Evaluation of myocardial sympathetic innervation in the 21st century: Is there a role for planar ^{123}I -MIBG imaging?

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Many cardiologists still consider the heart as no more than a rather complex hydraulic pump, whose sole function is to furnish the correct amount of blood and nourishment to the various organs. Accordingly, the majority of the measures of cardiac function that are currently employed in daily clinical practice are intended to directly [i.e., left ventricular (LV) ejection fraction] or indirectly reflect myocardial pumping ability. Similarly, the same indices of LV contractile function are often believed as the most relevant predictors of adverse cardiac prognosis,¹ guiding clinical decision-making as well as key sanitary interventions.² For example, despite the radical evolution in cardiological knowledge that has taken place in the last two to three decades, in many cardiac pathologies the presence of a significantly altered LV ejection fraction (i.e., less than 30% to 35%) is still considered as the most powerful indication for “implanted cardioverter defibrillator” (ICD) therapy.^{2,3} In this respect, while an increasing degree of LV systolic dysfunction actually represents a predictor of adverse cardiac events, most of the episodes of sudden cardiac death take place in patients with preserved LV ejection fraction,⁴ and the majority of ICD devices that are actually implanted will never deliver a therapy.⁵ Accordingly, in order to overcome the limitations of the currently employed cardiac functional indices, novel biomarkers that can

independently predict patients’ adverse outcomes are eagerly awaited.⁶

The evaluation of cardiac sympathetic innervation has been proposed as a useful tool to derive alternative measures of cardiac function that might integrate the information obtained from currently employed biomarkers.⁷ Accordingly, measures of cardiac sympathetic innervation have been consistently shown to predict adverse patients’ prognoses in different cardiac conditions, independently from other cardiac functional parameters, and, above all, additively to LV ejection fraction.⁷⁻⁹

As a matter of fact, despite the common beliefs, it has been clearly demonstrated that the heart is far from a simple hemodynamic pump, being constantly modulated by different adaptive systems, such as the nervous and the neurohormonal systems.¹⁰ In this respect, modest alterations of cardiac adrenergic tone may significantly modify prominent cardiac functional parameters, such as the heart rate and the muscle contractility, as an adaptation to conditions of increased metabolic demands. Nevertheless, while the acute effect of an adrenergic activation on myocardial functional status may seem beneficiary, a chronic surge of cardiac sympathetic tone has been clearly shown to associate to increased cardiac risk.⁷ For example, in patients with heart failure, irrespectively of the etiology, a sustained activation of cardiac sympathetic nervous system is frequent and is associated to disease progression, malignant arrhythmic events, and overall death.⁷⁻¹¹

Interestingly, despite its obvious relevance, the evaluation of cardiac adrenergic innervation has been frequently performed through indirect measures, such as the evaluation of baroreceptor sensitivity.¹² However, nuclear cardiac imaging has classically offered the chance to perform a direct, semi-quantitative assessment of myocardial adrenergic tone that can be performed with traditional cameras and with the use of a highly specific radiotracer represented by ^{123}I -metaiodobenzylguanidine

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(^{123}I -MIBG).⁷ Accordingly, in the last two decades, ^{123}I -MIBG scintigraphy has been proposed as the most accurate non-invasive test to assess cardiac adrenergic tone, which is able to give quantitative measures that could directly reflect the integrity of the myocardial sympathetic nervous terminals.^{9,11,13} The heart-to-mediastinum (H/M) ratio of ^{123}I -MIBG counts, as easily obtained through planar scintigraphic imaging, has been convincingly shown to represent a powerful marker of adverse cardiac prognosis in different cardiac pathologies and independently from LV ejection fraction.^{7,9} Specifically, evidence derived from the ADMIRE study has demonstrated that a significantly depressed H/M ratio of ^{123}I -MIBG, as a sign of impaired cardiac adrenergic activity, is strongly associated with increased cardiac death, frequently of arrhythmic origin.⁷

However, despite the apparent robustness of ^{123}I -MIBG planar scintigraphy and the solid experimental data in its favor, sympathetic innervation imaging has never obtained a wide clinical application, being rarely performed in daily clinical practice. This may in part derive from the intrinsic rudimentariness of planar nuclear imaging that, particularly in an era of “fancy” three-dimensional cardiac imaging modalities, might seem as relatively inappropriate for the characterization of a complex functional parameter such as myocardial sympathetic innervation. In particular, simple determination of the H/M ratio of ^{123}I -MIBG is only able to give a measure of the global cardiac adrenergic tone and does not allow the evaluation of the regional distribution of adrenergic nervous terminals and of the degree of inhomogeneity of cardiac sympathetic activity.^{11,14} In fact, measures of cardiac regional adrenergic inhomogeneity, rather than global planar measures, have been shown to better characterize patients submitted to ^{123}I -MIBG imaging and to better predict future adverse cardiac events.^{13,15} This is particularly true in patients with ischemic heart disease and post-ischemic LV dysfunction who frequently show areas of viable myocardium interposed within the regions of myocardial scar, and in whom an accurate evaluation of regional cardiac sympathetic innervation, as feasible with single-photon emission computed tomography (SPECT) imaging, seems mandatory.^{11,15}

Moreover, apart from those theoretical considerations, planar ^{123}I -MIBG imaging suffers from some other relevant technical limitation that might significantly impact the validity of its results.¹⁶ Above all, consistent evidence has demonstrated that the specific collimator used during planar ^{123}I -MIBG acquisitions may profoundly alter both overall image quality and data quantitation. The photon emission spectrum of ^{123}I isotopes is not homogeneous, presenting a mixture of 159 keV primary photons and 400 keV high-energy

photons. Accordingly, the use of low-energy (LE) collimators, specifically designed for $^{99\text{m}}\text{Tc}$ emitters, should be avoided in the case of ^{123}I -MIBG imaging, since the high-energy photons may easily penetrate the relatively thin septa of the collimator, degrading image quality and count validity. The use of medium-energy (ME) collimators has been clearly shown to represent the technical gold standard for planar ^{123}I -MIBG imaging, allowing the derivation of better estimates of H/M ratios compared with LE collimators.¹⁷ However, the greatest majority of the diagnostic and prognostic data regarding ^{123}I -MIBG imaging have been obtained with LE collimators, making the validity of the data obtained so far somehow questionable.⁷

In the present issue of the *Journal of Nuclear Cardiology*, Inoue et al. aimed to quantitate conclusively the impact of different collimators on the validity of the main output of planar ^{123}I -MIBG imaging, the H/M ratio, trying to derive effective conversion equations that could effectively correct the results obtained with LE collimators.¹⁸

In order to accomplish this task, 40 patients were sequentially submitted to planar ^{123}I -MIBG acquisition with various collimators of different vendors, and the results were compared with those gained with a ME collimator. The results obtained from this rather complex, tough, effective experimental protocol allowed to confirm the presence of a significant underestimation of H/M ratios obtained with non-ME collimators, particularly evident for higher values of this measure. Specifically, in the same patient, a normal H/M ratio (>1.6) obtained with a ME collimator could easily become significantly abnormal when the acquisition was performed with a non-ME collimator.

Interestingly, despite the inhomogeneity of the results, the authors succeeded in deriving a set of collimator-specific equations, which could effectively convert the results obtained with non-ME collimators into those gained with ME ones, addressing both the problems of septal penetration of high-energy ^{123}I photons and of random errors secondary to the variability in background (i.e., liver) activity. Finally, patient-based correction equations were accurately validated using a point source of ^{123}I , suggesting that the H/M ratios of ^{123}I -MIBG obtained with any non-ME collimator can be efficiently corrected using empirically derived equations.

The authors of the manuscript should be commended for the efforts made in trying to standardize an apparently simple, yet intricate, imaging test such as planar ^{123}I -MIBG imaging. Present and previous evidence, however, further underline some relevant limitations of the results obtained so far with this particular functional investigation. In fact, despite the

intrinsic disadvantages of the use of LE collimators in ¹²³I-MIBG imaging, the great majority of the most relevant studies performed on this matter have employed H/M ratios obtained with non-ME collimators.^{7,9} This fact, in particular, shades some doubts on the general validity of the clinical cut-off of H/M ratio (i.e., 1.6) that is currently employed in everyday practice.

On the other hand, in the last decade, it has been suggested that the traditional planar ¹²³I-MIBG scans should be integrated with separate SPECT acquisitions, as the sole way to obtain an accurate evaluation of cardiac regional adrenergic tone.^{11,13,14,19} In particular, if the clinical value of the H/M ratio has been classically reported, consistent evidence has been accumulating on the additive information given by measures of cardiac regional sympathetic inhomogeneity, as an independent marker of increased cardiovascular risk, particularly arrhythmic.^{11,13,20}

Moreover, it has been recently suggested how only SPECT-derived indices of cardiac adrenergic tone might correlate with relevant cardiac functional parameters (i.e., LV mechanical dyssynchrony)¹⁴ and guide specific cardiac interventions (i.e., ablation of ventricular arrhythmias).²⁰

Finally, SPECT imaging gives the chance to perform a comprehensive assessment of LV adrenergic innervation and perfusion within the same imaging session and with a significantly contained radiation burden, allowing obtaining integrated functional measures that can better characterize different subgroups of patients.^{13,14,19}

In conclusion, innervation imaging gives the possibility to evaluate what is one of the most elegant functional aspects of cardiac pathophysiology, the interaction between the brain and the heart. While planar nuclear imaging has represented the reference standard for the depiction of myocardial adrenergic tone, novel imaging modalities, particularly if performed with dedicated cardiac cameras, have been demonstrated to give a chance to understand the intricate interaction between LV innervation, function, and perfusion as never done before.^{13–15} This comprehensive evaluation has shown promise in deriving new integrated indices that might better individuate patients at increased cardiac risk, candidate to targeted medical interventions.^{11,19,20}

Disclosure

Drs Riccardo Liga and Veronica Della Tommasina have no conflicts of interest to disclose.

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