

EDITORIAL COMMENT

Is Cardiac Autonomic Neuropathy the Basis of Nonischemic Diabetic Cardiomyopathy?*

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Autonomic diabetic neuropathy is a common and serious complication of diabetes mellitus with variable multiple organ involvement, principally of the cardiovascular system, but also of the gastrointestinal and urogenital tracts (1). Cardiac autonomic neuropathy (CAN) causes alterations in heart rate control and vascular dynamics, which may result in disabling clinical and functional manifestations, including resting tachycardia, exercise intolerance, postural hypotension, enhanced intraoperative and

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perioperative cardiovascular instability, derangement in myocardial blood flow regulation, and left ventricular (LV) dysfunction. It is associated with poorer prognosis, with increased mortality and incidence of both silent myocardial ischemia and infarction, and complicates both type 1 and type 2 diabetes. CAN increases with age, poor glycemic control, and probably with the duration of diabetes (1).

In this issue of *JACC*, Sacre et al. (2) evaluate the association of CAN with LV dysfunction and regional LV parameters in asymptomatic patients with type 2 diabetes and no history of cardiovascular disease or other severe illness. In a mainly correlational analysis, the report described associations between various measures of cardiac autonomic function (spectral power of heart rate variability and cardiac reflex testing), cardiac sympathetic innervation (^{123}I -metaiodobenzylguanidine [^{123}I -mIBG] imaging), and echocardiographic measures (mainly tissue Doppler velocities) of systolic and diastolic function. The au-

thors found patients with CAN had lower systolic and diastolic function at rest, as well as systolic function after exercise. They also found an association between diastolic function and CAN, independent of metabolic factors and other contributors to LV dysfunction. Furthermore, they reveal that relative regional ^{123}I -mIBG deficits representative of local denervation were associated with regional diastolic dysfunction in the mid-ventricular portion of the anterior and lateral walls. The association between regional denervation and regional dysfunction are novel and interesting, and raise the possibility of a direct contribution of CAN to the LV functional abnormalities in diabetic patients.

The development of LV systolic, and particularly diastolic, dysfunction in diabetes has been traditionally attributed to CAN, interstitial myocardial fibrosis, microangiopathic, or metabolic changes. However, the independent association of CAN with diabetic cardiomyopathy has not been established because of related etiologies for both conditions. The relative predominance of sympathetic activity at the onset of CAN would stimulate the renin-angiotensin-aldosterone system, which not only increases the hemodynamic stresses and energetic requirements of the left ventricle by sodium retention and peripheral vasoconstriction but may also exert direct noxious effects on cardiomyocytes (apoptosis and regression to a fetal phenotype) and changes in the nature of the extracellular matrix (stimulation of myocardial fibrosis), which may further alter the architecture and impair the performance of the left ventricle. Such sympathetic hyperactivity, in combination with regional myocardial denervation present in a more advanced stage of CAN, has been recently shown to lead to diminished coronary blood flow reserve and diastolic dysfunction in diabetic patients with early microangiopathy (3,4).

The study by Sacre et al. (2) identifies only 14% of the patients with fully evolved CAN, and that may raise issues regarding the appropriateness of multivar-

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iate analysis in the small size group, especially considering the large number of covariables. In addition, as the authors acknowledge, the more adverse clinical status among their patients with CAN makes it difficult to isolate the direct effects of this complication on LV function, even after statistical adjustment.

The confirmation of the presence of CAN in otherwise healthy type 2 diabetes patients, and its independent association with resting diastolic dysfunction, is important. Several treatment interventions including graded exercise, cardioactive drugs, and intensification of treatment for the multiple risk factors for CAN that are shared with those for macrovascular disease have been shown to improve the functional deficiency in the autonomic nervous system. Therefore, noninvasive identification of early stages of CAN may emphasize the need for intensive control of cardiovascular risk factors, thereby reducing the risk of premature mortality.

Nuclear cardiology offers an attractive option with sufficient sensitivity to assess processes such as neurotransmission that take place at picomolar concentrations in the human heart (5-7). The sensitivity of radioisotope techniques to detect mild degrees of CAN may be superior to that of autonomic reflex tests. In fact, similar to what Sacre et al. (2) describe, a global decrease in ^{123}I -*m*IBG uptake has been identified both in type 1 and type 2 diabetic patients with and without abnormalities in autonomic reflex tests. In 1988, Kahn et al. (8) published the first report of cardiac sympathetic denervation by means of ^{123}I -*m*IBG in a patient with CAN. Subsequent scintigraphic investigations demonstrated that cardiac sympathetic disturbances are more frequently present in both types of diabetes than previously detected with conventional autonomic reflex tests. Several studies have shown decreased and heterogeneous myocardial ^{123}I -*m*IBG uptake in patients with CAN. The impairment of cardiac ^{123}I -*m*IBG uptake correlates with abnormal response to exercise, and may contribute to LV dysfunction before the appearance of irreversible damage and overt heart failure (9). Even diabetic patients with normal autonomic reflex tests and normal myocardium perfusion studies show reduced cardiac ^{123}I -*m*IBG uptake, which is more pronounced in the posterior myocardium and correlates with all indexes of heart rate variability at rest and during deep breathing (10). Therefore, the regional associations between diastolic impairment and sympathetic denervation found by Sacre et al. (2) in mid-anterior and lateral walls might have been even stronger with the inclusion in the analysis of inferior myocardial segments; the authors justify their exclusion as an inten-

tion to reduce the high incidence of artifacts secondary to mesenteric ^{123}I -*m*IBG uptake in the inferior wall.

The observation of cardiac sympathetic denervation both in patients with and without autonomic reflex tests indicative of CAN suggests that cardiac ^{123}I -*m*IBG imaging is a more sensitive means to detect CAN, particularly in early stages of the disease (11,12). Atherosclerosis of the large coronary arteries is not a prerequisite cause for these findings, as ^{123}I -*m*IBG defects are present even in the absence of coronary artery disease. However, the role of microvascular disease in CAN has not been well characterized so far. Although ^{123}I -*m*IBG decreased cardiac uptake is mainly localized in the LV inferior wall, it may be completely absent in advanced CAN. This pattern has also been observed using the norepinephrine analogue ^{11}C -hydroxyephedrine (^{11}C -HED) and positron emission tomography imaging (13). In cases of severe CAN, Stevens et al. (14) observed that cardiac retention of ^{11}C -HED was heterogenous, and as the extent of distal deficits increased, tracer retention became paradoxically increased in the proximal myocardial segments. This phenomenon may be related with the greater diastolic dysfunction described in mid than in basal segments in the current study (2).

Long-term poor glycemic control is strongly related with the process of LV adrenergic denervation (15), and several studies have investigated whether neuronal damage may be reversed by improved glycemic control. Muhr-Becker et al. (16) reported that cardiac sympathetic denervation in poorly controlled long-term type 1 diabetic patients is dominated by ^{123}I -*m*IBG-verified neuronal abnormalities. However, substantial metabolic improvement after 1 year of intensive insulin therapy partially restores cardiac sympathetic denervation, indicating the presence of a reversible component of cardiac sympathetic dysfunction. Ziegler et al. (17) observed that global and regional ^{123}I -*m*IBG defect scores in the inferior, posterior, and apical walls were increased in poorly controlled diabetic patients; well-controlled patients showed enhanced global ^{123}I -*m*IBG uptake compared with the poorly controlled group after 4 years.

Although CAN has been proposed to be the basis of LV dysfunction (18), demonstration of a cause and effect relationship in nonischemic diabetic cardiomyopathy may have significant therapeutic implications. A welcome manuscript by Sacre et al. (2) offers a strong argument.

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