Quantitative I-123 mIBG SPECT in differentiating abnormal and normal mIBG myocardial uptake

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Background. **The purpose of this study was to evaluate global quantitation of cardiac uptake on I-123 mIBG SPECT.**

Methods. **The study included a pilot group of 67 subjects and a validation group of 1,051 subjects. SPECT images were reconstructed by filtered backprojection, ordered subsets expectation maximization, and deconvolution of septal penetration, respectively. SPECT heart-to-mediastinum ratio (H/M) was calculated by comparing the mean counts between heart and mediastinum volumes of interest drawn on transaxial images. Receiver operating characteristic (ROC) analysis was used to assess the capability of each SPECT method to differentiate the heart disease subjects from controls in comparison with that of the planar H/M.**

Results. **In the validation group, the areas under the ROC curves were not significantly different between the SPECT and planar H/M. Order subsets expectation maximization had significantly larger area under the ROC curve than the other two SPECT methods.**

Conclusion. **H/M obtained from I-123 mIBG SPECT was equivalent to the planar H/M for differentiating between subjects with normal and abnormal mIBG uptake. Global quantification of cardiac I-123 mIBG SPECT may represent a viable alternative to the planar H/M. (J Nucl Cardiol 2012;19:92–9.)**

Key Words: Sympathetic nervous system • I-123 mIBG • SPECT • heart failure

See related editorial, pp. 16–18

INTRODUCTION

Assessment of sympathetic nerve activity using I-123 metaiodobenzylguanidine (mIBG) imaging in heart failure (HF) patients has been shown to provide important information for prognosis and therapy evaluation.[1-11] Numerous single-center studies have shown that reduced myocardial uptake of I-123 mIBG is an independent predictor of adverse long-term outcome.[12-17] This finding has recently been confirmed in the prospective multicenter AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial.[18] In that study, quantitation of I-123 mIBG myocardial uptake by the heart-to-mediastinum ratio (H/M) measured from planar imaging predicted prognosis for significant cardiac events in subjects with HF and significant left ventricular dysfunction.[18]

Most published studies have used planar imaging to measure I-123 mIBG myocardial uptake. While single-photon emission computed tomography (SPECT) imaging has been performed as part of many trials, data analysis has primarily focused on regional abnormalities, typically quantified from summed visual scores or polar plots, rather than global assessment analogous to the planar H/M.[19] However, a previous phantom study demonstrated that H/M measured from SPECT reconstructions more accurately reflected the true concentration of I-123 mIBG in the heart than that measured from planar images.[20,21] In addition, as I-123 decays with emission of multiple low-abundance, high-energy photons in addition to the primary 159-keV photopeak, there is septal penetration when low-energy collimators are used, which can affect quantitation of I-123 mIBG myocardial uptake. A mathematical technique [deconvolution of septal penetration (DSP)] was therefore

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developed for use in reconstruction of I-123 mIBG SPECT images, which reduces the contamination of I-123 high-energy photons and improves the accuracy of quantitation of I-123 mIBG myocardial uptake.[20,21]

The objective of this study was to measure I-123 mIBG myocardial uptake from SPECT images reconstructed with different algorithms and to evaluate these results for differentiating between abnormal and normal mIBG uptake in comparison to H/M measured from planar imaging.

MATERIALS AND METHODS

Patient Studies

Two groups of subjects were included in this study, a pilot group and a validation group. The pilot group was used as a training dataset for the operators to familiarize how to define heart volumes of interest (VOI) on the SPECT reconstructions, especially when the subjects had very low cardiac uptake of I-123 mIBG. The validation group was used for comparison of SPECT quantitation of mIBG uptake to that of the planar technique. None of the subjects in the pilot group came from the validation group.

The pilot group consisted of 67 subjects (53 ischemic heart disease (IHD), 14 controls) with I-123 mIBG SPECT images. The IHD subjects (mean age 65; 94% male) all had history of prior myocardial infarction and all but one had left ventricular ejection fraction (LVEF) $\leq$40%. The controls (mean age 36; 71% male) were normal volunteers without history of heart disease.

The validation group consisted of 1,051 subjects (957 HF patients and 94 controls) in the ADMIRE-HF trial who completed both planar and SPECT imaging in the trial. All HF subjects were in New York Heart Association functional class II or III due to ischemic or nonischemic cardiomyopathy with LVEF $\leq$35% and guidelines-based optimal medical therapy. The controls were age-matched normal subjects with low likelihood of heart disease. Details about the population and study design of the ADMIRE-HF trial were described in a previous publication.[18]

All subjects in the validation group received 10 mCi (370 MBq; ±10%) of I-123 mIBG (AdreView™, GE Healthcare, Princeton, NJ, USA) and underwent anterior planar and SPECT imaging beginning at 3-hour 50 minutes post-injection. Details of the imaging procedures were described in previous publications.[18,22] The subjects in the pilot group received various doses of I-123 mIBG from different manufacturers.

Image Processing and Analysis

The de-identified SPECT data were transferred to a core laboratory at Emory University for SPECT quantitation of I-123 mIBG myocardial uptake. The Emory core laboratory was blinded from the planar images and the planar H/M results.

The SPECT data were reconstructed using these algorithms: filtered backprojection (FBP), ordered subsets expectation maximization (OSEM), and OSEM with DSP. For FBP, the SPECT data underwent pre-reconstruction two-dimensional filtering on each projection using a Butterworth low-pass filter (critical frequency = 0.4 cycles/cm, power = 10). The images reconstructed by OSEM and DSP had no pre-reconstruction filtering, but post-reconstruction three-dimensional filtering using a Butterworth low-pass filter (critical frequency = 0.4 cycles/cm, power = 10). After reconstruction and filtering, the images were sent to the Emory Cardiac Toolbox (Emory University, Atlanta, GA, USA) for quantitation of I-123 mIBG myocardial uptake.

Figure 1 demonstrates the tool developed in the Emory Cardiac Toolbox for quantitation of I-123 mIBG myocardial uptake from SPECT images. The first step was to manually draw a heart range on the projection image at left anterior 45° that tightly included the heart (the upper left image in each panel). Then, the mediastinum range was automatically determined to include 7 slices in total, immediately above the heart range (the lower left image in each panel). Seven slices were used to form the mediastinum VOI so that it had a similar size to that of the mediastinum ROI validated for I-123 mIBG planar imaging, which was a square ROI with 7 × 7 pixels.[22] The center slices of the heart and mediastinum ranges were reconstructed and displayed beside the projections. The heart region of interest (ROI) was manually drawn on the heart transaxial image (the upper right image in each panel). The mediastinum ROI was automatically determined as a circle with a radius of 4 pixels centered at the image center (the lower right image in each panel). The heart and mediastinum VOIs were then constructed to include the pixels within the heart and mediastinum ROIs on the transaxial slices between the heart and mediastinum ranges, respectively. SPECT H/M was calculated by dividing the mean counts in the heart VOI divided by the mean counts in the mediastinum VOI.

Details about quantitation of I-123 mIBG myocardial uptake from planar images were described in previous publications.[18,22] In brief, the heart ROI was drawn manually to include all visible ventricular activity and a 7 × 7 pixel mediastinum ROI was drawn in the upper mediastinum, using the apices of the lungs as anatomic landmarks. The H/M was calculated as the ratio of the counts/pixel in the two ROIs.

Reproducibility

The intra- and inter-observer reproducibility of the tool of SPECT quantitation of I-123 mIBG myocardial uptake was evaluated using a subset (N = 50) of the validation group. A total of 50 subjects were randomly selected from the validation group. Two operators, who were blinded from each other, processed the 50 subjects and the FBP, OSEM, and DSP H/M results between them were then compared. After 1 week, one of the operators, blinded from previous results, re-processed the 50 subjects and compared the FBP, OSEM, and DSP H/M results to those from the first processing.

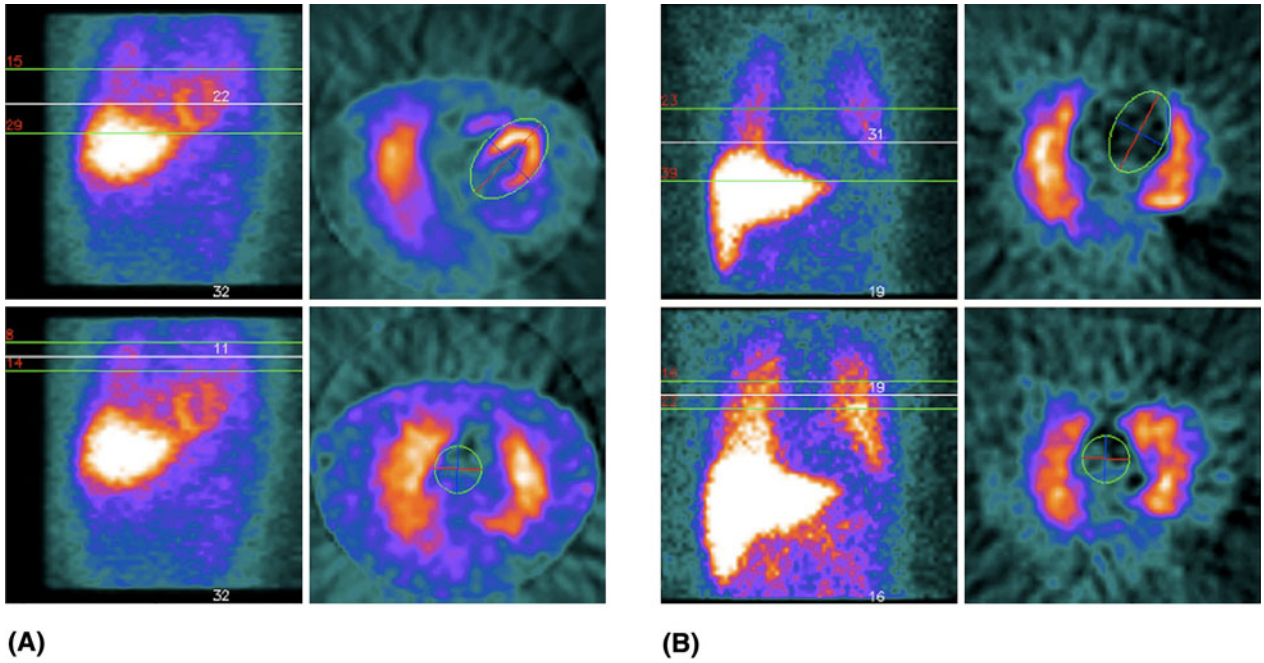

Figure 1. Examples of subjects with normal (**A**) and abnormal mIBG uptake (**B**) measured by I-123 mIBG SPECT imaging. In **A** and **B**, the heart ROI was manually drawn and the mediastinum ROI was automatically determined on the heart and mediastinum transaxial images (reconstructed using either FBP, OSEM, or OSEM with DSP), which corresponded to the *red lines* on the planar images next to them, respectively. The heart and mediastinum VOIs were then constructed to include the pixels within the heart and mediastinum ROIs in between the corresponding green lines, respectively. SPECT H/M was calculated by dividing the mean counts in the heart VOI divided by the mean counts in the mediastinum VOI.

Statistical Analysis

Receiver operator characteristics (ROC) curves were generated to evaluate the accuracy of the FBP, OSEM, and DSP H/M in differentiating the patients and controls in both pilot and validation groups, respectively. Areas under the ROC curve (AUC) were calculated for each SPECT method and compared to each other and to that for the planar technique. The optimal cutoff values for the FBP, OSEM, and DSP H/M in differentiating HF subjects and controls were calculated as the values giving the maximal accuracy. Sensitivity and specificity were then calculated using the optimal cutoff values and compared to those given by the planar technique.

RESULTS

Pilot Group

Table 1 shows the planar and SPECT H/M in the IHD and control subjects in the pilot group. For all SPECT reconstruction methods, the H/M values in the IHD patients were significantly smaller than those in the controls. Figure 2 shows the ROC curves of the SPECT H/M. Table 2 shows the optimal cutoff values, sensitivity, specificity, and AUC of the planar and SPECT H/M. There were no significant differences among the AUC, indicating that SPECT H/M had similar capability to differentiate normal and abnormal mIBG myocardial uptake as compared to the planar technique.

Validation Group

Thirty-five subjects (31 HF patients and 4 controls) were excluded from the analysis. Images from 27 subjects had less than the required 7 slices above the base of the heart for defining the mediastinum VOI. Studies on 4 subjects had non-circular orbit, and the orbit information was lost during data transfer. Studies on 2 subjects had corrupted data. One study had significant truncation of the heart region, and one study had incomplete acquisition that resulted in multiple blank projections. The validation group therefore consisted 1,016 subjects (926 HF patients and 90 controls).

Table 3 shows the planar and SPECT H/M in the HF and control subjects in the validation group. For all SPECT reconstruction methods, the H/M in the HF subjects were significantly smaller than those in the controls. Figure 3 shows the ROC curves and Table 4

Table 1. Planar and SPECT H/M in the pilot group

	Planar H/M	FBP H/M	OSEM H/M	DSP H/M
IHD patients (N = 53)				
Mean	1.46	1.99	1.85	2.76
SD	0.20	0.61	0.61	1.36
Controls (N = 14)				
Mean	2.46	5.43	4.25	9.13
SD	1.82	2.56	0.61	4.38
P	<.0001	<.0001	<.0001	<.0001

P value of the unpaired *t* test with unequal variance between the IHD patients and controls.
FBP, Filtered backprojection; *OSEM*, ordered subsets expectation maximization; *DSP*, deconvolution of septal penetration, *IHD*, ischemic heart disease; *SD*, standard deviation.

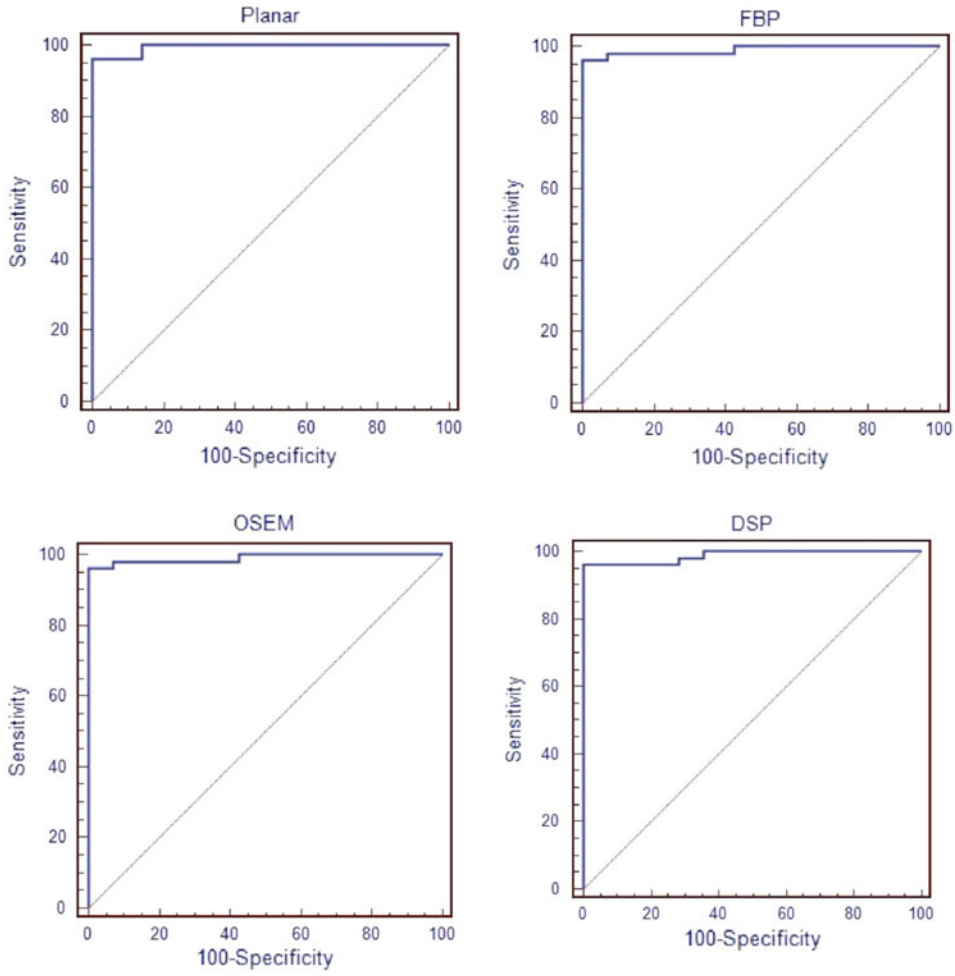

Figure 2. ROC curves of planar and SPECT H/M in differentiating the IHD and control subjects in the pilot group.

shows the optimal cutoff values, sensitivity, specificity, and AUC of the planar and SPECT H/M. There were no significant differences between the AUC values of the SPECT H/M and planar H/M. Among the SPECT methods, OSEM H/M had significantly larger AUC than FBP H/M and DSP H/M.

Figure 4 shows the results of the reproducibility analysis. The intra- and inter-observer correlation

Table 2. Optimal cutoff values, sensitivity, specificity, and AUC of planar and SPECT H/M in differentiating the IHD and control subjects in the pilot group

	Planar H/M	FBP H/M	OSEM H/M	DSP H/M
Optimal cutoff	1.82	3.10	2.90	4.90
Sensitivity	0.96	0.96	0.96	0.96
Specificity (%)	1.00	1.00	1.00	1.00
AUC (%)	0.99	0.99	0.99	0.99

FBP, Filtered backprojection; *OSEM*, ordered subsets expectation maximization; *DSP*, deconvolution of septal penetration; *AUC*, area under ROC curve.

Table 3. Planar and SPECT H/M in the validation group

	Planar H/M	FBP H/M	OSEM H/M	DSP H/M
HF patients (N = 926)				
Mean	1.44	2.41	2.18	3.47
SD	0.20	0.98	0.78	2.00
Controls (N = 90)				
Mean	1.77	3.87	3.67	6.49
SD	0.23	1.48	1.20	2.93
P	<.0001	<.0001	<.0001	<.0001

P value of the unpaired *t* test with unequal variance between the HF patients and controls.
FBP, Filtered backprojection; *OSEM*, ordered subsets expectation maximization; *DSP*, deconvolution of septal penetration; *HF*, heart failure; *SD*, standard deviation.

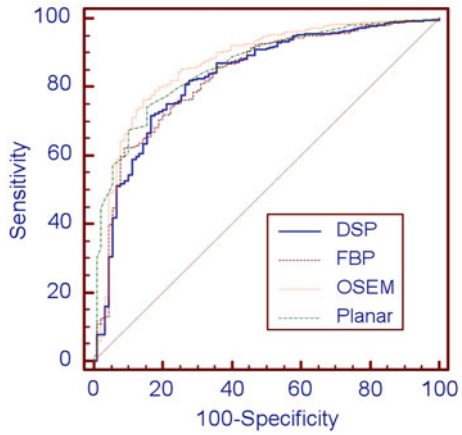

Figure 3. ROC curves of planar and SPECT H/M in differentiating the HF and control subjects in the validation group.

coefficients were 0.93 and 0.89 for FBP H/M, 0.91 and 0.90 for OSEM H/M, and 0.93 and 0.91 for DSP H/M, respectively.

DISCUSSION

This study presents a new quantitative tool for determining the H/M from I-123 mIBG SPECT images. Comparing the SPECT results to those from the planar H/M in a small pilot group and a large validation group, the capability to differentiate subjects with abnormal and normal mIBG uptake was equivalent, regardless of the SPECT reconstruction method used (FBP, OSEM, or DSP). In each group, SPECT H/M values were systematically larger than planar H/M values. The counts measured from planar images were summations of all pixels along the direction of the planar projection. Although such summations applied to both mediastinum ROI and heart ROI, it increased the mediastinum counts by more times than it did to the heart counts. Therefore, planar imaging overestimated the background more than the heart uptake, resulting in a smaller H/M than SPECT H/M. Moreover, in each group DSP H/M values were systematically larger than FBP H/M and OSEM H/M. DSP utilized system-specific point-spread functions to de-convolve the impact of high-energy photons associated with I-123 emission, and thus yielded images with less background counts. Since the background counts represented a higher portion of the mediastinum VOI counts than that of the heart VOI counts, reduction of the background counts in the image (as a result of DSP) yielded a higher H/M.

To date the majority of studies using I-123 mIBG SPECT imaging have primarily focused on regional

Table 4. Optimal cutoff values, sensitivity, specificity, and AUC of planar and SPECT H/M in differentiating the HF and control subjects in the validation group

	Planar H/M	FBP H/M	OSEM H/M	DSP H/M
Optimal cutoff	1.58	2.72	2.61	4.01
Sensitivity	0.78	0.72	0.76	0.72
Specificity (%)	0.79	0.78	0.86	0.83
AUC (%)	0.85	0.82	0.87	0.83
P (SPECT vs planar)		.0892	.7057	.1310
P (FBP or DSP vs OSEM)		<.0001		.0002

FBP, Filtered backprojection; *OSEM*, ordered subsets expectation maximization; *DSP*, deconvolution of septal penetration; *AUC,* area under ROC curve.

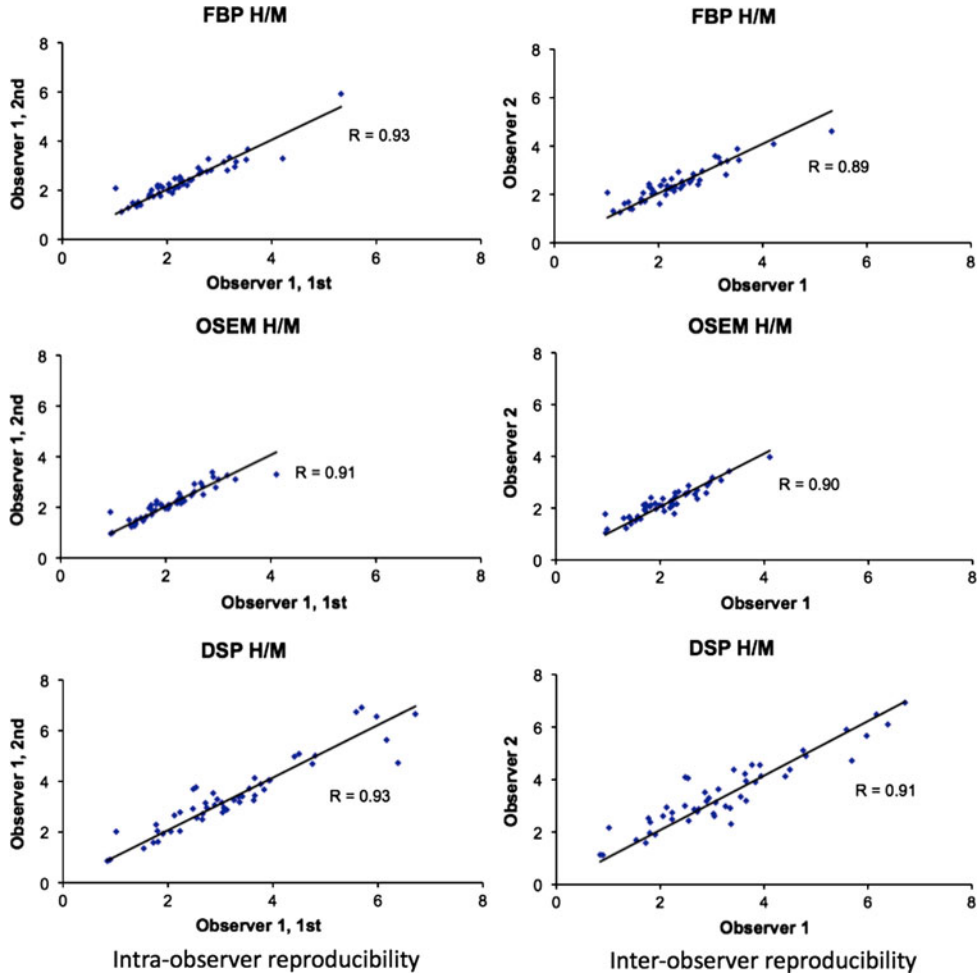

Figure 4. Intra- and inter-observer reproducibility of the tool for determining H/M from I-123 mIBG SPECT.

abnormalities, typically quantified from summed visual scores or polar plots, rather than global assessment analogous to the planar H/M. One study determined the ratio of LV myocardium to LV cavity on SPECT images but needed a LV cavity VOI and a blood sample as reference.[23] This is the first large study describing a practical SPECT global quantitation tool with discrimination capability equivalent to the well-studied planar

global quantitation of I-123 mIBG cardiac uptake. Such tool can have implications for users of small field-of-view cardiac cameras and new SPECT-only systems, from which conventional planar imaging cannot be obtained. Such tool can also allow not acquiring unnecessary planar imaging for future clinical applications, if any, where H/M is integrated with other SPECT parameters for certain clinical indications.

The SPECT quantitation tool involved manual procedures to obtain heart and mediastinum VOI. The major manual steps were to determine the slice range of the heart on the projection at left anterior 45° and to draw the ROI of the heart on the center transaxial slice in the slice range of the heart. Both manual steps can introduce operator-dependent variability to the mean heart counts calculated from the SPECT images. Once the heart VOI was determined, the mediastinum VOI was automatically defined as a cylinder with a radius of 4 pixels and a height of 7 slices (similar to that for the mediastinum ROI in I-123 mIBG planar imaging[22]), centered at the center of transaxial images and immediately above the slice range of the heart. The automatic definition of the mediastinum VOI minimizes operator-dependent variability to the mean mediastinum counts, and eventually, the SPECT H/M. As shown in the assessment of operator-dependent variability of SPECT H/M in the subset of 50 subjects in the validation group, the intra- and inter-operator correlation coefficients were about 0.90, indicating the SPECT H/M tool had satisfactory reproducibility. Note that the SPECT quantitation tool used heart VOI, not myocardial VOI, which would have required excluding the cavity from the measure of average heart counts. In order to define a myocardial VOI, more user interactions would be needed to define the center and radius of the ventricle, and the slices of the apex and base. In addition, an automated tool would be needed to define the epicardial and endocardial surfaces. For patients with severe HF, there can be very little uptake of mIBG in part of the myocardium. This can be very challenging for automatic definition of the epicardial and endocardial surfaces. Thus, for simplicity and reproducibility, the SPECT quantitation tool used a cardiac VOI, analogous to the whole-heart ROI typically used in determination of the planar H/M.

Even though the SPECT quantitation tool was designed to minimize the effect of manual processing, it must be noted that there were several factors that complicated image processing for I-123 mIBG SPECT. Most of the HF subjects had high liver and lung uptakes of I-123 mIBG adjacent to the heart region that made the definition of the heart VOI more difficult. Such difficulty was most prominent for studies with very low cardiac uptake of I-123 mIBG. Use of the pilot group as a training dataset allowed the image processors to become familiar with defining heart VOIs on the SPECT reconstructions, especially when the subjects had very low cardiac uptake of I-123 mIBG.

The ROC analysis in both pilot and validation groups showed that the SPECT H/M had equivalent capability to differentiate subjects with normal and abnormal cardiac uptake of I-123 mIBG, as compared to planar H/M. However, the ROC analysis in the pilot and validation groups yielded different optimal cutoff values to differentiate the normal and abnormal subjects. This in part reflected differences between the pilot group and the validation group. In particular, the pilot control group was small and considerably younger (mean age 36) than the validation controls (mean age 58), resulting in higher cardiac uptake of I-123 mIBG for the former group and minimal overlap with the IHD subjects in the ROC analysis. Moreover, since the main clinical utility of I-123 mIBG imaging is prognosis and therapy evaluation rather than diagnosis of IHD or HF, the optimal cutoff values determined in this study might not be relevant as a basis for use of I-123 mIBG imaging results in clinical practice. Care should also be taken when considering the differences among the SPECT reconstruction methods. Although OSEM H/M showed significantly larger AUC values in differentiating normal and abnormal subjects in the validation group, it remains to be determined whether OSEM should be the preferred reconstruction method for clinical use of I-123 mIBG SPECT imaging.

CONCLUSION

A highly reproducible tool has been developed and validated to measure H/M from I-123 mIBG SPECT images. It showed similar capability to the planar H/M to differentiate between heart disease and control subjects, regardless of the SPECT reconstruction method used (FBP, OSEM, or DSP). This tool could be a viable quantitative SPECT alternative to the planar H/M, which can have implications for users of small field-of-view cardiac cameras and new SPECT-only systems.

Disclosure

This study was supported in part by GE Healthcare. Dr Chen, Dr Garcia, and Mr Folks receive royalties from the sale of the Emory Cardiac Toolbox. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest practice. Dr Jacobson is an employee of GE Healthcare and owns shares in the General Electric Company.

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