25 years) mortality reported on causes of death in 48,000 urban adults and 32,000 rural adults from Tamil Nadu, India. This study reported death rates on the basis of "verbal autopsies" from 1996. For men age 35 to 69 years, death rates from all CVDs were 685 per 100,000 and for women of corresponding ages 428 per 100,000 (23). The substantially higher CV death rates in India compared with those reported in China over a similar time period may relate to a truly higher CV risk in India (1) and/or to differences in the accuracy of case ascertainment, the definitions of CVD used, and/or reporting methods. This study also found that 41% of urban male deaths and 37% of urban female deaths were due to CVDs, with proportions in rural areas of 25% for men and 22% for women. In contrast, for South Asians in California, the proportion of deaths due to CVDs from 1985 to 1990 was 23% for men and 20% for women (24).

CHANGING PREVALENCE OF RISK FACTORS. Historically, most populations from South Asia have documented low levels of CV risk factors, particularly blood lipid levels, diabetes, and hypertension. However, in recent decades, the prevalence of these risk factors has increased, especially in urban areas. For example, a survey of 6 major cities in India including 11,216 participants age ≥20 years reported a diabetes prevalence of 12.1% and an impaired glucose tolerance prevalence of 14.1% (25), in contrast to rates of diabetes reported in urban studies in the 1970s of 1% to 3% (26). There is also evidence that diabetes rates are increasing in rural areas. Recent rural studies from select states have reported diabetes rates as high as 13% (27). Similarly, rates of hypertension increased from about 5% in urban areas in the 1960s to 12% to 15% in the 1990s (28). Recent studies have also documented high rates of abdominal obesity in certain urban and rural areas. In our somewhat alarming survey of rural adults from Andhra Pradesh (n = 4,535), the prevalence of central obesity (waist circumference >90 cm in men and >80 cm in women) was 26.0%, and the prevalence of metabolic syndrome ranged from 24.6% to 30.2%, depending on the definitions used (29). The proportion of subjects classified as overweight and obese is even higher when using recently recommended lower body mass index cut points for Asian adults (30).

JACC Vol. 60, No. 14, 2012
October 2, 2012:1207–16

CV EVENT SURVEYS AND INSIGHTS FROM EARLY IMAGING STUDIES. There are few directly collected data on the incidence of CHD events in India. However, indirect comparisons of studies in which CHD incidence was defined using electrocardiography indicate that incidence is increasing (5). There is also some indication that CHD event rates in some regions of India may be higher compared with established market economies. In a cohort study of 4,151 participants age 25 to 64 years recruited in 1990 in Delhi, the incidence of CHD was approximately 19.7 per 1,000; in comparison, the incidence of CHD in Oxfordshire in the U.K. at a similar time was of the order of 3 per 1,000 (31). Some studies have also shown that South Asians acquire CHD at younger ages compared with other populations, and this appears to be explained by their higher levels of risk factors at younger ages (32).

Our recent study from rural India conducted in 2004 of 345 rural Indians found that carotid IMT, a measure of the burden of atherosclerotic disease that has been shown to be predictive of the risk for subsequent vascular events, was thicker in rural Indians compared with urban Australians (Fig. 2). This greater thickness was not explained by differences in CV risk factors between the groups. Our findings suggest that the vasculature of rural Indians may respond differently to some key CV risk factors. A particular susceptibility of South Asian Indians to pre-symptomatic atherosclerosis was also suggested in a study of Anand et al. (33) in 2000, examining carotid IMT in South Asian and Chinese immigrants to Canada. The finding of susceptibility to atherosclerotic risk factors in populations with rapid changes in their environments leading to exposure to risk factors is similar to that seen in a number of other migrant studies, such as of South Asians to the United Kingdom (34).

Africa. In sub-Saharan Africa, there is increasing evidence of a changing disease profile from infectious diseases and nutritional deficiencies to noncommunicable chronic diseases, including chiefly CVD (35). Even after incorporating recent estimates for the spread of HIV/acquired immune deficiency syndrome, projections of mortality and burden of disease suggest that by 2030, CVD will become the leading cause of death in low-income countries in Africa, contributing 13.4% of total deaths, compared with 13.2% from HIV/acquired immune deficiency syndrome. In addition, CHD is projected to rank fifth among the 10 leading causes of disability-adjusted life-years lost in low-income countries by 2030 (35).

A major factor in the increasing prevalence of atherosclerotic CVD in developing countries is the ongoing change in nutrition patterns, with progressive shifts to a westernized diet high in saturated fats and sugar, along with a more sedentary lifestyle. Furthermore, cigarette consumption is increasing significantly in most African countries (36). Also, hypertension is a major risk factor for CVD, particularly stroke, in sub-Saharan Africa, with an estimated prevalence of hypertension in adults of 30% (37).

Risk factors for CVD were examined in the INTERHEART Africa study, an international, standardized, case-control study that recruited 578 cases of first-time myocardial infarction and 785 controls from 9 sub-Saharan African countries (38). The participants, almost 75% of them men, included 36.3% black Africans, 46.7% colored Africans, and 17% European and other African peoples. Hypertension and diabetes stand out as particularly important in the black African population because of its higher population-attributable risk compared with that observed in the two other ethnic groups.

Although the major coronary risk factors in Africa are similar to those identified in other regions of the world, definitive data from Africa on the magnitude of the burden of CVD and CV risk factors, the strength of the associations among the various risk factors, and the incidence of myocardial infarction have generally been lacking. The INTERHEART Africa study represents presently the largest comprehensive study carried out in Africa. Even then, more than 80% of subjects enrolled in this study were from South Africa, known to be significantly more developed than the other countries of sub-Saharan Africa. This should caution against the generalization of these findings to the African continent overall.

Figure 2 Cardiovascular Testing in Rural India for Cardiovascular Risk Factors and Carotid Intima-Media Thickness, a Surrogate Marker of Early Atherosclerosis

Heart Failure

Heart failure in the developing world is due mainly to nonischemic causes; hypertensive heart disease, valvular and myocardial damage from rheumatic fever, and heart muscle diseases caused by certain infectious agents. These diseases include HIV cardiomyopathy (recently reviewed in detail elsewhere) (39) and certain region-specific cardiomyopathies, such as endomyocardial fibrosis (EMF) in Africa and Chagas' disease in Latin America, reviewed in the following discussion. Alcohol, thiamine deficiency, and peripartum cardiomyopathy are also well-recognized causes of heart failure in developing nations. Except where noted in the following, prevalence data for these causes of heart failure are often unavailable, and population-based studies in this regard are needed.

RHD. WORLDWIDE BURDEN. RHD accounts for most of the CV mortality and morbidity among young people in developing countries, with clinically apparent disease affecting about 20 million people and responsible for an estimated 250,000 premature deaths each year (40). Considering subclinical disease as well, the prevalence of RHD is likely 2 to 3 times higher than these estimates.

RHD is the result of valvular damage (and less frequently myocardial and/or pericardial involvement), caused by an immune response to group A streptococcal infection. Antigenic mimicry in association with an abnormal immune response is the cornerstone of pathophysiology. Acute rheumatic fever (ARF) classically occurs 3 weeks after streptococcal pharyngitis and can involve the joints, skin, brain, and heart. During ARF, about 50% of patients present with clinical carditis, with an audible cardiac murmur. The incidence of ARF, difficult to assess accurately in most developing countries, varies from 5 to 80 per 100,000 of the total population (41). Valve dysfunction in RHD most often develops insidiously after repeated or persistent ARF attacks (42).

EARLY DETECTION AND PREVENTION. RHD is the result of a preventable disease, as demonstrated by its exceedingly low prevalence in nonindigenous populations of developed countries. Prevention thus includes improvement of socioeconomic conditions with better hygiene and housing (primordial prevention), primary prevention through antibiotic treatment of streptococcal pharyngitis, and finally secondary prevention of ARF recurrence by penicillin prophylaxis against repeated or chronic ARF attacks.

In the 1970s and 1980s, large screening programs in schoolchildren were recommended by the World Health Organization and undertaken, in which diagnosis was based on clinical examination. However, cardiac auscultation may prove insensitive, especially for early disease. Small regurgitant volumes, especially posteriorly directed mitral regurgitation, simply may not be audible. Furthermore, functional murmurs are very common in children, especially in the presence of fever or anemia, as may be the case during common comorbidities in these regions, including malaria or sickle cell episodes. In a stepwise screening program conducted in Tonga, junior and experienced physicians' auscultation skills were compared (43). Whereas more experienced physicians had much higher specificity for detecting pathologic RHD murmurs, at least half the true cases of RHD were missed (43).

The emergence of echocardiography (including portable systems) as a means of detecting subclinical carditis has allowed more detailed assessment of subclinical RHD, and echocardiography may become a valuable tool in early detection (Fig. 3). In Cambodia and Mozambique, we have documented case detection rates by echocardiography that were 3 to 10 times higher than that that found by clinical examination among schoolchildren (44). (Fig. 4). Similar results have been observed by others (43). The likelihood that these subclinical changes are of pathologic significance is supported by recent data from New Zealand (45) demonstrating that such valve changes (even those considered minimal) were more frequent among high-risk populations.

CONTROVERSIES AND UNANSWERED QUESTIONS. Although echocardiography may prove a valuable tool in detecting cases at an early stage, fundamental issues remain unanswered: 1) the lack of standard echocardiography criteria to diagnose subclinical RHD; 2) the management of patients with mild valvular abnormalities; and 3) the practicalities of delivering echocardiographic screening programs (46).

Changes in echocardiographic criteria considerably alter the apparent RHD prevalence in screening surveys (47), also illustrating the difficulties in diagnosing subclinical RHD. Standardization of echocardiographic criteria is currently under way, by an international group of the World Heart Federation (48). Intuitively, secondary prophylaxis may prove most beneficial at the early stage of RHD, when valve damage is minimal, but this requires further research. In

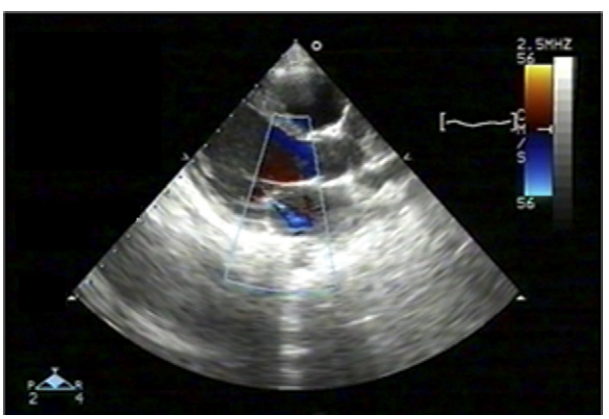

Figure 3 **Echocardiogram Showing Early, Subclinical Rheumatic Heart Disease**

The regurgitant flow across the mitral valve is shown in **blue**.

JACC Vol. 60, No. 14, 2012
October 2, 2012:1207–16

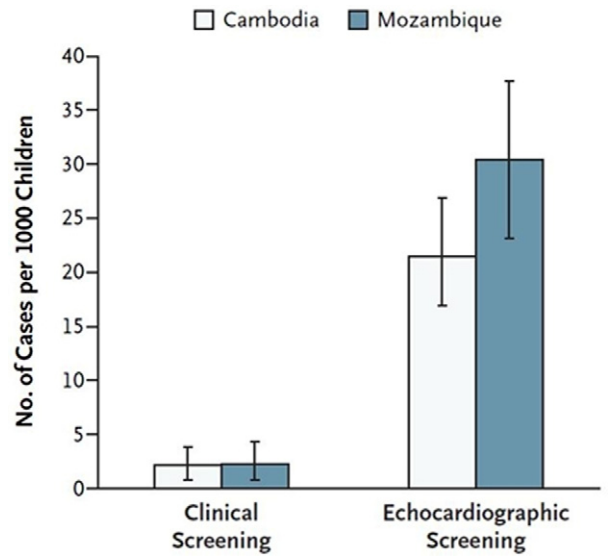

Figure 4 **Echocardiography Detects Significantly More Early Rheumatic Heart Disease Than Clinical Examination**

Reprinted, with permission, from Marijon et al. (46).

practice, antibiotic prophylaxis should currently be initiated only in cases of definite subclinical RHD.

EMF in the tropics. EMF is a neglected tropical disease that predominates in tropical and subtropical areas, affects mainly children and young adults of low socioeconomic status, and is recognized as an important cause of heart disease in Africa, India, and Brazil. First described in Uganda 70 years ago, EMF remains a somewhat mysterious and understudied disease entity (49). The distinctive pathologic feature of established EMF is endocardial thickening of 1 or both ventricles, more prominent at the apices and the inflow tracts, usually causing dysfunction of the atrioventricular valves, leading to restrictive ventricular filling and giant atria (Fig. 5). Rare epidemiologic studies have shown a very heterogenous distribution of the disease, with some areas having an extremely high prevalence (for unclear reasons) (50). For example, in the first large community echocardiography-based study carried out by the Maputo Heart Institute 100 miles north of Maputo, Mozambique, an area known to be endemic for EMF (50), the investigators demonstrated a prevalence of EMF in the community of 20% (markedly higher than the 9% previously found in the same area, using clinical criteria but without echocardiography) (51). The availability of portable echocardiography thus now provides the opportunity for early diagnosis and prospective studies in affected communities, which could ultimately allow better understanding of the natural history of the disease.

The pathogenesis of EMF remains unknown. Several hypotheses have been proposed and explored, including cardiotoxicity of the eosinophil, infectious agents, autoimmune processes, genetic predisposition, ethnicity, diet, and possible chemical factors. Echocardiography is now the standard technique for the diagnosis of this condition. The lack of association, however, between clinical and echocardiographic findings in EMF has previously been recognized and may partly explain the late presentation of patients in hospital-based series and why the diagnosis of EMF is

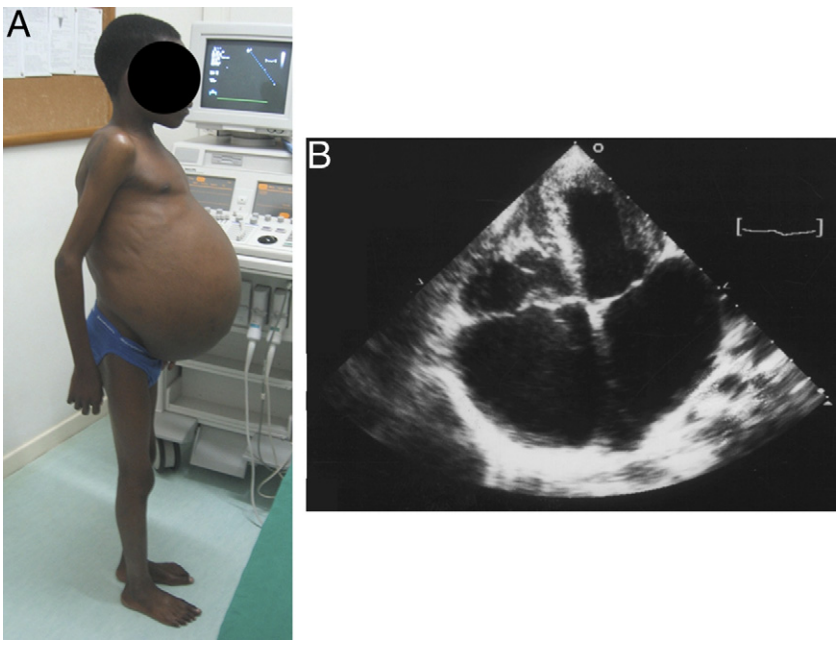

Figure 5 **A Young Male Patient With Restrictive Cardiomyopathy From Endomyocardial Fibrosis and a Typical Echocardiogram Showing Endomyocardial Fibrosis**

usually made in the late stages of the disease, when heart failure or its complications are already present and patients are thus more difficult to treat (with standard heart failure medications). Further study is required to know if early detection by echocardiography can facilitate early diagnosis, treatment, and possibly improved outcomes in this potentially devastating disease.

Chagas' disease in Latin America. Chagas' disease is endemic to Latin America and can result in cardiomyopathy during its chronic phase. The causative infection is usually acquired during childhood; the relevant organism *Trypanosoma cruzi* penetrates the skin or eye mucosa of people usually living in poor rural housing. Acute Chagas' disease is usually asymptomatic or presents as a nonspecific febrile illness. Acute myocarditis is rare in this phase. The chronic stage occurs decades later, and cardiac pathologic findings include mononuclear infiltrates, fibrosis, and myocytolysis (52). Complications include symptomatic left ventricular systolic and/or diastolic dysfunction and arrhythmia.

Disease control programs have significantly reduced the number of infected subjects, from approximately 16 million to 18 million in the early 1990s to 10 million to 12 million in the early 2000s (53). A substantially larger number (tens of millions), however, remain at risk for acquiring the pathogenic infection.

Chagas' disease in the chronic phase is diagnosed on serologic testing in patients who grew up in affected areas, and cardiac involvement is suspected when electrocardiography shows atrioventricular block, right bundle or left anterior hemiblock, and/or multifocal ventricular ectopic beats.

Echocardiography is extremely valuable in detailed characterization of cardiac involvement in chronic Chagas' cardiomyopathy, but no screening studies have yet been reported from community-based samples in endemic areas. Recent publications, however, have focused on the early identification of subjects with cardiac involvement, reasoning that this may lead to earlier treatment and thus potentially better outcomes. Heart failure and arrhythmias are treated along similar lines as other nonischemic cardiomyopathies, but the therapeutic role of antiparasite therapy in the chronic phase remains uncertain.

Garcia-Alvarez et al. (54) studied 54 patients and 44 controls and found that diastolic dysfunction (from mitral inflow and tissue Doppler measurements) and brain natriuretic peptide measurements were valuable in early case detection. Acquatella (53) reviewed relevant publications in this area in 2007 and concluded that echocardiographic results in those with positive serologic findings and electrocardiographic changes were frequently abnormal, often markedly so, even in asymptomatic subjects.

This common cause of potentially serious cardiac disease in Latin America is therefore only poorly studied. On the basis of published data, echocardiography should be undertaken in subjects with serologic evidence of disease and electrocardiographic findings suggestive of abnormality.

Malaria. Although it may not be immediately apparent why malaria is included in a review of CVD in developing countries, many of the pathogenic events in severely affected patients are due to the consequences of microvascular occlusion and consequent ischemia, as outlined in the following discussion. Therefore, in that sense, malaria is an important worldwide cause of "vascular disease" (although not of classic coronary or carotid artery disease).

WORLDWIDE BURDEN. Although the incidence of malaria has fallen recently with intensified malaria control measures, an estimated 2.3 billion people remain at risk for infection with *Plasmodium falciparum* (55), the most pathogenic species causing malaria. *P. falciparum* causes 350 million to 550 million infections (55) and most of the estimated 780,000 deaths from malaria each year. The majority of deaths arise from complications of tissue ischemia: metabolic acidosis, acute renal failure, respiratory distress, and multiple organ failure (56).

PATHOGENESIS OF FALCIPARUM MALARIA AND THE ROLE OF VASCULAR DYSFUNCTION. A central process in the pathogenesis of severe falciparum malaria is the cytoadherence of parasitized red blood cells to the endothelium, resulting in microvascular sequestration and obstruction, thereby causing tissue hypoxia and injury (57). Evidence includes autopsy studies in both adults and children (57) and clinical studies showing the obstruction of blood flow in both retinal (58) and rectal capillaries. Sequestration of parasitized red cells is exacerbated by concurrent endothelial activation (59).

Although the histopathologic evidence for microvascular obstruction in severe malaria dates back to the 19th century (60), the importance of vascular dysfunction in impaired microvascular perfusion has only recently been shown in a series of studies by our groups (61). Our recent studies in adults with severe and falciparum malaria have shown profound endothelial dysfunction associated with measures of impaired microvascular perfusion (61), which improves with clinical recovery (62). Endothelial dysfunction in severe malaria is associated with impaired nitric oxide (NO) bioavailability, which results from hypargininemia (L-arginine being the substrate for the enzyme synthesizing NO) (61), increased circulating concentrations of the NO synthase inhibitor, asymmetric dimethyl arginine, reduced expression of NO synthase 2, and NO quenching due to malaria-associated intravascular hemolysis (63). As well as functional effects on microvascular vasomotor regulation and perfusion, reduced endothelial NO bioavailability results in increased endothelial intercellular adhesion molecule-1 expression (64) and increased endothelial cell Weibel-Palade body exocytosis (59,65), with concentrations of the Weibel-Palade body products, angiopoietin-2, and von Willebrand factor being increased in severe and fatal malaria and inversely related to endothelial function (59). Angiopoietin-2 sensitizes endothelium to cytokine-induced expression of endothelial adhesion molecules, and von

JACC Vol. 60, No. 14, 2012
October 2, 2012:1207–16

Willebrand factor binds to platelets, enhancing CD36-mediated parasite cytoadhesion, with both linked to increased microvascular obstruction by parasitized red cells.

EARLY DETECTION OF VESSEL DYSFUNCTION AND THERAPEUTIC IMPLICATIONS. Noninvasive measures of endothelial and microvascular dysfunction have proven useful in providing proof of principle for candidate adjunctive agents targeting the endothelium in malaria and in identifying agents suitable for evaluation in larger clinical trials in severe malaria (61). Traditional gold-standard measures such as flow-mediated dilation are operator dependent and are logistically difficult in critically unwell patients in peripheral health facilities in malaria-endemic regions. A portable, operator-independent method, reactive hyperemia peripheral artery tonometry, is at least 50% dependent on NO production and has been used as a measure of endothelial function in a number of disease settings (66), including malaria (61). Because of the importance of vascular dysfunction in the pathogenesis of severe and fatal malaria (61), noninvasive measures of endothelial and microvascular dysfunction in patients presenting with severe malaria may prove to have a role identifying those with the greatest impairment of vessel dysfunction who may benefit most from adjunctive agents.

RATIONALE FOR ADJUNCTIVE THERAPIES. An important recent advance in the treatment of severe malaria has been the demonstration in 2 large randomized trials that the use of the most rapidly active antimalarial agent, artesunate, reduces case fatality in severe malaria in both adults and children. The results of these studies have changed global treatment policy from quinine to artesunate (67). Despite this major advance with antiparasitic drugs, there is no survival benefit in adults in the first 48 h (68), suggesting that additional therapies targeting underlying pathogenic processes are needed to further improve outcomes in this vital early time window. Although results of limited trials of adjunctive therapies to date have been disappointing, none have specifically targeted the endothelium or endothelial dysfunction. The ability of L-arginine to improve NO bioavailability and endothelial dysfunction in patients with moderately severe malaria (61) and its initial safety profile in malaria (69) have suggested the potential role of agents that increase NO bioavailability and/or endothelial function in severe falciparum malaria (61). Trials of L-arginine and inhaled NO in severe malaria are therefore in progress in Asia and Africa.

Conclusions

The burden of CVD is increasing sharply in developing countries, chiefly because of atherosclerosis-related illnesses. Data from China implicate urbanization, westernization of diet, and increasing rates of smoking, obesity, and diabetes in disease pathogenesis. Data from India suggest a possible particular susceptibility of South Asians to the atherogenic effects of metabolic risk factors. The paucity of epidemiologic data from these and many other poorer countries limits our knowledge, however, of CVD patterns and prevalence.

In addition, infectious and post-infectious illnesses remain common in developing countries, and many affect the heart and vessels. These diseases include RHD and malaria, and these impose a considerable burden of CVD on regions with relatively low per capita health budgets.

New developments in the noninvasive study of cardiac and vascular structure and function, particularly with ultrasound, have provided novel and valuable insights into the early stages of atherosclerotic, rheumatic, malarial, and cardiomyopathic diseases in affected regions, including in rural and remote settings. Such information has informed concepts about disease prevalences and pathogenesis and in some cases facilitated the possibilities of pre-symptomatic screening, early diagnosis, and potentially lifesaving early therapeutic intervention.

Reprint requests and correspondence: Prof. David S. Celermajer, Royal Prince Alfred Hospital, Department of Cardiology, Missenden Road, Camperdown, Sydney 2050, Australia. E-mail: david.celermajer@email.cs.nsw.gov.au.

REFERENCES

1. Mathers CD, Salomon JA, Ezzati M, Begg S, Vander-Hoorn S, Lopez AD. Global Burden of Disease and Risk Factors. New York, NY: Oxford University Press, 2006.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269–76.
3. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–5.
4. Chow CK, McQuillan B, Raju PK, et al. Greater adverse effects of cholesterol and diabetes on carotid intima-media thickness in South Asian Indians: comparison of risk factor-IMT associations in two population-based surveys. Atherosclerosis 2008;199:116–22.
5. Ahmad N, Bhopal R. Is coronary heart disease rising in India? A systematic review based on ECG defined coronary heart disease. Heart 2005;91:719–25.
6. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Lancet 1999;353:1547–57.
7. Wang W, Zhao D, Wu G. The trend of incidence rate of acute stroke event in urban areas, Beijing from 1984 to 1999 [article in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi 2001;22:269–72.
8. Zhao D, Wu Z, Wang W, Yue L, Zhou M. The trend of incidence rate of acute coronary events from 1984-1997 in Beijing area: Sino-MONICA project. Chin J Cardiol 2000;28:14–7.
9. Wu Y, Liu X, Li X, et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation 2006;114:2217–25.
10. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet 2006;368:647–58.
11. People's Republic of China–United States Cardiovascular and Cardiopulmonary Epidemiology Research Group. An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the People's Republic of China. Baseline report from the P.R.C.-U.S.A. Collaborative Study. Circulation 1992;85:1083–96.
12. Yang G, Fan L, Tan J, et al. Smoking in China: findings of the 1996 National Prevalence Survey. JAMA 1999;282:1247–53.

13. Wu Y. Current status of major cardiovascular risk factors in Chinese populations and their trends in the past two decades. Chin J Cardiol 2001;29:74–9.
14. Liu H, Yu JM, Pan CY, Chen F, Li J, Hu DY. Cross-sectional study on the prevalence of metabolic syndrome in patients with coronary heart disease in China [article in Chinese]. Zhonghua Yi Xue Za Zhi 2006;86:2095–8.
15. Gu D, Reynolds K, Wu X, et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365:1398–405.
16. Thomas GN, Ho SY, Janus ED, Lam KS, Hedley AJ, Lam TH. The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) prevalence of the metabolic syndrome in a Chinese population. Diabetes Res Clin Pract 2005;67:251–7.
17. Woo KS, McCrohon JA, Chook P, et al. Chinese adults are less susceptible than whites to age-related endothelial dysfunction. J Am Coll Cardiol 1997;30:113–8.
18. Woo KS, Chook P, Raitakari OT, McQuillan B, Feng JZ, Celermajer DS. Westernization of Chinese adults and increased subclinical atherosclerosis. Arterioscler Thromb Vasc Biol 1999;19:2487–93.
19. Woo KS, Robinson JT, Chook P, et al. Differences in the effect of cigarette smoking on endothelial function in Chinese and white adults. Ann Intern Med 1997;127:372–5.
20. Woo KS, Chook P, Yip TWC, et al. Folic acid and vitamin B-12 supplementation improves arterial function and structure in subjects with subnormal intake. Heart Lung Circ 2008;17:S201–2.
21. Woo KS, Chook P, Yu CW, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. Int J Obes Relat Metab Disord 2004;28:852–7.
22. Woo KS, Chook P, Yu CW, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. Circulation 2004;109: 1981–6.
23. Gajalakshmi V, Peto R, Kanaka S, Balasubramanian S. Verbal autopsy of 48 000 adult deaths attributable to medical causes in Chennai (formerly Madras), India. BMC Public Health 2002;2:7.
24. Wild SH, Laws A, Fortmann SP, Varady AN, Byrne CD. Mortality from coronary heart disease and stroke for six ethnic groups in California, 1985 to 1990. Ann Epidemiol 1995;5:432–9.
25. Ramachandran A, Snehalatha C, Kapur A, et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia 2001;44:1094–101.
26. Ramachandran A. Epidemiology of diabetes in India—three decades of research. J Assoc Physicians India 2005;53:34–8.
27. Chow CK. Cardiovascular Risk Factor Levels and Cardiovascular Risk Estimation in a Rural Area of India [dissertation]. Sydney, Australia: University of Sydney, 2007.
28. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens 2004;18:73–8.
29. Chow CK, Naidu S, Raju K, et al. Significant lipid, adiposity and metabolic abnormalities amongst 4535 Indians from a developing region of rural Andhra Pradesh. Atherosclerosis 2008;196:943–52.
30. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
31. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA, for the Oxford Myocardial Infarction Incidence Study Group. Coronary event and case fatality rates in an english population: results of the Oxford Myocardial Infarction Incidence Study. Heart 1998;80:40–4.
32. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA 2007;297:286–94.
33. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic Groups (SHARE). Lancet 2000;356:279–84.
34. Markus H, Kapozsta Z, Ditrich R, et al. Increased common carotid intima-media thickness in UK African Caribbeans and its relation to chronic inflammation and vascular candidate gene polymorphisms. Stroke 2001;32:2465–71.
35. Mensah GA. Ischaemic heart disease in Africa. Heart 2008;94:836–43.
36. Jha P, Ranson MK, Nguyen SN, Yach D. Estimates of global and regional smoking prevalence in 1995, by age and sex. Am J Public Health 2002;92:1002–6.
37. Dalal S, Beunza JJ, Volmink J, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. Int J Epidemiol 2011;40: 885–901.
38. Steyn K, Sliwa K, Hawken S, et al. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. Circulation 2005;112:3554–61.
39. Ntsekhe M, Mayosi BM. Cardiac manifestations of HIV infection: an African perspective. Nat Clin Pract Cardiovasc Med 2009;6:120–7.
40. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group a streptococcal diseases. Lancet Infect Dis 2005;5: 685–94.
41. Tibazarwa KB, Volmink JA, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. Heart 2008;94:1534–40.
42. Marijon E, Mirabel M, Celermajer D, Jouven X. Rheumatic heart disease. Lancet. 2012;379:953–64.
43. Carapetis JR, Hardy M, Fakakovikaetau T, et al. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. Nat Clin Pract Cardiovasc Med 2008;5:411–7.
44. Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med 2007;357:470–6.
45. Webb RH, Wilson NJ, Lennon DR, et al. Optimising echocardiographic screening for rheumatic heart disease in New Zealand: not all valve disease is rheumatic. Cardiol Young 2011;21:436–43.
46. Marijon E, Celermajer DS, Jouven X. Management of patients with subclinical rheumatic heart disease. Int J Cardiol 2009;134:295–6.
47. Marijon E, Celermajer DS, Tafflet M, . Rheumatic heart disease screening by echocardiography: the inadequacy of World Health Organization criteria for optimizing the diagnosis of subclinical disease. Circulation 2009;120:663–8.
48. Reményi B, Wilson N, Steer A, et al. World Heart Federation's criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol 2012;9:297–309.
49. Marijon E, Ou P. What do we know about endomyocardial fibrosis in children of Africa? Pediatr Cardiol 2006;27:523–4.
50. Ferreira B, Matsika-Claquin MD, Hausse-Mocumbi AO, Sidi D, Paquet C. Geographic origin of endomyocardial fibrosis treated at the central hospital of Maputo (Mozambique) between 1987 and 1999 [article in French]. Bull Soc Pathol Exot 2002;95:276–9.
51. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med 2008;359:43–9.
52. Dias E, Laranja FS, Miranda A, Nobrega G. Chagas' disease; a clinical, epidemiologic, and pathologic study. Circulation 1956;14: 1035–60.
53. Acquatella H. Echocardiography in Chagas heart disease. Circulation 2007;115:1124–31.
54. Garcia-Alvarez A, Sitges M, Pinazo MJ, et al. Chagas cardiomyopathy: the potential of diastolic dysfunction and brain natriuretic peptide in the early identification of cardiac damage. PLoS Negl Trop Dis 2010;4:e826.
55. Hay SI, Okiro EA, Gething PW, et al. Estimating the global clinical burden of Plasmodium falciparum malaria in 2007. PLoS Med 2010;7:e1000290.
56. Dondorp AM, Lee SJ, Faiz MA, et al. The relationship between age and the manifestations of and mortality associated with severe malaria. Clin Infect Dis 2008;47:151–7.
57. Pongponratn E, Turner GD, Day NP, et al. An ultrastructural study of the brain in fatal Plasmodium falciparum malaria. Am J Trop Med Hyg 2003;69:345–59.
58. Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME. Malarial retinopathy: a newly established diagnostic sign in severe malaria. Am J Trop Med Hyg 2006;75:790–7.
59. Yeo TW, Lampah DA, Gitawati R, et al. Angiopoietin-2 is associated with decreased endothelial nitric oxide and poor clinical outcome in severe falciparum malaria. Proc Natl Acad Sci U S A 2008;105:17097–102.
60. Marchiafava E, Bignami A. On Summer-Autumnal Fever. London: New Sydenham Society, 1894.
61. Yeo TW, Lampah DA, Gitawati R, et al. Impaired nitric oxide bioavailability and L-arginine reversible endothelial dysfunction in adults with falciparum malaria. J Exp Med 2007;204:2693–704.

62. Yeo TW, Lampah DA, Gitawati R, et al. Recovery of endothelial function in severe falciparum malaria: relationship with improvement in plasma L-arginine and blood lactate concentrations. J Infect Dis 2008;198:602–8.
63. Yeo TW, Lampah DA, Tjitra E. Relationship of cell-free hemoglobin to impaired endothelial nitric oxide bioavailability and perfusion in severe falciparum malaria. J Infect Dis 2009;200:1522–9.
64. De Caterina R, Libby P, Peng HB, et al. Nitric oxide decreases cytokine-induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest 1995;96:60–8.
65. Lowenstein CJ, Morrell CN, Yamakuchi M. Regulation of Weibel-Palade body exocytosis. Trends Cardiovasc Med 2005;15:302–8.
66. Celermajer DS. Reliable endothelial function testing: at our fingertips? Circulation 2008;117:2428–30.
67. World Health Organization. Guidelines for the Treatment of Malaria. 2nd ed. Geneva, Switzerland: World Health Organization, 2010.
68. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366:717–25.
69. Yeo TW, Lampah DA, Gitawati R, et al. Safety profile of L-arginine infusion in moderately severe falciparum malaria. PLoS One 2008;3:e2347.

Key Words: atherosclerosis ■ Chagas' disease ■ endothelium ■ malaria ■ rheumatic heart disease.