How to best appreciate the possible clinical role of cardiac ^{123}I -*m*IBG scintigraphy in heart failure patients: Trying not to get lost while going in the right direction!

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Cardiac ^{123}I -*m*IBG scintigraphy, a non-invasive imaging technique to assess cardiac sympathetic activity, has been shown to be of clinical value, especially for the assessment of prognosis in patients with chronic heart failure (CHF).^{1,2} The semi-quantification of the images is essential to differentiate normal and abnormal cardiac sympathetic activity and thereby identify respectively the low and high risk groups. In the ADMIRE-HF study ($n = 961$), so far the largest prospective multicenter study addressing the prognostic value of cardiac ^{123}I -*m*IBG scintigraphy, a predefined LEHR (low energy high resolution) collimator-derived late heart-to-mediastinum (H/M) ratio < 1.6 was shown to be an independent predictor of heart failure progression, cardiac death, and arrhythmia.¹ A pooled individual patient data meta-analysis showed that, in CHF patients ($n = 636$), the late H/M ratio is not only useful as a dichotomous predictor of events (high vs low risk) but also has prognostic implication over the full range of the outcome value for all event categories except arrhythmias.²

However, despite the abundance of evidence showing the prognostic value of cardiac ^{123}I -*m*IBG

scintigraphy, its role has yet not been acknowledged by the guidelines of the major clinical cardiology societies both in the United States and Europe. In part this lack of acknowledgement can be explained by the plethora of alternative potential “new” prognostic biomarkers and prediction models for CHF patients. These other tests, based on circulating molecules (i.e., biomarkers), are in general cheaper and more easily implemented in clinical practice compared with cardiac ^{123}I -*m*IBG scintigraphy.

As proposed by Maisel et al. the ideal biomarker should, amongst others, either be highly sensitive (for diagnostic purposes) or highly specific (for assessment of treatment effects), reflect abnormal physiology and serve as the basis for targeted therapy.³ In line with this definition, it can be argued that cardiac ^{123}I -*m*IBG scintigraphy should be regarded as an ideal biomarker. The key is to realize that the characteristics of each individual test depend on the clinical setting in which they are applied (i.e., what disease and under what circumstance: specific populations, etc.). Therefore tests should be chosen wisely including cost-effectiveness considerations.

Although it is of critical importance to be informed on the prognosis of individual CHF patients, the role of cardiac ^{123}I -*m*IBG scintigraphy in the risk assessment in daily clinical practice is mostly hampered by its difficult implementation and relatively high costs. Therefore the role of cardiac ^{123}I -*m*IBG scintigraphy may have potential in specific subpopulations of CHF patients. Despite therapeutic improvements the prognosis of CHF remains unfavourable partly due to sudden cardiac death (SCD). Implantable cardiac defibrillators (ICDs) applied for primary or secondary prevention of SCD reduce the relative risk of death by 20%. However, 3 years after ICD implantation for primary prevention, a remarkably

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high percentage (65%) of patients had never received appropriate ICD therapy.⁴ Moreover, the risk of malfunction, (post)operative complications and the relatively high cost of these devices urges for optimization of current ICD selection.⁵ In previous studies it has been suggested that cardiac ^{123}I -*m*IBG scintigraphy may have a cost-effective roll in selecting CHF patients for ICD implantation.⁶ Furthermore, when an ICD has reached its end of life (approximately 7 to 10 years after implantation), a decision has to be made with regard to either simply replace the ICD and downgrade to simpler type of pacemaker or decide that there is no need for any type of pacemaker anymore. Therefore, in these specific CHF patients it would be of help to have a biomarker to better estimate the risk of potential fatal arrhythmia or SCD, especially in patients referred for prophylactic (i.e., primary prevention) ICD implantation.

The long-term follow-up of the ADMIRE-HF study presented by Agostini et al. in this issue of the Journal of Nuclear Cardiology should be seen in this perspective. This retrospective study evaluated an extended follow-up of CHF patients from the original ADMIRE-HF study who were alive after the 2-year ADMIRE-HFX study.⁷ Six hundred six patients were followed for a median of 62.7 months. During this 5-year follow-up period 334 patients died, 233 deaths more than in the 2-year follow-up study. There was a stepwise and substantial increase in all-cause mortality as the H/M ratio decreased (20.9% with $\text{H/M} \geq 1.6$, 36.4% with $\text{H/M} 1.2\text{--}1.59$, and 53.3% with $\text{H/M} < 1.2$). Combined SCD or aborted life-threatening arrhythmias were less common when H/M was ≥ 1.60 (10.9%) vs < 1.60 (21.1%), $P = 0.0002$. There was no difference in the incidence of SCD alone between groups (9.5% vs 13.0%, respectively, $P = 0.06$). In contrast to mortality, the authors have chosen to show only a dichotomic distribution of the H/M ratio (i.e., late H/M ratio < 1.60 vs ≥ 1.60) of the combined endpoint SCD and aborted life-threatening therapy.

In a recent multicentre prospective study the prognostic value of cardiac ^{123}I -*m*IBG, using a standardized H/M ratio, in relation to appropriate ICD therapy was evaluated in 135 patients with stable CHF referred for prophylactic ICD implantation.⁸ During a median follow-up of 30 months (6–68 months), 24 subjects (17.8%) experienced a first cardiac event (appropriate ICD therapy [$n = 12$], HF progression [$n = 6$], cardiac death [$n = 6$]). In contrast to previous reported linear relationships between late H/M and overall prognosis, the results of this study showed a “bell-shape” curve for the relation between the late H/M ratio and appropriate ICD therapy. Most arrhythmic events occurred in the group with intermediate standardized late H/M ratio and these subjects were more likely to have appropriate ICD

therapy compared to patients with low and high late H/M ratios. The late H/M ratio was not associated with ICD therapy, although post hoc analysis showed that the combination of late H/M ratio (HR 0.461 [0.281–0.757]) and LVEF (HR 1.052 [1.021–1.084]) was significantly associated with freedom of appropriate ICD therapy ($P < 0.001$).

The mentioned “bell-shape” distribution of events is in line with a previous study by Agostini et al. showing that arrhythmias occurred in CHF patients with an intermediate late H/M ratio between 1.46 and 2.17 (using a LEHR collimator).⁹ In addition, Travin et al. concluded that the presumption of a monotonic increase in the risk of an arrhythmic event with increasing ^{123}I -*m*IBG SPECT defects may not be correct. This conclusion was based on the observation that in ischemic CHF patients, those with intermediate defects on ^{123}I -*m*IBG SPECT summed score appeared to be at the highest risk for cardiac events.¹⁰ Unfortunately the study by Agostini et al. in this journal show only a dichotomous distribution of the late H/M ratio (i.e., late H/M ratio < 1.60 vs ≥ 1.60) in relation to the combined endpoint SCD and aborted life-threatening therapy. It would have been of interest if the “bell-shape” distribution of these types of events was also present in the long-term follow-up of the ADMIRE-HF study.

Although H/M ratio is highly reproducible with small inter- and intra-observer variation,^{11,12} collimator choice is one of the most important factors causing variation among institutions and studies.^{13,14} Therefore, the use of medium energy (ME) collimators is recommended for the estimation of the H/M ratios, but low energy (LE) collimators are still commonly applied for cardiac ^{123}I -*m*IBG scintigraphy because of their wide availability.¹⁵ In addition, although the nomenclature of collimators is classified into two major groups of LE and ME collimators, various types of collimators have been developed depending on the clinical purpose. The variety in the collimator types used for cardiac ^{123}I -*m*IBG scintigraphy has hampered multicenter comparison of cardiac ^{123}I -*m*IBG scintigraphy-derived parameters, and the single center results could not easily be extrapolated to other institutions.¹⁶ Recently a phantom for planar cardiac ^{123}I -*m*IBG imaging has been developed to cross-calibrate different acquisition conditions.¹⁷ This phantom has been used to calculate conversion coefficients for frequently used gamma camera-collimator combinations in Japan and Europe.^{18,19} Standardization of H/M ratios will have an impact on patient medical treatment. Most importantly standardization of H/M ratio allows the development of a universal prognostic threshold and consequently clinical acceptance of cardiac ^{123}I -*m*IBG scintigraphy in daily practice. This could be established by reanalyzing databases from a number

of previously published cardiac ^{123}I -mIBG studies. In addition, future multicenter studies should aim for the use of a standardized H/M ratio, overcoming the impact of gamma camera and collimator differences.

In conclusion cardiac ^{123}I -mIBG scintigraphy should be regarded as an almost ideal biomarker in CHF patients. Especially in those patients where a decision is eminent with regard to prophylactic ICD (re)placement, it seems that cardiac ^{123}I -mIBG scintigraphy is a cost-effective tool to help facilitate patient management. So we should appreciate the strengths of this non-invasive technique and at the same time be aware of the possible caveats of the technique. In other words, trying not to get lost while going in the right direction.

Disclosure

Hein J. Verberne and Derk O. Verschure have no conflict of interest to declare.

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