Physica Medica 59 (2019) 163–169

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Impact of low-dose SPECT imaging on normal databases and myocardial perfusion scores

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ARTICLE INFO

Keywords:
Myocardial perfusion SPECT imaging
Iterative reconstruction
Normal databases
Patient dose

ABSTRACT

Purpose: We have recently demonstrated that iterative reconstruction algorithms with resolution recovery require the adoption of specific normal databases (NDBs) for perfusion SPECT quantification. This work was aimed at investigating the impact of patient low-dose imaging on NDBs and percent summed rest (SR%) and stress (SS%) scores.

Methods: Assuming that count statistics of shorter acquisition time may simulate that of lower patient dose, three simultaneous scans were acquired (BrightView, Philips) with different acquisition-time/projection: 30, 15 and 8 s (from 100% to 25% of the reference). Fifty-two normal patients with low likelihood of coronary artery disease were enrolled and three homemade NDBs were then generated and compared (Astonish™ algorithm with default parameters): 100%-HM-NDBs, 50%-HM-NDBs and 25%-HM-NDBs. SR% and SS% were subsequently calculated for another group of 38 patients (normal/abnormal = 5/33). SR% and SS% values of 100%-HM-NDBs were compared with those obtained with the NDBs available on the workstation. Moreover, the impact of the study count statistics on perfusion scores was evaluated using the count-specific NDBs.

Results: Significantly higher standard-deviation values were found for 25%-HM-NDBs compared to the other HM-NDBs ($p < 0.02$). Significantly higher SS% were also found for the 100%-HM-NDBs compared to the workstation NDBs (95%CI: 0.15–2.11%). Moreover, a post-hoc test showed significantly lower SR% and SS% for 25%-count statistics compared to 100%-HM-NDBs ($p < 0.03$).

Conclusions: NDBs and perfusion scores depend significantly on study count-statistics. A 50% reduction in patient dose is ultimately the limit for Astonish™ (with the default parameters) in order to prevent a significant variation in myocardial perfusion quantification.

1. Introduction

Commercial and academic software packages for myocardial perfusion imaging (MPI) have been continuously refined over recent decades [1–5]. One of the aims of these packages is to identify automatically the myocardial hypoperfused areas, providing global and regional measures of hypoperfusion at stress and rest. Although each package offers a unique set of features, there remains a common theme among them: the use of normal databases (NDBs).

The most currently used method for hypoperfusion quantification in single photon emission computed tomography (SPECT) is actually based on local comparisons of patient myocardial uptake with the perfusion distribution of a database created from normal scans.

In the Cedars-Sinai approach [1], an NDB is typically comprised of SPECT studies from 20 to 40 patients having a low likelihood of coronary artery disease (CAD) and who have undergone an MPI study which is visually normal [6]. For local hypoperfusion identification, a threshold below the normalised count mean among the NDB scans is used, such as 2.5 × the standard deviation (SD) among the normal scans.

In order to calculate correctly the hypoperfusion amount by a perfusion score, it is now well-established that the normal database must

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Abbreviations: MPI, myocardial perfusion imaging; IRR, iterative reconstruction algorithms with resolution recovery; LV, left ventricle; GP, general purpose; BMI, body mass index; SR%, percent summed rest score; SS%, percent summed stress score

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https://doi.org/10.1016/j.ejmp.2019.03.009
Received 3 December 2018; Received in revised form 6 March 2019; Accepted 11 March 2019

be specific to the type of SPECT system [7–9], collimator [10], and acquisition and reconstruction protocol used [11]. Aside from technological aspects that will influence the need for a specific normal database, the patient's characteristics, such as gender, must also be taken into account [12]. Moreover, a disease-specific normal database has been also built and has proved to be efficient for patients with end-stage renal disease [13].

In relation to the specificity of NDBs an open issue remains: the need for dose-specific databases of normality. Assuming that count statistics of shorter acquisition time (at the same patient dose) may simulate that of lower injected activity (at the same acquisition time), Lecchi et al. have shown that radiopharmaceutical activity can be reduced down to 25% of the reference without significant differences in perfusion quantification only in normal-weight subjects, while in overweight and obese patients a more conservative reduction of 50% should be preferred [14]. However, the authors used the same NDB for all simulated dose levels of the study and for both normal-weight and overweight groups of patients.

Nakazato et al. developed simulated count-specific NDBs by reframing the list-mode raw-data of normal patients who had undergone an MPI study on a latest-generation scanner with Cadmium Zinc Telluride (CZT) detectors [15]. In comparison to the use of the same NDBs for all simulated dose levels of the study, the count-specific NDBs facilitate a significant reduction in perfusion score bias when lowering the study count statistics. This is the only study that specifically investigated the effect of the reducing counts on myocardial perfusion quantification.

In a previous study, we demonstrated that the iterative reconstruction algorithm Astonish™ (Philips) with resolution recovery requires the adoption of the specific databases of normality available on the gamma-camera BrightView (Philips) in order to prevent incorrect risk-stratification with regard to cardiac event-free survival [16]. In fact, risk groups could be based on percent stress perfusion such as: normal or minimally abnormal for SS% less than 5%, from 5% to 9% mildly abnormal, from 10% to 14% moderately abnormal, and severely abnormal for SS% equal to 15% or greater [1]. However, no 25%-count specific NDBs were available on the workstation software.

This study was aimed at generating three homemade NDBs (HM-NDSs) with different study count-statistics (from 100% to 25% of the traditional reference) to investigate the impact of low-dose SPECT imaging on normal databases for myocardial hypoperfusion quantification and on the perfusion score calculation both in rest and stress studies using count-specific homemade NDBs.

2. Materials and methods

2.1. Creation of homemade normal databases

In order to create the HM-NDBs the following criteria were used at San Paolo Hospital (Milan, Italy): patients with low likelihood of CAD, no previous history of acute coronary disease and the pre-test probability of CAD was assessed, scoring several factors. Patients' gender and age were considered, along with ECG abnormalities and symptomatology, i.e. typical, atypical or non-specific chest pain. The presence of cardiovascular risk factors was also investigated, particularly diabetes, hypertension, dyslipidemia, smoking history, obesity and family history of CAD.

Table 1
Characteristics of normal patients of the homemade databases of normality.

NDB patient characteristics	
Patient number (Males)	52 (23)
Age (y)	63.5 ± 1.9
Weight (kg)	73.3 ± 2.0
BMI (kg/m^2)	26.9 ± 0.7
Stress activity (MBq)	607 ± 9
Rest activity (MBq)	613 ± 9
Effective dose (mSv)[*]	
Rest	4.9 [4.3–6.1]
Stress	4.2 [3.6–5.2]

[*] From ICRP Publication 53.

Patients had undergone both stress and rest ECG-gated SPECT with [^{99m}Tc]Tetrofosmin using 2-day imaging protocol. In both stress and rest studies, the injected activity was 550 MBq (± 10%) in patients weighing less than or equal to 70 kg, while in patients weighing more than 70 kg, the weight was multiplied by 8 to calculate the activity up to a maximum of 740 MBq (± 10%) [17]. The stress test was performed with incremental loads of 25 W every 2 min. Patients exercised until they achieved 85% of their maximal age-predicted heart rate or they complained of exercise-limiting fatigue, chest pain, or dyspnea. [^{99m}Tc]Tetrofosmin was injected intravenously at peak exercise. Patients who were unable to achieve the targeted heart rate or exercise were stressed pharmacologically. Dipyridamole was infused intravenously (0.56 mg/kg in 4 min) after an overnight fast and [^{99m}Tc]Tetrofosmin was injected 3 min after the end of dipyridamole infusion. Aminophylline was given 3 min after the radiopharmaceutical injection. The time between radiopharmaceutical injection and stress/rest acquisition was 30 min or more in order to reduce the hepatobiliary uptake. All patients signed an informed consent.

Patients performed an 8 bin/cycle ECG-gated SPECT acquisition with the 2-headed SPECT BrightView (Philips), equipped with low-energy high-resolution (LEHR) collimators, on a 64 × 64 matrix with a pixel size of 6.39 mm and over a 180° arc (64 projections, zoom = 1.46).

Three simultaneous scans (*100%-count scan, 50%-count scan* and *25%-count scan*) were started at the same time but with different acquisition-time/projection, i.e. 30, 15 and 8 s [14].

For each patient and each set of stress or rest projections with different count statistics, left-ventricular (LV) short-axis images were reconstructed using the Astonish™ algorithm with the manufacturer's default parameters (4 iterations, 8 subsets, cut-off frequency = 1 cycle/pixel). No attenuation or scatter correction was applied.

Starting from the LV short-axis images, three sets of HM-NDBs with different count-statistics were generated using the "Database" tool of the Quantitative Perfusion SPECT (QPS) software (Cedar-Sinai Medical Center, Los Angeles, USA) available on the workstation:

1. 100% homemade normal-databases (100%-HM-NDBs), created with the LV short-axis images of 100%-count scans;
2. 50% homemade normal-databases (50%-HM-NDBs), created with the LV short-axis images of 50%-count scans;
3. 25% homemade normal-databases (25%-HM-NDBs), created with the LV short-axis images of 25%-count scans.

Each of these three sets consists of four different normal databases: male/stress, male/rest, female/stress and female/rest.

2.2. Normal database comparison

In order to compare the 12 NDBs created, the LV polar map of each normal study was created and displayed using the QPS software. For each polar map and each of the 17 myocardial segments defined by the American Heart Association [18], the average of the normalised counts (displayed as 'raw data') was registered. For each NDB, the segmental mean and SD of the raw data were then calculated among all the normal studies matching the specific NDB.

The impact of the study count statistics on the normal mean and SD found was finally evaluated by 1-way-ANOVA analysis and Tukey test as post-hoc ($p < 0.05$).

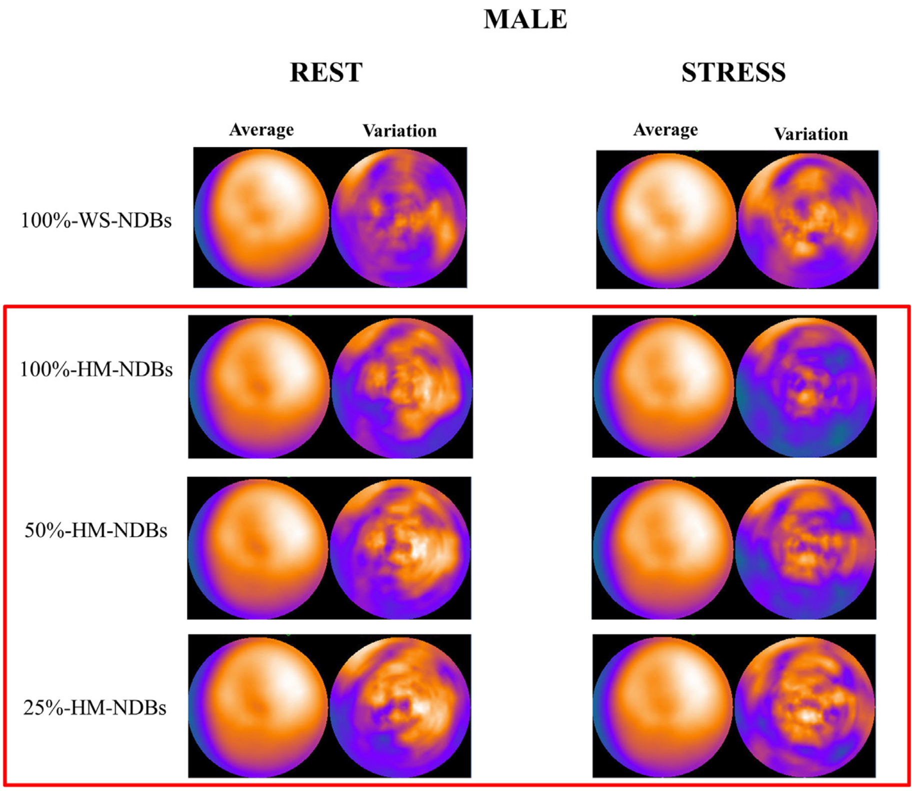

Fig. 1. Male/rest (left) and male/stress (right) HM-NDBs obtained for the different study count-statistics considered in this study (100%-count, 50%-count and 25%-count statistics). In the first raw, the normal databases available on the workstation were also reported (100%-WS-NDBs). Normal databases are shown as displayed (average and variation) by the QPS software used to create the NDB.

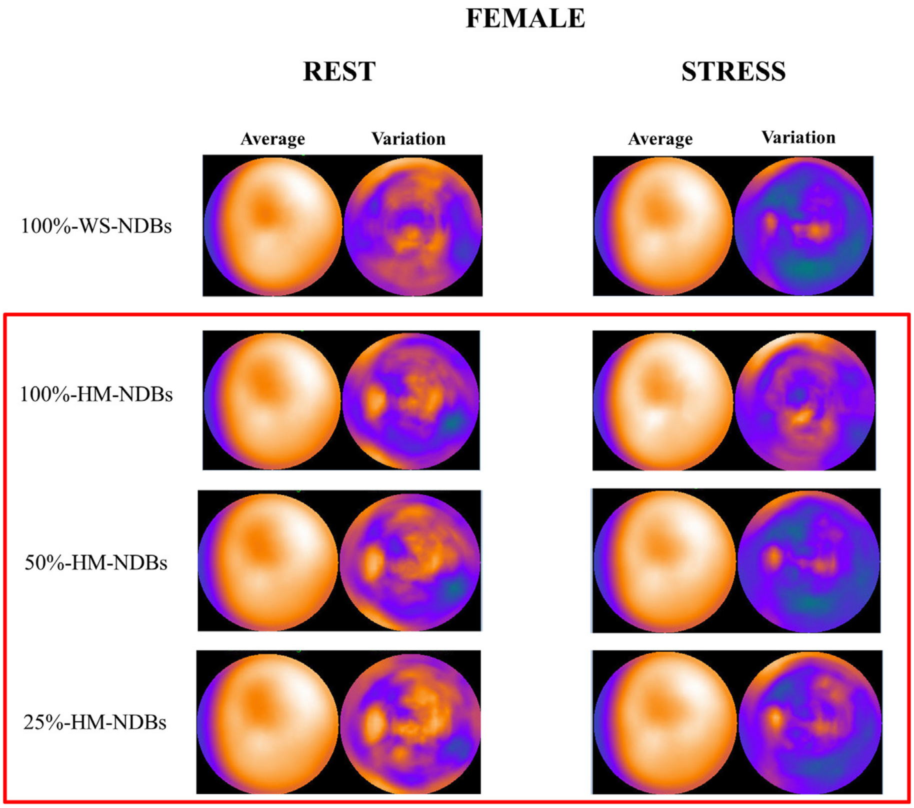

Fig. 2. Female/rest (left) and female/stress (right) HM-NDBs obtained for the different study count-statistics considered in this study (100%-count, 50%-count and 25%-count statistics). In the first raw, the normal databases available on the workstation were also reported (100%-WS-NDBs). Normal databases are shown as displayed (average and variation) by the QPS software used to create the NDB.

2.3. Patient group for perfusion score calculation

After the NDB creation, another group of consecutive MPI patients was considered. The following inclusion criteria were used: patients had undergone both stress and rest ECG-gated scan with [^{99m}Tc]Tetrofosmin using the 2-day imaging protocol described above (three simultaneous scans) and both the weight and height of the patients were recorded. All patients signed an informed consent.

The reconstruction protocol of this group was the same used for the patients enrolled for the creation of the normal databases. The LV short-

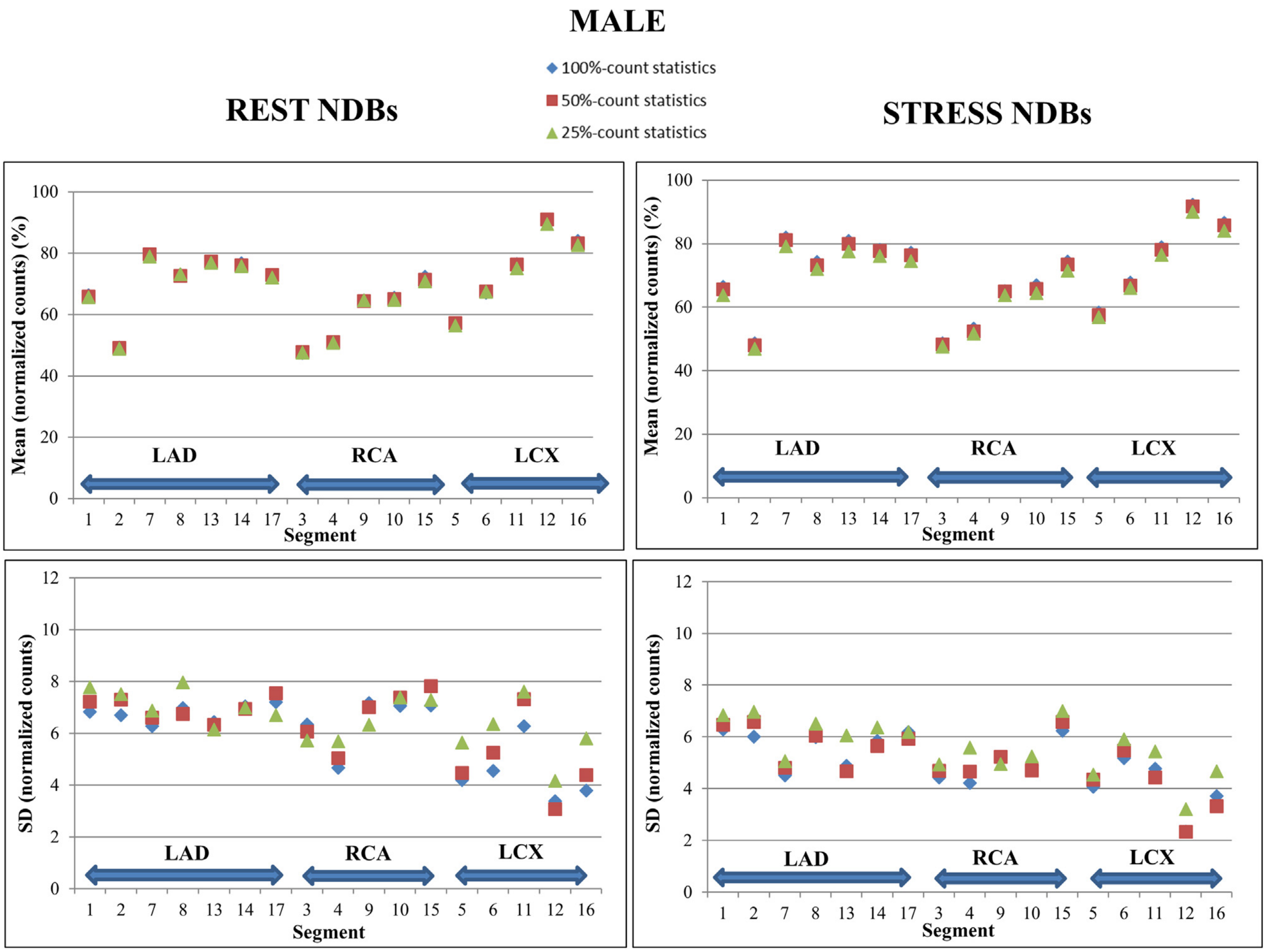

Fig. 3. Segmental means (top) and standard deviation (SD) values (bottom) for normal patients included in the male (a) and female (b) HM-NDBs with different study count statistics. For each NDB and for each myocardial segment, the mean and SD of the normalised counts were calculated among all the normal studies included in the specific NDB. The segments are ordered according to the three standard coronary branch territories: left anterior descending (LAD), right coronary artery (RCA) and left circumflex artery (LCX).

axis images were then used for calculating the percent summed rest (SR%) and stress (SS%) scores using the count-specific HM-NDBs, i.e. 100%-HM-NDBs for 100%-count scans, 50%-HM-NDBs for 50%-count scans and 25%-HM-NDBs for 25%-count scans.

An additional set of perfusion scores was calculated using the normal databases available on the workstation (100%-WS-NDBs) for the 100% study count statistics and Astonish™ algorithm with default parameters. In the software instructions, the manufacturer declares that the Astonish™ WS-NDBs were obtained from 80 patients (40 women and 40 men) acquired with either LEHR or general purpose collimators and Forte, SkyLight variable-angle or CardioMD fixed-ninety dual-detector camera. Moreover, MPI studies were performed using either one-day or two-day imaging protocol and ^{99m}Tc-sestamibi as radiopharmaceutical.

2.4. *Statistical analysis of the perfusion summed scores obtained from the different NDBs*

The degree of quantification agreement between 100%-HM-NDBs and 100%-WS-NDBs was assessed according to the Bland-Altman plot as the mean (bias) ± 1.96 (95% limits of agreement) × SD of the differences between the perfusion results obtained from the two methods.

Moreover, the impact of the study count-statistics on SS% and SR% calculated using the count-specific NDBs was evaluated by ANOVA analysis and Tukey test as post-hoc ($p < 0.05$).

When not mentioned, the results are presented as mean ± standard errors of the mean.

3. Results

3.1. *Normal databases creation and comparison*

The baseline characteristics of the 52 patients included in the study from February 2014 to June 2017 are summarised in Table 1. There were 23 male and 29 female patients and the range of body mass index (BMI) was 19.95–41.91 kg/m^2 (34 overweight and obese patients).

The [^{99m}Tc]Tetrofosmin activity mean was 613 ± 9 MBq and 607 ± 9 MBq for stress and rest exams, respectively, while the mean of the effective doses (from ICRP Publication 53) for stress plus rest studies was 9.1 mSv (range 7.9–11.1 mSv).

The HM-NDBs created are shown in Fig. 1 for males and in Fig. 2 for females as polar maps containing the average and relative variation among the normal patients (as displayed by QPS software). The normal databases available on the workstation are also reported.

With regard to the database average, HM-NDBs were visually different from 100%-WS-NDBs, while no differences in the average polar maps were appreciable or found statistically between the HM-NDBs ($p > 0.05$). Conversely, for database variation, an increasing variability was observed with the decreasing of the count statistics, particularly for the stress study. In fact, the highest SD among the HM-NDBs were found for female/stress NDB and segment no. 1 and 2 (basal segments) of the left anterior descending (LAD) territory (Fig. 3).

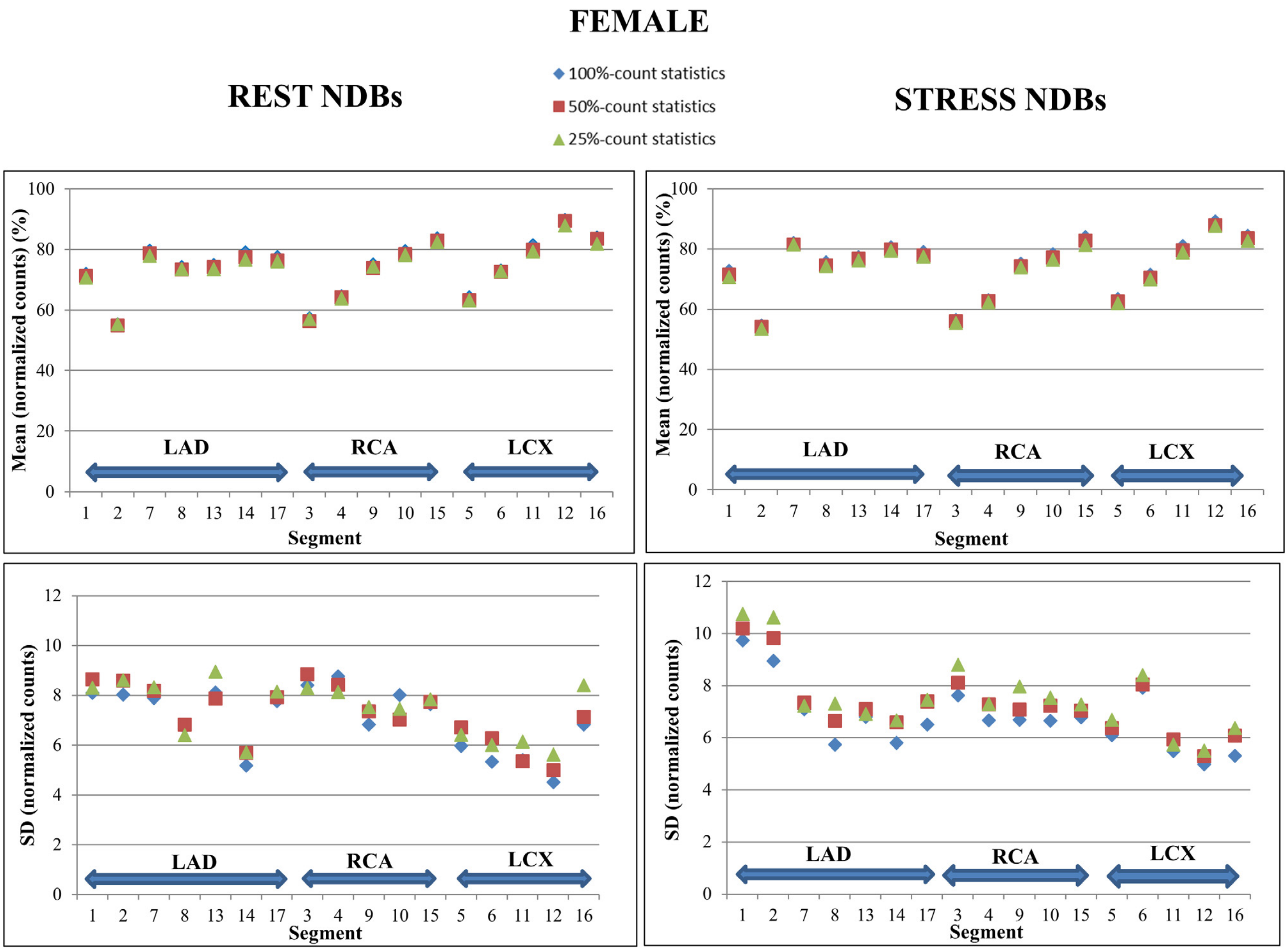

Fig. 3. (*continued*)

Table 2
Characteristics of patient group used to calculate the perfusion scores with the different NDBs considered in this study.

Characteristics	All patients	Overweight patients
Patient number (Males)	38 (27)	23 (18)
Age (y)	68.8 ± 1.4	68.7 ± 2.0
Weight (kg)	75.4 ± 2.3	83.7 ± 2.4
BMI (kg/m^2)	26.7 ± 0.7	29.3 ± 0.8
Standard stress activity (MBq)	610 ± 12	654 ± 14
Standard rest activity (MBq)	611 ± 12	653 ± 14
Effective dose (mSv)*		
Rest	4.9 [4.2–5.9]	5.2 [4.3–5.9]
Stress	4.2 [3.3–5.1]	4.5 [3.8–5.1]
Medical Report		
Negative	5	2
Abnormal	33	21

*From ICRP Publication 53.

Moreover, the study count-statistics showed a statistically significant impact on database SD for both males ($p < 0.001$ for stress and $p = 0.005$ for rest) and females ($p < 0.001$ for stress and $p = 0.013$ for rest). For female/stress NDB, the post-hoc test showed significantly higher SD stress values for 25%-count statistics compared to 50%- and 100%-count statistics ($p = 0.002$ and $p < 0.001$, respectively) and for 50%-count statistics compared to 100%-count statistics ($p < 0.001$). For male/stress NDB, significantly higher stress SD values were found only for 25%-count statistics as opposed to 50% and 100%-count statistics ($p = 0.001$).

With regard to the post-hoc test of the rest NDBs, significantly higher SD values were found for 25%-count statistics only compared to 100%-count statistics ($p = 0.001$ for males and $p = 0.005$ for females).

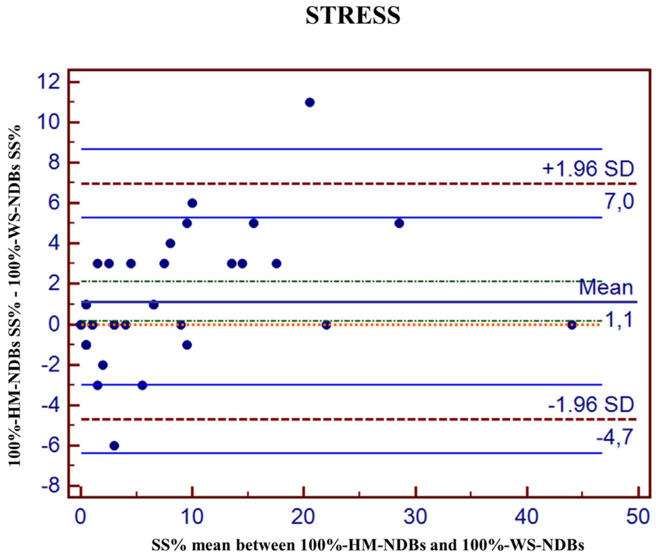

Fig. 4. Bland and Altman plot of SS% values obtained for 100%-HM-NDBs and 100%-WS-NDBs. Bias (mean) and limits of agreement (± 1.96 × SD) are shown.

3.2. Patient group for perfusion score calculation

The baseline characteristics of the 38 patients (27 males and 11

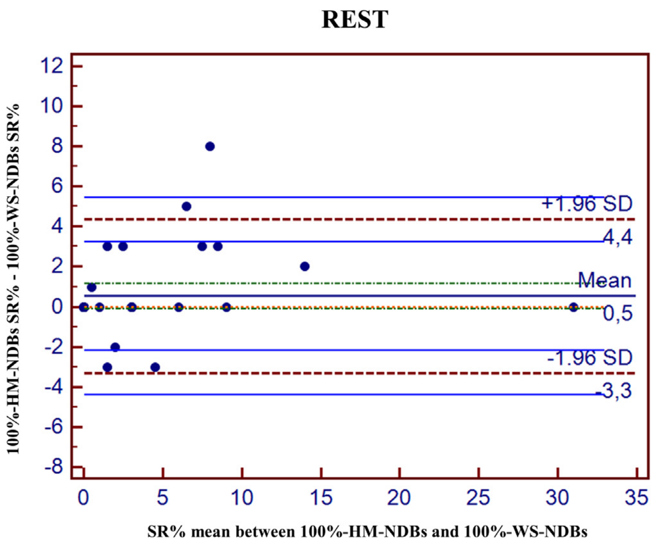

Fig. 5. Bland and Altman plot of SR% values obtained for 100%-HM-NDBs and 100%-WS-NDBs. Bias (mean) and limits of agreement (± 1.96 × SD) are shown.

Table 3
SR% and SS% results using the count-specific HM-NDBs for all patients and for the overweight patient group.

Description	All patients		Overweight patients	
	SR%	SS%	SR%	SS%
100%-WS-NDBs	2.87 ± 0.47	6.84 ± 1.43	3.13 ± 1.35	8.43 ± 2.12
100%-HM-NDBs	3.39 ± 0.98	7.97 ± 1.62	4.13 ± 1.44	10.43 ± 2.36
50%-HM-NDBs	3.18 ± 0.98	7.68 ± 1.67	3.74 ± 1.41	10.04 ± 2.44
25%-HM-NDBs	2.82 ± 0.97	6.94 ± 1.56	3.43 ± 1.46	9.00 ± 2.24

females) studied from July 2017 to June 2018 with the HM-NDBs are summarised in Table 2. The 3rd column refers to the 23 overweight patients of this second group. The BMI range was 19.6–40.2 kg/m^2 (23 overweight and obese patients). The mean [^{99m}Tc]Tetrofosmin administered activity was 610 ± 9 MBq and 611 ± 9 MBq for stress and rest exams, respectively. The mean of the effective doses for stress plus rest studies was 9.1 mSv (range 7.8–11.1 mSv). Perfusion defects were not observed in 5 patients, two of them being in the overweight and obese patient group.

3.3. Statistical analysis of the perfusion summed scores obtained from the different NDBs

Significantly higher SS% values were found for the 100%-HM-NDBs compared to 100%-WS-NDBs (mean diff.: 1.13% with a 95% confidence interval, CI, of 0.15–2.11%), as shown by the Bland and Altman plots of SS% values reported in Fig. 4. Conversely (Fig. 5), no significant difference was found for the rest score (mean diff.: 0.53% with a 95%-CI of −0.12–1.70%).

Restricting the results to the overweight patients group (Table 3), both significantly higher SS% and SR% values were found for the 100%-HM-NDBs compared to the 100%-WS-NDBs (SS%: mean diff. = 2.0% with a 95%-CI of 0.70–3.30%; SR%: mean diff. = 1.0% with a 95%-CI of 0.02–1.98%).

Higher upper limits of agreement for SS% were found for all the patients (6.97% with a 95%-CI, of 5.28–8.66%) and for the overweight group (7.88% with a 95%-CI of 5.63–10.13%) compared to the width of the groups at risk of cardiac death and myocardial infarction defined using SS%.

With respect to the impact of study count statistics on the perfusion scores (Table 3), a statistically significant difference was found for the SR% and SS% values calculated using the count-specific HM-NDB ($p = 0.03$ for the SR% and $p = 0.01$ for the SS%). The post-hoc test showed significantly lower SR% and SS% for 25%-HM-NDBs compared to 100%-HM-NDBs (SR%: $p = 0.02$; SS%: $p < 0.01$). These findings were confirmed in the overweight group of patients for SS% ($p = 0.01$).

4. Discussion

Normal databases represent the strength as well as the weakness of the myocardial perfusion quantification with SPECT. They have been shown to be very effective and reproducible, giving similar diagnostic predictions to those of a trained observer [19]. However, there are still several situations in which NDB-based quantification can introduce bias into the perfusion results due to the inherent patient non-specificity of NDBs. They may introduce inconsistencies in the presence of extreme heart geometry, such as Asiatic and female small hearts with reduced chamber size [20]. NDB-based methodology is also vulnerable with regard to patient-specific artefacts, such as scatter from subdiaphragmatic activity or hot spots due to regional myocardial hypertrophy (local increase in myocardial wall thickness) [21]. Moreover, the NDBs methodology confines the patient imaging protocol to the acquisition and reconstruction parameters used to create the NDBs available on the SPECT system [22]. The dependency of the NDB on radiopharmaceutical and camera type, rotation range and attenuation correction has been extensively investigated by the Japanese Society of Nuclear Medicine, but it has never evaluated the impact of patient dose on myocardial perfusion quantification [23].

To avoid the use of normal databases, alternative measures have been developed using stress and rest scans of the patients to obtain some measures of change in hypoperfusion [24]. In any case, the use of NDBs to define perfusion defects in SPECT MPI is now a mainstay in the nuclear medicine community. However, these NDBs are unknown objects on the gamma camera software and it is therefore difficult to investigate the NDB features and behaviour in relation to low-dose imaging.

Count statistics of MPI studies can be reduced by lowering the injected activity, consequently the patient dose, or by shortening the acquisition time. The resultant two effects on myocardial perfusion quantification are very similar if the other variable (time or activity) remains fixed and the patient position and radiopharmaceutical uptake remain unchanged [25]. In this study, low-count imaging was tested by acquiring three simultaneous scans with different acquisition times for each of the projection views after injecting the reference activity to the patients. In this way, we performed a realistic simulation of the low-dose effect on perfusion scores: same patient position, same radiopharmaceutical uptake and total scan times of about 16, 8 and 4 min for the 100%-, 50%- and 25%-count scans, respectively.

Three sets of homemade normal databases were firstly generated using polar maps obtained from 52 patients (23 male and 29 female, 34 overweight and obese patients) who had undergone ECG-gated SPECT (Figs. 1 and 2). We then evaluated the percent scores (SS% and SR%) on another group of 38 patients (27 males and 11 females, 23 overweight and obese patients) using the homemade NDBs and the normal databases available on the general-purpose gamma-camera Bright View (Philips) for Astonish™ algorithm with manufacturer's default parameters (4 iterations, 8 subsets, cut-off frequency = 1 cycle/pixel).

To the best of our knowledge, this is the first study evaluating the impact of study count-statistics on the features of normal databases in the case of a general-purpose gamma camera with sodium iodine heads and an iterative algorithm with resolution recovery.

A significant underestimation (about 14%) of the SS% was observed using the workstation NDBs for the 100%-count statistics rather than the corresponding homemade NDBs. Moreover, higher upper limits of agreement (Figs. 4 and 5) were found both for all patients and overweight patient groups compared to the width of the groups at risk with regard to cardiac event-free survival (5%). The use of the workstation normal databases, not user-specific (different gamma cameras and radiopharmaceutical), could lead to a different diagnostic judgment of the MPI examination.

In analysing the mean and standard deviation of the created NDBs, we found no difference in the average values of the normal myocardial segments among the different count statistics considered in this study, while the standard deviation values showed a statistical increase with the decreasing of the count density, particularly for the female stress basal segments (Fig. 3). These findings explain the impact of count statistics on the perfusion scores: the greater the standard deviation, the lower the hypoperfusion quantification with the same normal mean. These concerns concur with the results of Nakazato et al. for a CZT scanner [15]. In fact, the statistical analysis showed significantly lower SR% and SS% for 25%-HM-NDBs compared to the 100% reference (see Table 3).

Although the differences found may be acceptable from a clinical point of view (−17% for SR% and −13% for SS%), we chose to evaluate only the fully automated quantitative analysis as this method eliminates observer variability and bias. Moreover, it is useful for comparing sequential MPI studies.

The group of overweight and obese patients is of particular interest in MPI as these patients are more likely to suffer from cardiovascular diseases and cardiac mortality. Moreover, imaging of obese patients may lead to a higher incidence of attenuation artefacts and produce artificial perfusion defects compared to normal-weight patients [6]. In our study, the number of overweight and obese patients was too small to create weight-specific NDBs. However, specific normal limits for obese patients have been created in the past, showing no significant differences compared to normal-weight NDBs [12].

Scabbio et al. showed that, in overweight and obese patients, the reduction of count statistics to a quarter of the MPI reference influences negatively the perfusion quantification of the stress studies even if half-count normal limits are used [16]. The results of this study with count-specific HM-NDBs confirmed the past findings for the SS%, but also for SR%, in a patient group not restricted to overweight subjects.

Based upon the results of these studies, a 50% reduction in patient dose (~4.5 mSv) is ultimately the limit for the Astonish™ algorithm with the default parameters in order to prevent significant variations in the myocardial perfusion quantification.

5. Limitations

The results of this study are strictly dependent on the iterative reconstruction algorithm used and on the automatic quantification software available on our gamma-camera. Moreover, to avoid the introduction of misleading factors, we used the manufacturer's reconstruction recommendations for all the scans with different count statistics. The optimisation of the reconstruction strategy with low count density could provide better diagnostic image quality for myocardial perfusion imaging [26].

Furthermore, attenuation and scatter corrections were not applied, as routinely done in our centre, as TC is not available on our gamma-camera.

6. Conclusions

Both normal databases and perfusion scores depend significantly on study count-statistics. In particular, database variation was higher for the simulated low-dose scans with a statistically significant impact on the calculation of perfusion scores both at stress and rest. A 50% reduction in patient dose is ultimately the limit for the Astonish™ algorithm with the default parameters in order to prevent significant variations in the myocardial perfusion quantification.

Financial support

None.

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