Original article

The influence of number of counts in the myocardium in the determination of reproducible functional parameters in gated-SPECT studies simulated with GATE

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\textbf{ABSTRACT}

Myocardial perfusion gated-single photon emission computed tomography (gated-SPECT) imaging is used for the combined evaluation of myocardial perfusion and left ventricular (LV) function. The aim of this study is to analyze the influence of counts/pixel and concomitantly the total counts in the myocardium for the calculation of myocardial functional parameters.

\textbf{Material and methods:} Gated-SPECT studies were performed using a Monte Carlo GATE simulation package and the NCAT phantom. The simulations of these studies use the radiopharmaceutical \(^{99m}\text{Tc}\)-labeled tracers (250, 350, 450 and 680 MBq) for standard patient types, effectively corresponding to the following activities of myocardium: 3, 4.2, 5.4–8.2 MBq. All studies were simulated using 15 and 30 s/projection.

The simulated data were reconstructed and processed by quantitative-gated-SPECT software, and the analysis of functional parameters in gated-SPECT images was done by using Bland–Altman test and Mann–Whitney–Wilcoxon test.

\textbf{Results:} In studies simulated using different times (15 and 30 s/projection), it was noted that for the activities for full body: 250 and 350 MBq, there were statistically significant differences in parameters Motility and Thickness. For the left ventricular ejection fraction (LVEF), end-systolic volume (ESV) it was only for 250MBq, and 350MBq in the end-diastolic volume (EDV), while the simulated studies with 450 and 680 MBq showed no statistically significant differences for global functional parameters: LVEF, EDV and ESV.

\textbf{Conclusion:} The number of counts/pixel and, concomitantly, the total counts per simulation do not significantly interfere with the determination of gated-SPECT functional parameters, when using the administered average activity of 450 MBq, corresponding to the 5.4 MBq of the myocardium, for standard patient types.

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\textbf{Influencia del número de cuentas en el miocardio, en la determinación de los parámetros funcionales en los estudios de Gated-SPECT, simulados con GATE}

\textbf{RESUMEN}

La gammagrafía de perfusión miocárdica sincronizada con el electrocardiograma (Gated-SPECT) permite la evaluación de la perfusión miocárdica y la función ventricular izquierda. El objetivo de este estudio fue analizar la influencia de las cuentas/pixel y, las cuentas totales en miocardio en la determinación de los parámetros funcionales.

\textbf{Material y métodos:} Hemos simulado estudios Gated-SPECT, por el método Monte Carlo GATE y el uso de fantoma NCAT.

Las simulaciones de estos estudios han considerado un paciente estándar utilizando un radiofármaco marcado con \(^{99m}\text{Tc}\), con diferentes actividades (250, 350, 450 y 680 MBq) correspondientes a las siguientes actividades en miocardio: 3; 4.2; 5.4 a 8.2 MBq. Se simularon todos los estudios con un tiempo de 15 y 30 seg/proyección. Los datos simulados fueron reconstruidos, procesados y quantificados por el software Quantitative-Gated-SPECT. El análisis de la influencia de las cuentas en los parámetros funcionales se llevó a cabo utilizando la prueba de Bland-Altman y Mann-Whitney-Wilcoxon.

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Introduction

Myocardial perfusion gated-SPECT is an imaging technique that uses radiopharmaceuticals (e.g., $^{99m}$Tc-tetrofosmin) to evaluate the distribution of blood flow in cardiac muscle and the myocyte functional viability.1

The advantages of using this imaging technique is a combination of the characteristics of myocardial SPECT studies, which allows the assessment of myocardial perfusion of the LV and quantitative parameters of myocardial function, such as LV ejection fraction (LVEF), end-diastolic volume (EDV), end-systolic volume (ESV) and quantification of movement and systolic thickening of the LV myocardium.2,3

The optimization of such acquisition protocols is not yet fully accomplished.4 Based on the EANM Guidelines, there are several benchmarks in the activity (MBq) administered to “standard type patients”, taking into account the acquisition protocol used in Europe or the country where it is performed.1

Standard protocols of the myocardial perfusion gated-SPECT studies require an average of 20 min/study.1-3 The special position of the arms (raised above the head) to avoid artifacts of reconstruction and approaching the detectors as much as possible to the signal source – the myocardium – though uncomfortable for patients, a must to avoid movement artifacts during the acquisition.4 It is therefore important for the total duration of image acquisition to be reduced as much as possible. However, it is known that this reduction leads to decrease on counts statistics per projection and doubts arise about the validity of the functional parameters determined by quantitative gated SPECT/quantitative perfusion SPECT (QGS/QPS) program.

For these reasons decreasing acquisition time without compromising the results, especially in the quantification parameters of cardiac function, is important.

Due to ethical, logistical and economical reasons, the acquisition and analysis of real patients were a problem, so simulated studies were performed for this purpose.

A previous implementation of the Monte Carlo simulation of the basic features of the GE Millennium MG SPECT gamma camera was used. This has already been validated by comparing data from simulated studies with experimental studies, showing a good agreement between the results obtained.4

Under this scope, the simulation parameters used in a previous work,4 were used to simulate the gated-SPECT imaging of a healthy standard patient, using the NURBS phantom – based cardiac torso (NCAT).5

This phantom,5 known today as XCAT phantom,6 is a useful tool in the aid of the study of medical imaging modalities such as myocardial SPECT. It is a tridimensional matrix which can be used in Geant4 Application for Tomographic Emission (GATE), representing the whole body of a patient that can be modeled to simulate the physiological movements such as breathing and heartbeat.

NCAT phantom allowed the study of the activity in Bq/voxel in a myocardium with normal radiopharmaceutical biodistribution and derived the number of average counts per pixel and total counts in the myocardium, for which acquisition time per projection does not interfere in the determination of functional parameters determined with gated-SPECT studies.

The purpose of this study is to analyze the influence of the number of counts/pixel and concomitantly the total counts in the myocardium per acquisition, in the calculation of functional parameters of the myocardium: LVEF, EDV, ESV, motility and thickening of the LV myocardium.

Material and methods

NCAT is an application that allows generating phantoms in two different pixelated versions: the phantom with the distribution of the radionuclide and the phantom of attenuation coefficients for a desired energy.5 This application includes a parameter file that allows the user to change shape and time dependency and control the generation of both distributions. In this study the pixelated version of NCAT describing the distribution of the radionuclide was used. A parameter file to build a phantom of a healthy male patient having 40 internal organs, with his arms lifted above his head, with a matrix of $128 \times 128$ pixels, with a heart rate of 72 beats/min, in which each cardiac cycle was divided into eight intervals, was used. This represents typical acquisition conditions used in the acquisition protocol of real studies.

The attenuation phantom was not simulated.

For the use of the NCAT phantom in GATE, the voxelized source was specified and for each voxel or voxel interval the activity and the type of particles emitted were also indicated in the GE Millennium MG macro.4 $^{99m}$Tc-tetrofosmin was chosen because it is the mostly used radiopharmaceutical in the majority of nuclear medicine services in Portugal in real studies to assess myocardial perfusion and function. The following reference values for standard type patients, i.e. a male patient carrying a weight of 70 kg and 170 cm height, suggested by EANM Guidelines1 used were:

According to the recommendations made by national European regulatory authorities, national societies and others,1 250 MBq the lowest (the minimum) and 350 MBq as the highest (the maximum) are used as the protocol for most European countries, including Portugal.

Based on the study of Garcia et al,7 for the first study of one-day protocol a 450 MBq and 680 MBq were used.

To calculate the activity in Bq/voxel in the NCAT phantom myocardium, the average percentage that is fixed in this myocardium was used, 30–60 min after intravenous administration, which represents 1.2% of total administered activity.8

This activity was, then, equally redistributed by the total number of myocardial voxels in the NCAT phantom, which is approximately 11,005 voxels resulting in the values showed in Table 1.4,9
In this study only activity in the myocardium was simulated. Tomographic studies were simulated under identical conditions to those performed on real patients. All tomographic studies were simulated in a 32-bit based PC server system with 4 GB of RAM, two processors at 3.4 GHz. All studies were simulated using a double detector gamma camera equipped with low energy high resolution collimators. Each study consisted of several projections along a path of 202.5° around the patient’s longitudinal axis, as corresponds to the 78.75° configuration of the two detectors, frequently used in cardiac SPECT studies.

In each study, 72 projections, 36 projections/detector (in step-and-shoot mode) including 8 intervals per cardiac cycle were simulated, starting in right anterior oblique and ending in left posterior oblique view.

Bearing in mind that we wanted to evaluate the interference of the total number of counts in the value of different myocardial functional parameters, all studies were simulated within the time period, 15 s/projection and 30 s/projection with activity in the myocardium of 3 MBq, 4.2 MBq, 5.4 MBq and 8.2 MBq (corresponding to the injected activity of 250 MBq, 350 MBq, 450 MBq and 680 MBq), respectively. The image was simulated considering an energy window of 130–158 keV (i.e. 20% asymmetric high energy window over the 99mTc photopeak with 3% offset), and with an acquisition matrix of 64 × 64 pixels. The difference in acquisition times by projection arises because it is assumed that the activity corresponds to an activity double the time than the first simulated activity in the myocardium. The intention was to investigate whether if by increasing activity in the myocardium and decreasing the time per projection, the function parameters obtained with Gated-SPECT studies were not compromised.

All simulations were repeated five times, in order to obtain statistical data that could be, whenever possible, explored through descriptive and inferential statistical analysis.

Values of the functional parameters of the left ventricle myocardium – LVEF, EDV, ESV, motion and thickness – were determined for the simulated data using the commercial software QGS/QPS10 under the same processing conditions as real studies, i.e., reconstruction using filtered back projection with Butterworth filter with a cutoff frequency of 0.4 cm⁻¹, order 10, without attenuation correction. In all studies the slices were reoriented according to the anatomic axis of the heart. Multiple short-axis, horizontal and vertical long-axis slices were thus generated.

The analysis of the interference of the number of total counts per simulation in the LV myocardium functional parameters were allowed when Bland-Altman test11 and the Mann-Whitney Wilcoxon test12 were used. Bland-Altman test was used to compare the functional parameters (LVEF, EDV, ESV, motility and thickness) calculated with two sets of simulated studies (same activity per myocardium but different times by projection), and also whether these differences are within the confidence interval determined for each study, when using the 95% confidence interval. The Mann–Whitney–Wilcoxon test was applied to infer whether the two independent samples and small dimension (N = 5) were statistically significant relating to the values found for the different functional parameters. Differences were statistically significant for p value inferior to 0.05 (5% level).

Results

Data presented are the result of the simulations of myocardium gated-SPECT studies (Fig. 1) performed with the same acquisition conditions, except for the activity in the myocardium and the acquisition time per projection (Table 1).

![Fig. 1. Gated-SPECT study simulated by using the NCAT phantom.](image-url)

<table>
<thead>
<tr>
<th>Whole body activity (MBq)</th>
<th>Myocardium activity (1.2% of whole body activity) – (MBq)</th>
<th>Myocardium voxel activity ≈ Bq/voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>3.0</td>
<td>275</td>
</tr>
<tr>
<td>350</td>
<td>4.2</td>
<td>385</td>
</tr>
<tr>
<td>450</td>
<td>5.4</td>
<td>500</td>
</tr>
<tr>
<td>680</td>
<td>8.2</td>
<td>750</td>
</tr>
</tbody>
</table>

Table 1 Reference values for standard type patients, suggested by EANM guidelines: whole body activity (MBq), corresponding myocardium activity (MBq) and myocardium voxel activity (≈ myocardium activity/11,005 voxels).
Table 2
No. of counts/pixel and total counts by studies with different activities in myocardium and acquisition times by projection.

<table>
<thead>
<tr>
<th>Activity in myocardium (MBq)</th>
<th>Time acquisition s/projection</th>
<th>Total counts/pixel in myocardium (N=5) mean (SD)</th>
<th>Total counts in myocardium (N=5) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>15</td>
<td>10.5 (2.3)</td>
<td>3.2052E+5 (719)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>21.0 (3.1)</td>
<td>6.42277E+5 (950)</td>
</tr>
<tr>
<td>4.2</td>
<td>15</td>
<td>14.5 (1.5)</td>
<td>4.49754E+5 (671)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>25.0 (2.6)</td>
<td>8.99812E+5 (948)</td>
</tr>
<tr>
<td>5.4</td>
<td>15</td>
<td>19.5 (2.5)</td>
<td>5.84315E+5 (764)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>35.7 (3.3)</td>
<td>1.16492E+6 (1079)</td>
</tr>
<tr>
<td>8.2</td>
<td>15</td>
<td>23.5 (2.5)</td>
<td>8.74780E+5 (935)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>55.5 (4.1)</td>
<td>1.75210E+6 (1320)</td>
</tr>
</tbody>
</table>

Analysis of the effect of average counts per pixel and the total number of counts per myocardium in the values of the functional parameters of left ventricular myocardium

Based on the average counts per pixel and average number of total counts in the myocardium (Table 2) the functional parameters of the LV myocardium were obtained.

In Table 2 is also represented the SD which demonstrates the deviation of the number of counts for each study simulated (five times) with the same activity in myocardium and the same projection time.

Global functional parameters – LVEF, EDV and ESV

As for the Bland–Altman test the results from the simulated studies with 3 MBq and 4.2 MBq in myocardium (corresponding to the injected activity of 250 MBq and 350 MBq) with different times per projection (15 s and 30 s) show differences between the average values of LVEF (%) that not only deviate from zero but are also outside the 1.96SD confidence interval (±2.1 and ±0.9, respectively). When compared these results agree with the results from the Mann–Whitney–Wilcoxon test, where the value of LVEF showed significant differences statistically for p value < 0.05, (Table 3).

Although simulated studies with 5.4 MBq and 8.2 MBq show minor differences between the LVEF values for both time/projection, these results are within the range of acceptable average differences of ±1% (see Table 3), also confirmed by the Mann–Whitney–Wilcoxon test (p value: 0.06 and 0.59).

As for the determination of the EDV when using the Bland–Altman test, the only simulated study that does not show agreement between the two methods applied was simulated with 4.2 MBq in myocardium (corresponding to the injected activity of 350 MBq). These differences are also outside the 1.96SD confidence interval (±1.61 mL) and in agreement with the Mann–Whitney–Wilcoxon test results (p value < 0.01) (Table 3).

The ESV was the only functional parameter where the differences found between sets of simulated studies for all the myocardial activities of 3 MBq, 4.2 MBq, 5.4 MBq and 8.2 MBq (corresponding to the injected activity of 250 MBq, 350 MBq, 450 MBq and 680 MBq) were inside the 1.96SD confidence interval (±2.46 mL, ±1.12 mL, ±0.82 mL and ±1.28 mL, respectively).

Regarding the inferential analysis with the Mann–Whitney–Wilcoxon test, statistically significant differences were only found for simulated studies with 3.0 MBq (corresponding to the injected activity of 250 MBq) (p value = 0.03), and not significant for all the other simulated activities in myocardium (p value > 0.05) (Table 3).
Table 4

<table>
<thead>
<tr>
<th>Activity in myocardium (MBq)</th>
<th>15 s</th>
<th>30 s</th>
<th>Average difference ± 1.96SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility cm² (SD)</td>
<td>Thickness cm² (SD)</td>
<td>Motility cm² (SD)</td>
<td>Thickness cm² (SD)</td>
<td>Motility</td>
</tr>
<tr>
<td>3.0</td>
<td>30.4 (5.33)</td>
<td>35.5 (4.95)</td>
<td>21.4 (4.92)</td>
<td>21.4 (10.85)</td>
</tr>
<tr>
<td>4.2</td>
<td>26.8 (2.39)</td>
<td>16.0 (2.00)</td>
<td>26.2 (0.84)</td>
<td>27.6 (1.67)</td>
</tr>
<tr>
<td>5.4</td>
<td>17.0 (1.22)</td>
<td>20.0 (0.71)</td>
<td>20.8 (1.30)</td>
<td>24.8 (0.84)</td>
</tr>
<tr>
<td>8.2</td>
<td>26.6 (0.55)</td>
<td>15.6 (1.14)</td>
<td>25.0 (1.00)</td>
<td>25.8 (1.92)</td>
</tr>
</tbody>
</table>

Average ± SD motility (cm²) and thickness (cm²) in each 5 simulations with the activity in myocardium of 3, 4.2, 5.4, and 8.2 and with 15 s/projection. Statistically significant differences for p < 0.05.

Regional functional parameters – motility and thickness of the LV myocardium

Motility and thickness values of the myocardial wall of the LV, in studies with different simulated activity with different times by projection, are presented in Table 4.

The difference between the values of LV myocardial wall motility simulated with different time/projection with 3 MBq, 5.4 MBq and 8.2 MBq (corresponding to the injected activity of 250 MBq, 450 MBq and 680 MBq) is above the acceptable limit but for 3 MBq (corresponding to the injected activity of 250 MBq) this difference is more evident and significant regarding the reference value (±6.68 cm²).

The assessment of myocardial wall thickness showed values above the acceptable range of differences.

Discussion

From the analysis of average counts per pixel and the total number of counts per myocardium in the values of the functional parameters of left ventricular myocardium it is verified, that for the parameter LVEF, the images with 3 MBq and 4.2 MBq (corresponding to the injected activity of 250 MBq and 350 MBq), simulated with the time 15 s/projection, resulted in images with an unacceptable low counts (averaging between 10.5 and 14.5 counts/pixel) compromising significantly the LVEF values in the gated-SPECT studies. Thus, the limited temporal resolution is also one of the factors that may affect the quantification of this parameter.

As far as the parameter of EDV is concerned, the simulated studies using 4.2 MBq (corresponding to the injected activity of 350 MBq) showed significant differences mainly outside the range of acceptable average differences.

The results for the parameter ESV indicate that this functional parameter is poorly influenced by the number of counts in the myocardium.

By analyzing Table 3 and although in literature it is stated that the division of the cardiac cycle in eight projections, is not ideal for the evaluation of the systolic function, it was noted that there are no major differences compromising significantly the ESV values in the gated-SPECT studies (except for the activity in the myocardium with 3 MBq (corresponding to the injected activity of 250 MBq), average counts 10.5/pixel).

The inferential analysis of the differences between the values of motility determined from the results of the projections simulation revealed that there were significant differences for the simulated studies with 3.0 MBq, 5.4 MBq and 8.2 MBq (corresponding to the injected activity of 250 MBq, 450 MBq and 680 MBq).

A detailed analysis of the results from the Bland–Altman test demonstrate that the deviation from zero presented by this functional parameter is higher than in the results from all the activities compared with the previous parameters which may point out the influence of the number of counts in myocardium in the determination of reproducible myocardial wall motility of LV in gated-SPECT.

In the assessment of myocardial wall thickness and on the contrary to what happened with the analysis of ESV, all simulated studies showed values above the acceptable range of differences (Table 4). These differences may result, as pointed by Fakhri et al., from partial volume effects in small structures, such as the wall of the LV myocardium. In fact, considering that the thickness of the myocardium is determined based on the increase of counts per pixel between the phases of systole and diastole and the average system resolution is 19 mm while the wall thickness of the myocardium is 10 mm, it may easily be concluded that the quantification of myocardial wall thickness of the LV can be influenced by partial volume effect which may explain why the quantitative parameters of regional myocardial function of LV are considered relevant and important, as it has been demonstrated in several studies, and that’s why further investigation and development of software for the correction of the partial volume effect must still be improved in order to be fully accepted and trusted in and by nuclear medicine departments.

Additionally, we should highlight that the simulations are not totally realistic because the phenomena of attenuation and scattering of photons were not considered. The simulations only included the heart geometry, injected activity and acquisition conditions, excluding the tissues surrounding the heart. Making the simulations excluding the attenuation map can be interpreted as we have made a perfect correction of the effects of attenuation and dispersion; that way, the results can have validity when comparing with real data after corrections.

Considering the results presented and discussed, the total number of counts by simulation does not significantly interfere with the calculation of the global functional parameter: LVEF, EDV and ESV when myocardial activity is equal to or greater than 5.4 MBq (corresponding to the injected activity of 450 MBq), in order to obtain an average value per pixel greater than or equal to 19.5 counts/pixel. Following EANM Guidelines reference values for a standard patient, in Portugal, the recommended lowest value, in the first study of one-day protocol, for Millennium MG gamma camera, should be 450 MBq.

Conclusion

Simulation of myocardium gated-SPECT studies, using the digital NCAT phantom, indicate that for whole body with a total injected activity ≥450 MBq (≥5.4 MBq in myocardium), an average 19.5 counts/pixel, correspond to a total number of counts 5.84315E+5, which does not interfere significantly with the evaluation of most functional parameters of LV myocardium, with the exception of the quantitative assessment of myocardial motility and thickness.

Whenever the cooperation of the patient is not possible, an administered average activity of 450 MBq is acceptable, by reducing the time/projection and consequently the total counts in the acquisition, without compromising significantly the global functional
parameters in clinical daily studies of gated-SPECT. By contrast, when an activity is less than 450 MBq we must increase the number of cycles or time/projection, otherwise there will be a risk of compromised results.

**Conflict of interest**

The authors state that there were no conflicts of interests when the manuscript was written.

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