Cardiac Autonomic Denervation in Diabetes Mellitus

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The heart is heavily innervated with sympathetic and parasympathetic nerve fibers. Although both receptor types are present in the atria and ventricles, the cholinergic receptors are located mainly in the atria and the adrenergic receptors in the ventricles. The distribution of these receptors in the ventricles is not homogenous but follows apex-to-base and epicardium-to-endocardium gradients. The adrenergic receptors are localized in the myocardium and in the coronary arteries and are of several types and subtypes. The α-receptors constitute ≈15% of the total receptors and are both post- and presynaptic, whereas the β-receptors constitute ≈85% of the receptors and are postsynaptic. In the coronary arteries, α-1d and β-2 are most common, whereas in the left ventricular (LV) myocardium, α-1a and β-1 prevail.1

The stimulation of β-1 receptors induces positive inotropic and chronotropic effects, which ultimately lead to an increase in cardiac output, whereas β-2 stimulation activates antiapoptotic and cardioprotective pathways.2 The stimulation of α-1 receptors (abundant in the larger epicardial arteries) in normal, unlike in diseased, arteries does not lead to vasoconstriction or reduction in myocardial blood flow (MBF), most probably due to low receptor density and the opposing effect of nitric oxide. The stimulation of α-2 receptors (more abundant in the microvasculature) results in a decrease in MBF in both normal and diseased arteries.3 The β-receptors, on the other hand, induce coronary artery dilation, but treatment with β-blockers increases MBF perhaps because of increased diastolic time and a decrease in the abundance of α-receptors.1

In the nerve terminal, tyrosine from the blood is converted to dihydroxyphenylalanine, then to dopamine, and then ultimately to norepinephrine, which is stored inside vesicles awaiting a signal for release. Once released to the synaptic cleft, norepinephrine activates the adrenergic receptors and is cleared to the nerve terminal by an energy-dependent mechanism (uptake 1). A small amount is taken up by the myocardium through an energy-independent mechanism (uptake 2). The norepinephrine that reenters the nerve terminal is either restored to the vesicles or broken down to dihydroxyphenylglycol by the action of the enzyme monoamine oxidase and is then released to the blood stream.4

Imaging cardiac sympathetic innervations depends on radiolabeled analogs of neurotransmitters, and the one used with single-photon emission CT (SPECT) is the norepinephrine analog meta-iodobenzylguanidine, which is labeled with 123-iodine (123I-mIBG). The uptake and transport kinetics of 123I-mIBG are very similar to norepinephrine, but 123I-mIBG is not catabolized by monoamine oxidase or catechol-O-methyltransferase in the synaptic cleft, which allows for the accumulation of 123I-mIBG in the sympathetic nerve endings and the imaging of cardiac sympathetic innervation.5 Thus, 123I-mIBG may be viewed as an adrenergic presynaptic analog. Neurocardiac imaging with PET, using 11C-epinephrine as a true transmitter or 11C-hydroxyephedrine as an analog as well as other tracers, allows for adrenergic pre- and postsynaptic and parasympathetic imaging.

The most widely used parameter with 123I-mIBG imaging has been the heart/mediastinum (H/M) ratio obtained late (≈4 hours) after tracer injection from anterior projection images. The late H/M ratio is a composite number that reflects the early H/M ratio (≈15 minutes after injection) and the rate of washout. A ratio of <1.6 is considered abnormal because it is 2 SDs below the mean (2.2±0.3) for a normal population.6

Cardiac autonomic dysfunction due to structural and functional changes has been described in many disease states. The classical case of cardiac denervation exists after cardiac transplantation, but autonomic dysfunction is common in heart failure (HF), diabetes mellitus (DM), chronic kidney disease, myocardial ischemia and infarction, and hibernating myocardium.5,7 Studies have shown that patients with DM and evidence of sympathetic nerve dysfunction have reduced MBF response to cold pressor stimulation and to adenosine administration and that reinnervation after cardiac transplantation restores the reactivity of the coronary vasculature to autonomic stimulation.8–10 Despite these intriguing reports, the major interest in the study of cardiac denervation has been centered on its relation to outcome in patients with HF. Multiple single-center reports and meta-analyses have demonstrated a worse prognosis in patients with HF with an abnormal 123I-mIBG scan than in those with a normal scan.11

In the only prospective multicenter trial (the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure [ADMIRE-HF]) of 961 patients with New York Heart Association (NYHA) class II or III HF and LV ejection fraction (EF) ≤35%, the late H/M ratio was independently predictive of the primary end point of HF progression, arrhythmic cardiac events, and cardiac death (hazard ratio of H/M, ≥1.6 of 0.40; P<0.001).12

In this issue of Circulation: Cardiovascular Imaging, Gerson et al13 analyzed the role of late H/M ratio in predicting...
HF progression in patients with and without DM in the ADMIRE-HF study. Most (85%) patients with DM were taking insulin, oral agents, or both. HF progression, defined as an increase in NYHA class (from II to III/IV or from III to IV) as adjudicated by an independent committee, occurred in 22% of patients with DM compared to 14% in those without DM ($P=0.005$). As expected, the late H/M ratio was lower in patients with DM than in those without DM, and only 21% of patients in the study had a late H/M ratio $\geq 1.6$, which is consistent with cardiac autonomic dysregulation in patients with HF in general, regardless of the presence of DM.\(^\text{12}\) Although in patients with an H/M ratio $\geq 1.6$ the presence of DM had no influence on risk for HF progression, in those with H/M ratio $<1.6$, DM was associated with an increased risk of HF progression (relative risk [RR], 1.46; $P=0.006$). Importantly, patients with DM with an H/M ratio $<1.6$ were 3 times more likely to experience HF progression over 2 years compared to those with DM with normal $^{123}$I-mIBG uptake (RR, 2.99; $P<0.001$). Patients without DM with a reduced H/M ratio also experienced a higher risk of HF progression, although this did not reach statistical significance (RR, 1.64; $P=0.08$). The late H/M ratio was an independent, incremental predictor of HF progression in addition to B-type natriuretic peptide, LVEF, and NYHA class.

These observations therefore support the association of DM with alterations in cardiac structure and function and highlight the contribution of cardiac autonomic denervation to the development and progression of HF.\(^\text{14}\) Thus, DM is considered a risk factor for both systolic and diastolic LV dysfunction and the development of HF independently from coronary artery disease and hypertension.\(^\text{15–17}\) Gerson et al\(^\text{13}\) list multiple plausible mechanisms by which denervation may contribute to this process, including a malfunctioning warning system for myocardial ischemia, activation of the renin-angiotensin-aldosterone system, uninhibited sympathetic activity leading to tachycardia, orthostatic hypotension, and uncontrolled hypertension. Furthermore, because MBF is regulated by autonomic fibers, autonomic dysfunction can result in an alteration of MBF. PET imaging with $^{11}$C-hydroxyephedrine has shown that patients with sympathetic denervation have a lower MBF response to cold pressor stimulation\(^\text{4}\) and a lower coronary flow reserve.\(^\text{18}\)

One limitation of the H/M ratio for the assessment of cardiac autonomic function is its global index. Autonomic denervation in the human heart clearly could be regional. An attempt at measuring the regional variation in $^{123}$I-mIBG uptake was reported in the ADMIRE-HF trial by using visual qualitative SPECT imaging. This approach provided fewer prognostic data than the H/M ratio likely because of technical difficulties in the interpretation of $^{123}$I-mIBG SPECT and the fact that myocardial perfusion and $^{123}$I-mIBG images were interpreted separately rather than side by side. Whether automated quantitative interpretation of the SPECT images, alternative acquisition and processing techniques, or use of newer imaging systems that allow imaging in the semierect position (to minimize inferior wall attenuation by liver activity) would offer any advantage is currently speculative and worth further study. The late H/M ratio in Gerson et al\(^\text{13}\) as well as in other studies has provided superior prognostic information to the early H/M ratio and the washout rate.

There is intense interest in the imaging community to determine whether regional perfusion-innervation mismatch is predictive of sudden cardiac death and whether this information provides superior or incremental information to other variables that have been examined in relation to this dreadful end point. For example, perfusion-innervation mismatch in experimental, and clinical studies of hibernating myocardium have been linked to ventricular fibrillation and sudden death.\(^\text{7}\) In a prospective study by Tamaki et al,\(^\text{19}\) $^{123}$I-mIBG imaging (washout rate) was a powerful predictor of sudden cardiac death independently of LVEF in patients with HF, whereas other variables that have been used to measure cardiac autonomic dysfunction, such as heart rate variability, QT dispersion, and signal-averaged ECG, were not. An emerging variable that reflects cardiac autonomic dysfunction is the heart rate response to adenosine receptor agonists, which are widely used as stress agents for myocardial perfusion imaging.\(^\text{20}\) Because these agents directly stimulate the sympathetic nervous system, patients with cardiac autonomic denervation experience a blunted heart rate response to them.\(^\text{21–22}\) Although the heart rate response has been shown to provide prognostic information, it remains to be shown how it compares with $^{123}$I-mIBG variables or other measures of autonomic dysfunction. Currently, the late H/M ratio offers a simple and reproducible measurement that has been shown in multiple studies to carry prognostic information.

The study by Gerson et al\(^\text{13}\) demonstrates the prognostic power of $^{123}$I-mIBG for detecting the clinically relevant end point of HF progression. The study suggests that the H/M ratio can complement data derived from LVEF, B-type natriuretic peptide, and DM status for the prediction of HF progression. The use of HF progression as an end point, however, is not devoid of technical difficulties and may not be easily reproducible because changes in therapy (especially diuretic dose) could produce dramatic changes in short-term symptoms and HF classification. These findings can have an important clinical application in determining the prognosis of patients with HF due to the low rate of progression of HF in subjects with and without DM with a normal H/M ratio.

**Disclosures**

Dr Iskandrian is a consultant to GE Healthcare.

**References**


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