A key role for nuclear cardiac imaging in evaluating and managing patients with heart failure

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Congestive heart failure (CHF, HF) is a major health problem in the United States and much of the western world. More than 6 million Americans over age 20 have HF, with 1/5 people over 40 likely to develop HF sometime during their lives.¹ Despite significant advancements in evaluation and management, the death rate remains high, with about 50% of HF patients dying in 5 years, and HF mentioned as a contributing factor in 1/9 death certificates.^{2,3}

A variety of methods are used to assess patients with HF, including standard clinical techniques, i.e., history, physical examination, and laboratory measurements; a variety of non-invasive imaging procedures that include chest x-ray, echocardiography, equilibrium radionuclide angiography (ERNA), myocardial perfusion imaging with ECG-gated SPECT, cardiac CT methods, cardiac magnetic resonance imaging, and invasive procedures such as right and left heart catheterization, and coronary angiography. These methods diagnose HF, determine a likely etiology, classify its severity, identify additional contributing factors, and guide patient management in terms of remedying reversible causes, improving symptoms and patient well-being, and preventing additional adverse events ranging from frequent recurrent HF hospitalizations to dangerous cardiac arrhythmias to death. Recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Heart Failure guidelines

recommend comprehensive pharmacologic regimens, and describe when advanced mechanical device therapies such as biventricular pacemakers for cardiac resynchronization therapy (CRT), left ventricular assist devices (LVAD), and implantable cardiac defibrillators (ICD) should be considered, as well as when cardiac transplantation is the preferred option.⁴

Nevertheless, much remains unclear regarding the approach to patients with HF, a condition expected to increase in prevalence in coming years as the population ages.⁵ In particular, many of the beneficial advanced mechanical device therapies are costly and have risks. It is important to wisely select which patients should receive them. An issue of particular focus is who should get an ICD. Based on several multicenter, prospective randomized clinical trials, the ACCF/AHA HF guidelines assign a Class IA recommendation for implantation of an ICD as primary prevention of sudden cardiac death (SCD) in patients with New York Heart Association (NYHA) Class II-III symptoms and a left ventricular ejection fraction (LVEF) $\leq 35\%$.^{4,6-8} At the same time, while trials report significant reductions in mortality with ICDs, the absolute decrease in death is relatively small, from about 5.6%⁷ to 7.2%,⁶ with 11⁷ to 14⁶ patients needing to receive an ICD to save 1 life.⁹ There are risks associated with an ICD, including a 4% post-procedural complication rate,¹⁰ infections, device malfunction, worsened quality of life, psychiatric problems, and life style restrictions.^{11,12} ICDs are expensive, about \$28,000 per device, not including ICD follow-up costs.¹³ Thus, current methods for choosing which patients receive an ICD have limitations,¹⁴ and using LVEF as a major deciding parameter appears flawed.¹⁵

A key way to identify patients who are best managed with advanced mechanical therapies such as an ICD, and/or who should be referred for cardiac transplant, is effective risk stratification, better if one can adjust predicted outcomes for clinical status changes, including when a device is added. Using databases from multiple large HF studies, survival scores have been developed incorporating combinations of clinical variables. One such model, the Seattle Heart Failure Model (SHFM), uses routinely collected demographic, imaging, laboratory, and therapeutic parameters to generate a

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score that determines the likely 1-5-year mortality,^{16,17} predicts the mode of death, i.e., SCD versus progressive HF,¹⁸ and measures potential improved survival with mechanical devices.¹⁹ In response to demonstration by SCD-HEFT (SCD in HF)⁶ of improved survival with an ICD in Class II-III NYHA patients with LVEF $\leq 35\%$, a modified version of the model, i.e., SHFM-D was developed.²⁰ In particular, SHFM-D can identify not only subgroups of patients for whom ICD placement is most beneficial but also a subgroup that, while at high risk overall mortality, is so unlikely to have SCD that an ICD has no benefit. SHFM-D appears better than LVEF-based current approaches for deciding on an ICD.

Another technique consistently found to effectively risk stratify patients with advanced HF is cardiac imaging with ¹²³I-*m*IBG (*meta*iodobenzylguanidine), a radionuclide analogue of norepinephrine that provides information on the health of cardiac sympathetic innervation.^{21,22} Most commonly, global cardiac uptake is measured on delayed planar images, expressed as a ratio of cardiac activity to background, i.e., the heart-to-mediastinal ratio (H/M). Among the first to recognize ¹²³I-*m*IBG imaging as a potentially useful risk stratifying tool for patients with HF was Merlet et al,²³ finding that H/M was independent of and superior to cardiac size on chest x-ray, echocardiographic end-diastolic diameter, and LVEF in predicting survival in patients with NYHA Class II-III symptoms and LVEF $< 45\%$. Subsequently, various small single-center studies reported the potential value of cardiac ¹²³I-*m*IBG imaging in HF patients, followed by a 290 patient multicenter retrospective reanalysis study²⁴ and a 1,755 patient meta-analysis²⁵ that strengthened the belief by many that ¹²³I-*m*IBG imaging provides prognostic and therapeutic guiding value beyond standard clinical and laboratory parameters. These efforts culminated in the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial, a prospective, multicenter, international study of 961 patients with NYHA Class II-III HF and LVEF $\leq 35\%$.²⁶ At 17 months, an H/M < 1.6 more than doubled (from 15% to 37%) the incidence of worsening CHF, life-threatening arrhythmias, and cardiac death. Subsequent multivariate analysis showed that H/M was a predictor of cardiac and all-cause deaths independent of other clinical and image variables, including age, LVEF, and brain natriuretic peptide (BNP).²⁷

In the manuscript by Ketchum et al²⁸ appearing in this issue of the journal, the investigators examine enhancement of the risk stratification power of the SHFM-D model by the addition of ¹²³I-*m*IBG parameters for patients enrolled in ADMIRE-HF. In this cohort, SHFM-D was again a significant predictor of adverse outcome. At the same time, the H/M was an independent predictor of events, and added incremental risk stratification to

SHFM-D. When the authors dichotomized the patients by the median SHFM-D, each standard deviation (SD) increase in H/M ratio was associated with increased mortality. This was especially true for the cohort of patients with an SHFM-D score above the median (88.5% risk increase for each SD, $P < .0001$). Addition of the H/M ratio was superior to SHFM-D alone in effectively reclassifying patients, with a 14.9% net reclassification improvement for patients who died, and a 7.9% improvement for those who survived, with a net reclassification improvement of 22.7%.

Evidence in the literature suggests that neurohormonal activation is a key factor in HF that is proarrhythmic and contributes to remodeling. Although some SHFM-D variables, such as serum sodium and systolic blood pressure indirectly incorporate the prognostic value of neurohormonal factors, direct sympathetic innervation imaging using H/M is shown by the analyses of Ketchum et al to add important incremental risk stratification value. The additive prognostic utility of ¹²³I-*m*IBG imaging over SHFM-D should allow better selection of beneficial therapy.

What next? The manuscript by Ketchum et al adds to the wealth of available data consistently showing the strong and independent risk stratification ability of ¹²³I-*m*IBG imaging. Its prognostic power has just about always been found to be as good as, or better than, parameters such as LVEF and BNP upon which major therapeutic decisions are customarily made for HF patients. Nevertheless in the current era, for ¹²³I-*m*IBG imaging to become part of the standard evaluation of HF patients, demonstration of effective risk stratification will not be sufficient—imaging will have to be shown to be reliably useful for key therapeutic decision-making and ultimately improve outcome. Despite the reported high negative predictive values for death if the H/M ratio is above a certain value, many have expressed skepticism in using ¹²³I-*m*IBG imaging to decide not to place an ICD in a patient who meets guidelines. Currently in the US, although ¹²³I-*m*IBG is available it is not FDA approved for cardiac imaging, and therefore not reimbursable. The lack of convenient clinical availability has precluded large prospective studies that many say are required to show that imaging is a safe and effective way to decide on an ICD. There is concern that without such studies managing patients not in accordance with published guidelines is unwise, particularly because of the potential medical-legal implications of a patient meeting guidelines who, based on ¹²³I-*m*IBG imaging does not receive an ICD, and then suffers a SCD.

However, it is important to consider the limitations of guidelines.²⁹ In a critical discussion of practice guidelines, Diamond and Kaul write that they are “most often...constructed from a pastiche of expert consensus opinion, observational cohort studies, and randomized

control trials,” and “even when founded solely on direct empirical observations from well-designed randomized trials...the weighing of the evidence is inherently subjective and does not explicitly reflect the putative clinical importance of the wide spectrum of alternative outcomes and treatment effect.”³⁰ Guidelines for ICD use as primary prevention derive largely from four large randomized studies: Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-2),⁷ Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),⁸ Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE)³¹ and SCD-HeFT.⁶ From these, LVEF has become a principal variable for deciding who should receive a device. However, as described by Myerburg, “these trials, especially MADIT-II and SCD-HEFT, had broad enrollment criteria, with limited stratification of the study populations, and have shown relatively small absolute improvements in the outcomes.”³² Differences among EF entry criteria were large, and most enrolled patients had EFs well below the threshold ultimately used in guidelines. Buxton et al¹⁵ found that consideration of multiple factors beside LVEF provide more accurate prediction of SCD and mortality; he developed a model identifying patients who meet criteria but are unlikely to have improvement in 2-year survival. In addition, often patients with an LVEF > 30%, who would not receive an ICD based on guidelines are at high risk, with evidence that over half of patients who die suddenly have an LVEF > 30%.^{33–35} In fact, current guidelines based on LVEF do not identify the majority of those who might benefit from an ICD.

In part because of perceived limitations of guidelines, many clinicians are not following them. One study reported a 9% compliance rate in suitable patients post-myocardial infarction.³⁶ In contrast, a recent review of >100,000 patients in the National Cardiovascular Data Registry-ICD Registry found that 22.5% of ICDs did not meet evidence-based criteria.³⁷ Even when clinicians are well familiar with and do wish to follow guidelines, lack of clarity about a patient’s true LVEF, often documented solely as visual estimates “subject to bias and reader error,” often differ depending on the imaging method chosen, creating uncertainty.³² In one study 31% of patients with EF < 30% referred for ICD were not eligible after repeat imaging with ERNA showed a higher EF.³⁸

Given the recognized problems with guidelines, a simple imaging method that can be used with routinely obtained HF clinical parameters, well described by Ketchum et al and consistent with much previous work, should help more effectively manage this prevalent and high morbidity/mortality condition. Compared with LVEF, imaging with autonomic tracers depicts cardiac pathophysiology closer to the underlying basis of arrhythmias. ¹²³I-*m*IBG, and perhaps PET tracers such as

¹¹C-HED^{39,40} or an F-18-based tracer under investigation,⁴¹ would be expected to more precisely determine risk.

Most agree that prospective clinical effectiveness trials studies examining the clinical utility of autonomic imaging with ¹²³I-*m*IBG and other autonomic tracers are needed. Cardiac radionuclide imaging, while currently mostly confined to perfusion imaging, has promise in helping to show the underlying molecular basis of much cardiovascular disease, such as HF.⁴² Continuing the work of studies such as that of Ketchum et al has much potential for better directing patient management, thereby improving well-being and outcome.

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