EDITORIAL

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^{123}I-meta-Iodobenzylguanidine Imaging in Patients with Cardiac Resynchronization Therapy: Results are Intriguing, but Unknowns Remain

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Excess sympathetic activation and subsequent decrease in neuronal reuptake of norepinephrine due to receptor downregulation are important in the pathogenesis of congestive heart failure. ^{123}I-*meta*-iodobenzylguanidine (*m*IBG) scintigraphy has emerged as a method to measure cardiac sympathetic activity because ^{123}I-*m*IBG shares the same biological properties as norepinephrine, but is not metabolized by the body. Impaired sympathetic integrity is manifested by low cardiac ^{123}I-*m*IBG uptake relative to the mediastinal background, resulting in a low heart-to-mediastinal ratio (HMR). The comparison between early and delayed HMR is quantified by the washout rate, with high rates corresponding to increased sympathetic activity.[1,2]

^{123}I-*m*IBG imaging was first shown to have an important prognostic value in patients with heart failure in the early 1990s.[3] Since then, a number of studies have confirmed that late HMR is an independent predictor of cardiac events both as a dichotomous and a continuous variable.[4–6] Tamaki et al. have also demonstrated that abnormal ^{123}I-*m*IBG washout rate serves an independent predictor for sudden cardiac death.[7] Models have further incorporated late HMR and clinical variables to predict 2- and 5-year mortality,[8] with a recent study validating the 2-year risk model in those with heart failure at low and intermediate cardiac risk.[9]

Despite the current level of evidence, clinical use of ^{123}I-*m*IBG scintigraphy has remained limited, potentially because ^{123}I-*m*IBG activity can be affected by imaging and processing conditions, raising the need for protocol standardization.[10,11] With the advent of cadmium-zinc-telluride cameras, data have demonstrated that despite a good agreement between transaxial and planar HMR, the absolute HMR values obtained using a multi-pinhole cadmium-zinc-telluride camera were lower than those using conventional planar imaging.[12] However, Bateman et al. have shown that HMR of ^{123}I-*m*IBG is highly reproducible when subjects are imaged on the same camera.[13] In addition, the specific HMR thresholds for various patient populations and outcomes have remained sub-optimally defined in clinical studies.

In light of these considerations, efforts have been made to specifically focus on the subset of heart failure patients eligible for cardiac resynchronization therapy (CRT). Research has suggested that CRT is associated with improved washout rate and HMR.[14,15] A study of 30 patients by Nishioka et al. demonstrated that late ^{123}I-*m*IBG HMR can independently predict response to resynchronization with an optimal cutoff value of 1.36, yielding a sensitivity of 75% and specificity of 71%.[16] More recent data also highlight an association between global longitudinal strain improvement and increase in late HMR in patients with CRT.[17] However, the number of patients included in these studies was relatively small and they did not assess the presence of left bundle branch block (LBBB) as a variable.

In this issue of the Journal, Moreira et al. studied 121 patients with severe systolic dysfunction and primarily non-ischemic cardiomyopathy, also included in the BETTER-HF trial, who underwent CRT. Fifty-five patients also had ^{123}I-*m*IBG scintigraphy performed 6 months after implant placement. The mean follow-up

was approximately 2 years and 2 months. The main finding by the authors was that baseline late HMR was an independent predictor of echocardiographic CRT response, as defined by $\geq$ 15% reduction in end systolic volume (regression coefficient 2.906, 95% CI 0.293-3.903, p = 0.029), and the composite end point of cardiac mortality, cardiac transplant or hospitalization for heart failure (hazard ratio 0.066 (0.005-0.880) p = 0.040). The data also demonstrate significant correlation between improvement in late HMR and improvement in peak VO2. Further, in the 55 patients who had MIBG imaging 6 months after implant placement, only CRT responders had an increase in late HMR. Of caution, the absolute difference in HMR between responders and non-responders was relatively small with potential for overlap (1.36 ± 0.14 prior to CRT vs 1.42 ± 0.16 6 months after CRT, p = 0.039).

The present work by Moreira et al. is important because it adds to the growing knowledge that CRT response is associated with increase in HMR and includes more patients than the previous CRT studies. The data also suggest that HMR can predict echocardiographic response independent of the presence of LBBB, which may add value in the clinical dilemma in which patients with advanced heart failure but without a class I indication for CRT by the current guidelines (such as those without LBBB or with QRS durations < 150 ms) may still benefit from implantation.[18,19] Despite these results, important limitations remain including the study's relatively small size and observational design, use of only planar imaging, and the fact that fewer than half of the patients had follow-up ^{123}I-mIBG scintigraphy. The authors note that as 123I-mIBG imaging is highly dependent on acquisition and processing conditions, extrapolation of their results to other settings may be limited. Last, the study does not seem to provide an optimal cutoff of late ^{123}I-mIBG HMR for separating responders and non-responders.

In concordance with prior studies on ^{123}I-mIBG imaging in patients with heart failure and CRT, the results by Moreira et al. are promising. These data, however, demonstrate a need for larger trials and protocol standardization prior to translation to mainstream clinical practice.

Disclosure

Anisiia Doytchinova and Myron C. Gerson have no conflicts to disclose.

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