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ORIGINAL ARTICLE

Development and validation of a direct-comparison method for cardiac ^{123}I-metaiodobenzylguanidine washout rates derived from late 3-hour and 4-hour imaging

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Abstract
Purpose The washout rate (WR) has been used in ^{123}I-metaiodobenzylguanidine (MIBG) imaging to evaluate cardiac sympathetic innervation. However, WR varies depending on the time between the early and late MIBG scans. Late scans are performed at either 3 or 4 hours after injection of MIBG. The aim of this study was to directly compare the WR at 3 hours (WR_{3h}) with the WR at 4 hours (WR_{4h}).
Methods We hypothesized that the cardiac count would reduce linearly between the 3-hour and 4-hour scans. A linear regression model for cardiac counts at two time-points was generated. We enrolled a total of 96 patients who underwent planar ^{123}I-MIBG scintigraphy early (15 min) and during the late phase at both 3 and 4 hours. Patients were randomly divided into two groups: a model-creation group (group 1) and a clinical validation group (group 2). Cardiac counts at 15 minutes ($count_{early}$), 3 hours ($count_{3h}$) and 4 hours ($count_{4h}$) were measured. Cardiac $count_{4h}$ was mathematically estimated using the linear regression model from $count_{early}$ and $count_{3h}$.
Results In group 1, the actual cardiac $count_{4h}/count_{early}$ was highly significantly correlated with $count_{3h}/count_{early}$ (r= 0.979). In group 2, the average estimated $count_{4h}$ was 92.8± 31.9, and there was no significant difference between this value and the actual $count_{4h}$ (91.9±31.9). Bland-Altman analysis revealed a small bias of −0.9 with 95 % limits of agreement of −6.2 and +4.3. WR_{4h} calculated using the estimated cardiac $count_{4h}$ was comparable to the actual WR_{4h} (24.3± 9.6 % vs. 25.1±9.7 %, p=ns). Bland-Altman analysis and the intraclass correlation coefficient showed that there was excellent agreement between the estimated and actual WR_{4h}.
Conclusion The linear regression model that we used accurately estimated cardiac $count_{4h}$ using $count_{early}$ and $count_{3h}$. Moreover, WR_{4h} that was mathematically calculated using the estimated $count_{4h}$ was comparable to the actual WR_{4h}.

Keywords Cardiac ^{123}I-MIBG imaging · Washout rate · Cardiac sympathetic innervation · Linear regression model

Introduction

^{123}I-Labelled meta-iodobenzylguanidine (MIBG) cardiac scintigraphy has played an important role in the evaluation of heart failure and neurodegenerative disease [1–5]. The heart-to-mediastinum ratio (HMR) and washout rate (WR) have been used in MIBG imaging to evaluate cardiac sympathetic innervation. The HMR and WR are known to have good reproducibility in planar MIBG imaging [6]. Although quantitative measurement of cardiac MIBG uptake can be performed using HMR and WR, these indices are considerably influenced by collimator performance, processing of the region of interest (ROI) and acquisition conditions [7–10]. In particular, the WR varies depending on the time from the early to the late MIBG scan. Late scanning is alternatively

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performed at 3 or 4 h after injection of MIBG [11]. Consequently, the WR derived from different acquisition times cannot easily be compared. Therefore determination of the difference between two values is needed to obtain a standardized WR.

We propose a method for estimating cardiac WR at 4 h (WR_{4h}) using early (15 min) and late (3 h) planar images. This method should be useful for the direct comparison of WR at 3 h (WR_{3h}) and WR_{4h}. The aim of this study was to evaluate the efficacy of the method to compare the actual WR_{4h} with an estimated WR_{4h} in a group of consecutive patients who underwent cardiac ^{123}I-MIBG imaging at 15 min, 3 h and 4 h.

Material and methods

Consecutive patients

Consecutive patients (n=98) who underwent early and late MIBG scans were included in this study. All patients underwent planar imaging at 15 min, 3 h and 4 h after the injection of MIBG. Of the 98 patients, 2 were excluded because of inappropriate time intervals from the 3-h scan to the 4-h scan (27 and 37 min). Since all the patients were retrospectively enrolled, we randomly divided the remaining 96 patients into two study groups: group 1 for creation of a regression model (24 men and 24 women), and group 2 for clinical validation (22 men and 26 women). This study was performed from May 2010 to April 2011 in Okayama Kyokuto Hospital, Okayama, Japan. Informed consent was obtained from all patients before enrolment (in the hospital). The ethics committee approved this study.

Image acquisition

The anterior MIBG planar image was acquired with a dual-head gamma camera (Millennium VG; GE Healthcare Japan, Tokyo, Japan) equipped with an extended low-energy general-purpose collimator. MIBG at a dose of 111 MBq was injected intravenously. An early planar image and two late planar images were acquired at 15 min, 3 h and 4 h after injection. The acquisition time was approximately 3 min in both the early and late scans. Planar imaging was performed with a 256×256 matrix. A photopeak window of ^{123}I was centred at 159 keV with a 20 % energy window.

Image analysis

Cardiac count, mediastinal count, HMR and WR were calculated using dedicated software (smartMIBG; FUJIFILM RI Pharma, Tokyo, Japan) [8, 10]. The cardiac count was calculated with a circular ROI set manually at the centre of the heart. Using the size and position of the cardiac ROI, a rectangular mediastinal ROI was automatically determined in the upper mediastinum. Cardiac and mediastinal counts were provided as the mean count per pixel. HMR was expressed as the cardiac count divided by the mediastinal count. WR was expressed as the decrease in cardiac count between the early and late images divided by the cardiac count in the early image, and expressed as a percentage. The cardiac and mediastinal counts in the late image were mathematically corrected for decay using the time between the early and late scans. Using the mediastinal count as the background, WR with background correction was calculated by subtracting the background from the cardiac count, as proposed by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology [12].

Estimation of WR_{4h}

The WR_{4h} was estimated using cardiac and mediastinal counts in the early and 3-h images as follows:

1) In group 1, cardiac and mediastinal counts/pixel were measured. Counts at 3 h ($count_{3h}$) and 4 h ($count_{4h}$) were divided by the early counts ($count_{early}$). Time-decay correction was used for the compensation of radioactive decay.
2) A linear regression line for the relationship between cardiac $count_{3h}$ and $count_{4h}$ was generated using the following equation:

$$\frac{count_{4h}}{count_{early}} = a \times \frac{count_{3h}}{count_{early}} + b$$
$$\therefore count_{4h} = a \times count_{3h} + b \times count_{early}$$

where the variables a and b denote the slope and the y-intercept, respectively. A linear regression line for the mediastinal count was also generated.

3) WR_{4h} was calculated using the following equation:

$$WR_{4h} = \frac{H_{early} - H_{4h}}{H_{early}} = -\left(a \times \frac{H_{3h}}{H_{early}} + b - 1\right)$$

where the variables H_{early}, H_{3h} and H_{4h} denote the cardiac $count_{early}$, $count_{3h}$ and $count_{4h}$, respectively. WR_{4h} with background correction was also calculated using the following equation:

$$WR_{4h}(with\ background\ correction) = \frac{(H_{early} - M_{early}) - (H_{4h} - M_{4h})}{(H_{early} - M_{early})} = -\left(a \times \frac{H_{3h} - M_{3h}}{H_{early} - M_{early}} + b - 1\right)$$

where the variables M_{early}, M_{3h} and M_{4h} denote the mediastinal $count_{early}$, $count_{3h}$ and $count_{4h}$, respectively.

Statistical analysis

All continuous values are expressed as means ± standard deviation. Student's *t* test was used to analyse the differences among continuous variables. To analyse the differences between $count_{3h}$ and $count_{4h}$, a paired *t* test was used. Linear regression analysis was used to define the relationship between two continuous variables. The chi-squared test was used to compare the differences in categorical variables between groups. A one-way repeated measures analysis of variance was used to compare WRs among no correction, time-decay correction, and time-decay and background corrections. If the overall ANOVA was significant, then pair-wise comparisons were performed using the Bonferroni factor to correct the *p* values. Intraclass correlation coefficient (ICC) and Bland Altman analysis were used for the assessment of agreement. All statistical tests were two-tailed, and *p* values <0.05 were considered significant. These analyses were performed using MedCalc version 14.12.0 (MedCalc Software bvba, Ostend, Belgium) and JMP version 11.2.1 (SAS Institute Inc., Cary, NC).

Results

HMR and WR

The time intervals between scans, HMR and WR are shown in Table 1. The mean time interval between the 3-h and 4-h scans was 62±6 min in group 1 and 61±7 min in group 2 (*p*=ns). Both WR and HMR did not differ between the two groups (*p*=ns). When the time-decay correction and background correction were used for calculating WR, WR_{4h} was significantly greater than WR_{3h} ($p<0.0001$; Fig. 1a). HMR was significantly decreased in accordance with the time after the injection of MIBG ($p<0.01$; Fig. 1b).

Relationship between $count_{3h}$ and $count_{4h}$

The relationship between $count_{3h}$ and $count_{4h}$ is shown in Fig. 2. Cardiac $count_{4h}$ divided by $count_{early}$ was positively correlated with cardiac $count_{3h}$ divided by $count_{early}$ ($count_{4h}/count_{early} = 1.039 \times count_{3h}/count_{early} - 0.067$, $r=0.979$, $p<0.0001$; Fig. 2a). Mediastinal $count_{4h}$ divided by $count_{early}$ was also positively correlated with mediastinal $count_{3h}$ divided by $count_{early}$ ($count_{4h}/count_{early} = 0.967 \times count_{3h}/count_{early} - 0.003$, $r=0.892$, $p<0.0001$; Fig. 2b). Bland-Altman analysis revealed that the mean of the difference between $count_{4h}/count_{early}$ and $count_{3h}/count_{early}$ was −0.04 for the cardiac region and −0.03 for the mediastinal region (Fig. 2c, d).

Table 1 Time intervals between scans, HMR and WR in Groups 1 and 2

	Group 1	Group 2	*p* value
Men/women	24/24	22/26	ns
Mean age (years)	78.5±9.4	77.5±8.2	ns
Time interval between scans (min)			
Early to late 3 h	163±5	165±6	0.039
Early to late 4 h	224±5	226±6	ns
Late 3 h to late 4 h	62±6	61±7	ns
Heart-to-mediastinum ratio			
Early scan	1.96±0.45	2.03±0.44	ns
3-h scan	1.88±0.56	1.97±0.57	ns
4-h scan	1.86±0.57	1.93±0.56	ns
Washout rate (%)			
With time decay correction			
WR_{3h}	22.22±8.76	20.64±9.22	ns
WR_{4h}	25.94±9.29	25.08±9.74	ns
With time decay and background corrections			
WR_{3h}	32.23±22.61	28.33±21.54	ns
WR_{4h}	36.99±23.54	34.78±23.03	ns

Group 1 was used for creation of a regression model, and Group 2 was used for clinical validation

Estimated count and actual count

The mean of the actual $count_{4h}$ and estimated $count_{4h}$ was 91.9±31.9 and 92.8±31.9 in the cardiac region, respectively (*p*=ns), and 47.6±8.4 and 47.4±8.3 in the mediastinal region, respectively (*p*=ns). In the linear regression there was a positive association between the actual and estimated counts in both the cardiac region (Fig. 3a) and the mediastinal region (Fig. 3b). In the Bland-Altman analysis there was a bias of −0.9 with 95 % limits of agreement of −6.2 to +4.3 in the cardiac region (Fig. 3c), and a bias of 0.1 with 95 % limits of agreement of −2.7 to +3.0 in the mediastinal region (Fig. 3d). The ICC showed excellent agreement between the actual and estimated counts in the cardiac region (ICC(2,1)=0.996) and in the mediastinal region (ICC(2,1)=0.985).

Estimated WR and actual WR

The average estimated WR_{4h} with time-decay correction was not different from the actual WR_{4h} (24.3±9.6 % vs. 25.1±9.7 %, *p*=ns). Similarly, the average estimated WR_{4h} with time-decay and background corrections was also not different from the actual WR_{4h} (32.9±22.9 % vs. 34.8±23.0 %, *p*=ns). The correlation coefficients of the linear regression lines ranged from 0.970 to 0.978 (Fig. 4a, b). The ICC showed excellent agreement

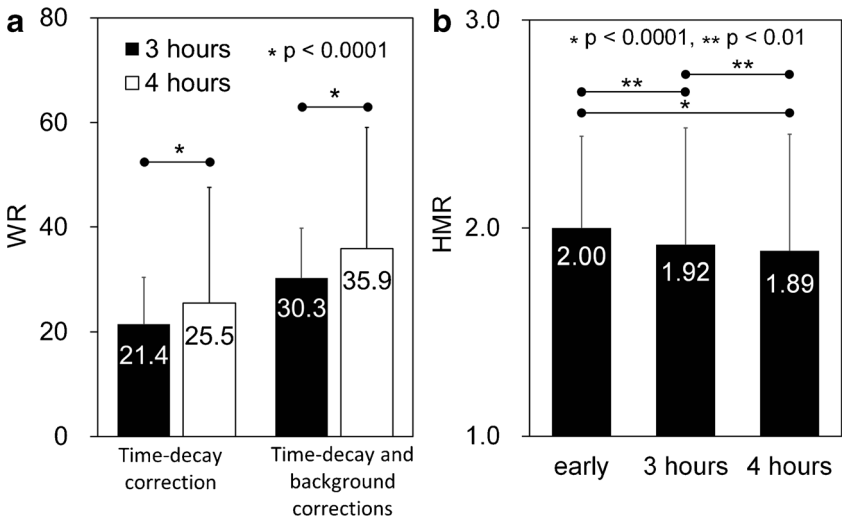

Fig. 1 Late 3-h (*black bars*) and 4-h WRs (*white bars*), and HMRs in the early and late scans in the 96 patients. Time-decay correction and time-decay and background corrections were used for calculating WR. The start time of the early and late scans influenced WR and HMR values

between the actual and estimated WRs with time-decay correction (ICC(2,1)=0.972), and with time-decay and background corrections (ICC(2,1)=0.967). In the Bland-Altman analysis there was good agreement between the estimated WR_{4h} and the actual WR_{4h} with time-decay correction (bias 0.8, 95 % limits of agreement −3.2 to + 4.7), and with both time-decay and background corrections (bias 1.8, 95 % limits of agreement −9.2 to +12.9; Fig. 4c, d).

Discussion

We designed this clinical MIBG study to develop a method for estimating WR_{4h} using early and 3-h planar images. Our results showed that the estimated WR_{4h} was equivalent to the actual WR_{4h}. This approach has the potential to allow direct comparison of WR_{3h} and WR_{4h}, and to standardize quantification of the WR in cardiac MIBG imaging.

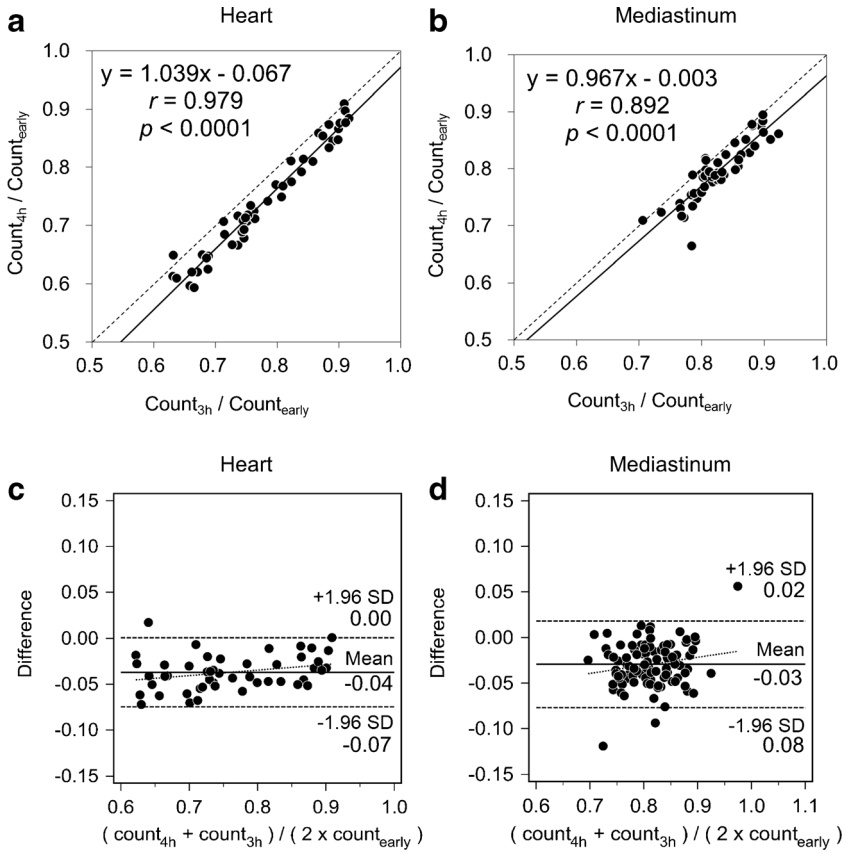

Fig. 2 Linear regression analysis of the relationship between $count_{3h}$ and $count_{4h}$, and the agreement between $count_{3h}$ and $count_{4h}$ by Bland-Altman analysis. The Bland-Altman analysis shows no correlation between the mean and difference in the heart region (r=0.281, p=ns) or the mediastinal region (r=0.178, p=ns)

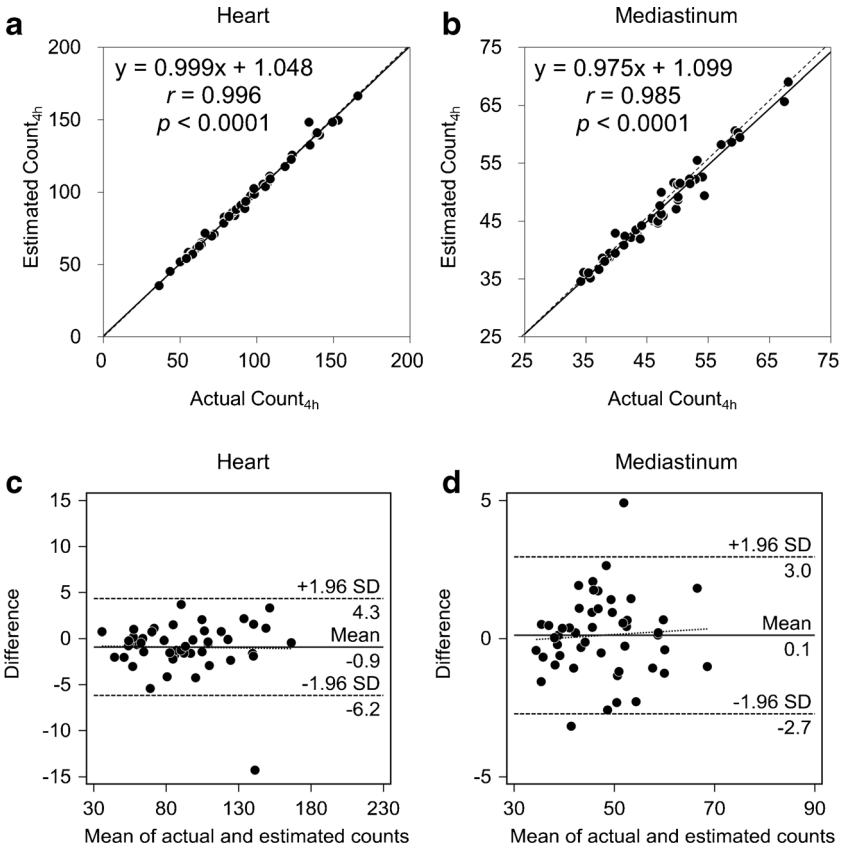

Fig. 3 Regression and agreement analysis of the relationship between the actual and estimated counts at 4 h in the heart and mediastinal regions. The Bland-Altman analysis shows no correlation between the mean and difference in the heart region (r=0.000, p=ns) or the mediastinal region (r=0.062, p=ns)

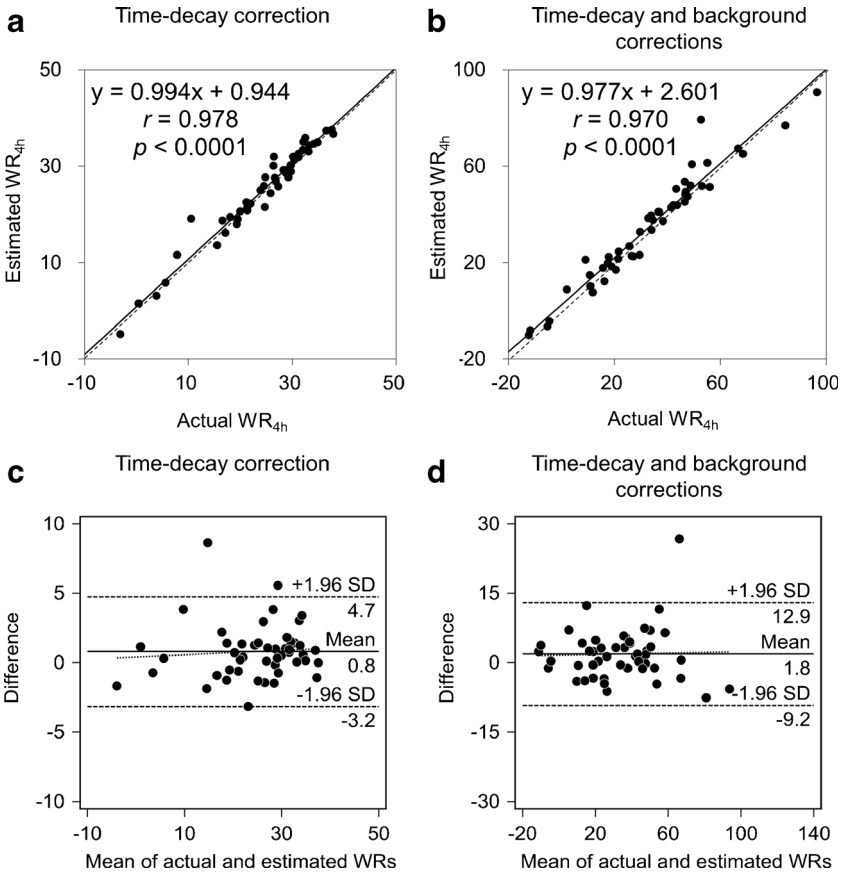

Fig. 4 Regression and agreement analysis of the relationship between the actual WR_{4h} and estimated WR_{4h}. Time-decay correction and both time-decay and background corrections were used in calculating WR. The Bland-Altman analysis shows no correlation between the means and differences in the actual WR_{4h} and estimated $WR_{4h}$with time-decay correction (r=0.074, p=ns) or with time-decay and background corrections (r=0.030, p=ns)

Cardiac kinetics of MIBG

The cardiac kinetics of MIBG after clearance of the initial nonneuronal uptake can be characterized by the equation: $A(t) = A_0 e^{-0.693t/T}$, where A_0 is the cardiac uptake of MIBG in the initial phase, and T is the half-time of the washout [13]. We calculated the cardiac $count_{4h}$/$count_{3h}$ ($count_{4/3}$) using this equation as follows: $count_{4/3}(T) = A(4)/A(3) = e^{0.693T}$. Glowniak et al. found an average T value of 19.0±11.8 in six cardiomyopathy patients and 7.98±4.2 in eight normal controls [14]. The $count_{4/3}$ for cardiomyopathy patients (T=19.0) and normal controls (T=7.98) were calculated as 0.982 and 0.958, respectively. We suspect that the changes in cardiac kinetics of MIBG at the two late time-points would be limited, even in cardiomyopathy patients and normal controls. Moreover, the slope of the linear regression line between cardiac $count_{3h}$ and $count_{4h}$ was 0.971 in our consecutive 96 patients, showing a similar tendency to the $count_{4/3}$ values (0.982 and 0.958).

WR with and without time-decay correction and background correction

Regarding the WR calculation using early and late images, we employed time-decay correction and background correction based on the proposed standardization of MIBG for cardiac sympathetic imaging [12]. We sought to determine experimentally the effect of these corrections in our preliminary study (Fig. 5). Decreasing kurtosis associated with background correction was observed in both WR_{3h} and WR_{4h}. Concerning the choice of the corrections for the image analysis, we suggest that time-decay correction would be useful based on histogram distribution.

WR_{3h} and WR_{4h}

WR_{4h} was significantly higher than WR_{3h} in our consecutive patients. Regarding normal WR values with time-decay correction in previous studies, Yoshita et al. found a WR_{3h} of 15.1±7.4 % in 10 normal volunteers [15], Lorberboym et al. found a WR_{4h} of 21±8 % in 7 normal volunteers [16], and Somsen et al. found a WR_{4h} of 23±6.4 % in 25 normal volunteers [17]. The normal WR_{4h} in these studies was also higher than WR_{3h}. Standardization of the time between early and late scans is necessary to compare normal WRs derived under different acquisition conditions. Furthermore, since we hypothesize that WR linearly increases between 3 h and 4 h, WR at any arbitrary time between 3 h and 4 h can be calculated by linear interpolation.

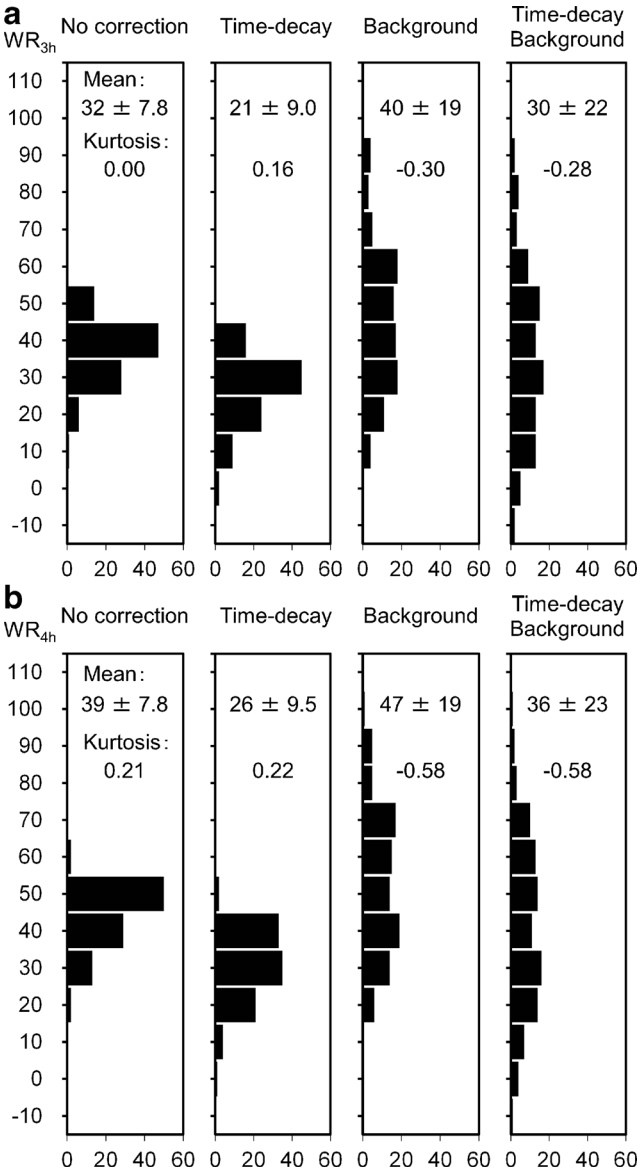

Fig. 5 WR_{3h} (**a**) and WR_{4h} (**b**) values with and without time-decay correction and background correction. Histograms were generated from the 96 consecutive patients (group 1+group 2). WR decreased with time-decay correction, but increased with background correction compared with WR with no correction (p<0.001). The histogram for WR with time-decay correction shows a narrower distribution (less kurtosis) than the histogram with background correction. The coefficient of variation of WR with time-decay correction was less than that with background correction and that with time-decay and background corrections (WR_{3h} 42 %, 48 % and 73 %, respectively; WR_{4h} 37 %, 40 % and 65 %, respectively)

Study limitations

Although both WR_{3h} and WR_{4h} can reasonably be used to evaluate cardiac sympathetic nerve activity, we used only WR_{4h} as a standard index of cardiac WR in this study. Since our method can also be used to estimate WR_{3h} from $count_{early}$ and $count_{4h}$, WR_{3h} can also be estimated. The regression line for the estimation of WR_{4h} was determined from the count

statistics within the cardiac and mediastinal ROIs. Therefore, patients with severe myocardial sympathetic nerve dysfunction, such as those with dementia with Lewy bodies and severe heart failure, frequently show cardiac MIBG uptake so low that our method may not provide a reliable estimate of WR_{4h}. However, inaccuracy in the determination of WR in patients with very low cardiac uptake is inherent in the calculation of WR, and high WR is usually calculated by the subtraction of background. Since our results are based on a single-centre study, further clinical validation of our method is needed in a multicentre study.

Conclusion

Using the linear regression model for the relationship between $count_{3h}$ and $count_{4h}$, WR_{4h} estimated from $count_{early}$ and $count_{3h}$ accurately corresponded with actual WR_{4h} in consecutive patients. This methodology would make it possible to directly evaluate WR_{3h} and WR_{4h}, and to provide WR of intermediate timing between 3 and 4 h. With further clinical validation, the estimation method could be applied to determine a standardized WR value in multicentre studies using ^{123}I-MIBG scintigraphy.

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Compliance with ethical standards

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Conflicts of interest K.N. does collaborative research work for the development of the software with FUJIFIL RI Pharma, Co. Ltd, Japan. Y.K. is employed by FUJIFIL RI Pharma, Co. Ltd, Japan, supplier of ^{123}I-MIBG in Japan.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55:2212–21.
2. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, Kasama S, et al. A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging. 2013;6:772–84.
3. Kashihara K, Ohno M, Kawada S, Okumura Y. Reduced cardiac uptake and enhanced washout of 123I-MIBG in pure autonomic failure occurs conjointly with Parkinson's disease and dementia with Lewy bodies. J Nucl Med. 2006;47:1099–101.
4. Yoshita M, Arai H, Arai H, Arai T, Asada T, Fujishiro H, et al. Diagnostic accuracy of 123I-meta-iodobenzylguanidine myocardial scintigraphy in dementia with Lewy bodies: a multicenter study. PLoS ONE. 2015;10:e0120540.
5. Nakajima K, Okuda K, Matsuo S, Yoshita M, Taki J, Yamada M, et al. Standardization of metaiodobenzylguanidine heart to mediastinum ratio using a calibration phantom: effects of correction on normal databases and a multicentre study. Eur J Nucl Med Mol Imaging. 2012;39:113–9.
6. Veltman CE, Boogers MJ, Meinardi JE, Al Younis I, Dibbets-Schneider P, Van der Wall EE, et al. Reproducibility of planar (123)I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy in patients with heart failure. Eur J Nucl Med Mol Imaging. 2012;39:1599–608.
7. Nakajima K, Okuda K, Yoshimura M, Matsuo S, Wakabayashi H, Imanishi Y, et al. Multicenter cross-calibration of I-123 metaiodobenzylguanidine heart-to-mediastinum ratios to overcome camera-collimator variations. J Nucl Cardiol. 2014;21:970–8.
8. Hasegawa D, Onishi H, Matsutomo N, Kangai Y. Validation of an optimal analysis method and reproducibility to calculate the heart-to-mediastinum ratio and washout rate in the iodine-123-labeled metaiodobenzylguanidine myocardial scintigraphy. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2014;70:1420–8.
9. Verschure DO, de Wit TC, Bongers V, Hagen PJ, Sonneck-Koenne C, D'Aron J, et al. (123)I-MIBG heart-to-mediastinum ratio is influenced by high-energy photon penetration of collimator septa from liver and lung activity. Nucl Med Commun. 2015;36:279–85.
10. Okuda K, Nakajima K, Hosoya T, Ishikawa T, Konishi T, Matsubara K, et al. Semi-automated algorithm for calculating heart-to-mediastinum ratio in cardiac iodine-123 MIBG imaging. J Nucl Cardiol. 2011;18:82–9.
11. van der Veen L, Scholte A, Stokkel M. Mathematical methods to determine quantitative parameters of myocardial 123I-MIBG studies: a review of the literature. Nucl Med Commun. 2010;31:617–28.
12. Flotats A, Carrio I, Agostini D, Le Guludec D, Marcassa C, Schafers M, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging. 2010;37:1802–12.
13. Glowniak JV. Cardiac studies with metaiodobenzylguanidine: a critique of methods and interpretation of results. J Nucl Med. 1995;36:2133–7.
14. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Woodward WR. Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. J Nucl Med. 1989;30:1182–91.
15. Yoshita M, Taki J, Yokoyama K, Noguchi-Shinohara M, Matsumoto Y, Nakajima K, et al. Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology. 2006;66:1850–4.
16. Lorberboym M, Lampl Y, Nikolov G, Sadeh M, Gilad R. I-123 MIBG cardiac scintigraphy and autonomic test evaluation in multiple sclerosis patients. J Neurol. 2008;255:211–6.
17. Somsen GA, Verberne HJ, Fleury E, Righetti A. Normal values and within-subject variability of cardiac I-123 MIBG scintigraphy in healthy individuals: implications for clinical studies. J Nucl Cardiol. 2004;11:126–33.