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EDITORIAL COMMENT

Early Identification and Monitoring Progression of Chagas' Cardiomyopathy With SPECT Myocardial Perfusion Imaging*

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In this issue of *iJACC*, Hiss et al. (1) report correlations of single-photon emission computed tomography (SPECT) perfusion defects with subsequent left ventricular dysfunction by echocardiography in patients with chronic Chagas' cardiomyopathy. In 36 patients with a 5.6-year follow-up period, the authors demonstrated a topographic association between SPECT perfusion defects at rest and subsequent development of regional left

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ventricular (LV) dysfunction. In the absence of demonstrable coronary artery disease by coronary angiography in these patients with Chagas' disease, stress perfusion defects by SPECT myocardial perfusion imaging (MPI) progressed to rest defects; and this disease progression evidenced by SPECT MPI was associated with a reduction in left ventricular ejection fraction (LVEF) assessed by echocardiography.

Chagas' disease is a model of microvascular dysfunction associated with perfusion abnormalities assessed as reversible perfusion defects in the absence of angiographic disease (2,3). Of the 36 patients in the study by Hiss et al. (1), all 20 patients with reversible perfusion defects had normal subsequent angiograms. The cardiomyopathy of Chagas' disease is thought to result from parasitism of myocardial fibers by *T. cruzi* and inflammatory effects of an autoimmune reaction that sets the stage for endothelial dysfunction, myocytolysis, and myocardial fibrosis (4). Both human and experimental studies support the suggestion that derangements of the coronary microcirculation are associated with this process (2,4). Progression of Chagas' disease is associated with more marked myocardial fibrosis, as demonstrated by cardiac magnetic resonance imaging (5), and likely accounts for the progression from vasodilator stress-induced defects to resting perfusion defects seen in the current observational study by Hiss et al. (1).

Camici and Crea (6) have provided an elegant review of the spectrum of coronary microvascular dysfunction in human diseases and suggest the potential for risk stratification and tracking treatment effectiveness by noninvasive assessment of coronary flow reserve. Coronary flow reserve, as well as its scintigraphic correlate myocardial perfusion reserve, is the ratio of maximal to resting coronary flow. Maximal flow is achieved with vasodilator stress interventions such as dipyridamole, adenosine, and the selective A2a agonists (6). Differences in coronary flow reserve in the absence of epicardial stenosis are likely due to endothelial dysfunction at the levels of the conduit arteries or the coronary arterioles (microvasculature). Diffuse arteriopathy and subtle reductions in luminal diameter associated with atherosclerosis, coronary inflammation, myocardial inflammation, or myocardial fibrosis as in Chagas' disease might impact flow reserve as well. The regional nature of Chagas' disease likely facilitated detection of disease with MPI on the basis of regional relative differences in myocardial perfusion reserve. Whether quantification of absolute flow by positron emission tomography will further identify disease progression and

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risk of events in Chagas' disease remains open for future investigation.

The techniques and findings of this study provide remarkable insights regarding the role of SPECT MPI to identify both the early onset and the progression of Chagas' cardiomyopathy. The slight, statistically significant decline in LVEF by echocardiography over 5 years from 55% to 50% was not influenced by technical measurement effects of subendocardial hypoperfusion on volume and EF calculations by electrocardiography (ECG)-gated radionuclide SPECT MPI. It can be expected that LV volume indexes likely increased as cardiomyopathy progressed, although these potent quantitative radionuclide prognostic indexes were not obtained in the current study, because ECG-gating of the SPECT images was not performed. Deterioration of LVEF over time and increases in LV volume indexes imply worse prognosis in cardiomyopathy, suggesting a potentially important role of ECG-gated SPECT MPI in providing greater risk stratification in Chagas' cardiomyopathy. Thus, ECG-gated SPECT MPI seems well suited to track alterations of myocardial perfusion, regional function, global EF, and volume indexes as mechanistic markers that correlate with the pathogenesis of myocardial injury in the progression of Chagas' cardiomyopathy. Despite not reporting ECG-gated LV volumes, this report by Hiss et al. (1) represents the first longitudinal study to demonstrate the correlation between myocardial perfusion disturbances and progression of regional and global LV systolic dysfunction in chronic Chagas' cardiomyopathy.

With this report by Hiss et al. (1), Chagas' disease joins a growing list of conditions as reviewed by Camici and Crea (6) that are associated with myocardial perfusion abnormalities detectable in the absence of angiographic coronary disease, such as coronary risk factors, atherosclerosis, diabetes, hypertension, hypertrophic cardiomyopathy, aortic and mitral valvular diseases, infiltrative diseases, and cigarette smoking (6). Endothelial dysfunction has emerged as a significant predictor of subsequent cardiovascular events (7–9) and is known to produce regional differences in myocardial perfusion, as evidenced by SPECT and positron emission tomography imaging techniques. In the case of coronary atherosclerosis, Schachinger et al. (8) have demonstrated that impressive vasospasm with vasomotor stress with adenosine or other interventions during coronary angiography correlates with the site-specific development of subsequent stenosis an average of 3.7 years later and best identified patients who clinically progressed to experience clinical events. As reported by Hiss et al. (1) in the current study of Chagas' disease, abnormalities of endothelial function imaged by stress SPECT imaging early in the course of the disease seem to predict site-specific progression of defects at rest, reflecting progressive fibrosis, and regional systolic dysfunction preceding a decline in calculated LVEF.

In summary, this study is an important contribution to the published data that correlates serial progression of stress and rest perfusion defects by SPECT MPI and subsequent regional and global LV dysfunction with the suspected pathophysiological progression of Chagas' cardiomyopathy from coronary microvascular dysfunction to fibrosis and frank chamber dilation and dysfunction. Beyond early detection of Chagas' disease, SPECT MPI offers promise to track subclinical progression of Chagas' cardiomyopathy. This study by Hiss et al. (1) offers real hope that we have in SPECT MPI a tool to identify early in Chagas' disease the effectiveness of future therapies designed to prevent the insidious and inexorable progression of cardiomyopathy before onset of intense cardiac chamber dilation, heart failure, malignant ventricular arrhythmia, and thromboembolic phenomena that characterize its devastating clinical course and poorly understood pathogenesis.

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Key Words: cardiomyopathy ■ myocardial perfusion scintigraphy ■ single-photon emission computed tomography ■ Chagas' disease.