Reliability of the ^{123}I-*m*IBG heart/mediastinum ratio: Results of a multicenter test–retest reproducibility study

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A quantitative measurement, the Heart-to-Mediastinum (H/M) ratio of counts derived from a planar acquisition approximately 4 hours after injection of ^{123}I-*m*IBG, is a strong predictor of outcomes in patients with stable class II-III heart failure and LVEF ≤ 35%. This study assessed the test–retest reproducibility of the H/M ratio in such patients. 47 subjects with class II-III systolic heart failure and LVEF ≤ 35% were tested at two time intervals separated by 5 to 14 days. Subjects were imaged twice on the same camera using the same radionuclide dose. Images were sent to a core analysis lab, where three nuclear technologists independently determined the H/M ratios. The primary endpoint was test–retest H/M ratio reproducibility calculated as the absolute difference in mean value determined by the three readers. Mean subject age was 65 ± 12 years, 85% were male, and mean BMI was 29 ± 6 kg/m^2. Mean injected activity was 10.18 ± 0.43 mCi for first dose and 10.09 ± 0.52 mCi for the second dose. The mean and SD values for first and repeat studies were almost identical: the 95% confidence interval of the mean test–retest difference was 0.055 to 0.076. Bland–Altman plots showed no systematic effect of the H/M ratio on the magnitude of the difference between replicate measurements. Inter-reader measurements were nearly identical. There were no serious adverse events despite exposure to ^{123}I-*m*IBG on 2 occasions in a short time period. The Heart-to-Mediastinum ratio of ^{123}I-*m*IBG is a consistent and highly reproducible measurement in stable Class II to III heart failure patients. (J Nucl Cardiol 2019;26:1555–65.)

Key Words: Iodine-123 • radionuclides • MIBG imaging • heart failure

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Abbreviations

^{123}I	Iodine 123
*m*IBG	meta-iodobenzylguanidine
H/M	Heart-to-mediastinum ratio
LVEF	Left ventricular ejection fraction
ROI	Region of interest
CI	Confidence interval

See related editorial, pp. 1566–1568

INTRODUCTION

Meta-iodobenzylguanidine is a norepinephrine analog processed by norepinephrine re-uptake receptors at sympathetic synapses and elsewhere. Its uptake in cardiac tissue can be measured scintigraphically when it is labelled with iodine-^{123}. ^{123}I-meta-iodobenzylguanidine (*m*IBG) uptake is robust in normal cardiac tissue. However, its uptake is markedly reduced in most patients with systolic heart failure. A strong relationship has been demonstrated between ^{123}I-*m*IBG uptake and prognosis in these patients. The ADMIRE-HF (AdreView™ Myocardial Imaging for Risk Evaluation in Heart Failure) study and its extension study ADMIRE-HFX showed that subjects with an abnormally low heart/mediastinum (H/M) ratio in ^{123}I-*m*IBG planar scintigraphic imaging have earlier and more frequent events than those with an H/M ratio in the normal range (H/M $\geq$ 1.60).[1,2]

A standard procedure for validating a diagnostic measurement is to establish that independent determinations made during a short interval with no change in patient condition are reproducible. This provides an indication of measurement stability and the degree to which a single determination can be used as the basis for further diagnostic or therapeutic action. Furthermore, test–retest reproducibility data are needed to establish the magnitude of change that represents a true change in patient clinical status.

The primary objective of this study was to assess the test–retest reproducibility of the ^{123}I-*m*IBG H/M ratio in heart failure subjects on planar imaging at 3 hours 50 minutes following its intravenous administration.

METHODS

Study Design

This was a 10-center study in which 47 subjects with stable New York Heart Association Class II or III chronic systolic heart failure and left ventricular ejection fraction $\leq$ 35% underwent planar imaging at approximately 4 hours after ^{123}I-*m*IBG injection in order to quantify the Heart/Mediastinum ratio of ^{123}I-*m*IBG uptake. All subjects were imaged twice, the second image performed with the same radionuclide dosage and on the same camera system. Three nuclear technologists working in a core analysis lab independently quantified the H/M ratios. The primary endpoint was test–retest H/M ratio reproducibility calculated as the absolute difference in mean value determined by the three readers. A safety analysis was also conducted as a secondary end-point of this study.

Subjects

Patients eligible for inclusion in the study had chronic systolic cardiomyopathy with left ventricular ejection fraction $\leq$ 35% as measured by radionuclide or contrast ventriculography, electrocardiographically gated SPECT myocardial perfusion imaging, cardiac magnetic resonance, or echocardiography. Measurements needed to be performed within 30 days of enrollment, and be consistent with at least one prior measurement $\geq$ 3 and $\geq$ 6 months earlier for ischemic and non-ischemic cardiomyopathies, respectively. All patients had clinically stable New York Heart Association class II or III heart failure for at least 3 months before enrollment, with no changes during this period in heart failure medications, no hospitalizations, and no change in symptoms. Patients had to be taking daily heart failure medications including at least a beta blocker and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist (unless there were clinical contraindications), and to have a history of compliance with their heart failure medications.

Subjects were excluded if they had previously received ^{123}I-*m*IBG, had any contraindications to ^{123}I-*m*IBG injection, were allergic to iodine, were pregnant or had a history of significant exposure to radiation. Other exclusion criteria included the following: prior heart transplant; defibrillation [via external or implantable cardioverter defibrillator (ICD)], antitachycardia pacing, or cardioversion to treat an arrhythmic event in the previous 90 days; cardiac revascularization, insertion of an ICD, or acute myocardial infarction in the previous 30 days; or renal insufficiency (creatinine $>$ 3 mg/dL). Subjects taking antidepressants that inhibit the norepinephrine transporter, antihypertensives that deplete norepinephrine stores or inhibit norepinephrine reuptake, and those with a history of using sympathomimetic amines or cocaine were ineligible. Subjects with a non-cardiac condition that causes a significant elevation of plasma catecholamines (e.g., phaeochromocytoma) were also ineligible.

Imaging Visits

At each imaging visit, subjects had a physical examination and a 12-lead electrocardiogram. Current medications and dosages were recorded. Thyroid blockade in accordance with the package insert and local regulations was permitted. Each subject then underwent ^{123}I-*m*IBG planar scintigraphy. If the subject's clinical condition remained stable, the imaging procedure was repeated 5 to 14 days later. Adverse events from the time of the administration of the first dose of ^{123}I-*m*IBG up to 24 hours after the second dose of ^{123}I-*m*IBG were recorded.

At each imaging visit, each subject received ~ 10 mCi (370 MBq) of ^{123}I-*m*IBG. A ± 10% tolerance of the nominal dose was allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) per administration. A subsequent injection of sterile 0.9% sodium chloride was permitted to ensure full delivery of the dose. Anterior planar 10-minutes scintigraphic images were acquired at 3 hours 50 minutes after injection of the ^{123}I-*m*IBG using a 128 × 128 matrix. For each subject, the same dual-detector Anger gamma camera fitted with low energy high-resolution collimators was used for both imaging sessions. The nominal dose of ^{123}I-*m*IBG, the imaging parameters, and the time points were specified to be the same for both imaging visits for each subject.

The resulting images were reviewed at each site by both that site's Principal Investigator or designate, and by a local site nuclear technologist who had been trained on the procedure. Image analysis was to ensure that all quality control requirements had been met and that patient positioning was adequate for measurement of the H/M ratio. Appropriate positioning entailed inclusion of the entire heart and upper mediastinum in the field of view. Images were also inspected on-site for motion artifacts, and any possible system malfunction. Images were then forwarded to a core imaging lab for quantitative measurements of the H/M ratio.

H/M Ratio Measurements

All of the H/M measurements reported in this study were performed at a core facility where each of the 94 images (two series of 47 acquisitions) was analyzed by three readers blinded to all clinical information. The 94 images were randomized, and the randomization number then defined the order in which the scans were read. Images were evaluated individually on Xeleris workstations version 2.1 (GE Healthcare, Chicago, IL). Reading was performed independently in different secure reading rooms with standardized lighting and computer screens standardized to pixel density and color display.

For each image, the blinded reader was instructed to process and to record the H/M ratio. The process used to derive the H/M ratio was pre-defined (see Figure 1).

First, either an elliptical or a free-hand region of interest (ROI) was to be drawn around the left ventricular (LV) myocardium (see upper middle image of Figure 1). The ROI was to be drawn as close to the myocardium as possible and not include photopenic areas around it. Because there can be a varying uptake throughout the myocardium due to ischemia, infarct or severe denervation, the ROI was to be placed so that it covered the entire LV myocardium and not only around the visible focal uptake. If the heart border could not be identified because all or the majority of the myocardium was not visualized, the ROI was to be drawn based upon the presumed location of the heart, using the medial aspects of the left and right lower lung for anatomic guidance. The total number of pixels and the average counts/pixel for this ROI was recorded on the Case Report Form (CRF).

Second, a horizontal line was to be drawn on the planar image between the apices of the lungs (see upper right image of Figure 1). Lung uptake may be reduced in certain subjects and the physical apices of the lungs may not be visible above the background activity. In these cases, the horizontal line was to be drawn 2 pixels below the thyroid (if visible) or at the approximate location of the physical lung apices based on visible anatomic landmarks. If the image was from a small FOV camera and the lung apices were not in the FOV, the horizontal line was to be drawn below any edge-packing artifacts at the top of the image.

Third, a vertical line was to be drawn from the horizontal line to the dome of the diaphragm between the lungs and spaced equidistant from each (see lower left image of Figure 1).

Fourth, counts were examined along the vertical line, beginning 4 pixels below the intersection point with the horizontal line and extending for a total of 15 pixels from that intersection. The pixel with the lowest counts was to be identified and then the reader was to draw a 7 × 7 pixels rectangular ROI (i.e., one having an area of 49 pixels) centered over the previously identified low count pixel located along the vertical line. The total number of pixels and the average counts/pixel for this mediastinal ROI was recorded on the CRF.

A separate, annotated version of the anterior planar image with the lines and ROIs drawn on it was saved. The H/M ratio was defined as the average counts per pixel in the heart ROI divided by the average counts per pixel in the mediastinal region of interest.

Independent Blinded Readers

The independent blinded readers were licensed nuclear medicine technologists with at least 5 years of clinical experience, including the processing of at least 500 nuclear cardiac images in a clinical setting. The readers underwent training in the measurement of the H/M ratio. They first viewed a live demonstration of the H/M calculation on up to 15 images and then performed the assessment independently on up to another 50 images (with the H/M known) with varying degrees of ^{123}I-*m*IBG uptake. To demonstrate successful completion of training and adequate competency in drawing heart and mediastinal regions of interest, each technologist had to pass an exam utilizing 20 planar images not shown in training and accurately assess the H/M ratio within 0.08 for at least 80% of the images.

Statistical Analysis

For each image, the mean of the H/M values provided by the three independent blinded readers was calculated. The primary outcome measure of this study was the absolute difference in the mean H/M values for the 3-hours 50-minutes image between the two visits for each subject. The 95% confidence interval [CI] of the mean of these absolute differences between the two visits was used as a measure of test stability. Bland–Altman analysis was conducted to assess whether the difference between the test and retest values at 3 hours and 50 minutes after ^{123}I-*m*IBG administration varies

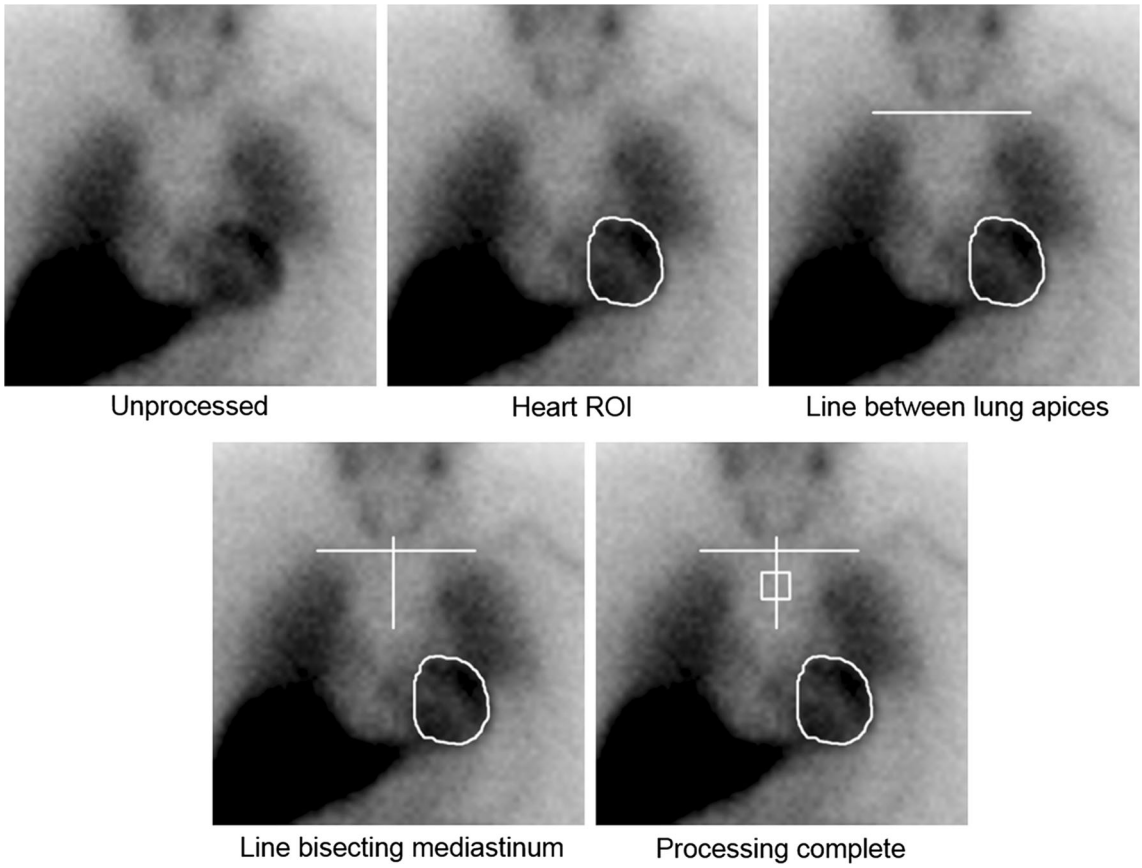

Figure 1. ROI Placement steps for anterior planar image.

according to the magnitude of the measurements. Scatter plots between H/M ratios on day 1 and day 2 by individual technologist and overall (average of 3 technologists) were also constructed.

A sample size of 45 evaluable subjects was chosen to provide a reasonably narrow 95% confidence interval for the mean absolute difference between the test and retest values for the H/M at 3 hours 50 minutes after ^{123}I-*m*IBG administration. After the first 25 subjects had completed both scans, a pre-specified interim analysis was performed to reassess the necessary sample size to ensure a 2-sided 95% CI around the mean difference in H/M ratio of half-length 0.05. The original sample size was deemed sufficient.

RESULTS

Subjects

Of the 63 subjects who provided informed consent, 12 withdrew prior to administration of ^{123}I-*m*IBG. The 51 subjects who received $\geq$ 1 dose of ^{123}I-*m*IBG were included in the safety analysis. Four subjects were withdrawn from the imaging evaluation because of protocol violations (1 because an imaging protocol had not been followed correctly, 2 because of changes in their clinical condition or medications, and 1 because of use of an excluded concomitant medication), leaving 47 subjects for the image evaluation.

The subject demographics are shown in Table 1. Of the 51 subjects in the safety population, 43 (84%) were male and 8 (16%) were female. The majority were caucasian (67%). Age ranged from 40 to 90 years, with a mean of 65.2 years. BMI ranged from 19 to 48, with a mean of 29. 81% of subjects had Class 2 heart failure, and 51% had an ischemic basis for their cardiomyopathy. There were no differences between the safety and the imaging populations.

All subjects in the imaging population were taking at least 2 medications of the 4 standard categories included in heart failure treatment guidelines: angiotensin-converting enzyme (ACE) inhibitors (29/47); angiotensin II receptor blockers (16/47); beta blockers (47/47); aldosterone antagonists (26/47). Forty-two subjects (89%) were taking either an ACE inhibitor or ARB.

The mean injected activity in the safety population was 10.18 mCi on dosing day 1 and 10.09 mCi on dosing day 2. Two subjects received doses outside of the prespecified range; one subject received 8.92 mCi on

Table 1. Subject demographics

Variable	Safety evaluation (*N* = 51)	Imaging population (*N* = 47)
Gender		
Male, *n* (%)	43 (84.3)	40 (85.1)
Female, *n* (%)	8 (15.7)	7 (14.9)
Race		
Asian, *n* (%)	2 (3.9)	2 (4.3)
African American, *n* (%)	14 (27.5)	13 (27.7)
White, *n* (%)	34 (66.7)	31 (66.0)
Middle eastern, *n* (%)	1 (2.0)	1 (2.1)
Age, years		
Mean ± SD	65.2 ± 12.5	65.6 ± 12.1
Range (Min, Max)	40, 90	43, 90
BMI, kg/m^2		
Mean ± SD	29.25 ± 6.0	29.46 ± 5.83
Range (Min, Max)	19.0, 48.2	21.2, 48.2
NYHA class		
II, *n* (%)	42 (83.4)	38 (80.9)
III, *n* (%)	9 (17.6)	9 (19.1)
HF etiology		
Ischemic, *n* (%)	28 (55)	24 (51.1)
Non-ischemic, *n* (%)	23 (45)	23 (48.9)
Diabetes		
Yes, *n* (%)	17 (33.3)	15 (31.9)
No, *n* (%)	34 (66.7)	32 (68.1)

N = Total number of subjects in that population
n = Number of subjects (out of N) for the variable
BMI, body mass index; *Max*, maximum; *Min*, minimum; *SD*, standard deviation; *HF*, heart failure

dosing day 1 and 8.95 mCi on dosing day 2 and another subject received 8.92 mCi on dosing day 2. These minor deviations did not affect image appearances and the subjects were included in the analysis. The mean interval between doses was 7.7 days. Table 2 shows the different camera systems and collimators that were used in this study. Each of the two image sets was in all cases acquired using the exact same camera.

Table 2. Camera systems included in study

Manufacturer	Model	Collimator
GE	Infinia	LEHR
	Millenium MG	LEHR
Phillips/ADAC	Cardio 60	VXGP
	Cardio MD	VXGP
	Forte	VXGP
	Vertex	VXGP
Siemens	e.CAM	LEHR

LEHR, Low energy, high-resolution; *VXGP*, Vertex general-purpose

Table 3 shows that important physiologic measurements including heart rate, blood pressure, and respiratory rate did not change between screening, visit 1, and visit 2. One subject did not have vital signs recorded at visit 1, explaining why data are complete for only 46 subjects. These data add confidence that the study population remained stable for the duration of this investigation.

Test–Retest Analysis

Table 4 shows that the mean (SD) between-visit difference in the mean H/M ratio for the images taken at 3 hours 50 minutes after administration of ^{123}I-*m*IBG was 0.065 (0.0348); the 95% CI for the mean between-visit difference was 0.055 to 0.076. Further, the Bland–Altman plot (Figure 2) of the H/M values obtained at 3 hours 50 minutes after administration of ^{123}I-*m*IBG showed that the size of the difference between the test and retest values for H/M did not vary in relation to the magnitude of the measurements. The plot shows two outliers. One was a subject with a history of intermittent

Table 3. Comparison of physiologic measurements across the study population between screening and the two imaging time-points

Parameter	Screening visit	1st imaging visit	2nd imaging visit
Systolic blood pressure (mmHg)			
n	47	46	47
Mean (SD)	118.9 (17.16)	119.5 (19.93)	121.1 (17.58)
Median	117	116.5	121
Min, max	88, 170	90, 180	91, 170
Diastolic blood pressure (mmHg)			
n	47	46	47
Mean (SD)	71.6 (9.16)	71.4 (8.76)	72.1 (9.50)
Median	70	70	70
Min, max	58, 94	51, 90	44, 90
Heart rate (beats/minute)			
n	46	46	47
Mean (SD)	71 (10.99)	67 (10.64)	69 (10.66)
Median	70	66.5	67
Min, max	51, 101	43, 96	42, 89
Respiratory rate (breaths/minute)			
n	46	46	47
Mean (SD)	17 (2.38)	17 (2.34)	17 (2.06)
Median	17	17	17
Min, max	12, 22	12, 24	12, 22

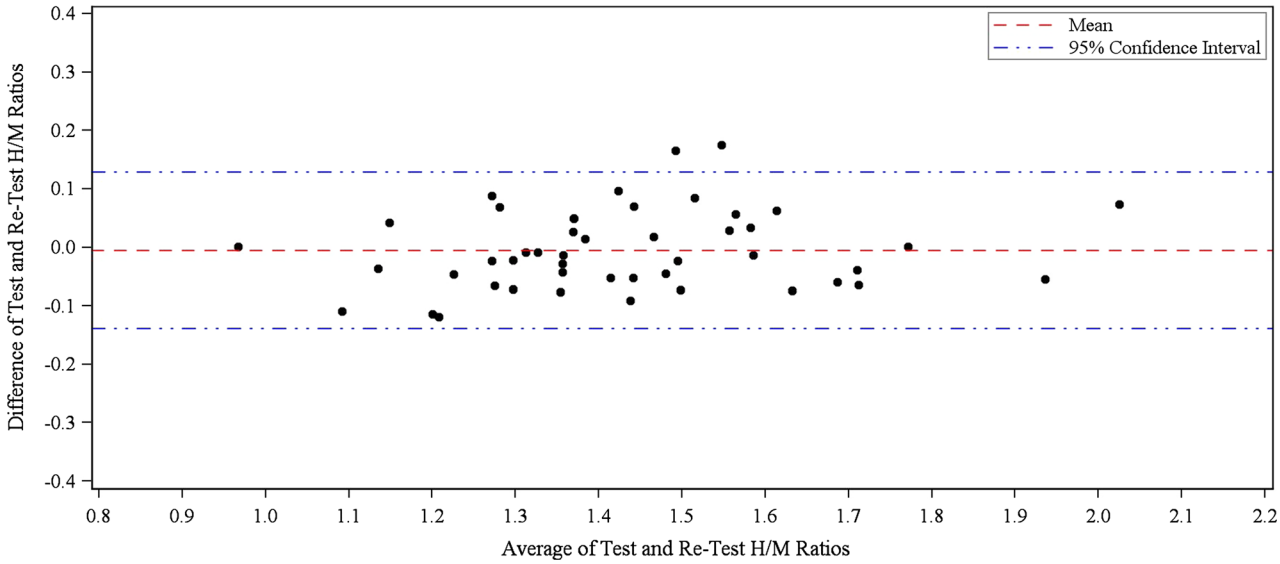

Figure 2. Bland-altman plot of averaged 3-reader test and retest values for H/M ratio on planar scintigraphy at 3 hours 50 minutes After ^{123}I-*m*IBG administration.

left bundle branch block (LBBB). Although the subject was clinically stable, the ECG during Visit 2 showed a LBBB pattern that was not present during Visit 1. Thus, the change in the H/M ratio may have represented a change in cardiac physiology, as opposed to variability in accuracy of the measurement of H/M. This subject's images are shown in Figure 3. The other subject's 3-hours 50-minutes H/M ratio was 1.57 during Visit 1 and

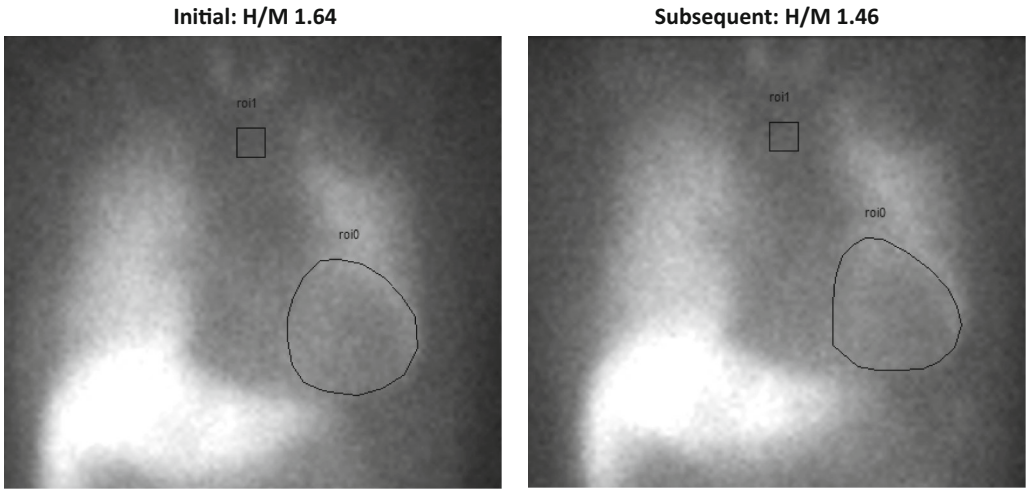

Figure 3. Patient who developed LBBB between initial and subsequent imaging.

1.41 during Visit 2. That subject had non-ischemic cardiomyopathy diagnosed 14 months earlier and a dual-chamber pacemaker inserted 8 months earlier.

Table 4 also shows that the mean [SD] values for the visit 1 and visit 2 H/M ratio determinations by the independent readers A, B, and C at 3 hours 50 minutes after ^{123}I-*m*IBG administration were almost identical [A: 1.435 (0.2238) vs 1.422 (0.2229); B: 1.430 (0.2220) vs 1.436 (0.2069); C: 1.427 (0.2115) vs 1.441 (0.1945); average: 1.429 (0.2160) vs 1.433 (0.2048)]. The mean of the absolute difference in H/M ratio at 3 hours 50 minutes after ^{123}I-*m*IBG administration for the 3 readers ranged from 0.060 to 0.070, and the SD ranged from 0.0413 to 0.0612.

Figure 4 shows scatter-plots of H/M ratios at the 2 time intervals by individual technologist. The absolute measurement correlation is shown to be strong for each technologist performing the measurement, with Pearson's correlation coefficient being greater than 0.9 in all cases (individual comparison and average of all readers).

Safety

There were no deaths or serious adverse events, and no subjects withdrew from the study as a result of an AE. Of the 51 subjects in the safety population, 4 (7.8%) experienced a total of 5 treatment-emergent adverse events. One of the events was classified as moderate in intensity (dizziness lasting 10.5 hours). The others were classified as mild: one subject had injection-site erythema after both injections, another subject reported a case of acne, and another subject reported diarrhea.

DISCUSSION

^{123}I-*m*IBG has been used since the 1970s for scintigraphic imaging of adrenergic tumors, such as pheochromocytoma and neuroblastoma. On the basis of the ADMIRE-HF[1] and ADMIRE-HFX[2] studies, ^{123}I-*m*IBG was also approved for assessment of myocardial sympathetic innervation in evaluation of patients with NYHA class II or III heart failure with an LVEF $\leq$ 35%. The current phase 4 study, which compared the results of two examinations performed 5 to 14 days apart, was performed to establish the test–retest reliability of the H/M ratio measured on planar scintigraphic images obtained after intravenous injection of ^{123}I-*m*IBG.

Test–retest variability can come from three sources: variability in the phenomenon being tested, intraobserver and interobserver variability, and the variability in the test itself. To minimize the variability in the phenomenon being measured (i.e., the sympathetic innervation of the myocardium), the present study enrolled heart failure subjects whose clinical condition had been stable over the previous few months and was expected to remain stable between imaging visits. To minimize variability in the calculation of the H/M, the same reader derived the value from both images for each subject. Thus, this study was designed to increase the likelihood that any discrepancy between the test and retest results would be due to variability in the measurement technique itself.

The results clearly demonstrate that the planar H/M ratio is a highly consistent measurement when the clinical circumstances are stable. The study population consisted of 47 stable Class II and III NYHA heart failure patients with LVEF shown to be stable at $\leq$ 35%. They each underwent two ^{123}I-*m*IBG

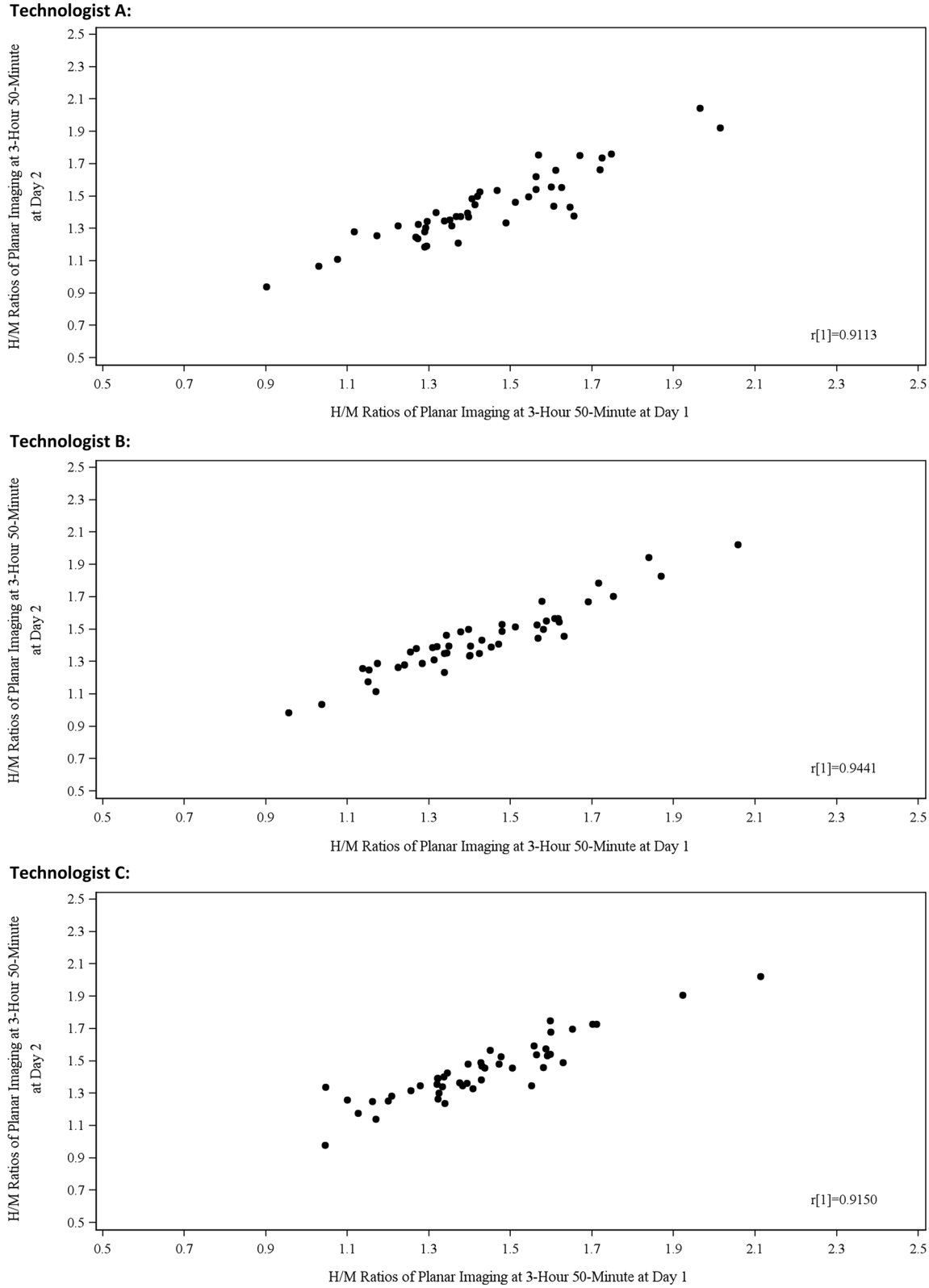

Figure 4. Scatter-plots of individual readers showing subject by subject H/M ratio results initial vs second image acquisitions.

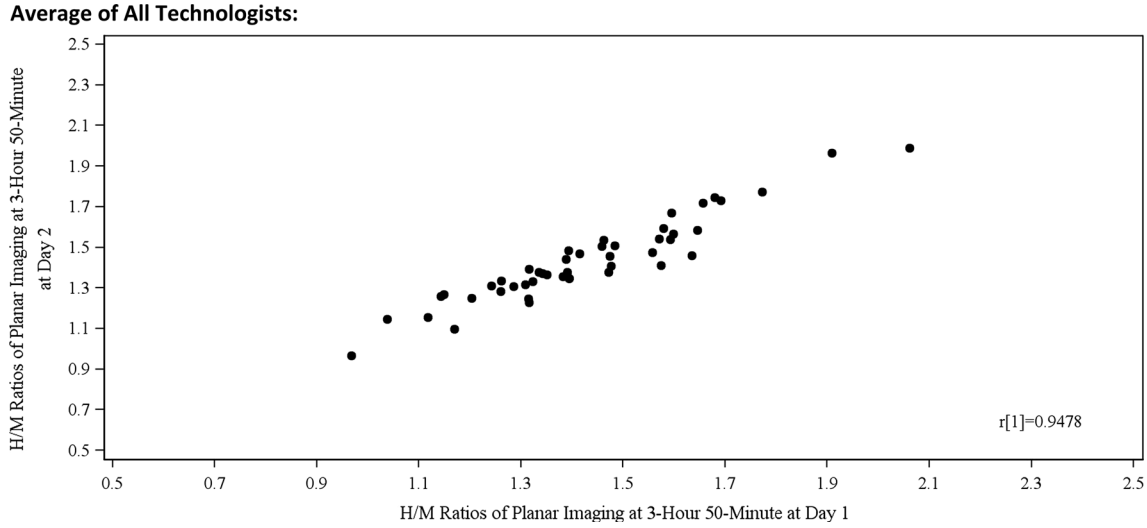

Figure 4. con tinued.

examinations on the same gamma camera within 5 to 14 days. Each imaging study was processed independently by three trained readers using standard procedures for defining heart and mediastinum ROIs, from which the H/M ratio was calculated. The mean 3-hours 50-minutes H/M ratio difference (absolute values) between the test and retest studies was 0.065, with 95% CI of (0.055, 0.076). The upper bound of the 95% CI was < 0.10. A mean absolute difference of > 0.1 between the paired H/M ratios would limit the clinical utility of the test for reliably identifying low-risk in patients whose results are near the predefined lower limit of normal (H/M = 1.6). Overall, the study was successful in demonstrating that the H/M ratio on 3-hours 50-minutes planar ^{123}I-*m*IBG imaging is highly consistent as the upper bound of the 95% CI on the mean test–retest difference in H/M ratio was < 0.10.

Inter-Reader Reproducibility

Although the procedure for deriving both myocardial and mediastinum average counts per pixel is detailed, the current study demonstrates the very high concordance that is achieved when trained nuclear technologists independently perform the measurements. The mean determinations for both initial and subsequent studies, and the differences between the two studies, were almost identical among the 3 readers, as shown by the tight standard deviations and ranges between readers in Table 2. The scatter-plots (Figure 4) demonstrate high correlation coefficients with few clinically significant differences between the two computations. Analysis of the few outliers determined that these were secondary to deviations from the specified protocol. Figure 5 shows one such case, where the mediastinum ROI is clearly misplaced. The accurate placement of heart and mediastinum ROI's can be clearly recognized upon visual review of the stored image.

To our knowledge, ours is the only study that has examined reproducibility of the H/M ratio in such a comprehensive manner—that is, the entire procedure including 2 image acquisitions separated by 5 to 14 days and three technologists independently placing heart and mediastinum regions of interest. The mean spread between the 3 technologists was only 0.017 (Table 4). Veltman et al.[3] had technologists rescore the same image set and reported an interobserver variability of 0.04 and an intraobserver variability of 0.008.

Prior Studies Examining Reproducibility of ^{123}I-*m*IBG Studies

Only a few studies have reported on the intrinsic variability of H/M results when the same patient has undergone sequential testing using the same or similar equipment and imaging protocol. Kasama et al.[4] reimaged 30 patients with stable dilated cardiomyopathy after 6 months. In the 15 patients treated with spironolactone, the H/M ratio improved from 1.64 ± 0.20 to 1.86 ± 0.27. In the other 15 patients who had no change in therapies between the sequential tests, the H/M ratio at rest was 1.65 ± 0.2 initially and 1.63 ± 0.15 after 6 months. In a similar study[5] of 50 patients tested at baseline and after 6 months, the 25 patients treated with candesartan had an improvement in H/M ratio from 1.87 ± 0.24 to 2.00 ± 0.22, compared to the 25 patients

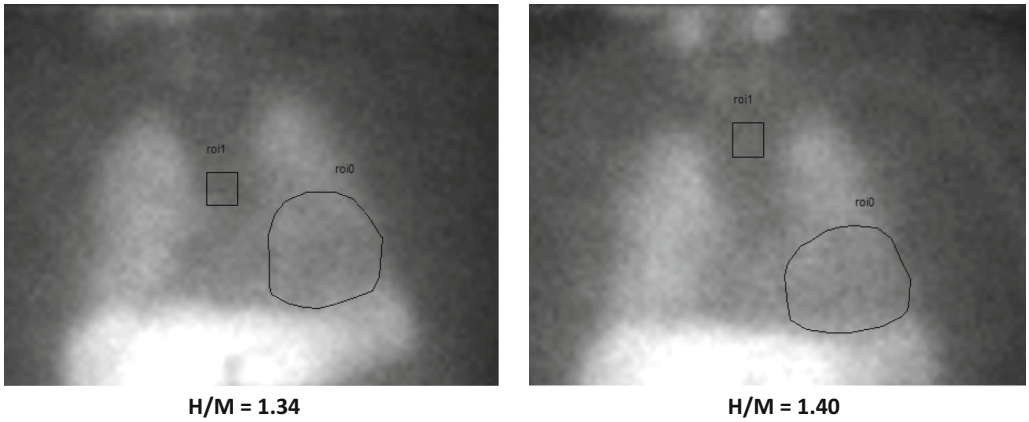

Figure 5. An example of an erroneously place mediastinal region of interest. The H/M ratio will be significantly affected if the prespecified analysis is not performed correctly.

Table 4. Test-retest analysis of heart/mediastinum (h/m) ratio on planar scintigraphy by individual blinded reader

Variable	Statistic	Reader A	Reader B	Reader C	Mean of A, B, and C[a]
H/M at 3 hours 50 minutes in Visit 1	N[b]	46	47	47	47
	Mean (SD)	1.435 (0.2238)	1.430 (0.2220)	1.427 (0.2115)	1.429 (0.2160)
	Median	1.401	1.400	1.408	1.395
	Min, max	0.90, 2.01	0.96, 2.06	1.05, 2.11	0.97, 2.06
	95% CI	1.368, 1.501	1.364, 1.495	1.365, 1.489	1.365, 1.492
H/M at 3 hours 50 minutes in Visit 2	N[b]	47	47	47	47
	Mean (SD)	1.422 (0.2229)	1.436 (0.2069)	1.441 (0.1945)	1.433 (0.2048)
	Median	1.376	1.395	1.401	1.392
	Min, max	0.94, 2.04	0.98, 2.02	0.98, 2.02	0.97, 1.99
	95% CI	1.356, 1.487	1.375, 1.497	1.384, 1.498	1.373, 1.493
Absolute difference in H/M at 3 hours 50 minutes between Visit 1 and 2 for each subject	N[b]	46	47	47	47
	Mean (SD)	0.070 (0.0612)	0.060 (0.0413)	0.067 (0.0537)	0.065 (0.0348)
	Median	0.050	0.054	0.057	0.062
	Min, max	0.00, 0.28	0.00, 0.17	0.01, 0.29	0.01, 0.18
	95% CI	0.052, 0.088	0.048, 0.072	0.051, 0.083	0.055, 0.076
	p value[#]	< 0.0001	< 0.0001	< 0.0001	< 0.0001

The 95% confidence intervals (CI) were estimated under the normal distribution assumption and were calculated as mean ± [1.96* standard deviation/square root of sample size]
CI, Confidence interval; *Max*, maximum; *Min*, minimum; *SD*, standard deviation
#*p* value is based on the one-sample *t* test
[a]Mean of the non-missing values from the 3 technologists. All non-missing evaluations were averaged per subject. These results were then summarized overall for all subjects
[b]*N* = Images deemed diagnostically evaluable by the technologist

whose therapy did not change in whom the H/M ratio was 1.84 ± 0.27 at baseline and 1.86 ± 0.27 at 6 months. In these studies, therefore, the mean H/M ratio variability of 0.02 is slightly smaller than our mean change of 0.065, but the standard deviation in our study was remarkably small considering the multicenter basis and the use of three independent readers.

This was the first prospective trial to examine the safety of two administrations of AdreView™ within a short time interval, and no safety signal was identified.

Fifty-one subjects received 101 administrations of AdreView™, and there were a total of five treatment emergent adverse events in four subjects. Only one was of moderate intensity and no adverse events were judged as related to the study drug. The most common one (injection site reaction, $n = 2$) was also the most commonly observed in the pivotal AdreView™ trials (AdreView™ PI). Consistent with previous prospective trials and more than 20 years of clinical experience, AdreView™ was well tolerated and there were no new safety concerns raised by the results of this study.

NEW KNOWLEDGE GAINED

The current study establishes that the H/M ratio as measured on the same Anger camera in stable heart failure patients on two different occasions is a robust measurement, varying by less than 0.1. Furthermore, it shows that with training and adherence to a structured approach, three technologists working independently can attain virtually identical H/M ratios.

LIMITATIONS

The calculations of the H/M ratios were done by trained nuclear technologists after undertaking comprehensive training and qualification based on test scores. Thus, the findings of reproducibility of H/M ratios demonstrated in the current study may not be generalizable to situations where technologists have not received formal training. However, the Veltman study referenced above[3] showed good agreement in derived H/M ratios between highly experienced technologists and one with 2 hours of formal instruction. Nevertheless, both studies serve to highlight a point that measurement variables employed in clinical decision making should undergo proper evaluation and quality control by individual laboratories. Hence each nuclear laboratory should train designated personnel in ^{123}I-*m*IBG scans and H/M calculation and put forth adequate quality control measures to ensure reproducibility in their clinical setting. Interpreting physicians should critically inspect the placement of the heart and mediastinum regions of interest as part of the image interpretation quality control.

When 3-hours 50-minutes H/M ratios are rounded to 1 decimal place (e.g., 1.3, 1.4, and 1.5), it is important to appreciate that as the 1.6 threshold for lower risk[2] is approached, exercise of due caution is advisable, due to the uncertainty indicated by the standard deviation and 95% CI on the mean absolute difference in H/M. The clinician should be circumspect in designation of patients as being above or below the 1.6 threshold demonstrated to dichotomize subjects into lower and higher event-risk subpopulations.

This study employed only Anger cameras with low-energy high-resolution collimators. As such, for purposes of determining changes in individual patients, the study results are only robust when the same patient is imaged using the same Anger camera with low-energy high-resolution collimation, and no attenuation correction. Further study is needed before extrapolating the findings to medium energy collimators and to non-Anger cameras.

CONCLUSION

This study has successfully established the reliability and the reproducibility of ^{123}I-*m*IBG planar image H/M ratio determinations on a replicate examination performed within 5 to 14 days on the same Anger camera with low energy high-resolution collimators. For the 10-minutes planar image obtained at 3 hours and 50 minutes, the upper bound of the 95% CI on the mean test–retest difference in H/M ratio was < 0.10. A mean absolute difference of > 0.10 between the paired H/M ratios would limit the clinical utility of the test for reliably identifying low-risk in patients whose results are near the predefined lower limit of normality (H/M = 1.6). Additionally, no safety concerns were raised in repeated administration.

Disclosure

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