J of Nuclear Medicine Technology, first published online April 5, 2021 as doi:10.2967/jnmt.120.258632

Interobserver Agreement In The Diagnosis Of Parkinson's Disease With Cardiac 123I -meta-iodobenzylbuanidine Scintigraphy.

Running Title

Interobserver Agreement in Cardiac MIBG.

Authors:

Robert W Foley [1], Stewart L Redman [1], Isabel J Laurence [2], Richard N Graham [1], David Little [1]

Affiliations:

[1] Department of Radiology, Royal United Hospitals Bath NHS Foundation Trust, United Kingdom.

[2] Department of Radiology, Southmead Hospital, North Bristol NHS Trust, United Kingdom.

Corresponding author:

Robert William Foley, Radiology Resident,

Department of Radiology, Royal United Hospitals Bath NHS Foundation Trust, Combe Park, Avon, Bath, BA1 3NG, United Kingdom

Email: rwjfoley@gmail.com

Phone: 01225 824368

Total Word Count: 2,458

Abstract

Rationale

The aim of this study was to analyse the interobserver agreement of visual and quantitative assessment of cardiac 123I-MIBG scintigraphy.

Methods

Planar images were acquired using a low-energy collimator. The heart-to-mediastinal ratio (HM ratio) was adjusted for the use of a low-energy collimator, using a published formula. Interpretation was undertaken on both visual interpretation and following the addition of adjusted HM ratios. Images were classified as normal, abnormal or borderline.

Results

The cohort consisted of 10 patients. On visual interpretation only, there was strong agreement on the interpretation of the scan, $\kappa = .82$, $p<0.01$. Adjusted HM ratios led to a significant increase in mean ratios, (1.79 vs 1.36, $p=0.02$) and when utilised in reporting, resulted in perfect agreement, $\kappa = 1.0$, $p<0.01$.

Conclusion

The use of quantified HM ratios, adjusted for low-energy collimator use improves upon visual assessment alone and allowed for excellent interobserver agreement.

Keywords:

MIBG Cardiac Scintigraphy; Parkinson Disease; Heart-to-mediastinum ratio; Collimator;

Introduction

Sympathetic input, via noradrenaline, augments the function of the heart as part of the autonomic nervous system. Patients with Parkinson's disease display altered noradrenergic function (*1*). I-123 metaiodobenzylguanidine (123I-MIBG) is a radioactive analog of noradrenaline, which localizes in the myocardial sympathetic nerve terminals, and thereby allows this altered function to be imaged (*2*).

Myocardial sympathetic denervation on cardiac 123I-MIBG scintigraphy has shown great promise in the differential diagnosis of Parkinson's disease (*3, 4*) and is included in the Movement Disorder Society diagnostic criteria for Parkinson's disease (*5*). A cardiac 123I-MIBG study can be assessed both visually and quantitatively. The quantitative data derived from this test is the heart-to-mediastinum (HM) ratio, which has been demonstrated to be significantly lower in patients with Parkinson's disease (PD), compared to other Parkinsonian syndromes (*6*).

The use of a low-energy collimator for cardiac 123I-MIBG scintigraphy produces significantly lower HM ratios than that of a medium-energy collimator (*7*). However, correlation between the two methods is excellent and the use of a simple formula allows for the conversion of HM ratios derived from a low-energy collimator cardiac 123I-MIBG study (*8*).

In the present study, we analyse the interobserver agreement in the reporting of cardiac 123I-MIBG studies using visual interpretation and quantitative data with HM ratios. We hypothesise that the use of a low-energy collimator conversion formula to calculate adjusted HM ratios will lead to improved interobserver agreement.

Materials and Methods

Study Design

A retrospective review was conducted of all patients who underwent cardiac 123I-MIBG scintigraphy at two nuclear medicine departments between 2015-2019. Patients who underwent the study for a non-neurological indication were excluded. 1. The institutional review board (Trust Audit Committee) approved this retrospective study and the requirement to obtain informed consent was waived.

Technical Information

Following intravenous injection of 100 MBq (2.7 mCi) of 123I-MIBG, planar images were acquired in the anterior view at both 15 minutes and 4 hours using a double-headed GE Infinia gamma camera (GE Healthcare, Chicago, Illinois, USA) and a low-energy collimator. Photopeak energy was centred on 159 keV with a 10% window and processed on Xeleris software (GE Healthcare, Chicago, Illinois, USA). The HM ratio was measured by 2 consultant radiologists on the anterior planar images for

image interpretation. A freehand region of interest (ROI) was drawn around the left ventricle, and a small rectangular ROI drawn in the mediastinum, as per Kashihara *et al.* (*6*). The average counts in the left ventricular ROI were divided by the mediastinal ROI to calculate the HM ratio. Both the early and delayed phase images were processed. Normal HM ratios may vary by patient population and there are no clearly defined normal values for HM ratios using low-energy or medium-energy collimators. However a normal HM ratio has been suggested of >2.0 on both the early and delayed imaging (*6, 9*), while it has also been demonstrated in healthy controls that a normal early HM ratio is > 2.07 and a normal delayed HM ratio is > 1.86 (*10*). We subsequently recalculated each patients HM Ratio for a medium-energy collimator, using the following published formula; Medium Energy HM Ratio = Low Energy HM Ratio / 0.41 - 0.63 (*8*).

Image Interpretation

Visual interpretation of each 123I-MIBG study was undertaken by 2 radiology consultants without access to the patient's HM ratio and blinded to the clinical information for each patient. Interpretations were classified as normal, abnormal or borderline in each patient (Fig. 1). Interpretation was then undertaken using the visual analysis *and* quantitative HM ratio data.

Statistical Analysis

Interobserver agreement was calculated using Cohen's Kappa. Interobserver agreement for the HM ratio measured by consultants, registrars and technicians was

performed via intraclass coefficient correlation (ICC) analysis. The mean HM ratio with low-energy collimators and the mean HM ratio after adjustment with the medium energy formula were compared using the paired t-test. Statistical analysis was performed in R software v3.3.3.

Results

The cohort consisted of 10 consecutive patients, with an average age of 71. There were 7 men and 3 women included in the study. The clinical diagnoses of the patient cohort were PD, n=7, multiple system atrophy, n=2, and dementia with Lewy bodies, n=1. On visual interpretation of each patient's cardiac 123I-MIBG study, there was a strong agreement between the 2 reporter's interpretation of the imaging, $\kappa = .82$, (95% CI, .510 to 1.00), $p<0.01$. There was disagreement in one patient (Fig. 2), in which Reporter 1 labeled the visual interpretation of the study as borderline, while Reporter 2 labeled the study as abnormal, see Table 1.

The mean HM ratio in this cohort was 1.36 using the low-energy collimators, while the mean HM ratio was 1.79 following the use of the medium-energy conversion formula (Fig. 3). This was a statistically significant increase ($p=0.02$). The interpretation of each cardiac 123I-MIBG study following the addition of the adjusted HM ratios led to perfect agreement between the 2 raters, $\kappa = 1.0$, (95% CI, 1.0 to 1.0), $p<0.01$. The patient, in whom there was disagreement between the raters

on visually assessment only, demonstrated a HM ratio of 1.78 on early imaging and a ratio of 1.58 on the delayed imaging. This patient was subsequently labeled as abnormal by both raters following the addition of the quantitative data to their interpretation.

Discussion

The use of cardiac 123I-MIBG scintigraphy in the diagnostic pathway for patients under investigation for Parkinson's disease has been well established in the literature. The gold standard for the diagnosis of Parkinson's disease is a clinical one, however in a systematic review of 2016 literature, the overall accuracy of clinical diagnosis is approximately 80-83% (*11*). Therefore, imaging retains a core role in the attempts to improve this accuracy. There have been a number of studies that have demonstrated significantly lower HM Ratios on cardiac 123I-MIBG scintigraphy in patients with PD (*6, 12*), but also in the other Lewy body diseases; dementia with Lewy bodies and pure autonomic failure (*6, 9, 12, 13*). This is in contrast to various patient populations with a normal HM ratio, which includes normal controls, vascular parkinsonism, drug-induced parkinsonism and the parkinson's plus syndromes; multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration (*6, 9, 12, 13*).

The results of the present study demonstrate that the interobserver agreement between two experienced readers in the visual interpretation of cardiac 123I-MIBG is strong. The interobserver agreement is further improved by the addition of quantitative data in the form of the HM ratio. Previous research has demonstrated that visual interpretation of cardiac 123I-MIBG studies was equivalent to that of quantitative HM ratios (*14, 15*). In the present study, we have demonstrated that the use of quantitative methods in combination with visual assessment in the reporting of 123I-MIBG studies leads to improved agreement between reporters.

Some authors recommend the use of the HM ratio as the primary method of interpretation (*16*), with the visual assessment used as a secondary tool, particularly in borderline cases. This technique would require the normal and abnormal cut-off for the HM ratio to be defined precisely in each centre. However, this is clearly not the case, with normal values demonstrating wide ranges in the literature, varying from 1.38 – 1.94 for the early imaging and from 1.34 – 2.40 on delayed images (*3*). Therefore we recommend a reporting strategy, which utilises both visual interpretation and the quantitative HM ratio data in tandem when interpreting cardiac 123I-MIBG scintigraphy.

The present study utilises a low-energy high-resolution collimator, as this was our practice for other I-123 studies. Inoue *et al.* demonstrated the average ratio in patients imaged with a medium energy collimator was 2.66 +/-0.74, while the average ratio with a low-energy collimator was 1.81 +/-0.29, $p<0.05$ (*7*). Therefore

the use of a low-energy collimator makes comparison with established cut-offs in the literature difficult. We have demonstrated that the use of low-energy collimator for cardiac 123I-MIBG studies can be adjusted via the formula derived by Brumberg *et al.* (*8*). If cardiac 123I-MIBG scintigraphy is performed using a low-energy collimator, this formula can be utilised in order to allow for meaningful comparisons of HM ratios with the published cut-offs in the literature. No such study, which compares the clinical interpretation of cardiac 123I-MIBG studies acquired using a medium-energy and a low-energy collimator has been undertaken, and this is a potential area for future research.

We acknowledge several limitations to the present study. This is a relatively small patient cohort under investigation. However, we have attempted to remedy this by including two nuclear medicine centres. We have not attempted to quantify the overall accuracy of this test in the diagnosis of PD. However, as previously discussed, there is myriad evidence for the utility of cardiac 123I-MIBG scintigraphy in the diagnostic pathway for patients under investigation for Parkinson's disease.

The present study adds to the body of evidence surrounding the use of cardiac 123I-MIBG scintigraphy in three ways. Firstly, we have demonstrated that interobserver agreement is improved by the use of visual assessment *and* HM ratio data. We therefore recommend that a visual and quantitative assessment take place in tandem for the reporting of cardiac 123I-MIBG studies. Secondly, we have demonstrated that the use of low-energy collimator for cardiac 123I-MIBG studies

can be adjusted via a published formula (*8*) to allow for comparisons with published HM ratios.

Conclusion

The use of HM ratios in Cardiac 123I-MIBG scintigraphy, adjusted for low-energy collimator use, improves upon visual assessment alone and allowed for excellent interobserver agreement in the present study.

References

1. Goldstein DS, Holmes C, Cannon RO, Eisenhofer G, Kopin IJ. Sympathetic cardioneuropathy in dysautonomias. *N Engl J Med*. 1997; 336:696–702.
2. Lucio GC, Cuccurullo V, Restuccia A, Tamburrini O, Rotondo A, Mansi L. Neurological applications for myocardial MIBG scintigraphy. *Nucl Med Rev*. 2013; 16:35–41.
3. Orimo S, Suzuki M, Inaba A, Mizusawa H. 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: A systematic review and meta-analysis. *Park Relat Disord*. 2012; 18:494–500.
4. Treglia G, Cason E, Stefanelli A, et al. MIBG scintigraphy in differential diagnosis of Parkinsonism: a meta-analysis. *Clin Auton Res*. 2012; 22:43–55.
5. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015; 30:1591–1601.
6. Kashihara K, Ohno M, Kawada S, Okumura Y. Reduced cardiac uptake and enhanced washout of123I-MIBG in pure autonomic failure occurs conjointly with Parkinson's disease and dementia with Lewy bodies. *J Nucl Med*. 2006; 47:1099–1101.
7. Inoue Y, Suzuki A, Shirouzu I, et al. Effect of collimator choice on quantitative assessment of cardiac iodine 123 MIBG uptake. *J Nucl Cardiol*. 2003; 10:623–632.
8. Brumberg J, Blazhenets G, Schröter N, et al. Imaging cardiac sympathetic

innervation with MIBG: linear conversion of the heart-to-mediastinum ratio between different collimators. *EJNMMI Phys*. 2019; 6:12.

9. Kawazoe M, Arima H, Maeda T, et al. Sensitivity and specificity of cardiac 123I-MIBG scintigraphy for diagnosis of early-phase Parkinson's disease. *J Neurol Sci*. 2019; 407:116409.
10. Roberts G, Lloyd JJ, Kane JPM, et al. Cardiac 123I-MIBG normal uptake values are population-specific: Results from a cohort of controls over 60 years of age. *J Nucl Cardiol*. 2019; [Epub ahead of print].
11. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease. *Neurology*. 2016; 86:566–576.
12. Yoshita M (1998) Differentiation of idiopathic Parkinson's disease from striatonigral degeneration and progressive supranuclear palsy using iodine-123 meta- iodobenzylguanidine myocardial scintigraphy. *J Neurol Sci*. 1998; 155:60–67.
13. Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. 123I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999; 67:189–194.
14. Tiraboschi P, Corso A, Guerra UP, et al. (2016) 123I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and 123I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with lewy bodies from other dementias: A comparative study. *Ann Neurol*. 2016; 80:368–378.
15. Sakamoto F, Shiraishi S, Tsuda N, et al. 123I-MIBG myocardial scintigraphy for

the evaluation of Lewy body disease: Are delayed images essential? Is visual assessment useful? *Br J Radiol*. 2016; 89:20160144.

16. Roberts G, Kane JPM, Lloyd JJ, et al. A comparison of visual and semiquantitative analysis methods for planar cardiac 123I-MIBG scintigraphy in dementia with Lewy bodies. *Nucl Med Commun*. 2019; 40:734–743.

Figure Legends

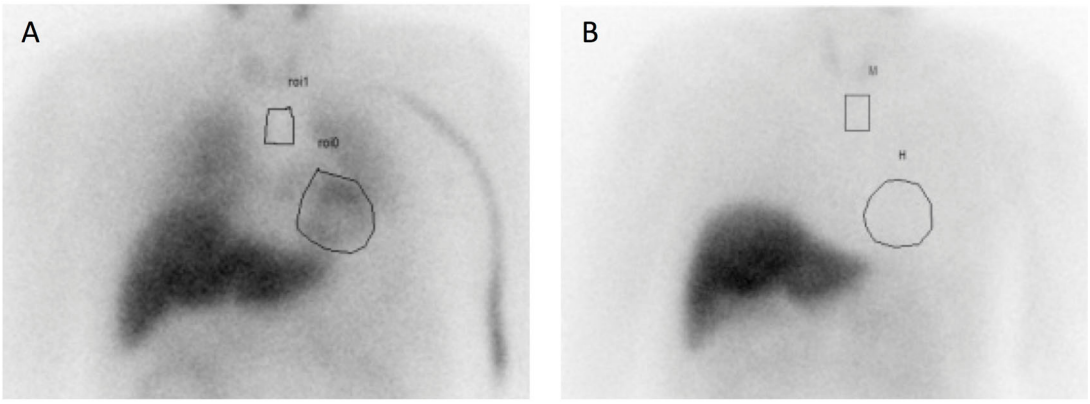

Figure 1

Cardiac 123I-MIBG scintigraphy interpreted as normal on visual assessment by both reporters (A) and a study interpreted as abnormal by both reporters (B). The heart-to-mediastinum ratios were 2.3 and 1.1 respectively, on the delayed phase images.

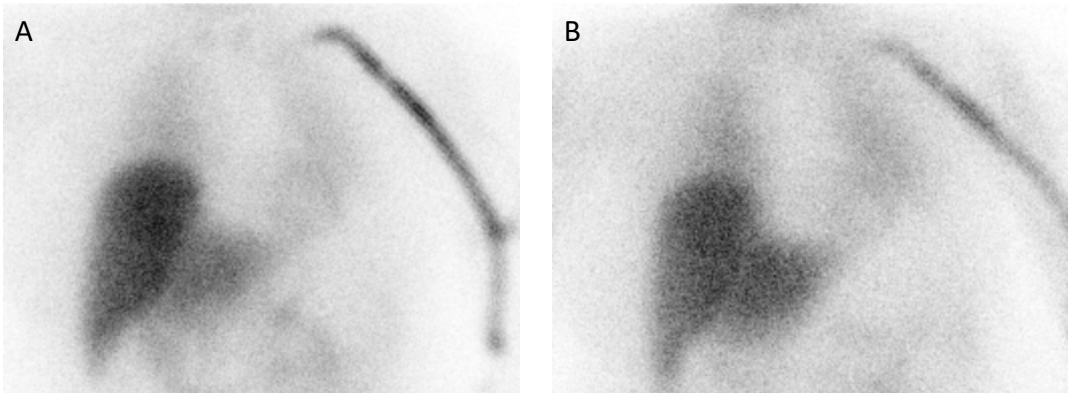

Figure 2

The early (A) and delayed (B) cardiac 123I-MIBG scintigraphy images interpreted as borderline by one reporter and abnormal by the second reporter on visual assessment. Following the addition of the heart-to-mediastinum ratios of 1.78 and 1.58 respectively, both reporters interpreted the study as abnormal.

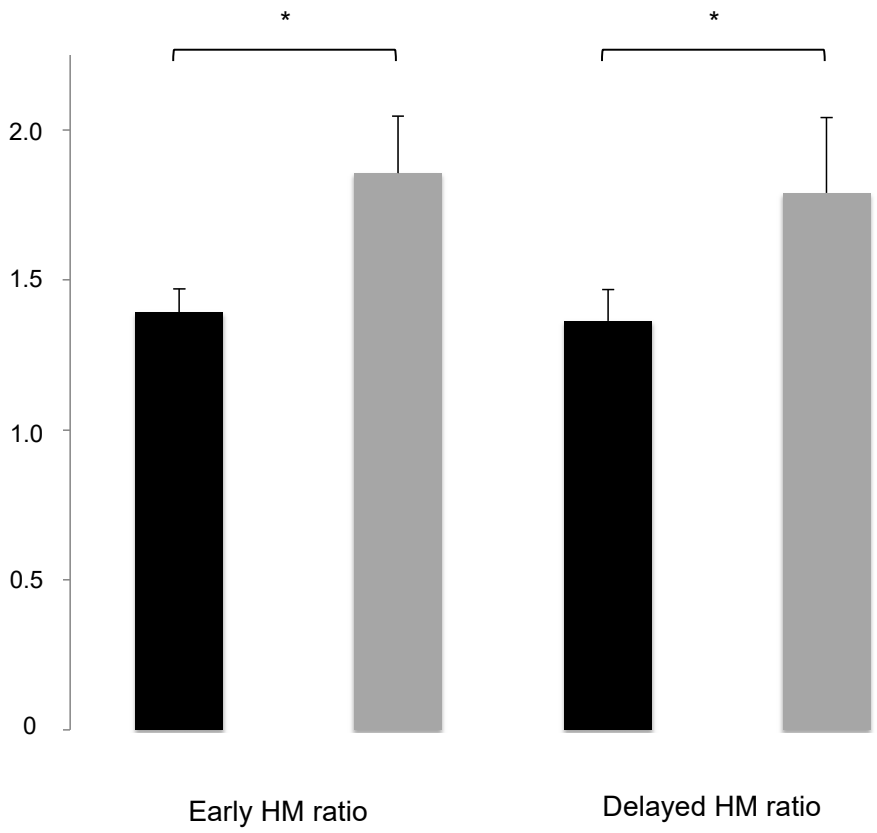

Figure 3

There was a significant increase in the average heart-to-mediastinal (HM) ratio, for both early and delayed phase imaging following application of the linear conversion formula (HM Ratio-medium = HM Ratio-Low/0.41 - 0.63). The original HM ratio is shown in black, with the corrected HM ratio in grey.

Table 1: Visual Interpretation Of The Study Cohort

Reporter 2	*Reporter 1*		
	Normal	Borderline	Abnormal
Normal	5	1	0
Borderline	0	0	0
Abnormal	0	0	4

Graphical Abstract