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EDITORIAL COMMENT

Does Cardiac Sympathetic Innervation Imaging Fulfill an Unmet Need for Managing Atrial Fibrillation?*

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Meta-iodobenzylguanidine (*m*IBG) is a structural analog of guanethidine that shares the same uptake and storage mechanisms as norepinephrine in nerve endings. By radiolabeling *m*IBG with iodine-123, the uptake and storage of *m*IBG can be imaged with a gamma camera. Because *m*IBG is not metabolized, its accumulation over several hours is a measure of neuronal integrity. *m*IBG was first used for myocardial imaging in 1987, but in the ensuing 20 years, it has not established a clinical role in cardiac imaging.

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Recently, *m*IBG imaging has been employed in studies of heart failure patients. Heart failure is associated with high sympathetic activity manifested in part by increased release of norepinephrine. That leads to a decrease in neuronal norepinephrine reuptake due to post-transcriptional down-regulation of the cardiac norepinephrine transporter. This increase in adrenergic nervous system activity of the heart is exhibited as decreased *m*IBG uptake relative to a background standard of the upper mediastinum or the heart/mediastinum ratio (H/M). In a recent report from the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study, a decrease in H/M was associated with the composite end point of heart failure progression, ventricular tachyarrhythmias, and death (1). Also, H/M was an independent predictor by multivariate analysis, adding to information obtained from brain natriuretic peptide (BNP), ejection fraction, and New York Heart Association functional class. That led the investigators to speculate that *m*IBG imaging may have a role in the management of heart failure patients.

In this issue of *iJACC*, there is a report by Akutsu et al. (2) of a study of *m*IBG imaging in 98 patients with paroxysmal atrial fibrillation, with relatively normal left ventricular systolic function and without symptoms of heart failure. They hypothesized that a reduced H/M would predict the development of heart failure and permanent atrial fibrillation (AF). They showed that a low H/M was a powerful independent predictor of the development of permanent AF alone and heart failure plus permanent AF. They concluded that increased adrenergic nervous system activity is associated with the development of permanent AF and heart failure in subjects with paroxysmal AF and no heart failure. Also, they suggested that *m*IBG may be useful for managing patients with paroxysmal AF.

Perhaps the most important contribution of this paper is the demonstration that increased cardiac sympathetic nervous system activity is related to the development of permanent AF. We know clinically that conditions associated with increased adrenergic activity, such as exercise, stress, and excess alcohol consumption, can be temporally related to the onset of AF, but little proof of the role of adrenergic activity exists. Also, we know that heart failure is associated with increased sympathetic activity. Thus, it is not surprising that the development of AF and heart failure were related to sympathetic activity in this study, and *m*IBG was an elegant way to document this relationship.

In this study, *m*IBG was the strongest predictor of AF and heart failure by multivariate analysis. However, left ventricular ejection fraction (LVEF)

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was also independently predictive of these events, and BNP predicted the development of permanent AF and heart failure. When the occurrence of heart failure and AF were examined by sensitivity, specificity, and receiver-operator characteristic curve areas, there was little difference in the predictive power of *m*IBG, LVEF, and BNP. In fact, for predicting death alone in a Kaplan-Meier analysis, BNP was best. Both BNP and *m*IBG have a relatively low specificity for predicting permanent AF and heart failure, so their positive predictive value is low. Conversely, their relatively high sensitivities mean that they are most useful when normal. This limits their role in therapeutic decisions.

The ability of LVEF to predict permanent AF is interesting since it was truncated at 50% in the selection criteria for the study. Echocardiography was used to assess LVEF for study entry, and patients with a value <50% were excluded. A value of 50% is just below the lower limit of normal of 55% by the American Society of Echocardiography criteria (3). Perhaps if patients with lower LVEF but no heart failure symptoms were allowed in the study, LVEF would have been more strongly predictive. Clearly, *m*IBG is a stronger predictor of permanent AF in patients with relatively normal LVEF.

There are many risk factors for the development of AF, yet it is clinically difficult to predict who will get permanent AF. In this study, the usual clinical practice of cardioversion and drug therapy were employed to keep patients in sinus rhythm if they relapsed, but nothing special was done for patients who did not relapse. The results of this study suggest that a low H/M in a paroxysmal AF patient should encourage prophylactic therapy, perhaps with at least beta-blockers to try to prevent the development of permanent AF. We would need a randomized trial to establish such a strategy, but preventing permanent AF would certainly be desirable.

Because most of the patients in this study had EFs in the normal range (>55%), it is likely that many of those who had heart failure had diastolic LV dysfunction. Diastolic parameters were not provided for the patients. That raises the question of whether such measures might also be predictive of the development of permanent AF and heart failure. If so, echocardiography is less expensive and does not involve radiation exposure in comparison with *m*IBG. Also, we may be on the verge of the clinical application of genetics to AF risk. Atrial fibrillation clearly has a genetic component and is much more prevalent among white Americans than among black Americans, despite a higher prevalence of more traditional AF risk factors among blacks (4). Whether *m*IBG will be useful in more racially diverse populations is unclear.

Finally, a barrier to the widespread application of *m*IBG imaging for the assessment of patients with paroxysmal AF is a lack of standardization of the technique between laboratories. Recently, Europeans have suggested a standardized technique, but it has not been widely accepted at this point (5). Hopefully, the American Society of Nuclear Cardiology will address this soon, as cardiac *m*IBG may be on the threshold of more wide utilization as our aging population is increasing the prevalence of AF and heart failure.

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