Introduction of New Tests: Low Are the Mountains, High the Expectations

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There has been a significant movement recently in a rather stagnant field of cardiovascular radionuclide imaging in the U.S. Two relatively large prospective clinical studies have just been completed with 123I-labeled beta-methyl-p-iodophenyl-pentadecanoic acid and 123I-labeled meta-iodobenzylguanidine (mIBG) for the assessment of ischemic memory and neuronal dysfunction, respectively. The results of these studies have been recently presented (1,2). A third agent, 18F-labeled pyridaben derivative, is also being investigated in a large clinical trial for myocardial perfusion imaging (3). However, before such tests are incorporated into the routine clinical practice, it would be mandatory to demonstrate that the management strategy including the novel imaging tools is distinctly superior to the standard of care.

Molecular imaging with mIBG, a false adrenergic neurotransmitter, was proposed for the assessment of the sympathetic neuronal system years ago (4) and represents one of the few imaging agents that has endured the arduous scientific journey from bench to bedside. mIBG shares the reuptake mechanism and endogenous storage with norepinephrine but is neither metabolized nor does it interact with postsynaptic receptors. Images of the heart acquired with radiolabeled mIBG provide sufficient spatial resolution to provide both anatomic localization and quantifiable functional attributes. 123I-mIBG was approved with a cardiac indication in Japan more than 15 years ago and has been used clinically with an established safety record. In Europe, it has been used almost for the same duration for assessing candidacy for cardiac transplantation. mIBG has received U.S. Food and Drug Administration (FDA) approval for imaging neuroendocrine tumors in the U.S. However, for the routine characterization of neuronal function in the heart, the FDA had requested 2 well-controlled trials to demonstrate that mIBG imaging results are indeed predictive of outcome in heart failure (HF) patients. The prospective evaluation was deemed necessary, because it was not available from the trial used to obtain approval in Japan, and the European approval was based only on literature but not on the prospective trial data.

As such, 2 multinational prospective open-label, multicenter, phase 3 studies evaluating the usefulness of 123I-mIBG imaging to identify symptomatic HF patients who are likely to experience a major adverse cardiac event (ADMIRE-HF [AdreView Myocardial Imaging for Risk Evaluation in Heart Failure] study) were performed (1). Almost 1,000 subjects with HF (New York Heart Association [NYHA] functional class II to III; left ventricular ejection fraction ≤35%) were recruited and followed for up to 2 years until the time to first occurrence of NYHA functional class progression, potentially life-threatening arrhythmic event (including implantable cardioverter-defibrillator [ICD] discharge), or cardiac death. Adverse events occurred in one-quarter of the patients; a 2-year event-free survival was 85% in subjects with normal mIBG uptake compared with 63% in subjects with abnormal imaging result (hazard ratio [HR]: 0.40; p < 0.001). HR for occurrence of HF progression, arrhythmic events, and cardiac death were all individually significant (HR: 0.49, p = 0.002; 0.37, p = 0.02; and 0.14, p = 0.006, respectively). Significant contributors to the multivariable model were the mIBG results, left ventricular ejection fraction, B-type natriuretic peptide, and NYHA functional class. This study validated information gathered from numerous smaller and single-center studies reported earlier (5).
The results of the prospective study suggested that a subset of patients who are likely to worsen rapidly or die a sudden death and would benefit from aggressive treatment, could be differentiated from those who do well.

Despite the reproducible benefits of aggressive management, such as with resynchronization and defibrillator device implantations, a large proportion of appropriately selected patients are not benefited. As such, the most appropriate and cost-effective application for a test such as $m$IBG would be to correctly identify patients who may benefit most from aggressive HF therapy including biventricular pacing to prevent progression to end-stage disease, and to select patients most deserving of a defibrillator insertion to prevent sudden arrhythmic deaths (6). With such an end in view, an $m$IBG single-photon emission computed tomography study was recently performed in 100 HF patients to address the predictability of life-threatening tachyarrhythmias for an appropriate ICD indication (7). In a 2-year follow-up period, an appropriate ICD discharge was documented in 20% of the patients and the $m$IBG defect score was an independent predictor. Patients with greater defect scores showed a 10-fold higher likelihood of appropriate ICD discharge therapy (50% vs. 5%, $p < 0.01$) than patients with smaller defects. The clinical trials of resynchronization and defibrillator therapy are currently recruiting patients with relatively mild HF, and such a trend is likely to substantially add to the cost of the health care expenditure. As such, the identification of subjects at high risk and deserving of high-cost devices has become significantly more important.

Assessment of the subclinical neuronal involvement may be relatively difficult and may require induction of neuronal stress. It has been proposed that competitive interference with the reuptake mechanism could accentuate $m$IBG defects and unmask subclinical dysfunction (8). Tricyclic antidepressants, such as amitriptyline, are bona fide inhibitors of human norepinephrine transporter 1–norepinephrine-dependent uptake in pre-synaptic neurons. A very small oral dose (25 mg) of amitriptyline was used in a small study of post-pharmacologic stress $m$IBG imaging in 6 patients. These patients had demonstrated a normal cardiac $m$IBG scan within the past week during work-up for movement disorders, and the serial imaging was performed 4 h after amitriptyline to assess any change in the regional $m$IBG distribution. Mean percentage of peak activity was calculated for each segment at rest and after pharmacologic stress; a >10% decrease in regional $m$IBG uptake was observed in 20% of myocardial segments. Whether uncovering such subclinical regional myocardial neuronal defects will identify subjects who are at a greater risk for developing HF in the future is yet to be determined. However, this strategy may parallel the clinical and prognostic implications of myocardial perfusion defects that are identified only with stress.

The role of neuronal imaging has also been explored for better decision making in specifically designed boutique studies. An $m$IBG study (9), presented in the current issue of $iJACC$, proposes that normalization of $m$IBG uptake may allow identification of subjects who have recovered from advanced HF and may be weaned from left ventricular assist devices. This study, in addition to providing patient-specific information also offers in vivo clarification of the pathogenetic mechanisms involved in adverse and reverse cardiac remodeling (10).

The new face of imaging is likely to be the identification of molecular targets—not as a marker of disease alone but also as a maker to identify selected subpopulations that might benefit from specific therapies and more importantly, guide such therapies. Techniques such as neuronal imaging may have the promise of offering some solutions to clinical problems that have defied classification with current techniques. The potential of new tests may only be realized once these tests become clinically available for innovative, investigator-initiated clinical studies providing improved disease definition, more intelligent choice of therapeutic intervention, and closer monitoring of response to therapeutic interventions. Thus, a debate is timely to compare the pros and cons of establishing all indications of a new test before it is approved by a regulatory process versus approval of a test (once proven to be safe in human use) to allow investigators to study its potential in numerous clinically relevant conditions.

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