Assessment of cardiac sympathetic innervation with $^{123}$I-mIBG SPECT comes to life: need for standardization!

Hein J. Verberne*

Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Heart failure (HF) is a life-threatening disease affecting ~26 million people worldwide. The lifetime risk for developing HF in economically developed countries can rise to 20% and is associated with increasing age. In the USA, total cost for HF was estimated to be $30.7 million in 2012. Of this total, 68% was attributable to direct medical costs. Projections show that by 2030, the total cost of HF will increase almost 127% to $69.7 billion from 2012. For Europe, these numbers are equally disturbing.

These projections give urge to the need for an optimized allocation of the available resources. Especially the high costs associated with implantable devices such as defibrillators (ICD) and resynchronization therapy (CRT) a worrisome. In general, these devices have improved the overall survival of HF patients. However, a substantial proportion of patients with these devices never has an (adequate) ICD discharge or does not improve after CRT. Therefore, a better identification of possible therapy responders from non-responders is essential.

HF is associated with high sympathetic activity manifested in part by increased release of norepinephrine. That leads to a decrease in neuronal norepinephrine reuptake due to post-transcriptional down-regulation of the cardiac norepinephrine transporter. Meta-iodobenzylguanidine (mIBG) is a structural analogue of guanethidine that shares the same uptake and storage mechanisms as norepinephrine in nerve endings. By radiolabeling mIBG with iodine-123 ($^{123}$I), the uptake and storage of mIBG can be imaged with a gamma camera. Because $^{123}$I-mIBG is not metabolized, its accumulation over several hours is a measure of neuronal integrity. The increase in adrenergic nervous system activity of the heart is exhibited as decreased $^{123}$I-mIBG uptake relative to a background standard of the upper mediastinum or the heart/mediastinum ratio (H/M). In a recent report from the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study, a decrease in the late H/M was associated with the composite end point of HF progression, ventricular tachyarrhythmias, and death. These findings were in line with a meta-analysis, and therefore, it is tempting to speculate that $^{123}$I-mIBG imaging may have a role in the management of HF patients. Indeed a prediction model for 5-year cardiac mortality in patients with HF using $^{123}$I-mIBG has been developed.

The formula for predicting 5-year mortality was created using a logistic regression model. By including the late H/M in the model, the net reclassification improvement analysis for all subjects was 13.8% ($P < 0.0001$). The inclusion of the late H/M was most effective in the down reclassification of low-risk patients.

In addition to these data, it has been shown that increased adrenergic nervous system activity as assessed with $^{123}$I-mIBG is associated with the development of permanent atrial fibrillation (AF) and HF in subjects with paroxysmal AF and no HF. Perhaps the most important contribution of this paper is the demonstration that increased cardiac sympathetic nervous system activity is related to the development of permanent AF. This implies that the impact of the assessment of the cardiac sympathetic activity extents to an even larger population than the HF patients alone.

Although convincing, it is important to realize that these $^{123}$I-mIBG imaging findings are based on planar data only (2-dimensional). As preclinical and animal studies have suggested that myocardial regions with damaged or dysfunctional neurons but preserved perfusion can be a source for arrhythmia development, volumetric data like SPECT acquisition and reconstruction (i.e. 3-dimensional data) may be of added value. However, the prognostic value of $^{123}$I-mIBG SPECT alone or in combination with myocardial perfusion has not yet been fully established. This is most likely related to the fact that these $^{123}$I-mIBG SPECT studies have been limited by visual or suboptimal automated analysis and have not identified uniform prognostic criteria based on the degree of abnormal $^{123}$I-mIBG SPECT uptake.

In this issue of Eur Heart J—Cardiovascular Imaging, there is a report by Clement et al. of a study on the use of a computer quantitation method for myocardial $^{123}$I-mIBG SPECT studies. They sought to assess the incremental prognostic significance of $^{123}$I-mIBG SPECT imaging on all-cause and cardiac mortality for subjects in the ADMIRE-HFX study by exploring the interactions...
between dysinnervation ($^{123}$I-mIBG SPECT) and abnormal perfusion ($^{99m}$Tc-tetrofosmin SPECT) with a focus on differences between patients with ischaemic (I) and non-ischaemic (NI) HF. Highest cardiac mortality risk for IHF subjects was seen with perfusion defects involving 20–40% of the myocardium. By comparison, NIHF subjects with smaller perfusion abnormalities (<20% of myocardium), but with a large discrepancy between $^{123}$I-mIBG and $^{99m}$Tc-tetrofosmin defect sizes, were at highest risk of cardiac death. They concluded that $^{123}$I-mIBG SPECT in combination with $^{99m}$Tc-tetrofosmin SPECT can be effectively analysed quantitatively for use in prognostic assessments of HF patients.

The most important contribution of this paper is not the demonstration that increased cardiac sympathetic nervous activity as assessed with $^{123}$I-mIBG SPECT is related to the prognosis in HF patients. The merit of this paper lies in the fact that the majority of the limitations of previous studies have been overcome (i.e. suboptimal automated analysis and not uniform prognostic criteria). However, the authors rightfully state that future studies are necessary to define the role of innervation SPECT imaging in clinical assessment and management of HF patients.

This further proves that standardization of the technique to assess the outcome parameters of $^{123}$I-mIBG myocardial scintigraphy is essential. The technique is highly reproducible and has a small inter- and intra-observer variation. However, the lack of standardization between different institutions is one of the factors that have hampered the wide scale clinical implementation of $^{123}$I-mIBG myocardial scintigraphy. Some initial efforts have been made to harmonize and standardize myocardial $^{123}$I-mIBG scintigraphy. These recommendations include proposals for patient preparation, administered amounts of $^{123}$I-mIBG activity, scanning parameters (e.g. choice of collimators), and analysis of the acquired data to obtain the most used semi-quantitative parameters (i.e. early and late heart-to-mediastinum ratio and myocardial washout). To further the role of $^{123}$I-mIBG scintigraphy, a strict use of these recommendations is essential.

In conclusion, it appears that imaging of the cardiac autonomic innervation offers unique benefits over other options. However, it is essential to standardize the $^{123}$I-mIBG scintigraphy. Especially as our ageing population is increasing, the prevalence of AF and HF will increase, and therefore, the use of $^{123}$I-mIBG scintigraphy may be on the threshold of a more wide utilization.

**Conflict of interest:** none declared.

**References**


**CORRIGENDUM**

doi:10.1093/ehjci/jeu002


In the above article the name of author Bas M van Dalen was incorrectly given as “Bas van Dalen”. This has now been corrected online.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2016. For permissions please email: journals.permissions@oup.com.