Eur J Nucl Med Mol Imaging (2009) 36:555–559
DOI 10.1007/s00259-008-0976-x

EDITORIAL COMMENTARY

How to use myocardial ^{123}I-MIBG scintigraphy in chronic heart failure

Denis Agostini · Ignasi Carrio · Hein J. Verberne

Published online: 7 November 2008

Introduction

Cardiac sympathetic neuronal function and activity can be assessed noninvasively by the use of ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), an analogue of norepinephrine [1]. In the past two decades, a large number of investigators have demonstrated decreased myocardial ^{123}I-MIBG uptake in patients with chronic heart failure (CHF) and have shown that those with the lowest uptake tend to have the poorest prognosis [2–12]. There have also been findings suggesting that abnormalities of myocardial ^{123}I-MIBG uptake may be predictive of increased risk of ventricular arrhythmia and sudden cardiac death [13, 14]. One factor that has constrained acceptance of cardiac ^{123}I-MIBG imaging as a clinical management tool in heart failure has been the variability of the technical aspects of the procedure. Although most reports include the heart-to-mediastinum (H/M) ratio as the measure of myocardial uptake, the methods used to obtain this parameter have shown considerable variation. However, the influence of procedural and acquisition parameters on the reproducibility of this measurement technique have only occasionally been considered.

This Editorial commentary refers to the article doi:10.1007/s00259-008-0971-2.

D. Agostini (✉)
Department of Nuclear Medicine, CHU Côte de Nacre,
14000 Caen, France
e-mail: agostini-de@chu-caen.fr

I. Carrio
Department of Nuclear Medicine, Hospital of San Pau,
Barcelona, Spain

H. J. Verberne
Department of Nuclear Medicine, Academic Medical Center,
Amsterdam, The Netherlands

How to use myocardial ^{123}I-MIBG scintigraphy in clinical routine

Planar ^{123}I-MIBG imaging

In order to block thyroid uptake of free radioactive iodide either 500 mg potassium perchlorate or 200 mg potassium iodide (10% solution) is orally administered. After 30 min approximately 185 or 370 MBq of ^{123}I-MIBG is administered intravenously for planar and/or SPECT imaging, respectively. ^{123}I-MIBG is internalized by presynaptic nerve endings of postganglionic neuronal cells through the energy-dependent uptake-1 system. A 15% energy window is usually used, centred on the 159-keV ^{123}I photopeak. Anterior planar scintigraphic images are obtained 10 min (early) and 4 h (late) after injection and stored in a 128×128 matrix. Two SPECT images can be acquired (20 min each) just after early and late planar imaging.

Semiquantitative parameters

The commonly used myocardial ^{123}I-MIBG indices are the H/M ratio and myocardial washout. On anterior planar images regions of interest (ROIs) are drawn over the heart and the mediastinum. The mean count density in each ROI is obtained and the H/M ratio (specific activity/nonspecific activity) is calculated. Myocardial ^{123}I-MIBG washout is calculated as follows:

$$\left\{\frac{(\text{early H/M} - \text{late H/M})}{\text{early H/M}}\right\} \times 100\%$$

The early H/M ratio probably reflects the integrity of presynaptic nerve terminals and uptake-1 function. The late H/M ratio combines information on neuronal function from uptake to release through the storage vesicle at the nerve terminals. Myocardial ^{123}I-MIBG washout is an index of the degree of sympathetic drive. This implies that increased sympathetic activity is associated with high myocardial ^{123}I-MIBG washout and low myocardial ^{123}I-MIBG delayed uptake.

Impact of ROI definition

For ^{123}I-MIBG there are several ways to define the mediastinal (size and placement) and myocardial ROIs (i.e. myocardium including the left ventricular cavity vs. myocardium excluding the left ventricular cavity). However, there are limited data on the impact of ROI definition on H/M ratios and myocardial washout. Somsen et al. demonstrated in 25 healthy volunteers that ^{123}I-MIBG semiquantitative parameters using a ROI of the myocardium including the left ventricle showed the lowest interindividual and within-subject variability [15]. In a large retrospective study a uniform analysis with clear definition of the myocardial ROI (variable in size, including the left ventricular cavity) and the mediastinal ROI (fixed size) showed remarkable consistency in interpretation between three blinded image evaluators (Fig. 1) [16]. These findings suggest that rigorous and uniform analysis of cardiac ^{123}I-MIBG semiquantitative parameters minimizes inter- and intra-individual variation.

Influence of collimation

The most well-validated influence on the measured late H/M ratio is the collimator type. In addition to the prime emission of 159-keV photons, ^{123}I emits high-energy photons of more than 400 keV (approximately 2.87%, main contributor 529 keV, 1.28%). These high-energy photons lead to penetration of the collimator septa and cause scatter detected in the 159-keV energy window. Septal penetration affects estimation of the H/M ratio in ^{123}I-MIBG imaging with a low-energy (LE) collimator [17]. Nevertheless, LE collimators are frequently used for imaging ^{123}I-MIBG [12, 18]. Medium-energy (ME) collimators have been shown to provide better quantitative accuracy in ^{123}I studies [17–19]. Therefore, in order to minimize the effects of septal penetration the ME collimator is preferred. However, the use of ME collimation provides relatively low spatial resolution which may hamper accurate estimation of activity in small regions through a partial volume effect. In brain SPECT imaging with ^{123}I-labelled agents, collimation with LE high resolution is preferred. High spatial resolution leads to a more or less homogeneous scatter in head and brain tissue imaging, and the regions are mostly equidistant from the gamma camera. In cardiac scintigraphy with ^{123}I-labelled agents, however, H/M ratios are assessed from counts in relatively large regions, the thorax and abdomen produce inhomogeneous scatter, and the myocardium is not equidistant from the gamma-camera, especially in SPECT imaging. In cardiac scintigraphy with ^{123}I-labelled agents the trade-off between spatial resolution and septal penetration is therefore in favour of low septal penetration. Moreover, as shown by Inoue et al. in a checker phantom, the use of ME collimation in cardiac scintigraphy with ^{123}I showed a contrast accuracy similar to that with ^{99m}Tc [19].

While these results would suggest that semiquantitative cardiac ^{123}I-MIBG imaging might be best performed using ME collimators, there are practical limitations to such a recommendation. Almost all nuclear medicine procedures are now performed on a multihead gamma camera, and many dedicated dual head cardiac cameras are not supplied with ME collimators.

Triple energy window scatter correction

Various methods of scatter correction have been described to improve image quality and quantitative accuracy [20]. The triple energy window (TEW) scatter correction method estimates the scatter component in the prime photopeak from counts in a window just below and above the prime photopeak window [21]. Data on the effect of this TEW scatter correction method in ^{123}I studies on semiquantitative cardiac analysis are limited [17, 19]. Although TEW scatter correction increases all planar ME collimated H/M ratios, TEW scatter correction does not improve the contrast between the ME collimated H/M ratios.

In a clinical setting of heart failure, myocardial count densities are generally low. TEW scatter correction, however, reduces the already low count density which increases the uncertainty in ratio determination. Moreover, the reduction in count density induced by TEW scatter correction hampers the identification of endo- and epicardium and will therefore influence the definition of the myocardial ROIs. This decreases the reproducibility of the ratios. In addition, TEW scatter correction introduces noise, again increasing the uncertainty of the generated ratios.

In addition to theoretical limitations, the TEW method has a limited availability in various gamma camera systems because TEW requires special hardware and software. Rather than try to filter unwanted counts by a post-acquisition scatter correction method, it is preferable to acquire data directly with less scatter. ME collimation without scatter correction is straightforward to implement and is therefore preferred in cardiac ^{123}I scintigraphy.

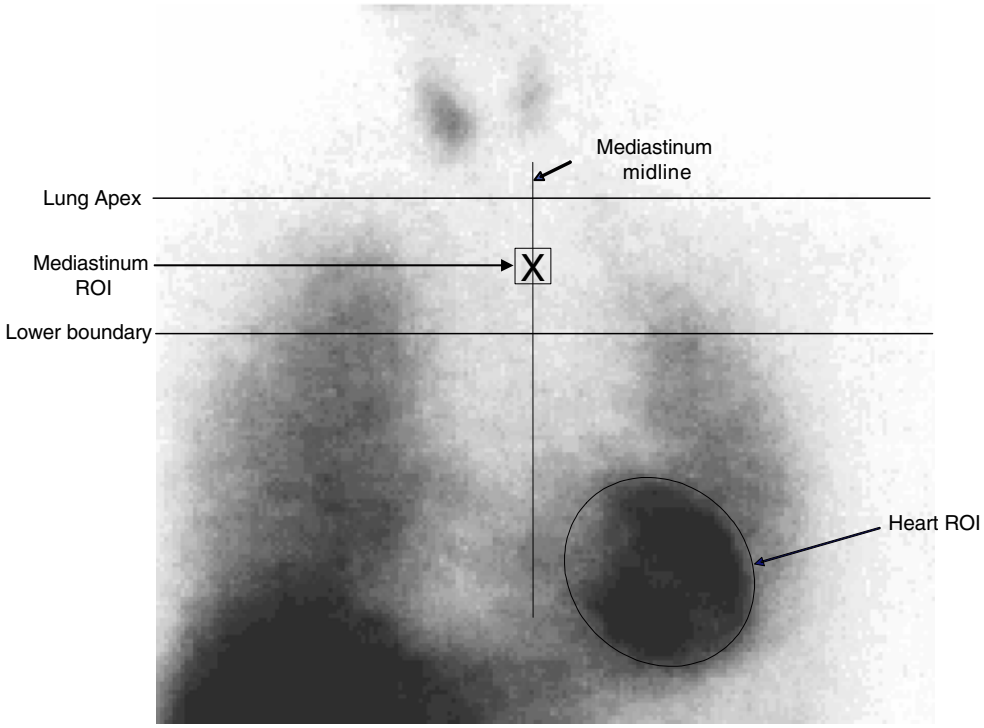

Fig. 1 Example of processing procedure for late planar ^{123}I-MIBG images. The positioning of the mediastinal ROI was standardized in relation to the lung apex, the lower boundary of the upper mediastinum, and the midline between the lungs

Acquisition parameters

In a heterogeneous population of patients with heart failure, the most important determinant of cardiac uptake of ^{123}I-MIBG is the degree of impairment of the norepinephrine transporter function in presynaptic adrenergic neurons [2–10]. As such, considerable variation in late H/M ratio would be expected between patients with otherwise similar clinical presentations (NYHA class, LVEF, etc). Nevertheless, a relative small proportion of the variation in the late H/M ^{123}I-MIBG can also be explained by differences in acquisition duration. Of particular interest, factors contributing to this variation differ for different ranges of late H/M ratio [22].

^{123}I-MIBG SPECT

Planar imaging is most commonly used in myocardial ^{123}I-MIBG scintigraphy. Nevertheless, there are known limitations to this technique: superposition of noncardiac structures, and lack of segmental analysis. Although SPECT may overcome these limitations, it must be taken into account that in patients with severe CHF myocardial ^{123}I-MIBG uptake may be severely reduced. This reduced myocardial uptake may hamper adequate image reconstruction (i.e. short-axis, horizontal long-axis and vertical long-axis slices). However, it seems of paramount importance to couple ^{123}I-MIBG SPECT to perfusion imaging in order to understand the real regional myocardial uptake of MIBG in both ischaemic and nonischaemic cardiomyopathy, and therefore the possible pathophysiological mechanism of ventricular tachyarrhythmias.

^{123}I-MIBG and perfusion SPECT imaging

Recently the inducibility of ventricular arrhythmias during electrophysiology (EP) testing in patients with previous myocardial infarction has been explored using both ^{123}I-MIBG and myocardial perfusion scintigraphy [23].

In a multivariable analysis the 4-hour ^{123}I-MIBG SPECT defect score was the only independent predictor of EP results. A 4-hour ^{123}I-MIBG SPECT defect score of ≥37 yielded a sensitivity of 77% and specificity of 75% for predicting the EP results.

The results of this pilot study suggest that the extent of denervated myocardium, as assessed by ^{123}I-MIBG SPECT, is correlated with the inducibility of ventricular tachyarrhythmias during EP testing. Data from two ongoing major prospective trials in the US and Europe may support the additional value of the combined use of ^{123}I-MIBG and myocardial perfusion scintigraphy in patients with heart failure for the prediction of ventricular tachyarrhythmias. The results of these trials are expected in 2009. Furthermore, it is tempting to speculate whether patients with mismatches between perfusion and innervation are more prone to the development of ventricular tachyarrhythmias (Fig. 2). This may imply that those patients with mismatches are especially eligible for implantation of an implantable cardioverter defibrillator.

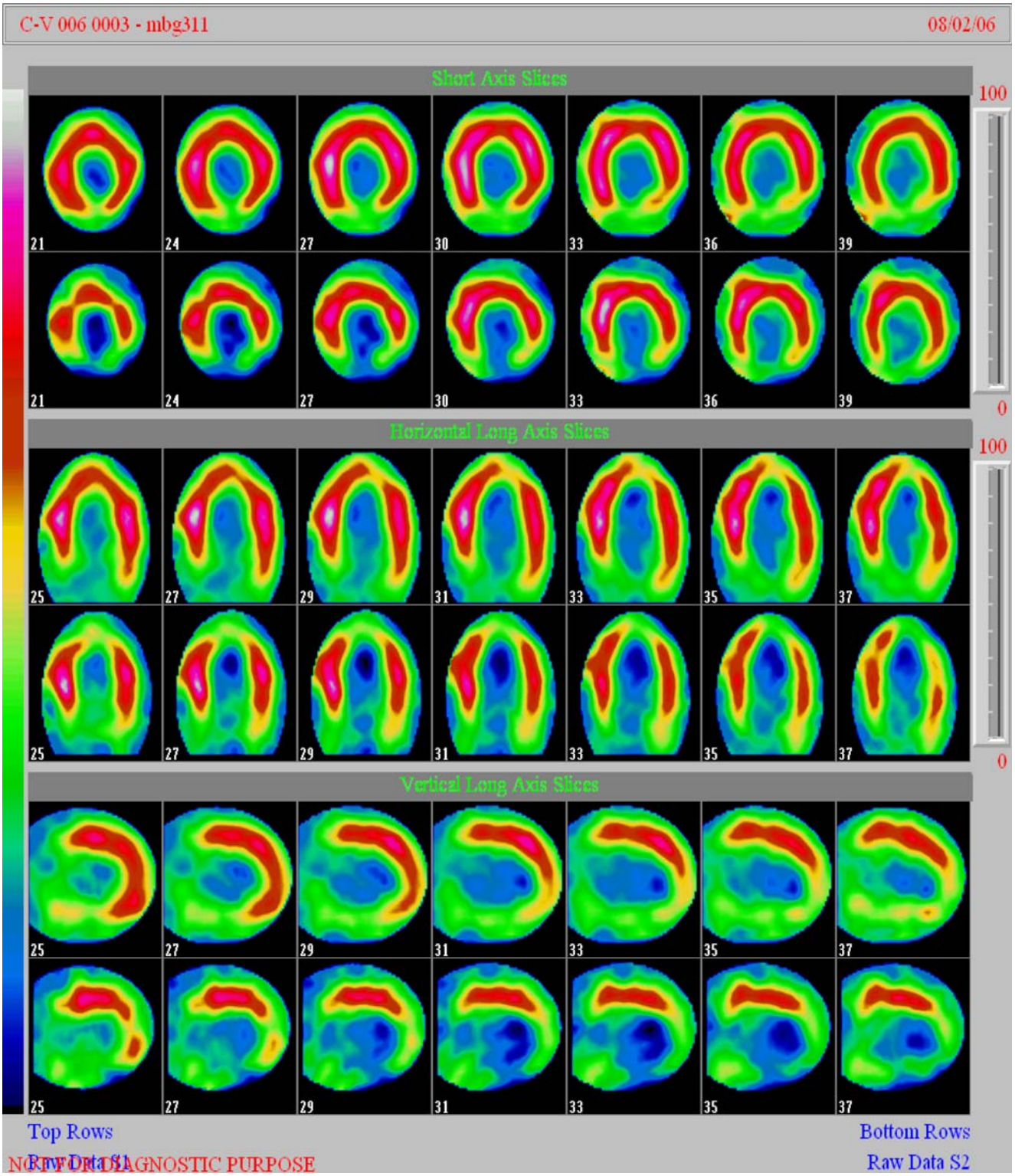

Fig. 2 MIBG and tetrofosmin SPECT studies in a patient with ischaemic cardiomyopathy (inferior myocardial infarction, LVEF 33%) show a mismatch between perfusion (tetrofosmin *top panel*) and innervation (MIBG *bottom panel*) in inferior, lateral and apical walls. There is a larger defect in innervation than in perfusion imaging

Conclusion

The absence of published guidelines for cardiac ^{123}I-MIBG imaging, makes standardization of procedures among individual users of this radiopharmaceutical even more important. Given the current data, myocardial ^{123}I-MIBG scintigraphy is preferred with adapted collimation without scatter correction, adequate acquisition duration and simple but robust analysis of the semiquantitative parameters and innervation score on 17 LV segments. The use of both myocardial perfusion and myocardial innervation SPECT seems to be promising in identifying those patients with heart failure at risk of developing ventricular tachyarrhythmia.

References

1. Patel AD, Iskandrian AE. MIBG imaging. J Nucl Cardiol 2002;9:75–94.
2. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992;33:471–77.
3. Merlet P, Benvenuti C, Moyse D, Pouillart F, Dubois-Rande JL, Duval AM, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. J Nucl Med 1999;40:917–23.
4. Momose M, Kobayashi H, Iguchi N, Matsuda N, Sakomura Y, Kasanuki H, et al. Comparison of parameters of 123I-MIBG scintigraphy for predicting prognosis in patients with dilated cardiomyopathy. Nucl Med Commun 1999;20:529–35.
5. Cohen-Solal A, Esanu Y, Logeart D, Pessione F, Dubois C, Dreyfus G, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. J Am Coll Cardiol 1999;33:759–66.
6. Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. J Nucl Med 2001;42:1757–67.
7. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, et al. Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. J Nucl Med 2002;43:1279–85.
8. Yamada T, Shimonagata T, Fukunami M, Kumagai K, Ogita H, Hirata A, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. J Am Coll Cardiol 2003;41:231–8.
9. Kyuma M, Nakata T, Hashimoto A, Nagao K, Sasao H, Takahashi T, et al. Incremental prognostic implications of brain natriuretic peptide, cardiac sympathetic nerve innervation, and noncardiac disorders in patients with heart failure. J Nucl Med 2004;45:155–63.
10. Nakata T, Wakabayashi T, Kyuma M, Takahashi T, Tsuchihashi K, Shimamoto K. Cardiac metaiodobenzylguanidine activity can predict the long-term efficacy of angiotensin-converting enzyme inhibitors and/or beta-adrenoceptor blockers in patients with heart failure. Eur J Nucl Med Mol Imaging 2005;32:186–94.
11. Manrique A, Bernard M, Hitzel A, Bauer F, Ménard JF, Sabatier R, et al. Prognostic value of sympathetic innervation and cardiac asynchrony in dilated cardiomyopathy. Eur J Nucl Med Mol Imaging 2008;35:2074–81
12. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BLF. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J 2008;9:1147–59.
13. Arora R, Ferrick KJ, Nakata T, Kaplan RC, Rozengarten M, Latif F, et al. I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator. J Nucl Cardiol 2003;10:121–31.
14. Paul M, Schafers M, Kies P, Acil T, Schafers K, Breithardt G, et al. Impact of sympathetic innervation on recurrent life-threatening arrhythmias in the follow-up of patients with idiopathic ventricular fibrillation. Eur J Nucl Med Mol Imaging 2006;33:866–70.
15. Somsen GA, Borm JJ, Dubois EA, Schook MB, van der Wall EE, van Royen EA. Cardiac 123I-MIBG uptake is affected by variable uptake in reference regions: implications for interpretation in clinical studies. Nucl Med Commun 1996;17:872–6.
16. Agostini D, Verberne HJ, Burchert W, Knuuti J, Povinec P, Sambuceti G, et al. I-123-mIBG myocardial imaging for assessment of risk for a major cardiac event in heart failure patients: insights from a retrospective European multicenter study. Eur J Nucl Med Mol Imaging 2008;35:535–6.
17. Verberne HJ, Feenstra C, de Jong WM, Somsen GA, VAN Eck-Smit BL, Busemann Sokole E. Influence of collimator choice and simulated clinical conditions on 123I-MIBG heart/mediastinum ratios: a phantom study. Eur J Nucl Med Mol Imaging 2005;32:1100–7.
18. Dobbeleir AA, Hambye AS, Franken PR. Influence of high-energy photons on the spectrum of iodine-123 with low- and medium-energy collimators: consequences for imaging with 123I-labelled compounds in clinical practice. Eur J Nucl Med 1999;26:655–8.
19. Inoue Y, Suzuki A, Shirouzu I, Machida T, Yoshizawa Y, Akita F, et al. Effect of collimator choice on quantitative assessment of cardiac iodine 123 MIBG uptake. J Nucl Cardiol 2003;10:623–32.
20. Buvat I, Benali H, Todd-Pokropek A, Di Paola R. Scatter correction in scintigraphy: the state of the art. Eur J Nucl Med 1994;21:675–94.
21. Ichihara T, Ogawa K, Motomura N, Kubo A, Hashimoto S. Compton scatter compensation using the triple-energy window method for single- and dual-isotope SPECT. J Nucl Med 1993;34:2216–21.
22. Verberne HJ, Habraken JB, van Eck-Smit BLF, Agostini D, Jacobson AF. Variations in 123I-metaiodobenzylguanidine (MIBG) late heart mediastinal ratios in chronic heart failure: a need for standardisation and validation. Eur J Nucl Med Mol Imaging 2008;35:547–53.
23. Bax JJ, Kraft O, Buxton AE, Fjeld JG, Parizek P, Agostini D, et al. 123I-mIBG scintigraphy to predict inducibility of ventricular arrhythmias on cardiac electrophysiology testing. A prospective multicenter pilot study. Circulation Cardiovasc Imaging 2008; 1:131–40