OPEN
Original article

Nuclear Medicine Communications

Can early phase cardiac [^{123}I]mIBG images be used to diagnose Lewy body disease?

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Purpose **Some studies have suggested that cardiac [123I]metaiodobenzylguanidine images obtained 15–20 min after tracer administration are as accurate for dementia with Lewy bodies (DLB) diagnosis as standard images acquired after a delay of 3–4 h; some suggest delayed imaging is preferable. We compare early and delayed heart-to-mediastinum ratios (HMR) in a well-characterised research dataset and make recommendations for clinical practice.**

Methods **Images were acquired using a Siemens gamma camera with medium energy collimators. Early images were obtained at 20 min and delayed at 4 h (± 30) min. In total 167 pairs of images were reviewed: 30 controls, 39 people with dementia and 98 with mild cognitive impairment. HMR normal cutoff values derived from control data were ≥2.10 for early imaging and ≥1.85 for delayed.**

Results **HMR tended to drop between early and delayed for abnormal images, but increase for normal images. Histograms of early and delayed HMR showed a slightly better separation of results into two groups for delayed imaging. Accuracy results were slightly higher for delayed imaging than early imaging (73 vs. 77%), sensitivity 63 vs. 65% and specificity 82 vs. 88%. However, this was not statistically significant – in total only 8/167 (5%) of scans changed designation between early and delayed imaging.**

Conclusion **We suggest that a delayed image could be acquired only if the early result is borderline. This removes the need for delayed imaging in about 70% of patients. Adopting this protocol in clinical practice would reduce the time most patients have to wait and could free up scanner time.** ***Nucl Med Commun*** **43: 770–777 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

Nuclear Medicine Communications 2022, **43**:770–777

Keywords: Cardiac mIBG, dementia with Lewy bodies, heart-to-mediastinum ratio, sympathetic denervation

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Received 24 January 2022 **Accepted** 12 April 2022

Introduction

Many studies using cardiac [123I]metaiodobenzylguanidine ([123I]mIBG) for the assessment of Lewy body disease acquire both early images (acquired 15–20 min after mIBG administration) and delayed images (3–4 h after administration). The heart-to-mediastinum ratio (HMR) is usually calculated on the delayed images because these are thought to reflect the function of the cardiac sympathetic nerves and early images the distribution of the nerves [1,2]. However, we have noted little difference between HMR obtained on cardiac mIBG images acquired at 20 min postinjection and those acquired at around 4 h after injection [3,4], suggesting that the initial capability for uptake of mIBG by sympathetic neurons is impaired at the same time as storage mechanisms. Autopsy studies report a loss of sympathetic nerve fibres in Lewy body disease cases [5,6], suggesting that cardiac mIBG uptake should be reduced on both early and delayed imaging. This was indeed the case in the only study to date to report autopsy findings in patients with cardiac mIBG imaging during life [7], where cardiac mIBG uptake was reduced on early images in 91% of Lewy body disease cases and on the delayed images in 96%.

Three recent cardiac mIBG studies in Lewy body disease carried out by separate groups [8–10] have demonstrated no significant difference between diagnostic accuracy of early or delayed imaging, suggesting that early images alone could be sufficient. Acquiring early images alone would benefit both patients and clinical departments and would also make the test much more convenient than [^{123}I] 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT), which requires a 3–6 h uptake period before scanning. This would be particularly helpful for patients with more advanced dementia symptoms, who may find a lengthy period spent in an

unfamiliar environment unsettling. Even if the delayed image could only be omitted in a subset of cases such a protocol could be worthwhile. Although most articles presenting a statistical comparison between early and delayed HMR show no significant differences [8–11], Yoshita *et al.* [12] demonstrated that HMR values in Parkinson's disease were significantly lower on delayed images than early images, whereas control HMR values were the opposite and were higher on the delayed images. The differences between early and late HMR were statistically significant.

In our previous work, we failed to find evidence for a significant difference between the diagnostic accuracy of early and delayed imaging [3,4]. It is possible that there is a true difference in the accuracy of early and delayed imaging but that the study dataset was too small for our results to reach statistical significance. Several of the subjects included had quite different uptake levels on delayed imaging compared to early, although this did not usually affect normal/abnormal categorisation with the optimal receiver operating characteristic (ROC) cut-offs applied [4]. Furthermore, we tended to see greater differences in mean HMR between our dementia with Lewy bodies (DLB) and non-DLB groups on delayed imaging compared with early, which is in keeping with previous studies, including those that demonstrated no statistically significant difference in diagnostic accuracy between early and delayed imaging [10,11].

The objective of this work is to bring together cardiac mIBG images from two research cohorts [3,13] to assess the utility of early imaging in a large group of well-characterised cases of Lewy body disease and Alzheimer's disease. The difference between early and delayed HMR is explored for the whole dataset, providing a wide range of cardiac uptake values as well as for the individual clinical groups. The diagnostic accuracy of early and delayed imaging is compared in both mild cognitive impairment and dementia and for combined Lewy body disease and non-Lewy body groups.

Materials and methods

Participants

We obtained 167 pairs of early and delayed cardiac mIBG scans: 137 in individuals with cognitive impairment and 30 in controls with normal cognition and normal scan appearances. All cases were used to compare early and delayed HMR values.

To compare HMR between clinical groups and to compare diagnostic accuracy, 30 participants with less certain clinical diagnoses (i.e. possible dementia or possible mild cognitive impairment with Lewy bodies) were excluded. The 30 controls were also excluded so that specificity would reflect that of clinical cases. The diagnoses used were the most up-to-date available for each participant. Either baseline, 1 or 2 year clinical symptoms and dopaminergic imaging results were used depending on the date of entry into the study. The 107 patients included therefore have a consensus clinical diagnosis of either probable DLB, probable mild cognitive impairment (MCI) with Lewy bodies (MCI-LB), dementia due to Alzheimer's disease or probable MCI due to Alzheimer's disease (MCI-AD). The numbers in each group are given in Table 1.

Participants were grouped as MCI-AD when they had none of the four core Lewy bodies features, a normal FP-CIT scan, and decline characteristic of Alzheimer's disease, that is, fulfilling the National Institute on Ageing–Alzheimer's Association (NIA-AA) criterion of "aetiology of MCI consistent with Alzheimer's disease pathophysiologic process."[14] This makes Alzheimer's disease the most likely cause, although other non-Lewy body causes cannot be excluded. Alzheimer's disease-specific biomarkers were not used as we aimed to exclude Lewy body disease rather than confirm Alzheimer's disease pathology [13].

Image acquisition

All individuals were administered 111 MBq (±10%) [^{123}I] mIBG via slow intravenous injection. Potassium iodate tablets (170 mg) were given before and after injection to minimise uptake of free iodine by the thyroid. Ten-minute anterior planar images were acquired at 20 min (early) and at 4 h (± 30 min) after injection (delayed). All images were acquired on a dual-headed Siemens Symbia Intevo or Siemens Symbia gamma camera (Siemens Healthcare, Munich, Germany) with medium energy low penetration (MELP) collimators with an energy window of 159 keV ± 10%, matrix size 128×128 and no zoom applied [3,13].

Comparison between imaging time points

Early and delayed planar cardiac mIBG images were processed independently by two operators to obtain HMR values [4]. The relationship between early and delayed imaging was assessed using linear regression, taking the mean HMR from the two operators for each image. The mean of just two operators was taken as previous work on inter-operator repeatability showed variability was low [4]. Bland-Altman plots were used to compare the difference between early and delayed images over the full HMR range more closely.

Comparison between mean early and mean delayed heart-to-mediastinum ratios for Lewy bodies and Alzheimer's disease groups

Table 1 Number of patients included in the Lewy body disease and Alzheimer's disease groups for each category

	Lewy body disease	Alzheimer's disease
Mild cognitive impairment	35	40
Dementia	17	15
Combined groups	52	55

The dementia and MCI groups [3,13] were analysed separately and combined into larger Lewy body and Alzheimer's disease groups. The mean HMR values and SD for early and delayed images were calculated. Paired *t*-tests were used to determine whether a statistically significant difference between early and delayed HMR exists. A linear mixed-effects model was used to show whether the relationship between early and delayed HMR was different for Lewy body and non-Lewy body groups.

Accuracy of early and delayed planar imaging for Lewy bodies and Alzheimer's disease groups

Thirty healthy controls with normal images were used to derive HMR cut-offs for early and delayed imaging, defined as two SDs below the mean HMR. The normal HMR cutoffs of ≥2.10 for early images and ≥1.85 for delayed were used to assign each scan as normal or abnormal. Sensitivity, specificity and overall accuracy were calculated for each of the clinical groups described above. Because sensitivity and specificity values are expressed as a percentage, binomial confidence intervals for proportions were calculated using the "Exact Binomial and Poisson Confidence Intervals" online tool available at http://statpages.info/confint.html

Results

Comparison between imaging time points

The goodness-of-fit parameters between early and delayed HMR (Table 2), show R^2 values of around 85%, suggesting 15% of the variance in delayed HMR is not predicted by early HMR (Fig. 1). The Bland–Altman plots in Fig. 2 show that for normal HMR values there is a trend for HMR to be lower on early imaging than on delayed, particularly at HMR values above 3. However, abnormal scans are much more likely to show a drop in HMR between early and delayed imaging. The HMR histograms in Fig. 3 show a slightly clearer separation of the data into two distinct normal and low uptake groups on delayed imaging and a slightly wider range of HMRs.

Comparison between mean early and mean delayed heart-to-mediastinum ratios for Lewy bodies and non-Lewy bodies groups

Paired *t*-tests showed no significant difference in the group means between early and delayed imaging for controls or Alzheimer's disease cases (Table 3). Although the mean control HMR is the same for early and delayed imaging, the abnormal cutoff is 2.10 for early and 1.85 for delayed, due to increased variation in the control HMRs at the delayed time point.

There was, however, a significant difference for both probable DLB and probable MCI-LB cases, with the delayed image HMR lower by 0.19 (11%) on average for probable DLB and 0.12 (6%) for MCI-LB.

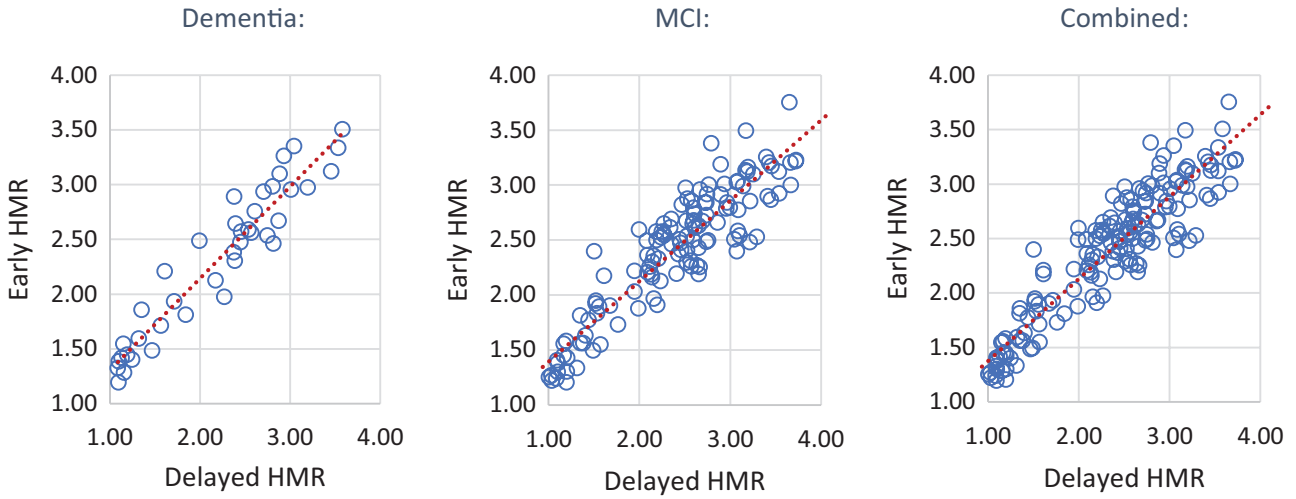
The linear-mixed effects model showed that the diagnostic group (Lewy body disease or non-Lewy body disease)

Table 2 Goodness-of-fit parameters for linear regression analysis between early and delayed time points

Dataset	R^2 (% explained variance)	Standard error of regression (in units of HMR)
Dementia	91	0.21
MCI	84	0.24
Combined	85	0.24

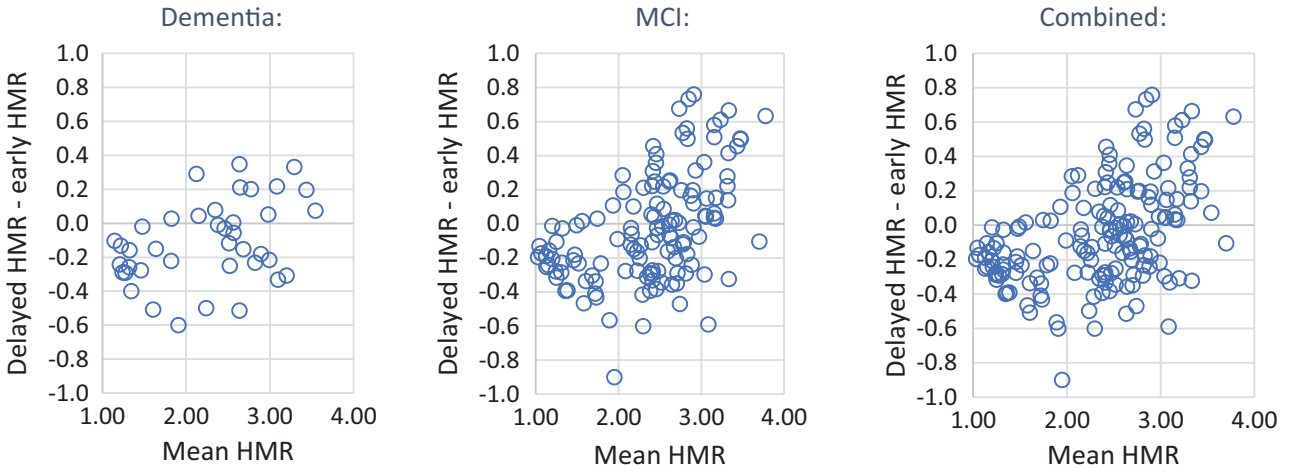
MCI, mild cognitive impairment.

Fig. 1



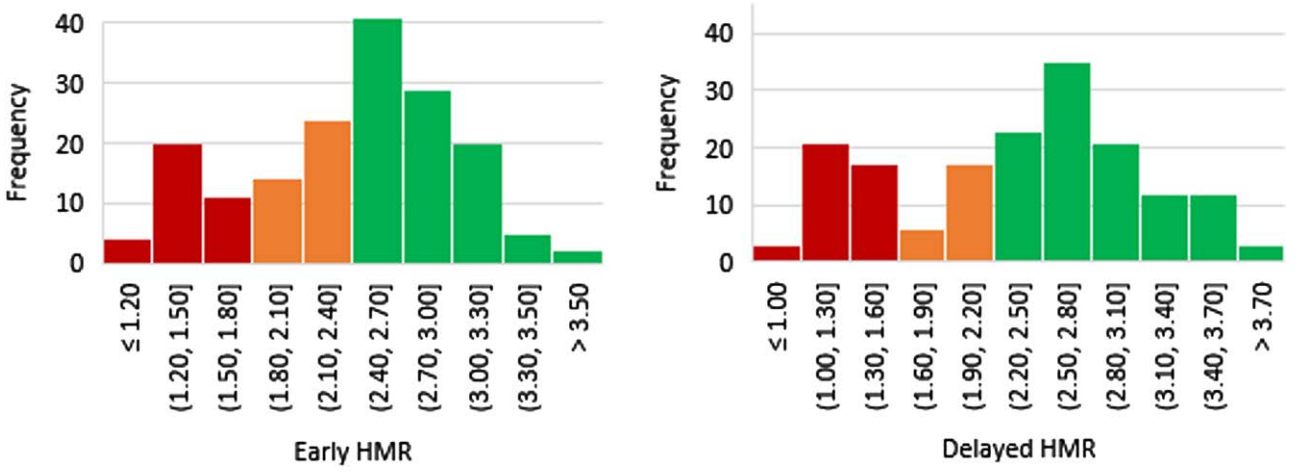
Correlation between early and delayed images (mean of both operator heart-to-mediastinum ratios) for the dementia and MCI datasets and for the two studies combined. MCI, mild cognitive impairment.

Fig. 2



Bland–Altman plots of the difference between delayed and early heart-to-mediastinum ratios for dementia, MCI and both datasets. MCI, mild cognitive impairment.

Fig. 3



Histograms for early and delayed heart-to-mediastinum ratios– for all cases. The red categories are below the normal cut-offs, orange borderline and green normal.

was a significant factor in the regression between early and delayed HMR ($F = 1224$; $P < 0.001$).

Accuracy of early and delayed planar imaging for Lewy body disease and non-Lewy body disease groups

The categorisation of scans into normal or abnormal groups is given in Table 4 for probable DLB and Alzheimer's disease and probable MCI-LB and MCI-AD with the sensitivities and specificities in Table 5. In all but six cases (6/107; 6%) the categorisations are the same on both early and delayed images (two with dementia and four with MCI). One probable DLB case had a borderline-normal HMR on early imaging (2.15; cutoff 2.10), which fell to 1.61 on delayed imaging (delayed cutoff 1.85). One Alzheimer's disease dementia case had a borderline-abnormal early HMR of 2.01, increasing to a clear normal 2.26 on delayed imaging. From the MCI dataset, all discrepancies were in the MCI-AD group. One MCI-AD case with an early HMR of 2.17, dropping to 1.61 on delayed images. The images were reviewed and this does appear to be a true difference, rather than a collimator or processing error. Two MCI-AD cases had borderline-abnormal HMRs on early images and normal HMRs on delayed (1.97 vs. 2.15 and 1.91 vs. 2.19). The final discordant MCI-AD case was abnormal on early images (1.88) and borderline-normal on delayed (1.99).

Table 3 Difference between mean heart-to-mediastinum ratios on early and delayed images for the different clinical groups

	n	Mean early HMR	Mean delayed HMR	Mean difference	Mean % difference	*P* value (paired *t*-test)
Controls	30	2.71	2.78	0.07	3	0.24
Prob MCI-AD	40	2.44	2.48	0.04	2	0.51
Prob AD	15	2.47	2.48	0.01	0	0.5
All prob AD	55	2.48	2.49	0.02	1	0.67
ProbMCI-LB	35	1.97	1.85	-0.12	−6	0.01
Prob DLB	17	1.88	1.69	-0.19	−11	<0.01
All Prob LB	52	1.95	1.8	-0.14	−8	<0.01

AD, Alzheimer's disease; HMR, heart-to-mediastinum ratios; LB, Lewy body; MCI, mild cognitive impairment.

Table 4 Early and delayed normal-abnormal categorisation for prob DLB, Alzheimer's disease, prob MCI-LB and MCI-AD groups

		Early				Early	
Prob DLB		normal > 2.10	abnormal < 2.10	AD		normal > 2.10	abnormal < 2.10
Delayed	normal > 1.85	5	0	Delayed	normal > 1.85	12	1
	abnormal < 1.86	1	11		abnormal < 1.85	0	2

		Early				Early	
Prob MCI-LB		normal > 2.10	abnormal < 2.10	MCI-AD		normal > 2.10	abnormal < 2.10
Delayed	normal > 1.85	13	0	Delayed	normal > 1.85	32	3
	abnormal < 1.85	0	22		abnormal < 1.85	1	4

Discrepancies between early and delayed results occur on the positive diagonal.
MCI, mild cognitive impairment.

Table 5 Sensitivity, specificity and overall accuracy figures for the diagnosis of Lewy body disease on early and delayed cardiac mIBG imaging, with 95% confidence intervals calculated using the binomial distribution

	Dementia		MCI		Combined data	
	Early	Delayed	Early	Delayed	Early	Delayed
Sensitivity	65% (38–86%)	71% (44–90%)	63% (45–79%)	63% (45–79%)	63% (49–76%)	65% (51–78%)
Specificity	80% (52–96%)	87% (60–98%)	83% (68–93%)	88% (74–96%)	82% (70–91%)	88% (76–95%)
Accuracy	72% (53–86%)	78% (60–91%)	74% (62–83%)	76% (65–85%)	73% (64–81%)	77% (68–84%)

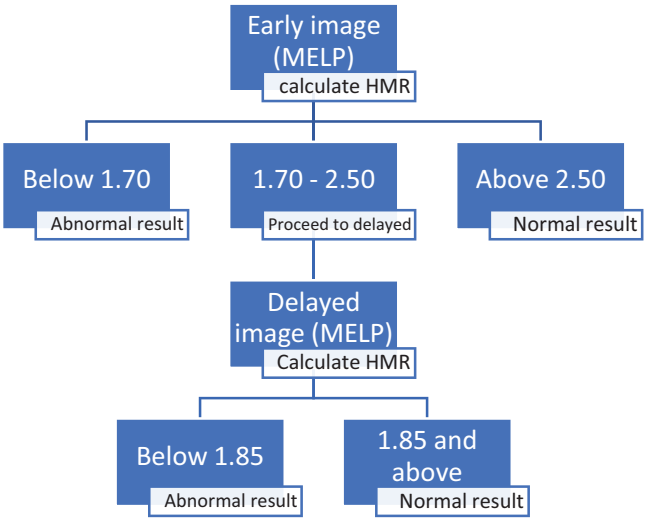
MCI, mild cognitive impairment; mIBG, metaiodobenzylguanidine.

The specificity for diagnosing Lewy body disease (Table 5) appears slightly lower for early imaging than delayed imaging at 82 vs. 88% with the MCI and dementia datasets grouped together but this was not statistically significant (95% CI, 70–91% early; 76–95% delayed). The overall sensitivity is similar for early and delayed imaging (63 vs. 65%, Table 5). With only 6/107 discordant cases, McNemar's test shows no statistically significant difference between early and delayed image outcomes ($P=0.69$).

Discussion

Bland–Altman plots of the pooled cardiac mIBG scans in our dementia and MCI studies revealed a difference between early and delayed imaging for low HMR values only, with no apparent difference between early and delayed HMR for scans with normal cardiac uptake. Paired *t*-tests on well-characterised subsets of the data confirmed that in healthy controls and Alzheimer's disease there was on average no difference between early and delayed HMR, whereas in probable Lewy body disease early HMR was significantly higher than delayed HMR, particularly for the DLB cases. It may be that the early images contain a higher degree of nonspecific uptake in the cardiac region, which washes out later and is not so apparent on delayed images. This reduction in nonspecific uptake would have more effect when the level of specific uptake is low (or zero), which may explain why the DLB patients had lower HMRs on delayed images. The histograms of HMR distribution also suggested a slightly clearer distinction between normal uptake and low uptake groups on delayed imaging than on early imaging. While this is evidence in favour of delayed imaging in principle, a larger separation between Lewy body and non-Lewy body groups does not necessarily equate to superior diagnostic accuracy – the accuracy of early imaging may be equivalent in practice if the smaller separation between groups is more than adequate. We see in our dataset that the vast majority of scan results (normal or abnormal) do not change category between early and delayed. These results also suggest that the exact timing of the early and delayed

Fig. 4



Flow chart for suggested approach to omitting delayed imaging if early imaging result is clear-cut. The heart-to-mediastinum ratios values are suitable for images acquired on Siemens gamma cameras fitted with medium energy low penetration (MELP) collimators.

imaging is not critical, which is useful to know in clinical practice as it can be difficult to schedule a patient for an exact timeslot.

Previous studies [8–10] have shown no statistically significant difference in the area under the ROC curve between early and delayed imaging. However, the objective of these articles was to show that early imaging could be used instead of delayed so the null hypothesis of no difference is not valid. Insufficient evidence to conclude that delayed imaging has better accuracy than early imaging does not prove that there is no difference in accuracy. One of the studies provides weak evidence, rather than no evidence, for delayed imaging being more accurate (area under the curve 0.871 early, 0.893 delayed; $P=0.091$) [9]. These three studies were quite large with 453, 111 and 192 cases included. However, they were all done retrospectively, on clinical patients attending for diagnostic testing and as such the results are likely to have influenced the clinical groupings whereas in our studies diagnosis was assigned blind to mIBG findings and mIBG ratings were blind to clinical information.

Because only a small proportion of the cases included in the accuracy comparison (6/107, 6%) changed their normal-abnormal designation between early and delayed imaging we can conclude that the accuracies of early and delayed imaging must be similar. A small difference in accuracy is not clinically important, especially in the context of other factors which might contribute to larger variations in the mIBG data, such as obesity, cardiac disease and physiologic fluctuations in uptake. However, it is clear from reviewing the 95% confidence interval that this study is not powered to detect clinically important differences in sensitivity or specificity between early and delayed imaging even using all our study data from our MCI and dementia studies. A power calculation (assuming 80% power and a 5% significance level) using Lehr's method [15] suggests that in total around 1300 scans (650 subjects) would be required to be confident that our 4% difference in accuracy is real. This takes into account the observed differences in proportions of abnormal scans on early and delayed imaging (0.02) and the correlation between early and delayed outcomes (phi coefficient 0.88). Here the correlation between early and delayed imaging is strong, so a large sample would be required to demonstrate a difference.

Our results suggest that we should assume that delayed imaging is likely to be slightly more accurate than early imaging, although the majority of the time the outcome on the early image will be the same. The question is then, what range of early HMR results can we accept as being definitively normal or abnormal (when requiring a binary result) and which range should be regarded as equivocal?

We suggest that an early HMR of >2.50 should be taken as unequivocally normal. None of the 83 people with early HMRs above 2.50 had abnormal delayed HMRs below 1.85, the closest was an HMR of 2.50 on early imaging dropping to 2.00 on delayed. We can also assume that any case already below 1.70 on early imaging with medium energy collimators (well below the 2.10 normal cutoff) is very likely to be below the abnormal cutoff of 1.85 on delayed imaging. In our full dataset of 167 scans acquired with MELP collimators, 31 people had early HMRs below 1.70, none of which were over 1.85 on delayed imaging. Only one of the scans below 1.70

on early imaging saw any increase in HMR; from 1.55 on early imaging to 1.57 on delayed.

Applying this method in clinical practice, any patient with an early HMR below 1.70 or above 2.50 does not need delayed imaging, as we are confident of the outcome. In our dataset, we could therefore have omitted the delayed image in 114 cases (68%) and have still been confident in predicting the delayed outcome. This system would be practical to implement as the HMR is very quick to calculate, so it would be feasible to inform the patient within around 10 min of the early scan being completed as to whether they needed to return for delayed imaging. The decision flow chart following the approach suggested above is summarised in Fig. 4.

Of the remaining 54 scans in the full dataset, there were eight where the early and delayed results differed: three changed from normal on early images (≥2.10) to abnormal on delayed (<1.85) and five changed from abnormal to normal.

Sensitivity and specificity values using HMR cut-offs derived from healthy controls are very similar for early and delayed imaging, showing that any difference in diagnostic accuracy between the time points is very small. In total, only 5% of scans (8/167) changed designation between early and delayed imaging. However, there is some suggestion from our data that the later imaging could separate Lewy body and non-Lewy body groups better than the early imaging; there would be some theoretical support for this view as nonspecific uptake will wash out later.

Considering that much of the literature uses delayed imaging and there are theoretical reasons to prefer it, we would recommend that imaging 3–4 h after injection remains the reference standard. However, we suggest that in clinical practice centres could omit the delayed image if the early results were unequivocal and have provided suggested ranges for this, valid for Siemens gamma cameras with medium energy collimators. Further work is required to determine whether these values are applicable to other gamma camera models fitted with medium energy collimators. In our dataset, 68% of cases would count as nonequivocal on early imaging. Adopting this approach in clinical practice would remove the need for the delayed image in the majority of cases, with negligible potential impact on diagnostic accuracy.

A key strength of our work is that diagnoses were made as part of research studies and performed entirely independently of cardiac mIBG imaging; however, a limitation is the relatively small sample size, especially when only the patients with more certain diagnoses are included. We included patients with MCI as well as patients with dementia, but in current clinical practice people with MCI are not referred for cardiac mIBG imaging. A further limitation is that we present data for Siemens medium energy collimators only; normal cutoffs may be camera and population dependent [16].

Conclusion

In the majority of cases, cardiac [^{123}I]mIBG imaging at 20 min after tracer administration gives the same outcome as imaging at 3–4 h. Centres that routinely image at both time points could omit the delayed image if the early result is clear.

Acknowledgements

The authors would like to acknowledge the support of Ms Helen Kain in the undertaking of this study, and the NIHR Clinical Research Network North East and Cumbria for their support in recruiting participants.

This work was supported by Alzheimer's Research UK (ARUK-PG2015-13) and by the NIHR Newcastle Biomedical Research Centre. GR was supported by an Alzheimer's Society clinical fellowship. JOB is supported by the NIHR Cambridge Biomedical Research Centre.
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study received ethical approval from an ethical standards committee on human experimentation –the National Research Ethics Service Committee North East – Newcastle & North Tyneside 2 (Research Ethics Committee Identification Number 15/NE/0420). Informed consent was obtained from all individual participants included in the study.

A.J.T., J.L., G.R., M.F., G.S.P. and J.O'B. contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.R., J.P.M.K., J.L, and M.F.. The first draft of the manuscript was written by G.R. and all authors commented on previous versions of the manuscript. All authors read and approved the final article.

Conflicts of interest

G.R. has received honoraria from GE Healthcare for delivering educational workshops on FP-CIT imaging. G.S.P. has received honoraria from GE Healthcare for delivering educational workshops on FP-CIT imaging and fees for backup reporting from GE Healthcare. J.-P.T. has received honoraria from GE Healthcare for delivering educational presentations on Lewy body disease and has consulted for Sosei-Heptares and Kyowa-Kirin. J.O'B. has acted as a consultant for Axon Neuroscience, TauRx,

GE Healthcare, Lilly and Eisai, has been a recipient of grant support from Alliance Medical, GE Healthcare and Merck and received honoraria for talks for GE Healthcare. A.J.T. has received support for investigator led studies and honoraria from GE Healthcare. For the remaining authors, there are no conflicts of interest.

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