123I-mIBG assessed cardiac sympathetic activity: standardizing towards clinical implementation

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$^{123}$I-$m$IBG heart-to-mediastinum ratio is influenced by high-energy photon penetration of collimator septa from liver and lung activity

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**ABSTRACT**

**Aim**
The $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG)-derived late heart-to-mediastinum (H/M) ratio is a well-established prognostic parameter in patients with chronic heart failure (CHF). However, $^{123}$I presents imaging problems owing to high-energy photon emission leading to penetration of collimator septa and subsequent reduction in image quality. Most likely this affects the H/M ratio and may subsequently lead to incorrect patient risk classification. In this prospective study we assessed the intrapatient variation in late H/M ratio between low-energy high-resolution (LEHR) and medium-energy (ME) collimators in patients with CHF.

**Materials and methods**
Fifty-three patients with CHF (87% male, age 63 ± 8.3 years, LVEF 29 ± 7.8) referred for cardiac $^{123}$I-mIBG scintigraphy were enrolled in the study. In each patient, after the administration of 185 MBq $^{123}$I-mIBG, early (15 min after injection) and late (4 h after injection) planar anterior thoracic images were acquired with both LEHR and ME collimators. Early and late H/M ratios were calculated on the basis of the mean count densities from the manually drawn regions of interest (ROIs) over the left ventricle and a predefined fixed ROI placed in the upper mediastinum. Additional ROIs were drawn over the liver and lungs. Liver/lung to myocardium and liver/lung to mediastinal ratios were calculated to estimate the effect of collimator septa penetration from liver and lung activity on the myocardial and mediastinal ROIs.

**Results**
The mean LEHR collimator-derived parameters were lower compared with those from the ME collimator (late H/M ratio $1.41 \pm 0.18$ vs. $1.80 \pm 0.41$, $p < 0.001$). Moreover, Bland–Altman analysis showed that with increasing late H/M ratios the difference between the ratios from the two collimator types increased ($R^2 = 0.73$, $p = 0.001$). Multivariate regression analysis showed that almost 90% of the variation in the difference between ME and LEHR late H/M ratios could be explained by scatter from the liver in both the mediastinal and myocardial ROIs ($R^2 = 0.90$, $p = 0.001$). Independent predictors for the difference in the late H/M ratio between ME and LEHR collimator were the liver-to-heart ratio and the liver-to-mediastinum ratio assessed by ME collimator (standardized coefficient of $-1.69$ and $1.16$, respectively) and LEHR collimator (standardized coefficient of $1.24$ and $-0.90$, respectively) ($p < 0.001$ for all).

**Conclusion**
Intra-patient comparison in H/M ratio between the ME and LEHR collimators in patients with CHF showed that with increasing H/M ratio the difference between the ratios increased in favour of the ME collimator. These differences could be explained by septal penetration of high-energy photons from both the liver and the lung in the mediastinum and myocardium, being lowest when using the ME collimator. These results strengthen the importance of the recommendation to use ME collimators in semiquantitative $^{123}$I-mIBG studies.
INTRODUCTION

Myocardial $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG) scintigraphy has been used extensively to assess cardiac sympathetic activity in patients with chronic heart failure (CHF). Numerous single-centre studies have demonstrated that a low late heart-to-mediastinum (H/M) ratio in CHF patients is an independent predictor for ventricular arrhythmia\(^1\), appropriately ICD therapy\(^2\), sudden cardiac death\(^3\) and mortality\(^4\). The prognostic value of the late H/M ratio has been confirmed in the large prospective multicentre ADMIRE-HF study\(^5\). Although reproducibility and inter- and intraobserver variability have been proven to be adequate\(^6-8\), the methods used to obtain the H/M ratio show substantial variation in both acquisition and image analysis\(^9\). These interinstitutional differences have hampered multicentre comparison of H/M ratio and have made the extrapolation of single-centre results difficult\(^9\). The relatively recent proposal by Flotats et al. to standardize cardiac sympathetic imaging with $^{123}$I-mIBG scintigraphy will most likely reduce the interinstitutional variation\(^11\).

Of special concern with $^{123}$I scintigraphy is the fact that, in addition to the main photopeak of 159 keV (83%), $^{123}$I emits high-energy photons of 529 keV (1.4%). These high-energy photons may lead to septal penetration of the collimator and cause scatter that is detected in the 159 keV energy window. In patients with CHF the myocardial uptake of $^{123}$I-mIBG can be low. This means that, especially when there is relatively high $^{123}$I-mIBG uptake in other organs in the direct vicinity of the myocardium (i.e. liver and lungs), septal penetration will degrade image quality and the quantitative accuracy of the H/M ratio (Figure 1)\(^12,13\).

Medium-energy (ME) collimators have thicker septa compared with low-energy (LE) collimators; ME collimators are therefore better equipped to stop high-energy photons. The effect of collimator selection has been evaluated in a number of phantom studies, and significantly higher H/M ratios have been demonstrated when using the ME collimator compared with the LE collimator\(^11,13-15\). Recently, Inoue et al. demonstrated the same difference in H/M ratio between low-energy high-resolution (LEHR) and low-to-medium-energy collimators in 40 patients with neurodegenerative disorders\(^11\). However, data on the impact of collimator type on H/M ratio in patients with CHF are limited. Fletcher et al. demonstrated the difference between ME and low-energy high-sensitivity collimator types in 100 CHF patients\(^17\). However, the planar $^{123}$I-mIBG images were not assessed as proposed by Flotats et al.\(^11\) Therefore, data on direct intra-individual comparison between collimators in CHF patients assessed on planar $^{123}$I-mIBG imaging 15 min and 4 h after injection of $^{123}$I-mIBG are still lacking.

The primary objective of this prospective study was to assess the intra-individual variation of collimator choice on planar $^{123}$I-mIBG early and late H/M ratios in CHF patients. As a secondary objective, an estimation of septal penetration by high-energy photons emerging from other organs than the myocardium (i.e. liver and lungs) was tested as a possible explanation for the inter-individual differences.


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MATERIALS AND METHODS

Study population
The study population consisted of CHF patients with New York Heart Association functional class II–III/IV and an impaired left ventricle ejection fraction (LVEF) of less than or equal to 35% who were referred for $^{123}$I-mIBG myocardial scintigraphy to the department of Nuclear Medicine at the Diakonessenhuis, Utrecht, the Netherlands, and the Wilhelminenspital, Vienna, Austria. Both centres are larger teaching hospitals with a large regional adherence area. All patients were optimally treated according to the European guidelines for heart failure.\textsuperscript{18}

Data acquisition
All patients were pretreated with 250 mg of oral sodium perchlorate 30 min before intravenous injection of 185 MBq $^{123}$I-mIBG (AdreView\textsuperscript{TM}, GE Healthcare, Eindhoven,
**I-123-mIBG scintigraphy and influence of collimators**

The Netherlands) to block uptake of free $^{123}$I by the thyroid gland. $^{123}$I-mIBG planar images were acquired with the patient in the supine position. A duration of 15 min (early images) and 4 h (late images) after intravenous injection of $^{123}$I-mIBG, 10-min planar images were acquired from an anterior thoracic view using a zoom factor of 1 and a matrix of $256 \times 256$. All images were acquired with a 15% energy window centred at the 159 keV photopeak of $^{123}$I. Images were acquired using a dual-headed gamma camera (Philips Skylight; Philips, Milpitas, California, USA and Siemens Symbia T6; Siemens, Erlangen, Germany). Per-time-point images were acquired using an LEHR collimator, directly followed by image acquisition using an ME collimator. In one centre (Diakonessenhuis, Utrecht) a dual-headed gamma camera was used. By mounting an LEHR collimator on one head of the gamma camera and the ME collimator on the second gamma camera head it was possible to quickly switch between two different acquisitions. After the LEHR acquisition the heads of the gamma camera rotated so that the ME collimator was in the same anterior position as the earlier LEHR acquisition. In the second centre (Wilhelminenspital, Vienna) the dual-headed gamma camera could only be mounted by one type of collimator. Therefore, the collimators had to be changed before the next acquisition could be made. In both situations, care was taken that the positioning of the patient was left unchanged between the LEHR and ME collimated acquisitions.

**Planar $^{123}$I-mIBG images analysis**

All planar $^{123}$I-mIBG images were analyzed by one experienced observer from the Academic Medical Center in Amsterdam using post-processing software (Hermes Hybrid Viewer v1.4; Hermes Medical solutions, Stockholm, Sweden). The observer was blinded to patient data. All regions of interest (ROIs) except the cardiac ROI were predefined. The cardiac ROI was manually drawn over the myocardium including the left ventricular cavity. The mediastinal ROI with a rectangular shape ($10 \times 5$ pixels) was placed on the upper part of the mediastinum. The location of the mediastinal ROI was determined in relation to the lung apex, the lower boundary of the upper mediastinum and the midline between the lungs.$^{10}$ H/M ratio was calculated by dividing the mean count density in the cardiac ROI by the mean count density in the mediastinal ROI.$^{11}$ The $^{123}$I-mIBG washout (WO) was calculated using the early and late H/M ratio with the following formula:

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

Additional ROIs were placed over the liver and both lungs (Figure 2). The liver ROI with a rectangular shape ($13 \times 8$ pixels) was placed on the right liver lobe. Left and right lung ROIs with a rectangular shape ($12 \times 8$ pixels) were placed on the mid part of each lung. The mean count density in the liver and in both lung ROIs was used to calculate the liver/heart (Li/H) ratio, the liver/mediastinum (Li/M) ratio, the lung/heart (Lu/H) ratio and the lung/mediastinum (Lu/M) ratio.
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Statistical analysis
All continuous variables are expressed as average ± SD. The difference in ratio of each collimator type was evaluated with a paired t-test. Bland–Altman analysis was used to compare the differences between the LEHR and ME collimators for both mean early and mean late H/M ratios. Multivariate logistic forward regression analysis was performed to investigate several early and late parameters (i.e. Li/H, Li/M, Lu/H and Lu/M derived from both collimator types) as possible independent predictors for the difference between LEHR and ME collimators for the early and late H/M ratios. All statistical analyses were performed using the software package SPSS, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Figure 2. Example of post-processing planar $^{123}$I-mIBG images. The positioning of the predefined mediastinum ROI (M) is determined in relation to the lung apex, the lower boundary of the upper mediastinum and the midline between the lungs. The manually drawn cardiac ROI (H) is placed over the myocardium, including the left ventricular cavity. The predefined liver ROI (Li) is placed over the right liver lobe. The predefined left and right lung ROIs (L) are placed over the mid part of both lungs. ROI, region of interest.
RESULTS

Study population
A total of 53 patients with CHF were included in the study and they underwent early and late $^{123}\text{I-mIBG}$ scintigraphy (35 patients in Utrecht and 18 patients in Vienna). The majority of patients were male (87%) with a mean age of 63 ± 8.3 years (Table 1). The mean New York Heart Association functional class was 2.3 ± 0.4 and the mean LVEF was 29 ± 8.0%. The majority of patients had an ischaemic origin of CHF ($n$ = 38, 72%). Medication use consisted of β-blockers (89%), angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blocker (ARB) (98%), diuretics (76%) and lipid-lowering agents (72%). Planar $^{123}\text{I-mIBG}$ images analysis Figure 1 illustrates increase septal penetration of high-energy photons when using an LEHR collimator with increased background noise and consequently decreased image quality compared with the ME collimator. The LEHR collimator-derived early and late H/M ratios were significantly lower compared with the ME collimator derived ratios (early H/M ratio 1.51 ± 0.23 vs. 2.08 ± 0.42, $p < 0.001$, and late H/M ratio 1.41 ± 0.18 vs. 1.80 ± 0.41, $p < 0.001$, for LEHR and ME, respectively). Interestingly, Bland–Altman analysis showed a linear increase in the difference between LEHR and ME collimators with increasing mean early H/M ratio ($R^2$ = 0.391, $p < 0.001$). For the late H/M ratio a similar pattern between LEHR and ME collimators was seen ($R^2$ = 0.733, $p < 0.001$) (Figure 3).

The additionally calculated ratios using ROIs of the liver and lung compared with those of the mediastinum and the heart are shown in Table 2. In line with the H/M ratio, the additional ratios derived from the late planar images using the ME collimator are significantly higher than those obtained with the LEHR collimator. However, the early Lu/H and Lu/M ratios showed no significant difference between the ME and LEHR collimators. In addition to the early and late H/M ratios, the $^{123}\text{I-mIBG WO}$ derived with the ME collimator was significantly higher compared with that obtained with the LEHR collimator (13.5 ± 10.6 vs. 5.4 ± 17.2, $p = 0.001$, respectively, for ME and LEHR).

Multivariate regression analysis
Multivariate regression analyses showed that Li/H and Li/M ratios from both collimator types and the Lu/H and Lu/M ratios from the ME collimator were independent predictors of the difference in early H/M ratio between the LEHR and ME collimators. The combined model containing variables of early Li/H, early Li/M from both LEHR and ME collimators and early Lu/M from the ME collimator explained ~90% of the variation in the early H/M ratio difference between the two collimator types (adjusted $R^2$ = 0.888, $p = 0.001$). The difference in late H/M ratio between the two collimator types could be independently explained by Li/H and Li/M from both collimators. As for the difference in early H/M ratio, the combined model explained ~ 90% of the variation in the late H/M ratio difference between the two collimator types (adjusted $R^2$ = 0.897, $p < 0.001$). As the $^{123}\text{I-mIBG WO}$ is
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Table 1. Patient characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>((n = 53))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), ([n (%)])</td>
<td>46 (87)</td>
</tr>
<tr>
<td>Age mean ± SD (years)</td>
<td>63 ± 8.3</td>
</tr>
<tr>
<td><strong>Heart failure characteristics ([n (%)])</strong></td>
<td></td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>38 (72)</td>
</tr>
<tr>
<td>Non-ischaemic cardiomyopathy</td>
<td>15 (28)</td>
</tr>
<tr>
<td>NYHA functional class (mean ± SD)</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>LVEF (mean ± SD)(%)</td>
<td>29 ± 8.0</td>
</tr>
<tr>
<td><strong>Clinical cardiovascular risk factors ([n (%)])</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>34 (64)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (64)</td>
</tr>
<tr>
<td><strong>Medication ([n (%)])</strong></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>47 (89)</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>52 (98)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>40 (76)</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>38 (72)</td>
</tr>
</tbody>
</table>

ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Table 2. Mean ratios derived from early (15 min after injection) and late (4 h after injection) planar \(^{123}\)I-\textit{mIBG} acquisition using LEHR and ME collimator.

<table>
<thead>
<tr>
<th></th>
<th>LEHR</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early acquisition (mean ± SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver/Heart</td>
<td>1.97 ± 0.51</td>
<td>2.74 ± 1.01</td>
</tr>
<tr>
<td>Liver/Mediastinum</td>
<td>2.95 ± 0.71</td>
<td>5.43 ± 1.46</td>
</tr>
<tr>
<td>Lung/Heart</td>
<td>1.34 ± 0.82</td>
<td>1.51 ± 0.53</td>
</tr>
<tr>
<td>Lung/Mediastinum</td>
<td>1.99 ± 1.27</td>
<td>3.02 ± 0.87</td>
</tr>
<tr>
<td><strong>Late acquisition (mean ± SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver/Heart</td>
<td>2.42 ± 0.75</td>
<td>3.52 ± 1.11</td>
</tr>
<tr>
<td>Liver/Mediastinum</td>
<td>3.35 ± 0.73</td>
<td>6.05 ± 1.53</td>
</tr>
<tr>
<td>Lung/Heart</td>
<td>1.19 ± 0.32</td>
<td>1.53 ± 0.65</td>
</tr>
<tr>
<td>Lung/Mediastinum</td>
<td>1.64 ± 0.30</td>
<td>2.58 ± 0.74</td>
</tr>
</tbody>
</table>

LEHR: low-energy high-resolution; ME: medium-energy.
determined by the early and late H/M ratios, the difference in $^{123}$I-mIBG WO between the two collimator types depends on the combination of all variables explaining the difference in both early and late H/M ratios between the ME and LEHR collimators. The large numbers of variables make the multivariate regression analyses for the difference between the two collimator types for $^{123}$I-mIBG WO less reliable and were therefore not assessed.
DISCUSSION

Cardiac sympathetic activity can be adequately assessed with $^{123}$I-mIBG scintigraphy. $^{123}$I-mIBG is a norepinephrine (NE) analogue that shares the same presynaptic uptake, storage and release mechanism as NE. The most commonly used semiquantitative measurements of myocardial $^{123}$I-mIBG uptake are the calculated early and late H/M ratios and $^{123}$I-mIBG WO derived from planar $^{123}$I-mIBG images. The early H/M ratio reflects the integrity of sympathetic nerve terminals. The late H/M ratio offers information about neuronal function resulting from uptake, storage and release. It has been suggested that $^{123}$I-mIBG WO reflects the neuronal integrity of the sympathetic tone/drive.\(^\text{11}\)

Numerous single-centre studies have demonstrated that the late H/M ratio is an independent predictor of cardiac mortality and morbidity in CHF patients.\(^\text{3,5,9,19}\) However, when comparing studies, variability in the methods used to calculate the H/M ratio leads to substantial variation in the values obtained. This variation affects the clinical impact; that is, the H/M ratio may be wrongly calculated, resulting in incorrect risk classification. The major factor causing these variations in H/M ratio is the collimator choice. For example, the Japanese standard $^{123}$I-mIBG databases showed significant difference in healthy human H/M ratios: 2.39 ± 0.21 and 2.49 ± 0.25 for early and late imaging using an LE collimator and 2.76 ± 0.31 and 3.01 ± 0.35 using an ME or low-to-medium-energy collimator, respectively ($p < 0.0001$ for both early and late H/M ratios).\(^\text{20}\) The difference between collimator types can be explained by septal penetration of high-energy photons of $^{123}$I-mIBG. The septa of LE collimators are less thick than those of ME collimators, leading to increased septal penetration of high-energy photons (Figure 1). Methods for scatter correction in $^{123}$I-mIBG scintigraphy to improve the image quality and compare different collimator types have been described, but clinical use is very limited.\(^\text{14,21,22}\) In addition, correction for penetration may be essential for adequate comparison between collimators; however, these data are currently not available.

Phantom studies have demonstrated significant difference in H/M ratios between different collimator types.\(^\text{13,15,23}\) Specifications of collimators can vary both within the same manufacturer and among different manufacturers. This causes interinstitutional differences in the effect of septal penetration and consequently in estimations of H/M ratio. Therefore, Nakajima et al. developed a correction method using a phantom to provide comparable H/M ratio values between the different LE, low-to-medium-energy and ME-type collimators.\(^\text{23}\) However, studies on H/M ratio difference between different collimator types in humans with CHF are limited and contain a small number of patients. The present study is the first prospective study including more than 50 CHF patients using both LEHR and ME collimators for the acquisition of planar $^{123}$I-mIBG images.
In the current study, early and late H/M ratios derived from planar $^{123}$I-mIBG images using an ME collimator were significantly higher compared with the LEHR collimator-derived H/M ratios. These results are in line with previous phantom studies and comparable to small patient studies comparing different collimator types. Interestingly, there was a linear increase in difference with increasing H/M ratio. In planar LEHR collimator-acquired images, septal penetration of high-energy photons caused increased counts in both mediastinum and heart ROIs, leading to a regression to the mean when calculating H/M ratio. As the ME collimator has thicker septa leading to less septal penetration, the calculation of H/M ratio is less affected by a regression to the mean resulting in higher H/M ratio, and therefore most likely these H/M ratios more accurately reflect the real biodistribution of $^{123}$I-mIBG.

The ratios between the liver, lung and heart and mediastinum were higher when using an ME collimator compared with an LEHR collimator (Table 2). This confirms that mediastinum and heart ROIs are less affected by septal penetration of scattering of high-energy photons from the liver and lung when using an ME collimator. Multivariate regression analysis showed that 90% of the difference in early and late H/M ratios could be explained by scatter from the liver. In early acquisition, scatter from the lungs also contributes to differences in the early H/M ratio. However, scatter from the lungs did not contribute to the difference in late H/M ratios between collimator types. This can easily be explained by the biodistribution of $^{123}$I-mIBG, showing decreasing lung uptake over time. On the late images this results in a relatively higher contribution of scatter of high-energy photons and consequently septal penetration of the liver compared with the lungs.

The ADMIRE-HF was the first large multicentre study that showed that the late H/M ratio was an independent predictor of cardiac morbidity and mortality.\(^5\) In this study a predefined cutoff value for late H/M ratio of 1.6 was chosen using an LEHR collimator. Late H/M ratio less than 1.6 was associated with progression of heart failure, hospitalization, arrhythmia and mortality. Extrapolation of these results to institutions using ME collimators is unclear. Although Nakajima et al. have developed a correction method to translate H/M ratio derived with an LEHR collimator to an ME collimator value in a phantom, translating these findings to a clinical setting may be hampered by inter-individual and intra-individual variation of $^{123}$I-mIBG uptake in the liver and the lung.\(^23\)

As proposed by Flotats et al. standardization of acquisition is essential to compare $^{123}$I-mIBG scintigraphy results between different institutions and they recommended the use of ME collimators.\(^7\) This study underlines that the use of an ME collimator results in H/M ratios being less influenced by scatter from septal penetration. However, many institutions continue to use LEHR collimators because of availability and the relative inconvenience of changing collimators from study to study in daily practice.
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LIMITATION

The primary limitation of the present study is that the early and late acquisition with ME collimators was performed \( \sim 15 \) min after the acquisition with the LEHR collimator. As in time after injection \(^{123}\text{I}-\text{mIBG}\) uptake changes, this could have influenced the H/M ratio outcomes leading to underestimation of H/M ratio with the LEHR collimator. However, the difference in H/M ratios between the two collimator types is too large to be explained by the delay between the different acquisitions alone. Second, although collimators from two different vendors were used (Siemens and Philips), there was no difference in the impact that the LEHR and ME collimators from each vendor had on the H/M ratio (data not shown). Finally, this study only focussed on planar images, and therefore the influence of scatter due to septal penetration on the regional sympathetic innervation/activity as assessed by SPECT remains uncertain. This regional information appears to be of additional clinical value to the planar-derived parameters and should be assessed in future studies.

CONCLUSION

Early and late H/M ratios and subsequently \(^{123}\text{I}-\text{mIBG}\) WO derived from planar \(^{123}\text{I}-\text{mIBG}\) images are significantly lower when using an LEHR collimator compared with an ME collimator. This difference is caused by septal penetration of high-energy photons mainly from the liver and shows a linear increase with increasing H/M ratio. The thicker septa of the ME collimator reduce septal penetration and most likely result in a more realistic reflection of cardiac sympathetic activity. These results strengthen the importance of the recommendation to use ME collimators in semiquantitative \(^{123}\text{I}-\text{mIBG}\) studies.
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