ORIGINAL ARTICLE

Impact of non-specific normal databases on perfusion quantification of low-dose myocardial SPECT studies

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Aim. **To evaluate the impact of non-specific normal databases on the percent summed rest score (SR%) and stress score (SS%) from simulated low-dose SPECT studies by shortening the acquisition time/projection.**

Methods. **Forty normal-weight and 40 overweight/obese patients underwent myocardial studies with a conventional gamma-camera (BrightView, Philips) using three different acquisition times/projection: 30, 15, and 8 s (100%-counts, 50%-counts, and 25%-counts scan, respectively) and reconstructed using the iterative algorithm with resolution recovery (IRR) Astonish™ (Philips). Three sets of normal databases were used: (1) full-counts IRR; (2) half-counts IRR; and (3) full-counts traditional reconstruction algorithm database (TRAD). The impact of these databases and the acquired count statistics on the SR% and SS% was assessed by ANOVA analysis and Tukey test ($P < 0.05$).**

Results. **Significantly higher SR% and SS% values (> 40%) were found for the full-counts TRAD databases respect to the IRR databases. For overweight/obese patients, significantly higher SS% values for 25%-counts scans (+19%) are confirmed compared to those of 50%-counts scan, independently of using the half-counts or the full-counts IRR databases.**

Conclusions. **Astonish™ requires the adoption of the own specific normal databases in order to prevent very high overestimation of both stress and rest perfusion scores. Conversely, the count statistics of the normal databases seems not to influence the quantification scores. (J Nucl Cardiol 2019;26:775–85.)**

Key Words: Myocardial perfusion imaging • gated SPECT • iterative reconstruction • normality databases • patient dose

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Abbreviations

IRR	Iterative reconstruction algorithms with resolution recovery
TRAD	Traditional reconstruction algorithm database
LV	Left ventricle
GP	General purpose
CZT	Cadium zinc telluride
BMI	Body mass index
SR%	Percent summed rest score
SS%	Percent summed stress score
FBP	Filtered back projection
OSEM	Ordered subset expectation maximization

See related editorial, pp. 786–789

INTRODUCTION

Quantitative analysis of myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) has become a mainstay in nuclear cardiology practice because it eliminates observer bias and inter-observer variability and it is helpful for comparing sequential myocardial perfusion studies.[1]

Automatic quantitative algorithms developed by several groups are now commercially available and are routinely used.[2–4] These tools can automatically compute important clinical parameters, such as the amount of hypoperfusion at stress and rest, using perfusion scores. These scores are based on the evaluation of the differences between the patient-specific distribution of myocardial counts and the corresponding mean in normal population as a function of normal variability. Both normal mean and its variability depend on a number of factors, including patient related variables, image reconstruction algorithm used, and image noise. Thus, a potential limitation of this quantitative approach is the need for system, protocol, gender, and dose-specific databases of normality.[5–7]

Using an anthropomorphic phantom, Zoccarato et al.[8] found that the comparison of the perfusion data obtained from different systems requires the adoption of the specific normal databases developed for each systems, coupled with the reconstruction method employed. They found also that the mean segmental uptake as well as the associated variability are not affected by the reduction in count statistics up to 25% of the in-vivo reference (6 Mcounts) for the general-purpose (GP) gamma-cameras and the reconstruction algorithms with resolution recovery (IRR). However, the left ventricular (LV) insert of a phantom is geometrically fixed, while there is a great variability of the LV volume and normal uptake among the patients.

Using an advanced cadmium-zinc-telluride (CZT) camera, Nakazato et al. found that a progressive decrease of the LV counts leads to an increase of the inter-patient variation of the normal limits.[9] However, in the advanced CZT systems, the amount of acquired LV counts is fixed a priori (reference count statistics is typically 1 Mcounts) and thus, it is independent of the specific patient undergoing the cardiac examination, while in a GP gamma-camera the resulted LV counts depend on patient characteristics (degree of radiopharmaceutical uptake and patient weight), as well as injected activity and acquisition time of the study. Thus, the variability in normal polar maps could be different.

In a recent study, Lecchi et al. has demonstrated that the 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.[10] However, the authors used the same databases of normality for all the dose level of the study and for both normal-weight and overweight groups of patients.

Further studies may be needed to consolidate our knowledge regarding the use of normal databases in low-dose MPI studies with GP gamma-cameras and IRR algorithms, and in the presence of overweight and obese patients.

In the present study, the impact of non-specific databases of normality (reconstruction algorithms and different study count statistics) on the clinical estimates of the percent summed scores at stress (SS%) and rest (SR%) was investigated using the GP gamma-camera Bright View (Philips) and the IRR algorithm Astonish™ (Philips). Two different populations were considered, one of 40 normal-weight patients and another of 40 overweight or obese patients. First, an anthropomorphic phantom was used to compare normal LV polar maps of different levels of acquired count statistics and from different reconstruction algorithms, using an automated quantification tool (Autoquant™ ver. 7.0).

MATERIALS AND METHODS

Anthropomorphic Phantom Study

Phantom preparation and acquisition. An anthropomorphic phantom of the chest (Torso Phantom™ and Cardiac Insert™, Data Spectrum Corporation, Hillsborough, NC, USA), with inserts simulating lungs, liver, LV wall, and LV chamber, was used. The phantom chambers were filled with different ^{99m}Tc-radioactivity concentrations consistent with a normal distribution of the radiopharmaceutical in a stress cardiac study.[11] The phantom was acquired with a GP 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), starting from the *in-vivo* reference study count statistics of 6 Mcounts. This value of count statistics was established from a prior multicenter clinical database as detailed in a previous phantom study.[11]

Three acquisitions corresponding to 100% (6 Mcounts), 50% (3 Mcounts), and 25% (1.5 Mcounts) of the reference count statistics were acquired by, changing in each step only the acquisition time.

Image reconstruction and quantitative analysis of polar maps. For each acquisition, three sets of SPECT images were then reconstructed with three different algorithms:

(1) filtered back projection (FBP) with Butterworth filter (cut-off frequency = 0.5 cycles/pixel and order = 10);
(2) ordered subset expectation maximization (OSEM) with Butterworth filter (2 iterations and 8 subsets, cut-off f. = 0.5 cycles/pixel and order = 5);
(3) Astonish™, the IRR algorithm available at our center, with Hanning filter (default manufacturer's parameter: 4 iterations, 8 subsets, cut-off f. = 1 cycles/pixel and order 1).

No scatter or attenuation correction was applied.

The QPS algorithm of the Autoquant™ software (ver. 7.0) was used in order to analyze the different polar maps obtained from the three sets of phantom images. Each polar map was automatically divided into 17 segments and for each segment, the percentage ratio (*segmental uptake*) between the mean value and the corresponding maximum was considered.[2]

Statistical analysis. The impact of the different relative levels of count statistics, reconstruction algorithms, and coronary branch territories (left anterior descending, LAD, right coronary artery, RCA, and left circumflex artery, LCX) on the segmental uptake was assessed by three-way analysis ANOVA in order to understand also the apparent non-uniformity of polar maps. Relative levels of count statistics, reconstruction algorithms, and coronary branch territories were considered as independent variables, while the segmental uptake was considered as the dependent variables.

If a significant F value was found for one independent variable, then this was referred as a main effect and a post-hoc test (Tukey pairwise for multiple contrasts) was performed to identify the main source of variability.

Statistical analysis was performed using the software R Studio (Version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria). Differences were considered significant when P-value were ≤ 0.05.

Patients Study

Clinical study design and ECG-gated SPECT acquisitions. Among the patients referred in 2014 for a diagnostic MPI examination to the Nuclear Medicine Unit of the 'San Paolo' Hospital, Milan, Italy, a dataset of exams was retrospectively extrapolated. The main inclusion criteria (see reference[10] for more details) were: patient had undergone both stress and rest ECG-gated SPECT with [^{99m}Tc]Tetrofosmin using a 2-day imaging protocol and both weight and height of the patient was known. The main characteristics of the two patient groups, (1) 40 consecutive patients with normal-weight and (2) 40 consecutive overweight patients are summarized in Table 1.

All patients performed an 8 bin/cycle ECG-gated SPECT acquisition with the same GP 2-headed SPECT used for phantom (same acquisition protocol).[10] Assuming that count statistics of shorter-acquisition time (at the same patient dose) may simulate that of lower injected activity if the shorter projection views are obtained for each projection angle, three simultaneous scans (*100%-counts scan, 50%-counts scan*, and *25%-counts scan*) were started at the same time but with different acquisition time/projection, i.e. 30, 15, and 8 s, respectively.

Image reconstruction and assessment of summed scores. For each patient and each set of stress or rest projections with different count statistics, short-axis LV images were reconstructed using Astonish™ algorithm with default manufacturer parameters (4 iterations, 8 subsets, cut-off f. = 1 cycles/pixel). No attenuation or scatter correction was applied. Then, the corresponding polar map was created using Autoquant™ software.

For each LV polar map, three set of perfusion scores (SR% or SS%) were created using, one at a time, the following normal databases available in Autoquant™ software (for a total of 9 combinations of databases/count statistics for each patient):

(1) full-time normal LV images reconstructed with Astonish™ and default manufacturer parameters *(full-counts IRR*);
(2) half-time normal LV images reconstructed with Astonish™ and default manufacturer parameters *(half-counts IRR*);
(3) full-time normal images reconstructed without Astonish™, but with other traditional algorithms without resolution recovery (*full-counts traditional reconstruction algorithm database - TRAD*):
   - for stress images, iterative reconstruction algorithm provided by the manufacturer with 12 iterations and Butterworth filter (order = 5 and cut-off f. = 0.66 cycles/pixel);

Table 1. Description of the two patient groups considered in this study

Characteristics	Normal-weight group	Overweight group
N.	40	40
Age (y)	65.2 (SD 12.8)	64.1 (SD 11.4)
Male/Female (N.)	28/12	26/14
Weight (kg)	66.2 (SD 6.7)	82.9 (SD 14.2)
BMI (kg/m^2)	23.4 (SD 1.4)	29.4 (SD 4.0)
Stress type (n.)		
Exercise	38	33
Pharmacologic	2	7
Activity (MBq)		
Rest (100% reference)	588 (SD 50)	659 (SD 80)
Stress (100% reference)	591 (SD 47)	659 (SD 74)

- for rest images, FBP with Butterworth filter (order = 10 and cut-off f. = 0.50 cycles/pixel).

In the manual of the Autoquant™ software, it is reported that all the patients selected for the inclusion in a database had a low likelihood of CAD (< 5%), based on age, sex, pre-test symptoms, and risk factor. All had normal stress and rest myocardial perfusion SPECT images. All of the perfusion studies were of good to excellent quality, exhibited normal ventricular volumes, wall motion and global systolic function, and showed no evidence of transient ischemic dilatation. Quarter time IRR databases are not available on the software.

Statistical analysis. As for the phantom study, the impact of the different level of acquired count statistics and normality databases were assessed by ANOVA analysis and post-hoc test (Tukey pairwise for multiple contrasts) for both the normal-weight and the overweight groups of patients.

Moreover, the degree of quantification agreement between two different combinations of study count statistics and normal databases was assessed according to Bland and Altman as the mean (bias) ± 1.96 (95% limits of agreement) × standard deviation (SD) of the differences between the perfusion results obtained from the two methods. The perfusion results of 100%-counts scans were considered as reference when full-counts IRR databases were used for the automatic quantification.

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

RESULTS

Anthropomorphic Phantom Study

From a qualitative point of view (see Figure 1), no difference is evident for the same reconstruction method between the polar maps obtained from the different levels of study count statistics. On the contrary, the polar maps reconstructed with the IRR algorithm Astonish™ show a count reduction in the apical region (at the center of the polar maps) compared to the other reconstructions, independently of the level of count statistics. However, this difference is not statistically significant ($F = 0.02$), while coronary branch territory was a main effect with a statistically significant impact on the segmental uptake ($F = 5.73$, $P < 0.01$, Figure 2). Post-hoc test of coronary branch territories showed a significant increase in the segmental uptake from LCX to LAD areas ($P < 0.01$) and from RCA to LAD areas ($P < 0.05$), whilst no significant differences were detected between RCA and LCX ($P = 0.80$).

Patients Study

Perfusion quantification results. The detailed comparison between the perfusion results in relation to the normality databases and the level of study count statistics are reported in Tables 2 and 3.

Databases of normality. For both normal-weight and overweight groups of patients, the selection of the normal databases had a statistically significant impact on the SR% and SS% values. Post-hoc test showed significantly higher SR% and SS% for full-counts TRAD databases respect to both full-counts and half-counts IRR databases (Figure 3).

For both groups of patients, the Bland and Altman plots of SR% and SS% results for 100%-counts scans between full-counts TRAD databases and full-counts

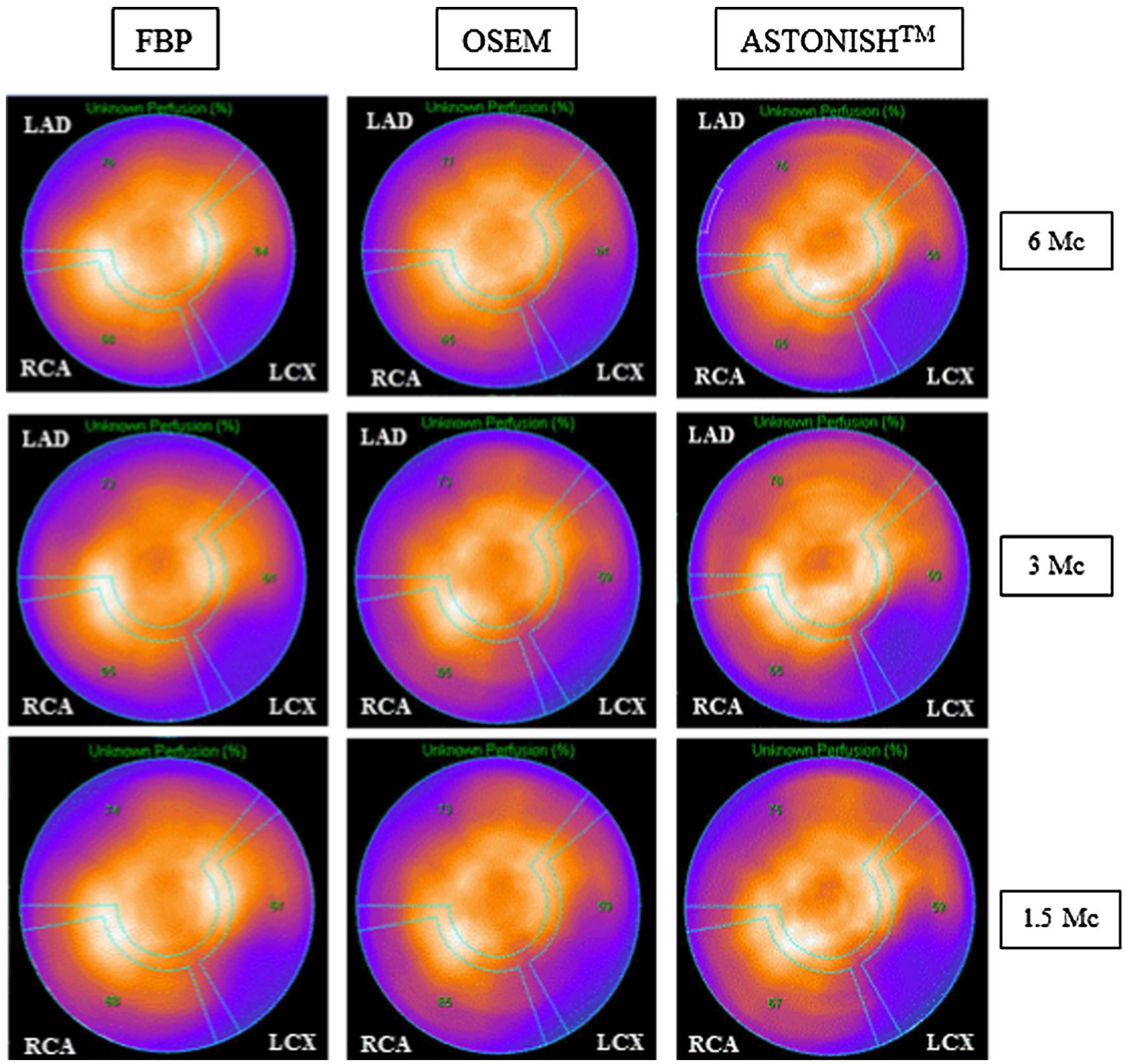

Figure 1. Phantom polar maps obtained for the three different reconstruction methods considered in this study (FBP, OSEM, and Astonish™) starting from different levels of count statistics chosen (6Mc, 3Mc, and 1.5 Mc).

IRR databases are shown in Figure 4. A trend in the differences among the SR% and the SS% values was not evident and the variability remained consistent across the average values. However, higher upper limits of agreement for SS% were found for both normal-weight group (9.68% with a 95% confidence interval, CI of 8.02–11.35%) and for the overweight group (9.46% with a 95% CI of 7.65–11.28%) compared to the width of the groups of risk for cardiac death and myocardial infarction defined using SS%.[2] Risk groups based on the percent stress perfusion are: less than 5% (normal or minimally abnormal), 5%–9% (mildly abnormal), 10%–14% (moderately abnormal), and 15% or greater (severely abnormal).

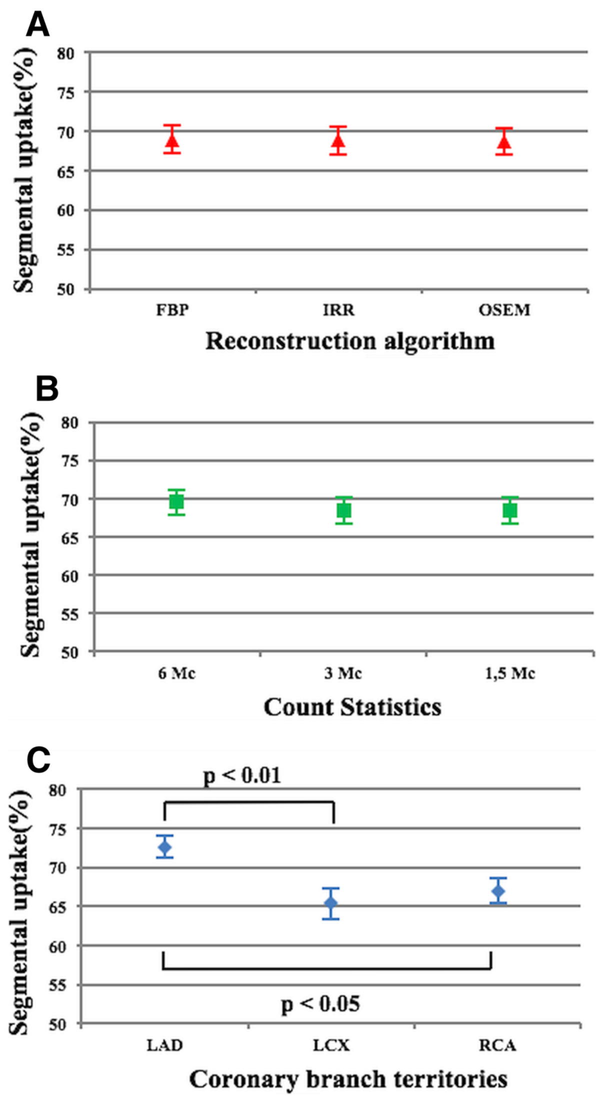

Figure 2. Segmental uptake as a function of reconstruction method (**A**), count statistics (**B**), and coronary branch territory (**C**). Points represent mean values (considering the entire dataset) and vertical bars represent 95% confidence intervals (P = probability from the post-hoc test).

Relative level of count statistics. For both normal-weight and overweight groups of patients, the SR% did not depend on the level of the study count statistics ($F = 0.37$ and $F = 0.18$, respectively). For normal-weight patients, also SS% values did not depend on the level of study count statistics ($F = 0.71$), while for the overweight group of patients the level of study count statistics was a main effect with statistically significant impact on SS% ($F = 8.33$). The post-hoc test demonstrated significantly higher SS% from 25%-counts scans to 50%-counts scans (5.45 ± 0.61 vs. 4.58 ± 0.59, $P = 0.013$), whereas no significant difference was found between 100%-counts scans and 50%-counts scans (4.60 ± 0.59 vs. 4.58 ± 0.59, $P = 0.996$) (Figure 5).

For overweight group of patients, Bland and Altman plots of SS% values between 100%-count scans/full-counts IRR databases and 25%-counts scans/(full-counts or half-counts) IRR databases are shown in Figure 6. A trend in the differences among the SS% values was not appreciable and the variability remained consistent across the average values. Similar values for mean and upper/lower limits were found between the two plots with different normality databases (full-counts vs. half-counts). The upper limits are higher than 4%, although not statistically significant.

DISCUSSION

Dedicated CZT scanners, multifocal collimators, or advanced reconstruction algorithms, as well as stress-first or low-radiotracer-dose protocol (half dose or less than half dose) allow a significant reduction of patient dose in MPI.[12] The use of CZT cameras allows to conjugate high diagnostic performance[13] with significant decrease in patient dose,[14] but the availability of such equipment is still limited mainly because they are scanners dedicated only to nuclear cardiology.

Table 2. Normal-weight patients: statistical results for SR% and SS% in relation to study count statistics and normal databases

Main effect	Description	SR%	SS%
Normal databases	Full-counts IRR	4.45 ± 0.71	7.97 ± 0.87
	Half-counts IRR	4.21 ± 0.69	7.78 ± 0.85
	Full-counts TRAD	6.52 ± 0.77	11.04 ± 0.90
	ANOVA: *P-value*	$<10^{-4}$	$<10^{-4}$
Study count statistics	100% counts	5.13 ± 0.75	8.78 ± 0.91
	50% counts	5.06 ± 0.70	8.88 ± 0.88
	25% counts	4.98 ± 0.74	9.13 ± 0.87
	ANOVA: *p-value*	n.s. (0.68)	n.s. (0.46)

Table 3. Overweight or obese patients: statistical results for SR% and SS% in relation to study count statistics and normal databases

Main effect	Description	SR%	SS%
Normal databases	Full-counts IRR	2.22 ± 0.52	3.88 ± 0.57
	Half-counts IRR	2.14 ± 0.52	3.92 ± 0.56
	Full-counts TRAD	3.18 ± 0.56	6.83 ± 0.63
	ANOVA: *P-value*	<0.01	<0.001
Study count statistics	100% counts	2.53 ± 0.54	4.60 ± 0.59
	50% counts	2.47 ± 0.53	4.58 ± 0.59
	25% counts	2.54 ± 0.53	5.45 ± 0.61
	ANOVA: *P-value*	n.s. (0.81)	<0.001

Zoccarato et al. demonstrated, in an anthropomorphic phantom study, that the application of the advanced algorithms with resolution recovery to conventional gamma-cameras hold the promise of significantly reducing patient dose until 75% of the reference.[11] However, according to our previous study,[10] the reduction of the patient dose to such a low limit influenced negatively the automatic quantification of hypoperfusion in overweight or obese patients when the full-dose normal limits were used.

Some open issues remain in relation to low-dose MPI studies with a conventional gamma-camera and an IRR algorithm, mostly in the presence of overweight and obese patients. In particular, the need of dose-specific databases of normality should be clarified.[1,15] Moreover, to the best of our knowledge, no study has evaluated the potential clinical outcome of using non-specific normal databases for the automatic perfusion quantification of cardiac images reconstructed with the advanced reconstruction algorithms.

In the present study, we first investigated the influence of reconstruction method (FBP, OSEM, and IRR algorithms), level of study count statistics (100%, 50% and 25%) and coronary branch territory on normal segmental uptake using an anthropomorphic phantom and a clinical quantification software based on QPS algorithm.[2] We found that the polar maps reconstructed with the IRR algorithm Astonish™ present a count reduction in the apical region, even if not statically significant, compared to the conventional polar maps (with FBP or OSEM), as a result of the different LV contour defined by the software on the reconstructed images (Figure 7). The inclusion of the resolution recovery and noise regularization in the iterative reconstruction yields an improvement in spatial resolution, contrast, and background variability of cardiac images compared to conventional OSEM,[8] that seems to influence the outcome of the quantification software.

On the contrary, no variation was found between the polar maps with different count statistics for the same reconstruction method, while the statistical analysis showed significant differences in segmental uptake between LCX and LAD and between RCA and LAD due to photon attenuation in the phantom (Figure 2). A previous study documented that attenuation correction

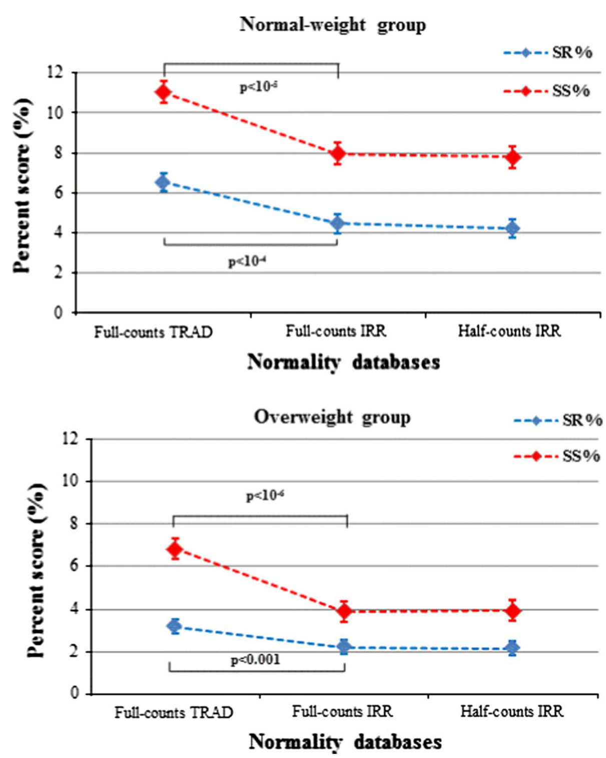

Figure 3. Percent rest score (SR%) and percent stress score (SS%) values as a function of normal databases for normal-weight (*top*) and overweight (*bottom*) groups of patients. Points represent means and vertical bars represent Fisher's least significant differences (P = probability from the post-hoc test).

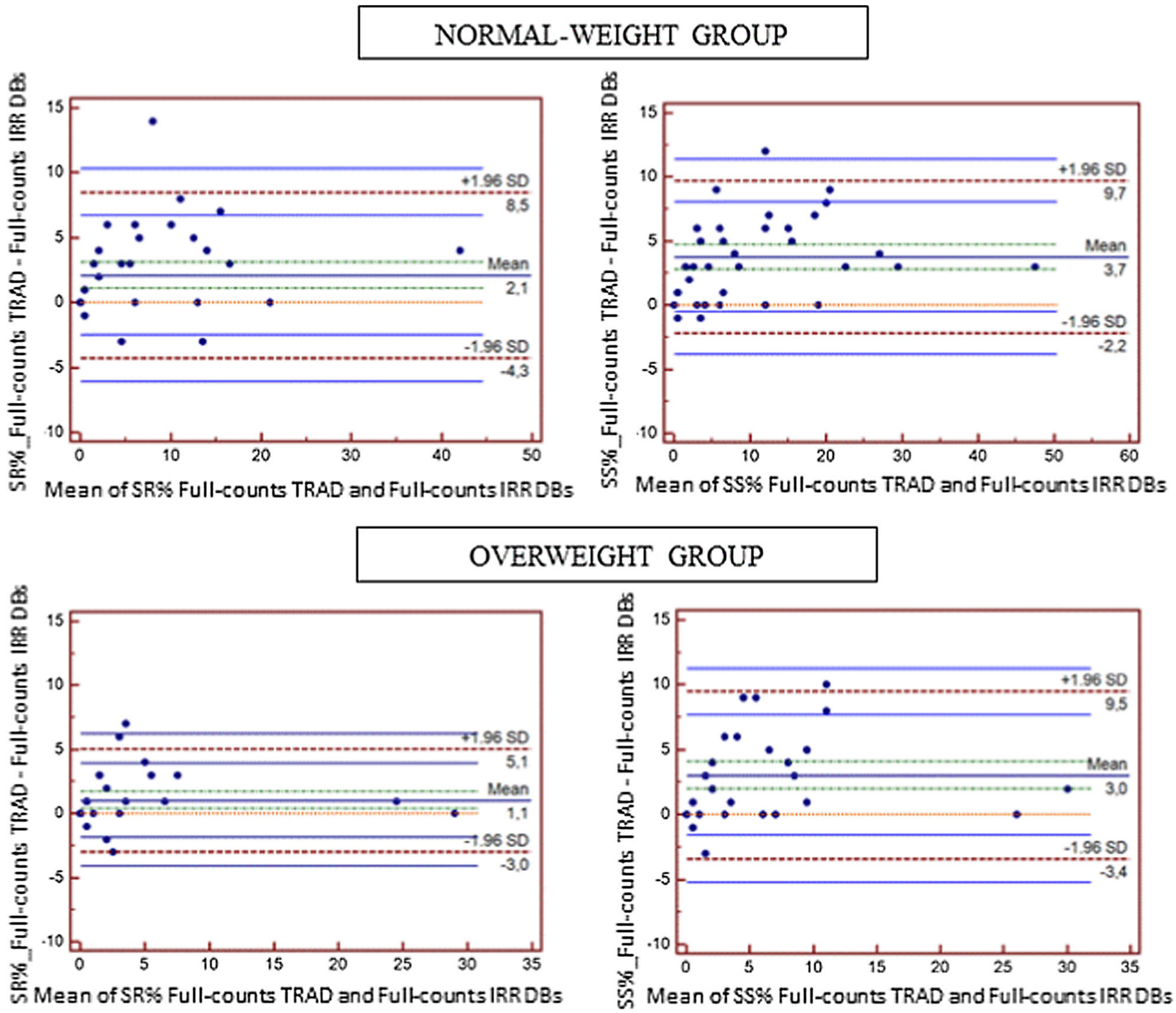

Figure 4. Bland and Altman plots of SR% (*left*) and SS% (*right*) values obtained from the 100%-counts scans of normal-weight (*top*) and overweight/obese (*bottom*) patients between full-counts TRAD databases and full-counts IRR databases. Bias (mean) and limits of agreement (± 1.96 × SD) are shown (DBs = databases).

increases the uniformity of polar maps both in obese men and women.[16]

Although a phantom study is a useful test for evaluating the differences in relative perfusion distribution of normal myocardium uptake, it is less applicable for testing the inter-patient variation. Thus, a series of 40 normal-weight and 40 overweight or obese patients were considered and the different normal databases available on the GP gamma-camera Bright View (Philips) were investigated (full-counts IRR, half-counts IRR and full-counts TRAD databases). Low-dose imaging was tested by acquiring three simultaneous scans with different acquisition times (100%, 50%, and 25%-counts scans). Based on the results of the phantom study, only the Astonish^{TM} algorithm was considered for patient reconstruction.

The results of the patient study showed that, for all the level of acquired count statistics considered, both SR% and SS% are overestimated (> 40%) when normal databases based on a reconstruction method other than the IRR algorithm were used (Figure 4). This appears related to an incorrect quantification of perfusion defects. Defects were more extensive, more severe, or both. As shown in Figure 8, the use of normal databases not based on the IRR algorithm, results in an overestimation of the defect number and size, since some variations considered within normal threshold were considered below such threshold when the non-specific

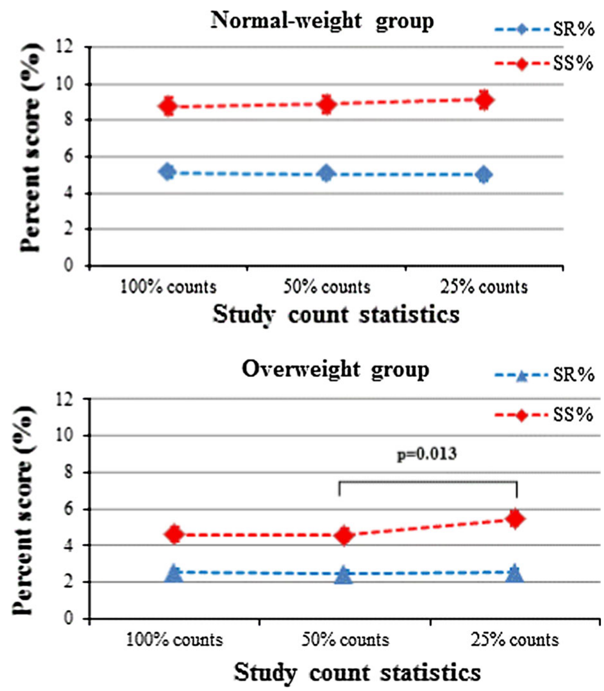

Figure 5. Percent rest score (SR%) and percent stress score (SS%) values as a function of study count statistics for normal-weight (*top*) and overweight (*bottom*) groups of patients. Points represent means and vertical bars represent Fisher's least significant differences (*P* = probability from the post-hoc test).

normal databases were used. Moreover, in the last case, higher upper limits of agreement were found both for normal-weight and overweight groups of patients compared to the width of the group of risk with regard to cardiac event-free survival (4%). This could produce the worsening of the diagnostic judgment of the MPI examination with a subsequent wrong risk-stratification of the patients.

A significant overestimation (about 19%) of the SS% for 25%-dose protocol was confirmed for the overweight group of patients even though normal scans with half-counts were used to build the database of normality (Figure 6).

In our nuclear medicine unit, we used 2-day imaging protocol. The alternative choice of one-day protocol entails different amount of radiopharmaceutical activity at both stress and rest studies. Thus, different normal databases are required for 1-day imaging protocol as a result of the different count statistics of the normal scans. However, the count statistics of the normal databases seems not to influence the quantification scores.

LIMITATIONS

For SPECT systems other than the one used in the current study, validations with other clinical studies are necessary. The results are also strictly dependent on the automatic quantification software (and databases of

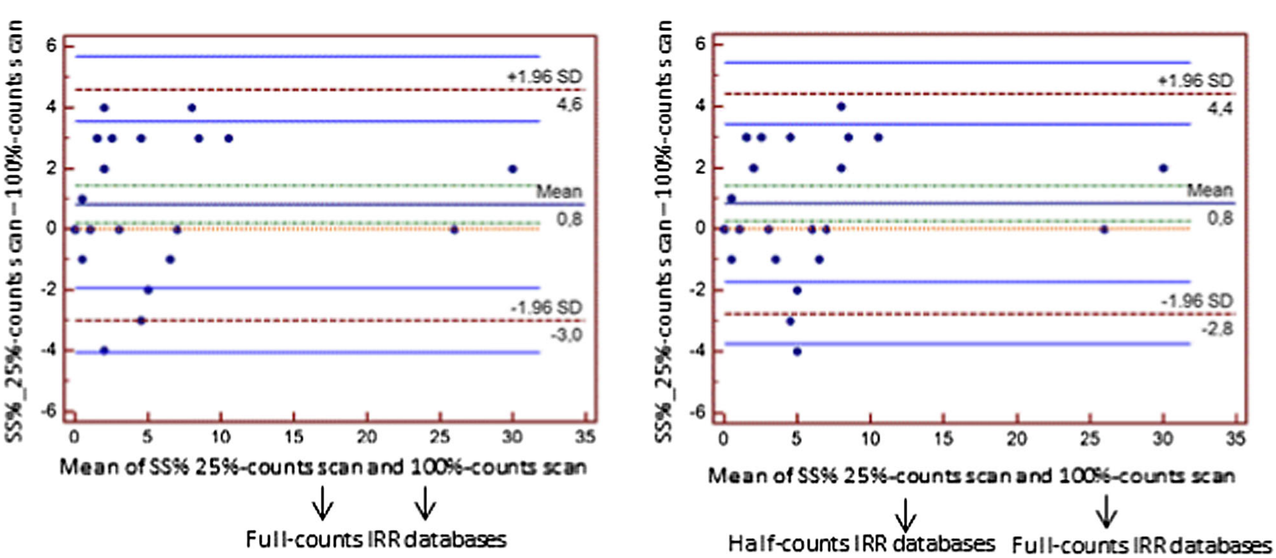

Figure 6. Bland and Altman plots of SS% values between 100%-counts scans (full-counts IRR databases) and 25%-counts scans (full-counts IRR normality databases on the *left* and half-counts IRR normality databases on the *right*) for overweight group of patients. Bias (mean) and limits of agreement (± 1.96 × SD) between are shown.

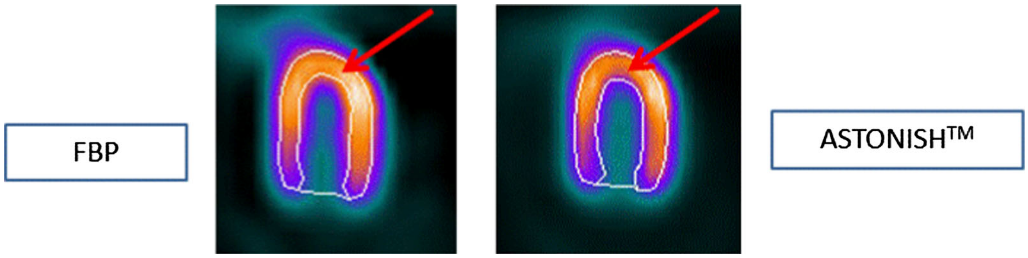

Figure 7. Horizontal long-axis images of the cardiac phantom reconstructed with FBP (*left*) or the IRR algorithm Astonish^{TM} (*right*).

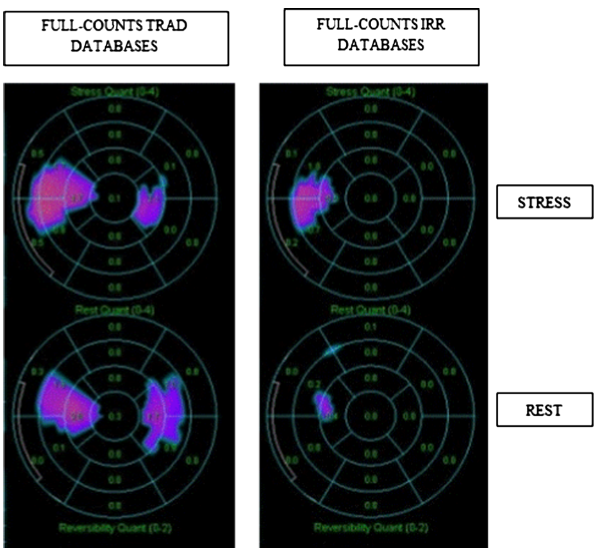

Figure 8. Different hypoperfusion areas from the same 100%-counts scans of a man with BMI = 26.56 kg/m^2 using the corresponding full-counts IRR databases (*right*) or the full-counts TRAD databases (*left*).

normality) available on the specific gamma-camera.[17] Moreover, to avoid the introduction of misleading factors, we used the manufacturers' recommendations for IRR parameters for the scans with different count statistics. The optimization of reconstruction strategy with count density could provide better diagnostic image quality for myocardial perfusion imaging.[18] Finally, image quality was not assessed in the present study. Image quality is likely to vary between the standard and shorter-acquisition scans, especially in the overweight patient group.

NEW KNOWLEDGE GAINED

The clinical outcome of using non-specific normal databases for the automatic perfusion quantification of the cardiac images reconstructed with an IRR algorithm is very important as it resulted in a very high overestimation of both stress and rest perfusion scores (> 40%) respect to the same data obtained from the specific normal databases. This is due to the improved image quality for the IRR algorithms compared to the conventional reconstruction methods (different contours of LV signal).

CONCLUSIONS

The IRR algorithm Astonish^{TM} (Philips) requires the adoption of the specific databases of normality available on the GP gamma-camera for the reconstruction method in order to prevent wrong risk-stratification with regard to cardiac event-free survival. The count statistics of the normal scans of these databases seems not to influence the perfusion quantification results. 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-counts normal limits were used.

Disclosure

C. Scabbio, O, Zoccarato, S. Malaspina, G. Lucignani, A. Del Sole and M. Lecchi declare that they have no conflict of interest.

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