

**Evaluation of the Left Ventricular Ejection Fraction with gated IQ-SPECT
Myocardial Perfusion Imaging.**

Troels Joergensen, MSc, Susanne Haase Hansson, MD.

Department of Clinical Physiology and Nuclear Medicine, Naestved Hospital,
Naestved, Denmark.

Correspondent author:

Troels Joergensen, MSc, Department of Clinical Physiology and Nuclear Medi-
cine, Naestved Hospital, Ringstedgade 61, 4700 Naestved, Denmark.

Phone: 0045 56514926

Fax: 0045 56513759

troe@regionsjaelland.dk

Word Count: 5469

Financial support: None

Abstract:

Background. The aim of this study was to evaluate the assessment of the left ventricular ejection fraction (LVEF) in patients by gated IQ-SPECT (Siemens Medical System).

Methods. 28 patients were examined using gated ^{99m}Tc -sestamibi IQ-SPECT. Using the same projection data, two different reconstruction datasets were created. The number of iterations, subsets and Gaussian filtering were based on two different recommendations from the manufacturer.

For each dataset end diastolic volume (EDV), end systolic volume (ESV) and LVEF were calculated using 4DMSPECT. A multigated planar equilibrium radionuclide ventriculography (MUGA) study with ^{99m}Tc –labeled red blood cells was used as a reference for the LVEF.

Results. The values of the different datasets were tested using the Bland-Altman analysis method. The calculated mean and 95% limits of agreement for the LVEF comparing dataset one and two was -1.1%, and 14%-points to -16%-points, comparing dataset one with MUGA the mean was calculated to -3.1%-points and 14%-points to -20%-points for the 95% limits of agreement, and comparing dataset two and MUGA gave a mean of -4.2%, and a 95% limits of agreement of -22%-points to 14%-points.

Conclusion. None of the two gated reconstructed datasets analyzed with 4DMSPECT were comparable to LVEF estimated by MUGA with a tendency to overestimate LVEF. However, large random variations of the EDV, ESV and LVEF between the two gated reconstructed datasets were found. The reconstructed datasets were not interchangeable. Thus, these values should only be used with great caution when evaluating the functional state of the heart.

Keywords:

Ejection fraction, IQ-SPECT, gated blood pool, myocardial perfusion imaging.

Introduction

As a diagnostic technique in coronary artery disease (CAD), electrocardiography (ECG)-gated single photon emission computed tomography (gSPECT) data acquisition is an established method. Reconstruction and analysis of the data provides information of left ventricular perfusion, wall motion, wall thickness and quantification of parameters as left ventricular end diastolic/systolic volumes (EDV, ESV) and ejection fraction (LVEF). The study is normally performed using dual or triple headed gamma camera system with low energy all purpose or low energy high resolution (LEHR) collimators installed and with a "90°" or "L" detector-configuration (1). To generate adequate imaging statistics the overall acquisition time can be 20-30 min. Developments in hardware and software, continue improving gSPECT image quality (2, 3). In December 2008, Siemens Healthcare announced the FDA clearance of their newly developed hardware and software package called IQ-SPECT with the purpose to shorten the acquisition time considerably. The Siemens IQ-SPECT system consists of SMARTZOOMTM collimators (magnifying collimators with a complex design), gantry movement control and special reconstruction software. SMARTZOOMTM collimators center on the heart, collecting up to 4 times more counts than LEHR collimators. These collimators magnify the heart while still capturing counts from the entire field of view (4, 5). IQ-SPECTs cardio-centric orbit

is centered on the heart instead of the gantry's mechanical center. This ensures that the heart is always in the SMARTZOOMTM collimators' magnification area. Thus the system is able to reduce acquisition time from approximately 20 minutes to approximately 5 minutes with the same patient dose (6, 7).

In our department the IQ-SPECT system has been used routinely for clinical gated and non-gated myocardial perfusion imaging (MPI) studies since the installation in 2011. The use of the new system has led to suspicion that the reliability of the LVEF using IQ-SPECT may be questioned. The aim of this study was to evaluate the LVEF using IQ-SPECT with two different reconstruction settings (Siemens^{Original} and Siemens^{New}) and to explore how these values relate to the LVEF using multigated planar equilibrium radionuclide angiography (MUGA). MUGA is a well-established method first reported in 1971 by Strauss et al (8) and it has earlier shown to be a simple, reproducible and highly accurate method for determination of LVEF (9,10).

Methods

Patients.

28 patients (12 males, 16 females; mean age 65 years, range 43-82) scheduled for routine MPI using ^{99m}Tc-Sestamibi IQ-gSPECT/CT were prospectively included. Exclusion criteria included pregnancy, arrhythmia and if the patient was not able to give written commitment. 17 patients were referred with suspected

CAD and 11 with known CAD. In 12 patients the stress test was performed as a physiological treadmill test, and 16 patients had a pharmacological stress test with dipyridamol. None of the patients required longer acquisition time or higher dose and Siemens quality control check was met (11). A 2-days SPECT/CT protocol was applied. gSPECT was only performed for the stress MPI. The stress test was performed according to the international guidelines (1). If the stress MPI was normal the rest MPI was not performed. A MUGA study was performed in addition to the MPI 3.4 ± 0.5 days (range, 3-6 days) later as a method of reference for the LVEF. All patients were informed orally and in writing. Written consent was given by all the patients. The study was approved by The Regional Committee on Health Research Ethics.

Method A: Gated stress ^{99m}Tc -Sestamibi SPECT/CT study.

Acquisition. Gated stress MPI acquisition was acquired using a Symbia T16 SPECT/CT (Siemens AG, Erlangen, Germany) equipped with SMART-ZOOMTM collimators. The acquisition was performed approximately 115 ± 20 minutes (range, 73-234 min) after injection of in average 650 ± 50 MBq (range, 600-705 MBq) ^{99m}Tc -Sestamibi. Gated IQ-SPECT images were acquired over 208° cardiac-centric orbits with 17 views per detector of 14 sec. The radius of the orbit was 280 mm. The total acquisition time for the study was only 6 min (including CT). Images were acquired with low-dose CT for attenuation correc-

tion for the non-gated images. Attenuation correction for gated images was not supported by the manufacturer. Additional acquisition settings are given in Table 1.

Reconstruction. After data acquisition was completed the study was transferred to a Siemens Syngo Processing workstation for reconstruction. The projection data was reviewed for motion, and motion correction was applied, if necessary. The manufacturer's original recommendation for the reconstruction was used: Siemens Flash3D iteration reconstruction algorithm, 15 iterations, 2 subsets, 10 mm Gaussian filtering (Siemens^{original}). Processing steps included determining of myocardial axes and boundaries and masking of the myocardium.

The Siemens Flash3D technology is based on the maximum likelihood reconstruction using ordered subset. It uses a 3D beam model for collimation in the iterative process providing increased accuracy over earlier models (OSEM 2D). Correctly modelling the collimation beam enables the distribution of the activity over the slices to be more accurately reconstructed. The Flash3D has furthermore been modified to include SMARTZOOMTM collimator and gantry movement. The Gaussian filtering is applied to the reconstructed images to reach the desired trade-off of resolution versus image noise.

Data analysis. The reconstructed gated dataset was loaded into the 3rd program 4DMSPECT (University of Michigan Center, version 2010.1.0.56, 28 April

2011). This program measures the EDV, ESV and LVEF and is described elsewhere (12). Automatic processing was initially used for all software. Tracing of the ventricular walls was visually evaluated by an experienced operator and if necessary the ventricular border surrounding the ventricle was modified and reprocessed.

Two experienced nuclear medicine physicians processed each dataset independently, beginning with the projection images and continued through reconstruction and gated SPECT analysis. The average of the values was calculated and used for further analysis. The interobserver variability was 1-3 %-points for all LVEF (data not presented here).

Method B: Gated stress ^{99m}Tc-Sestamibi SPECT/CT study.

The same projection data acquired in method A was used to create a new reconstruction for all patients. The manufacturer's new recommendation for the reconstruction was used: Siemens Flash3D iteration reconstruction algorithm, 12 iterations, 1 subset, 10 mm Gaussian filtering (Siemens^{new}). Data analysis is as described in method A.

Method C: Multigated Blood-Pool Imaging.

International guidelines for determination of the LVEF using planar equilibrium radionuclide angiography was followed (13).

Acquisition. The patients red blood cells were labeled in vitro with 740 ± 45 MBq (range, 680-810 MBq) ^{99m}Tc and reinjected in the patient. After the injection of the labeled red blood cells, the MUGA was performed in the left anterior oblique projection ($30-45^\circ$). The data was acquired using a 64×64 matrix using a Symbia S gamma camera (Siemens AG, Erlangen, Germany) with LEHR collimators. 16 frames per R-R interval were used and the R-R interval tolerance window was set to 20%.

Data Analysis. LVEF was measured by the standard program supplied by the manufacturer (eSoft MI Apps VE50A, Siemens Medical Solution). Ventricular and background ROIs were created semiautomatic by the operator, with support of the cine loop and phase image for an accurate definition of valvular planes. Butterworth 0.55, volume curve smoothing and curve fitting were used.

Statistics.

Mean values and standard deviation, SD, were calculated for LVEF for each method and for EDV and ESV for method A and B. Scatterplots were drawn and linear regression analysis was performed by least squares fitting. The coefficient of determination, R^2 , and the Pearson correlation coefficient, r , were calculated ($r = \sqrt{R^2}$).

The similarity of the methods was tested according to the method of Bland-Altman (14–19).

The mean of the differences, the 95% limits of agreement and the confidence intervals, CI, for the mean and the 95% limits of agreement were calculated.

The distribution of the differences was compared to a normal distribution using the Kolmogorov-Smirnov test. The differences among the LVEF results were shown in absolute LVEF units, called “%-points”, not by percentage of LVEF. The statistical analysis was done using Microsoft Excel 2003.

To help us in the interpretation of the method comparison, we predefined a medical accepted limit. LVEF is an important parameter for prediction of poor long-term prognosis and the accuracy and reproducibility of the estimated LVEF is of great importance (20-22). The current guidelines for treating patients with cardio toxic chemotherapy states that chemotherapy should be considered discontinued if the patient represents with a drop in LVEF of 10%-points or more (23).

Therefore, if the new method for measuring the LVEF is unlikely to give readings for a subject who differs more than 10%-points from those obtained using the old method, we would rely on the measurements made by the new method, as differences smaller than this would not be affected in the clinical interpretation of the result. On the other hand, differences of 10%-points or more would not be satisfactory as an error of this magnitude could lead to a change in pa-

tient management. For the Bland-Altman plot this means that the $\pm 1.96SD \leq 10\%$, or actually that the upper/lower CI for the 95% limit of agreement $\leq 10\%$.

Results

For the 28 patients included in the study the mean of the LVEF was respectively $68 \pm 26\%$, $69 \pm 22\%$ and $64 \pm 24\%$ for method A, method B and method C. The range of the LVEF was approximately 20-83 %, Table 2. Most of our patients had normal LVEF, as only one was below 50%.

Comparison of volumes:

The results of the statistical analysis of EDV and ESV are summarized in Table 2-4 and Figure 1-2.

When comparing EDV and ESV for method A and B, the Pearson's correlations coefficient are in both cases high, $r=0.99$, and showed good correlation. From the Bland-Altman plots, Figure 1-2, we found that EDV has a systematic error of 11 mL and the systematic error of ESV is 4 mL. EDV and ESV are therefore estimated lower in method B compared to method A. The Bland-Altman analysis reveals high limits of agreement, 22 mL for EDV and 20 mL for ESV, shown in Figure 1-2.

Comparison of LVEF:

On the Bland-Altman plots, Figure 3-5, we found that the highest systematic error for the LVEF is 4.2%-points comparing method B with C, followed by 3.1%-points comparing method A with C, and the smallest systematic error is 1.1%-points comparing method A with B. In addition to the systematic error, the Bland-Altman plots indicated a significant random variance. For LVEF the range of limits of agreement are unacceptable high, respectively $\pm 15\%$ -point, $\pm 17\%$ -points and $\pm 18\%$ -points for method A vs. B, A vs. C and B vs. C. There is a poor correlation between the method A and B for assessment of the LVEF, ($r=0.71$) Table 5, and LVEF values calculated from 4DMSPECT showed poor to modest correlation with MUGA ($r=0.86$ and $r=0.67$).

Discussion

This study evaluates the estimation of LVEF using IQ-gSPECT with different reconstruction settings.

MUGA was chosen as the method of reference, because it remains a generally accepted standard, against which other LVEF measurement techniques are evaluated (24–26), and the method has been shown to be as good as MRI (27).

28 patients were included in the study. At this number we estimated that the width of the 95% limit of agreement was so high, that increasing the number of patients would only reduce the CIs-intervals and not contribute to reduce the fluctuations around the mean to the medical accepted tolerance.

When the IQ-SPECT system was introduced in 2011, recommendations from the manufacturer for processing of gated studies was to use Siemens Flash3D iterative reconstruction algorithm with 15 iterations and 2 subsets. This resulted in reconstruction times of 10-12 minutes per study. To reduce reconstruction time a new method was later suggested, reducing the number of iterations from 15 to 12 and the number of subsets from two to one. In order to see the effect of changing reconstruction parameters, we compared method A with B. This study reveals only a modest correlation ($r=0.83$, $y=0.7$, $b=20$) between the two methods.

Using the Bland-Altman analysis the mean is calculated to -1.1%-points. Such a small systematic difference is within our predefined medical limits, however, the variations around the mean cause problems. As seen in Bland-Altman plot in figure 3 the differences between the two methods are widely spread and the values for the $\pm 1.96SD$ are high, with values of $\pm 15\%$ -points. These variations around the mean tell us how far apart measurements by the two methods are likely to be.

Thus, for 95% of the patients the LVEF determined by method B will be within a range of +14%-point and -16%-point of the LVEF determined by method A.

As shown in Figure 3 the 95% limits of agreement are much wider than the medically accepted limits (the gray area). To accept the two methods to be in-

terchangeable, the width of the 95% limits of agreement (and its lower/upper CI) needs to be less or equal to the predefined medical limit. In our case the width of the 95% limits of agreement is 30%-points (40% with the CI) which are three times (four times with the CI) larger than our tolerance.

The statistical analysis of the EDV and ESV is summarized in table 2-4 and figure 1 and 2. There is a large systematic error of 11 mL for the estimation of the EDV between the two methods, and only a small systematic error of 4 mL for the ESV. The limits of agreement are in both cases approximately 20 mL indicating large fluctuation around the mean. The large limit of agreement for the LVEF between method A and B is due to the large systematic error of the EDV and due to the variations in both EDV and ESV.

To demonstrate this an example of reconstructed IQ-gSPECT data using method A and B loaded into 4DMSPECT is displayed in figure 6 and 7. Method A has better/more clearly defined borders than method B, and the volume of the myocardium seems to be smaller. As the number of iterations and subsets increase, the level of details in the image (including edge sharpness and conspicuity) is expected to improve but also the noise to increase. Using the same Gaussian filtering the images in method B are in this case over smoothed (reducing the Gaussian filtering has little effect). In figure 7 the 4DMSPECT seems to have a problem, particularly in method B, with the definition of the borders used for volume estimation.

Overall this shows that with even the most optimistic interpretation there are considerable discrepancies between the two methods, and we think that the disagreement is unacceptable for clinical use.

Another question to be answered is whether the LVEF measured by any of the two methods A and B is comparable to the method of reference. When comparing method A with method C the scatterplot in figure 4 and table 5 shows that the correlation between the two methods is poor. The Pearson's correlation coefficient is only 0.77, with a y-intercept at 12 and a gradient of 0.86. The deviation from the identity line is obvious. From the Bland-Altman analysis the mean difference is calculated to -3.1%-points which are within our predefined limit.

As before the variations around the mean is high and the $\pm 1.96SD$ is equal to $\pm 17\%$ -points. In this case we can estimate that for 95% of the patients examined, the LVEF determined by method A will be between 14%-point above the method of reference and 20%-points below. The limit of our medical accepted error of 10%-points is thus exceeded by a factor of more than three. This implies that method A can NOT be used as an alternative for estimation of the LVEF compared to method C.

Comparing method B and C is even worse. The Pearson's correlation coefficient is as low as 0.70, and visual inspection of the scatterplot in figure 5 confirms that the correlation is poor. The mean difference is calculated to -4.2%-

point, and the limits of agreement are $\pm 1.96SD = \pm 18.2\%$ -points. Once again we estimate that for 95% of the subjects the LVEF determined by method B will be between 14%-points above method of reference and 22%-points below. The predefined medical limit is exceeded with a factor close to four, and we must conclude that method B and C are NOT interchangeable.

In summary, none of the values EDV, ESV and LVEF generated by the methods A, B and C are comparable because of the large variations.

To the best of our knowledge most of the studies performed with IQ-SPECT are non-gated SPECT MPI, comparing image quality with conventional SPECT MPI (28-31). Onishi et al (31) has shown that the spatial resolution in the center of the scanner and image quality of the IQ-SPECT is comparable to the conventional SPECT (in a radius of 28 cm), suggesting that IQ-SPECT would be the optimal technology for MPI because of the reduced acquisition-time. However, IQ-gSPECT's ability to quantify the EDV, ESV and LVEF was not investigated as gated phantom studies were not performed. Corbette et al. (28) found in a single-center clinical trial that IQ-SPECT provided better image quality than conventional SPECT, but again gated studies were not performed. F. Caobelli et al. (29,30) concluded that MPI with IQ-SPECT protocol can be acquired using about a quarter the scan time normally needed without disagreement compared to full time scan acquisition performed with standard protocols, but only

for non-gated studies. A paper from Siemens Healthcare, P. Hawman et al (7) evaluated several patient studies to describe the differences between conventional SPECT and IQ-SPECT, but none of the studies were done as gSPECT and estimation of EDV, ESV and LVEF is lacking. An earlier paper from Siemens (11) compared the IQ-gSPECT with LEHR conventional gSPECT for estimation of the LVEF analyzed with 4DMSPECT. We have not asked Siemens Healthcare for permission to transmit the results. Talleruphuus et al (32) has also compared the quantification of the EDV, ESV and LVEF between IQ-gSPECT and conventional LEHR gSPECT. For conventional gSPECT the values for LVEF, ESD, and EDV were (60.8 ± 3.0) %-points, (44.2 ± 6.6) %-points and (101.6 ± 10.1) %-points. For IQ-gSPECT the corresponding values were (66.0 ± 4.2) %-points, (32.2 ± 6.2) %-points and (79.2 ± 9.3) %-points. They concluded that IQ-gSPECT studies exhibit systematic deviations from conventional studies concerning EDV, ESV and LVEF (as estimated by QGS).

A follow-up of our study would be to compare the LVEF estimated with other software packages (e.g. QGS, Emory toolbox) and try to optimize the reconstruction settings to see, if it is possible to obtain values for the LVEF, that are comparable to the LVEF estimated by method C.

Some limitations of this study should be noted. First, most of our patients had normal LVEF. The correlation in patients with impaired LV function should be

further evaluated in the 15% to 50% range. Second, the acquisition of gSPECT was performed more than one hour after the pharmacological stress test. The effect of myocardial stunning in the state of post-stress was unknown. Third, there are known variations in the estimation of EDV, ESV and LVEF between 3rd. party Cardiac Software packages, caused by differences in the way the contours that identify the cardiac surfaces are generated (33). Only the software package 4DMSPECT has been used here. Fourth, quantification of LVEF is dependent of the number of gates pr. cardiac cycle. In method A and B, 8 gates pr. cardiac cycle are used and in method C 16 gates pr. cardiac cycle are used. In 1995, Germano et al. (34) showed that the use of 8 gates per cardiac cycle instead of 16 resulted in a constant and predictable 4%-points decrease in LVEF. However, this should not influence our results. The main problem is the LVEF variations between the two methods.

Conclusion

Some differences in the measurement of LVEF can be expected when using different imaging techniques. To evaluate if two methods were interchangeable we defined an acceptable clinical change for the total deviation of LVEF, which was set to 10%-point. With this limit in mind we can conclude that changing the reconstruction settings for the iterative algorithm has a large impact on the estimation of EDV, ESV and LVEF using IQ-gSPECT. Therefore, method A

and B are NOT interchangeable. Furthermore, we can conclude that neither LVEF using method A or method B (estimated with 4DMSPECT) is comparable with LVEF estimated by MUGA and this is not suitable for evaluation of LVEF in critical settings e.g. in control of chemotherapy or evaluation of cardiac pumping efficiency.

Disclosure

No potential conflict of interest relevant to this article was reported.

References

1. Hesse B, Tagel K, Cuocolo A, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. *Eur J Nucl Med Mol Imaging*. 2005;32:855–897.
2. Slomka PJ, Patton JA, Berman DS, Germano G. Advances in technical aspects of myocardial perfusion SPECT imaging. *J Nucl Cardiol*. 2009;16:255–276.
3. DePuey E. Advances in SPECT camera software and hardware: Currently available and new on the horizon. *J Nucl Cardiol*. 2012;19:551-581.
4. Zeintl J, Rempel TD, Bhattacharya M, Malmin RE, Vija AH. Performance characteristics of the SMARTZOOM collimator. *Nuclear Science Symposium and Medical Imaging Conference*. IEEE, New York, USA. 2011;2426-2429.
5. Rajaram R, Bhattacharya M, Xinhong D, Malmin R. Tomographic performance characteristics of the IQSPECT system. *Nuclear Science Symposium and Medical Imaging Conference*. IEEE, New York, USA. 2011;2451 – 2456.
6. Vija AH, Malmin R, Yahil A, et al. A method for improving the efficiency of myocardial perfusion imaging using conventional SPECT and SPECT/CT imaging systems. *Nuclear Science Symposium Conference Record*). IEEE, New York, USA. 2010;3433-3437.
7. Hawman P, Ghosh P. *IQ-SPECT: A technical and clinical overview*. White paper. Siemens Medical Solutions, USA Molecular Imaging; 2012.

8. Strauss HW, Zaret BL, Hurley BJ, Natarajan TK, Pitt B. A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterize. *Am J Cardiol.* 1971; 28:575-580.
9. Hains AD, Khawaja IA, Hinge DA, Lahiri A, Raftery EB. Radionuclide left ventricular ejection fraction: a comparison of three methods. *Br Heart J.* 1987;57:232-236.
10. Wackers FJT, Berger HJ, Johnstone DE, et al. Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *Am J Cardiol.* 1979;43:1159-1166.
11. Siemens Healthcare. *IQ -SPECT Hints and Tips. Software Version VA60A.* Siemens HealthCare Headquarters, Erlangen, Germany. 2011.
12. Ficaro EP, Lee BC, Kritzman JN, Corbett JR. Corridor4DM: the Michigan method for quantitative nuclear cardiology. *J Nucl Cardiol.* 2007;14:455-465.
13. Hesse B, Lindhardt TB, Acampa W, et al. EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging.* 2008;35:851-885.
14. Blandi JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res.* 1999;8:135-160.
15. Blandi JM, Altman DG. Measurement in medicine: the analysis of method comparison studies. *Statistician.* 1983;32:307-317.

16. Blandi JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;307-310.
17. Blandi JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet*. 1995; 346:1085-1087.
18. Dewitte K, Fierens C, Stöckl D, Thienpont LM. Application of the Bland-Altman plot for the interpretation of method-comparison studies: a critical investigation of its practice. *Clin Chem*. 2002;48:799-801.
19. Stöckl D, Rodriguez D, Cabaleiro, Uytfanghe K, Thienpont LM. Interpreting method comparison studies by use of the Bland–Altman plot: Reflecting the importance of sample size by incorporating confidence limits and predefined error limits in the graphic. *Clin Chem*. 2004;50:2216-18.
20. Hammermeister KE, de Rouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease: selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation*. 1979;59:421–430.
21. White HD, Norris RM, Brown MA, Brandt PW, Whitlock M, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44–51.

22. Yamaguchi A, Ino T, Adachi H, Murata S, Kamio H. Left ventricular volume predicts postoperative course in patient with ischemic cardiomyopathy. *Ann Thorac Surg.* 1998;65:434–438.
23. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiology. *Am J Med.* 1987;82:1109-1118.
24. Hacker M, Hoyer X, Kupzyk S, La Fougere C, Kois J, Stempfle HU. Clinical validation of the gated blood pool SPECT QBS processing software in congestive heart failure patients: correlation with MUGA, first-pass RNV, and 2D-echocardiography. *Int J Cardiovasc Imaging.* 2006; 22:407–16.
25. Bondt PD, Winter OD, Sutter JD, Dierckx RA. Agreement between four available algorithms to evaluate global systolic left and right ventricular function from tomographic radionuclide ventriculography and comparison with planar imaging. *Nucl Med Commun.* 2005;26:351–359.
26. Mondelli JA, Di Luzio S, Nagaraj A, Kane BJ, Smulevitz B, Nagaraj AV. The validation of volumetric real-time 3-dimensional echocardiography for the determination of left ventricular function. *J Am Soc Echocardiogr.* 2001;14:994–1000.

27. Alberto J, Candell-Rierab J, Arnolda R, et al. Quantitative Analysis of Left Ventricular Function as a Tool in Clinical Research. Theoretical Basis and Methodology. *J Nucl Med*. 2005;46:1256-1263.
28. Corbett J, Meden J, Ficaro E. Clinical validation of attenuation corrected cardiac imaging with IQSPECT SPECT/CT [abstract]. *J Nucl Med*. 2010; 51(suppl 2):1722.
29. Caobelli F, Pizzocaro C. Evaluation of patients with coronary artery disease. IQ-SPECT protocol in myocardial perfusion imaging: Preliminary results. *Nuklearmedizin*. 2013; 52:178-185.
30. Caobelli F, Pizzocaro C, Massetti V, et al. Possible use of IQSPECT protocol in myocardial perfusion imaging in the evaluation of patients with suspected or known coronary artery disease: preliminary results [abstract]. EANM 2013; op231.
31. Onishi H, Matsutomo N, Kangai Y, Saho T, Amijima H. Differential impact of multifocus fan beam collimation with Lmode and conventional systems on the accuracy of myocardial perfusion imaging: Quantitative evaluation using phantoms. *Asia Oceania J Nucl Med Biol*. 2013;1:28-34.
32. Talleruphuus U, Davidsdottir ML, Lonsdale MN. How smart is SMART-ZOOM? A direct comparison between IQ-SPECT and traditional clinical myocardial perfusion SPECT [abstract]. EANM 2013;op232.

33. Wolak A, Slomka PJ, Fish MB, Lorenzo S, Acampa W, Berman DS, Germano G. Quantitative myocardial-perfusion SPECT: Comparison of three state-of-the-art software packages. *J Nucl Cardiol.* 2008;15:27-34.
34. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med.* 1995;36:2138-2147.

FIGURE LEGENDS

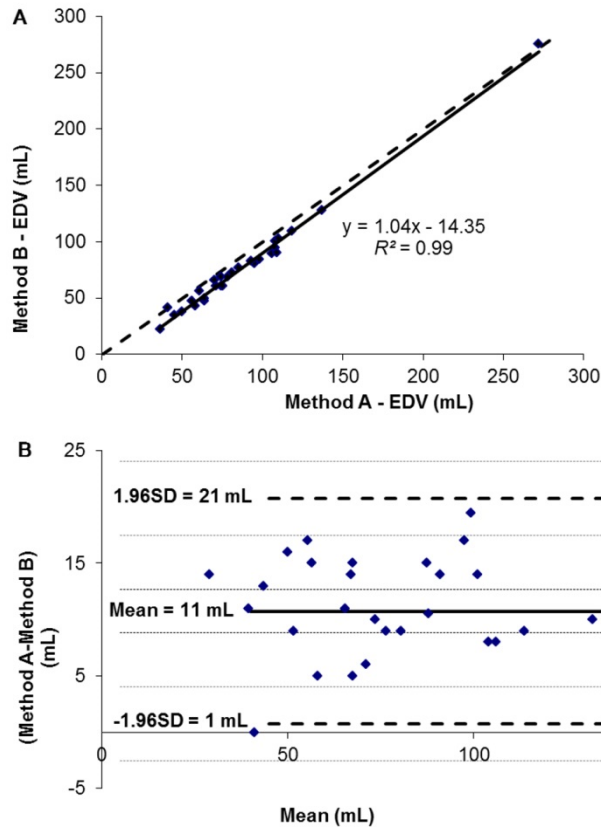


FIGURE 1. Method A vs B for EDV. A: Scatterplot. Linear regression calculated and shown as the full curve and line of equality illustrated by the dotted curve. B: Bland-Altman plot. Bold curve, The mean of the differences. Dotted curve, $\pm 1.96SD$. Small dotted curves, The CIs of the mean and the CIs of the limit of agreement. Notice that one point in the Bland-Altman plot is omitted due to scaling of the x-axis.

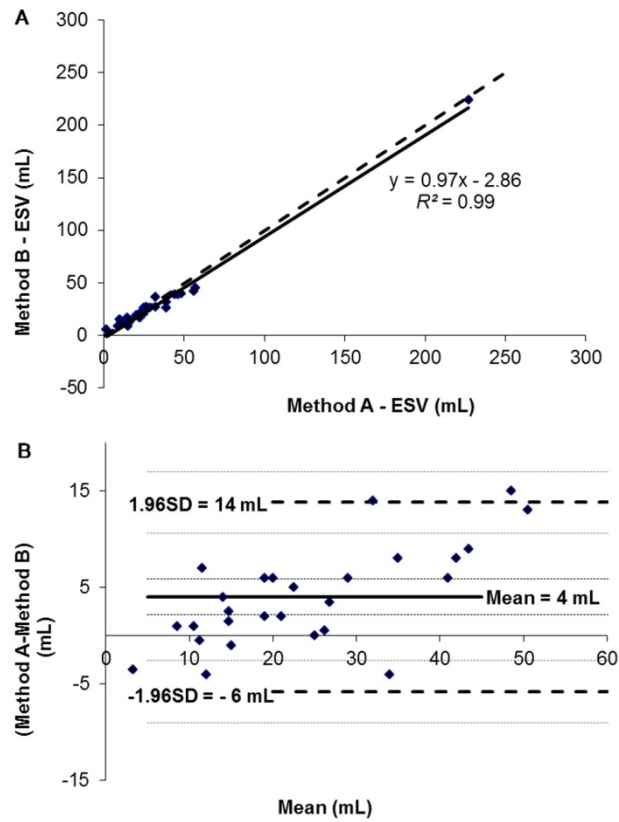


FIGURE 2. Method A vs B for ESV. A: Scatterplot. Linear regression calculated and shown as the full curve and line of equality illustrated by the dotted curve. B: Bland-Altman plot. Bold curve, The mean of the differences. Dotted curve, $\pm 1.96SD$. Small dotted curves, The CIs of the mean and the CIs of the limit of agreement. Notice that one point in the Bland-Altman plot is omitted due to scaling of the x-axis.

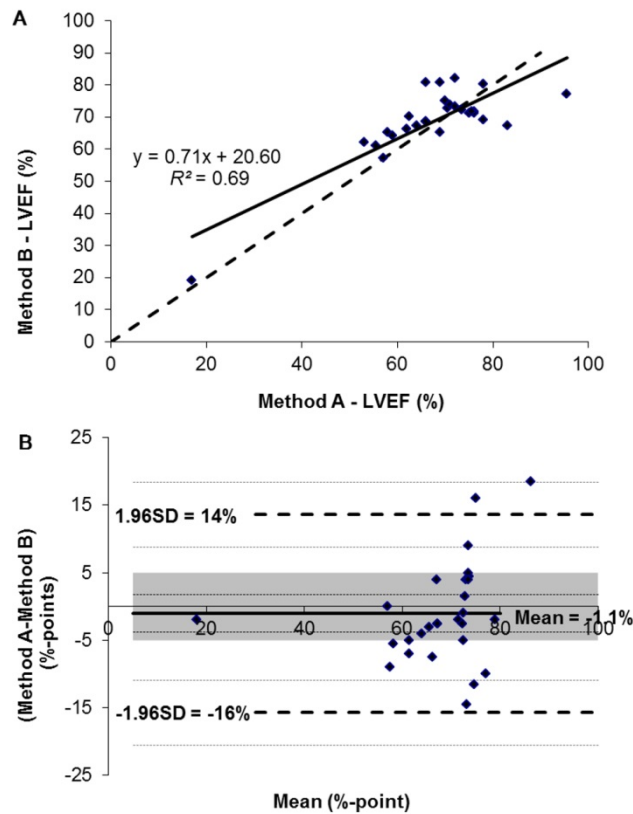


FIGURE 3. Method A vs B for LVEF. A: Scatterplot. Linear regression calculated and shown as the full curve and line of equality illustrated by the dotted curve. B: Bland-Altman plot. Bold curve, The mean of the differences. Dotted curve, $\pm 1.96SD$. Small dotted curves, The CIs of the mean and the CIs of the limit of agreement. Gray-area, Predefined medical limits of 10-% points.

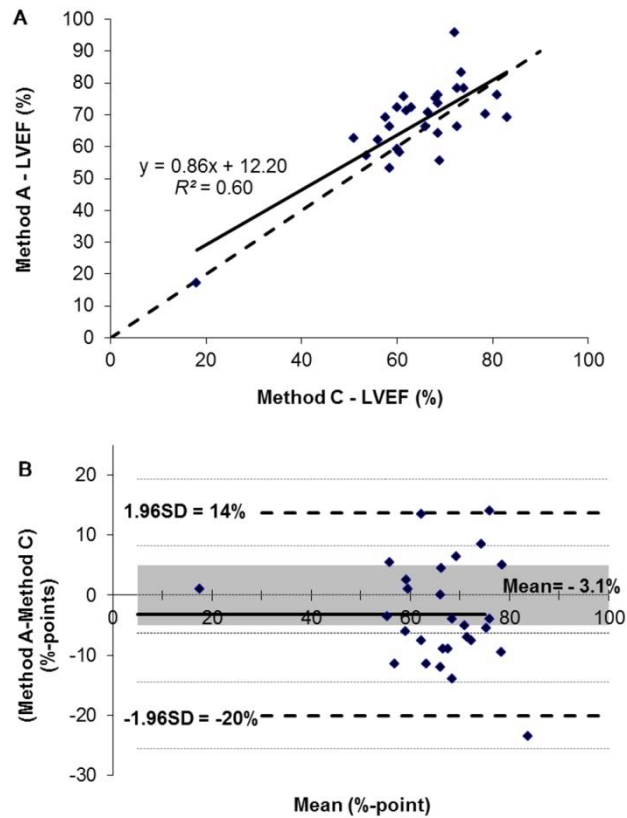


FIGURE 4. Method A vs C for LVEF. A: Scatterplot. Linear regression calculated and shown as the full curve and line of equality illustrated by the dotted curve. B: Bland-Altman plot. Bold curve, The mean of the differences. Dotted curve, $\pm 1.96SD$. Small dotted curves, The CIs of the mean and the CIs of the limit of agreement. Gray-area,

Predefined medical limits of 10-% points.

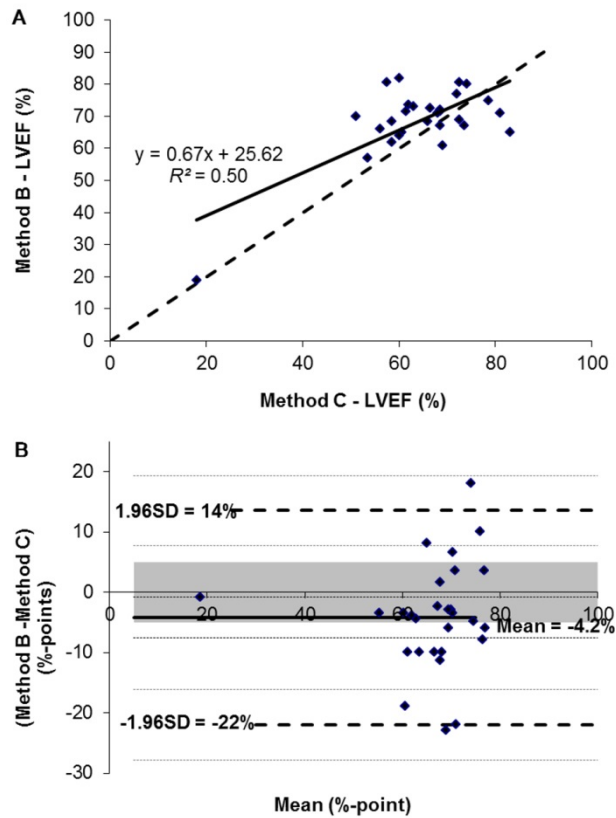


FIGURE 5. Method B vs C for LVEF. A: Scatterplot. Linear regression calculated and shown as the full curve and line of equality illustrated by the dotted curve. B: Bland-Altman plot. Bold curve, The mean of the differences. Dotted curve, $\pm 1.96SD$. Small dotted curves, The CIs of the mean and the CIs of the limit of agreement. Gray-area, Predefined medical limits of 10-% points.

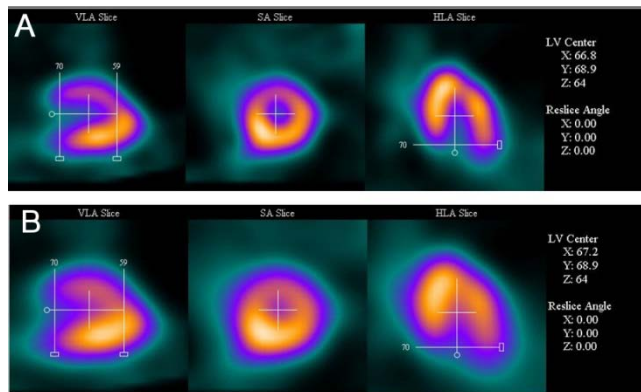


FIGURE 6. Screen Capture of the tap "Setup" in 4DMSPECT. Determination of the position of the LV center, and the apical and basal limits. A: Results for method A. B: Results for method B. The quality of the images in method B is in this case reduced. Notice that the Gaussian filtering in method A and B is equal.

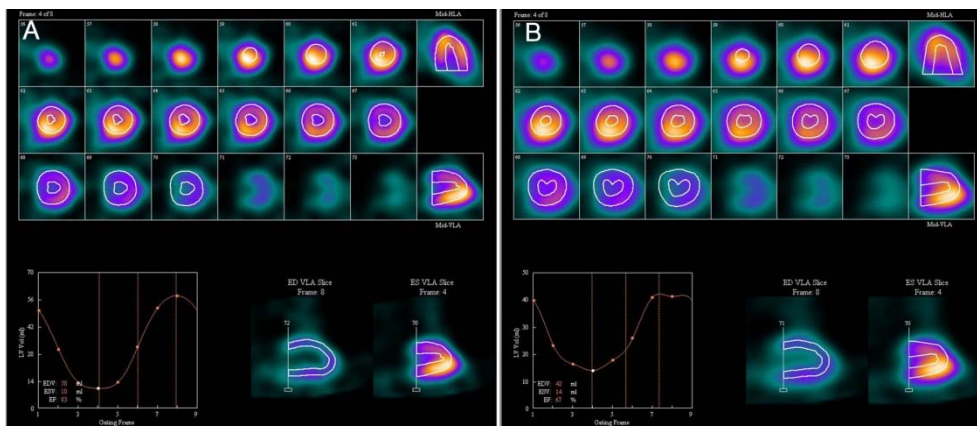


TABLE 1. Settings for acquisition and data processing for the three methods.

Method	A	B	C
Radiopharmacy	^{99m} Tc-Sestamibi	^{99m} Tc-Sestamibi	^{99m} Tc-Ultratag
Dose (±2SD)	650±50 MBq	650±50 MBq	740±45 MBq
Collimator	SMARTZOOM	SMARTZOOM	LEHR
Bins pr. cardiac cycle	8	8	16
Acq. time	5 min	5 min	20 min
Matrix	128*128	128*128	64*64
Pixel size	4.8 mm	4.8 mm	5.4 mm
Zoom	1	1	1.78
Camera position	2 det., 208°, 17 views	2 det., 208°, 17 views	Single head 45° LAO / best septal separation be- tween ventricles by adjustment
Processing Software	4DMSPECT	4DMSPECT	Siemens esoft (MIApps)
Reconstruction Alg.	Iterative Flash3D (15i2s)	Iterative Flash3D (12i1s)	-
Filtering	Gaussian 10 mm	Gaussian 10 mm	Lowpass filtering

TABLE 2. Average value, SD, and range for LVEF, EDV and ESV for all patients and for each of the methods applied. EDV and ESV can't be estimated in a MUGA study.

Method			
	A	B	C
EDV	[mL]	[mL]	
Mean±SD	87.0±44.2	76.3±46.3	-
Range	36-276	22-223	-
ESV	[mL]	[mL]	
Mean±SD	33.3±40.7	29.3±40.0	-
Range	1.5-227	5-223	-
LVEF	[%]	[%]	[%]
Mean±SD	67.5±13.4	68.6±11.4	64.4±12.1
Range	18-83	19-82	18-83

TABLE 3. Results of the Kolmogorov-Smirnov test for each method. If the data is normally distributed then, the critical value $D(n,\alpha)$ will be larger than $D(n)$. $D(n,\alpha)$ is found in the Kolmogorov-Smirnov table, for $n=28$ and $\alpha = 0.05$ $D(n,\alpha)=0.24$. $D(n)$ is calculated for each method comparison, and is in all cases lower than $D(n,\alpha)$. All data is normal distributed.

Methods				
	A vs. B		A vs. C	B vs. C
	$D(n)$	$D(n,\alpha)$	$D(n)$	$D(n,\alpha)$
LVEF				
KS-test	0.05	<0.24	0.09	<0.24
			0.10	<0.24
EDV				
KS-test	0.06	<0.24	-	-
ESV				
KS-test	0.08	<0.24	-	-

TABLE 4. Results of the statistical analysis for EDV and ESV for comparison between method A and B.

Methods		
	A vs. B	A vs. B
Bland Altman analysis		
	EDV [mL]	ESV [mL]
Mean $\pm$ 2SD	10.8 $\pm$ 22	4.0 $\pm$ 20
CI of mean	$\pm$ 1.9	$\pm$ 1.9
CI of limits	$\pm$ 3.3	$\pm$ 3.2
Linear regression (y=ax+b)		
a	1.04	0.97
b	-14	-2.8
R ²	0.98	0.99
r	0.99	0.99

TABLE 5. Results of the statistical analysis for LVEF for each comparison between method A, B and C.

Methods			
	A vs. B	A vs. C	B vs. C
Bland Altman analysis			
	[%-points]	[%-points]	[%-points]
Mean $\pm$ 2SD	-1.1 $\pm$ 15.0	-3.1 $\pm$ 17.2	-4.2 $\pm$ 18.2
CI of mean	$\pm$ 2.8	$\pm$ 3.3	$\pm$ 3.4
CI of limits	$\pm$ 4.9	$\pm$ 5.6	$\pm$ 5.9
Linear regression (y=ax+b)			
a	0.71	0.86	0.67
b	20.6	12.2	25.6
R ²	0.69	0.60	0.50
r	0.83	0.77	0.70