ORIGINAL ARTICLE

Cardiac 123I-MIBG Parameters at 4 Hours Derived from Earlier Acquisitions Times

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Abstract

Background: The clinical implementation of cardiac 123Iodine-meta-iodobenzylguanidine (123I-MIBG) scintigraphy for the evaluation of prognosis in patients with heart failure (HF) is still limited. This may partially be related to the long examination time with an almost 4 hour delay between the early and late acquisition. Additionally, outcome derived at different late acquisition times cannot be compared with each other. To assess whether earlier acquisition time of the late image is justified, the aim of present study was to evaluate in a HF patient cohort whether a developed direct comparison method for cardiac 123I-MIBG imaging enables comparison of washout rates and late heart-to-mediastinum (H/M) ratios from 1 to 3 hours post injection (pi) with measurements at 4 hours pi.

Methods: Forty-eight patients with HF were clinically referred for cardiac 123I-MIBG scintigraphy. The washout rate and late H/M ratio at 4 hours pi were estimated with a previous published linear model from heart and mediastinal counts at 1, 2 and 3 hour pi and compared with the actual values at 4 hour pi.

Results: The estimated washout rate and late H/M ratio at 4 hours pi from counts at 1 hour pi demonstrated large differences. However, the average estimated late H/M ratio at 4 hours pi derived from 2 and 3 hours pi did not differ with the actual late H/M ratio at 4 hours pi (P=0.84 and P=0.06). As well as, the actual washout rate at 4 hours pi and estimated washout rate at 4 hours pi derived from 3 hours pi did not differ significantly (P=0.22). Yet, the mean estimated washout rate at 4 hours pi derived from the acquisition at 2 hours pi showed a difference compared with the actual washout rate at 4 hours pi (25 ± 19 vs. 34 ± 17, P<0.001).

Conclusions: The direct comparison method for cardiac 123I-MIBG imaging enables accurate estimation of the actual late H/M ratio and washout rate at 4 hours pi derived from the acquisitions at 3 hours pi. The acquisition at 2 hours pi should only be performed in exceptional cases when clinically necessary because of the existing difference between the actual and estimated washout rate at 4 hours pi derived from 2 hours pi.

Keywords: 123Iodine-meta-iodobenzylguanidine, Heart-to-mediastinum ratio, Washout rate, Estimation, Acquisition, Heart failure
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The increasing prevalence of heart failure (HF) worldwide is a major healthcare problem (1). In patients with HF the cardiac sympathetic nervous system is activated, which can be visualized with ^{123}Iodine-meta-iodobenzylguanidine (^{123}I-MIBG) imaging (2); the procedure of ^{123}I-MIBG imaging consists of an early acquisition (15 minutes post-injection [pi]) and a late acquisition (varying between 3 and 4 hours after tracer injection). Different parameters can be extracted from these images. First, the late heart-to-mediastinum ratio (H/M ratio), which is calculated by dividing the cardiac ^{123}I-MIBG uptake by the mediastinal ^{123}I-MIBG uptake (3). It represents the relative distribution of cardiac sympathetic nerve terminals, offering information about neuronal function from uptake to release. The other ^{123}I-MIBG parameter is the myocardial washout rate representing the tracer washout between the early and late planar ^{123}I-MIBG acquisition and therefore the washout rate provides an index of the sympathetic drive.

Several studies have shown that patients with HF and a low late H/M ratio and/or an increased washout rate, are at increased risk for cardiac death and arrhythmic events (4-6). However, the clinical implementation of this technique is still limited. This may partially be related to the long examination time with an almost 4 hour delay between the early and late acquisition. Additionally, outcome derived at different late acquisition times cannot be compared with each other. This is of importance since most Japanese studies in contrast to Western studies perform the late acquisition at 3 hours pi (7,8).

Recently, a more time-efficient cardiac ^{123}I-MIBG protocol demonstrated only small differences between the late H/M ratio 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi, suggesting that the late imaging can be performed at an earlier stage (9). This will shorten the acquisition time and may increase patient comfort. However, the differences between the washout rates were larger and increased over time, which makes comparison of the washout rate measured at different acquisition times difficult. Okuda et al. recently developed a linear model to ease comparison of the washout rate at 3 hours pi with 4 hours pi (10). Yet, no external validation has taken place in a HF cohort and it is unknown whether this model can be applied to estimate the washout rate and the late H/M ratio at 4 hours pi from even earlier acquisitions times than 3 hours pi.

To assess whether earlier acquisition time of the late image is justified, the present study evaluated whether the linear model based formula enables comparison of washout rates and late H/M ratios determined from acquisition times at 1 to 3 hours pi with the actual measurements at 4 hours pi in a cohort of HF patients.

Methods

Patients

The study population consisted of patients included in a previous study focusing on the change in late H/M ratio between 1, 2 and 3 hours pi in comparison with the late H/M ratio at 4 hours pi (9). The inclusion criteria for the study population were age between 18 and 74 years and symptoms of HF New York Heart Association class (NYHA) II-IV. Excluded for that study were patients with severe shortness of breath who were unable to lie flat for several times under a gamma camera. Previous study concentrated on the determination of the late H/M ratio at 1, 2, 3 and 4 hours pi. The current evaluation will focus on a recently developed direct comparison method for cardiac ^{123}I-MIBG imaging to evaluate whether this method provides an accurate estimation of the late H/M ratio and washout rate at 4 hours pi derived from earlier (1, 2 and 3 hours pi) acquisitions to overcome differences in late H/M ratios and washout rates between different acquisitions. The population consisted of 50 patients with HF and NYHA II-IV from two centers (Leiden, Netherlands and Pisa, Italy) clinically referred for cardiac ^{123}I-MIBG scintigraphy between 2012-2015. The study was approved by the Medical Ethical Committee from the Leiden University Medical Centre (the Netherlands) and the Medical Ethical Committee from the Fondazione Toscana/CNR Gabriele Monasterio (Italy) and complied with the Declaration of Helsinki. All patients signed the informed consent form.

^{123}I-MIBG data acquisition and analysis

The protocol of the ^{123}I-MIBG data acquisition and analysis have been described in detail (9). In brief, after an intravenous bolus injection of 185 MBq ^{123}I-MIBG (AdreView; GE Healthcare, Princeton NJ) 5 frontal planar images of the chest were obtained 15 minutes pi (early scan) and 1, 2, 3 and 4 hours pi (late scans). All examinations were performed with a Siemens ECAM (Pisa, Italy) or a Toshiba GCA 7200/PI (Leiden, The Netherlands) scanner with dual head gamma cameras in combination with low-energy high-resolution collimators with a matrix 256 x 256. The Siemens ECAM scanner has a 1.23 zoom factor and 1.9 mm pixel size and the Toshiba scanner a 1.5 zoom factor and 1.4 mm pixel size.

Post-processing enhanced a manually drawn polygonal region-of-interest (ROI) over the myocardium including the left cavity and a rectangular ROI upon the upper half of the mediastinum. The H/M ratio was calculated by dividing the mean counts per pixel within the cardiac ROI by the mean counts per pixel in the mediastinal ROI. The washout rate with correction for background and physical decay of ^{123}I was calculated with the following formula: $WR_{BKG\ and\ decay\ corrected} = [(\{H\}_e - \{M\}_e) - (\{H\}_l - \{M\}_l \times {}^{123}I\ decay\ correction)] / (\{H\}_e -$

{M}$_e$) x 100.

In this formula {H} represents the mean counts per pixel in the cardiac ROI and {M} represents the mean counts per pixel in the mediastinal ROI in the early ($_e$) and late ($_l$) images (11).

Estimation of ^{123}I-MIBG parameters

To estimate the mean cardiac counts per pixel of ^{123}I-MIBG at 4 hours derived from acquisitions at 1, 2 and 3 hours pi, the following formula was extracted from the linear regression model between 3 and 4 hours pi, provided by Okuda et al. (10): $\{H\}_{ih\text{-}estimated} = (1.039^{i\text{-}j} \times \{H\}_{jh\text{-}actual}) - ((1.039^{i\text{-}j\text{-}1} + 1.039^{i\text{-}j\text{-}2} + ... + 1) \times 0.067 \times \{H\}_e)$. $\{H\}_{ih\text{-}estimated}$ represents the estimated mean count density in the cardiac ROI at i hours pi and $\{H\}_{jh\text{-}actual}$, the actual mean count density in the cardiac ROI at j hours. $\{H\}_e$ represents the mean count density in the cardiac ROI of the early image at 15 minutes. Thus, the formulas for the estimated mean cardiac counts per pixel of ^{123}I-MIBG at 4 hours from acquisitions at 1, 2 and 3 hours pi were:

Cardiac counts at 1 hour pi: $\{H\}_{4h\text{-}estimated} = (1.122 \times \{H\}_{1h\text{-}actual}) - (0.209 \times \{H\}_e)$,

Cardiac counts at 2 hours pi: $\{H\}_{4h\text{-}estimated} = (1.080 \times \{H\}_{2h\text{-}actual}) - (0.137 \times \{H\}_e)$,

Cardiac counts at 3 hours pi: $\{H\}_{4h\text{-}estimated} = (1.039 \times \{H\}_{3h\text{-}actual}) - (0.067 \times \{H\}_e)$.

In addition, to estimate the mean mediastinal counts per pixel of ^{123}I-MIBG at 4 hours derived from acquisitions at 1, 2 and 3 hours pi the following formula was extracted from the linear regression model between 3 and 4 hours pi, provided by Okuda et al(10): $\{M\}_{ih\text{-}estimated} = 0.967^{i\text{-}j} \cdot \{M\}_{jh} - ((0.967^{i\ i\text{-}j\text{-}1} + 0.967^{i\ i\text{-}j\text{-}2} + ... + 1) \times 0.003 \times \{M\}_e)$. $\{M\}_{ih\text{-}estimated}$ represents the estimated mean count density in the mediastinal ROI at i hours pi and $\{M\}_{ih\text{-}actual}$, the actual mean count density in the cardiac ROI at j hours. $\{M\}_e$ represents the mean count density in the mediastinal ROI of the early image at 15 minutes. Consequently, the formulas to calculate the estimated mean mediastinal counts per pixel of ^{123}I-MIBG at 4 hours from acquisitions at 1, 2 and 3 hours pi were:

Mediastinal counts at 1 hour pi: $\{M\}_{4h\text{-}estimated} = (0.904 \times \{M\}_{1h\text{-}actual}) - (0.009 \times \{M\}_e)$,

Mediastinal counts at 2 hour pi: $\{M\}_{4h\text{-}estimated} = (0.935 \times \{M\}_{2h\text{-}actual}) - (0.006 \times \{M\}_e)$,

Mediastinal counts at 3 hour pi: $\{M\}_{4h\text{-}estimated} = (0.967 \times \{M\}_{3h\text{-}actual}) - (0.003 \times \{M\}_e)$.

Afterwards, the late H/M ratio and myocardial washout rate with background and decay correction at 4 hours pi were calculated from the estimated mean cardiac and mediastinal counts per pixel at 4 hours pi.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation and non-normally distributed variables as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

To evaluate the differences in estimated and actual measured cardiac and mediastinal counts at 4 hours pi, the following analyses were performed. First, the estimated cardiac and mediastinal counts derived from 1, 2 and 3 hours pi were compared with the actual cardiac and mediastinal counts at 4 hours pi using a paired samples t test. In addition, the agreement of the estimated and the actual cardiac and mediastinal counts at 4 hours was evaluated with the Pearson's correlation and Bland Altman analysis. Similarly, these analyses were repeated for the comparison of the estimated and actual late H/M ratios and washout rates.

Furthermore, the sensitivity and specificity for the threshold of ＜1.6 of the actual late H/M ratio were calculated for the estimated late H/M ratio at 4 hours pi derived from the 1-, 2- and 3-hour scan (4). As well as, the sensitivity and specificity for the threshold of ≥27% of the actual washout rate at 4 hours pi were computed for the estimated washout rate at 4 hours pi derived from the 1-, 2- and 3-hour scan (12).

Statistical analysis was performed using SPSS software (Version 22.0, SPSS IBM Corp., Armonk, New York, USA). A two-sided P-value of ＜0.05 was considered statistically significant.

Results

Patients

The clinical characteristics of the patients are depicted in Table 1. Of the study population 2 patients (4%) were excluded since 1 patient withdrew his informed consent after the examination and 1 patient did not have an acquisition 4 hours pi due to logistic reasons. The final population comprised 48 patients with HF of which 77% (37/48) were male with a mean age of 64 ± 9 years.

Planar ^{123}I-MIBG image analysis

Results of the planar ^{123}I-MIBG images of the early and late scans at 1, 2, 3 and 4 hours pi and the actual acquisition time-intervals after ^{123}I-MIBG injection are shown in Table 2. In the total study population the late H/M ratio decreased over time and was 1.60 ± 0.18 at 1 hour, 1.56 ± 0.19 at 2 hours pi and 1.54 ± 0.19 at 3 hours pi and differed all significantly from the late H/M ratio of 1.52 ± 0.20 at 4 hours pi (P<0.001, P<0.001 and P=0.02, respectively). The washout rate increased over time from 11 ± 11 at 1 hour pi, 21 ± 16 at 2 hours pi, 28 ± 17 at 3 hours pi to 34 ± 17 at 4 hours pi. The washout rate at 1, 2 and 3 hours were all significantly different from the washout rate at 4 hours pi (all P<0.001).

Estimated and actual ^{123}I-MIBG parameters

The estimated mean cardiac and mediastinal counts per

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Table 1 Characteristics of the study population

Patient characteristic	Total group (N=48)
Age (years)	64 ± 9
Sex (male)	37 (77%)
Height (cm)	176 ± 9
Weight (kg)	85 ± 14
Cardiovascular risk factors	
Diabetes mellitus[*]	7 (15%)
Obesity, BMI ≥ 30 (kg/m²)	7 (15%)
Family history of CVD[†]	19 (40%)
Hypercholesterolemia[‡]	26 (54%)
Hypertension[§]	29 (60%)
Current smoker	8 (17%)
Ejection fraction (%)	31 (IQR 25-37)
CRT-D / ICD therapy	31 (65%)
Medication	
ACE-/AT II-inhibitor	44 (92%)
Beta blocker	39 (81%)
Calcium antagonist	3 (6%)
Lipid-lowering agent	34 (71%)
Antiplatelet/OAC therapy	41 (85%)
Diuretics	37 (77%)
Oral antidiabetics	8 (17%)
Insulin	3 (6%)
Nitrates	3 (6%)
Ischemic CMP	25 (52%)
NYHA class	
I	11 (23%)
II	26 (54%)
III	11 (23%)
NT-proBNP (pg/L)	811 (IQR 419-1265)

Abbreviations: ACE: angiotensin converting enzyme inhibitor; AT-II: angiotensin-II; BMI: Body Mass Index, CRT-D: cardiac resynchronization therapy defibrillator; CVD: cardiovascular disease; HF: heart failure; ICD: implantable cardioverter defibrillator; IQR: interquartile range; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; OAC: oral anticoagulant.
Definitions: [*]Self-reported history of Diabetes Mellitus and/or treatment with antidiabetics, [†]presence of coronary artery disease in first-degree family members at age <55 years in men and <65 years in women, [‡]Self-reported history of hypercholesterolemia and/or treatment with lipid-lowering drugs, [§]Self-reported history of hypertension and/or use of antihypertensive medication, or a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.

Table 2 ^{123}I-MIBG scintigraphy results

MIBG scintigraphy	Total group (N=48)
Actual acquisition time after injection (in minutes)	
Early scan	15 (IQR 13-19)
Late scan 1H	66 (IQR 62-71)
Late scan 2H	118 (IQR 115-122)
Late scan 3H	177 (IQR 176-182)
Late scan 4H	239 (IQR 236-245)
Heart/mediastinum ratio	
Early scan	1.60 ± 0.15
Late scan 1H	1.60 ± 0.18
Late scan 2H	1.56 ± 0.19
Late scan 3H	1.54 ± 0.19
Late scan 4H	1.52 ± 0.20
Washout rate[a] (%)	
Late scan 1H	11 ± 11
Late scan 2H	21 ± 16
Late scan 3H	28 ± 17
Late scan 4H	34 ± 17

Abbreviations: H: hour(s); HF: heart failure; IQR: interquartile range.
Definitions: Washout rate with ^{123}I-decay and background correction

pixel for 4 hours pi determined from the cardiac and mediastinal counts at 1, 2 and 3 hours pi are depicted in Table 3.

The Pearson's correlation was excellent between the estimated cardiac counts at 4 hours pi determined from the late acquisitions at 1, 2 and 3 hours pi and the actual cardiac counts at 4 hours pi (r=0.995, r=0.996 and r=0.996; all P <0.001, Fig. 1). In the Bland-Altman analysis there was a bias of -11.4 (95%CI-30.4；7.6), -5.8 (95%CI-15.8；4.2) and -2.5 (95%CI -9.0；4.0) between the actual and estimated cardiac counts at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively.

Depicted in Fig. 2, the estimated mediastinal counts at 4 hours pi determined from the late acquisitions at 1, 2 and 3 hours pi and the actual mediastinal counts at 4 hours pi demonstrated excellent Pearson's correlations (r=0.994, r= 0.994, r=0.995, respectively, all P <0.001). In the Bland-Altman analysis there was a bias of -6.1 (95%CI-16.2；4.1), -3.7 (95%CI-10.1；2.7) and -1.9 (95%CI -6.5；2.7) between the actual and estimated mediastinal counts at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively.

Estimated and actual late H/M ratio

The mean estimated late H/M ratio at 4 hours pi derived from the counts at 1, 2 and 3 hour pi were 1.58 ± 0.19, 1.52 ± 0.20 and 1.50 ± 0.20, respectively. Compared with the actual late H/M ratio at 4 hours pi (1.52 ± 0.20) the differences with the estimated late H/M ratio at 4 hours pi from 1, 2 and 3 hours pi were 0.06, 0.002 and -0.015, respectively (P<0.001, P=0.84 and P=0.06, respectively).

There was a positive correlation between the actual late H/M ratio at 4 hours pi and estimated late H/M ratio at 4 hours

Table 3　Actual and estimated cardiac and mediastinal counts per pixel at 4 hours calculated from 1, 2 and 3 hours pi.

	Estimated counts at 4 hours pi	Actual counts at 4 hours pi	Difference between estimated and actual counts at 4 hours pi	P value
cardiac counts per pixel				
H_1	55 ± 39	44 ± 30	11 (95%CI 9;14)	<0.001
H_2	50 ± 34	44 ± 30	6 (95%CI 4;7)	<0.001
H_3	47 ± 32	44 ± 30	2 (95%CI 1;3)	<0.001
Mediastinum counts per pixel				
M_1	35 ± 23	29 ± 19	6 (95%CI 5;8)	<0.001
M_2	33 ± 21	29 ± 19	4 (95%CI 3;5)	<0.001
M_3	31 ± 20	29 ± 19	2 (95%CI 1;3)	<0.001

Abbreviations: H_1: mean heart counts per pixel from 1 hour pi, H_2: mean heart counts per pixel from 2 hour pi, H_3: mean heart counts per pixel from 3 hour pi, M_1 mean mediastinal counts per pixel from 1 hour pi, M_2 mean mediastinal counts per pixel from 2 hour pi, M_3 mean mediastinal counts per pixel from 3 hour pi.
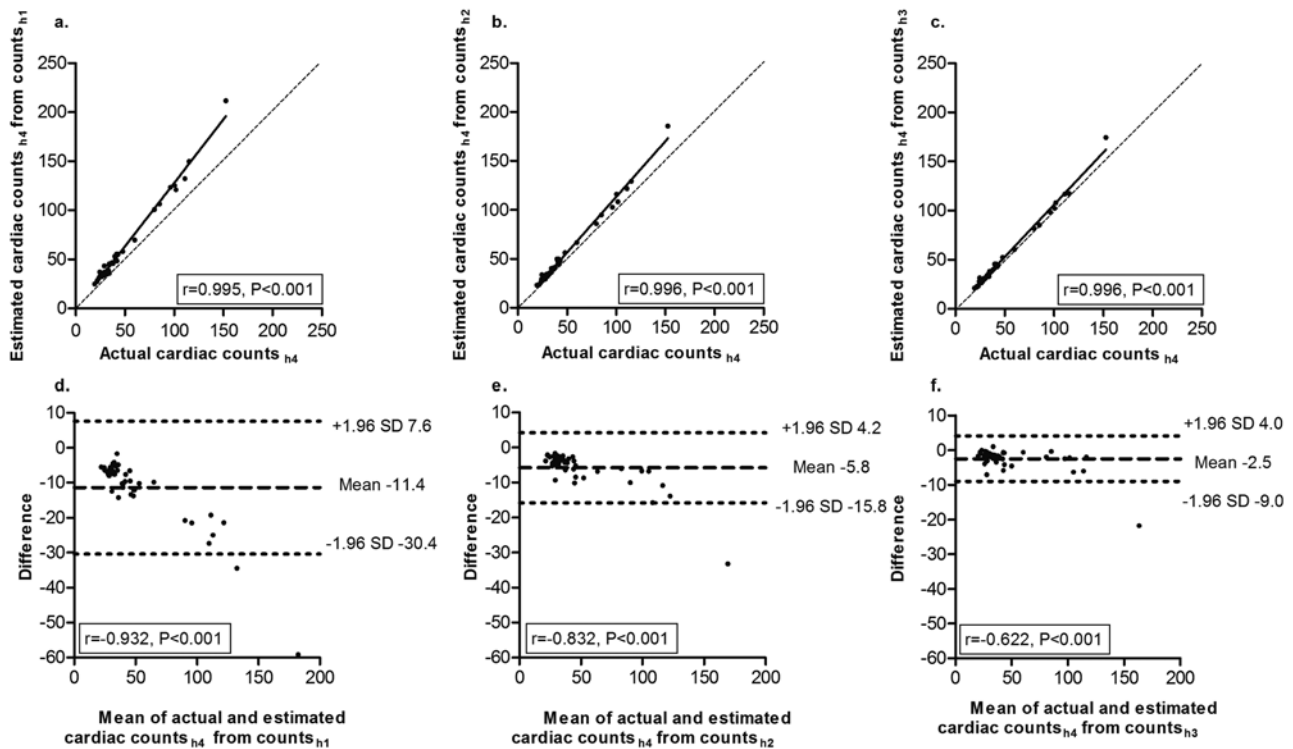
Fig. 1　Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated cardiac counts at 4 hours pi from the cardiac counts at 1, 2 and 3 hours pi.

pi derived from the scans at 1, 2 and 3 hours pi (Fig. 3). The Pearson's Correlation was excellent between the estimated late H/M ratio at 4 hours pi derived from 1, 2 and 3 hours pi and the actual late H/M ratio at 4 hours pi, r=0.914, r=0.950 and r=0.965, respectively (all P<0.001). In the Bland-Altman analysis there was a bias of -0.059 (95%CI-0.216; 0.098), -0.0018 (95%CI-0.124; 0.121) and 0.015 (95%CI-0.087; 0.117) between the actual and estimated late H/M ratio at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively. No correlation existed between the difference and the mean of the actual and estimated late H/M ratios

obtained from 1, 2 and 3 hours pi.

Of the 34 patients with an actual late H/M ratio <1.6, 25 (74%), 29 (85%) and 31 (91%) patients had an estimated late H/M ratio at 4 hours pi <1.6 derived from 1, 2 and 3 hours pi, respectively. The sensitivity and specificity for the actual late H/M ratio <1.6 for the estimated late H/M ratio at 4 hours pi derived from the 1-hour scan were 74% and 93%, respectively. For the estimated late H/M ratio at 4 hours pi derived from 2 and 3 hours pi the sensitivity and specificity were 85% and 93%, 91% and 86%, respectively.
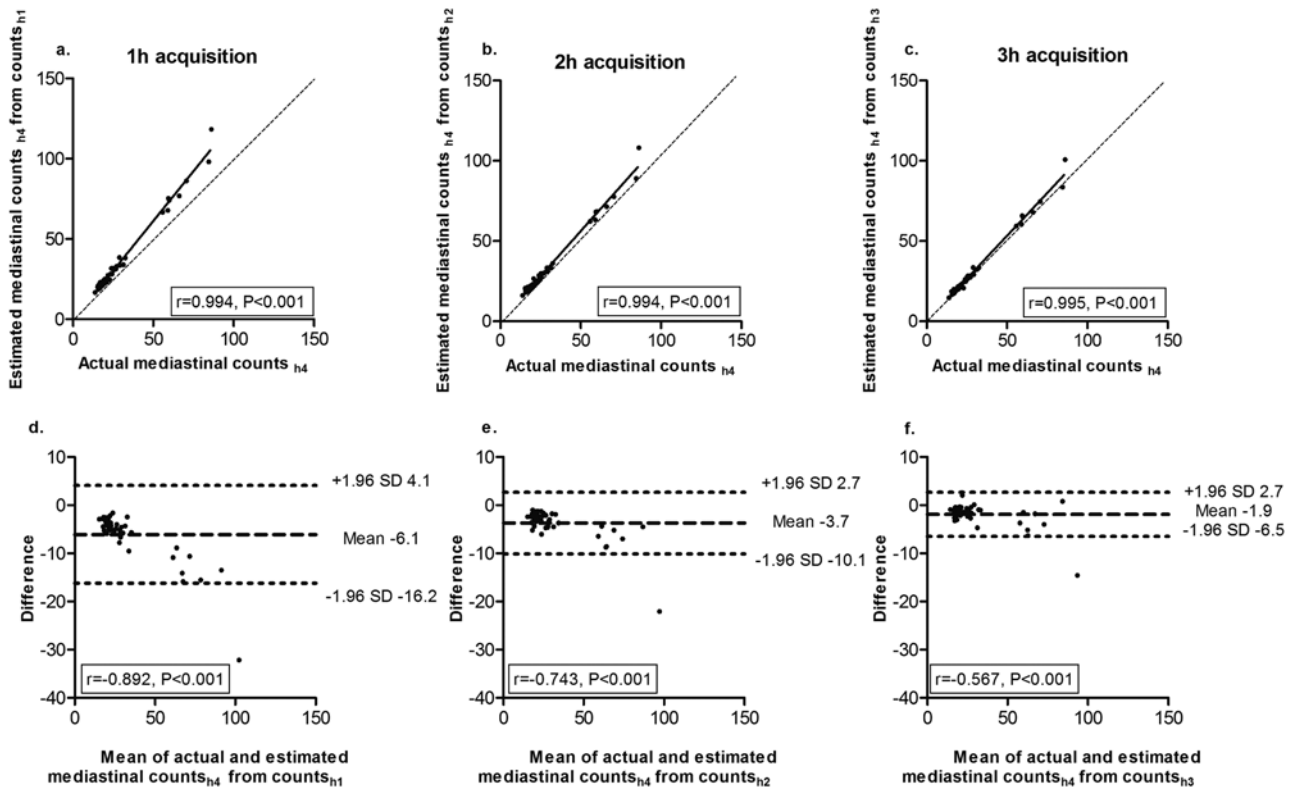
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Fig. 2 Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated mediastinal counts at 4 hours pi from the mediastinal counts at 1, 2 and 3 hours pi.
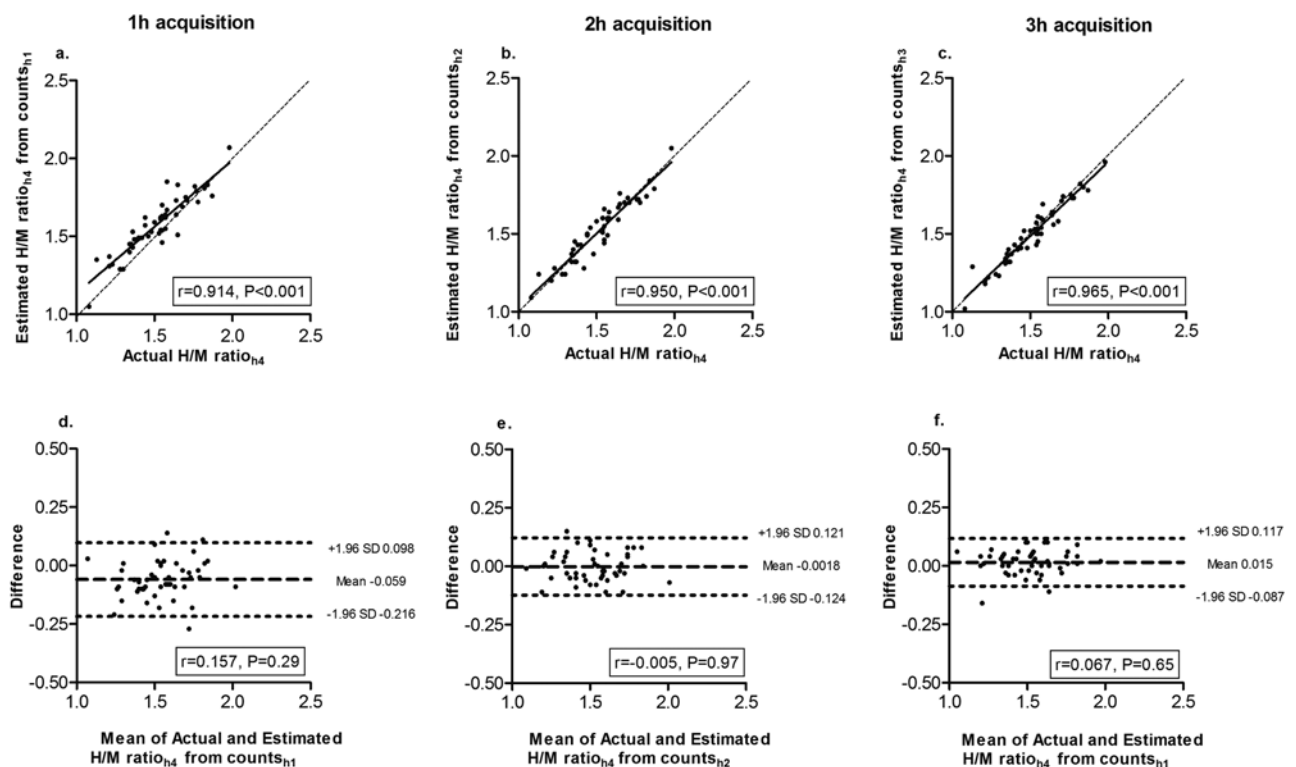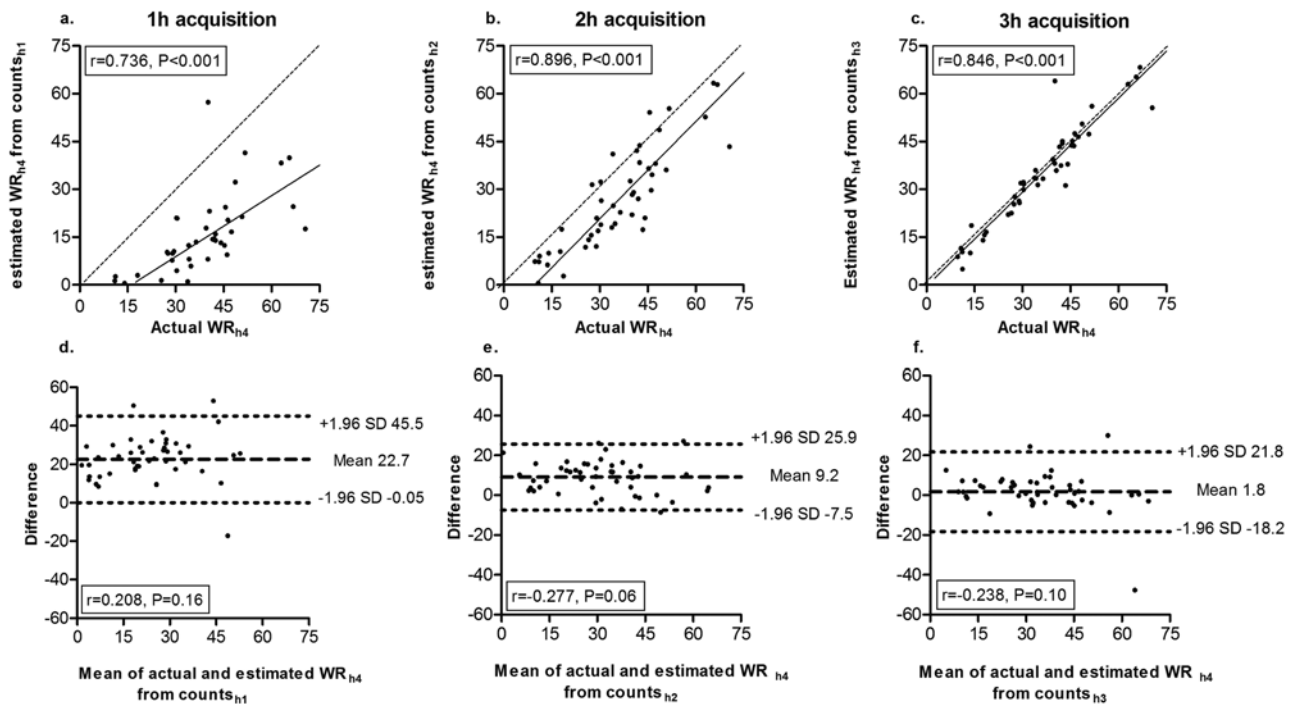

Fig. 3 Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated heart-to-mediastinum ratio at 4 hours pi from the cardiac and mediastinal counts at 1, 2 and 3 hours pi.

Fig. 4 Pearson's correlation and Bland-Altman analysis of the relationship between the actual washout rate at 4 hours and estimated washout rate at 4 hours from the late acquisitions at 1, 2 and 3 hours pi.

Estimated and actual washout rate

The mean estimated washout rate (with background and ^{123}I-decay correction) at 4 hours pi calculated from the acquisitions at 1 and 2 hours pi differed significantly from the actual washout rate at 4 hours pi, 12 ± 15 and 25 ± 19 in comparison with 34 ± 17 (both $P<0.001$). The mean estimated washout rate at 4 hours pi derived from 3 hours pi did not differ significantly with the actual washout rate at 4 hours pi, 32 ± 19 and 34 ± 17, respectively ($P=0.22$). There was a positive correlation between the actual washout rate at 4 hours pi and the estimated washout rate at 4 hours pi derived from 1, 2 and 3 hours pi (Fig. 4). The Pearson's Correlation of the actual washout rate at 4 hours and the estimated washout rate at 4 hours obtained from the scan at 1 hour pi was strong ($r=0.736$) and excellent for the estimated washout rate at 4 hours from the 2- and 3-hour pi scan ($r=0.896$ and $r=0.846$, respectively). In the Bland-Altman analysis for the actual and estimated washout rate there was a bias of 22.7 (95%CI 0；45), 9.2 (95%CI -7.5；25.9) and 1.8 (95%CI -18.2；21.8) between the actual and estimated washout rate at 4 hours pi calculated from cardiac and mediastinum counts at 1, 2 and 3 hours pi. No correlation existed between the difference and the mean of the actual washout rate at 4 hours pi and the estimated washout rate at 4 hours pi derived from 1,2 and 3 hours pi.

Of the 35 patients with an actual washout rate at 4 hours pi $\geq 27\%$, 8 (23%), 22 (63%) and 31 (89%) patients had an estimated washout rate at 4 hours pi $\geq 27\%$ derived from 1, 2 and 3 hours pi, respectively. The sensitivity and the specificity for the estimated washout rate at 4 hours pi derived from the 1-hour scan were 23% and 100% to determine the actual washout rate $\geq 27\%$. For the estimated washout rate at 4 hours pi derived from 2 and 3 hours pi the sensitivity was 63% and 89%, respectively with at both scanning times a specificity of 100%.

Discussion

The present study demonstrated that by using the direct comparison method for cardiac ^{123}I-MIBG imaging, it is possible to provide an accurate estimation of the actual late H/M ratio and washout rate at 4 hours pi, derived from acquisitions at 3 hours pi.

The timing to acquire late planar myocardial ^{123}I-MIBG images is still 4 hours pi (11). However, several studies calculated the late H/M ratio and/or washout rate from acquisitions at 3 hours pi (7). Recently, we demonstrated in patients with HF only small differences (≤ 0.05) between the late H/M ratio determined at 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi (9). In addition, in the present study the late H/M ratio at 4 hours pi could be accurately estimated from the ratio at 2- and 3-hour scan pi by means of a linear model, in contrast to the 1-hour scan pi. In addition, the sensitivity and specificity of the estimated late H/M ratio derived from 2 and 3 hours pi to determine the actual late H/M ratio at 4 hours pi <1.6 were high. These findings may allow a more time-efficient cardiac ^{123}I-MIBG-imaging protocol.

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The washout rate between the early and several late acquisition times increased from 11±11 between 15 minutes and 1 hour pi to 34±17 between 15 minutes and 4 hours pi. This increase in washout rate over time was also observed by Henderson et al. This study demonstrated in patients with severe dilated cardiomyopathy that the global myocardial ^{123}I-MIBG concentration reduced from 117±41 at 15 minutes to 85±35 and 52±14 at 85 and 240 minutes, respectively (13).

To correct for the increasing washout rate over time Okuda et al. developed a linear model using the early and 3-hour planar image which makes comparison of the washout rate determined at 3 hours pi with 4 hours pi possible (10). In that study, the total population (n=96) was randomly divided into two groups: one group for the creation of a linear regression model between the heart and mediastinal counts at 3 and 4 hours pi and group 2 for the clinical validation. The results demonstrated that the estimated washout rate at 4 hours pi by the linear regression model determined from the early and 3-hour pi scan did not differ from the actual washout rate at 4 hours pi.

Similar results were detected in present HF cohort between the actual and estimated washout rate at 4 hours pi from the 3-hour scan pi. In addition, the sensitivity and specificity for the threshold of ≥27% of the actual washout rate at 4 hours pi were high for the estimated washout rate at 4 hours pi derived from 3 hours pi. Only small differences were found between the actual and estimated washout rate at 4 hours pi from the 2-hour scan pi. Although the specificity for the threshold of ≥27% of the actual washout rate at 4 hours pi was high (100%) for the estimated washout rate at 4 hours pi derived from 2 hours pi, the sensitivity was relatively low (63%). This means that patients with an estimated washout rate ≥27% at 4 hours derived from the 2-hour scan do not need a second scan at 4 hours pi. Within present study population, 22/48 (42%) patients could be excluded for a second scan at 4 hours pi.

A large difference was observed between the actual and estimated washout rate at 4 hours pi derived from the 1-hour pi scan. Therefore, the formula seems not useful for the estimation of the washout rate from the 1-hour pi scan.

In the created formula for the cardiac and mediastinal counts at the acquisition at 1, 2 and 3 hours pi to estimate the counts at 4 hours pi, it is assumed that the clearance of ^{123}I-MIBG is linear over time and that extra-neuronal ^{123}I-MIBG uptake plays no pivotal role. This is in line with data showing that ^{123}I-MIBG clearance has a clear distinction between an early more accelerated phase and a slower linear phase (14). These findings are corroborated by an earlier study by Morozumi et al, which demonstrated in 15 healthy subjects that the mean counts per pixel in the cardiac and upper mediastinal ROI were linear over time (15). In addition, Dae et al. concluded that non-neuronal uptake does not seem to be

operational in humans since there was no ^{123}I-MIBG uptake on early and late planar images present in post-cardiac transplant patients (16). However, in the present study there was an overestimation of the estimated cardiac and mediastinal counts at 4 hours from the 1-hour scan pi which resulted in a lower estimated washout rate and a significant higher mean late H/M ratio compared to the actual numbers. Possibly, the cardiac ^{123}I-MIBG uptake at 1 hour pi and in some extent at 2 hour pi is affected by attenuation of the liver, which is more present at the early hours pi since the clearance time of ^{123}I-MIBG in the liver is shorter (15,17).

Limitations

Since there were differences between the actual and the estimated washout rate at 4 hours pi calculated from the scan 2 hours pi, implementation of the late scan at 2 hours pi to estimate the washout rate at 4 hours pi needs to be evaluated in larger cohorts.

Conclusion

By using the direct comparison method for cardiac ^{123}I-MIBG imaging it is possible to accurately estimate the actual late H/M ratio and washout rate at 4 hours pi, derived from acquisitions at 3 hours pi. This will allow a more time efficient protocol, increase the clinical implementation in patients with HF and ease comparison of ^{123}I-MIBG parameters from acquisitions from 3 with 4 hours pi. The acquisition at 2 hours pi should only be performed in exceptional cases when clinically necessary because of the existing difference between the actual and estimated washout rate at 4 hours pi derived from 2 hours pi.

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