^{123}I-*m*IBG: Simplicity and reproducibility

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> Frustra fit per plura quod potest fieri per pauciora
> (It is futile to do with more things that which can be done with fewer)
> –William of Ockham

The activity of the sympathetic nervous system increases in patients with heart failure to compensate for decreased output. Norepinephrine and epinephrine improve forward flow but have long-term detrimental effects by increasing myocardial work, oxygen demand, and afterload. The stimulation of norepinephrine and epinephrine leads to the down-regulation of corresponding receptors in the myocardium and depleted levels of norepinephrine in myocardial cells.[1]

The clinical applications of radiolabeled iodobenzylguanidine agents, which are analogs of guanethidine, a norepinephrine analog used as an antihypertensive agent, have been under investigation for decades. These agents allow for noninvasive characterization of the adrenergic nervous system.[2] Modifications have been made to the structure of these radiolabeled tracers and ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) was found to be a useful, clinically relevant agent, given its long half-life, ease of imaging, and lack of catabolism. *m*IBG utilizes the same storage and release mechanisms as norepinephrine, but its lack of catabolism by the same enzymes as norepinephrine provides its ability to noninvasively evaluate the sympathetic nervous system.[3] Specific to the cardiac uses of this agent, it provides insight into the myocardial sympathetic nervous system and its impact of different disease states.[4] The myocardial uptake of these agents was first described in canine subjects in 1980[5] and in human subjects in 1981.[6] Clinical applications of these agents have expanded rapidly.

Abnormalities of myocardial uptake of ^{123}I-*m*IBG in patients with severe dilated cardiomyopathy were reported separately by Henderson et al[7] and Schofeld et al.[3] In the following years, there was a vigorous debate on how best to evaluate abnormal *m*IBG uptake. Initial, 4, and 24 hours images as well as washout were evaluated but none seemed to perform as well as the simple heart-to-mediastinal (*H*/*M*) ratio. Clinical interest in using *m*IBG as a prognostic tool was rekindled by Merlet et al who reported that *H*/*M* was a very powerful prognostic indicator: more robust than radionuclide left ventricular ejection fraction, x-ray cardiothoracic ratio, and M-mode echocardiography.[8] The utility of the mediastinum as a reliable reference area was validated in a subsequent study by Inoue and colleagues who found that the easily calculated *H*/*M* ratio correlated well with other dose-normalizing methods, including incorporating body size and injected dose.[9]

Several different techniques to calculate the *H*/*M* ratio have been published.[10-12] The differences between the techniques come with the region of interests selected for the myocardium and the mediastinum. Despite these differences, all three techniques have lead to similar results.[4] In response to several calls to standardize the technique,[13,14] a standardization proposal by the European Association of Nuclear Medicine and the European Council of Nuclear Cardiology was developed.[15] This called for the *H*/*M* ratio to be determined using the average counts per pixel in a myocardial region of interest to the average counts per pixel in the mediastinum (excluding the thyroid).[15] Despite this, significant variation among different publications has been described.[16]

The largest, multicenter trial evaluating *m*IBG *H*/*M* ratio was the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial.[17] This multicenter investigation validated the additive prognostic value of the *H*/*M* ratio among HFrEF patients. In this study, the threshold for an abnormal *H*/*M* ratio was defined as 1.6 which was 2 standard deviations below

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the mean of a group of normals. Patients below this level had an increased event rate of worsening New York Heart Association functional class, potentially life-threatening arrhythmic event, or cardiac death over a median follow-up of 17 months. The *H*/*M* ratio added independent discrimination in addition to left ventricular ejection fraction and B-type natriuretic peptide.[17] The ADMIRE-HFX trial extended this follow-up to a median of 24 months and showed the added prognostic benefit of *m*IBG *H*/*M* ratio to models utilizing left ventricular ejection fraction, but not a significant increase in models utilizing B-natriuretic peptide.[18] Evidence from this trial and others has led to the class I recommendation in the Japanese Circulation Society for the clinical use of cardiac nuclear medicine supporting the use of *m*IBG imaging in the severity assessment and prognosis of heart failure patients.[19]

But, it seems the world was not yet ready to accept such a simple measure as the last word on evaluating myocardial adrenergic activity. The ADMIRE-HF trial exhaustively evaluated and did not discover any further benefit from analyzing washout, or analyzing the relation between *m*IBG uptake and MPI. Regional assessment of tracer uptake has been described, but regional differences in uptake (even among healthy subjects) and frequent lack of acceptable image quality have limited clinical applications of this technique.[4,20] Lung uptake of *m*IBG has also been evaluated for its prognostic value in patients with heart failure with reduced ejection fraction.[21,22] Kamiyoshi et al reported that the lung/heart ratio was found to be an independent predictor of cardiac events.[22] Gerson and colleagues also published evidence of the prognostic utility of the lung/mediastinum ratio.[21]

It is ironic that the highly sophisticated imaging and reconstruction techniques introduced over the past decade or two have provided no further advantage when imaging with *m*IBG when compared to the comparatively primitive *H*/*M* ratio. This ratio is, in its essence, a simple measure of global adrenergic activity of the heart. It is analogous, therefore, to other global measures such as the ejection fraction or BNP. It is also not without precedent; the lung/heart ratio obtained after thallium imaging has been shown to be perhaps the strongest indicator of poor prognosis in patients with coronary disease, eclipsing perfusion defects, and EKG and catheterization results.[23]

The clinical utility of a test will also depend on two more factors. The first is inter-observer variability. Veltman et al demonstrated high intra-observer and inter-observer reliability, even among both experienced and inexperienced technologists.[24] A subsequent study by Pellegrino et al also demonstrated high intra-observer and inter-observer reproducibility among experienced readers.[25]

The study by Bateman et al in this volume of the Journal addresses the second factor.[26] It explores the reproducibility of *m*IBG *H*/*M* ratio among clinically stable New York Heart Association classes II-III patients with left ventricular ejection fraction $\leq$ 35%.[26] 47 Patients at 10 study centers were studied at two separate time intervals 5-14 days apart on the same camera using the same dose of radionuclide to assess the reliability of this measure. The protocol described by the authors to determine the *H*/*M* ratio was consistent with previously described protocols and outlined in the package insert for the medication. The results show for the first time that there is a high degree of consistency for the *H*/*M* ratio among clinically stable patients. They also demonstrated a very low inter-observer variability, though it should be noted that the readers in this study underwent extensive training beforehand.

This trial by Bateman et al adds an important finding that will help expand clinical indications for *m*IBG imaging. The reproducibility of the *H*/*M* ratio shows that it is a reliable marker that has the potential to assess the response to medical therapy. Multiple studies have already evaluated changes in *m*IBG after different therapeutic interventions. Pharmacologic studies have shown improvement in the *H*/*M* ratio in serial *m*IBG studies when HFrEF patients were treated for at least 6 months with carvedilol,[27] valsartan,[28] and the combination of spironolactone and candesartan.[29] Another study by Gould et al assessed the effects of bi-ventricular pacing on patients after a 2-week interval.[30] By showing that the *H*/*M* is both stable and reproducible in clinically stable patients, Bateman et al support the use of *m*IBG as a marker of clinical improvement in heart failure patients. A crucial, and as of yet, unanswered question is whether an improvement in the *H*/*M* ratio translates into increased survival.

In one sense, the simplicity of the *H*/*M* highlights the fundamental importance of myocardial adrenergic activity in the clinical course of patients with heart failure. The reproducibility of the *H*/*M* ratio as has now been demonstrated by Bateman et al, supports *m*IBG imaging as an important tool in the evaluation of patients and assessing their response to therapy.

Disclosure

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