

UNIVERSITY OF RIJEKA

FACULTY OF PHYSICS

Dea Dundara Debeljuh

**CHARACTERIZATION OF MYOCARDIAL
PERFUSION IMAGING SYSTEMS
THROUGH PHYSICAL DESCRIPTORS**

DOCTORAL DISSERTATION

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Supervisor: Prof. Slaven Jurković, PhD

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SVEUČILIŠTE U RIJECI

FAKULTET ZA FIZIKU

Dea Dundara Debeljuh

**KARAKTERIZACIJA SUSTAVA ZA
OSLIKAVANJE U PERFUZIJSKOJ
TOMOGRFIJI MIOKARDA NA
TEMELJU FIZIKALNIH DESKRIPTORA**

DOKTORSKA DISERTACIJA

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Rijeka, 2026.

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Doktorski rad obranjen je dana _____ u/na _____

_____, pred povjerenstvom u sastavu:

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There are three people who have profoundly shaped my professional life and my academic choices.

First, I would like to express my deepest gratitude to my high school physics teacher, Renzo Nicolini, who inspired me to choose physics as my life's path.

I am immensely grateful to Prof. Renata Longo, who introduced me to medical physics. Her lectures were the exact spark that opened my eyes to this field.

Heartfelt thanks go to my supervisor, Prof. Slaven Jurković, for giving me the opportunity to live my dream and become a medical physicist. He shaped my professional and personal growth by providing unwavering support throughout the years and encouraging me to do research.

I would also like to thank...

Roberta Matheoud, for her dedication and availability throughout these years. She walked this path with me, sharing knowledge and bringing kindness to every step.

Marco Brambilla for his warm hospitality and fruitful collaboration.

Prof. Michael Ljungberg for his support and the chance to work together on this project.

Miroslava Radić-Wolfl, for guiding me through my first steps in the application of physics in nuclear medicine.

My fellow physicists at the Clinical Hospital Center Rijeka and other collaborating institutions, and my colleagues from the General Hospital Pula, for their support.

All my friends, for being part of my life.

Finally, I am profoundly grateful to my family, Boris, Alba, Emma, Micol and Mija, for their unconditional love, their smiles and support throughout this journey and in everyday life.

I also hold a special place in my heart for those who would have loved to be here but sadly are no longer with us.

This investigation was performed within the scope of projects IAEA CRO6021 and UniRi-Iskusni-Prirod-23-8.

Characterization of myocardial perfusion imaging systems through physical descriptors

Abstract

Myocardial Perfusion Imaging (MPI) relies on the application of physics in diagnostic imaging and on gamma-ray detection. It is performed using scintillator or semiconductor detector systems, characterized by different collimation systems, detector and acquisition geometries, reconstruction algorithms and corrections performed, to determine the distribution of radiopharmaceuticals within the heart muscle.

The aim of this investigation is to introduce a novel approach for the characterization of *MPI systems* to extend and further advance current MPI quality metrics. Firstly, a characterization through physical descriptors related to image quality and myocardial perfusion data is performed by simulating clinical conditions with a semi-anthropomorphic phantom. In the second part of the investigation, the perfusion defect (PD) detection ability is evaluated for different *MPI systems* by image analysis performed with a quantitative post-processing algorithm. Standard perfusion descriptors have shown strong dependence on attenuation artifacts, and may lead to misinterpretation of image data. Additionally, partial volume effect and limited spatial resolution of respective systems influence detection of small PD. For these reasons, a new physical descriptor, the defect perfusion index (DPI), is introduced. Evaluation of the DPI is performed on image data obtained experimentally using a semi-anthropomorphic static phantom and also by Monte Carlo simulation of dynamic conditions in voxelized anthropomorphic phantom. DPI values obtained may be considered as reference values of the ability of an *MPI system* to detect PDs under controlled conditions. The results of this investigation provide new insights into MPI system performances.

Keywords: myocardial perfusion imaging, SPECT, physical descriptors, image quality, defect perfusion index, perfusion defect detection ability

Karakterizacija sustava za oslikavanje u perfuzijskoj tomografiji miokarda na temelju fizikalnih deskriptora

Sažetak

Oslikavanje perfuzije miokarda počiva na primjeni fizike u slikovnoj dijagnostici i na detekciji gama zračenja. Provođi se uporabom scintilacijskih i poluvodičkih detektora u svrhu određivanja nakupljanja radiofarmaka u srčani mišić. Detektori su određeni različitim sustavima za kolimaciju, geometrijskim konfiguracijama, geometrijama akvizicije, rekonstrukcijskim algoritmima te primjenjenim korekcijama.

Cilj istraživanja je osmišljavanje novog pristupa u svrhu nadogradnje i proširenja postojeće metrike kvalitete u oslikavanju perfuzije miokarda. Karakterizacija sustava je prvo učinjena na temelju fizikalnih deskriptora vezanih za kvalitetu slike i podataka o perfuziji miokarda, simulirajući klinički uvjete pomoću semi-antropomornog statičkog fantoma. U drugom dijelu istraživanja vrednovana je sposobnost detekcije perfuzijskog defekta putem analize slikovnih podataka koristeći kvantitativne algoritme za naknadnu obradu podataka. Standardni parametri perfuzije miokarda pokazali su snažnu ovisnost o atenuacijskim artefaktima što može dovesti do pogrešnog tumačenja slikovnih podataka. Efekt parcijalnog volumena i ograničena prostorna rezolucija kod određenih sustava dodatno utječu na detekciju malih perfuzijskih defekata. Zato je osmišljen novi fizikalni deskriptor, *perfuzijski indeks defekta*. Vrednovanje perfuzijskog indeksa defekta provedeno je na temelju eksperimentalno dobivenih slikovnih podataka statičkog fantoma, te Monte Carlo simulacijama dinamičkih uvjeta u vokseliziranom antropomornom fantomu.

Dobivene vrijednosti perfuzijskog indeksa defekta predstavljaju referentne vrijednosti sposobnosti sustava da u kontroliranim uvjetima detektira perfuzijske defekte. Rezultati ovog istraživanja pružaju novi uvid u performanse sustava za oslikavanje perfuzije miokarda.

Ključne riječi: oslikavanje perfuzije miokarda, SPECT, fizikalni deskriptori, kvaliteta slike, perfuzijski indeks defekta, sposobnost detektiranja perfuzijskog defekta

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List of abbreviations

attenuation correction (AC)	4	lookup table (LUT)	25
cadmium-zinc-telluride (CZT)	3	low-energy high-resolution (LEHR)	12
computed tomography (CT)	4	Magnetic Resonance Imaging (MRI)	37
contrast to noise ratio (CNR)	7	maximum likelihood/expectation maximization (MLEM)	5
coronary artery disease (CAD)	1	Monte Carlo (MC)	7
defect perfusion index (DPI)	32	Myocardial Perfusion Imaging (MPI)	1
ejection fraction (EF)	41	National Electrical Manufacturers Association (NEMA)	10
electrocardiographically gated myocardial perfusion SPECT (GSPECT)	37	non-circular detector orbit (NCO)	3
end-diastolic volume (EDV)	42	ordered subset expectation maximization (OSEM)	3
end-systolic volume (ESV)	42	perfusion defect (PD)	4
extended Cardiac-Torso phantom (XCAT)	37	poly (methyl methacrylate) (PMMA)	19
field of view (FOV)	12	Positron Emission Tomography (PET)	76
filtered back projection (FBP)	3	Quantitative Gated and Perfusion SPECT (QGS-QPS)	30, 73, 75
gated myocardial perfusion SPECT (GSPECT)	7	region of interest (ROI)	15
global uniformity (GU)	32	scatter and attenuation corrections (SCAC)	22
iterative reconstruction algorithms with resolution recovery (IRR)	3	scatter correction (SC)	22
law of propagation of uncertainty (LPU)	44	Single Photon Emission Computed Tomography (SPECT)	1
left ventricle (LV)	1	thallium-activated sodium iodide crystal NaI(Tl)-crystal	3
left ventricular inner chamber (LVIC)	25		

1. Introduction

The application of ionizing radiation in medicine began at the end of the 19th century. Over the years, ionizing radiation has been introduced into various diagnostic and therapeutic procedures. Today, modern medicine is almost unimaginable without its use.

Nuclear medicine is an area of medicine in which radionuclides are administered to the patient either in pure form or bound to different types of organic molecules (radiopharmaceuticals) for imaging and therapy. The aim of imaging is to diagnose and stage specific diseases, as well as to monitor the response to therapy. In imaging, pharmaceuticals labelled with gamma-ray emitters are used. Single Photon Emission Computed Tomography (SPECT) is a nuclear medicine imaging modality which gives an estimate of the three-dimensional in-vivo activity distribution. Activity distribution image data are used to obtain information about organ function and to detect physiological and metabolic changes before any anatomical changes become visible.

Myocardial Perfusion Imaging (MPI) is a nuclear medicine imaging procedure used to identify early asymptomatic coronary artery disease (CAD) and to assess the clinical impact of previously diagnosed disease. It is based on gamma-ray detection used to assess blood flow through the left ventricle (LV) of the heart muscle and to locate areas where blood flow is reduced. Image data are obtained by synchronizing image data acquisition with the patient's electrocardiogram, in the so-called electrocardiographically gated myocardial perfusion SPECT (GSPECT).

MPI procedures rely on various technological solutions that have been implemented through the years. They are mainly defined by the type of detector, the collimation system, the acquisition path and the reconstruction algorithm along with the corrections performed. The different combinations of tomographic imaging devices, reconstruction algorithms and correction modalities will be referred to as *MPI systems* hereafter.

The diversity of available *MPI systems* requires a comprehensive assessment of their performance, identification of limitations, and system validation. The characterization of such complex imaging systems through evaluation of the image data is the most important step in optimizing the MPI procedure. It ensures high quality of both the acquired data and the resulting diagnostic information.

In this investigation, a characterization of *MPI systems* was performed in image data obtained both experimentally, using a semi-anthropomorphic static phantom and by Monte Carlo simulation on voxelized anthropomorphic phantoms. Descriptors related to image quality and defect detection ability used in this

investigation will be referred to as physical descriptors hereafter. A new descriptor for the quantification of perfusion defect is introduced to extend and further improve current MPI quality metrics.

1.1. Outline of the thesis

In Chapter 1, “Introduction”, a brief description of detectors and technological solutions used in MPI is given. An overview of current knowledge and previous research is presented, with focus on the necessity of a comprehensive characterization of *MPI systems*, aimed to understand, analyze, and predict their behavior. The hypotheses and subsequent objectives are stated.

Research materials and methods are described in Chapter 2. The scintillation crystal and solid-state detector systems used in this investigation are presented in more detail. The static semi-anthropomorphic phantom used to mimic the patient and the experimental methodology are described. Next, the MC simulation aimed at evaluating *MPI systems* under dynamic conditions is presented. The formalism for image data evaluation is introduced. Finally, the statistical methods used for the uncertainty analysis are presented.

Chapter 3, “Results and Discussion”, is divided into sections following the research process. Results of the comprehensive characterization of *MPI systems* are presented and discussed. Firstly, initial measurements used to complement results from the literature are presented. Results of the evaluation of perfusion defect detection ability and intrinsic characteristics of *MPI systems*, aimed at better understanding the origins of image degradation and the limitations of the respective systems, are shown. Next, a new approach to extend and further improve current MPI quality metrics is presented. Finally, results of the MC simulation are shown.

In Chapter 4, the main points of this research are summarized and conclusions are drawn.

Finally, in Appendix A, a detailed description of the 4D XCAT model used for the simulation of one frame of the GSPECT is provided.

1.2. Myocardial Perfusion Imaging systems: an overview of technological solutions, characteristics and limitations

Currently, MPI is performed using dual-detector SPECT systems with thallium-activated sodium iodide (NaI(Tl)) crystal detectors and parallel-hole collimators, dual-detector cardio-centric SPECT/CT systems with NaI(Tl)-crystal detectors and multifocal collimators, and cadmium-zinc-telluride (CZT) detector systems with either parallel-hole or multi-pinhole collimators.

The SPECT system with an NaI(Tl)-crystal detector and parallel-hole collimators is considered the standard technology. The detector's ability to distinguish between adjacent point sources at a given distance is determined by the collimator resolution, and is also limited by the finite number of photomultiplier tubes [1]. Additionally, due to the geometry of the collimator, spatial resolution decreases as the distance between the source and the detector increases, resulting in increased image blurring. Therefore, a non-circular detector orbit (NCO) is used to minimize the distance between the patient and the detector. As the radius of rotation changes during acquisition, the position of the volume of interest also changes during imaging. This can lead to artifacts in the image data due to differences in spatial resolution [2]. Several deep learning-based reconstruction methods have been proposed in recent years to enhance SPECT image resolution [3]. Additionally, system sensitivity is limited because only a small portion of the detector area is used for data acquisition from the region of interest. The standard filtered back projection (FBP) analytical algorithm performs filtering of data in the frequency or spatial domain, and back-project the filtered data [4, 5]. Low-pass filters used in FBP may smooth the image significantly by reducing noise, but this comes at the expense of reduced contrast and spatial resolution [4, 6]. The performance of systems with NaI(Tl)-crystal detectors has been improved by the development and introduction of statistical iterative reconstruction algorithms with resolution recovery (IRR), which allow 3D collimator response function modelling and account for the system's spatial resolution during reconstruction [7-9]. The IRR algorithm used in the reconstruction process of image data from NaI(Tl)-crystal detector systems is an ordered subset expectation maximization (OSEM-IRR) algorithm. In the OSEM-IRR algorithm, 3D collimator response function modelling enables image data processing using the detector's and collimator's physical and geometric characteristics, as well as the detector orbit shape and radius, and the patient-to-detector distance [8, 10-12]. This approach improves the accuracy of the estimated activity distribution obtained from reconstructed image data [13]. Furthermore, a number of image-degrading factors, including noise, scatter, and attenuation, can be corrected [1, 8, 10, 14].

In general, image data acquired in SPECT imaging may suffer from high levels of noise. The number of counts per projection depends on the limited acquisition time, making the projection image data prone to statistical uncertainty. Noise in SPECT imaging arises from randomness in the number of radioactive nuclei that decay during the acquisition time, the number of photons that interact with tissue or the detector, and the number of counts generated in the detector in response to these interactions.

The scatter component of gamma rays caused by surrounding tissues reduces the quality of image data. Therefore, it should be estimated and corrected using multiple energy windows or modelling [14, 15]. In nuclear medicine imaging, systems with high energy resolution enable better discrimination of low-energy photons (scatter) from high-energy photons (photopeak), resulting in improved image quality.

One of the major limitations of MPI is soft tissue attenuation of photons which may lead to misinterpretation of image data and artificially mimic true perfusion defects (PDs) [16]. Due to the various attenuation paths from the radionuclide source volume to the detector, attenuation results in both underestimation of radiopharmaceutical uptake and an inhomogeneous bias in the distribution of activity [17, 18]. The problem of photon attenuation by soft tissue can be compensated using computed tomography (CT) data acquired in so-called transmission measurements. Attenuation correction (AC) for MPI based on CT data is still an open issue due to potential mismatch between emission and transmission image data on fused image data caused by the heart's rapid movement, which may result in artifacts caused by AC [19]. In cardio-centric SPECT/CT systems, CT is required, but both AC and non-corrected reconstructed image data are used for diagnosis [20].

Multifocal collimators increase the sensitivity (by a factor of two) and resolution of NaI(Tl)-crystal detector systems due to the specific convergent collimator geometry in the center of the detector area [21, 22]. This increases the portion of the detector area used for imaging the region of interest, enabling better sensitivity over the heart, while surrounding tissues are imaged by the parallel-hole part of the collimator. In addition, cardio-centric acquisition and multifocal collimators allow a reduction in administered activity or acquisition time [21], which may contribute to improve image data quality by reducing artifacts caused by organ and patient motion.

Due to the intrinsic properties of semiconductors that enable direct energy conversion into electrical signals, CZT detectors have better sensitivity (threefold to sevenfold higher), spatial resolution, and energy resolution (Figure 1) compared to NaI(Tl)-crystal detector systems, where the measured signal is based on light production, transport, and conversion [20, 22-25].

A CZT detector consists of compact, pixelated modules, with each pixel smaller than the intrinsic spatial resolution of a NaI(Tl)-crystal system at 10 cm from the source. CZT detector systems achieve twice the energy resolution of conventional NaI(Tl)-crystal detector systems. Depending on the *MPI system* design, different types of tungsten collimators are incorporated into CZT detectors [26]. In some *MPI systems*, multi-pinhole collimators are used. Pinhole collimators are typically used to obtain projections of small regions of interest with a magnification effect. However, sensitivity is limited by the specific collimator design. To increase sensitivity, multiple pinholes are focused toward the heart region.

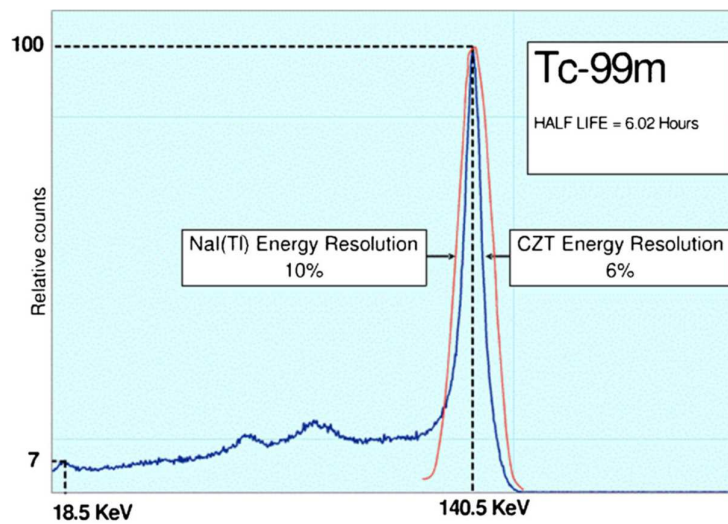


Figure 1. Differences in energy resolution between NaI(Tl)-crystal detector systems and CZT detector systems [24].

Image data obtained with CZT detectors are reconstructed using a maximum likelihood/expectation maximization (MLEM) reconstruction algorithm. Some CZT systems are available in SPECT/CT configurations, but many CZT detector systems are not equipped with CT. In these situations, the interpretation of perfusion patterns may be compromised due to the inability to perform AC [16, 27, 28]. In CZT systems, more options for AC have been introduced. These options enable the use of fluorescence X-ray AC technology [29], an external CT system, or an AC algorithm powered by artificial intelligence [30].

1.3. Myocardial perfusion assessment

Reconstructed image data are used for quantitative analysis of myocardial perfusion. The 3D perfusion distribution, presented as a 2D polar map, is obtained using quantitative post-processing algorithms developed for segmentation, visualization, and assessment of LV function and perfusion. The myocardial perfusion distribution is derived from LV short-axis image data as circumferential count profiles. These count profiles are mapped in concentric rings from the base of the LV (outer ring) to the apex (center of the polar map) forming the polar map, as shown in Figure 2 [31]. By comparing perfusion polar maps with the corresponding normal myocardial perfusion database, usually obtained from image data of patients with a low likelihood of coronary artery disease, a quantitative myocardial perfusion assessment can be made.

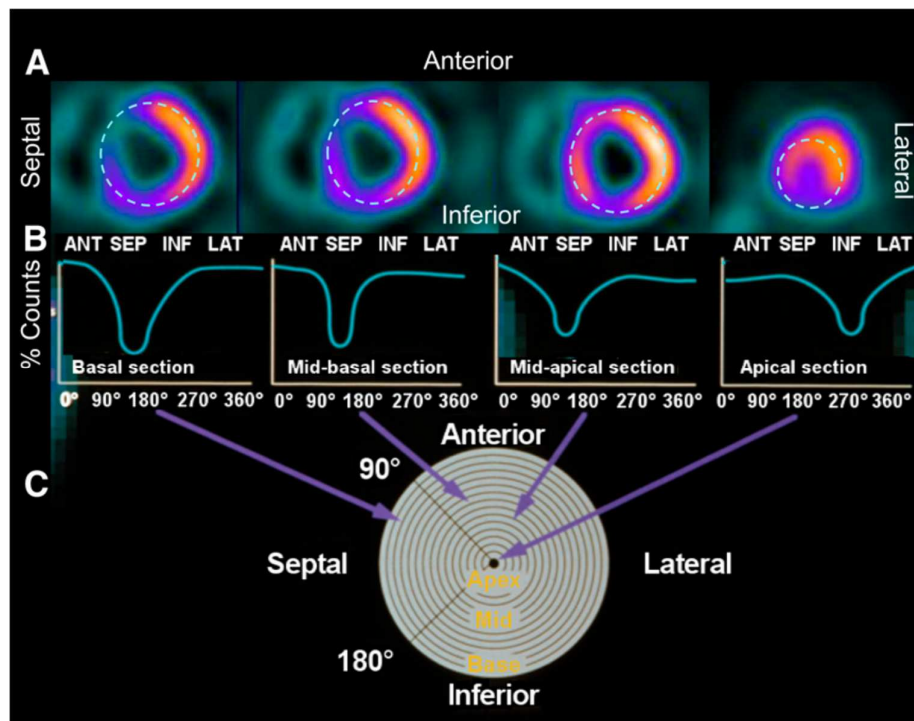


Figure 2. Schematic representation of the method used to create polar maps by using LV short-axis image data [31].

The normal myocardial perfusion database is selected based on information related to the imaging system used for MPI, the reconstruction algorithm used, the corrections applied, the type of population, and the patient gender.

1.4. Research motivation, aim and hypothesis

Several studies have been conducted to evaluate parameters related to image quality, such as spatial resolution, contrast, contrast-to-noise ratio (CNR), background variability, sensitivity, and uniformity [10, 22, 25, 32-34]. A review of the literature has shown that image quality evaluation requires additional measurements, related to spatial resolution and contrast, to complete the results for NaI(Tl)-crystal detector systems and multifocal collimators. In this investigation, spatial resolution and contrast values were obtained using a semi-anthropomorphic phantom by simulating normal and pathological myocardial perfusion conditions. Respective contrast analysis results were used to evaluate the perfusion defect detection ability of the *MPI systems* studied.

Other authors have investigated the results of quantitative analysis of myocardial perfusion in terms of segmental uptake and global uniformity of polar maps [35]. Results were obtained only for simulations of normal myocardial perfusion condition with a phantom. In this investigation, additional simulations of pathological myocardial perfusion conditions were performed to evaluate differences in segmental uptake values in the PD region between different *MPI systems*.

To take a step forward, and to perform a comprehensive characterization of *MPI systems*, an evaluation of the systems' PD detection ability through quantitative myocardial perfusion analysis is performed. This is first carried out using standard clinical descriptors for perfusion assessment, such as the extent of the PD and summed score values. To enable comparison between different *MPI systems* and improve agreement in the analysis of polar maps, system-specific normal myocardial perfusion databases are created for each *MPI system* evaluated, as suggested by Zoccarato et al. [35]. The results show that the clinical descriptors used in this investigation strongly depend on attenuation artifacts, and their use without caution may lead to misinterpretation of myocardial perfusion results. Furthermore, system perfusion defect detection ability may also be related to the quantitative post-processing algorithm used for perfusion assessment. To evaluate the systems' intrinsic performance in terms of PD detection ability under reproducible and controlled clinical conditions, a new approach and an extension of current quality metrics are proposed. A new physical descriptor, the defect perfusion index, is introduced and evaluated.

The final part of the investigation is dedicated to dynamic simulations of GSPECT. Since dynamic anthropomorphic phantoms are not available, Monte Carlo (MC) simulations of the imaging process are performed to produce realistic image data [36]. For this purpose, the MC-based code SIMIND [37] and the voxelized anthropomorphic phantom 4D XCAT are used [38].

The SIMIND MC-based code has shown its usefulness, enabling investigation of important imaging system parameters when measurements are difficult or impossible to perform [37, 39-41]. It enables MC simulation of radiation transport, which allows, among other things, detailed investigation of the causes of the degradation of SPECT image data. The 4D XCAT voxelized anthropomorphic phantom is used to model patient data with both normal and pathological myocardial perfusion conditions. Dynamic MC simulation of GSPECT is performed and the results are analyzed in terms of the ability of *MPI system* to detect PD. Results of dynamic MC simulations are associated and correlated to data obtained in the experimental sessions with a static semi-anthropomorphic phantom. Descriptors related to image quality and defect detection ability used in this investigation will hereafter be referred to as physical descriptors.

During this investigation, some important conclusions have been reached. A comprehensive characterization of *MPI systems*, in addition to image quality assessment, should also include evaluation of systems' intrinsic performance in terms of their ability to detect PDs. Conclusions should be drawn on the basis of results under both static and dynamic conditions.

This doctoral dissertation has one research hypothesis:

- A new approach for the characterization of systems used in myocardial perfusion imaging will improve and extend current quality metrics. This will be performed through a comprehensive evaluation of image data through physical descriptors. A new physical descriptor, the defect perfusion index, will be introduced for upgrade assessment of the *MPI system* performance and further characterize the quality of the image data.

The hypothesis has been examined through the following three specific objectives:

- Evaluation of MPI data using a comprehensive set of physical descriptors related to contrast, spatial resolution, and uniformity of polar maps.
- Introduction of a new descriptor for the quantification of perfusion defects to eliminate dependence on the quantitative algorithm and attenuation artifacts, and to assess the intrinsic performance of the imaging system in terms of perfusion defect detection ability with the use of a system-specific normal myocardial perfusion database.
- Characterization of *MPI systems* through evaluation of image data obtained both experimentally, using a semi-anthropomorphic static phantom, and by Monte Carlo simulation with virtual dynamic phantoms.

The main results presented in this Dissertation have been published in three scientific papers:

1. Dundara Debeljuh D, Matheoud R, Zoccarato O, Pribanić I, Brambilla M, Jurković S. Characterization of myocardial perfusion imaging systems - an extension of quality metrics. *Phys Med.* 2024 Sep;125:104510. <https://doi.org/10.1016/j.ejmp.2024.104510>
2. Dundara Debeljuh D, Matheoud R, Pribanić I, Brambilla M, Jurković S. Evaluation of Single-Photon Emission Computed Tomography Myocardial Perfusion Detection Capability through Physical Descriptors. *Applied Sciences.* 2024; 14(12):5283. <https://doi.org/10.3390/app14125283>
3. Gomez Villegas S, Dundara Debeljuh D, Calcaterra D, Pribanić I, Leva L, Garrou F, D'Alessio A, Matheoud R, Brambilla M. Half-count myocardial imaging on the D-SPECT camera: phantom validation and clinical agreement for perfusion and function. *Br J Radiol.* 2026; tqag201. <https://doi.org/10.1093/bjr/tqag201>

1.5. Overview of the previous research

Several studies have evaluated reconstructed image data from different *MPI systems* using image quality descriptors related to spatial resolution, contrast, CNR, sensitivity, and uniformity. System spatial resolution is determined by both detector properties and image acquisition settings. It is influenced by pixel or voxel spacing and is affected by the partial volume effect at the borders between different tissues. Spatial resolution can be determined according to standard National Electrical Manufacturers Association (NEMA) guidelines and by using phantom image data to evaluate MPI-specific descriptors such as LV wall thickness and sharpness index [10, 21, 25, 42, 43]. In the review article by Brambilla et al. [8], the authors summarized the impact of IRR algorithms, innovative collimators, and cardiac-dedicated systems with CZT detectors on different physical descriptors related to image quality. Several authors have evaluated LV wall thickness on NaI(Tl)-crystal detector systems with parallel-hole collimators or multifocal collimators, and CZT detector systems. However, sharpness index results for NaI(Tl)-crystal detector systems with multifocal collimators are still lacking.

Contrast is a physical descriptor defined by differences between pixel values. In MPI, contrast relates to the systems' ability to distinguish myocardial regions with different radiopharmaceutical accumulation and localize changes despite background activity. The contrast between the LV wall and the LV inner chamber, and the contrast of the PD with respect to the LV wall were evaluated in image data from semi-anthropomorphic phantom acquisitions [8, 10, 21, 25, 43]. Intrinsic contrast and net contrast have been evaluated by Zoccarato et al. on two *MPI systems* [44], but a review of the literature does not provide experimental data for intrinsic and net contrast for other NaI(Tl)-crystal detector systems with parallel-hole collimators, and, more importantly, data for NaI(Tl)-crystal detector systems with multifocal collimators are missing.

Another parameter related to object detectability is the CNR, which reflects the ability of the *MPI system* to generate image contrast not attributable to noise fluctuations. CNR is influenced by the signal level above the noise level (background), which is more critical for small objects, and limited spatial resolution. Some authors have determined CNR in both phantom and patient studies [22, 25, 34]. Tomographic count sensitivity has been determined by several groups [22, 23]. To evaluate noise, the percent coefficient of variation of the mean number of counts per voxel, i.e. the background variability, was determined [10]. Other aspects previously investigated include administered activity, count statistics, motion artifacts, acquisition time, and the complete acquisition set-up and image processing parameters [5, 11, 21, 32, 44-51].

Results of image quality analysis have been used in the preparation of several MPI procedure guidelines [20, 52-55].

Positional soft-tissue attenuation patterns in patient MPI image data obtained on CZT systems have also been studied by some authors. Evaluation was performed for a CZT system in supine and semi-reclining positions [16], and in a forward-leaning biker-like position [56].

Some research groups have been working on the assessment of LV function and perfusion with standard clinical descriptors, such as the extent and volume of the perfusion defect, the summed score (SS), severity of perfusion defect, wall motion and thickening, and LV ejection fraction [57-59].

One group has performed polar map analysis of image data obtained from anthropomorphic phantom image data [25]. Parameters such as segmental uptake and its uncertainty, global uniformity and regional uniformity have been evaluated under normal myocardial perfusion conditions on NaI(Tl)-crystal detector systems with parallel-hole collimators or multifocal collimators, and CZT detector systems [25]. Some authors have investigated the potential benefit of applying deep learning denoising for PD detection in clinical data [60].

Simulations of pathological myocardial perfusion conditions should be performed to evaluate the perfusion detection ability of *MPI systems*. Additionally, as pointed out by Zoccarato et al. [35], system-specific normal myocardial perfusion databases should be implemented to improve agreement in the analysis of polar maps from different *MPI systems*. This analysis method should allow a comprehensive comparison of the performance between different *MPI systems*. Evaluation of the ability in detecting PDs should be performed, while minimizing the influence of attenuation artifacts, regardless of the quantitative post-processing algorithm used.

Some authors have used a dynamic cardiac insert in a static phantom to simulate gated acquisitions and assess LV function and volumes on different *MPI systems* [61, 62]. To produce rather realistic image data, the MC-based code SIMIND [37, 39] could be used along with voxelized dynamic phantoms and a 4D cardiac model to simulate gated MPI acquisition [38, 57]. The MC-based code SIMIND has been validated and extensively used to model different *MPI systems* [63-65].

2. Research materials and methods

2.1. MPI systems with NaI(Tl)-crystal detectors

The NaI(Tl)-crystal detector system with parallel-hole collimators is considered the standard technology used in MPI. Due to its physical characteristics, the NaI(Tl)-crystal serves as the standard material for scintillation detectors used in nuclear medicine imaging, although it has limitations in mechanical stability, hygroscopic properties and linearity of light response to ionizing radiation. Parallel-hole collimators consist of thousands of precisely aligned channels (holes), allowing only gamma rays with energies in the pre-selected energy window and impinging perpendicular to the detector to reach the detector surface. Gamma rays emitted in other directions are mostly absorbed by the septa between the holes. In this investigation two dual-head NaI(Tl)-crystal detector systems with parallel-hole collimation system were used (Figure 3): two SPECT/CT systems Symbia T (Siemens Healthineers) with parallel-hole collimators dedicated to low-energy high-resolution (LEHR) imaging, available at Clinical Hospital Center Rijeka and Clinical Hospital Center Split.

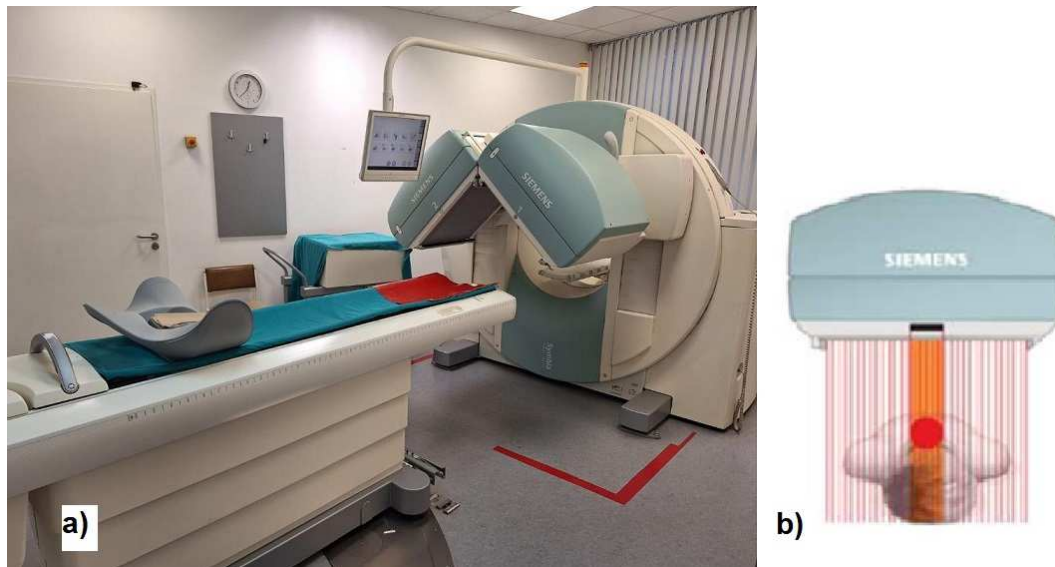


Figure 3. Siemens Symbia T system (a) and a schematic representation of parallel-hole collimator geometry (b) [66].

In both institutions, the computed tomography options available on the SPECT/CT systems were not used for AC in MPI. The detector field of view (FOV) for Symbia T systems is 53.3 cm × 38.7 cm. The detectors perform an NCO orbit.

The LEHR collimator has 148000 hexagonal channels, each with a diameter of 1.11 mm and a length of 24.05 mm, and a septal thickness of 0.16 mm. The NaI(Tl)-crystal thickness is 9.5 mm. Attached to the crystal are 59 photomultiplier tubes (53 with a diameter of 7.6 cm, and 6 with a diameter of 5.1 cm) arranged in a hexagonal array. The photomultiplier tubes are equipped with bi-alkali high-efficiency box-type dynodes. The nominal planar system sensitivity and spatial resolution at 10 cm are 91 cps/MBq and 7.5 mm, respectively. The nominal reconstructed spatial resolution with scatter for LEHR collimators and FBP reconstruction at 15 cm is ≤ 10.7 mm. Without scatter, the nominal reconstructed spatial resolution is ≤ 10.2 mm. If IRR is used the nominal reconstructed spatial resolution is ≤ 5.8 mm with scatter and ≤ 4.4 mm without scatter [67].

An advanced MPI-dedicated option for NaI(Tl)-crystal detector system is IQ SPECT technology. In this investigation, one IQ SPECT system was used: a SPECT/CT Symbia Intevo Excel (Siemens Healthineers) available at the General Hospital Pula, with SmartZoom collimators (Figure 4).

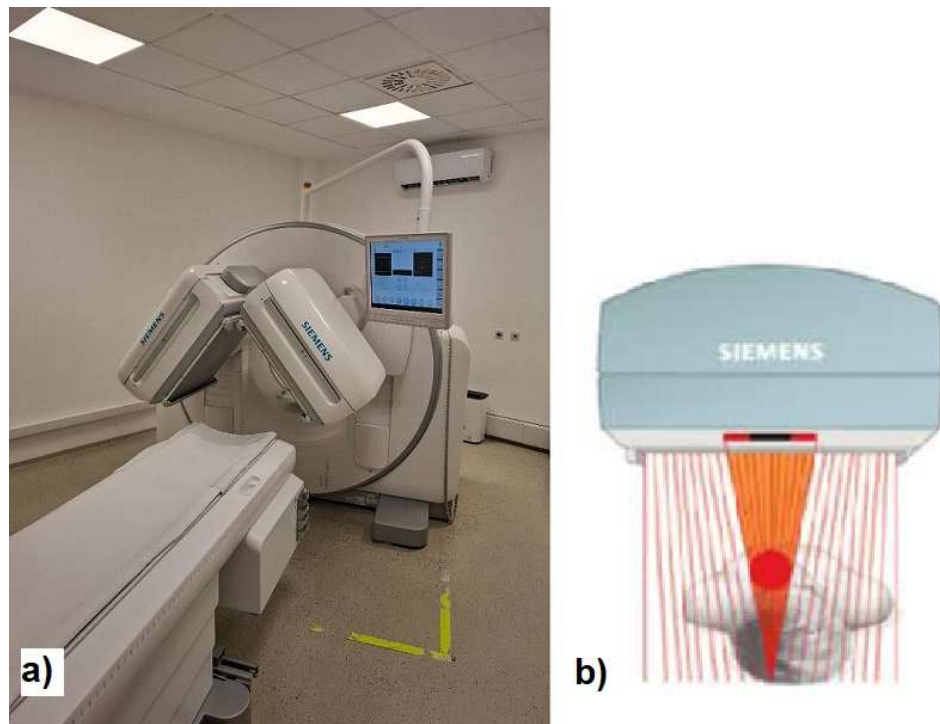


Figure 4. Siemens Symbia Intevo Excel system (a) and a schematic representation of SmartZoom collimator geometry that enable a cardio-centric detector orbit (b) [66].

The IQ SPECT system uses the same NaI(Tl)-crystal detector as conventional systems (Figure 5), but with new collimators featuring variable focus, the multifocal SmartZoom collimators.

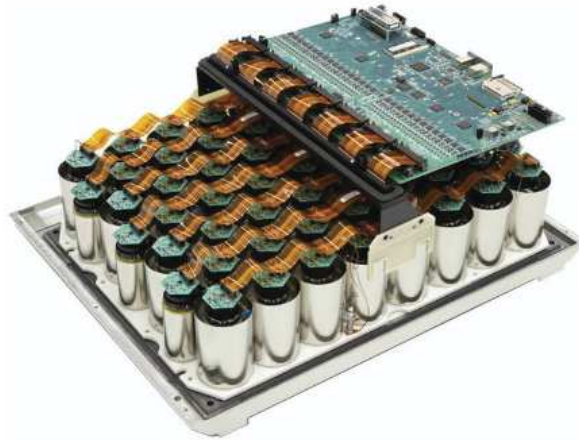


Figure 5. Example of a NaI(Tl)-crystal detector for Siemens Symbia Intevo Excel [68].

In multifocal collimators, the holes are focused at the center of the detector and nearly parallel at the detector edges, resulting in high sensitivity for the target region, which is always in the magnification area. The SmartZoom collimator has 48000 hexagonal holes with a diameter of 1.95 mm and a length of 40.25 mm. The septal thickness is variable, between 0.2 mm and 0.4 mm. The myocardium must be positioned within the region of largest magnification of the multifocal collimators [43]. This is achieved by marking the center of the heart on two projection image data visualized on the positioning monitor. The detector orbit is cardio-centric and the radius of rotation is fixed. The nominal planar system spatial resolution and sensitivity of the SmartZoom collimators at 10 cm are 7.4 mm and 128 cps/MBq, respectively [69]. The nominal system sensitivity at 28 cm is 365 cps/MBq. Since IRR is used, the system with SmartZoom collimators, is generally equivalent to the system with LEHR collimators mentioned above.

2.2. MPI systems with solid-state detectors

In this investigation two different CZT solid-state detector systems were used: a D-SPECT (Spectrum Dynamics, Caesarea Israel) with wide parallel-hole collimators installed at the University Hospital “Maggiore della Carità”, Novara (Italy), and a Discovery NM 530c (GE Healthcare, Haifa Israel) with Alcyone technology and multi-pinhole collimation system available at the Scientific Institute of Veruno (Italy).

The D-SPECT (Figure 6) has a stationary, curved gantry with nine rotating CZT detector columns (Figure 7.a). Each detector column can rotate independently with programmable angular orientations of up to 110 degrees around its long axis. The curved gantry is designed to accommodate the heart, situated on the left side of the thorax. Each detector column measures 40 mm × 160 mm, corresponding to four modules of 16 × 16 pixelated CZT crystals, for a total of 16 × 64 pixels. The CZT crystal thickness is 5 mm. The columns of CZT detectors are aligned with tungsten wide-angle square parallel-hole collimator. The collimator has square holes with a diameter of 2.26 mm and a length of 21.7 mm. The nominal reconstructed spatial resolution with scatter at 15 cm is ≤ 5 mm [70].

To ensure correct positioning of the heart within the field of view (FOV) during imaging, a pre-scan lasting 30 to 60 seconds is performed before acquisition. On the pre-scan image, a region of interest (ROI) that includes the heart must be contoured. This ROI enables a process known as region-centric acquisition (Figure 7.b).



Figure 6. D-SPECT solid-state detector system.

The Discovery NM 530c (Figure 8) has 19 blocks of stationary CZT detectors, each measuring 8 cm × 8 cm. The single square CZT module is identical to that in the D-SPECT, but the geometric configuration of the detector is different (Figure 9).

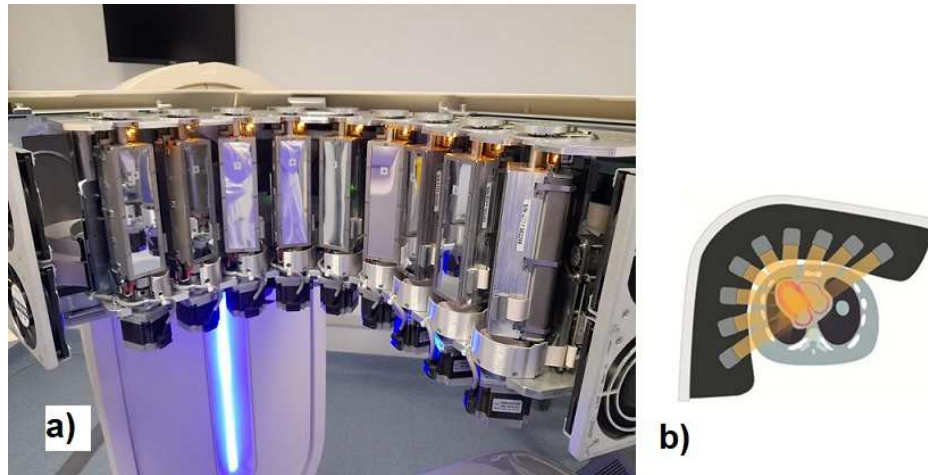


Figure 7. Detector configuration in the D-SPECT solid-state system (a) and schematic representation of the region-centric acquisition (b) [71].



Figure 8. Discovery NM 530c solid-state detector system.

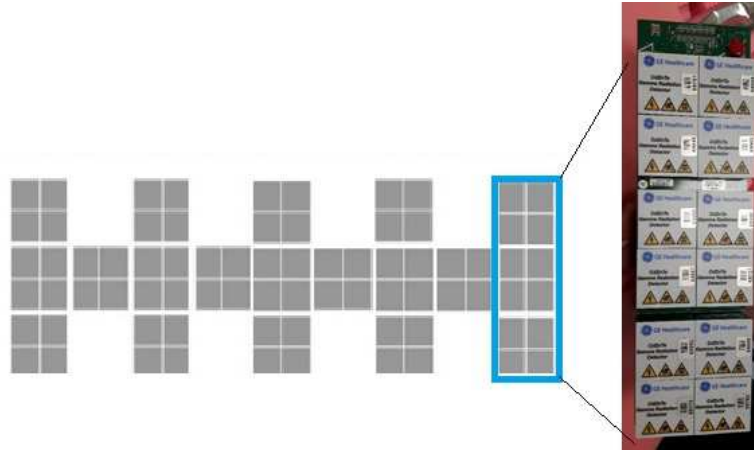


Figure 9. Detector geometric configuration in Discovery NM 530c and CZT detector modules.

This specific imaging detection geometry reduces the projected size of the imaged object on the detector surface (Figure 10). Each module consists of a 32×32 pixelated CZT crystal (pixel size $2.46 \text{ mm} \times 2.46 \text{ mm}$). The CZT modules are paired with pinhole collimators (Figure 10.b), forming a focused multi-pinhole collimator system that improves sensitivity and detection efficiency.



Figure 10. Detector configuration in Discovery NM 530c (a) and schematic representation of the detectors' field of view (b) [72].

The detectors are aligned to share a common focal point [72, 73]. The effective FOV is defined by a sphere with a diameter of 19 cm. Once the patient is positioned on the imaging table, the gantry position is adjusted so that the myocardium is close to the center of the FOV. The operator is guided by an automatic algorithm to achieve optimal positioning [73]. Within the virtual sphere, sensitivity varies because of the pinhole collimators. This variable sensitivity

reduces the contribution of gamma rays emitted from organs adjacent to the myocardium due to their distance from the focal point. The oblique angles of gamma-ray incidence further improve the energy resolution of the CZT system [49]. The nominal reconstructed spatial resolution with scatter is ≤ 6.5 mm [74].

2.3. The semi-anthropomorphic phantom

The human upper body was simulated using a semi-anthropomorphic phantom made from polymethyl methacrylate (PMMA) (Torso PhantomTM with Cardiac InsertTM, Data Spectrum Corporation, Hillsborough, NC, USA). It includes a large body-shaped volume with inserts that mimic the liver, lungs, spinal cord, and myocardium (Figure 11.a). The myocardial insert consists of a fillable chamber that mimics the LV wall, and a cavity that simulates the inner chamber of the LV (Figure 11.b and c).

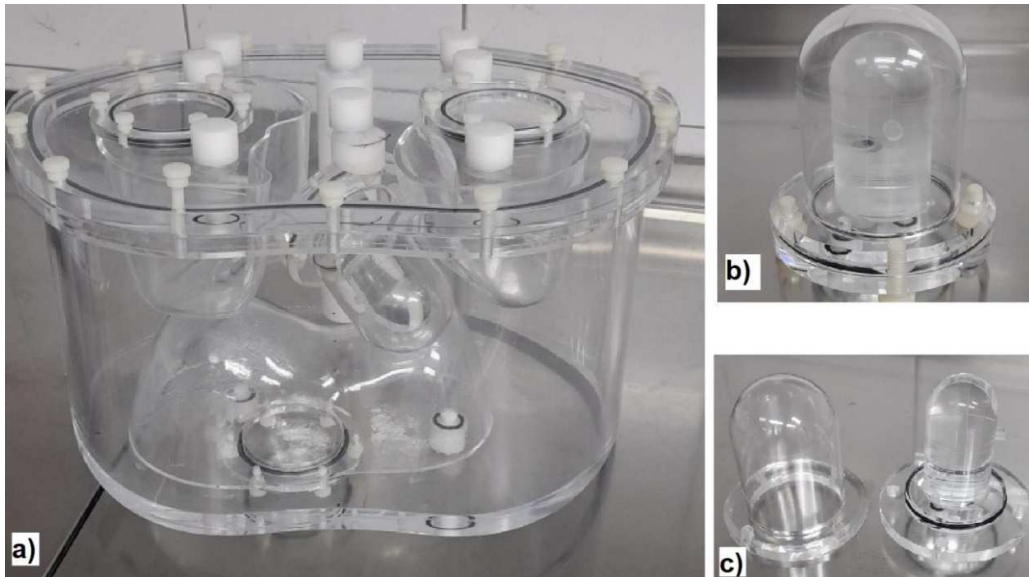


Figure 11. The semi-anthropomorphic phantom (a) with the myocardial insert (b). The myocardial insert consists of a fillable chamber that mimics the LV wall, and a cavity that simulates the inner chamber of LV (c).

The distribution of the radiopharmaceutical ^{99m}Tc -tetrofosmin in the body during MPI was simulated according to the reported ratios of activity concentration with respect to the thorax [10, 25]. To compute the activities needed to achieve the required organ activity concentrations, the volumes of the various fillable compartments were determined experimentally (Table 1). Volumes were measured using graduated laboratory glassware and syringes of various sizes. For each insert, a different syringe was used to prepare the activity. The activities were prepared to achieve the activity concentrations at the reference time (t_{ref}) shown in Table 2.

The full syringe activity a_i was measured at time t_i , the activity was dispensed into the phantom insert, and the residual syringe activity (b_i) was measured. The total activity in the phantom at t_{ref} was calculated using the radioactive decay law:

$$A_{phantom}(t_{ref}) = (a_i - b_i)e^{-\lambda(t_{ref}-t_i)} \quad (1)$$

where λ is decay constant for ^{99m}Tc .

The two lung inserts, filled with water and Styrofoam® beads, simulate low density lung tissue. The spinal cord insert is a Teflon®-made, non-fillable organ. An activity free (cold) insert filled with water was inserted into the myocardial wall at predefined positions to mimic a PD. It simulates a section of the myocardial wall without radiopharmaceutical uptake.

Insert	Type of tissue	Volume (mL)
LV wall without perfusion defect	normal	122.9
LV inner chamber	normal	64.7
Perfusion defect	pathologic	3.8
Liver	normal	1308.9
Thorax (background)	normal	9050

Table 1. Volumes of different inserts of the semi-anthropomorphic phantom and type of tissue.

Insert	Activity concentration (MBq/mL)	Activity concentration ratio
LV wall	0.08338	20.4
LV inner chamber	0.00401	1.0
Liver	0.04981	12.2
Thorax	0.00409	-

Table 2. Activity concentrations used in the preparation of the semi-anthropomorphic phantom for the experimental session. Activity concentrations in different organs were selected to obtain proper activity concentration ratio with respect to the thorax.

In this investigation a PD located in the middle of the LV wall was simulated using a PD insert with the following characteristics: dimensions of $45^\circ \times 2$ cm (coverage angle of 45° in the short-axis plane, 2 cm in the long-axis plane) and volume $V=2.7$ mL (Figure 12.a and b). The PD was positioned in four different locations within the LV wall: anterior, lateral, posterior and septal (Figure 12.c and d). The physical dimensions of the PD were determined by measuring its volume and calculating the surface area of the PD insert. The dimensions of the PD with respect to the myocardium insert are: 3.1% of the volume of the LV wall and 3.6% of the outer surface of the LV wall.

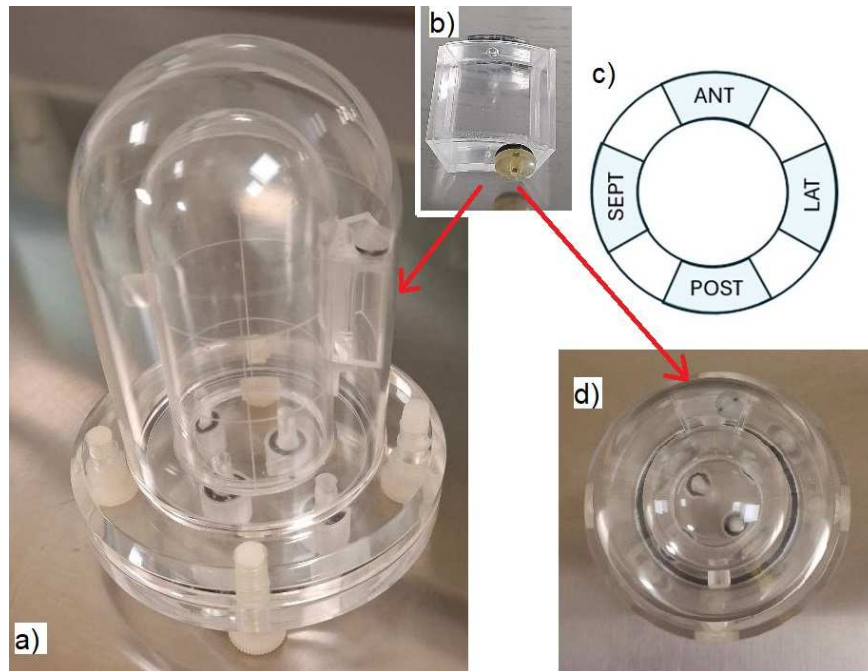


Figure 12. The myocardial insert (a) with the perfusion defect of dimension of $45^\circ \times 2$ cm (b). The PD may be positioned in four locations inside the LV wall: anterior, lateral, posterior and septal (c). An example of anterior positioning of the PD in the myocardial insert wall (d).

2.4. Experimental set-up and measurements

To simulate clinical conditions, acquisitions on *MPI systems* were performed using standard clinical acquisition parameters (Table 3). Reconstructions were performed using both FBP and IRR algorithms. When the IRR algorithm was used, reconstructed datasets were created both with scatter correction (SC) and without scatter correction. IQ SPECT acquisitions performed on Symbia Intevo Excel were performed in hybrid modality using CT imaging parameters as follows: 130 kV, reference tube current-exposure time product 55 mAs (Care Dose 4D, Siemens Healthineers), collimation 2×4 mm, pitch 1.0, reconstructed slice thickness 5 mm. Image data obtained by Symbia Intevo Excel were reconstructed using the IQ SPECT dedicated IRR algorithm. Reconstructed image data were corrected for both scatter and attenuation (SCAC). Non-corrected IQ SPECT image data were also evaluated. In institutions that use CZT systems, attenuation correction of image data was not available. Image data were reconstructed with system-specific iterative reconstruction algorithms.

In this investigation five myocardial wall perfusion conditions were simulated. In the simulation of normal myocardial perfusion, hereafter referred to as the *normal phantom (norm)* the semi-anthropomorphic phantom was filled with ^{99m}Tc solution according to Table 2. Acquisitions of the semi-anthropomorphic phantom were repeated at least 10 times for each *MPI system* with repositioning between acquisitions to simulate patient variability.

In pathological myocardial perfusion simulations, hereinafter referred to as the *pathological phantom (path)*, the phantom was prepared with the same activity concentrations as in the normal myocardial perfusion simulations (Table 2) with the PD filled with water (cold PD). Acquisitions were performed with the PD in four LV wall positions: anterior, lateral, posterior, and septal (Figure 12.c). For each PD position, the acquisitions were repeated at least three times on each *MPI system*, with phantom repositioning between acquisitions.

The phantom was positioned according to the MPI patient positioning protocol of each investigated *MPI system* to simulate patient position during clinical MPI: supine position and feet first for Siemens Symbia T and Siemens Symbia Intevo Excel, supine and upright position for the DSPECT, and supine position and head first for Discovery NM 530c.

Phantom image data were acquired to achieve an appropriate level of count statistics recommended for clinical routine: 3×10^6 total counts for the Symbia T and 10^6 counts in the LV for other *MPI systems* [10, 35].

Projection views obtained at different angles (Figure 13) were reconstructed using the parameters shown in Table 3.

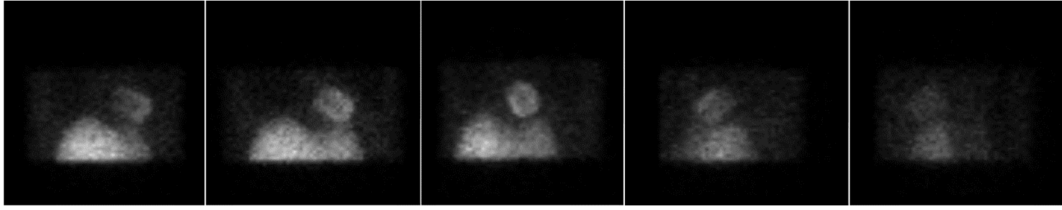


Figure 13. Example of projection views obtained during the semi-anthropomorphic phantom acquisition.

Reconstructed image data were subsequently realigned according to the myocardial axis: short-axis, vertical long-axis and horizontal long-axis. Figure 14 shows an example of reconstructed image data.

The aim of the study was to assess the performance of *MPI systems* under standard clinical acquisition and reconstruction parameters. Different imaging devices with specific acquisition and reconstruction parameters (Table 3), in combination with different correction modalities, were considered as seven different *MPI systems*: Symbia-FBP, Symbia-IRR, Symbia-IRR+SC, SymbialQ+SCAC, SymbialQ, DSPECT, and D530c.

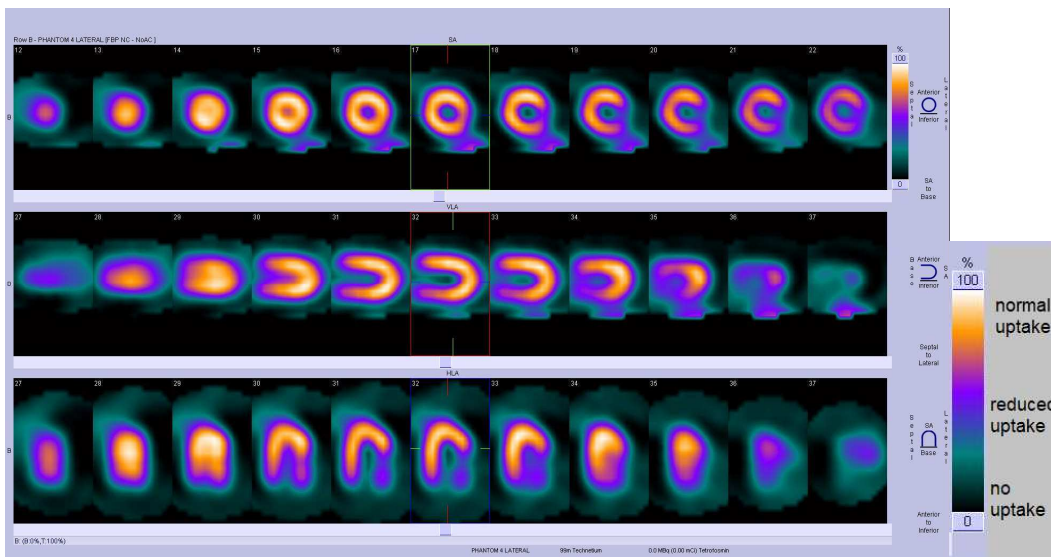


Figure 14. Example of reconstructed image data displayed along myocardial short-axis, vertical long-axis and horizontal long-axis.

Imaging device	Symbia T	Symbia Intevo Excel	D-SPECT	Discovery NM 530c
Collimator	LEHR	SmartZoom	Wide-angle parallel-hole	Multi-pinhole
Matrix size	64×64	128×128	64×64	32×32
Pixel size (mm)	6.6	4.8	4.2	2.46
Number of projections	64	34	120 (×9 blocks)	19
Angular range	180	208	110	180
Orbit	Non-Circular Orbit	Cardio-Centric	Rotating detector column blocks	Fixed detectors
Energy window	photopeak and lower scatter	photopeak and lower scatter	photopeak	photopeak
Reconstruction algorithm and settings	1. FBP 2. Flash 3D OSEM IRR: 15 iterations, 8 subsets	IQ Flash 3D OSEM IRR: 10 iterations, 3 subsets	Iterative 3D modified MLEM IR: (4+3) iterations, 32 subsets	Iterative 3D MLEM IR: 60 iterations, 1 subset
Filters	1. Butterworth filter, cut-off 0.4, order 5 2. 13.2 mm Gaussian post-reconstruction filter	10 mm Gaussian post-reconstruction filter	Iteration filter, kernel 0.125 mm + Post reconstruction Normalization filter*	Green OSL noise regularization ($\alpha=0.51$; $\beta=0.3$) + Post-reconstruction Butterworth filter: order 7, cut-off 0.37 cm^{-1}
Corrections	No corrections SC (only Flash 3D)	No corrections SCAC	No corrections	No corrections
*Proprietary information				

Table 3. Acquisition and reconstruction parameters.

2.5. Image quality analysis

An evaluation of MPI data using a comprehensive set of physical descriptors related to contrast, spatial resolution, and uniformity of polar maps was performed to assess and compare the performance of different *MPI systems*. Reconstructed and reoriented short-axis image data were used to assess image quality. Contrast was assessed by calculating the contrast between the LV wall and the LV inner chamber, the contrast of the PD with respect to the LV wall, the intrinsic contrast and the net contrast. Spatial resolution assessment was performed through evaluation of LV wall thickness and the sharpness index. Fiji edition of the ImageJ open-source software (National Institutes of Health, Bethesda, Maryland, USA) was used. The short-axis image data were opened as 32-bit files in ImageJ and the freehand option was used to draw regions of interest (ROIs). The ROIs for each *MPI system* were saved and used during the analysis, to ensure consistency within each MPI system. The lookup table (LUT) “cool” was applied when displaying short-axis image data.

The contrast between the LV wall and the LV inner chamber (LVIC), $C_{LV/LVIC}$, was determined in image data of the *normal phantom*. It is defined as the ratio between the contrast determined in the reconstructed image data ($C_{LV/LVIC,meas}$) and the contrast defined by the preparation of the *normal phantom* ($C_{LV/LVIC,phantom}$):

$$C_{LV/LVIC}(\%) = \frac{C_{LV/LVIC,meas}}{C_{LV/LVIC,phantom}} \times 100 \quad (2)$$

$C_{LV/LVIC,meas}$ was determined as:

$$C_{LV/LVIC,meas} = \frac{\overline{\eta_{LV}} - \overline{\eta_{LVIC}}}{\overline{\eta_{LV}} + \overline{\eta_{LVIC}}} \quad (3)$$

where $\overline{\eta_{LV}}$ and $\overline{\eta_{LVIC}}$ are the mean number of counts per voxel in the LV wall and LV inner chamber, respectively [10]. $C_{LV/LVIC,meas}$ was evaluated in the short-axis image data of the *normal phantom*. Figure 15 shows an example of ROIs used in the determination of $C_{LV/LVIC}$.

$C_{LV/LVIC,phantom}$ is a function of the activity concentrations in the LV wall and in the LV inner chamber, AC_{LV} and AC_{IC} , respectively. $C_{LV/LVIC,phantom}$ was defined as:

$$C_{LV/LVIC,phantom} = \frac{AC_{LV} - AC_{LVIC}}{AC_{LV} + AC_{LVIC}} \quad (4)$$

In this investigation, $C_{LV/LVIC,phantom} = 0.91$.

By definition, the contrast $C_{LV/LVIC}(\%)$, in the hypothetic case of an ideal detector system, is 100%.

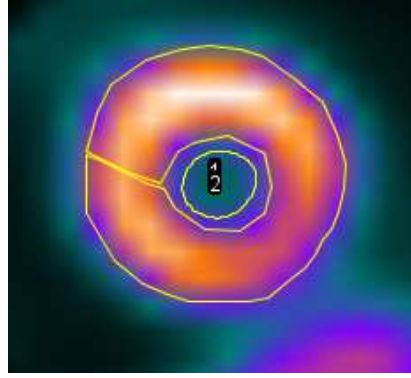


Figure 15. Example of the regions of interests used in the determination of the contrast between the LV wall and the LV inner chamber. ROI 1 and ROI 2 indicate the LV wall and LV inner chamber, respectively.

The contrast of the PD with respect to the LV wall, C_{PD} , was calculated in *pathological phantom* image data. Considering the activity concentration used for the preparation of the phantom, $C_{PD,phantom}$ is defined as:

$$C_{PD,phantom}(\%) = \frac{AC_{LV} - AC_{PD}}{AC_{LV} + AC_{PD}} \times 100 \quad (5)$$

where AC_{LV} and AC_{PD} are the activity concentrations in the LV wall and in the PD, respectively [44]. As described above, simulation of a pathological myocardial perfusion was performed by inserting the PD filled with water into the LV wall. In this case, $C_{PD,phantom}(\%) = 100\%$. Thus, the contrast between the PD and the LV wall was determined as:

$$C_{PD}(\%) = \frac{\overline{\eta_{LV}} - \overline{\eta_{PD}}}{\overline{\eta_{LV}} + \overline{\eta_{PD}}} \times 100 \quad (6)$$

where $\overline{\eta_{LV}}$ and $\overline{\eta_{PD}}$ are the mean number of counts per voxel in the LV wall and in the PD, respectively [44]. The contrast between the PD and the LV wall was

evaluated in three short-axis slices where the PD was clearly visualized. Figure 16 shows an example of ROIs used in the determination of C_{PD} .

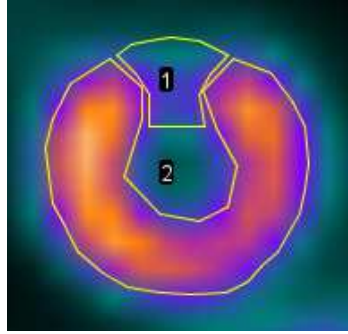


Figure 16. Example of the regions of interests used in the determination of the contrast of the PD with respect to the LV wall. ROI 1 and ROI 2 indicate the PD and the LV wall, respectively.

Using the same ROIs as for $C_{PD}(\%)$ evaluation, the contrast of the regions where the PD was positioned relative to the LV wall was also assessed in the corresponding short-axis image data of the *normal phantom*. This was done to estimate the intrinsic contrast (IC) that can be obtained with the *MPI system*. The IC was used as a measure of system-dependent effects, such as self-attenuation and scatter properties, finite spatial resolution and other system-related effects. It was determined as:

$$IC(\%) = \frac{\overline{\eta_{LV,norm}} - \overline{\eta_{PD,norm}}}{\overline{\eta_{LV,norm}} + \overline{\eta_{PD,norm}}} \times 100 \quad (7)$$

where $\overline{\eta_{LV,norm}}$ and $\overline{\eta_{PD,norm}}$ are the mean counts per voxel in the LV wall and in the position corresponding to the PD in *normal phantom* image data, respectively [44]. Figure 17 shows an example of ROIs used in the determination of the IC .

The net contrast (NC) was determined for each type of *MPI system* and each PD position as:

$$NC(\%) = C_{PD}(\%) - IC(\%) \quad (8)$$

NC is an image quality descriptor associated with the *MPI system's* perfusion defect detection ability. NC values obtained for each *MPI system* and different PD positions, should be used as reference values for the maximum achievable contrast between the PD and the LV wall [44]. In the case of an ideal *MPI system* without system-dependent degrading effects, $IC = 0$, meaning that $C_{PD}(\%) = 100\%$ and, consequently, $NC(\%) = 100\%$.

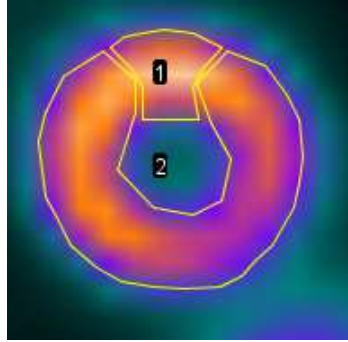


Figure 17. Example of the regions of interests used in the determination of intrinsic contrast. ROI 1 and ROI 2 indicate position corresponding to the PD and LV wall, respectively.

LV wall thickness was assessed as the full width at half maximum (FWHM) of the central count profile of the myocardial signal in the mid-ventricular section of the LV wall short-axis image data of the *normal phantom*. The FWHM was calculated by convolving the central count profile at the septal position with a Gaussian function [10, 25] (Figure 18). According to the phantom specifications, the wall thickness is 1 cm.

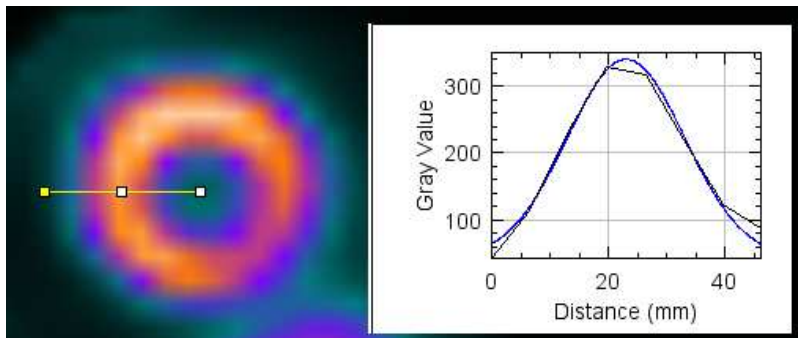


Figure 18. Example of determination of the LV wall thickness: the count profile (right) was obtained at the septal position (left) in the short-axis image data.

The sharpness index (cm^{-1}) was determined as the maximal slope of the horizontal profile of the mid-ventricular short-axis image data of the *normal phantom* at the lateral position [22, 25]. The maximal slope was calculated by fitting a linear function model to two points, at the position corresponding to the maximal slope. The sharpness of the myocardial contours is strongly related to the spatial resolution of the *MPI system*, for example the larger the sharpness index, the better the spatial resolution [22]. Figure 19 shows an example of the determination of the sharpness index.

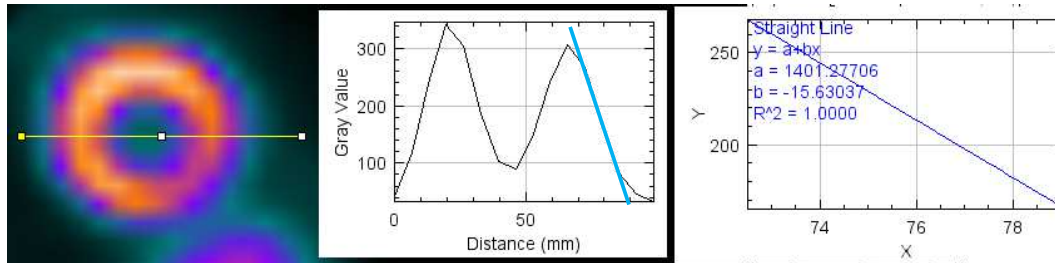


Figure 19. Example of determination of the sharpness index: the horizontal profile of the mid-ventricular short-axis image was is used (right). The position of the maximal slope at the lateral position is marked by the light blue line (center), and an example of results are shown on the right.

2.6. Quantitative myocardial perfusion analysis

Quantitative analysis was performed using standard quantitative post-processing algorithm for perfusion assessment. Corridor4DM (Invia Medical Imaging Solutions) was used for perfusion assessment in the case of Siemens systems and D530, while Quantitative Gated and Perfusion SPECT (QGS-QPS, Cedars-Sinai Medical Center) was used for DSPECT. Figure 20 shows an example of quantitative analysis performed with QGS-QPS.

At least ten acquisitions of the phantom simulating normal myocardial perfusion (*normal phantom*) were used to generate normal myocardial perfusion databases for each *MPI system*. Reconstruction of image data and subsequent use of the standard quantitative post-processing software allowed the definition of ten corresponding polar maps. Polar maps obtained from image data of the phantom simulating pathological myocardial perfusion (*pathological phantom*) were quantified using system-specific normal myocardial perfusion databases. Each quantitative post-processing algorithm provides results for a set of myocardial perfusion descriptors. In this investigation, extent and summed score parameters, as provided by both quantitative post-processing algorithms used, were considered.

According to Garcia et al. [31], the extent of PD is defined as the percentage of LV voxels outside the normal range when the normal range of perfusion is set at 2.5 standard deviations below the mean value of perfusion intensity for each segment in the normal myocardial perfusion database. This allows one to quantify the percentage size of the perfusion abnormality. The size of the perfusion defect correlates with the extent of CAD. The extent can be categorized as small (<10% of LV wall), medium (10-20%) or large (>20%) [55].

Perfusion defect severity correlates with the severity of CAD [55]. The severity of PD in each of the 17 segments is scored on a 0-4 scale. The summed score (SS) takes into account both the extent and severity of the perfusion defect. The SS is defined as the sum of the individual perfusion scores from the 17 segments of the polar map. Perfusion is regarded as normal or minimally abnormal if the SS value is less than 4; mildly abnormal if the SS value is between 4 and 8; moderately abnormal if the SS value is between 9 and 13; and significant extensive ischaemia is present if the SS value is 13 or higher.

The segmental uptake in the specific segment n , SU_n , was calculated as the percentage ratio between the mean value of perfusion in segment n , $mean_n$, and the maximum among the 17 segments of the polar map, max [35]:

$$SU_n(\%) = \frac{mean_n}{max} \times 100 \quad (9)$$

The SU_n was evaluated on polar maps obtained by image data for both *normal phantom* and *pathological phantom*.

An example of perfusion value for 17 segments of the polar map is shown in Figure 21.

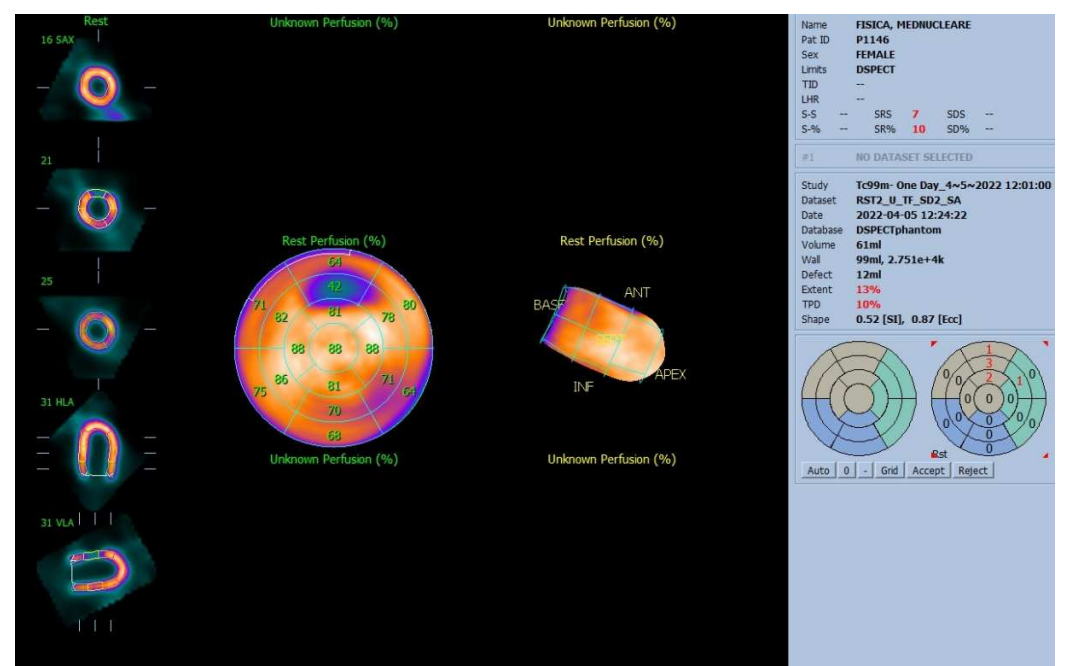


Figure 20. Example of results display when the quantitative analysis is performed using QGS-QPS.



Figure 21. Example of perfusion value for 17 segments of the *normal phantom* polar map.

The global uniformity (GU) of a set of polar maps was calculated as the percentage coefficient of variation of the segmental uptake across 17 segments [35]:

$$GU(\%) = \frac{SD_{SU_n}}{\overline{SU_n}} \times 100 \quad (10)$$

where SD_{SU_n} and $\overline{SU_n}$ are the standard deviation and the mean value of the segmental uptake in the segment n , respectively. GU was evaluated on polar maps obtained from image data for the *normal phantom*.

Finally, a new descriptor called the defect perfusion index (DPI) was introduced as a part of the metric for evaluation of performances in assessing perfusion defects. The DPI was defined as:

$$DPI (\%) = \frac{\sum_i mean_{norm,i} - \sum_i mean_{path,i}}{\sum_i mean_{norm,i}} \times 100 \quad (11)$$

where i refers to the segments included in the PD region, $mean_{norm,i}$ is the mean perfusion value of segment i in the normal myocardial perfusion database and $mean_{path,i}$ is the mean perfusion value of segment i in the polar map representation obtained from the image data of the phantom with the PD. The segments i to be considered in the calculation of the DPI should be identified based on the specific experimental set-up, as well as on the dimension and position of the PD. Figure 22.a-d shows an example of polar plot representations obtained in this investigation with the PD in different positions. A schematic representation of segments included in the calculation of the DPI for the specific set-up used in this investigation is also shown (Figure 22.e).

Specifically, with the experimental set-up described previously, the perfusion defect regions for the anterior position of the PD included segments $i = 1, 7$; segments $i = 5, 6, 11, 12$ for the lateral position; segments $i = 4, 10$ for the posterior position; and segments $i = 2, 3, 8, 9$ for the septal position. In this investigation the PD was located in the middle of the myocardial insert, thus the apical region was not affected by the PD. Segments corresponding to the apex (segments 13-17) were not considered in the calculation of the DPI .

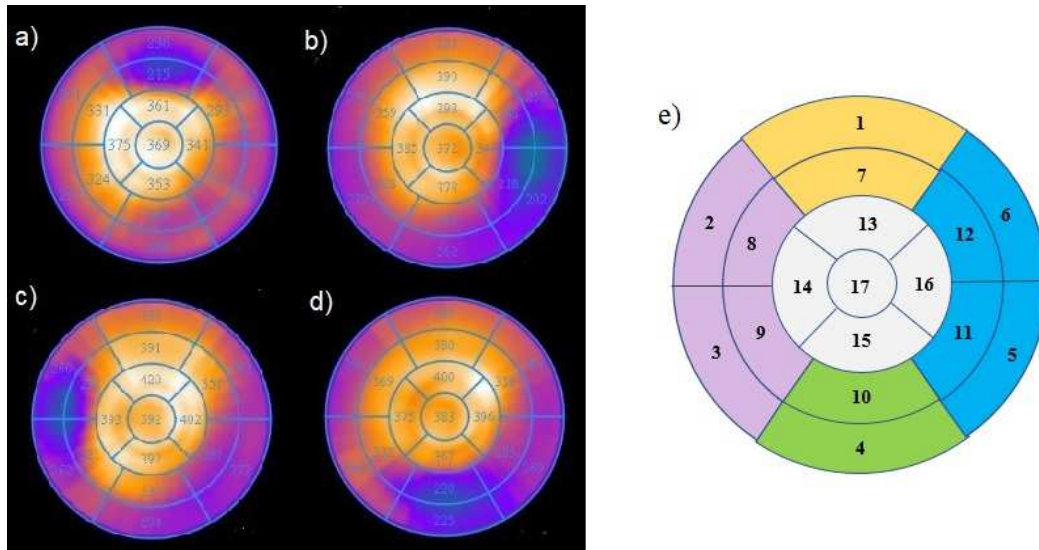


Figure 22. Examples of polar maps with PD in different positions: anterior (a), lateral (b), septal (c) and posterior (d). A schematic representation of segments included in the *DPI* calculation is shown (e) for the anterior position (yellow), lateral position (blue), septal position (purple) and posterior position (green). Apical region is shown in white (segments 13-17).

2.7. Simulations of GSPECT with Monte Carlo-based code

2.7.1. The SIMIND MC-based code and the 4D XCAT voxelized anthropomorphic phantom

MC simulation is a statistical method that uses random numbers as the basis for simulating of specified situations [75]. A physical process can be simulated by an MC-based code once the system and the physical process are modelled from known probability density functions. The SIMIND MC-based code enables quantitative simulation of nuclear medicine imaging procedures according to physical principles. It simulates the transport of gamma rays emitted from the source volume by using sampling algorithms for the occurrence, type and outcome of interactions, and for tracking secondary particles [37]. A decay position within the virtual phantom is sampled at the beginning of each gamma-ray track, known as the photon history.

The photon history can be divided into one primary photon history and histories of photons scattered in the phantom, depending on the selected number of scatter orders, i.e. the maximum number of scattering interactions (coherent and incoherent) of a photon within specific regions. The primary photon is "forced" to penetrate the phantom and proceed towards the detector within a predetermined acceptance angle, which is typically derived from the collimator-hole properties, without other interactions [75]. The probability of the photon to reach the crystal or other compartments depends on the accumulated attenuation coefficients along the photon path to the border of the phantom. To avoid bias in the results when comparing with real isotropic emission, the probability for scattering into the desired direction followed by a penetration is calculated and assigned as a weight that is part of the photon history. If detection occurs at a position corresponding to an image pixel, the weight is added to the total number of counts representing that pixel. In a real measurement, a value of one would have been added. This variance reduction method thus improves the efficiency of the simulations, especially when simulating a NaI(Tl)-crystal system with a collimator with low sensitivity.

When simulating histories of scattered photons, an isotropic direction is initially sampled at the decay point. A photon path is calculated. At the end of the sampled path (if inside the phantom), the scattered photon is split into two parts. The first part is directed towards the detector by applying Compton scattering in a forced direction. This scattered photon is then forced to escape the phantom without interaction and is then followed until termination (forced detection technique). The type of interaction for the second part of the scattered photon is weighted to be either Compton scattering or coherent scattering and this photon is followed in the phantom, step-by-step. This simulation procedure is repeated until the total

number of selected scattering orders has been simulated. At all of the steps above, the photon weight is adjusted along the path. Interactions are also simulated in the detector cover, the collimator, the crystal, and the backscattering compartment, but without photon-splitting.

A large number of simulated histories is required to obtain accurate estimates of the parameters to be calculated and to achieve reasonable statistical uncertainty. When simulating photon interactions, the differential cross-section data provide the information required to calculate the path length and the interaction type. The probability of a certain interaction type to occur is given by the individual attenuation coefficients for the photoelectric effect (τ), Compton scattering (σ_{inc}), coherent scattering (σ_{coh}), and pair production (κ). The sum of the individual attenuation coefficients is called the linear attenuation coefficient (μ):

$$\mu = \tau + \sigma_{inc} + \sigma_{coh} + \kappa \quad (12)$$

or mass-attenuation coefficient if normalized by the density $\mu(h\nu, Z)/\rho$. For simulation purposes in SIMIND, cross sections and attenuation coefficients have been calculated using the XCOM database (National Institute of Standards and Technology, Gaithersburg, MD, USA) in steps of 0.5 keV up to 3 MeV. For elements the database provides differential cross sections for scattering, photoelectric absorption and pair production, total cross sections, differential and total mass attenuation coefficients. For materials of different elements or even compounds materials, XCOM provides methods to weight the differential and total mass attenuation coefficients, which are equal to the product of the corresponding cross sections and the number of target molecules per unit mass of the materials.

The linear attenuation coefficient is used to sample the distance d a photon travels before its next interaction by the formula:

$$d = \frac{\ln(R)}{\mu(Z, h\nu)_{max}} \quad (13)$$

where R is a uniformly distributed random number between 0 and 1, $\mu(Z, h\nu)_{max}$ is the largest possible value of the attenuation coefficient within the volume of interest.

The type of interaction is determined by allowing a random number to decide among the possible interaction processes according to their relative probabilities. The coordinates of the end of the gamma-ray path must be calculated to determine whether the photon escapes the volume of interest or not. The path

length depends on the energy of the simulated gamma ray and the material density and composition.

An example of a flow diagram of the main steps of the simulation of a photon history in the scintillation crystal is shown in Figure 23.

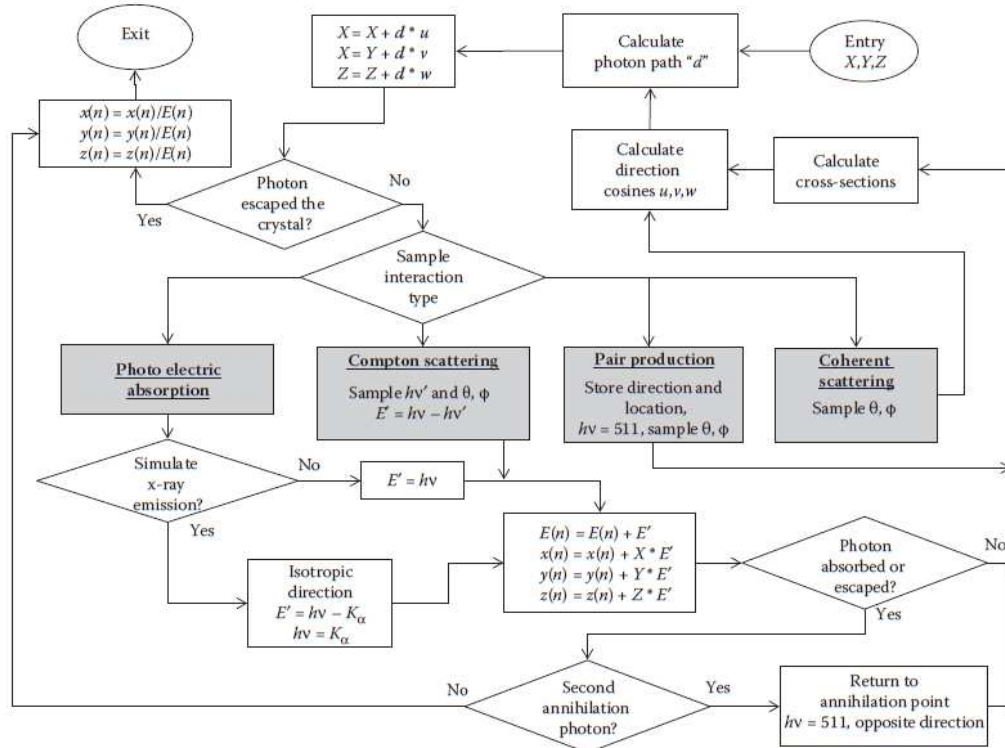


Figure 23. A general schematic representation of the simulation of a photon history in a material [75].

In gamma-ray imaging simulations, the energy released by secondary electrons is considered to be locally absorbed at the interaction site in the crystal.

To simulate an acquisition, a virtual phantom representing the radiopharmaceutical distribution is required. For this purpose, anthropomorphic voxel-based virtual phantoms are used, and digital image data are used to simulate a source distribution [75]. Each voxel represents the density at a specific location in the phantom. Radioactive decays are generated according to the voxel values of density. The relative pixel location from the center indicates the location of each decay. The linear attenuation coefficient is calculated as the product of the density ρ taken from the voxel map, and mass attenuation coefficients provided by the XCOM database. Voxel-based maps of both attenuation and source are then created.

The 4D extended Cardiac-Torso (XCAT) phantom used in this investigation is a hybrid-type phantom, that combines voxel-based and mathematical phantoms [38]. It was initially defined from segmented patient data and therefore provides a realistic model of patient anatomy. 4D tagged Magnetic Resonance Imaging (MRI) image data and high-resolution respiratory-gated CT provided the high-resolution three-dimensional human anatomy information necessary to construct a realistic volume-segmented phantom. The segmented structures were then fitted with continuous, smooth surfaces. These surfaces can be manipulated to model anatomical variation and motion. This phantom allows definition of the activity distribution in various organs and parameters such as heart and perfusion defect dimensions, specification of cardiac or respiratory patient motion, patient size and anatomic variations (Figure 24).

GSPECT is clinically used to evaluate LV function (contraction) and to distinguish between a true perfusion defect and an artifact. The cardiac cycle is divided into temporal frames, and image data for each frame are acquired and stored separately. Image data for each frame are then summed during processing to produce a dynamic representation of the LV. To simulate GSPECT, multiple datasets consisting of separate simulations for source and attenuation were created for each frame. Simulations were then combined in the final SIMIND file. In addition to the GSPECT dataset, non-gated datasets were obtained from the corresponding MC-simulated gated image data by summing the data for all phases of the cardiac cycle.

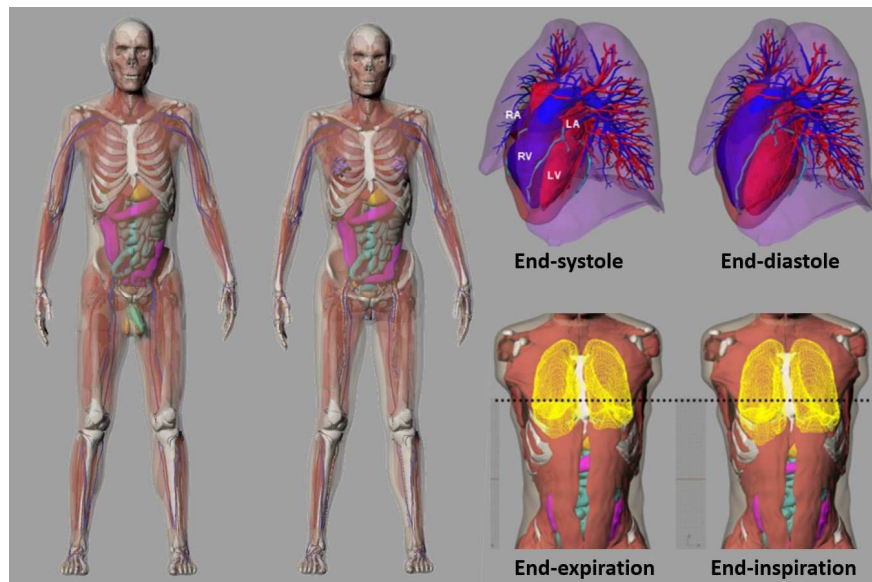


Figure 24. Examples of 4D XCAT voxelized anthropomorphic phantom model for male and female patients, and available cardiac and respiratory patient motion options [76].

2.7.2. Monte Carlo simulations of GSPECT on NaI(Tl)-crystal detector system with parallel-hole collimators

As described above, in the experimental session a static semi-anthropomorphic phantom was used to characterize imaging systems. The main objective of the MC simulation session was to extend the characterization also to dynamic conditions. For that reason, GSPECT was simulated for the SPECT system with NaI(Tl)-crystal detector and parallel-hole collimators, considered the standard technology.

In this investigation, input parameters for the simulations were selected according to standard acquisition parameters for GSPECT on Siemens Symbia T (Siemens Healthineers): 64 projections, matrix size 64×64, pixel size 6.6 mm, angular range 180°, non-circular detector orbit, and cardiac cycle divided into 8 temporal frames. A normal size 4D XCAT male model (body mass index=20 kg/m²) was used. The activity distribution per organs was simulated according to previously published data [41], scaled on the basis of quantitative evaluation of counts in relevant regions of interest in clinical patient cases. The activity concentrations in organs are shown in Table 4.

	Activity concentration (kBq/mL)
LV myocardium	65
RV myocardium	39
liver	26
lungs	3
gall bladder	163
kidneys	91
spleen	14
stomach	2
remaining thorax	1

Table 4. Activity concentrations in the 4D XCAT phantom used in the MC simulation session.

A normal myocardial perfusion condition was simulated according to activity distribution from Table 4. For each MC simulated GSPECT, a CT dataset was also created. Figure 25 shows examples of transversal, sagittal and coronal views.

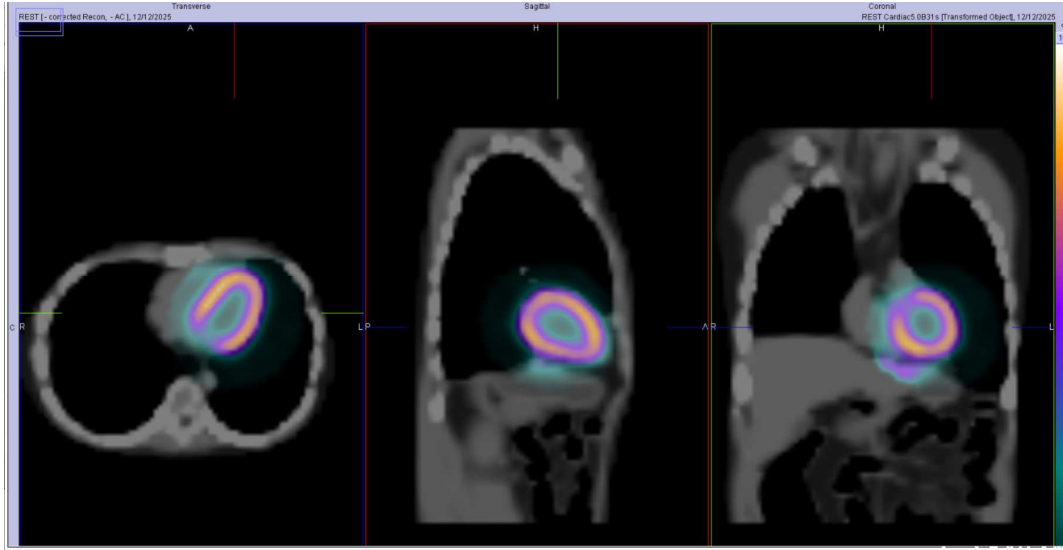


Figure 25. An example of a GSPECT MC simulation for normal myocardial perfusion condition: transversal, sagittal and coronal views.

Additionally, four pathological myocardial perfusion conditions were simulated with a cold defect in four different positions in the myocardial wall: anterior, lateral, posterior and septal. The positions of the defects were selected to match the conditions used in the experimental session, taking into account the volume changes due to cardiac motion in GSPECT. Table 5 shows the values used to create the 4D XCAT models of the pathological heart.

The dimensions of the myocardial LV and right ventricle (RV) set for the MC simulation of the normal myocardial perfusion condition are described in Table 6. The dimensions of the heart chambers vary between frames to simulate contraction of the myocardium. The dimensions of the PDs were selected to match the volume of the PD with relative to the wall in the semi-anthropomorphic phantom (3.1%). Relative PD dimensions for the four simulated pathological myocardial perfusion conditions (PD in the anterior, lateral, posterior and septal positions) are shown in Table 7. A detailed description of the 4D XCAT model used for the simulation of one frame of the GSPECT can be found in Appendix A.

For each myocardial perfusion condition, one GSPECT MC simulation was generated, and five different versions of the noise distributions were performed, i.e., five noise realizations. In total, five datasets were created for each myocardial perfusion condition.

Position of PD	XCAT notation							
	h1	h2	h3	h4	h5	h6	h7	h8
Anterior	10	50	0.38	25	1	0	10	5
Lateral	100	50	0.38	25	1	0	10	5
Posterior	190	50	0.38	25	1	0	10	5
Septal	280	50	0.38	25	1	0	10	5

h1 = theta center in degree (between 0 and 360)

h2 = theta total width in degree (between 0 and 360 deg.)

h3 = x center (for heart 0.0=base, 1.0=apex)

h4 = x width, total in mm's

h5 = fraction of the outer wall transgressed by the lesion

h6 = scales the motion of the defect region in the heart (1 = normal motion, < 1 = reduced motion), altered motion blends with normal

h7 = longitudinal width (in terms of number of control points) of transition between abnormal and normal motion of heart lesion

h8 = radial width (in terms of number of control points) of transition between abnormal and normal motion of heart lesion

Table 5. Specifications of the 4D XCAT models used for the simulation of GSPECT in SIMIND. Four pathological myocardial perfusion conditions were simulated by positioning the perfusion defect in anterior, lateral, posterior and septal position in the LV wall. 4D XCAT notation (h1, h2, h3, h4, h5, h6, h7, h8) are specified for each 4D XCAT model.

Frame	1	2	3	4	5	6	7	8
Volume (mL)								
LV wall	128.18	134.44	135.84	135.26	135.65	132.79	127.48	125.58
LV chamber	130.16	94.24	72.20	61.28	65.00	106.58	133.19	141.59
RV wall	29.38	27.84	26.45	25.67	25.93	28.34	29.61	29.93
RV chamber	102.97	85.87	74.12	67.93	70.17	91.95	104.20	108.03

Table 6. Volumes of the LV wall, LV chamber, RV wall and RV chamber for the MC simulated normal myocardial perfusion condition at 8 temporal frames.

Frame	1	2	3	4	5	6	7	8
PD position	Volume of the PD respect to the LV wall (%)							
ANT	2.96	3.24	3.46	3.49	3.43	3.12	2.89	2.81
LAT	3.23	3.24	3.31	3.28	3.27	3.20	3.16	3.12
POST	3.55	3.72	3.88	3.88	3.83	3.61	3.46	3.41
SEPT	3.07	2.96	2.87	2.78	2.83	2.96	3.00	2.94

Table 7. Volumes of the perfusion defect (PD) respect to the LV wall for the four MC simulated pathological myocardial perfusion conditions at 8 temporal frames.

The MC simulated projection image data in DICOM format were imported into the clinical processing workstation Symbia.net (Siemens Healthineers, Erlangen, Germany) and reconstructed using Flash 3D OSEM IRR with 15 iterations, 8 subsets and 13.2 mm Gaussian post-reconstruction filter. GSPECT image data were reconstructed without scatter and attenuation corrections, as performed clinically.

Quantitative analysis of the MC simulated image data was performed using the quantitative post-processing algorithm Corridor4DM (Invia Medical Imaging Solutions). The five datasets corresponding to normal myocardial perfusion condition were used to create the normal myocardial perfusion database for simulated GSPECT. The resulting polar maps were used to calculate DPI values for MC simulated GSPECT. When calculating DPI according to Equation 11, $mean_{norm,i}$ was the mean perfusion value of segment i in MC simulated normal myocardial perfusion GSPECT (normal myocardial perfusion database) and $mean_{path,i}$ was the mean perfusion value of segment i in the polar map representation obtained from the image data of MC simulated pathological myocardial perfusion GSPECT.

The segments included in the calculation of DPI for GSPECT MC simulations were the same as those used in DPI evaluation of experimental image data (Figure 22.d). The PD regions for the anterior position of the PD included segments $i=1,7$; segments $i=5,6,11,12$ for the lateral position; segments $i=4,10$ for the posterior position; and segments $i=2,3,8,9$ for the septal position. Evaluation was performed on both GSPECT and SPECT simulated image data. Additionally, LV volume curves obtained from both 4D XCAT inner chamber known volumes at each time frame of the GSPECT and the volumes obtained in the quantitative analysis with Corridor4D were compared. The ejection fraction (EF) was calculated as:

$$EF(\%) = 100 * \frac{EDV - ESV}{EDV} \quad (14)$$

where EDV and ESV are the largest and smallest 4D XCAT phantom volumes corresponding to the end-diastolic and end-systolic volumes, respectively. EF is used to estimate the percentage of blood the LV pumps out with each contraction.

2.8. Statistical analysis and uncertainty estimation of experimental data

Experiment is the essence of the natural sciences, which are based on measurements. Measurements are subject to uncertainty, and therefore the assessment and minimization of these uncertainties make a substance of the accuracy of the estimation of physical quantities.

In nuclear medicine, image quality is described through physical parameters evaluated over regions of interest in which counts are detected by the imaging system detector. The uncertainty of image quality parameters (e.g. signal-to-noise ratio, spatial resolution, contrast, noise, etc.) depends on both the uncertainty related to the preparation of the experimental session and the uncertainty related to the imaging system used.

There are two ways of estimating uncertainties: Type A evaluations and Type B evaluations. In Type A evaluations, uncertainties are estimated using statistical methods (σ^{stat}). In Type B evaluations, uncertainties are estimated from non-statistical methods (σ^{system}) such as calibration certificates, manufacturer's specifications, and scientific publications [77].

In nuclear medicine imaging, both Type A and Type B uncertainties should be considered when calculating the total uncertainty of the mean number of counts per voxel ($\bar{\eta}$) obtained in image analysis.

The following uncertainties shall be considered:

- Activity meter/activity measurement (Type B)
- Volume assessment/phantom compartments (Type B)
- Phantom positioning (Type A)
- Image reconstruction/SPECT acquisition (Type A)
- ROI positioning (Type A)
- ROI count statistics (Type A)

To mimic clinical conditions, phantom compartments shall be filled with a solution of predetermined activity and uncertainties related to the activity measurements (σ_A) correspond to uncertainties related to the accuracy of the activity meter used in phantom preparation.

The volumes of different phantom compartments are measured using syringe or graduated laboratory glassware. The uncertainty related to the scale on the syringe or glassware should be considered (σ_{vol}).

In the experimental session with the semi-anthropomorphic phantom of the present research, the phantom was repositioned between acquisitions to simulate patient variability. Variability in phantom positioning on the imaging

system is included in the standard deviation of repeated measurements of the mean number of counts per voxel σ_{pos} .

SPECT image reconstruction is not automatic and depends on the selection of reconstruction volume and axes realignment. The acquired phantom dataset should be reconstructed multiple times to account for variability in image reconstruction (σ_{recon}).

Image analysis is usually performed by manually drawing and positioning ROIs on the structures of interest, introducing variability in the ROI total count. Analysis should be performed multiple times to account for variability in ROI content ($\sigma_{ROI-pos}$).

Additionally, the uncertainty related to the distribution of the count statistics in the ROI ($\sigma_{ROI-stat}$) should be considered.

Since all the variables described above are assumed to be mutually independent and uncorrelated, the total uncertainty in the mean number of counts per voxel can be calculated:

$$\sigma_{\bar{\eta},tot} = \sqrt{\sigma_A^2 + \sigma_{vol}^2 + \sigma_{pos}^2 + \sigma_{recon}^2 + \sigma_{ROI-pos}^2 + \sigma_{ROI-stat}^2} \quad (15)$$

In the present study, $\sigma_{pos}^2 + \sigma_{recon}^2 + \sigma_{ROI-pos}^2 + \sigma_{ROI-stat}^2$ can be included in a unique term called σ_{stat}^2 . The σ_{stat} is calculated as the standard deviation for the measurements repeated n times.

In conclusion, the following equation can be used:

$$\sigma_{\bar{\eta},tot} = \sqrt{\sigma_A^2 + \sigma_{vol}^2 + \sigma_{stat}^2} \quad (16)$$

2.8.1. Uncertainty in the physical descriptors

Measured mean number of counts per voxel values are used to calculate the physical descriptors related to contrast and spatial resolution. The uncertainty in the descriptor related to contrast is obtained by applying the law of propagation of uncertainty (LPU) to the equation used to determine the physical descriptor [78].

Contrast between the LV wall and the LV inner chamber. $C_{LV/LVIC}$ is calculated as the ratio between the contrast measured on the reconstructed image data, $C_{LV/LVIC,meas}$, and the contrast defined by the preparation of the phantom,

$C_{LV/LVIC,phantom}$ (Equation 2). The uncertainty in the contrast between the LV wall and the LV inner chamber is obtained by applying LPU.

If the uncertainties in the activity and in the volumes of the LV and LVIC are assumed to be fixed and defined as relative values, the uncertainty in the activity concentration AC_x can be set as:

$$\sigma_{AC_x} = AC_x \cdot \sigma_{RelAC} \quad (17)$$

where σ_{RelAC} is a fixed relative uncertainty for each activity concentration. The uncertainty in the contrast between the LV wall and the LV inner chamber is calculated as:

$$\sigma_{C_{LV/LVIC}} = \left(\left(\left(\frac{2\overline{\eta_{LVIC}}}{(\overline{\eta_{LV}} + \overline{\eta_{LVIC}})^2} \right)^2 \sigma_{\overline{\eta_{LV}},tot}^2 + \left(-\frac{2\overline{\eta_{LV}}}{(\overline{\eta_{LV}} + \overline{\eta_{LVIC}})^2} \right)^2 \sigma_{\overline{\eta_{LVIC}},tot}^2 \right) \times \frac{1}{C_{LV/LVIC,phantom}^2} + 8 \frac{AC_{LV}^2 AC_{LVIC}^2}{(AC_{LV} + AC_{LVIC})^2} \sigma_{RelAC}^2 \frac{C_{LV/LVIC,meas}^2}{C_{LV/LVIC,phantom}^2} \right)^{\frac{1}{2}} \quad (18)$$

where $\sigma_{\overline{\eta_{LV}},tot}$ and $\sigma_{\overline{\eta_{LVIC}},tot}$ are the total uncertainties in the mean number of counts in the LV and the LVIC, respectively.

Net contrast. The NC is calculated according to Equation 8, thus the uncertainty in the NC is obtained by:

$$\sigma_{NC} = \sqrt{\sigma_{C_{PD}}^2 + \sigma_{IC}^2} \quad (19)$$

Where $\sigma_{C_{PD}}$ and σ_{IC} are the uncertainty in C_{PD} and IC , respectively.

The uncertainty in C_{PD} is calculated as:

$$\sigma_{C_{PD}} = \sqrt{\left(\left(\frac{2\overline{\eta_{PD}}}{(\overline{\eta_{LV}} + \overline{\eta_{PD}})^2} \right)^2 \sigma_{\overline{\eta_{LV}},tot}^2 + \left(-\frac{2\overline{\eta_{LV}}}{(\overline{\eta_{LV}} + \overline{\eta_{PD}})^2} \right)^2 \sigma_{\overline{\eta_{PD}},tot}^2 \right)} \quad (20)$$

where $\sigma_{\overline{\eta_{LV}},tot}$ and $\sigma_{\overline{\eta_{PD}},tot}$ are the total uncertainties in the mean number of counts in the LV and PD, respectively.

The uncertainty in the intrinsic contrast is calculated by using:

$$\sigma_{IC} = \left(\left(\frac{2\overline{\eta_{PD,norm}}}{(\overline{\eta_{LV,norm}} + \overline{\eta_{PD,norm}})^2} \right)^2 \sigma_{\overline{\eta_{LV,norm}},tot}^2 + \left(-\frac{2\overline{\eta_{LV,norm}}}{(\overline{\eta_{LV,norm}} + \overline{\eta_{PD,norm}})^2} \right)^2 \sigma_{\overline{\eta_{PD,norm}},tot}^2 \right)^{1/2} \quad (21)$$

where $\sigma_{\overline{\eta_{LV,norm}},tot}$ and $\sigma_{\overline{\eta_{PD,norm}},tot}$ are the total uncertainties in the mean counts per voxel in the LV wall and in the position corresponding to the perfusion defect on *normal phantom* image data, respectively.

Considering, above equations, the uncertainty in the net contrast can be calculated as:

$$\sigma_{NC} = \left(\left(\frac{2\overline{\eta_{PD}}}{(\overline{\eta_{LV}} + \overline{\eta_{PD}})^2} \right)^2 \sigma_{\overline{\eta_{LV}},tot}^2 + \left(-\frac{2\overline{\eta_{LV}}}{(\overline{\eta_{LV}} + \overline{\eta_{PD}})^2} \right)^2 \sigma_{\overline{\eta_{PD}},tot}^2 + \left(\frac{2\overline{\eta_{PD,norm}}}{(\overline{\eta_{LV,norm}} + \overline{\eta_{PD,norm}})^2} \right)^2 \sigma_{\overline{\eta_{LV,norm}},tot}^2 + \left(-\frac{2\overline{\eta_{LV,norm}}}{(\overline{\eta_{LV,norm}} + \overline{\eta_{PD,norm}})^2} \right)^2 \sigma_{\overline{\eta_{PD,norm}},tot}^2 \right)^{\frac{1}{2}} \quad (22)$$

Wall thickness and sharpness index. For the descriptors related to spatial resolution, Type A uncertainties were calculated (see 2.8.2), while Type B uncertainties were not considered. The reason is the definition of these descriptors (Figures 18 and 19). The uncertainties of the measurements repeated n times should be considered. With appropriate count statistics, no other uncertainties contribute to the total uncertainty.

Segmental uptake, global uniformity, extent of PD, SS and DPI. To calculate descriptors related to the myocardial perfusion, mean perfusion values obtained in the quantitative analysis were used. The uncertainty in the results obtained by quantitative post-processing algorithms was calculated considering only the Type

A uncertainty derived from the statistical analysis (see 2.8.2). The quantitative post-processing algorithms do not allow for additional considerations in terms of Type B uncertainties. The uncertainties of the measurements repeated n times should be considered (Type A).

2.8.2. Statistical analysis of data

The influence of the type of *MPI system* on contrast between the LV wall and the LV inner chamber, wall thickness, sharpness index and global uniformity was evaluated separately using one-way ANOVA. The type of *MPI system* was considered the independent variable, and the image quality descriptors (contrast between the LV wall and the LV inner chamber, wall thickness, sharpness index and global uniformity) were considered the dependent variables.

The impact of the type of *MPI system* and defect position on net contrast, extent of PD, SS and *DPI* was evaluated using two-way ANOVA. The type of *MPI system* and lesion position were considered the independent variables, and lesion net contrast, extent of PD, SS and *DPI* were considered the dependent variables.

If a significant F value was found for an independent variable, this was referred to as a main effect. When a main effect was found, a post-hoc test (Scheffé test) compared levels of a factor 2×2 for a particular dependent variable, thus identifying the main sources of variability.

The analysis was performed using Statistica version 14.1 (StatSoft Inc., Tulsa, OK, USA) with a two-sided type I error of $p=0.05$. Least square means, standard errors and 95% confidence intervals were calculated for all descriptors (Type A uncertainties). In the calculation of total uncertainty for the contrast between the LV wall and the LV inner chamber, intrinsic contrast and net contrast (Equations 18, 21 and 22), the standard errors were treated as Type A uncertainties.

Results from two Symbia T systems with LEHR collimators and FBP algorithms were compared using t-test for independent variables to assess the possibility of pooling results into a single *MPI system*. The null-hypothesis was that the means of the image quality descriptors obtained on the two *MPI systems* were not statistically significantly different.

3. Results and Discussion

3.1. Uncertainty estimation of experimental data

In the statistical analysis of experimental data, standard deviations, standard errors and 95% confidence intervals were calculated and shown in the graphs (Type A uncertainty). Additionally, for the physical descriptors as contrast between the LV wall and the LV inner chamber, intrinsic contrast and net contrast, both Type A and Type B uncertainties were calculated to estimate the total uncertainty. Tables 8, 9 and 10 present a detailed uncertainty analysis for the three descriptors related to the contrast.

$C_{LV/LVIC}$			
<i>MPI system</i>	Type A uncertainty (%)	Type B uncertainty (%)	Total uncertainty (%)
Symbia-FBP	1.1	3.6	3.8
Symbia-IRR	1.4	2.9	3.2
Symbia-IRR+SC	1.4	2.5	2.9
SymbialQ+SCAC	1.2	2.3	2.6
SymbialQ	1.2	3.9	4.0

Table 8. Results of the uncertainty analysis for the contrast between the LV wall and the LV inner chamber. Uncertainties are calculated for different *MPI systems*. Values are rounded to one significant digit.

The t-test for independent variables used for two Siemens Symbia T systems with LEHR collimators showed that the mean values of image quality descriptors of the two systems are not significantly different, as the null-hypothesis could not be rejected when comparing image quality descriptor data from the two systems. Therefore, assuming the results come from the same population, they were pooled.

<i>IC</i>												
<i>MPI system</i>	Type A uncertainty (%)				Type B uncertainty (%)				Total uncertainty (%)			
	ANT	LAT	POST	SEPT	ANT	LAT	POST	SEPT	ANT	LAT	POST	SEPT
Symbia-IRR	0.7	0.7	0.7	0.8	5.1	3.6	4.1	3.3	5.2	3.6	4.1	3.4
Symbia-IRR+SC	0.7	0.7	0.7	0.7	3.8	3.2	2.9	3.6	3.8	3.2	3.0	3.7
Symbia IQ+SCAC	0.5	0.5	0.5	0.5	6.0	5.1	4.4	4.3	6.0	5.1	4.4	4.3
Symbia IQ	0.5	0.5	0.5	0.5	6.3	6.7	6.0	6.2	6.3	6.7	6.0	6.2

Table 9. Results of the uncertainty analysis for the intrinsic contrast. Uncertainties are calculated for different *MPI systems* and different positions of the PD. Values are rounded to one significant digit.

<i>NC</i>												
<i>MPI system</i>	Type A uncertainty (%)				Type B uncertainty (%)				Total uncertainty (%)			
	ANT	LAT	POST	SEPT	ANT	LAT	POST	SEPT	ANT	LAT	POST	SEPT
Symbia-IRR	1.8	1.4	1.4	1.8	5.7	6.1	4.8	4.3	6.0	6.3	5.0	4.7
Symbia-IRR+SC	1.2	1.2	1.2	1.2	4.8	3.9	2.6	6.1	4.9	4.1	2.9	6.3
Symbia IQ+SCAC	1.4	1.2	1.8	1.8	6.5	7.8	4.8	4.4	6.7	7.9	5.1	4.8
Symbia IQ	1.4	1.2	1.8	1.8	7.1	7.6	6.5	6.4	7.3	7.7	6.7	6.6

Table 10. Results of the uncertainty analysis for the net contrast. Uncertainties are calculated for different *MPI systems* and different positions of the PD. Values are rounded to one significant digit.

3.2. Evaluation of *MPI systems* through physical image quality descriptors and descriptors related to the quality of myocardial perfusion data

In the first part of the investigation, the objective was to perform a comprehensive evaluation of *MPI systems* through a set of physical descriptors related to contrast, spatial resolution and uniformity of polar maps. As noted in the paragraph „Overview of previous research”, results for IQ SPECT systems had not been published, therefore a complement of results from literature was required. The evaluation was performed on *MPI systems* available at the Clinical Hospital Center Rijeka, Clinical Hospital Center Split and the General Hospital Pula. In the first two institutions, the *MPI system* used clinically was Symbia-FBP, but the implementation of IRR was also tested for optimization purposes. In the third institution, both SymbialQ+SCAC and SymbialQ had already been implemented in clinical practice.

This part of the investigation was therefore performed on the following *MPI systems*: Symbia-FBP, Symbia-IRR, Symbia-IRR+SC, SymbialQ+SCAC and SymbialQ.

Normal perfusion myocardial conditions were simulated with a semi-anthropomorphic phantom. Figure 26 shows an example of short-axis image data acquired with the different *MPI systems*.

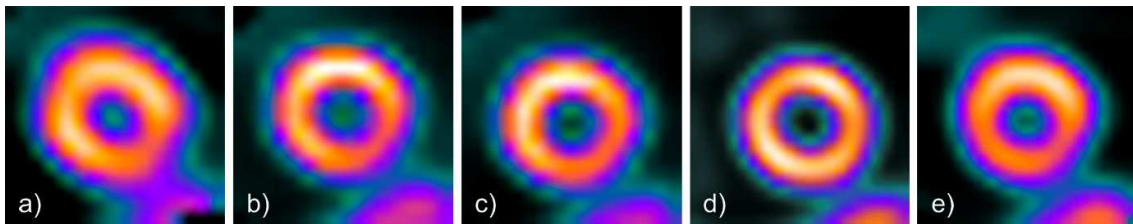


Figure 26. Examples of short-axis image data of the *normal phantom* acquired with different *MPI systems*: Symbia-FBP (a), Symbia-IRR (b), Symbia-IRR+SC (c), SymbialQ+SCAC (d) and correction free SymbialQ (e).

3.2.1. Contrast between LV wall and LV inner chamber, LV wall thickness, sharpness index, segmental uptake and global uniformity

Contrast between the LV wall and LV inner chamber. The type of *MPI system* was a main effect with a statistically significant impact on the contrast between the LV wall and LV inner chamber ($F=57.5$, $p<0.001$). The post-hoc Scheffé test identified the statistically significant differences shown in Figure 27. No

CONTRAST BETWEEN LV WALL AND LV INNER CHAMBER (%)

MPI SYSTEM	Contrast (%)	p-value (vs Symbia-FBP)
Symbia-FBP	47.0	-
Symbia-IRR	57.5	$p < 0.0001$
Symbia-IRR+SC	64.0	$p < 0.0001$
SymbialQ+SCAC	70.5	$p = 0.0004$
SymbialQ	54.5	$p = 0.03$

MPI SYSTEM

LV wall thickness and sharpness index. The type of *MPI system* was a main effect with a statistically significant impact on both LV wall thickness ($F=36.5$, $p<0.001$) and sharpness index ($F=72.2$, $p<0.001$). LV wall thickness values decreased from Symbia-FBP to SymbialQ+SCAC. When no corrections were applied, the SymbialQ results were comparable to those acquired with Symbia-FBP. The post-hoc Scheffè test of the different *MPI systems* showed no statistically significant differences in LV wall thickness values between the following pairs: Symbia-FBP and Symbia-IRR, Symbia-FBP and SymbialQ, Symbia-IRR and Symbia-IRR+SC, and Symbia-IRR+SC and SymbialQ, as shown in Figure 28. For the sharpness index, no statistically significant differences were found between Symbia-FBP and Symbia-IRR, Symbia-IRR and SymbialQ and between Symbia-IRR+SC and SymbialQ (Figure 29).

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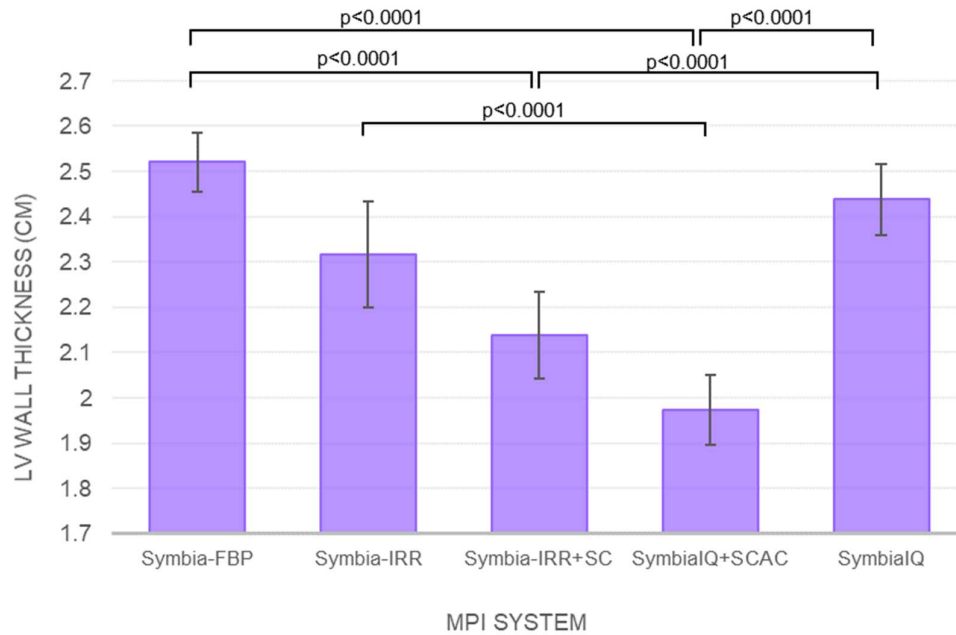


Figure 28. LV wall thickness values for different *MPI systems*. Values represent least square means; vertical bars represent 95% confidence intervals.

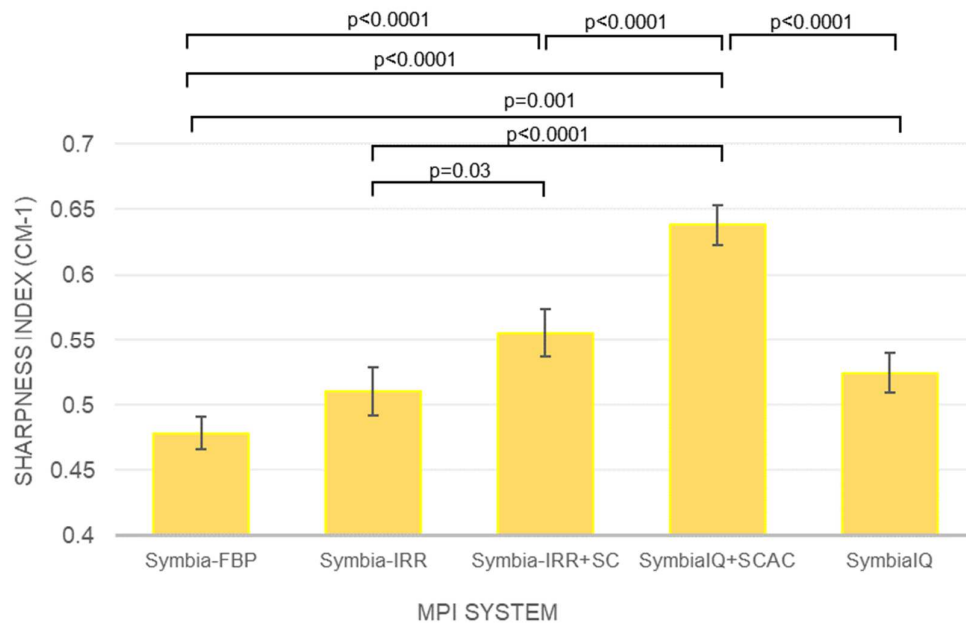


Figure 29. Sharpness index values for different *MPI system*. Values represent least square means; vertical bars represent 95% confidence intervals.

Segmental uptake and global uniformity. SU_n values for different *MPI* systems are shown in Figure 30. Values are shown for 17 segments of the polar map. Segments from 1 to 6 represent the basal section of the LV, segments from 7 to 12 represent the mid-section, and segments from 13 to 17 represent the apical section.

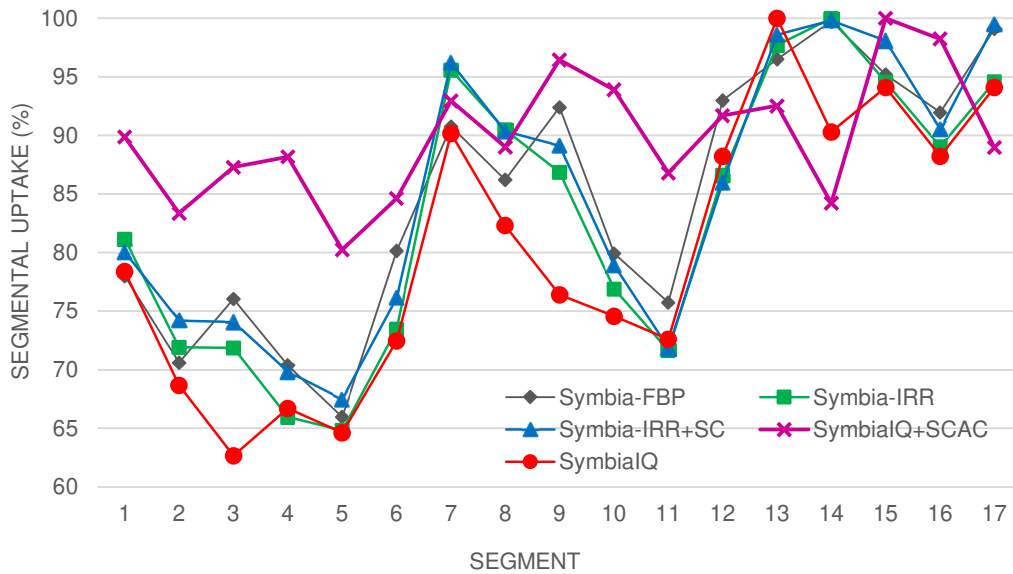


Figure 30. Segmental uptake values for 17 segments of the polar map and different *MPI* systems. Values represent least square means. For clarity vertical bars representing 95% confidence intervals were omitted (standard errors<1.5%).

One-way ANOVA analysis identified a statistically significant difference in *GU* between different types of *MPI* systems ($F=62.24$, $p<0.001$). Scheffé post-hoc analysis showed statistically significant differences between *GU* values for all types of *MPI* systems compared with SymbialQ+SCAC (Figure 31).

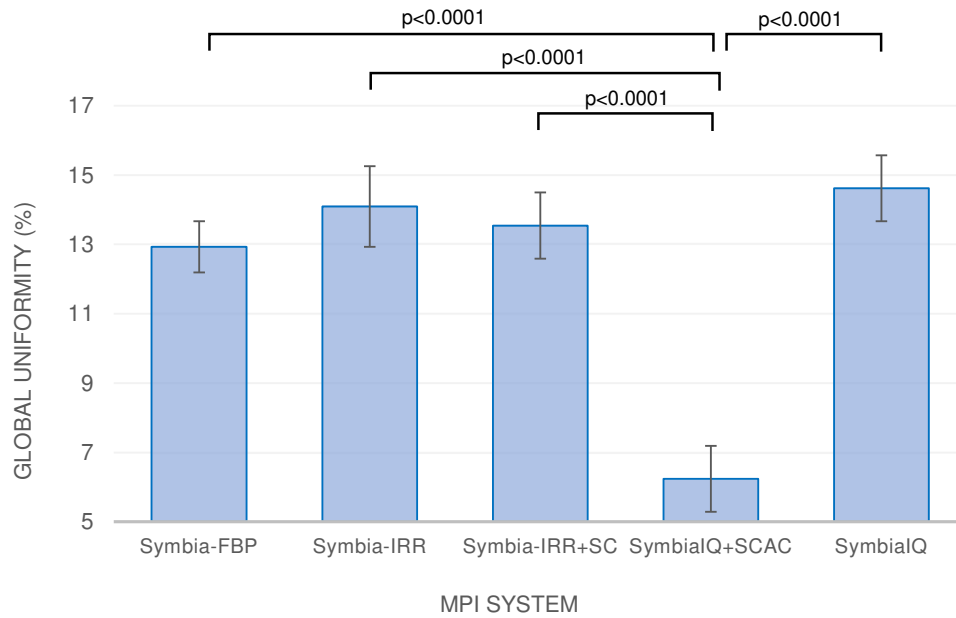


Figure 31. Global uniformity values for different *MPI systems*. Values represent least square means; vertical bars represent 95% confidence intervals.

Discussion

The percentage $C_{LV/LVIC}$ represents the ability of the *MPI system* to detect and image the contrast between chambers relative to the contrast defined during phantom preparation. Compared with the other *MPI systems* assessed, this part of the investigation showed that the SymbialQ+SCAC system outperformed the others in terms of contrast, with statistically significantly larger values of $C_{LV/LVIC}$ (Figure 27). The Symbia-FBP system produced the lowest contrast values. The mean $C_{LV/LVIC}$ increased by more than 10% on average when switching from FBP to IRR in the case of Symbia system. Although these differences were not statistically significant, overall, Symbia-IRR+SC exhibited a larger $C_{LV/LVIC}$ than Symbia-IRR ($63.8 \pm 1.4\%$ vs. $57.4 \pm 1.4\%$). If scatter and attenuation corrections are not performed for SymbialQ, $C_{LV/LVIC}$ is reduced by over 15%. Caobelli et al. [21] observed a similar pattern, reporting a larger contrast in IQ SPECT image data corrected for attenuation and scatter compared with image data without corrections. However, the results of Caobelli et al. [21] reported considerably higher values (~20%) than the $C_{LV/LVIC}$ values obtained in this investigation. Differences between the SymbialQ system without corrections and Symbia-IRR

are not statistically significant, which is in line with the results reported by Imbert et al [22]. The total uncertainty values in $C_{LV/LVIC}$ (2.6% - 4.0%) are included in the 95% confidence intervals shown in the graphs and do not alter the above conclusions.

The LV wall thickness analysis showed a substantial overestimation of wall thickness for all *MPI systems*, with values 2 to 2.5 times larger than the specified value (1 cm). Such overestimations were expected due to the position of the insert in the phantom and the presence of background activity. It is worth noting that Symbia-IRR performs better than Symbia-FBP, with mean wall thickness values more than 2 mm smaller (Figure 28). Liu et al. [23] used a different methodology to determine wall thickness and reported results for conventional imaging devices with IRR of the same order of magnitude. Differences in LV wall thickness values depending on the reconstruction algorithm used in NaI(Tl)-crystal detector systems were also shown by Zoccarato et al. [10], but the wall thickness values for NaI(Tl)-crystal detector systems obtained in this investigation were larger than those reported by that group. Additionally, even though smaller mean wall thickness values were obtained for Symbia-IRR+SC compared with Symbia-IRR, no statistically significant difference was found between these two *MPI systems*. This finding might suggest that the use of SC does not significantly affect wall thickness measurement when IRR is used. The lowest thickness values were detected for SymbialQ+SCAC and were considerably better than those of any other *MPI system*, although substantial overestimation is still present. The analysis also showed that correction free SymbialQ performs similarly to Symbia-FBP, despite differences in collimator design and the shorter acquisition time. The results of this investigation are comparable with those presented by Caobelli et al. [43] on IQ SPECT, despite the use of a different methodology to determine wall thickness. However, this investigation has shown a considerable impact of SC and AC on spatial resolution in the SymbialQ system and the superiority of SymbialQ+SCAC compared with correction free SymbialQ. Regarding the sharpness index, SymbialQ+SCAC was again found to be significantly superior to all other *MPI systems* used in this investigation (Figure 29). This demonstrates an improvement in spatial resolution when multifocal SmartZoom collimators are used in combination with CT. Additionally, the results suggest that the introduction of IQ SPECT technology has led to a significant improvement in *MPI system* spatial resolution, with sharpness index values comparable to those reported for advanced CZT systems [23, 25]. Correction-free SymbialQ was found to behave similarly to Symbia-IRR and Symbia-IRR+SC. Scatter correction significantly increased the sharpness index for Symbia-IRR, resulting in better spatial resolution in terms of sharpness index when a dual energy window is used. The lowest overall sharpness index was found for Symbia-FBP; however, the observed differences were not statistically

significant when compared with the values obtained by the Symbia-IRR. To the best of our knowledge, there are no published results for sharpness index evaluated on IQ SPECT systems, and the results of this investigation for SymbialQ+SCAC and SymbialQ could be considered as a complement to the available data.

Spatial resolution was found to be significantly superior for SymbialQ when both SC and AC corrections were applied. This investigation demonstrated that SymbialQ+SCAC has similar performances in terms of spatial resolution to the respective CZT dedicated systems [25].

Polar maps display the local radiopharmaceutical distribution and are used as a conventional representation of quantitative assessment of myocardial perfusion [55]. Apart from SymbialQ+SCAC, for the other *MPI systems* it is evident that, in the posterolateral part of both the basal and mid-section of the heart (segments 5 and 11) uptake values are lower and non-uniformity of the polar map due to attenuation artifacts is visible (Figure 30). This is also apparent when short-axis image data acquired with different *MPI systems* are compared (Figure 26). On Symbia-FBP, Symbia-IRR, Symbia-IRR+SC and SymbialQ, the posterolateral part of the LV suffers from underestimation of signal intensity. By contrast, image data obtained with SymbialQ+SCAC provide a higher level of signal intensity uniformity throughout the short-axis image data. This should be considered when interpreting clinical image data. As expected, the results show smaller segmental uptake values in the basal section and higher values in the apical section [19]. When SymbialQ-SCAC is used, differences in mean SU_n values are less pronounced, with SU_n values higher than 80% demonstrating the superiority of this *MPI system*. The results of this investigation confirm findings presented by other authors [21, 35, 43, 79], supporting the conclusion that non-uniformity of polar maps can be significantly reduced by IQ SPECT systems when appropriate SC and AC corrections are applied.

SymbialQ+SCAC was found to produce the lowest GU values with statistically significant differences compared with the other examined *MPI systems* (Figure 31). All other *MPI systems* were found to perform similarly in terms of GU , with differences between them not statistically significant. The results for SymbialQ+SCAC are in accordance with those reported by Zoccarato et al. [35], making it possible to conclude that SymbialQ+SCAC produces LV image data that are more uniform in terms of polar map analysis than those from the other *MPI systems* evaluated in this part of the investigation.

Results obtained in this initial part of the investigation showed generally better contrast, spatial resolution and polar map uniformity for Symbia-IRR+SC compared with Symbia-FBP. When these results were obtained, it was decided

to optimize the reconstruction parameters, and iterative reconstruction with resolution recovery was implemented in clinical practice.

3.3. Evaluation of system-dependent properties and perfusion defect detection ability of the *MPI* system through physical image quality descriptors

In the evaluation of physical descriptors presented in the section 3.2., the Symbia-FBP system exhibited inferior performance compared with the other *MPI* systems. Therefore, the Symbia-FBP system was excluded from further investigation. The second part of the investigation was consequently conducted on four *MPI* systems: Symbia-IRR, Symbia-IRR+SC, SymbialQ+SCAC and SymbialQ.

This part of the investigation focused on contrast, self-attenuation properties and system-dependent effects, and perfusion defect detection ability. Normal and pathological myocardial perfusion conditions were simulated using a semi-anthropomorphic phantom. For brevity, the different myocardial perfusion conditions in the phantom will be referred to as the *normal phantom* and *pathological phantom*, respectively. Intrinsic contrast was evaluated in short-axis image data of the *normal phantom*. Additionally, pathological myocardial perfusion conditions were simulated by using the semi-anthropomorphic phantom with the myocardial insert containing perfusion defects. Figure 32 shows an example of a short-axis image of the *pathological phantom* with the PD in four positions: anterior, lateral, posterior, and septal. Image data of both *normal phantom* and *pathological phantom* were used to evaluate the net contrast.

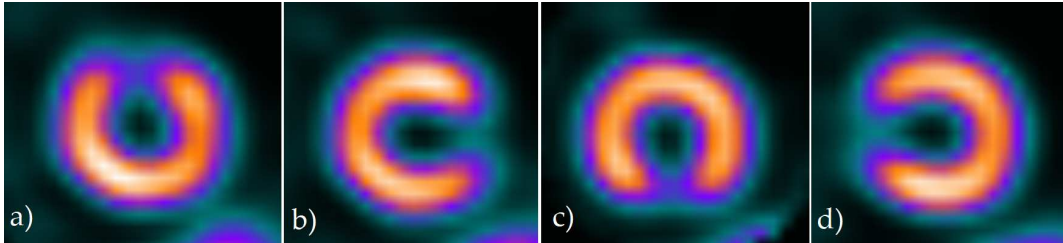


Figure 32. Example of short-axis image data of the *pathological phantom* obtained on SymbialQ+SCAC. Different PD positions are shown: anterior (a), lateral (b), posterior (c) and septal (d).

3.3.1. Intrinsic contrast and net contrast

Intrinsic contrast. Intrinsic contrast values at four PD positions are shown in Figure 33 for *MPI* systems evaluated.

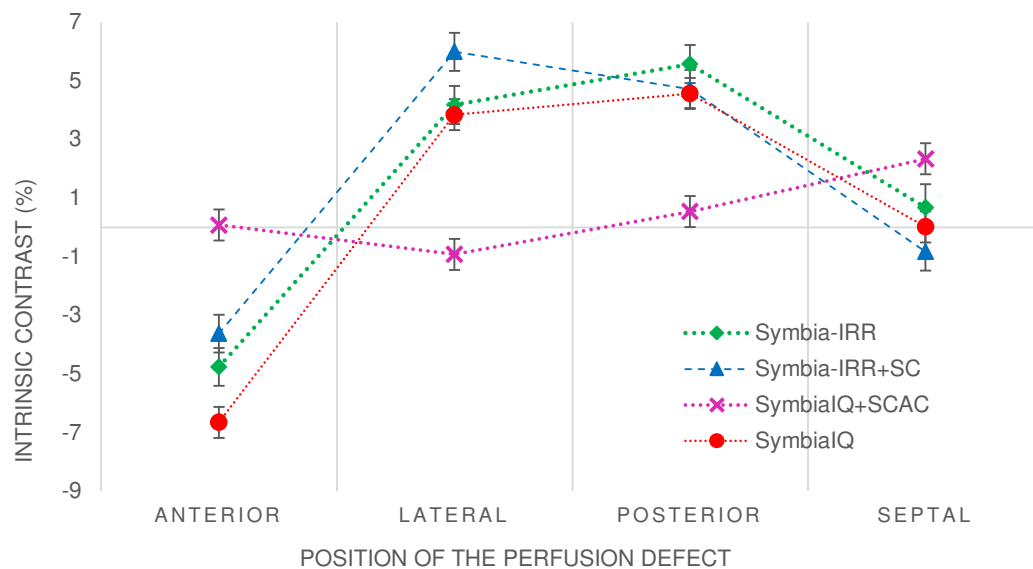


Figure 33. Intrinsic contrast values for evaluated *MPI systems* calculated at different positions of the myocardial wall. Values represent least square mean values; vertical bars represent 95% confidence. For clarity points are connected by dashed lines.

Net contrast. The *MPI system* and perfusion defect position were main effects on net contrast ($F=5.72$, $p=0.002$ and $F=37.23$, $p<0.001$, respectively). Post hoc analysis outlined a statistically significant difference in net contrast values between pairs of *MPI system*, as presented in Figure 34.

Statistically significant differences were found between the following *MPI systems* pairs: Symbia-IRR+SC and SymbialQ, and SymbialQ+SCAC and SymbialQ.

Net contrast values for each *MPI system*, and at the four PD positions, are shown in Figure 35.

Scheffé post-hoc analysis revealed a statistically significant difference between net contrast mean values obtained for different *MPI systems* at the four PD positions. Mean net contrast values for the different lesion positions are shown in Figure 36.

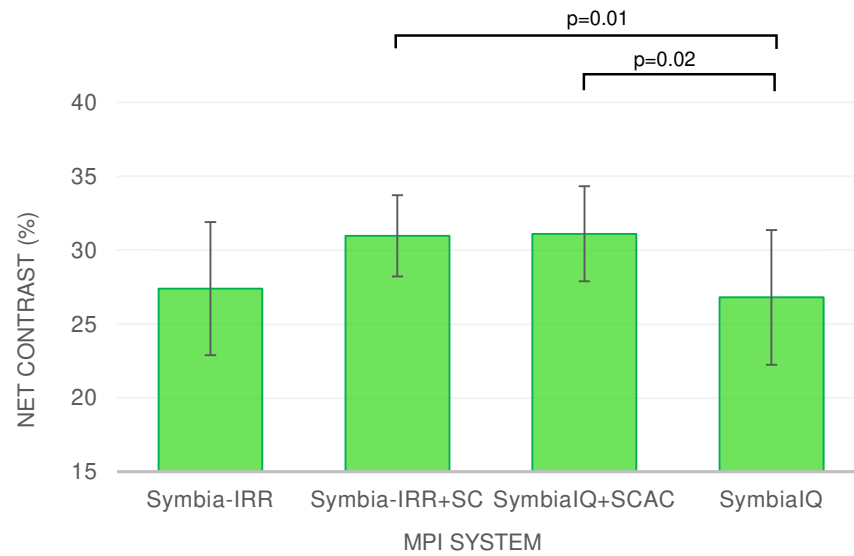


Figure 34. Net contrast values obtained for different *MPI systems*. Values represent least square mean values; vertical bars represent 95% confidence intervals.

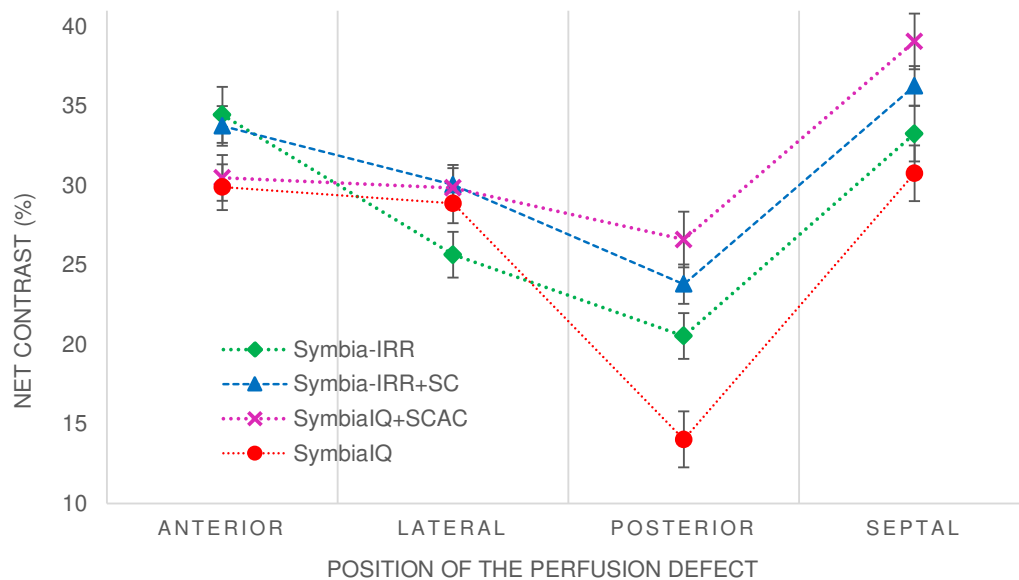


Figure 35. Net contrast values at anterior, lateral, posterior, and septal position of the myocardial wall for different *MPI systems*. Values represent least square mean values; vertical bars represent 95% confidence. For clarity points are connected by dashed lines.

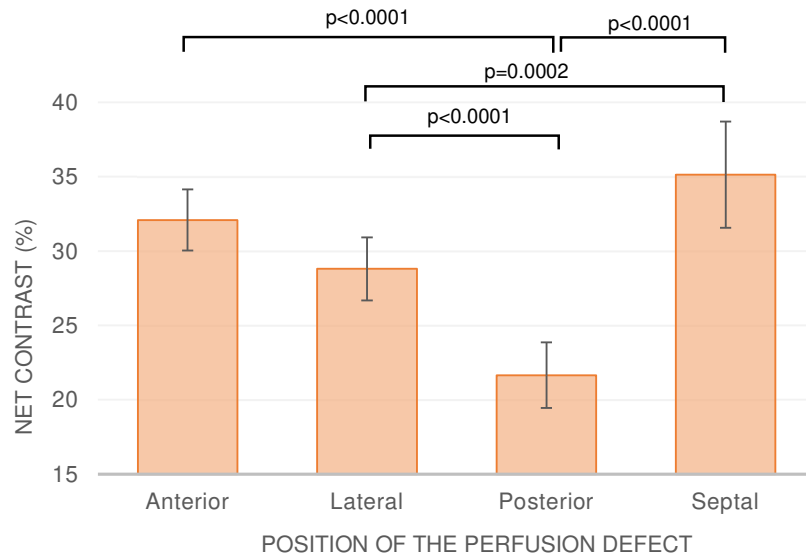


Figure 36. Net contrast values for different position of the perfusion defect. Values represent least square mean values; vertical bars represent 95% confidence intervals.

Discussion

By assessing the intrinsic contrast, an indirect measure of the *MPI system* - dependent effects was carried out. Results for the *IC* were used to correct the measured contrast between the PD and the LV wall, providing reference values for the maximum achievable contrast for each *MPI system* and different PD position. Regarding the intrinsic contrast, except for Symbia-IRR+SC, negative *IC* values in the anterior position and positive *IC* values in the lateral and posterior positions were observed for the majority of the *MPI systems*, except for the Symbia-IRR+SC, indicating relative regional differences in the reconstructed count distribution. For Symbia-IRR+SC and SymbialQ, non-uniformity of the reconstructed count distribution is more noticeable in the anterior and lateral positions, respectively. The observed differences in reconstructed count distribution in the lateral and posterior positions for most *MPI systems* could be related to the farthest location of this area of the myocardium insert from the detector and correlated with attenuation characteristics.

The importance of using scatter and attenuation corrections for the SymbialQ system is underlined by the reported relative regional differences in the reconstructed count distribution. In SymbialQ+SCAC, a uniform reconstructed count distribution was obtained in the anterior, lateral, and posterior positions, but

an unexpected positive IC value was found in the septal position. Attenuation artifacts are position-dependent and should be more noticeable when using multifocal collimators as opposed to LEHR collimators [20]. Nevertheless, non-uniformity of the reconstructed count distribution in the LV wall can be substantially corrected if AC and SC are applied to image data obtained on IQ SPECT systems. Slight septal non-uniformity of the reconstructed count distribution could be a result of the application of the AC, which seems to overcorrect values in the septal position. Interpretation of IC results (Figure 33) should be treated with caution, due to the total uncertainty of the experimental data shown in Table 9 (3.0 - 6.7%).

To determine reference values for the maximum achievable contrast for each MPI system and different PD positions, NC was calculated. Statistical analysis showed that both the MPI system and PD position were main effects on NC , while PD position had a dominant effect on NC variability. The largest NC mean values were obtained for SymbialQ+SCAC and Symbia-IRR+SC, followed by Symbia-IRR and SymbialQ (Figure 34). Differences between Symbia-IRR and Symbia-IRR+SC were not statistically significant, mainly due to the relatively large variation in results obtained with Symbia-IRR. Therefore, if least square mean values are considered, Symbia-IRR performs similarly to Symbia IQ without corrections. Nevertheless, substantial differences in NC values at different PD positions were observed between Symbia-IRR and SymbialQ (Figure 35). For SymbialQ, NC values are uniform in the anterior, lateral, and septal positions, while a decrease of up to 15% in the posterior position was observed. This decrease is probably due to loss of sensitivity in the area farthest from the detector when using multifocal collimators. It is also noteworthy that in the anterior and lateral positions, no differences in NC values were found between SymbialQ+SCAC and SymbialQ. On the other hand, corrections are crucial in the posterior and septal positions, allowing the cardio-centric system to detect PDs more accurately in these regions, which are highly influenced by attenuation and scatter. Applying AC can correct attenuation artifacts, which are particularly noticeable with multifocal collimators. Compared with Symbia-IRR, mean NC values for the lateral, posterior, and septal positions increase for Symbia-IRR+SC. Interpretation of NC results shown in Figure 35 should be performed with caution, considering the total uncertainty of the experimental data shown in Table 9 (2.9 - 7.9%).

Regarding the effect of lesion position on NC , the posterior position produced the lowest values, with statistically significant differences between the posterior and all other lesion positions (Figure 36).

The perfusion defect detection ability of *MPI systems* in the posterior region of the heart remains the lowest, despite the fact that the correction for intrinsic contrast was taken into account when calculating the *NC*. Results for *NC* obtained in this part of the investigation can be used as reference values for the maximum achievable contrast between the PD and LV wall.

3.4. Evaluation of the perfusion defect detection ability of the *MPI system* through quantitative myocardial perfusion analysis

In the first part of the investigation, the objective was to evaluate *MPI systems* through a set of physical descriptors and to complement the results for IQ SPECT systems with multifocal collimators. The results of this evaluation were used to optimize the imaging procedures in terms of reconstruction methodology (see 3.2.1.). In the second part of the investigation, the perfusion defect detection ability of the *MPI system* was evaluated through image quality descriptors. Once image quality had been evaluated, the next step was to implement a methodology for comparison of the *MPI systems* in reproducible and controlled clinical conditions. A semi-anthropomorphic phantom was used to simulate a range of patients, thus both normal and pathological myocardial perfusion conditions were simulated. In clinical practice, patient image data are reconstructed and post-processed to obtain myocardial perfusion assessment. Quantitative myocardial perfusion analysis was performed using a quantitative post-processing algorithm. In addition to Siemens *MPI systems* available in Croatia, the investigation was extended to CZT detector systems available in collaborating institutions in Italy: D-SPECT (Spectrum Dynamics, Caesarea, Israel) and Discovery NM 530c (GE Healthcare, Haifa, Israel). In total, six *MPI systems* were characterized in terms of perfusion defect detection ability: Symbia-IRR, Symbia-IRR+SC, SymbiaQ+SCAC, SymbiaQ, DSPECT and D530c.

Image data obtained in simulations of normal myocardial perfusion condition were used to create a normal myocardial perfusion database for each *MPI system* evaluated in this part of the investigation. These normal myocardial perfusion databases, were then used for quantitative analysis of polar maps obtained from *pathological phantoms* with PD at different positions. In this part of the investigation, the extent of PD, summed score and segmental uptake were evaluated for polar maps obtained from *pathological phantom* image data. Global uniformity was calculated using data from *normal phantom* polar maps.

3.4.1. Extent of perfusion defect, summed score, segmental uptake and global uniformity

Extent of PD. The type of *MPI system* and the position of the PD were the main effects on the extent of PD ($F=10.036$, $p<0.0001$ and $F=5.4653$, $p=0.0031$, respectively). Post hoc analysis showed a statistically significant difference in the values of extent of PD between D530c and all other systems (Figure 37.a). If the results for D530c were excluded, there would also be statistically significant differences in the values for the extent of PD between Symbia-IRR and other *MPI systems* ($p=0.006$, $p<0.0001$, $p=0.012$, $p<0.0001$ for Symbia-IRR+SC,

SymbialQ+SCAC, SymbialQ and DSPECT, respectively). Differences in mean values of extent of PD between lateral and posterior PD positions and between posterior and septal PD positions were statistically significant (Figure 37.b). Mean values for the extent of PD at different PD positions for the *MPI systems* used in this study are shown in Figure 38.

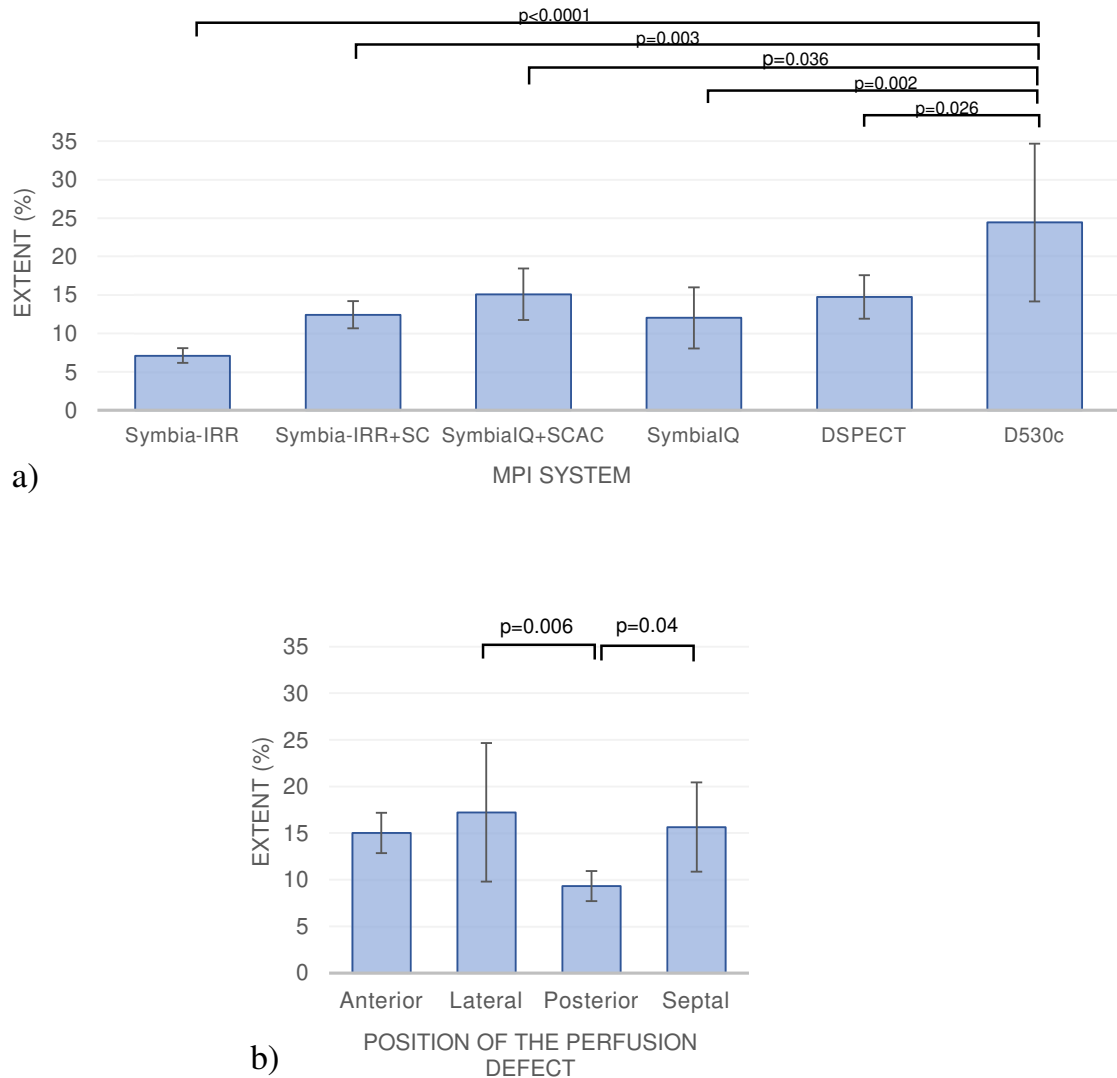


Figure 37. Extent of the perfusion defect for different *MPI systems* (a) and for different positions of the perfusion defect (b). Values represent least square means; vertical bars represent 95% confidence intervals.

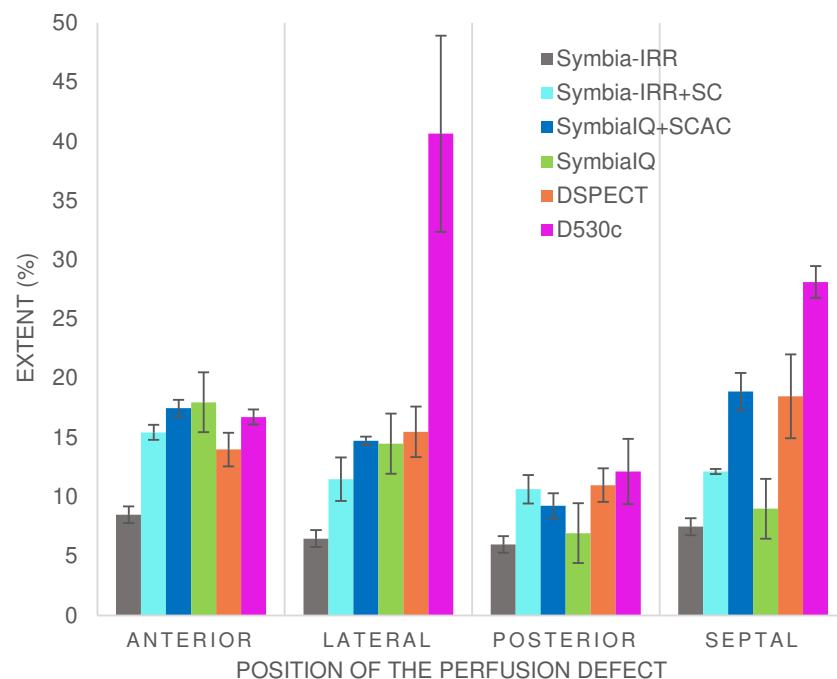


Figure 38. Extent of the perfusion defect at anterior, lateral, posterior and septal position of the myocardial wall for different *MPI systems*. Values represent least square means; vertical bars represent standard deviations.

Figure 39 shows an example of phantom polar maps with the PD in the anterior position.

Summed score. The type of *MPI system* and the position of the PD were main effects on the SS ($F=4.450$, $p<0.003$ and $F=3.1405$, $p=0.036$, respectively). Post hoc analysis revealed a statistically significant difference between SS values for DSPECT and Symbia-IRR+SC ($p=0.010$) and between DSPECT and SymbialQ+SCAC ($p=0.025$) (Figure 40.a). No statistically significant differences in mean values of SS were observed at different lesion positions (Figure 40.b).

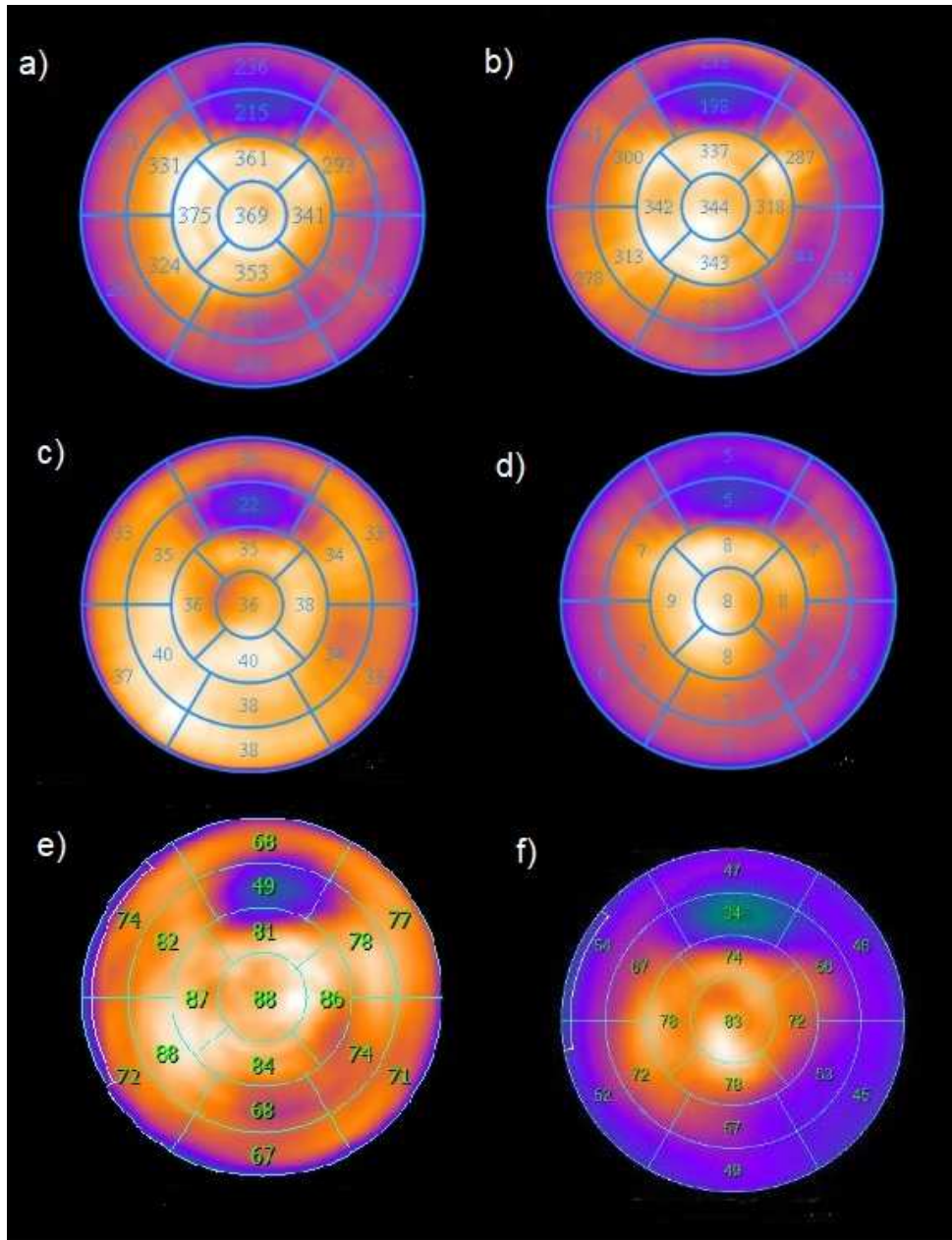


Figure 39. Examples of phantom polar maps in the case the PD is in the anterior position for different *MPI systems*: Symbia-IRR (a), Symbia-IRR+SC (b), SymbialQ+SCAC (c), SymbialQ (d), DSPECT (e), and D530c (f).

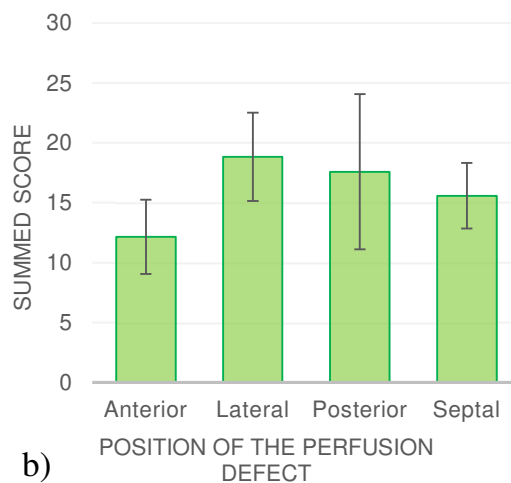
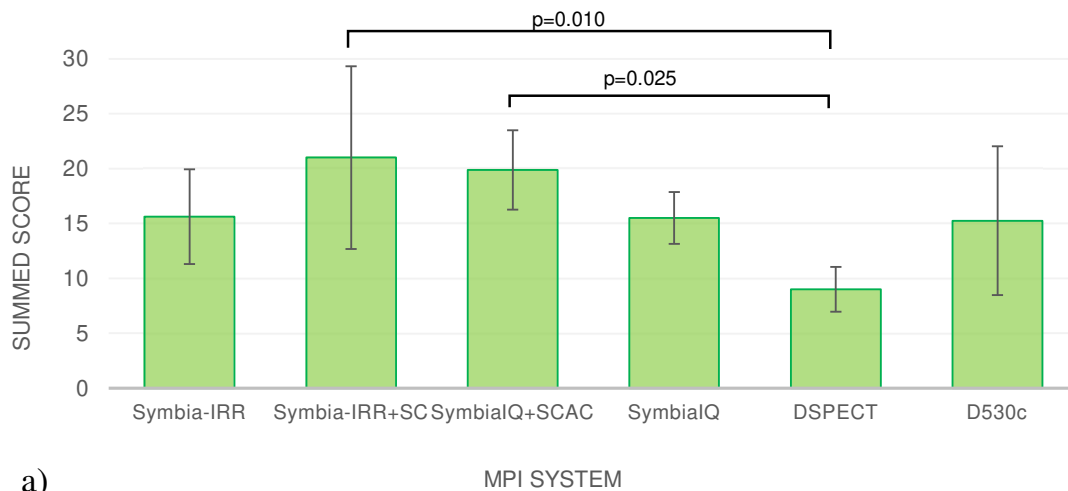


Figure 40. Summed score values for different *MPI systems* (a) and for different position of the perfusion defect (b). Values represent least square means; vertical bars represent 95% confidence intervals.

Segmental uptake. Figures 41.a–d show the segmental uptake results. The segments were divided into five regions: anterior (ANT), anterolateral and posterolateral (LAT), posterior (POST), anteroseptal and posteroseptal (SEPT), and apical (APICAL). A separate graph was prepared for each region, except for the apical one, because segments in this region were not affected by the PD. The order of the segments in the graphs was determined by the position of the PD.

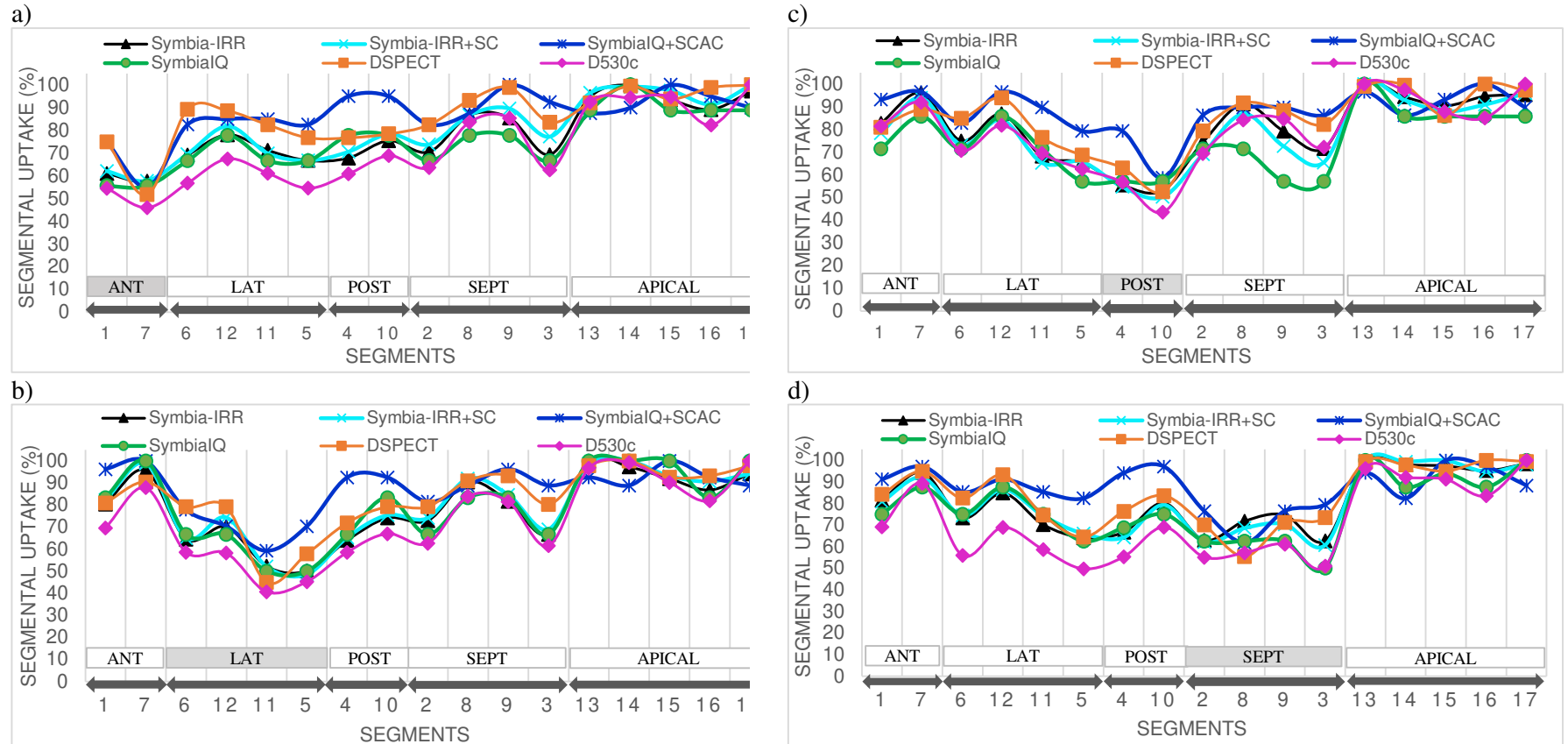


Figure 41. Segmental uptake values for 17 segments of the polar map and different *MPI* systems. The perfusion defect is in the anterior (a), lateral (b), posterior (c) and septal (d) positions. Segments in the apical region (13-17) are not involved in the PD position. Values represent least square means. For clarity vertical bars representing 95% confidence intervals were omitted (standard errors<1.5%).

Global uniformity. Global uniformity was calculated for all *MPI systems* used in this part of the investigation. Results for Symbia-IRR, Symbia-IRR+SC, SymbialQ-SCAC and SymbialQ are derived from calculations performed in the previous section. The best level of uniformity was obtained for SymbialQ+SCAC ($6.2\% \pm 0.5\%$), followed by DSPECT ($11.3\% \pm 0.9\%$), Symbia-IRR+SC ($13.5\% \pm 0.5\%$), Symbia-IRR ($14.1\% \pm 0.6\%$), and D530c ($17.5\% \pm 1.8\%$).

Discussion

Results for the extent of PD showed that different *MPI systems* estimate the size and severity of PD in different ways. The D530c system exhibited the largest mean values of extent of PD, while Symbia-IRR showed the smallest extent. The differences between D530c and the other *MPI systems* were statistically significant (Figure 37.a). The percentage size of the PD was estimated as small for Symbia, large for D530c, and medium for the other systems. On the other hand, while the SS values for the other *MPI systems* showed the presence of significant extensive ischaemia ($SS > 15$), the lowest SS values were obtained with DSPECT, indicating only moderately abnormal perfusion ($SS = 9$). Differences in SS values were statistically significant between DSPECT and Symbia+SC and between DSPECT and SymbialQ+SCAC (Figure 40.a). Differences in SS values between different PD positions were not statistically significant, but a difference between the anterior position and the other positions was found when evaluating the severity of the PD. The smallest SS value was obtained in the anterior position (Figure 40.b). At first sight, the results for extent and SS were unexpected, and some considerations should be addressed to explain them.

All systems have finite reconstructed spatial resolution, and are subject to the partial volume effect (PVE). In this investigation a small cold defect (PD) was inserted in a hot background (LV wall), causing the well-known spill-in effect of activity from the LV wall into the PD area. As a consequence, activity in the PD can be overestimated and PD severity underestimated. Additionally, PVE induces blurring at the myocardial wall edges, causing the quantitative post-processing algorithm to estimate smaller volumes and miscalculate surfaces. The effect of PVE becomes significant when the size of the object is less than 2-3 times the expected tomographic spatial resolution of the *MPI system* [80]. Spatial resolution values measured according to NEMA NU-1 2001 protocol are given by Brambilla et al. [8]: 15 mm, 8.6 mm and 6.7 mm for NaI(Tl)-crystal system with IRR, DSPECT and D530c, respectively. In this investigation, the PD has a coverage angle of

45° over the short-axis plane, 2 cm over the long-axis plane and 1 cm thickness, and the LV wall has a nominal thickness of 1 cm, so the influence of PVE was expected for all systems but with different effects depending on the *MPI system*. In general, the application of scatter and attenuation corrections for the NaI(Tl)-crystal system and, on the other hand, the better spatial and energy resolution of CZT detector systems enable improved accuracy in volume and size estimation [62].

For the selected small PD insert, limitations of the Symbia-IRR system result in a smaller percentage size of the PD and only apparently better accuracy in estimated PD size. Extent is a measure of the percentage size of the PD in terms of voxels outside the normal range, and a direct comparison between extent and physical dimensions could not be performed.

D530c showed the largest value of the extent of PD (Figure 37.a). Additionally, D530c results showed large variability in mean extent values at different PD positions (Figure 38), with a large extent in the septal and lateral positions. This effect might arise from a D530c limitation related to the intrinsic properties of this CZT system due to its particular acquisition geometry. The multi-pinhole collimation system can lead to position-dependent attenuation, sensitivity and resolution variation [81]. Specifically, D530c is known to show reduced sensitivity in the area of the FOV farthest from the detector [28, 82] and an expanded area of attenuation artifacts from the lateral to the septal region [62], as illustrated in Figure 39.f.

For all *MPI systems*, the smallest values of the extent were obtained in the posterior PD position. Furthermore, SymbiaIQ results demonstrated that, compared to SymbiaIQ+SCAC, a lower extent of PD in the septal position is obtained if no scatter and attenuation corrections are applied (Figure 38).

Due to the reduced dimensions of the PD, PVE and differences in spatial and energy resolution, the size and severity of PD were estimated differently by the investigated *MPI systems*. Furthermore, the findings of this study showed that attenuation artifacts had a substantial impact on the extent of the PD. Results for Symbia-IRR could not be visually confirmed on the polar maps, as the smaller extent of the PD for this system compared to other *MPI systems* could not be detected visually. Thus, besides quantitative values, it is also important to visually analyze image data and consider differences in attenuation patterns between *MPI system* and systems limitations when interpreting image data, to avoid misestimation of PD size.

Segmental uptake was calculated for each of the 17 segments in order to further examine variations in PD visualization and identification between *MPI systems*. Segments affected by the defect are easily visualized due to their lower segmental uptake (Fig. 41a-d). For the four PD positions used in this investigation, the D530c system showed lower segmental uptake values,

suggesting a high capacity to identify PDs. However, with the exception of the apical area, D530c often showed the lowest segmental uptake values across the polar map. The reason for such low uptake values in D530c is a large band of attenuation artifact that covers almost all basal segments (segments 1-6), from the posterolateral to the posteroseptal region (Figure 39.f). The presence of this large attenuation artifact was also the main cause of the high *GU* value for D530c. With segmental uptake values larger than 80% (Figures 41.a-d) and the lowest *DPI* value, SymbialQ+SCAC demonstrated a high degree of uniformity in the PD-free region of the polar map (Figure 39.c). As noted previously [79], a typical apical underestimation was observed for SymbialQ+SCAC (segments 14 and 17). For Symbia IQ, attenuation artifacts occurred in the posterolateral and posteroseptal regions, similar to Symbia-IRR and Symbia-IRR+SC (Figures 39.a, 39.b, and 39.d).

When considering PD-free regions, DSPECT systems displayed higher segmental uptake values in the lateral and septal regions compared to NaI(Tl)-crystal detector systems. Compared to the Symbia systems, DSPECT exhibits less severe attenuation artifacts in the posterior region (segmental uptake >70%).

3.5. Evaluation of the ability of *MPI systems* in detecting perfusion defects: an extension of the quality metrics

The *DPI* was established and used as a quantitative metric for assessing the PD detection performance of an *MPI system*, regardless of the two clinical quantitative post-processing algorithms used. This was made possible by the creation of a specific normal myocardial perfusion database for each *MPI system* within the quantitative post-processing algorithm (Corridor4DM for Siemens systems and D530, QGS-QPS for DSPECT). These databases account for the attenuation properties of the phantom and the system-specific response to the attenuating object. Additionally, *DPI* is determined in segments covered by the PD. In this way, attenuation artifacts in the remaining part of the polar map do not directly contribute to the results.

3.5.1. Defect perfusion index

Defect perfusion index. The type of *MPI system* and the position of the PD were the main effects on the *DPI* ($F=10.024$, $p<0.0001$ and $F=34.408$, $p<0.0001$, respectively). Post-hoc analysis showed a statistically significant difference between *DPI* values for D530c and all other *MPI systems*, as shown in Figure 42.a. Statistically significant differences were also observed between *DPI* mean values at different lesion positions (Figure 42.b): anterior-lateral, anterior-posterior, anterior-septal, and posterior-septal. *DPI* values at different PD positions are shown in Figure 43 for the *MPI systems* used in this part of the investigation.

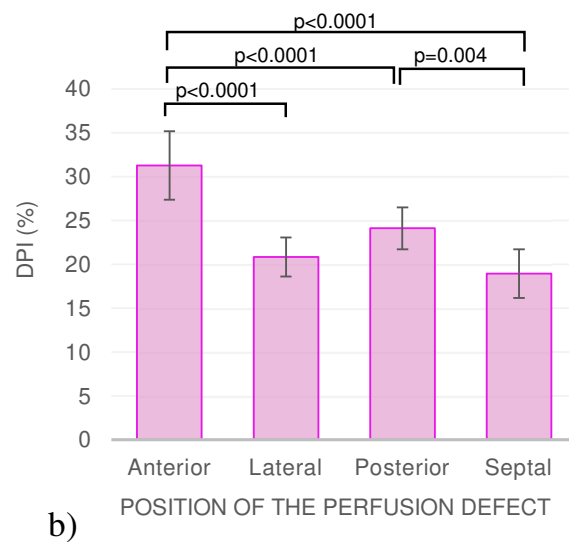
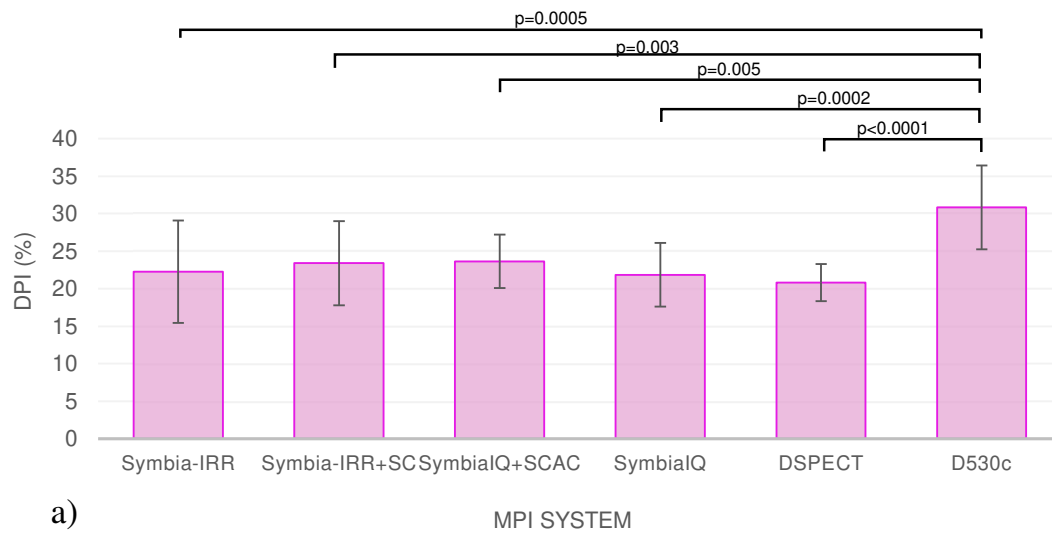


Figure 42. Defect perfusion index for different *MPI systems* (a) and at anterior, lateral, posterior, and septal positions of the PD (b). Values represent least square means; vertical bars represent 95% confidence intervals.

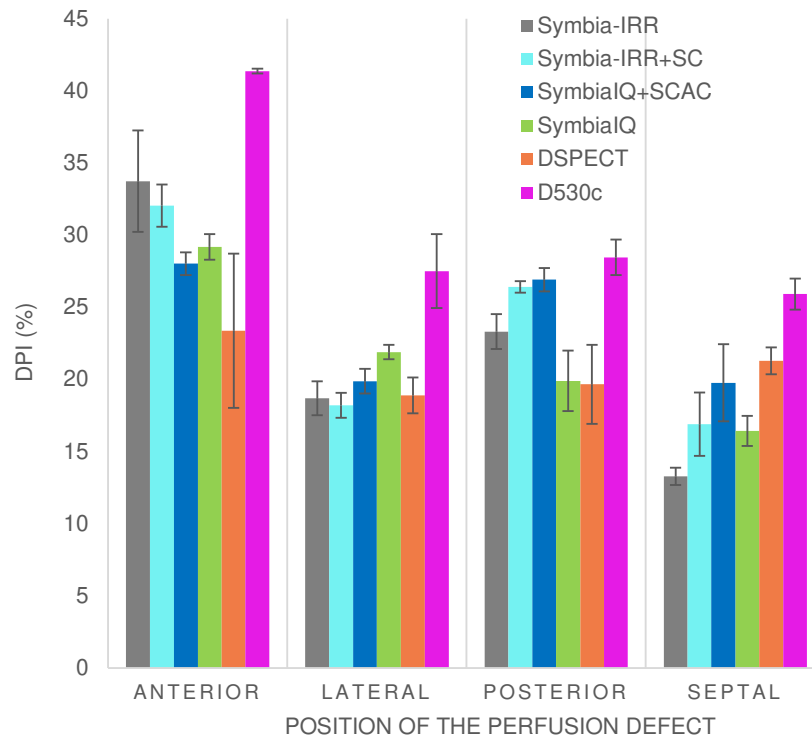


Figure 43. Defect perfusion index at anterior, lateral, posterior, and septal positions of the PD for different *MPI systems*. Values represent least square means; vertical bars represent standard deviations.

Discussion

The quantitative analysis showed that the estimated extent of the PD was strongly affected by attenuation artifacts, potentially leading to misinterpretation of image data. From Figure 39, attenuation artifacts can be visualized for *MPI systems* used in this part of the investigation. Therefore, a new descriptor called *DPI* was defined to reduce the dependence of the results on attenuation artifacts. Additionally, two distinct quantitative post-processing algorithms were used in this part of the investigation: Corridor4DM was used for perfusion assessment in the case of Siemens systems and D530c, while the QGS-QPS was used for DSPECT. *DPI* was defined and calculated as the deviation from each MPI system's own normal myocardial perfusion database. It is useful for assessing the deviation from normal myocardial perfusion within a given MPI system and its specific system/processing framework. *DPI* appears to make it possible to examine the intrinsic performance of the system in detecting variations in perfusion values.

The *DPI* results for several *MPI systems* in the experimental setup employed in this study revealed that D530c performed best in terms of its ability to detect PD in all PD positions used. The *DPI* values for D530c were the highest (Figures 42.a and 43). Differences in *DPI* values between D530c and the other *MPI systems* investigated were statistically significant, while no statistically significant differences were observed among other the *MPI systems* (Figure 42.a). Compared with the other systems, DSPECT showed lower mean *DPI* values, suggesting that this CZT system performed surprisingly poorly in terms of its intrinsic capacity to identify perfusion abnormalities.

Dependence on the PD position was observed, and the ability to detect PDs was not consistent across regions (Figure 42.b). When the various PD positions were taken into account, larger mean *DPI* values were found when the PD was in the anterior and posterior positions, suggesting a deeper perfusion defect in these positions. Lateral and septal positions yielded lower *DPI* values, indicating a general limitation for all *MPI systems* (Figure 42.b). When DSPECT was compared with other *MPI systems*, *DPI* dependence on PD position was less noticeable in DSPECT (Figure 43). After attenuation artifacts in the posterior region were reduced by using the database for quantitative analysis and selecting only segments in the PD region, DSPECT showed good uniformity of *DPI* values across the entire polar map. D530c showed particularly higher *DPI* values in the anterior position compared with other *MPI systems* and small variability in *DPI* values between lateral, posterior and septal regions (Figure 43). This could be related to the fact that the multi-pinhole collimation system appears to allow the most accurate PD detection in the anterior position, which is closest to the pinhole collimator.

DPI has an advantage over standard clinical descriptors such as SS and the extent of PD: it is calculated only for segments covered by the PD. In this way, the contribution of attenuation artifacts outside the PD can be reduced, and artifacts do not directly contribute to *DPI* results. Furthermore, *DPI* may also be used in the characterization of Positron Emission Tomography (PET) and PET/CT systems for MPI in experimental studies and controlled conditions where the segments covered by the perfusion defect have been specifically identified.

3.6. Monte Carlo simulations of GSPECT on NaI(Tl)-crystal detector system with parallel-hole collimators

Using the MC-based code SIMIND with the 4D XCAT phantom, simulations of both gated image data (GSPECT-SIMIND) and non-gated image data (SPECT-SIMIND) for the Symbia system with LEHR collimators and IRR were performed. Figure 44 shows an example of the quantitative analysis of the MC simulated image data for the normal myocardial perfusion condition.

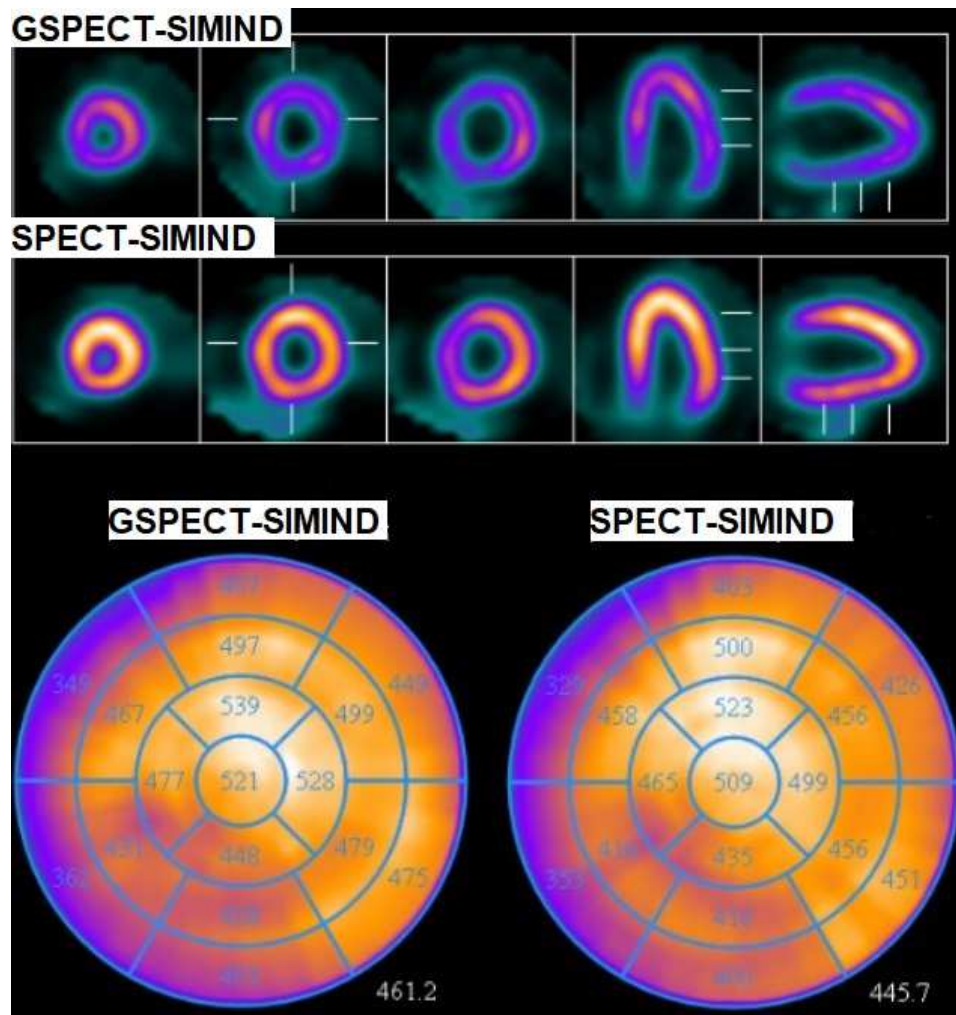


Figure 44. Example of Corridor4DM quantitative analysis of the MC-simulated image data for the normal myocardial perfusion condition on the Symbia-IRR system. Short-axis, vertical long-axis and horizontal long-axis image data are shown for simulated GSPECT and SPECT. For MC-simulated image data, polar maps are created and evaluated.

3.6.1. Defect perfusion index, LV volume curves and ejection fraction

Defect perfusion index. Post hoc analysis showed no statistically significant difference between *DPI* values for simulated GSPECT ($29.8\% \pm 1.0\%$) and SPECT ($29.5\% \pm 1.0\%$). However, lesion position was the main effect on *DPI* values ($F=181.5$, $p<0.001$). Statistically significant differences were found between mean *DPI* values at different PD positions (Figure 45): anterior-lateral, anterior-posterior, anterior-septal, lateral-posterior and posterior-septal.

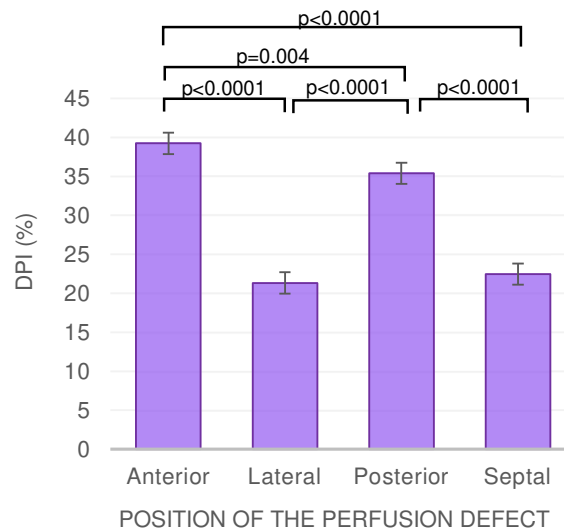


Figure 45. Defect perfusion index for MC-simulated MPI acquisitions at anterior, lateral, posterior, and septal positions of the PD. Values represent least square means; vertical bars represent 95% confidence intervals.

Figure 46 shows results for both MC-simulated GSPECT (GSPECT-SIMIND) and SPECT (SPECT-SIMIND). For comparison, values obtained in the experimental session with the semi-anthropomorphic phantom are also shown.

Figure 47.a-d shows an example of polar map representations obtained from MC-simulated GSPECT image data with PD in different positions: anterior, lateral, posterior and septal.



Figure 46. Defect perfusion index at anterior, lateral, posterior, and septal positions of the PD for MC-simulated acquisitions on the NaI(Tl)-crystal detector system with parallel-hole collimators. Symbia-IRR are values obtained in the experimental session with the semi-anthropomorphic phantom. Values represent least square means; vertical bars represent standard deviations.

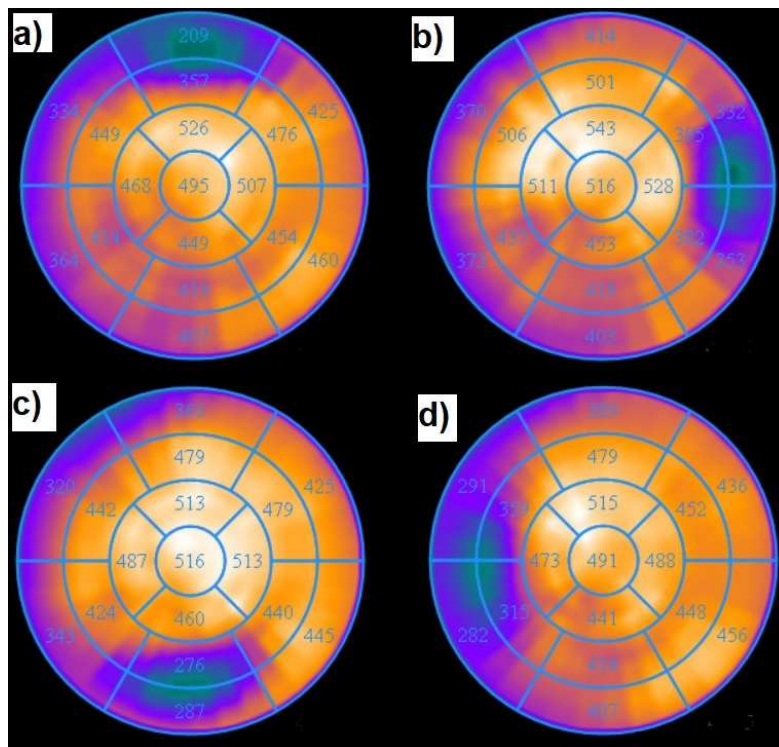


Figure 47. Examples of GSPECT polar maps with PD in different positions: anterior (a), lateral (b), posterior (c) and septal (d).

LV volume curves and ejection fraction. LV volume curves obtained from both true XCAT volumes and volumes obtained in the quantitative analysis with Corridor4D are shown in Figure 48. *EF* was calculated according to Equation 14.

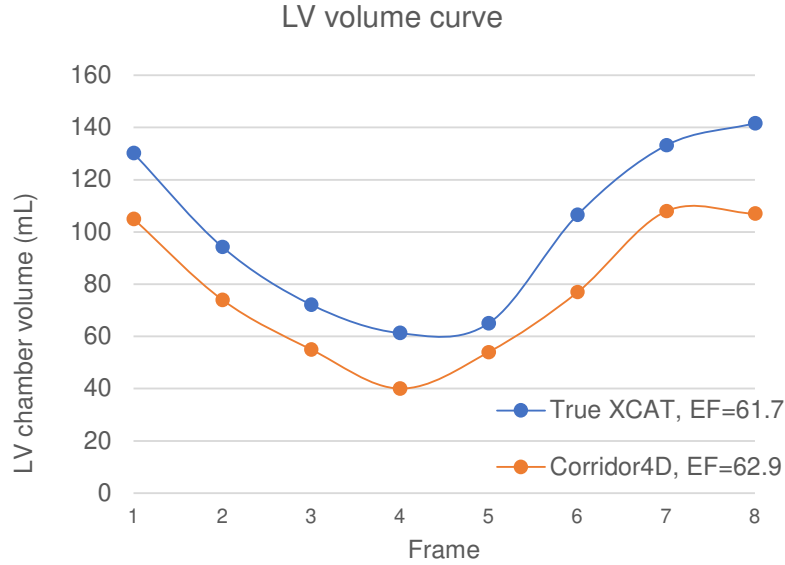


Figure 48. LV volume curves obtained from XCAT true inner chamber volumes at different time frames (true XCAT) and volume curve obtained from the quantitative analysis in Corridor4D, with corresponding ejection fraction values.

Discussion

The main objective of the MC simulation was to enable the characterization of *MPI systems* under dynamic conditions. For that reason, GSPECT was simulated for the SPECT system with a NaI(Tl)-crystal detector and parallel-hole collimators, considered the standard technology (Figure 44). The experimental session demonstrated that the *DPI* enables comparison of performance in detecting perfusion defects, while minimizing the influence of attenuation artifacts and the quantitative post-processing algorithm used. Therefore, the new descriptor was used to evaluate image data obtained by the MC simulation. A normal myocardial perfusion database was created with five datasets, and the *DPI* was calculated for both MC-simulated GSPECT and SPECT.

No statistically significant differences between *DPI* values for GSPECT-SIMIND and SPECT-SIMIND were found. This was expected, since non-gated image data are obtained from the corresponding gated image data by summing together

image data for all phases of the cardiac cycle. A dependency on the PD position was found, with larger mean *DPI* values when the PD was in the anterior and posterior positions (Figure 45). *DPI* values for different PD positions are in accordance with results from the experimental session with the semi-anthropomorphic phantom (Figure 42.b), except that in the simulated image data a statistically significant difference in *DPI* values was revealed also between the lateral and posterior PD positions. Results of MC simulations with the 4D XCAT phantom and measurements with the semi-anthropomorphic phantom could not be directly compared, since the phantoms used are different. The semi-anthropomorphic phantom has a geometrical heart (Figure 11.b), which cannot be considered realistic. Differences in heart shape and dimensions should result in *DPI* value differences. However, the XCAT phantom is a realistic representation of the human body (Figure 25.), and the results of the simulation session could be considered as a reference for the population described by the XCAT model used. The results show good agreement between experimental data and MC simulation data when the PD was in the anterior and lateral positions (Figure 46). Disagreement was relevant when the PD was in the posterior and septal positions, probably due to differences between the geometrical and simulated myocardium, as already mentioned.

The results obtained show that, if used in the properly, the new approach with the *DPI* can serve as a valuable method for the characterization of *MPI systems* in both static and dynamic controlled conditions, where the segments covered by the perfusion defect have been specifically identified.

In Figure 48, differences between true XCAT volumes and volumes obtained in the quantitative analysis are clearly noticeable. Volumes obtained by Corridor4D are smaller than the true ones with differences between 17% and 35%. These discrepancies are likely related to the limited spatial resolution of the imaging system, which affects image segmentation and results related to LV function and volumes. Limited spatial resolution and partial volume effects, along with automated border detection in Corridor4D, can result in an underestimation of the LV inner chamber volume due to inadequately defined endocardial boundaries.

3.7. Limitations

The results of the present investigation should be interpreted in the context of the study limitations. Specifically, most results were obtained using a static phantom acquired on different MPI systems, using acquisition and reconstruction parameters routinely used in the collaborating institutions for clinical studies (Table 3). The aim of this investigation was to characterize MPI systems under simulated clinical conditions. It would be of interest to study the influence of different acquisition and reconstruction parameters on the descriptors used in this investigation. At present, several additional options for attenuation correction are available for CZT systems. Advanced CZT systems can perform attenuation correction using either external CT systems or artificial intelligence software, which offers a promising option for reducing patient absorbed dose. In the MC simulation session, GSPECT acquisitions were simulated only for the NaI(Tl)-crystal detector system with parallel-hole collimators, considered the standard technology. Extending the research to other *MPI systems* could be of interest.

For DSPECT, the quantitative post-processing software QGS-QPS was used, while for all other *MPI systems* Corridor4DM was used. The choice for DSPECT was dictated by the fact that QGS-QPS is the only quantitative post-processing software available at that institution, and it is used in clinical practice. In this investigation, a characterization of seven combinations of imaging devices with specific acquisition and reconstruction parameters and different correction modalities, i.e. seven different MPI systems used clinically, was performed. In the experimental session, a specific set-up was used: a cold insert with a fixed size at fixed positions was used to mimic the PD. If inserts of different dimensions and different PD positions are used, to determine *DPI*, segments *i* should be identified based on the specific set-up. Additionally, the phantom was prepared according to specific activity concentrations, and a standard number of counts was acquired. Monte Carlo simulations of GSPECT were performed using a normal-size 4D XCAT male model (body mass index=20 kg/m²). Extending of the investigation with additional experimental and MC simulation studies may help to evaluate results over a wider range of potential situations.

4. Conclusion

Myocardial perfusion imaging uses gamma-ray detection to evaluate the presence, extent, and severity of myocardial ischaemia or infarction (perfusion) defects, which are quantified by comparing stress and rest image data. It is performed on different SPECT systems, mainly defined by the type of detector, the collimation system, the acquisition path, and the reconstruction algorithm, along with the corrections applied. For decades, the MPI procedure has been performed on standard multipurpose NaI(Tl)-crystal detector systems with parallel-hole collimators. This standard system has some limitations when MPI is performed: limited spatial resolution and sensitivity, attenuation artifacts, and long acquisition time. To improve spatial resolution, iterative reconstruction methods with resolution recovery have been developed, pushing the FBP method into the background. Over the years, advanced cardio-dedicated technology has been developed to further increase both spatial resolution and sensitivity on NaI(Tl)-crystal detector system by enabling a cardio-centric detector orbit and by using multifocal collimators. This advanced cardio-dedicated technology has allowed a significant reduction in administered activity or acquisition time compared to the standard system. Additionally, attenuation by soft tissue has been minimized by using CT. However, AC based on CT image data is not an ideal solution due to the possibility of mismatch between SPECT and CT, and artifacts caused by AC, with consequent misinterpretation of image data. For that reason, AC image data are always displayed as a complement to non-corrected data. Additionally, CT causes an increase of the total absorbed dose to the patient in the thoracic region. The introduction of solid-state detector systems has enabled high-quality gamma-ray detection. Cardio-dedicated solid-state systems have shown improved image quality and diagnostic performance compared to NaI(Tl)-crystal detector systems. Solid-state detector systems enable both faster acquisition (reducing patient motion and increasing patient throughput) and lower administered radiopharmaceutical activity. The limitation of cardio-dedicated solid-state detectors is that they are used for only one specific procedure and present challenges in obese patients due to the limited FOV and acquisition geometry. Additionally, when multi-pinhole collimation system is implemented, image data are subjected to position-dependent attenuation, sensitivity and resolution variations.

The diversity of available *MPI systems* requires a comprehensive assessment of their performance, identification of limitations, and also system validation based on the application of formalisms and metrics of radiation physics. The characterization of such complex imaging systems through evaluation of the image data is the most important step in optimizing the MPI procedure. This type

of evaluation is required to ensure high quality acquired data and diagnostic information.

In this investigation, image data were evaluated through physical descriptors related to image quality, perfusion data, and the ability of the system to detect perfusion defects. Image data in static myocardial conditions were obtained by imaging a semi-anthropomorphic phantom simulating both normal and pathological myocardial perfusion. Dynamic myocardial conditions were generated by Monte Carlo simulations along with a 4D voxelized anthropomorphic phantom.

Image quality analysis for NaI(Tl)-crystal systems demonstrated superiority of SymbialQ+SCAC in both normal and pathological myocardial perfusion conditions. Contrast and spatial resolution reached high levels when multifocal collimators were used in combination with SC and AC. An extended quantitative evaluation of system-dependent effects and perfusion defect detection ability of different NaI(Tl)-crystal systems was performed based on intrinsic contrast and net contrast. This investigation shows minimal attenuation artifacts and better reconstructed count distribution uniformity in the LV wall across the short-axis when SymbialQ+SCAC is used, with the exception of the septal position (positive intrinsic contrast value). Regarding perfusion defect detection ability, net contrast values for *MPI systems* were found to be dependent on perfusion defect position. Results show that SymbialQ+SCAC and Symbia-IRR+SC generally have the highest net contrast means. For SymbialQ+SCAC it was found that corrections make the difference in posterior and septal positions. This enables better perfusion defect detection ability across short-axis images for SymbialQ+SCAC and minimizes the lack of accuracy of that *MPI system* in the posterior part of the heart that would otherwise be present. If corrections are not applied on SymbialQ, a substantial deterioration of the quality of image data is observed and performances becomes comparable to standard NaI(Tl)-crystal systems with parallel-hole collimators. Results of this investigation suggest that dual energy window for scatter correction in NaI(Tl)-crystal systems with IRR also provides benefits in terms of image quality and perfusion defect detection ability.

Evaluation of perfusion defect detection ability of *MPI system* through quantitative myocardial perfusion analysis was performed on both NaI(Tl)-crystal detector systems and solid-state detector systems. The size and severity of perfusion defects were estimated differently by different *MPI systems* due to the small dimensions of the PD, limited spatial resolution, PVE, and attenuation artifacts. PVE induced blurring at the myocardial wall edges and spill-in effects, resulting in smaller volumes and miscalculation of the size of the PD. Because of the large attenuation artifacts belt from basal posterolateral to basal posteroseptal regions and position-dependent sensitivity, the D530c showed the highest extent of PD, generally the lowest segmental uptake values, and the highest *GU* value.

SymbialQ+SCAC revealed a high level of uniformity of polar maps, with SU_n values higher than 80% and the lowest GU value. The DSPECT system yielded the lowest SS value, while Symbia-IRR+SC revealed the highest SS value.

D530c outperforms other *MPI systems* in terms of ability of the system in detecting perfusion defect, showing the highest DPI value. DSPECT showed good uniformity of DPI values across the entire polar map and DPI mean values comparable to those obtained for NaI(Tl)-crystal systems.

Dependency on the PD position was observed, and the ability to detect PDs was not consistent across regions. Larger mean DPI values were found when the PD was in anterior and posterior positions, suggesting a deeper perfusion defect in these positions, i.e. a larger deviation of measured perfusion from the normal reference. Lateral and septal positions yielded lower DPI values, indicating a general limitation of *MPI systems* in assessing perfusion defects located in these positions.

DPI mean values obtained for MC-simulated GSPECT and non-gated SPECT were larger compared to measurements with a semi-anthropomorphic phantom and a geometrical heart in static conditions. Statistically significant differences were found between mean DPI values for MC-simulated acquisitions at different PD positions, showing that even in dynamic conditions the ability to detect PDs is not uniform across the LV wall. Larger mean DPI values were found in posterior and septal positions compared to measurements in static conditions.

In phantom and simulation studies presented here, DPI has proven to be a physical descriptor that enables the extension and further advancement of current MPI quality metrics. Results obtained in this investigation may be considered reference values of the ability of the *MPI system* to detect PDs in controlled static and dynamic conditions.

Results of the characterization of *MPI systems* performed in this investigation show that each *MPI system* has some advantages but also several limitations that must be considered when interpreting clinical image data. Compared to other systems, SymbialQ+SCAC, DSPECT and D530c have shown higher performance with reduced acquisition time.

Awareness of *MPI system* characteristics and understanding their advantages and limitations are essential for achieving high-quality image data in MPI in every specific situation.

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Appendix A

*** DYNAMIC XCAT PHANTOM, version 2.0 in C***

```
-----  
PARAMETERS: (dynamic XCAT version 2.0 in C)  
-----  
act_phan_each = 1 (activity phantom each frame saved)  
act_phan_ave = 0 (time-average activity phantom NOT saved)  
atten_phan_each = 1 (atten. coeff. phantom each frame saved)  
atten_phan_ave = 0 (time-average atten. coeff. phantom NOT saved)  
Beating heart motion included only  
Total Output Period =      1.0000 secs  
Total Output Frames = 16  
==>Time Per Frame =      0.0625 secs  
  
beating heart period =      1.0000 secs  
Respiratory period =      5.0000 secs  
maximum diaphragm motion =      2.0000  
heart scale x =      1.0000  
heart scale y =      1.0000  
heart scale z =      1.0000  
lung_scale =      1.0000  
phantom height scale =      1.0000  
phantom long axis scale =      1.0000  
phantom short axis scale =      1.0000  
head height scale =      1.0000  
head x scale =      1.0000  
head y scale =      1.0000  
head skin x scale =      1.0000  
head skin y scale =      1.0000  
chest_skin_long_axis_scale =      1.0000  
chest_skin_short_axis_scale =      1.0000  
torso_long_axis_scale =      1.0000  
torso_short_axis_scale =      1.0000  
abdomen long axis scale =      1.0000  
abdomen short axis scale =      1.0000  
arms length =      1.0000  
arms circumference scale =      1.0000  
arms skin circumference scale =      1.0000  
legs length =      1.0000  
legs circumference scale =      1.0000  
legs skin circumference scale =      1.0000  
li_air_flag = 5  
si_air_flag = 1  
Right kidney thickness parameter set to -1.000000  
Left kidney thickness parameter set to -1.000000  
breast_type = 1 (prone position model)  
which_breast = 0 (no breasts, male)  
right breast_long_axis_scale =      1.0000  
right breast_short_axis_scale =      1.0000  
right breast_height_scale =      1.0000  
left breast_long_axis_scale =      1.0000  
left breast_short_axis_scale =      1.0000  
left breast_height_scale =      1.0000
```

```

rdiaph_liv_scale =      1.0000
ldiaph_scale =      1.0000
pixel width =  0.1500 (cm/pixel)
slice width =  0.1500 (cm/pixel)
voxel volume (pixel width^2)(slice_width) =  0.003375 ml
x_array_size = 256
y_array_size = 256
subvoxel_index = 1 => 1 subvoxels per voxel
starting slice number   = 565
ending slice number     = 1064

```

Main orientation of heart:

```

zy_rotation (beta)=    0.00 (deg)
xz_rotation ( phi)=    0.00 (deg)
yx_rotation ( psi)=    0.00 (deg)

```

Translation of heart:

```

X translation   =    0.00 (cm)
Y translation   =    0.00 (cm)
Z translation   =    0.00 (cm)

```

activity_unit = 0 (no scaling of activity values)

radionuclide energy (keV)= 120.0000

Calculating bones with a water fraction of 0.500000

Linear Attenuation Coefficients (1/cm):

```

Body (water)   =    0.1614
Muscle         =    0.1679
Adipose (fat)  =    0.1481
Lung           =    0.0479
Spine Bone     =    0.1965
Rib Bone       =    0.2397
Blood          =    0.1697
Heart          =    0.1682
Kidney         =    0.1681
Liver          =    0.1696
Lymph          =    0.1657
Pancreas       =    0.1667
Spleen         =    0.1697
Intestine      =    0.1652
Skull          =    0.2130
Cartilage     =    0.1756
Brain          =    0.1671
Iodine blood   =    0.1838
Aluminum       =    0.4131
Graphite       =    0.2617
Lead           =   39.7790
Iron           =    2.1165
PMMA           =    0.1852
Titanium       =    0.9521
Air            =    0.0002
Mammary        =    0.1634
Skin           =    0.1744
Eye Lens       =    0.1699
Ovary          =    0.1684
Red Marrow     =    0.1645

```

Yellow Marrow	=	0.1571
Testis	=	0.1669
Thyroid	=	0.1692
Bladder	=	0.1669

Linear Attenuation Coefficients (1/pixel):

Body (water)	=	0.0242
Muscle	=	0.0252
Adipose (fat)	=	0.0222
Lung	=	0.0072
Spine Bone	=	0.0295
Rib Bone	=	0.0360
Blood	=	0.0255
Heart	=	0.0252
Kidney	=	0.0252
Liver	=	0.0254
Lymph	=	0.0249
Pancreas	=	0.0250
Spleen	=	0.0255
Intestine	=	0.0248
Skull	=	0.0320
Cartilage	=	0.0263
Brain	=	0.0251
Iodine Blood	=	0.0276
Skin	=	0.0262
Eye Lens	=	0.0255
Ovary	=	0.0253
Red Marrow	=	0.0247
Yellow Marrow	=	0.0236
Testis	=	0.0250
Thyroid	=	0.0254
Bladder	=	0.0250

Activity Ratios

```

background = 0.000000
myoLV_act = 65.000000
myoRV_act = 39.000000
myoLA_act = 16.000000
myoRA_act = 16.000000
bldplLV_act = 0.000000
bldplRV_act = 0.000000
bldplLA_act = 0.000000
bldplRA_act = 0.000000
body_activity = 0.000000
skin_activity = 0.000000
rbreast_activity = 0.000000
lbreast_activity = 0.000000
muscle_activity = 0.000000
brain_activity = 0.000000
liver_activity = 0.000000
gall_bladder_activity = 0.000000
right_lung_activity = 0.000000
left_lung_activity = 0.000000
esophagus_activity = 0.000000

```

esophagus_contents_activity = 0.000000
thyroid_activity = 0.000000
larynx_activity = 0.000000
laryngopharynx_activity = 0.000000
st_wall_activity = 0.000000
st_cnts_activity = 0.000000
pancreas_activity = 0.000000
right_kidney_cortex_activity = 0.000000
right_kidney_medulla_activity = 0.000000
left_kidney_cortex_activity = 0.000000
left_kidney_medulla_activity = 0.000000
adrenal_activity = 0.000000
right_renal_pelvis_activity = 0.000000
left_renal_pelvis_activity = 0.000000
spleen_activity = 0.000000
rib_activity = 0.000000
cortical_bone_activity = 0.000000
spine_activity = 0.000000
spinal_cord_activity = 0.000000
bone_marrow_activity = 0.000000
yellow_marrow_activity = 0.000000
art_activity = 0.000000
vein_activity = 0.000000
coronary_art_activity = 0.000000
coronary_vein_activity = 0.000000
bladder_activity = 0.000000
prostate_activity = 0.000000
asc_large_intest_activity = 0.000000
trans_large_intest_activity = 0.000000
desc_large_intest_activity = 0.000000
small_intest_activity = 0.000000
rectum_activity = 0.000000
sem_activity = 0.000000
vas_def_activity = 0.000000
penis_activity = 0.000000
test_activity = 0.000000
epididymus_activity = 0.000000
ejac_duct_activity = 0.000000
pericardium_activity = 0.000000
cartilage_activity = 0.000000
intest_air_activity = 0.000000
ureter_activity = 0.000000
urethra_activity = 0.000000
lymph_activity = 100.000000
trach_bronch_activity = 0.000000
airway_activity = 0.000000
sinus_activity = 0.000000
uterus_activity = 0.000000
vagina_activity = 0.000000
right_ovary_activity = 0.000000
left_ovary_activity = 0.000000
fallopian_tubes_activity = 0.000000
parathyroid_activity = 0.000000
thymus_activity = 0.000000
salivary_activity = 0.000000
pituitary_activity = 0.000000
eye_activity = 0.000000

```

Corpus_Callosum_act = 0.000000
Caudate_act = 0.000000
Internal_capsule_act = 0.000000
Putamen_act = 0.000000
Globus_pallidus_act = 0.000000
Thalamus_act = 0.000000
Fornix_act = 0.000000
Anterior_commissure_act = 0.000000
Amygdala_act = 0.000000
Hippocampus_act = 0.000000
Lateral_ventricle_act = 0.000000
Third_ventricle_act = 0.000000
Fourth_ventricle_act = 0.000000
Cerebral_aqueduct_act = 0.000000
Mamillary_bodies_act = 0.000000
Cerebral_peduncles_act = 0.000000
Superior_colliculus_act = 0.000000
Inferior_colliculus_act = 0.000000
Pineal_gland_act = 0.000000
Periacqueductal_grey_outer_act = 0.000000
Periacqueductal_grey_act = 0.000000
Pons_act = 0.000000
Superior_cerebellar_peduncle_act = 0.000000
Middle_cerebellar_peduncle_act = 0.000000
Substantia_nigra_act = 0.000000
Medulla_act = 0.000000
Medullary_pyramids_act = 0.000000
Inferior_olive_act = 0.000000
Tegmentum_of_midbrain_act = 0.000000
Midbrain_act = 0.000000
cerebellum_act = 0.000000
white_matter_act = 0.000000
grey_matter_act = 0.000000
lens_activity = 0.000000
lesn_activity = 100.000000

```

```

-----
Using user-specified startslice and endslice parameters.
Phantom Offset: -3.181046, -14.125237, 572.118469

```

```

-----
Phantom rotation
----Center of Rotation = 185.615997, 191.999985, 375.000000 mms
----Angles (x, y, z) = 0.000000 0.000000 0.000000 degrees

```

-----Phantom Dimensions and Weight-----

```

Total Body
  Height      1693.3594 mm
  Weight      73913.2734 mL
Head
  Short axis (AP)  201.5176 mm
  Long axis (LAT)  147.8051 mm
  Circumference    569.2609 mm
Chest
  Short axis (AP)  247.8446 mm

```

Long axis (LAT)	350.0001 mm
Circumference	962.3762 mm
Waist	
Short axis (AP)	223.2767 mm
Long axis (LAT)	340.0259 mm
Arms	
Length (shoulder to wrist)	565.6652 mm
Arms (upper, midpoint)	
Short axis (AP)	100.9742 mm
Long axis (LAT)	87.0986 mm
Circumference	305.4509 mm
Arms (lower, midpoint)	
Short axis (AP)	69.8128 mm
Long axis (LAT)	58.9631 mm
Circumference	217.5253 mm
Legs	
Length (from crotch)	2315.2646 mm
Legs (Thigh, below buttocks)	
Short axis (AP)	171.2564 mm
Long axis (LAT)	166.0656 mm
Circumference	533.9200 mm
Legs (Calf, below knee)	
Short axis (AP)	101.9351 mm
Long axis (LAT)	100.4205 mm
Circumference	315.3637 mm
Rib Cage	
Short axis (AP)	205.4858 mm
Long axis (LAT)	290.6466 mm
Right Diaphragm	
Height	103.3050 mm
Left Diaphragm	
Height	68.6565 mm
Right Kidney	
Approximate Cortex Thickness	11.9677 mm (obtained by taking samples, medulla vary inside so this is approximate and can be an overestimate)
Left Kidney	
Approximate Cortex Thickness	11.4242 mm (obtained by taking samples, medulla vary inside so this is approximate and can be an overestimate)
Breasts (prone)	
Short axis (AP)	22.4770 mm
Long axis (LAT)	35.4655 mm
Height	42.6781 mm
Breasts (supine)	
Short axis (AP)	22.4770 mm
Long axis (LAT)	35.4655 mm
Height	42.6781 mm
-----Heart Orientation Angles-----	
YX_rotation	-53.805725
XZ_rotation	-27.856049
ZY_rotation	-102.700287
-----LV Size (Diastole)-----	
Length	99.7908 mm's
Radius	32.9552 mm's

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-----
-----LV Size (Systole)-----
Length      88.3247 mm's
Radius      29.6450 mm's
-----
-----LV Volumes at Different Phases-----
V1 (end-diastole)      146.1263 mL
V2 (end-systole)       55.9024 mL
V3 (beg. quiet phase)  91.5068 mL
V4 (end quiet phase)   121.3379 mL
V5 (red. filling, diastole) 136.4043 mL
-----
-----
CREATING FRAME #1 ...

Time = 0.062 seconds
Current heart phase index = 0.062 (LV contracting, 16% contracted)
Current resp phase index = 0.000 (full exhalation)

RESPIRATION PARAMETERS -----
diaphragm motion = 0.00 mm
delta AP diameter = 0.00 mm

hrt_translation_x = 0.00 mm
hrt_translation_y = 0.00 mm
hrt_translation_z = 0.00 mm

hrt_rot_zy = 0.00 degrees
hrt_rot_xz = 0.00 degrees
hrt_rot_yx = 0.00 degrees

right_kidney_translation_y = 0.00 mm
right_kidney_translation_z = 0.00 mm
left_kidney_translation_y = 0.00 mm
left_kidney_translation_z = 0.00 mm

ORGAN VOLUMES:
Total = 41094.317776 ml
skin = 0.000000 ml
skeleton = 1622.656279 ml
muscle = 10338.290856 ml
cartilage = 356.275159 ml
arteries = 195.274144 ml
veins = 291.610153 ml
lung tree = 81.644633 ml
marrow = 2302.502844 ml
airway air = 0.000000 ml
intestinal air = 798.319201 ml
small intestine = 810.118202 ml
large intestine = 461.878919 ml
salivary glands = 82.076633 ml
stomach contents = 87.469883 ml
bladder contents = 51.937880 ml
esophagus contents = 28.063128 ml
bile = 9.608626 ml
right kidney = 242.412773 ml

```

left kidney = 246.283898 ml
larynx = 34.705128 ml
uterus = 37.534367 ml
vagina = 29.463768 ml
r_fallopian_tubes = 0.806624 ml
r_fallopian_tubes = 0.313875 ml
l_fallopian_tubes = 0.266625 ml
l_fallopian_tubes = 0.938249 ml
r_ovary = 4.441553 ml
l_ovary = 4.539429 ml
brain = 37.038094 ml
Cerebellum = 106.225479 ml
Temporal_left = 6.577961 ml
Temporal_right = 4.681181 ml
Occipital_left = 5.838825 ml
Occipital_right1 = 4.556304 ml
Temporal_lobe_left = 3.898169 ml
Temporal_lobe_right = 0.796499 ml
Occipital_lobe_left = 8.653619 ml
Occipital_lobe_right = 8.295863 ml
Fourth_ventricle = 1.863012 ml
Pons = 4.910685 ml
Superior_cerebellar_peduncle = 0.539999 ml
Superior_cerebellar_peduncle = 0.573749 ml
Middle_cerebellar_peduncle = 2.500897 ml
Middle_cerebellar_peduncle = 2.338895 ml
Medulla = 4.421302 ml
Medullary_pyramids = 0.394875 ml
Medullary_pyramids = 0.415125 ml
Inferior_olive = 0.452249 ml
Inferior_olive = 0.431999 ml
Tegmentum_of_midbrain = 3.074656 ml
basilar = 0.108000 ml
vertebral_left = 0.485999 ml
vertebral_right = 0.259875 ml
posterior_inferior_cerebellar_right = 0.209250 ml
anterior_inferior_cerebellar_left = 0.135000 ml
anterior_inferior_cerebellar_right = 0.118125 ml
superior_cerebellar_left = 0.027000 ml
internal_carotid_left = 3.226534 ml
internal_carotid_right = 9.213878 ml
superior_sagittal_sinus = 0.698624 ml
sigmoid_sinus_left = 0.911249 ml
sigmoid_sinus_right = 1.390505 ml
lateral_sinus_left = 2.632524 ml
lateral_sinus_right = 3.729417 ml
lateral_sinus_right = 0.060750 ml
straight_sinus = 0.506249 ml
rlung = 2244.981201 ml
llung = 2201.101318 ml
liver = 1596.226807 ml
pancreas = 103.011780 ml
stomach = 119.876114 ml
esophagus = 34.117847 ml
laryngopharynx = 16.105707 ml
spleen = 258.311646 ml
gall_bladder = 9.946264 ml

r_adrenal	=	12.842060 ml
l_adrenal	=	12.069173 ml
r_ureter	=	2.544773 ml
l_ureter	=	2.490772 ml
r_renal_pelvis	=	10.118392 ml
l_renal_pelvis	=	10.428897 ml
bladder	=	22.789799 ml
urethra	=	0.003375 ml
r_thyroid	=	11.755293 ml
l_thyroid	=	10.239894 ml
r_sup_parathyroid	=	0.050625 ml
r_inf_parathyroid	=	0.023625 ml
l_sup_parathyroid	=	0.050625 ml
l_inf_parathyroid	=	0.020250 ml
thymus	=	32.301556 ml
pituitary_ant	=	0.070875 ml
tonsils	=	2.021640 ml
tonsils	=	1.987889 ml
l_eye	=	0.371250 ml
l_sclera	=	0.823499 ml
l_cornea	=	0.054000 ml
l_retina	=	0.445499 ml
r_eye	=	0.185625 ml
r_sclera	=	0.189000 ml
r_retina	=	0.178875 ml

Volume of LV myocardium	=	128.175079 ml
Volume of RV myocardium	=	29.376041 ml
Volume of LA myocardium	=	10.989156 ml
Volume of RA myocardium	=	15.602854 ml
Volume of LV chamber	=	130.161301 ml
Volume of RV chamber	=	102.967941 ml
Volume of LA chamber	=	44.829918 ml
Volume of RA chamber	=	64.949844 ml

Volume of TOTAL HEART = 1055.872225 ml

Maximum activity per voxel	=	65.000000
Total activity	=	2935039.000000

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