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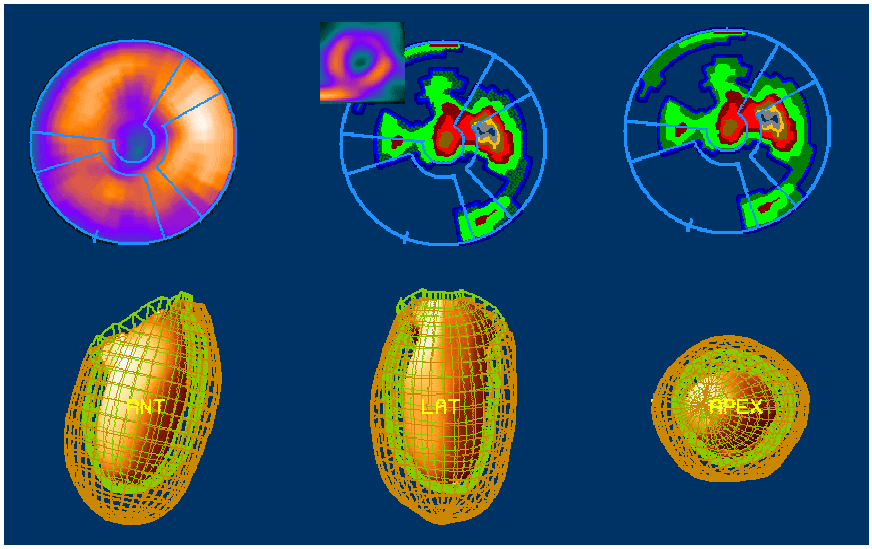
Faculty of Medicine and Health Sciences

Clinical value of Gated SPECT imaging in patients with left ventricular dysfunction and in the elderly



Olivier F.M.A. De Winter

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Clinical value of Gated SPECT imaging in patients with left ventricular dysfunction and in the elderly

Klinische waarde van Gated SPECT beeldvorming bij patiënten met linker ventrikel dysfunctie en ouderen

Olivier F.M.A. De Winter

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Voor Ibe en Frederic

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General introduction

Coronary artery disease (CAD) is the leading cause of mortality in the Western world. Complications of myocardial infarction are the most important cause of mortality in patients with CAD [1]. Therefore, risk assessment for future cardiac events is an important clinical question in these patients. Multiple prognostic parameters including infarct size, ischemia detection, left ventricular ejection fraction (LVEF) and left ventricular (LV) cardiac volumes have been introduced for management and follow-up of patients with CAD. During the past decades radionuclide myocardial perfusion imaging (MPI) using 201-thallium, first with planar and later with single photon emission computed tomography (SPECT) images, has proven to be of high diagnostic and prognostic utility in predicting future cardiac events [2,3]. Detecting CAD using radionuclide MPI is based on the visualisation of the coronary flow reserve. The coronary blood flow is primarily regulated at the arteriolar level. In normal epicardial arteries a minimal resistance to flow is observed [4]. During exercise, the myocardial oxygen demands increase, which results in arteriolar vasodilatation allowing blood flow to increase 2-fold to 3-fold [5]. In patients with CAD, many factors may increase epicardial resistance, including the severity and length of the stenosis [6,7], the presence of sequential arterial lesions [8] and intrinsic epicardial vasomotion [9]. Regardless of the mechanism of vascular resistance altering, the resting myocardial perfusion is generally maintained even when obstructions occlude 80-90% of the arterial cross-sectional area [6]. The capability for further hyperaemia during physical exercise or during pharmacological stress is however decreased. During exercise, the relative myocardial radionuclide concentration will be greater in the vascular beds supplied by a normal coronary artery compared with those perfused by an artery with a severe obstruction.

Since the late eighties 99m-technetium labelled perfusion tracers were developed and showed to be as valuable as 201-thallium for perfusion imaging [10,11]. The favourable imaging characteristics (high count density) of 99m-technetium make it possible to perform an electrocardiogram-gated cardiac SPECT during the acquisition of myocardial perfusion [12], which not only improves the specificity for the detection of CAD [13], but also enables to assess simultaneously LV functional parameters including LVEF and LV volumes [14,15]. It is well-known that LV functional data provide prognostic information in CAD patients. One of the most powerful prognostic parameters in patients with CAD is the LVEF. This measure is not a pure measure of intrinsic myocardial contractility since its value depends on and is affected by other parameters, such as heart rate and cardiac loading conditions. Despite this, LVEF has been found to be an extremely useful correlate of survival and thus a determinant of therapeutic decisions in a broad variety of cardiovascular disorders [16]. Multiple studies demonstrated the prognostic value of this parameter using different imaging modalities [17-21]. In particular both resting and exercise LVEF determined by radionuclide angiography (RNA) and other techniques are major determinants of long-term survival in patients with known CAD. Since the

development of RNA, multiple studies have reported its important prognostic value as a non-invasive tool [19,20,22,23]. However, during the last decade short and long-term survival rates after acute myocardial infarction improved markedly with the introduction of new reperfusion strategies [24]. This made it necessary to re-evaluate the prognostic value of LVEF estimated by RNA. In 1998, Shaw et al. [21] showed that also in the present era, LVEF determined using RNA at rest and during peak exercise provided information highly predictive of cardiac death (both $p < 0.0001$) in 863 consecutive patients with known CAD, of which 68% had a prior history of myocardial infarction.

Not only the LVEF, also LV cardiac volumes assessment provides information for the prediction of future cardiac events and cardiac death. Already in 1987, White et al. found that cardiac volumes and most importantly LV end-systolic volumes, in this study assessed by X-ray left ventriculography during catheterisation, had a high predictive value for future cardiac death during a mean follow-up of 78 months in 605 male patients after a first or recurrent acute myocardial infarction ($x^2 = 82.9$, $p< .001$). Using the same technique, a study by Hamer et al. showed comparable results in a population of 193 patients after coronary artery bypass grafting. The invasiveness of catheterisation and the assumption of an ideal ellipsoidal geometry of heart chambers to estimate cardiac volumes makes the assessment of myocardial function during catheterisation less suitable for follow-up of patients with known CAD [25]. Therefore, non-invasive imaging techniques are generally preferred for cardiac functional imaging.

A large and growing variety of non-invasive imaging methods is available to assess global LV function and volumes, including echocardiography, radionuclide techniques (RNA and myocardial gated SPECT) and cardiac magnetic resonance imaging (MRI). Each of these techniques is characterised by a variety of strengths and pitfalls. The ideal technique for imaging global LV function should not only offer highly accurate and reproducible measurements of both LVEF and LV volumes but also be time and cost efficient, non-invasive and widely available. Currently global LV function is, due to clinical circumstances, most commonly investigated by transthoracic echocardiography, which is widely available, readily accessible and inexpensive.

M-mode echocardiography and 2-dimensional echocardiography, like all not truly 3-dimensional (3D) techniques, assume an ideal ellipsoidal geometry of the heart chambers to estimate cardiac volumes. After myocardial infarction though, LV shape may be altered radically both due to infarct extension and the following remodelling process [26], which makes it difficult to make a good estimation of cardiac volumes and LVEF when assuming an ideal ellipsoid heart shape. Truly 3D techniques, like 3D echocardiography and 3D MRI but also gated SPECT, do not require assumptions of a normal heart shape for accurate estimation of LV volumes. All these tomographic methods have shown to be highly accurate and highly reproducible for the measurement of LV volumes and LVEF.

Cardiac MRI is, due to its high resolution and intrinsic 3D tomographic acquisition considered the ideal imaging modality for measuring cardiac volumes and changes in cardiac volumes over time. However there are few studies investigating the prognostic value of these volumetric data. Wu et al. investigated a small population of 44 patients early after myocardial infarction and found that there was a significant rise in LV end-diastolic and end-systolic volumes over a 6 month period post infarction in patients with a microvascular obstruction compared to patients without obstruction [27]. In an even smaller study, Sandstede et al. investigated 12 patients after myocardial infarction both with resting and stress cardiac MRI [28]. Patients who had a lower LV end-systolic volume and a higher LVEF on stress imaging compared to rest imaging had a greater improvement of global LV function after revascularisation than patients with a higher LV end-systolic volume and a lower LVEF. Up-to date, there are however no large studies focussing on the long term prognostic value of cardiac MRI.
Using myocardial gated SPECT, Sharir et al. showed in a retrospective study in a large population of 1680 patients who underwent rest 201-thallium/ stress 99m-technetium sestamibi that functional data obtained during gated MPI provide incremental prognostic information above myocardial perfusion data [29].

Prognosis in CAD patients

Prognosis in CAD patients is determined by clinical risk factors, the extent and severity of CAD and the degree of LV dysfunction. Using gated SPECT, it is possible to visualise extent and severity of CAD and LV function routinely. In this thesis, we used myocardial gated SPECT for functional imaging because this technique has proven to be accurate, operator independent and reproducible for the assessment of global LV function. Another advantage of myocardial gated SPECT imaging is that the functional data can be assessed at little or no extra cost during a myocardial perfusion study. In October 1998, we started collecting data for the Ghent Gated SPECT Database. Since then, clinical data, perfusion SPECT and functional SPECT data in patients referred routinely for 2 day stress-rest gated SPECT imaging in the Ghent University Hospital are being collected prospectively.
In this thesis we focussed on the outcome of patients with CAD and LV dysfunction and on the elderly population. We selected these patient populations because they become a growing proportion of the patients in the cardiology department:
- The proportion of patients with CAD and LV dysfunction is growing as a result of increasing life expectancy and a longer survival of patients with CAD in particular.
- Similarly, due to aging of the population and better medical and revascularisation treatment, more and more elderly patients are seen for diagnostic cardiac work-up.

Outline of this thesis

In the first chapter, we investigated relevant technical issues considering cardiac gated SPECT imaging.

In chapter 2, we investigated the value of combined perfusion and function imaging in patients with CAD and poor LV function in the prediction of future cardiac events. Secondly, patients with CAD and a severely depressed LV function are possible candidates for resynchronisation treatment. In these patients, we investigated the prevalence of non-viable tissue in the inferolateral wall, the region were pacing leads for cardiac resynchronisation treatment are commonly placed. Since non-viable tissue is electromechanically non-functional (30), placement of the lead in the inferolateral region could lead to ineffective pacing in these patients (31).

In chapter 3, we investigated the predictive value of combined perfusion and function imaging for cardiac death and all-cause mortality in the elderly population, a growing proportion of the patients in the cardiology department.
Amino-terminal pro brain natriuretic peptide (Nt-proBNP) is a valuable tool in the diagnosis and has prognostic value in CAD patients. It is known that increasing age is associated with higher serum brain natriuretic peptide levels. We investigated which clinical, myocardial perfusion and function parameters are determinants of Nt-proBNP in elderly patients with stable CAD.

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Chapter 1

Technical aspects of cardiac gated SPECT imaging

1.1 Introduction

In the first chapter we investigated technical variabilities concerning gated myocardial and bloodpool single photon emission computed tomography (SPECT) imaging.
Myocardial gated SPECT is increasingly used for left ventricular (LV) functional imaging in coronary artery disease (CAD) and has been validated against other cardiac imaging modalities [1-8]. However, little is known about the variability of LV functional measurements using this imaging modality. Serial reproducibility of the measurement of LV volumes and ejection fraction (LVEF) by gated SPECT has been shown to be very good on repeated processing of the same gated raw data [7]. Also global LV kinetic parameters assessed by repeated scanning (twice scanning a patient after a single tracer injection) using a 99m-technetium ligand has been shown to be highly reproducible [9]. However, when measurements in patients are performed to monitor changes over time in LV dimensions and function, the difference between two measurements is subject to interstudy variability. This interstudy variability may be of technical and biological origin. This variability should be assessed in serial tests rather than by repeat analysis of a single image [10]. In the first part of this chapter we investigated the day- to day variability of myocardial gated SPECT imaging in CAD patients with a reduced LVEF. The knowledge of this variability is important since gated SPECT is routinely used for follow-up over time of LV perfusion and function in these patients.

In the second part, we studied the agreement between different software algorithms for the evaluation of global left and right ventricular function in bloodpool SPECT imaging and compared these with planar bloodpool imaging. Recently, different programs are being developed to process tomographic radionuclide ventriculography [11-14]. These programs provide left and right ventricular volumes and ejection fractions, but validation of these parameters, mostly of the right ventricle, remains scarce. We therefore wanted to compare LVEFs calculated from planar radionuclide ventriculography with values from tomographic radionuclide ventriculography, calculated by four different software programs: QBS, QUBE, 4D-MSPECT and BP-SPECT. Furthermore, we compared left ventricular and right ventricular stroke volumes, calculated from tomographic radionuclide ventriculography from QBS, QUBE and BP-SPECT, as a method of validation of left ventricular and right ventricular volumetric parameters.

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1.2.
Day-to day variability of global left ventricular functional and perfusional measurements by Quantitative Gated SPECT using ^{99m}technetium tetrofosmin in patients with heart failure due to coronary artery disease.

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Abstract

Background: Although myocardial gated SPECT is routinely used for functional measurements in patients with coronary artery disease (CAD) and heart failure, day-to day variability of left ventricular ejection fraction (LVEF), left ventricular (LV) volumes and global perfusion scoring have not yet been investigated.
Methods: In 20 consecutive patients with CAD and a LVEF < 40% who routinely underwent a resting tetrofosmin gated single photon emission computed tomography (SPECT) study, we performed an additional gated SPECT at rest 1-5 days later under the same circumstances. LV volumes and LVEF were calculated from the gated SPECT data by commercially available software (QGS®). Myocardial perfusion was scored visually using a 20-segment, 5 point score method. For global LV function and perfusion, agreement between data was investigated using Bland-Altman plotting.
Results: The 95 % limits of agreement found by Bland-Altman analysis were –0.9 ± 6.0 % for LVEF, +3 ± 20 ml for LVEDV and +4 ± 20 ml for LVESV.
Conclusion: In CAD patients with a LVEF < 40 %, day-to day variability of measurements of global myocardial function and perfusion is quite similar as inter- and intraobserver variability. Day-to day variability of global LV functional parameters obtained by gated cardiac SPECT is fairly small, which indicates that myocardial gated SPECT can be used in daily clinical practice to determine changes in global LV function and perfusion over time in patients with a diminished LV function.

Introduction

Global left ventricular (LV) functional parameters assessed by myocardial gated Single Photon Emission Computed Tomography (SPECT) are routinely used for follow-up in patients with heart failure due to coronary artery disease (CAD) [1,2]. The accuracy of global LV functional indices calculated by gated cardiac SPECT has been validated against many other imaging techniques like cardiac magnetic resonance imaging (MRI) [3,4], echocardiography [5,6], planar RNA [6-9] and contrast angiography during catheterisation [10]. Serial reproducibility of the measurement of LV volumes and left ventricular ejection fraction (LVEF) by gated SPECT has been shown to be very good on repeated processing of the same gated raw data [9]. Also global LV kinetic parameters assessed by repeated scanning (twice scanning a patient after a single tracer injection) using a ^{99m}Technetium (^{99m}Tc) ligand has been shown to be highly reproducible [11]. However, when measurements in patients are performed to monitor changes over time in LV dimensions and function, the difference between two measurements is subject to interstudy variability. This interstudy variability may be of technical and biological origin. Technical factors include variability in data acquisition and analysis. Biologic variations such as loading conditions, adrenergic drive, heart rate, may cause variations in LV dimensions and function. This

variability should be assessed in serial tests rather than by repeat analysis of a single image [12]. A real day-to day variability of global LV functional parameters assessed by gated SPECT has never been investigated in patients with a reduced LVEF. However, it is of significant clinical importance to have an idea of the day-to day variability when evaluating a possible deterioration or amelioration of functional and perfusional parameters over time or after an intervention such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. The aim of this study is to investigate the day-to day variability of global functional and perfusional LV parameters assessed with myocardial gated SPECT in patients with a severely depressed LV function due to CAD.

Materials and methods

Patient population

In 20 patients (17 males/ 3 females; mean age 69 ± 8 y, mean body mass index 28 ± 8) with known CAD and a resting LVEF < 40 % calculated by Quantitative Gated SPECT software (QGS®, Cedars-Sinai, Los Angeles) [9] who routinely underwent a resting ^{99m}Tc tetrofosmin gated SPECT study (study 1) in a 2 day high dose stress/rest protocol, we performed an additional gated SPECT under the same circumstances. The patients returned for a repeat myocardial gated SPECT study in resting condition 1-5 days after the first study (mean 3.65 days) (study 2). The injected dose and acquisition protocol was the same in study 1 and 2. Patients were included when they had known CAD and a resting LVEF < 40 % determined by myocardial gated SPECT.

Fourteen patients (70 %) had a history of myocardial infarction and 8 (40%) a history of coronary artery bypass grafting. One patient was in atrial fibrillation but with a ventricular rhythm that made adequate electrocardiogram (ECG) gating possible. Two patients showed left bundle branch block on the resting ECG. Regarding medication, 12 patients (60%) were on beta-blockers and 18 (90%) on Angiotensin Converting Enzyme Inhibitors. Mean heart rate was 71 ± 12 beats/' in study 1 versus 66 ± 12 beats/' in study 2 (p = not significant). Mean systolic blood pressure was 127 ± 20 mmHg and mean diastolic blood pressure was 79 ± 9 mmHg. The clinical status remained unchanged between the first and the second scan for all patients.

The study was approved by the local Ethics Committee of the Ghent University Hospital. Written informed consent was obtained from all included patients prior to the study, after the nature of the study had been fully explained.

Gated SPECT Acquisition and reconstruction

In resting condition we administered 900 Mega Becquerel (MBq) (25 milli Curie) of ^{99m}Tc tetrofosmin intravenously in both study 1 and 2. Gated SPECT acquisition was performed over 360° (120 sectors of 3°) and was started between 30 and 45 minutes after tracer injection using a triple-headed camera (Picker Prism 3000, Marconi, Philips, Cleveland, Ohio) with a low energy all purpose collimator. In this way 40 step-and-shoot images were acquired for each detector, with 30 s per step and intervals of 3°, a matrix size of 64 x 64. Acquisitions were gated for 8 frames per cardiac cycle. Gated SPECT data were reconstructed using filtered back projection (ramp filter) over 180° (selected reconstruction angle from -45° to +135 °) and post-filtered using a low pass filter (order 5, cut-off frequency .21). There was a 20 % acceptance window around the 140 keV photo peak. Attenuation correction, background subtraction and beat rejection were not performed. The left ventricle was reoriented manually by a physician to obtain short axis, horizontal long axis and vertical long axis gated and ungated images. Data of study 1 and 2 were processed independently. To determine the interobserver variability of LVEF and LV volumes, data of study 1 were reconstructed and reoriented independently by a second physician using the same reconstruction parameters, but without knowledge of the reorientation of the first physician. To determine the intraobserver variability, raw data of study 1 were reprocessed one month after the first processing by the same physician who processed study 1.

Calculation of LV volumes and LVEF

The QGS® software automatically calculates left ventricular volumes (including left ventricular end diastolic volume [LVEDV] and left ventricular end systolic volume [LVESV]) by summing the area of the short axis slices following the Simpson rule [9]. LVEF is calculated by the formula [LVEDV-LVESV/ LVEDV].

Grading of myocardial perfusion

Rest perfusion scans were visually graded on polar plots of the ungated data using a 20 segment, 5 point scoring method (0: normal uptake, 4 absent uptake) [13,14]. Summed perfusion score (SPS) at rest [13], which can be considered global indices of resting myocardial perfusion, were calculated by summing the perfusion score of the 20 segments for each scan. No semi-quantitative software was used for perfusion scoring. Intraobserver, interobserver and day-to day variability was calculated for the SPS. Intra- and interobserver variability was determined by rescoring the data of the first study of every patient.

Statistical analysis

Bland-Altman analyses were performed to determine the 95 % limits of agreement for LVEF, LVESV, LVEDV and SPS [15]. Measurements of LVEF, LVEDV and LVESV were normally distributed (tested by the Shapiro-WilkTest [16]). Differences of mean were investigated using a Student t-test.

Results

QGS® succeeded in automatic edge detection and calculation of LV volumes and LVEF in 37/ 40 scans (92%). In 3 scans were automatic border detection failed due to high extra cardiac activity, masking of the extra cardiac activity on the short axis images was necessary to make accurate automatic border detection by the QGS® software possible. The manual border detection tool provided by the QGS® software program was not used. Mean values for global LV function and perfusion are shown in table 1. Values ranged from 18-38 % for LVEF, from 101-377 ml for LVEDV and from 70-277 ml for LVESV (study 1). No significant difference was found between the samples.

a) Global LV function

Bland-Altman plots of the day-to day variability of LVEF, LVEDV and LVESV are shown in figure 1. The 95 % limits of agreement for global LV function for day-to day, inter and intraobserver variability are shown in table 2. As expected 95 % limits of agreement were broader for day-to day than for interobserver variability and broader for interobserver variability than for intraobserver variability. For day-to day variability 95 % limits of agreement were ± 6.0 % for LVEF and ± 20 ml for both LVEDV and LVESV.

b) Global perfusion scoring

Bland-Altman plotting of day-to day variability of SPS is shown in figure 2. The 95 % limits of agreement for day-to day, inter and intraobserver variability are shown in table 2. The SPS scores ranged from 21-70 in study 1 and from 19-67 in study 2. Eighty is the theoretically maximum SPS score in a 20 segment, 5 point scoring method like we used. Similar as for global functional parameters, 95 % limits of agreement were broader for day-to day than for interobserver variability and broader for interobserver variability than for intraobserver variability. For day-to day variability of the SPS, 95 % limits of agreement were ± 9.1 on Bland-Altman plotting in this patient population with severe perfusion abnormalities.

Discussion

In this study we showed that day-to day variability of global LV functional indices assessed by gated SPECT in patients with severe heart failure due to CAD is reasonably small. We found 95 % limits of agreement on the Bland-Altman plot were ± 6% for LVEF and ± 20 ml for LVEDV and LVESV. To our knowledge, there are no full text articles and only one abstract by Johnson et al. [17] where a real day-to day variability (where the acquisition was investigated by scanning on 2 separate days after tracer injection in resting state) for gated SPECT measurements was investigated. Johnson et al. found 95 % limits of agreement on the Bland-Altman plot were ± 5.3 % for LVEF, ± 12 ml for LVEDV and ± 13 ml for LVESV. The population (16 patients) investigated by this group however was much less uniform and patients with a normal LV function were also included. Patients with more extensive CAD, like the population we investigated, frequently show cardiac regions with severely diminished tracer accumulation. The myocardium of these patients is more difficult to realign and it can be more difficult for the automatic software to define accurately the myocardial border in large areas with severe hypoperfusion. Therefore, it is expected that variability of functional measurements will be larger in patients with extensive CAD than in a less severely diseased population. Up till now, variability of gated SPECT measurements had only been investigated by repeated scanning after a single tracer injection (twice consecutively scanning on the same day after a single tracer injection). Using ^{99m}Tc bound ligands, this variability is small after stress, with 95 % limits of agreement being ± 5.3-6.4 % for LVEF , ± 14.1-14.4 ml for LVEDV and only ± 9.4-11.2 ml for LVESV [11,18-20]. There are to our knowledge no articles investigating the variability of measurements of global LV function in resting condition . Using ^{201}Tl, repeated scanning (1 tracer injection, twice consecutively scanning on the same day) has broader levels of agreement for global LV functional measurements with 95 % limits of agreement being ± 12 % for resting LVEF, ± 29 ml and ± 19 ml for LVEDV and LVESV respectively. This makes gated myocardial perfusion SPECT using ^{201}Tl less suitable for follow-up of alterations in global LV function in CAD patients [21].

When raw gated SPECT data study are reprocessed by the same observer (intraobserver variability) or by a different observer (interobserver variability), correlation is very high between measurements of global LV function [22]. However, a high correlation is logical when processing two consecutive times the same volumes by a single technique. It is thus not appropriate to use correlation or regression analysis when measuring agreement. Few studies performed Bland-Altman plotting which makes it impossible to make a good comparison with our results for intra- and interobserver variability. The interobserver variability was smaller in the study performed by Hyun et al. with 95 % limits of agreement for post stress LVEDV being ± 9 ml (versus ± 20 ml in our study) and ± 8 ml for LVESV (versus ± 17 ml in our study) [11]. Limits of agreement for LVEF though were slightly narrower in our study (± 4.4 % versus ± 3.0 % in our study). These broader limits of agreement

for LV volumes can be explained by the fact that the population described in our paper had a much more severely depressed LV cardiac function (mean LVEF 41 ± 14 % versus 28 ± 6 % in our study), had larger cardiac volumes (mean LVEDV 120 ± 52 ml versus 231 ± 77 ml in our study) and more severe perfusion abnormalities in the LV wall. These severe perfusion abnormalities may cause more problems to accurately realign the myocardium manually during processing and may possibly also influence the accuracy of the definition of the endocardial cavity by the automatic software.

It is important to know the intra- and interobserver variability of a technique. However, when measurements in patients are performed to monitor changes over time in LV dimensions and function for follow-up of remodeling in CAD, the difference between two measurements is not only subject to variability of technical origin, but also of biological origin. Technical factors include variability in data acquisition and analysis. Biological variations, such as variation by loading conditions, adrenergic drive and heart rate, may also cause variations in LV dimensions and function [12]. We preferred to perform a repeat study on an alternate day to investigate the real day- to day variability of the technique, because this situation reflects the daily clinical practice in the most accurate manner. In general one would expect day-to day variability to be at least as high as the variability of a repeated acquisition using a single tracer injection. This study shows that day-to day variability of global LV functional parameters obtained by gated cardiac SPECT is quite similar as inter- and intraobserver variability. Because 95 % limits of agreement for day-to day variability are reasonably small both for LVEF and LV volumes measured by gated SPECT, this technique can be used to monitor changes in LV function over time.

In table 3 we compared our data with the 95 % limits of agreement of day-to day variability of studies of other imaging techniques that investigated intraobserver, interobserver and day-to day variability in heart failure patients [23-25]. Due to its intrinsic higher resolution, MRI is considered the reference method for global LV function. However there is a comparable intra- and interobserver variability for gated SPECT and even smaller limits of agreement for LVEF. This can be explained by the fact that processing of gated SPECT data is almost entirely automatic and thus much less susceptible to variability caused by the processing. Planar RNA is very reproducible for LVEF, but LV volumes are more difficult to measure by this technique.

Conclusions

Day-to day variability of global indices of cardiac function assessed by ^{99m}Tc tetrofosmin myocardial gated SPECT is fairly small in patients with a diminished LV function due to CAD. The 95 % limits of agreement were –0.9 ± 6.0 % for LVEF, 3 ± 20 ml for LVEDV and 4 ± 20 ml for LVESV. This makes gated myocardial SPECT useful for follow-up of alterations in global cardiac function over time due to medical treatment or evolution of CAD.

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Tables

Abbreviations in the tables

3D-echo: 3- dimensional echocardiography
LVEDV: left ventricular end diastolic volume
LVEF: left ventricular ejection fraction
LVESV: left ventricular end systolic volume
MRI: (cardiac) MRI
Ns: not significant
RNA: radionuclide angiography
SPECT: single photon emission computed tomography
SPS: summed perfusion score

Table 1

Mean ± standard deviation of global LV indices and summed perfusion score values

	Study 1		Study 2		P
	Mean	Range	Mean	Range	
LVEF	27.9 ± 5.8 %	18-38 %	27.5 ± 5.3 %	19-38 %	Ns
LVEDV	231 ± 77 ml	101-377 ml	234 ± 80 ml	84-366 ml	Ns
LVESV	169 ± 65 ml	70-277 ml	172 ± 66 ml	59-281 ml	Ns
SPS	42 ± 14	21-70	42 ± 15	19-67	Ns

Table 2

The 95 % limits of agreement for global LV functional and perfusional measurements

		95 % limits of agreement
LVEF	intraobserver	- 0.15 ± 1.6 %
	interobserver	- 0.60 ± 3.0 %
	day-to-day	- 0.85 ± 6.0 %
LVEDV	intraobserver	+ 0.6 ± 14 ml
	interobserver	- 3.8 ± 22 ml
	day-to-day	+ 2.7 ± 20 ml
LVESV	intraobserver	+ 0.4 ± 12 ml
	interobserver	- 1.6 ± 17 ml
	day-to-day	+ 3.8 ± 20 ml
SPS	intraobserver	- 0.1 ± 4.1
	interobserver	- 0.8 ± 5.4
	day-to-day	+ 0.5 ± 9.1

Table 3

The 95 % limits of agreement for variability of global LV functional indices using different imaging techniques

		3D-echo [23]	MRI [24]	RNA [25]	Gated SPECT
LVEF	Intraobserver	5.6 %	4.4 %	2.4 % *	1.6 %
	Interobserver	7.6 %	6.6 %	3.0 % *	3.0 %
	day-to-day	1.8 %	5.0 %	2.0 %	6.0 %
LVEDV	Intraobserver	29 ml	12 ml	-	14 ml
	Interobserver	32 ml	24 ml	-	22 ml
	day-to-day	11 ml	15 ml	-	20 ml
LVESV	Intraobserver	27 ml	13 ml	-	12 ml
	Interobserver	21 ml	19 ml	-	17 ml
	day-to-day	7 ml	13 ml	-	20 ml

*data from pts with a normal + abnormal LVEF

Figures

Abbreviations in the figures

Diff. : Difference
LVEF : left ventricular ejection fraction
LVEDV : left ventricular end-diastolic volume
LVESV : left ventricular end-systolic volume
SPS: summed perfusion score

Figure 1

Bland-Altman plot: Day-to day variability of LVEF, LVEDV and LVESV by gated SPECT

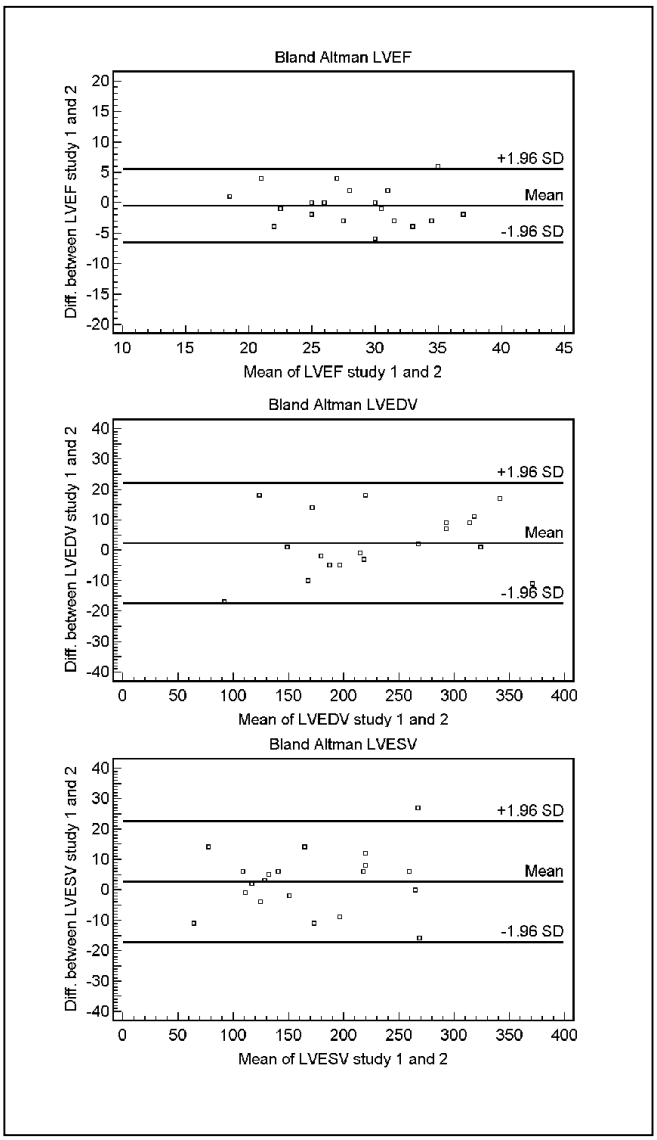
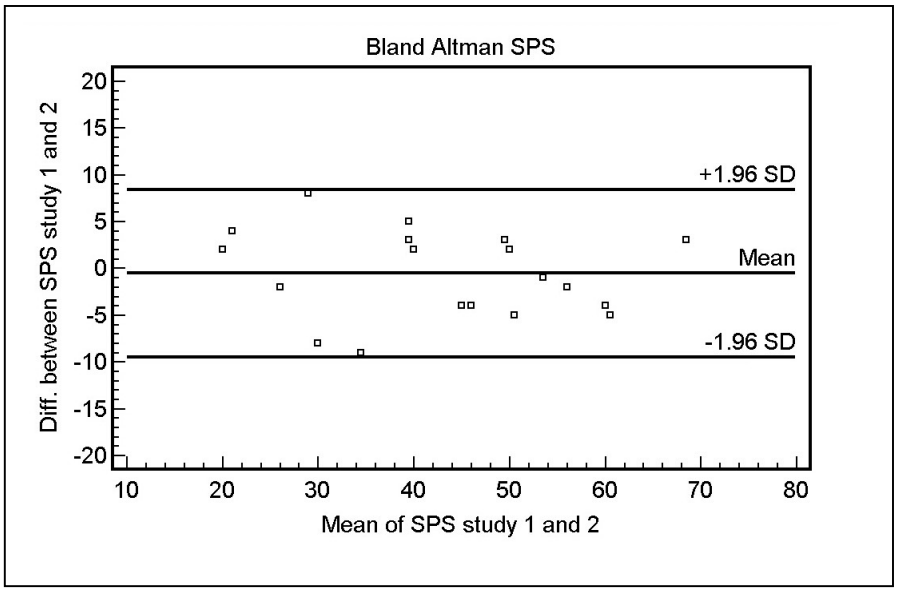


Figure 2

Bland-Altman plot of SPS of study 1 and 2



1.3
Agreement between four available algorithms to evaluate global systolic left and right ventricular function from tomographic radionuclide ventriculography and comparison with planar imaging.

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Abstract

Background: Left and right ventricular ejection fractions (LVEF and RVEF) and end-diastolic and end-systolic volumes (LVEDV, RVEDV, LVESV and RVESV) can be calculated from tomographic radionuclide ventriculography (TRV). We wanted to validate and compare these parameters from four different TRV software's (QBS, QUBE, 4D-MSPECT and BP-SPECT).
Methods: We compared LVEF from planar radionuclide ventriculography (PRV) with LVEF from TRV from the four different software's in 166 patients. Furthermore, ventricular volumes from TRV (QBS, QUBE and 4D-MSPECT) were compared with those from BP-SPECT, the latter being the only method with a validation of ventricular volumes in literature.
Results: Correlation for LVEF between PRV and TRV was good for all methods, being 0.81 for QBS, 0.79 for QUBE, 0.71 for 4D-MSPECT and 0.79 for BP-SPECT. Mean difference ± standard deviation (SD) was 3.16 ± 9.88, 10.72 ± 10.92, 3.43 ± 11.79 and 2.91 ± 10.39 respectively. Correlation for RVEF between BP-SPECT and QUBE and QBS was poor, being 0.33 and 0.38 respectively.
LV volumes calculated from QBS, QUBE and 4D-MSPECT correlated well with those from BP-SPECT (0.98, 0.90 and 0.98 respectively) with mean difference ± SD being 7.31 ± 42.94, -22.09 ± 36.07, -40.55 ± 39.36 respectively, whereas RV volumes correlated worse between QBS and BP-SPECT and between QUBE and BP-SPECT (0.82 and 0.57 respectively).
Conclusion: LVEF calculated from TRV correlates well with those from PRV but is not interchangeable with values from PRV. Volume calculations, for LV and RV, and RVEF need further validation before it can be used in clinical practice.

Introduction

Recently, different programs are being developed to process tomographic radionuclide ventriculography (TRV) [1-4]. These programs are fast, provide left (LVV) and right ventricular volume (RVV) and ejection fractions (EF), but the validation of these parameters, mostly of the RV, remains scarce. We therefore wanted to compare LVEF calculated from planar radionuclide ventriculography (PRV) with values from TRV, calculated by four different programs, QBS [2], QUBE [3], 4D-MSPECT [4] and BP-SPECT [1]. For LVV and RVV calculations, we compared values from QBS, QUBE and 4D-MSPECT with those of BP-SPECT, the latter being the only algorithm with MRI-validation of volumetric parameters in literature [1,5]. For the algorithm 4D-MSPECT, only parameters of the LV were available. Furthermore, we wanted to compare LV and RV stroke volumes, calculated from TRV from QBS, QUBE and BP-SPECT, as a method of validation of LV and RV volumetric parameters.

Materials and methods

Data acquisition

All images were acquired on two three-headed gamma camera's (IRIX and Prism 3000, Marconi-Philips, Cleveland, Ohio) equipped with low energy high-resolution collimators. PRV data were acquired over a 5 minute period, in 16 electrocardiographic gated frames, 64 x 64 matrix, zoom 1.333 (pixel size 7 mm) and with a beat acceptance window at 20 % of the average R-R interval calculated just before the acquisition was started. The gamma camera was positioned in left anterior oblique projection in order to obtain the best "septal view". Parameters of TRV acquisition were as follows: 360° step-and-shoot rotation, 40 stops per head, 30 seconds per stop, 64 x 64 matrix, zoom 1.422 (pixel size 6.5 mm), and 16 time bins per R-R interval, with a beat acceptance window at 20% of the average R-R interval. Projection data were pre-filtered using a Butterworth filter (cutoff frequency: 0.5 cycles/cm; order: 5) and reconstructed by filtered backprojection using an x-plane ramp filter. Data were then reoriented into gated short axis tomograms. The resulting gated short axis data sets were then used as input for the four algorithms.
From a database of 203 patients, who underwent PRV and TRV between 2001 and 2004, 37 patients were excluded because the best septal view in left anterior oblique position was not reached during PRV, and these were all patients after heart transplantation. None of the patients had proven intracardiac or intrapulmonary shunting.
From the remaining 166 patients (100 men, 66 women) clinical indications were pre-chemotherapy (55, 33%), post-chemotherapy (67, 40%), heart failure (8, 5%), acute myocardial infarction (7, 4%), pulmonary hypertension (3, 2%), congenital heart diseases (2, 1%) and other (24, 14%).

Processing

For the processing of the images, we used four software's: QBS (Quantitative Bloodpool SPECT® software from Cedars-Sinai Medical Center, Los Angeles, USA), QUBE (Free University of Brussels, Brussels, Belgium), 4D-MSPECT (University of Michigan Medical Center in Ann Arbor, Michigan, USA) BP-SPECT (algorithms from Columbia University, New York, USA).
For the validation of LVEF, we used PRV as the gold standard. PRV was processed with Multi-Gated Analysis, version march 2001, on an Odyssey workstation, Philips Medical Systems, The Netherlands. For the comparison of LVV and RVV, we compared data from QBS, QUBE and 4D-MSPECT with BP-SPECT, since this program is the only one available with validation of volumetric parameters.

Statistical Analysis

Results were reported as mean values ± 1 standard deviation (SD). Correlations (r) between the different methods to calculate LVEF, LVV, RVEF and RVV were expressed as the Pearson coefficient. Variability about the regression line was expressed as the standard error of the estimate (SEE). Bland-Altman analysis of differences versus means of paired values was used to search for trends and systematic errors. Statistical significance was defined as $p<0.05$. Histograms and Box and whisker diagrams were used to show the distribution of the stroke volume index for the different techniques.

Results

Global results

All gated short axis tomograms were processed on a pc, Pentium 4, 1.8 GHz, 512 Mb RAM. Mean processing times were 105 sec, 18 sec, 19 sec and 15 sec for QBS, QUBE, 4D-MSPECT and BP-SPECT respectively. The automatic option for all programs was first performed, followed by a visual inspection of the delineation of both ventricles. This was done by reviewing the dynamic images, slices into short, horizontal long and vertical long axis images with the calculated outlines of both ventricles superimposed on it.
QBS could successfully process the images automatically in 130 patients. From the other 36 patients, only 6 could be corrected by the manual option. The manual option for QBS is defining a ROI around the LV. After trying the automatic and manual option, in 3 patients there could be no satisfactory delineation of the LV and in 16 cases for the RV. For 11 patients, no result could be calculated at all.
For QUBE, 114 patients were correctly processed by the automatic option. The manual intervention included masking, defining RV limit, condense number of gates or define septum and this revealed a good LV and RV delineation in 51 patients. Only in 1 patient, no result could be achieved for both ventricles.
Seventy-one patients could be processed correctly with the automatic program of 4D-MSPECT, in 85 patients, the atrioventricular border has to be adjusted manually, or a ROI around the LV had to be drawn. In 10 patients, no result could be calculated. No results for the RV were available.
BP-SPECT could process the images completely automatic in 99 patients, whereas in the other 67 scans a satisfactory result could be achieved by drawing an end-diastolic and an end-systolic ROI in the vertical long axis slice through the RV and LV together with one ROI through the short axis of both chambers.

Validation of LVEF

Mean ± SD for LVEF from PRV and TRV are displayed in Table 1. Values of LVEF from all the methods to process TRV were significantly higher ($P<0.001$) compared to PRV. Furthermore, LVEF from QUBE was significantly higher ($P<0.001$) compared to the other methods of TRV. Regression and Bland-Altman analysis were performed for LVEF calculated with the four methods, compared to PRV (Figure 1). Correlation between PRV and TRV was good for all methods, being 0.81 for QBS, 0.79 for QUBE, 0.71 for 4D-MSPECT and 0.79 for BP-SPECT. The standard error of the estimate (SEE) was smallest for QBS (9.86) and BP-SPECT (9.79), somewhat larger for QUBE (10.79) and for 4D-MSPECT (12.18). From Bland-Altman analysis, no significant trend was seen for all methods across the range of LVEF.

Validation and comparison of LVV, RVV and RVEF

Mean ± SD for LVEDV, LVESV, RVEDV and RVESV from TRV are displayed in Table 1.

Regression and Bland-Altman analysis were performed for LVV calculated with QBS, QUBE and 4D-MSPECT, compared to LVV from BP-SPECT (Figure 2). LVV calculations from QBS, QUBE and 4D-MSPECT correlated well (0.98, 0.90 and 0.98) with values from BP-SPECT. All calculations of LVV, LVEDV and LVESV, showed the smallest values with 4D-MSPECT and largest with BP-SPECT. The values of LVEDV and LVESV from all the software's differed significantly ($P<0.001$) with every other technique, except LVESV from QBS compared to BP-SPECT. In the Bland-Altman analysis, no significant trend was observed between LVV calculated by QBS and BP-SPECT, but there was between QUBE and BP-SPECT and even more obvious between 4DM-SPECT and BP-SPECT, with a growing underestimation of LVV for QUBE and 4D-MSPECT for larger volumes. Furthermore, a lot of outliers were observed, especially between 4D-MSPECT and BP-SPECT and especially for larger volumes, and the variation of all methods depended strongly on the magnitude of measurements, by means that for large volumes difference between the two methods is often lying outside the 95% confidence interval (Figure 2).

For RVV, correlation was slightly lower for QBS (0.82), but with an acceptable mean difference and confidence interval on Bland-Altman plot, and much lower for QUBE (0.57) compared to the values found by BP-SPECT (Figure 3). When considering RVEDV, no significant difference was found between QBS, QUBE and BP-SPECT, whereas for RVESV, only significant higher values were found for QUBE, compared to QBS and BP-SPECT, and not between values of QBS and BP-SPECT.

For RVEF, significant differences were found between QBS and BP-SPECT and between QUBE and BP-SPECT and a poor correlation was found, 0.38 and 0.33 respectively (Figure 4).

Since the stroke volume (SV) is equal in LV and RV, proportion of stroke volumes (stroke volume index, SVI) has to be ideally 1. Histogram and Box and whisker

diagrams with the distribution of the SVI for the different techniques are shown in Figure 5. Mean SVI ± SD for BP-SPECT, QBS and QUBE were 1.01 ± 0.43, 0.99 ± 0.38 and 1.11 ± 0.51 respectively. Half of the patients show a difference between LVSV and RVSV more then 40% for BP-SPECT, 39% for QBS and 54% for QUBE.

Discussion

QBS is a very straightforward program but with only very limited possible manual intervention. After automatic processing, the visual interpretation of the delineation of the ventricles is not optimal in 22% of the patients, this is mostly the case in the lateral wall of the left ventricle and in the inferior wall of both ventricles. Another error seen was the inclusion of atrial structures in the LV or RV. Only in 17% of these cases, the manual option (defining LV in short axis, horizontal long axis and vertical long axis) resulted in a satisfactory result, mostly for the LV. Nevertheless, this program is easy to use and the result page is visually attractive, with display of bull's eye analysis of wall motion, similar to the well-known gated myocardial perfusion analysis software, QGS [6].
QUBE is more validated [3,7-9] and is nowadays distributed by Segami coporation. The reconstruction software is directly linked to the software itself, with the obvious advantage of easily making corrections in realignment of the short axis images, zooming, masking and condensing 16 time frames into 8. The manual options gave satisfactory results in nearly all the cases, for LV as well as for RV. Additional results are presented like 3D phase analysis and RV fraction shortening, but these items remain unvalidated.
4D-MSPECT is known for its analysis of gated myocardial perfusion [10], and it also includes a possibility to process TRV. At the moment of analysis, only the option of processing LV was available. The manual intervention is very fast and accurate in most of the cases, and the program is very flexible and open, which makes it possible to create own databases of normal patients and to export every parameter to a text-file to create an extensive and quantitative report. Wall motion is not only directly calculated in a predefined bull's eye (3, 5, 9, 13, 17, 19 or 20 segment polar map), but can be scored as well as normal, mild hypokinesis, moderate hypokinesis, severe hypokinesis, akinesis or dyskinesis by predefined cut-offs. Only, there is a subjective impression that wall motion in the apex is relatively underestimated, compared to visual analysis of the images. Most of the scans needed manual intervention (51%), but this was easily done by adjusting the valve plane in end-diastolic and end-systolic position. The way these programs define the valve plane is a critical point and influences volume calculations extensively. The method used to detect the valve plane is not described by the manufacturers and can be completely automatically in one program and not adjustable (e.g. QBS), and visually less accurate and easily adjustable in another program (e.g. 4D-MSPECT).

BP-SPECT is the only software with validation of LVV and RVV [1,5] which is absolutely necessary for this kind of software. During processing, RV results are first calculated and when these are accepted, LV delineation is done. Drawing ROI's in end-diastolic and end-systolic images for RV as well as LV, was successful in all clinical cases where the automatic program couldn't define the ventricular outline properly.

For the calculation of LVEF, all programs supply good results with correlation coefficients between 0.71 and 0.81. These values are lower than those mentioned in other publications about comparison of LVEF between PRV and TRV (Table 2.), although consistent with the finding that LVEF from TRV is higher compared to LVEF from PRV, probably because of atrial overlap with LV in PRV [11]. A larger correlation is mainly found in papers with smaller patient groups, which makes it less representative for a large group of clinical patients or is found with a relative manual or semi-automatic technique, like the programs NuSMUGA [12] and TMUGA [13]. Like NuSMUGA, drawing LV ROI's is all short axis slices in every time bin can derive accurate volume measurements when using an optimal cutoff, but you need an experienced user and it is clear that such a way of processing is very time-consuming and will not be popular in clinical practice. Moreover, there is to our knowledge no possibility to process the RV with NuSMUGA in contrast to TMUGA, with even a comparison of LV and RV cardiac output measurements from TRV compared with the thermodilution method [13]. The more the software is automatic (and reproducible), the more errors it produces and on the contrary, the more manual, the more time-consuming it is.

For LVV calculations, the difference between the program with smallest values (4D-MSPECT) and largest values (BP-SPECT) is almost double. The difference between 4D-MSPECT and BP-SPECT in volume calculation was also shown in a four-chamber cardiac phantom experiment (submitted) whereas BP-SPECT overestimated LVV in another biventricular cardiac phantom experiment [14].

The discussion about what technique gives the exact EF is inferior to the fact that TRV gives additional information, like each tomographic examination gives more information then a planar one. In this view it is also important to stress that, when describing a TRV, visual analysis of global and regional kinetic function of both ventricles should be included, even before delineation of ventricular volumes, without the influence of any (computerized) calculation. There were patients included in this study with a lower LVEF on PRV who showed a good contractility on TRV, and this is probably the cause of the "overestimation" of LVEF on TRV compared to PRV, but analysis of the gated reconstructed short axis slices showed a perfect contractility.

Limitations

Using PRV as gold standard for LVEF is acceptable but validation of TRV, a technique that can produce volumes and EF of both ventricles, is better done by MRI, but this was not available in our database of patients.
The relatively limited number of patients with impaired LV function (73% were cancer patients studies pre- and post chemotherapy) should also be stressed.

Conclusion

LVEF calculated from TRV with the four described methods correlate well with those from PRV and can be applied in clinical practice, although the values are not interchangeable with other techniques and even not within the same technique with other types of software.
Volume calculations from TRV, especially from the RV, need further validation, mainly with other techniques, such as MRI, before they can be applied in clinical practice

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Tables

Abbreviations in the tables

BP-SPECT: bloodpool SPECT
LVEDV: left ventricle end-diastolic volume
LVEF: left ventricle ejection fraction
LVESV: left ventricle end-systolic volume
M: manual method
PRV: planar radionuclide ventriculography
RVEDV: right ventricle end-diastolic volume
RVEF: right ventricle ejection fraction
RVESV: right ventricle end-systolic volume
SD: standard deviation
TRV: tomographic radionuclide ventriculography

Table 1

Mean ± SD for PRV and TRV for all programs with paired T-test results for TRV compared to PRV.

	PRV	TRV			
		QBS	QUBE	4D-MSPECT	BP-SPECT
LVEF	51.95±15.81	55.87±16.53*	62.87±17.40*	55.47±15.14*	54.86±16.01*
LVEDV		129.55±81.43**	114.92±72.95**	88.10±63.16**	141.53±77.66
LVESV		65.20±72.65	50.28±67.40**	44.12±55.74**	70.40±71.82
RVEF		51.35±11.87**	47.47±13.51**		55.57±12.71
RVEDV		133.96±40.92	141.81±55.39**		138.23±47.65
RVESV		66.06±28.86	76.33±41.09**		62.85±32.44

*: significant ($p<0.05$) difference compared to PRV
**: significant ($p<0.05$) difference compared to BP-SPECT

Table 2

Comparison of LVEF from PRV with TRV in literature

	year	N° pts	Software	Corr	Linear Regression y = TRV; x = PRV	Highest value	SEE	Ref.
Our results		166	QBS	0.81	y = 0.86x + 10.51	TRV	9.1	
			QUBE	0.79	y = 0.87x + 17.18	TRV	9.7	
			4D-MSPECT	0.71	y = 0.67x + 20.66	TRV	11.5	
			BP-SPECT	0.79	y = 0.80x + 13.46	TRV	9.8	
Nichols	**2004**	422	QBS	0.81	y = 0.98 x + 5	PRV	10	5
			BP-SPECT	0.83	y = 0.95 x + 7	TRV	9	
Slart	**2004**	22	NuSMUGA (M)	0.90		TRV		15
			NuSMUGA (A)	0.88		PRV		
Wright	**2003**	50	QBS	0.80		-		16
Ficaro	**2002**	56	4D-MSPECT	0.97	y = 1.06 x – 1.58	-	-	4
Daou	**2001**	29	QBS	0.99	y = 0.92 x	TRV	6.8	17
			TMUGA	0.98	y = 0.82 x	TRV	8.1	
			M	0.98	y = 0.84 x	TRV	8.4	
Groch	**2001**	178	NuSMUGA	0.92	y = 1.04 x + 6.1	TRV	5.4	18
Vanhove	**2001**	53	QUBE	0.78	y = 0.94 x + 6.33	TRV (EF> 50%)	8.8	3
Vanhove	**2001**	92	QUBE	0.82	y = 1.04 x – 4.75	TRV	8.8	8
			QBS	0.80	y = 0.98 x + 4.42	PRV	9.4	
Daou	**2004**	29	QBS	0.62		TRV		19
Van Kriekinge	**1999**	89	QBS	0.89	y = 1.01x + 2.00	TRV		2
Chin	**1997**	18	M	0.96		TRV	6.7	20
Bartlett	**1996**	23	Reprojection image	0.89	y = 1.4 x - 8	TRV	8	11
Mariano-Goulart	**1998**	30	TMUGA	0.93	y = 0.99 x + 4.17	TRV	5.9	13

Figures

Figure Legends

1. Figure 1
   - **a.** Title: Linear regression and Bland-Altman analysis of left ventricular ejection fraction calculation of the four methods (QBS, QUBE, 4DM and BP-SPECT), compared with LVEF from PRV.
   - **b.** First row: Results for QBS
     Second row: Results for QUBE
     Third row: Results for 4D-MSPECT
     Fourth row: Results for BP-SPECT

2. Figure 2.
   - **a.** Title: Linear regression and Bland-Altman analysis of left ventricular volumes (EDV and ESV) calculation of three methods (QBS, QUBE and 4DM), compared with left ventricular volumes from TRV (BP-SPECT)
   - **b.** First row: Results for QBS
     Second row: Results for QUBE
     Third row: Results for 4D-MSPECT

3. Figure 3.
   - **a.** Title: Linear regression and Bland-Altman analysis of right ventricular volumes (EDV and ESV) calculation of two methods (QBS and QUBE), compared with right ventricular volumes from TRV (BP-SPECT).
   - **b.** First row: Results for QBS
     Second row: Results for QUBE

4. Figure 4
   - **a.** Title: Linear regression and Bland-Altman analysis of right ventricular ejection fraction (RVEF) calculation of two methods (QBS and QUBE), compared with RVEF from TRV (BP-SPECT).
   - **b.** First row: Results for QBS
     Second row: Results for QUBE

5. Figure 5.
   - **a.** Title: Histogram and Box and Whisker diagrams showing the distribution of the stroke volume index calculated by the three software's. (Numbers above the Box and whisker diagrams being the lower whisker, lower hinge, median, upper hinge and upper whisker respectively)
   - **b.** First row: Results for BP-SPECT
     Second row: Results for QBS
     Third row: Results for QUBE

Figure 1

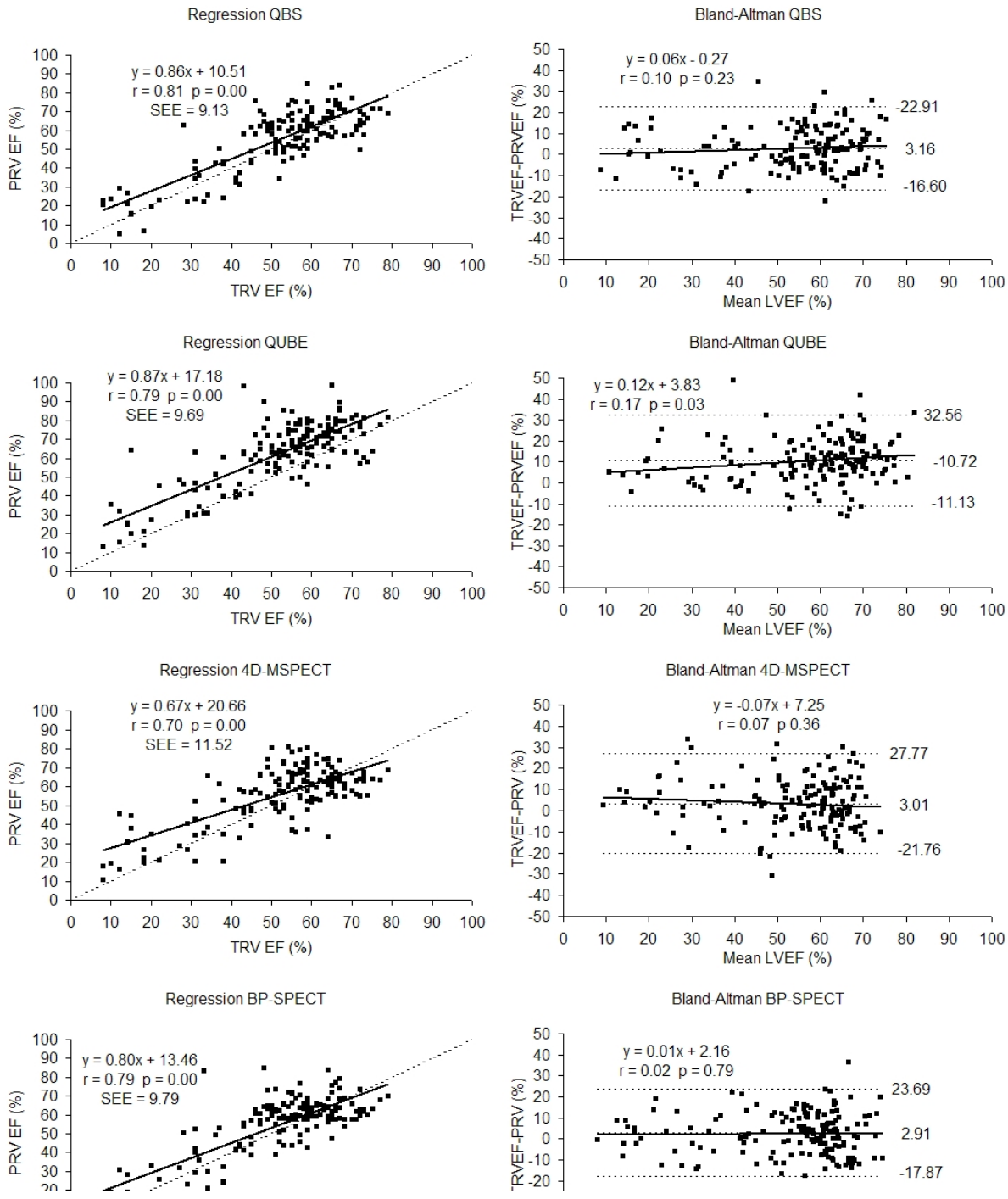

Regression QBS
y = 0.86x + 10.51
r = 0.81 p = 0.00
SEE = 9.13
PRV EF (%)
TRV EF (%)
Bland-Altman QBS
y = 0.06x - 0.27
r = 0.10 p = 0.23
-22.91
3.16
-16.60
TRVEF-PRVEF (%)
Mean LVEF (%)
Regression QUBE
y = 0.87x + 17.18
r = 0.79 p = 0.00
SEE = 9.69
PRV EF (%)
TRV EF (%)
Bland-Altman QUBE
y = 0.12x + 3.83
r = 0.17 p = 0.03
32.56
-10.72
-11.13
TRVEF-PRVEF (%)
Mean LVEF (%)
Regression 4D-MSPECT
y = 0.67x + 20.66
r = 0.70 p = 0.00
SEE = 11.52
PRV EF (%)
TRV EF (%)
Bland-Altman 4D-MSPECT
y = -0.07x + 7.25
r = 0.07 p 0.36
27.77
3.01
-21.76
TRVEF-PRV (%)
Mean LVEF (%)
Regression BP-SPECT
y = 0.80x + 13.46
r = 0.79 p = 0.00
SEE = 9.79
PRV EF (%)
Bland-Altman BP-SPECT
y = 0.01x + 2.16
r = 0.02 p = 0.79
23.69
2.91
-17.87
TRVEF-PRV (%)

Figure 2

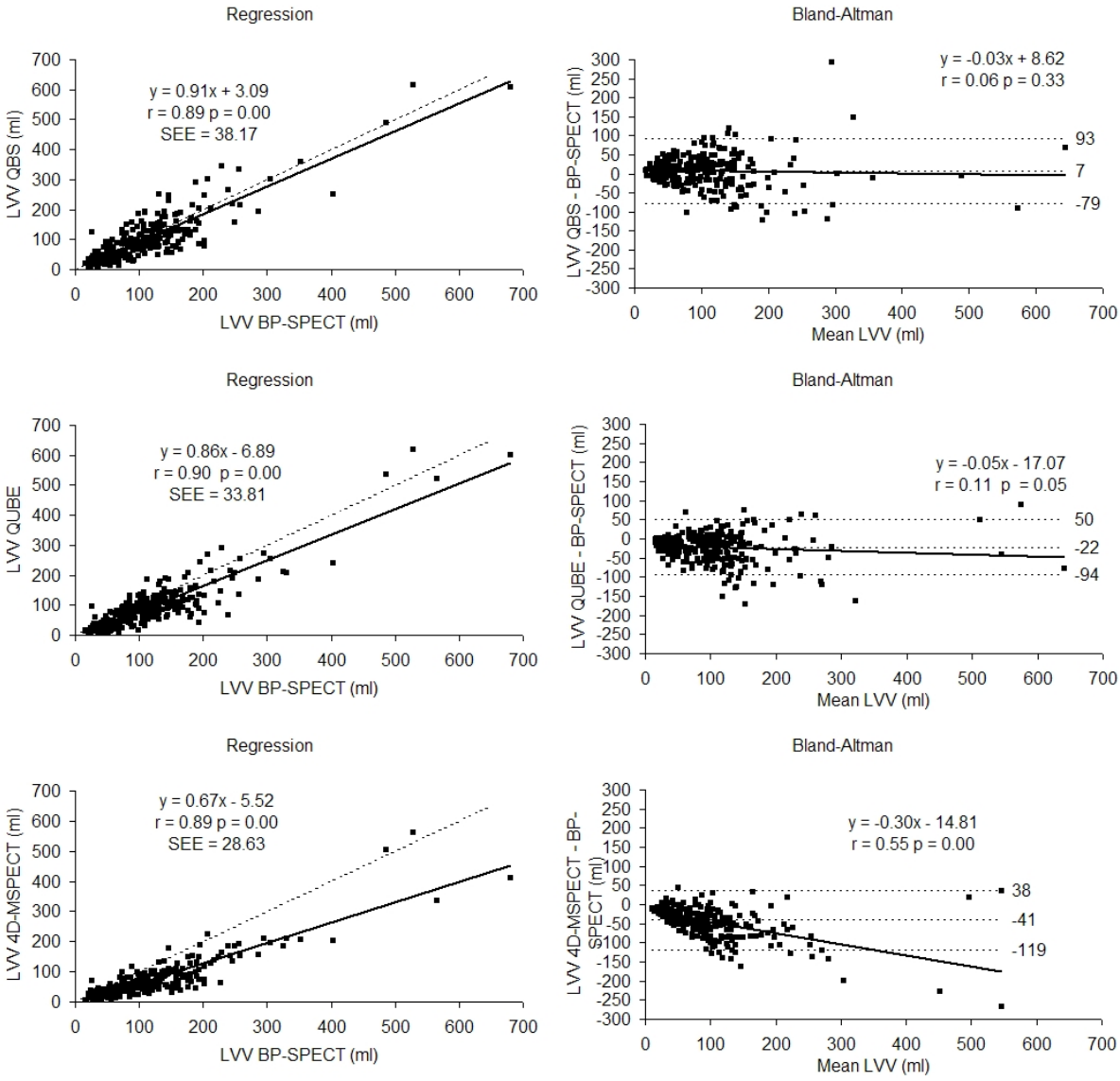

Regression
y = 0.91x + 3.09
r = 0.89 p = 0.00
SEE = 38.17
LVV QBS (ml)
LVV BP-SPECT (ml)
Bland-Altman
y = -0.03x + 8.62
r = 0.06 p = 0.33
93
7
-79
LVV QBS - BP-SPECT (ml)
Mean LVV (ml)
Regression
y = 0.86x - 6.89
r = 0.90 p = 0.00
SEE = 33.81
LVV QUBE
LVV BP-SPECT (ml)
Bland-Altman
y = -0.05x - 17.07
r = 0.11 p = 0.05
50
-22
-94
LVV QUBE - BP-SPECT (ml)
Mean LVV (ml)
Regression
y = 0.67x - 5.52
r = 0.89 p = 0.00
SEE = 28.63
LVV 4D-MSPECT (ml)
LVV BP-SPECT (ml)
Bland-Altman
y = -0.30x - 14.81
r = 0.55 p = 0.00
38
-41
-119
LVV 4D-MSPECT - BP-SPECT (ml)
Mean LVV (ml)

Figure 3

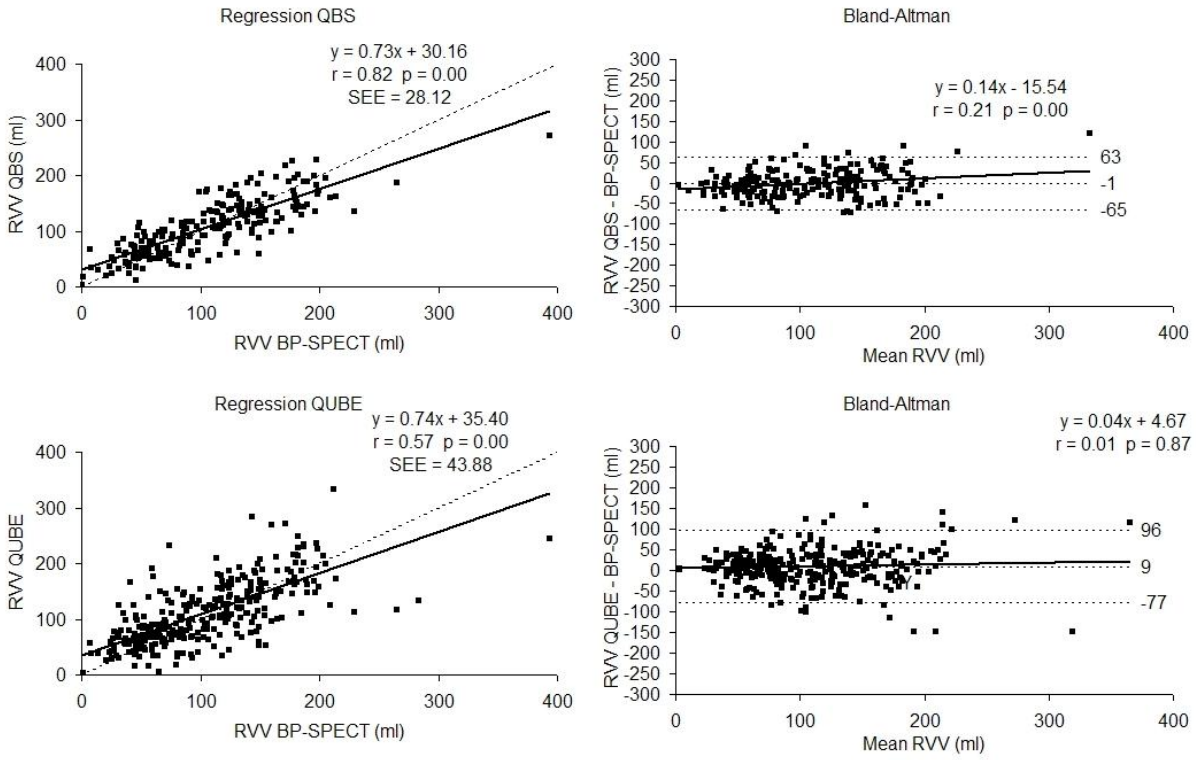

Regression QBS
y = 0.73x + 30.16
r = 0.82 p = 0.00
SEE = 28.12
RVV QBS (ml)
RVV BP-SPECT (ml)
Bland-Altman
y = 0.14x - 15.54
r = 0.21 p = 0.00
RVV QBS - BP-SPECT (ml)
63
-1
-65
Mean RVV (ml)
Regression QUBE
y = 0.74x + 35.40
r = 0.57 p = 0.00
SEE = 43.88
RVV QUBE
RVV BP-SPECT (ml)
Bland-Altman
y = 0.04x + 4.67
r = 0.01 p = 0.87
RVV QUBE - BP-SPECT (ml)
96
9
-77
Mean RVV (ml)

Figure 4

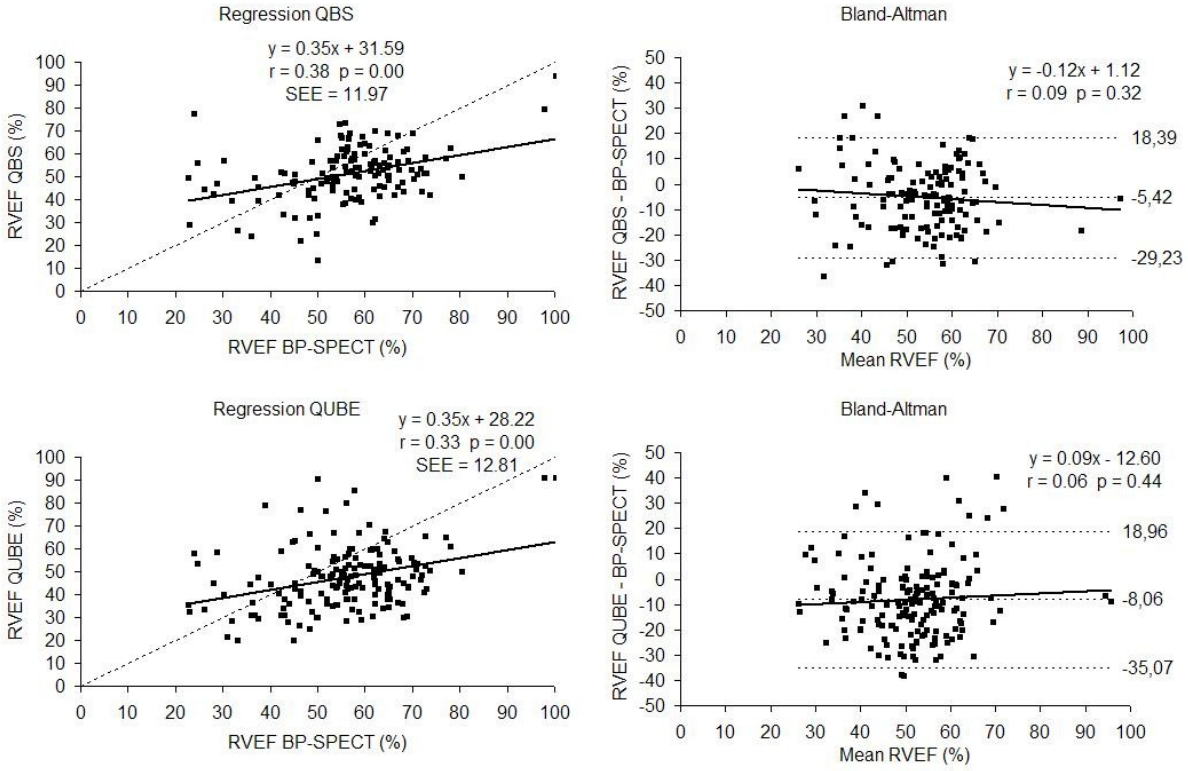
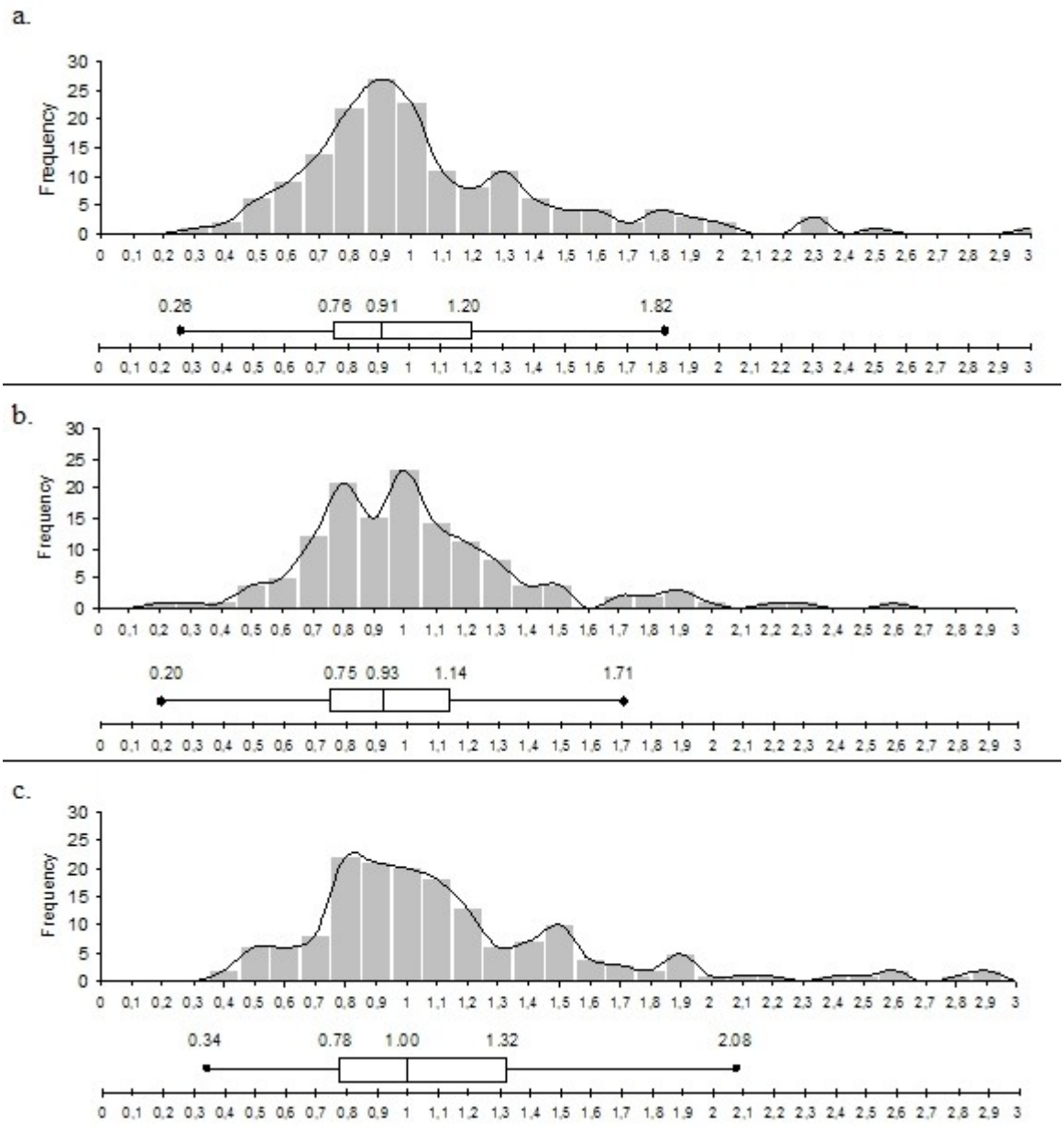

Regression QBS
y = 0.35x + 31.59
r = 0.38 p = 0.00
SEE = 11.97
RVEF QBS (%)
RVEF BP-SPECT (%)
Bland-Altman
y = -0.12x + 1.12
r = 0.09 p = 0.32
18,39
-5,42
-29,23
RVEF QBS - BP-SPECT (%)
Mean RVEF (%)
Regression QUBE
y = 0.35x + 28.22
r = 0.33 p = 0.00
SEE = 12.81
RVEF QUBE (%)
RVEF BP-SPECT (%)
Bland-Altman
y = 0.09x - 12.60
r = 0.06 p = 0.44
18,96
-8,06
-35,07
RVEF QUBE - BP-SPECT (%)
Mean RVEF (%)

Figure 5


a.
Frequency
0.26
0.76
0.91
1.20
1.82
b.
Frequency
0.20
0.75
0.93
1.14
1.71
c.
Frequency
0.34
0.78
1.00
1.32
2.08

Chapter 2

Human studies in patients with coronary artery disease and left ventricular dysfunction

2.1. Introduction
Clinical relevance of left ventricular volume assessment by gated myocardial SPET in patients with coronary artery disease: a review.

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Abstract

Coronary artery disease (CAD) is the leading cause of mortality in the Western world. Multiple parameters have been investigated to predict prognosis in CAD patients. The prognostic value of the assessment of LVEF in patients with CAD is well established. More recently left ventricular (LV) volumes also showed a prognostic value. The development of 99m-technetium (^{99m}Tc)-labelled myocardial perfusion tracers make it possible, due to the favourable imaging characteristics of ^{99m}Tc (high-count density) to perform an electrocardiogram gated acquisition during routine myocardial perfusion imaging. This enables us to assess LVEF and LV volumes during a myocardial perfusion scintigraphy. This review aims to overview the possible prognostic abilities of LV volume assessment by gated cardiac SPET.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in the Western world. Multiple prognostic parameters including left ventricular ejection fraction (LVEF) and left ventricular (LV) cardiac volumes have been introduced for management and follow-up of patients with CAD. During the past decades radionuclide myocardial perfusion imaging using ^{201}thallium (^{201}Tl), first with planar and later with single photon emission tomography (SPET) images, has proven to be of high diagnostic and prognostic utility in predicting future cardiac events [1,2]. Since the late eighties ^{99m}Tc-labelled perfusion tracers were developed and showed to be as valuable as ^{201}Tl for perfusion imaging [3,4]. The favourable imaging characteristics (high count density) of ^{99m}Tc make it possible to perform an electrocardiogram-gated (ECG-gated) cardiac SPET during the acquisition of myocardial perfusion [5], which does not only improve the specificity for the detection of CAD [6], but also enables to assess LV functional parameters including LVEF and LV volumes [7,8]. This review aims to overview clinical relevant technical issues and the potential clinical and prognostic role of cardiac volume assessment with gated SPET in patients with CAD.

Evaluation of cardiac volumes: Overview of different techniques and technical issues

A large and growing variety of methods is available to assess global LV function and volumes, including echocardiography, radionuclide techniques (radionuclide angiography (RNA) and myocardial gated SPET), magnetic resonance imaging (MRI) and cardiac angiography. Each of these techniques is characterised by a variety of strengths and pitfalls. The ideal technique for imaging global LV function should not only offer highly accurate and reproducible measurements of both LVEF and LV volumes but also be time and cost efficient, non-invasive and widely available. Currently global LV function is, due to clinical circumstances, most commonly investigated by transthoracic echocardiography, which is widely available, readily accessible and inexpensive. M-mode echocardiography and 2-dimensional (2D) echocardiography, like all not truly 3-dimensional (3D) techniques, assume an ideal ellipsoidal geometry of the heart chambers to estimate cardiac volumes. After myocardial infarction though, LV shape may be altered radically both due to infarct extension and the following remodelling process [9], which makes it impossible to make a good estimation of cardiac volumes and LVEF when assuming an ideal ellipsoid heart shape. Transthoracic echocardiography is also limited by the need to obtain adequate acoustic windows, the fact that the measurements are operator dependent, sensitive to subjective analysis and have a poor reproducibility. This poor reproducibility, operator dependency and assumption of a normal ellipsoid heart shape make echocardiography less attractive as follow-up tool of the remodelling heart. Truly 3D techniques, like 3D echocardiography and 3D MRI but also gated SPET, do not require assumptions of a normal heart shape for accurate estimation of LV volumes. All these tomographic methods have shown to be highly accurate and highly reproducible for the measurement of LV volumes and LVEF. For example Chuang et al. compared 2D and 3D (volumetric) measurements, both with echocardiography and MRI in 35 persons, 10 healthy volunteers and 25 patients with a dilated cardiomyopathy [10]. The 3D techniques yielded very reproducible values and correlation between LV volumes and LVEF obtained by 3D echocardiography and 3D MRI was very high with narrow limits of agreement on Bland-Altman plot (2 standard deviations (SD) = mean ± 5% for LVEF) [11]. In contrast, agreement between LVEF and volumes estimated by the 2D methods and those obtained by the 3D techniques was poor although the mean values were comparable. Agreement between both 2D techniques was very poor and so was reproducibility. However because 3D MRI and 3D echocardiography require multiple cross-sectional views of the heart, they are very time consuming. Thus even for these techniques biplane methods, requiring only two views and minimal data acquisition and analysis times, remain the method of choice in daily practice. On the other hand, calculation of volumes by gated SPET is fully automated and easy to perform in daily clinical practice. Multiple automated methods have been developed to obtain functional information

out of a gated acquisition [5,7,8]. The most widespread method, Quantitative Gated Spect (QGS) is developed at Cedars Sinai, Los Angeles [5]. In this software package, different LV volumes during the cardiac cycle are measured by detecting the endocardium and valve planes in three dimensions, based on asymmetric Gaussian fitting of count profiles across the myocardium and identification of endo- and epicardial surfaces. This provides series of contiguous short axis slices. Cardiac volumes, most importantly LVESV and LVEDV, are measured by summing the area of the cavity in these slices following Simpson rule approximations. In this method, volumes are calculated by summing LV surfaces of contiguous tomographic slices. Simpson rules approximations may be applied to data from any tomographic method for calculation of cardiac volumes and is used for volume estimation by all 3D techniques. Stroke volume (SV = LVEDV minus LVESV) and LVEF (LVEF = SV/ LVEDV) are calculated. This makes ^{99m}Tc gated SPET an operator independent methodology with a very high reproducibility (the algorithm applied twice to the same dataset) [12,13] and repeatability [14-16]. Other advantages of gated SPET include the fact that function and quantitative perfusion are simultaneously acquired and displayed in the same image preventing misregistration errors, that acquisition is intrinsically tomographic and encompasses the entire ventricle in three-dimensional fashion and that acquired data are inherently digital, lending itself to quantitative analysis [17].

Validation of global functional measurements by gated myocardial SPET versus other imaging techniques

Multiple studies have been performed to validate measurements of LV function as estimated by gated cardiac SPET against other methods [5,7,8, 18-26]. LVEF estimated by automated gated cardiac SPET has a very good agreement with other techniques. There is a good to excellent correlation in different comparatory patient studies with RNA, both equilibrium and first-pass, with r correlation values between 0.82 and 0.94 [5,7,8,20,22,23]. Even in patients with large perfusion defects there is a very good correlation (r = 0.94) between LVEF measured by RNA and gated SPET [24]. This is explained because there is usually a minimal tracer uptake even in infarcted regions, which makes it possible to detect the endocardium accurately. In contrast with these excellent correlations Vallejo et al. found only a fair correlation (r = 0.61) for LVEF between gated SPET (using QGS [5]) and first-pass RNA in 400 patients [25]. The fair correlation found by this group can be explained by the fact that cardiac studies were performed using both high dose (925-1110MBq) and low dose (444-555 MBq) injections. Correlation between RNA and gated SPET was considerably better in studies with high dose injection versus those with low dose (r = 0.81 vs 0.61). Also, automated border detection failed in 9% of the studies due to high extra cardiac activity, leading to totally false border detection and volume measurements. When they excluded studies where automatic border detection failed, overall correlation was better (r = 0.74).

Furthermore when comparing the means of LVEF estimated by gated SPET (using 8 intervals) and RNA (using 16 intervals) they found that gated SPET underestimated LVEF by 4%. This underestimation was already shown by Germano et al. who showed that LVEF assessed by gated SPET using 8 instead of 16 intervals underestimates LVEF by approximately 4% because of a smoothing of the time volume curve [5]. This underestimation is quite uniform over a wide range of values (LVEF range: 10-80%) and can be taken into account when interpreting LVEF values [5]. Vallejo et al. also found that LVEF obtained by gated SPET overestimates LVEF at high values compared with RNA [25]. This overestimation with gated SPET is found in small hearts and is caused by the relative limited spatial resolution of SPET, which makes endocardial border definition at end-systole difficult in small hearts [27]. This leads in small hearts to an underestimation of the LVESV and thus to an overestimation of the LVEF. On the other hand correlation of LVEF determined by gated SPET and RNA tends to be higher for patients with a low LVEF [24] and in this population assessment of LV functional parameters gives the most significant prognostic information. Border detection and estimation of endocardial surface can also be affected by the amount of background activity, the injected dose and the presence of a perfusion defect [18,28].

Bavelaar-Croon et al. compared LV parameters over a wide range of values (LVEF range: 10-80%) in 21 patients with gated SPET (16 intervals) and 3D-MRI, which is considered the reference standard for assessing global LV function due to its high resolution combined with a 3D technique [26]. Correlation between gated SPET and 3D MRI was good for LVEF (r = 0.85), LVESV (r = 0.95) and LVEDV (r = 0.94). Bland-Altman plotting [11] did not reveal a significant over- or underestimation of LVEF. There was a slight underestimation of volumes obtained by gated SPET in comparison with MRI, which is explained by the fact that calculation of LV volumes in cardiac MRI includes the outflow tract while this is never part of LV volumes acquired by gated SPET. Because both the LV volumes, LVESV and LVEDV, are slightly underestimated by gated SPET this does not affect LVEF significantly. Other comparatory studies yielded also good correlations between gated SPET and MRI for the assessment LVEF (r = 0.82-0.93), LVESV (r = 0.87-0.99) and LVEDV (r = 0. 81-0.97) [8,29-34]. It must be mentioned that although there are many studies investigating correlation coefficients between measurements by gated SPET and other techniques, few studies used Bland-Altman plotting. A significant correlation will always be found between two similar methods on repeated measurements in the same objects. Bland-Altman plotting is necessary to investigate if the difference between measurements by two methods is small and to detect significant over- or underestimation of one technique opposed to another [11].

Are ^{201}Tl and ^{99m}Tc ligands equivalent for volume assessment by myocardial gated SPET?

^{99m}Tc ligands are ideal for gated acquisition during myocardial perfusion imaging due to their high count rate and image quality. Recently Germano et al. reported the feasibility of a gated acquisition during myocardial perfusion SPET [35]. Few studies though investigated the accuracy of LVEF and LV volumes assessed by ^{201}Tl myocardial gated SPET and study data are conflicting. Tadamura et al. [34] found a good correlation between LVEF (r= 0.92), LVEDV (r= 0.85) and LVESV (r= 0.94) determined by ^{201}Tl gated SPET versus 3D cardiac MR. Bland-Altman analysis revealed no significant under- or overestimation. Cardiac studies by this group were performed with high dose ^{201}Tl (138 MBq) and a long acquisition time (16 minutes). There are however no validation studies for LVEF and LV volume measurements by low dose ^{201}Tl gated SPET and it is not clear if results by a high dose protocol can be extrapolated towards lower doses (maximum dose is 74 MBq in the UK) and a reduced count rate. Furthermore Lee et al. [36,37] found that repeatability of LVEF and LV volume measurements by ^{201}Tl gated SPET (111 MBq) is not as good as that assessed by ^{99m}Tc gated SPET. On the Bland-Altman plot 2 SD is much larger in LVEF and LV volume measurements assessed by ^{201}Tl versus ^{99m}Tc MIBI (925 MBq) measurements (table 1). This poorer repeatability makes that ^{201}Tl gated SPET is less suited for the follow-up of changes in LV volumes and LVEF over time and also that it is less suited for prognostic purposes.

Limits of normality

To be useful as a diagnostic and follow-up tool, global functional information estimated by gated cardiac SPET requires determination of normative data. Several institutes have proposed normal values for global LV functional measurements obtained by gated SPET at rest [38-41]. All these institutes performed gated SPET studies using 8 intervals. Patients were included if they had a low pre-test likelihood of CAD [38-40] or no signs of CAD during the stress test (normal exercise capacity, normal ECG, no chest pain) in combination with a normal scan (perfusion and wall motion) [41]. A summary is given of normative functional data found by different groups (Table 2). Data are expressed as mean ± SD. Limits for normality can be calculated by mean ± 2 SD (Table 3). Important differences are seen between sexes: women have a significantly higher mean resting LVEF and significantly lower LVESV and LVEDV [38-41]. LVEF and LVEDV are significantly related with body surface area (BSA), with a higher LVEDV and a lower LVEF when BSA increases [39]. There is no significant relationship observed between LVEF or cardiac volumes and age or heart rate [38,39].

There are also no significant differences in normal limits of LVEF and LV volumes obtained after injection of ^{201}Tl or ^{99m}Tc MIBI [41] or between measurements

acquired by different cameras (dual-headed Elscint CardiaL vs dual-headed ADAC CardioEpic vs triple-headed Picker Prism 3000 XP) [41]. Finally it has to be mentioned that gated SPET measurements of global LV function acquired post stress differ significantly from those acquired in resting condition (a higher LVEF and a smaller LVESV), so these data can not be used interchangeably [15, 38, 42].

Prognostic studies

One of the most powerful prognostic parameters in patients with CAD is LVEF. This measure is not a pure measure of intrinsic myocardial contractility since its value depends on and is affected by other parameters, such as heart rate and cardiac loading conditions. Despite this, LVEF has been found to be an extremely useful correlate of survival and thus a determinant of therapeutic decisions in a broad variety of cardiovascular disorders [43]. In particular both resting and exercise LVEF determined by radionuclide and other techniques is a major determinant of long-term survival in patients with known CAD. Since the development of RNA multiple studies have reported its important prognostic value as a non-invasive tool [44-47]. However during the last decade short and long-term survival rates after acute MI improved markedly with the introduction of new reperfusion strategies [48]. This made it necessary to re-evaluate the prognostic value of LVEF estimated by RNA. Recently Shaw et al. [49] reported on 863 consecutive patients with known CAD, of which 68% had a prior history of MI. All these patients underwent RNA, both at rest and during peak exercise, and cardiac catheterisation within 90 days. LVEF determined at rest and during peak exercise provided information highly predictive of cardiac death (both $p < 0.0001$). Patients with a resting LVEF ≤ 30% were stratified to exercise LVEF and had a hazard rate of 0.6 (for an exercise LVEF 31-50%) and 3 (for an exercise LVEF ≤ 30%) deaths annually per 100 ($p < 0.0001$). In 759 patients with a resting LVEF > 30%, there were 2, 6 and 19 deaths annually per 100 patients for an exercise LVEF > 50%, 31-50% and ≤ 30% respectively. When all non-invasive information was considered, both resting and exercise LVEF contained significant predictive information for cardiac death ($p < 0.0001$). In the prediction of cardiac death, rest and exercise RNA data also provided a significant incremental prognostic value above the anatomical information provided by cardiac catheterisation.

Shigeyama et al. [50] retrospectively investigated 419 consecutive patients after acute MI who underwent an exercise RNA before hospital discharge. Of these patients 306 (73%) received reperfusion therapy, being either trombolytic therapy (201 patients) or percutaneous transluminal coronary angioplasty (105 patients). After a mean follow-up of 4.6 years, 24.1% of the patients had cardiac events as determined by recurrent myocardial infarction, unstable angina, congestive heart failure and ventricular tachycardia. Death associated with cardiac events occurred in 4.3%. Both peak exercise LVEF ($p = 0.0140$) and peak work load ($p = 0.0018$)

during exercise RNA were significantly lower in the group with cardiac events than in the group without events. Regardless of the presence or absence of reperfusion therapy, a lower peak LVEF was associated with a decrease in event free survival rate. Resting LVEF was also lower in the group with cardiac events, but this difference was not statistically significant ($p = 0.2274$). These 2 recent studies indicate that even with current reperfusion strategies resting and peak stress LVEF can be used to predict future cardiac events in patients with CAD. LVEF is by definition calculated out of the measured LVEDV and LVESV (conf. supra). Therefore is it possible that 2 patients with a comparable LVEF have totally different cardiac volumes. Figure 1 shows the cumulative distribution of LVEDV at rest in 343 patients with CAD and LVEF $\leq 40\%$ (data from our Ghent gated SPECT database). It can be noticed that a wide range of volumes can be found in patients with a reduced LVEF. Even in patients with the same LVEF this wide range of volumes still exists. This is illustrated in figure 2 where LVEDV and LVESV of 22 patients with CAD and a calculated LVEF equal to 35 % are shown. For example we show end diastolic short axis slices (figure 3) and summed perfusion bull 's eye images (figure 4) of 3 patients with a reduced LVEF of 29 % due to ischemic heart disease. Although LVEF is equal in these 3 patients, they have totally different cardiac volumes, a different infarct extension and probably different prognostic prospectives. The first patient has a small infarcted area and mildly dilated volumes; the second patient has a moderate infarcted area with larger cardiac volumes. Patient 3 has much larger cardiac volumes, a large infarcted area and has inducible ventricular arrhythmias wherefore an implantable cardioverter defibrillator was indicated.

Many studies have demonstrated the important prognostic value of dilated heart chambers, both for predicting cardiac events and cardiac death [51-67]. In 1987 White et al. investigated the prognostic value of LVEF and cardiac volumes in 605 male patients after first or recurrent MI [51]. LVEF and cardiac volumes in this study were obtained during catheterisation (X-ray left ventriculography). Patients were followed for a mean period of 78 months (range 15-165 months) during which there were 101 cardiac deaths of which 70 % were sudden. Patients who suffered from morbid events had larger LVEDV and LVESV than those who did not. By multivariate analysis, LVESV ($\chi^2 = 82.9$) had a greater predictive value for survival than LVEDV ($\chi^2 = 59.0$) or LVEF ($\chi^2 = 46.6$). Moreover, once the relationship between survival and LVESV had been fitted, there was no significant additional value neither for LVEDV or LVEF. Similarly, Hamer et al. investigated a population of 193 patients after coronary artery bypass grafting (CABG) and followed them for a mean period of 133 months with a comparable result [52]. It has to be mentioned that the invasiveness of the procedure and the need of assumption of an ideal ellipsoidal geometry of heart chambers to estimate cardiac volumes by left ventriculography during catheterisation, makes this technique less suitable for follow-up of patients after cardiac events.

Although many studies investigated the prognostic value of different functional echocardiographic measurements in patients with CAD [53-56,58-60, 63,64], and other echocardiographic studies investigated the evolution of LV volumes in CAD (with or without medical treatment) [68-70], very few investigated the prognostic meaning of augmented LVESV and LVEDV. Romano et al. [65] investigated LV volumes and LVEF by 2D echocardiography in 192 patients (143 males) after a first non-Q wave infarction and followed them for short-term outcome (events during the in-hospital period). 35 patients had hard events (death, reinfarction, recurrent angina or severe heart failure). Indicators for poor short-term prognosis were higher age, worse wall motion and more frequent presentation with ST-depression, but also a significant lower LVEF ($p < 0.01$) and higher LVESV ($p < 0.01$). There was a trend towards higher LVEDV volumes in patients with a poor prognosis, but this was not statistically significant. It is however not clear if the assessment of global left ventricular function in this study had in incremental value above other parameters (age, ECG). A large multi-centre prognostic study was performed by Nicolosi et al. (GISSI-3 trial) [66]. They investigated the prognostic value of global LV functional measurements by predischarge 2D echocardiography in a large population (8606 patients). Six hundred of these patients (=7%) had hard events (263 deaths and 337 non-fatal late clinical congestive heart failures) during a 6 months follow-up period. Patients were classified in quartiles according to the LV volumes and LVEF. They found that patients with LVEDV or LVESV in the highest quartile and LVEF in the lowest quartile had a significant augmented risk for death and non-fatal late ($p < 0.01$).

Cardiac MRI is, due to its high resolution and intrinsic 3D tomographic acquisition considered the ideal imaging modality for measuring cardiac volumes and changes in cardiac volumes over time. However there are few studies investigating the prognostic value of these volumetric data. Wu et al. [67] investigated a small group of 44 patients with cardiac MRI early after AMI (10 ± 6 days). All but 2 received thrombolytics or direct angioplasty in the acute period. In the early period after MI, patients with a microvascular obstruction had comparable LVEF and cardiac volumes compared to those without obstruction. A second cardiac MRI study was performed 6 months after MI in a very small group of 17 patients, of whom 8 had microvascular obstruction in the early episode post infarction. In patients with microvascular obstruction there was a significant rise in LVEDV (% rise 89.0 ± 77.8 versus 9.8 ± 26.8%, $p < .02$) and LVESV (% rise 165 ± 199.6% versus 3.0 ± 19.8 %, $p < .04$) compared with patients without obstruction. For LVEF the difference was not statistically significant. Sandstede et al. investigated in a short follow-up study only 12 patients after MI both with a resting and stress MRI. Patients who had a lower LVESV and a higher LVEF on stress imaging compared to rest imaging had a greater improvement of global LV function after revascularisation than patients with a higher LVESV and a lower LVEF [71].

More recently Sharir et al. retrospectively investigated the prognostic value of post stress LVEF and volumes obtained by gated cardiac SPET in patients with known or suspected CAD [62]. A large population of 1680 patients underwent a rest ^{201}Tl/ stress ^{99m}Tc MIBI myocardial gated SPET and were followed-up for a duration of 569 $\pm$ 106 days. They found that functional measurements obtained by ^{99m}Tc MIBI gated cardiac SPET after stress had an incremental prognostic value over perfusion data. Most importantly LVEF and LVESV were strongly correlated with patient outcome. Patients with a LVEF > 45% had mortality rates < 1% / year regardless of the severity of perfusion abnormalities, whereas patients with a LVEF < 45% had high mortality rates (9.2%/year) even with only mild to moderate perfusion abnormalities. Similarly, a LVESV $\leq$ 70 ml was related to a low cardiac death rate (< 1.2%/y), whereas patients with a LVESV > 70 ml and only mild or moderate perfusion abnormalities had high death rates (8.2%/y), both regardless of the severity of perfusion abnormalities. Most importantly, in patients with a LVEF < 45%, a LVESV $\leq$ or > 70 ml distinguished between those at low and high risk for future cardiac events (cardiac death rate 1.7 %/y vs 7.9%/y). Patients with LVEF > 45% had low cardiac event rates. The grouping criteria of LVEF < 45% and LVESV > 70ml in this study were derived from ROC analysis afterwards. Multivariate analysis showed that in the prediction of total coronary events, perfusion variables and LVESV were independent and powerful predictors. For the prediction of cardiac death and cardiac death or MI, post stress LVEF and LVESV were independent predictors and had an incremental value above perfusion data.

Future prospects

Myocardial gated SPET is an accurate, operator independent and reproducible technique for the assessment of global LV function in patients with CAD. Multiple centres around the world perform ECG gating during acquisition of myocardial SPET in daily practice. These considerations make gated myocardial SPET a promising tool for the follow-up of changes in LV function and thus also for the assessment of prognostic information in patients with CAD. There is however still a lot of work to do. The retrospective analysis by Sharir et al. [62] is very promising but the prognostic value of LV functional parameters both at rest and after stress as assessed by gated SPET still has to be shown in large prospective studies. Also, prognostic abilities of global function assessed by gated SPET must be investigated in high-risk populations of patients with CAD, such as the elderly and patients with heart failure due to CAD. Furthermore it needs to be investigated whether patients with a significant decline of LVEF post stress in comparison to resting LVEF have a worse prognosis. Finally a formal analysis of cost effectiveness of incorporating gated SPET perfusion imaging routinely into imaging protocols has not yet been reported. However, because gated SPET software is fully automated and gating is already routinely acquired in order to improve specificity of perfusion imaging, the extra cost of gated SPET for assessing global LV function conjunction with standard perfusion imaging should be relative modest, in comparison with a separate assessment of ventricular function by other techniques.

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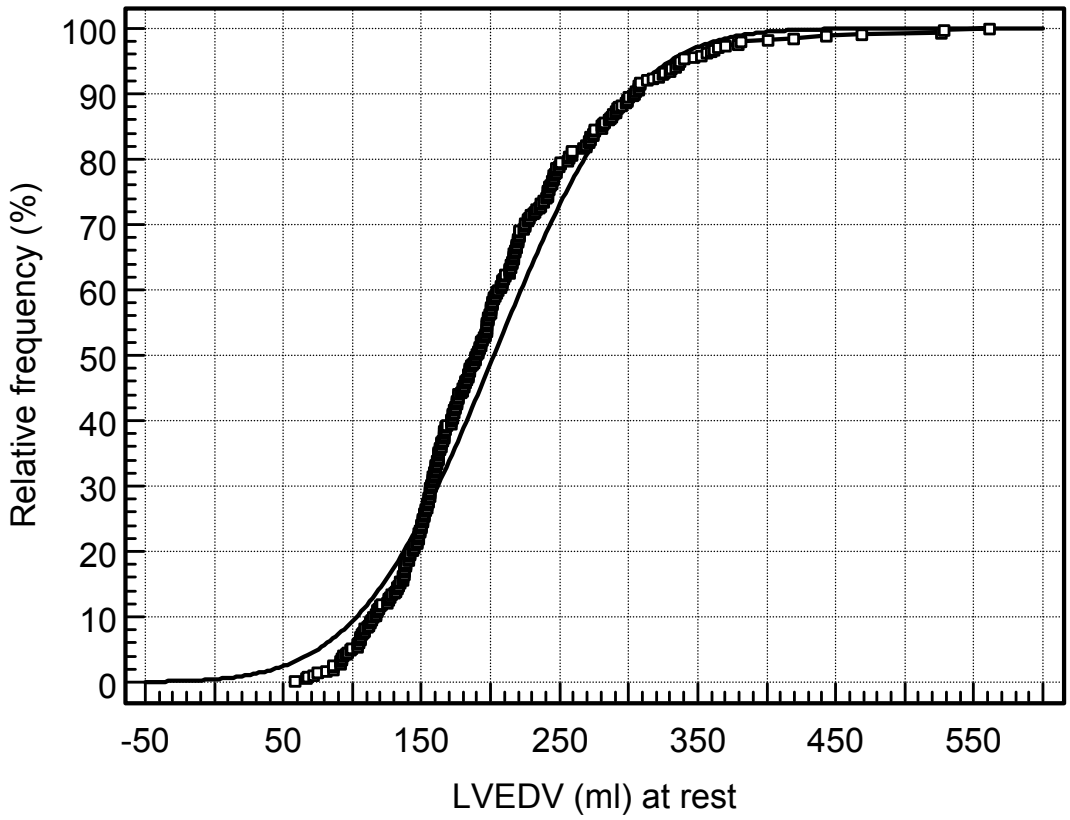
Figures

Figure 1

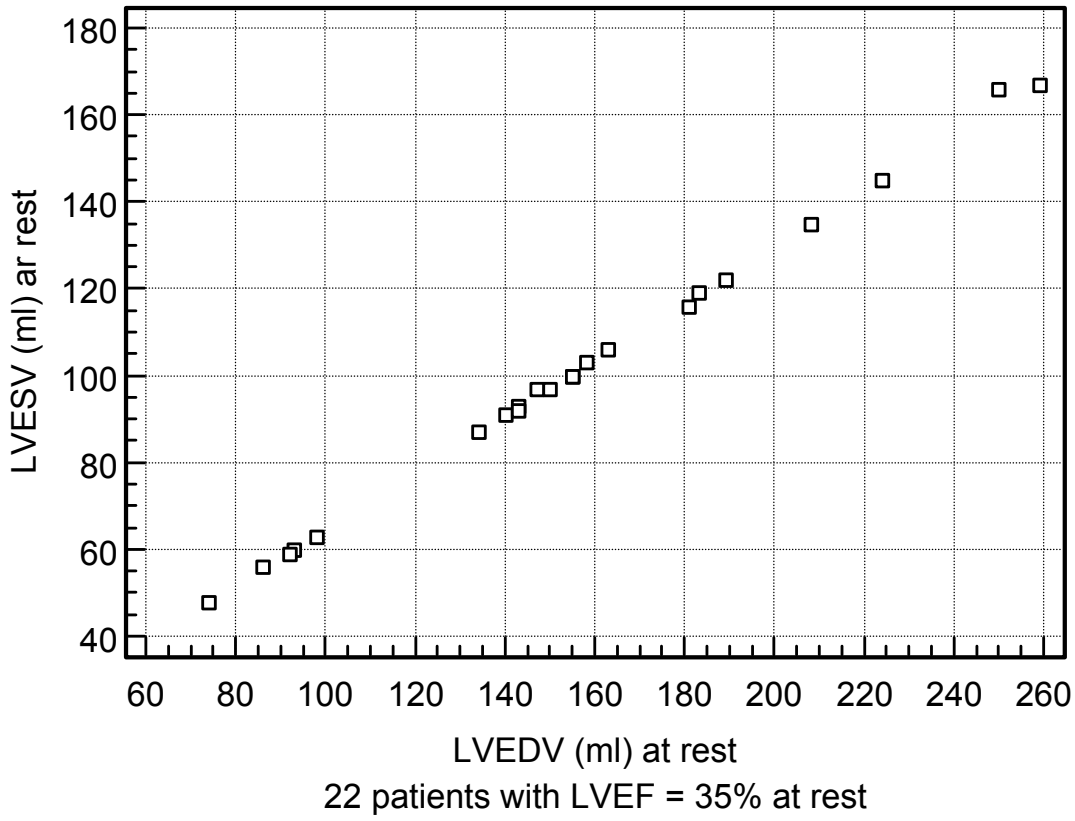
Cumulative distribution of LVEDV at rest in 343 patients with CAD and LVEF ≤ 40%.



Data from the Ghent gated SPECT Database:
2500 pts. (1850 males) with known or suspected CAD investigated by tetrofosmin gated SPECT

Figure 2

Distribution of LVEDV and LVESV in 22 patients with CAD and a calculated LVEF of 35%.



Data from the Ghent gated SPECT Database
2500 pts. (1850 males) with known or suspected CAD investigated by tetrofosmin gated SPECT

Figure 3

Short axis end diastolic images of 3 patients with a LVEF equal to 29% with totally different cardiac volumes.

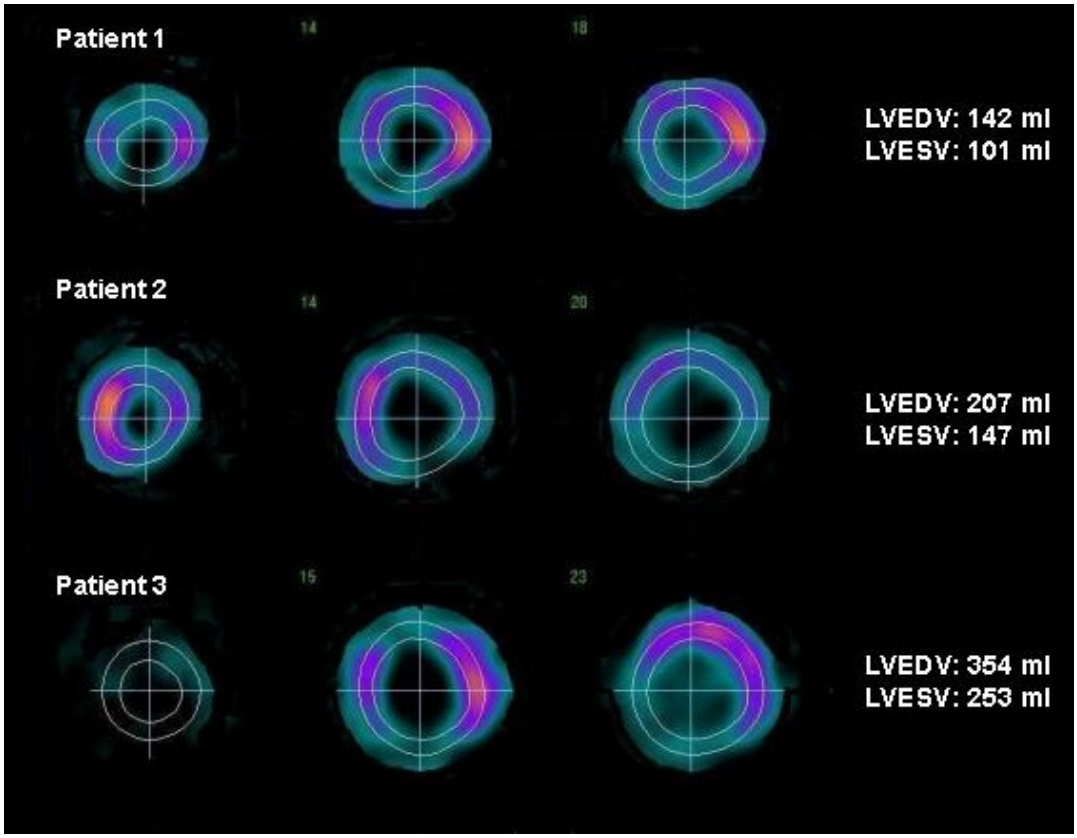
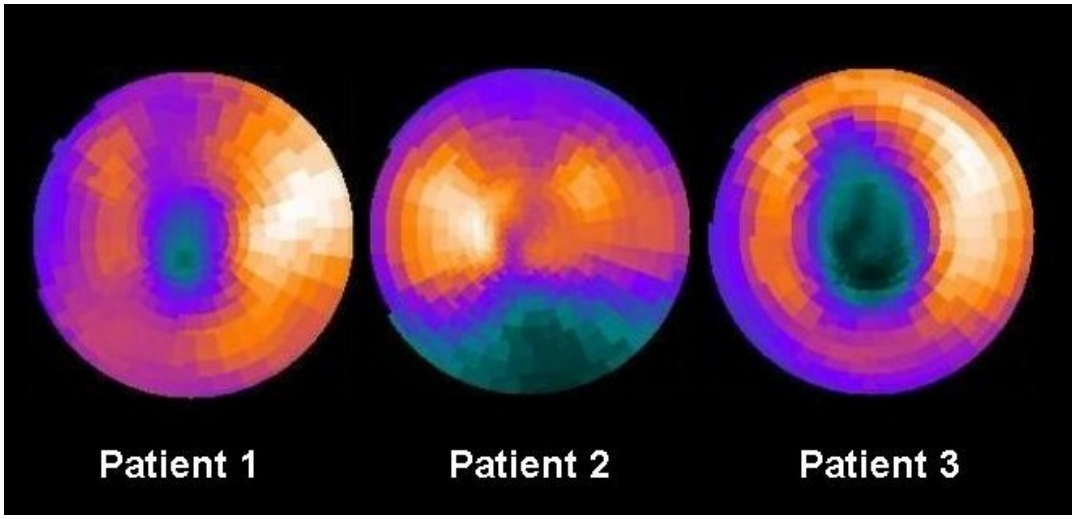


Figure 4

Summed perfusion bull's eye images of 3 patients with a LVEF equal to 29%.



2.2
Post stress left ventricular ejection fraction is an independent predictor of major cardiac events in patients with coronary artery disease and impaired left ventricular function

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Abstract

Aim: To investigate the prognostic value of myocardial perfusion and function SPECT imaging in patients with coronary artery disease (CAD) and poor left ventricular (LV) function.

Methods: We studied 261 patients (231 men, age 66±10 year) with CAD and a resting LV ejection fraction (LVEF) ≤40% assessed during myocardial gated SPECT. Perfusion defect extent was calculated using 4D-MSPECT® software (Michigan University). Ischemia scoring was performed visually. Considered end points were 1) major cardiac events (MACE: cardiac death, non-fatal myocardial infarction or late revascularisation), 2) MACE or the need for hospitalisation due to heart failure (MACE-HF) and 3) cardiac death or non-fatal myocardial infarction.

Results: During a median follow-up of 31 months, 52 patients (20%) died (35 cardiac deaths), 50 (19%) developed a MACE and 69 (26%) a MACE-HF. In a clinical model, diabetes and angina status were the only predictors of MACE (χ^2= 19.3; p<.001). By multivariate analysis, post stress LVEF (χ^2–gain of 6.4; p=.008) and presence of ischemia (χ^2–gain of 5.8; p=.018) were predictive of MACE. Similary, diabetes mellitus (χ^2= 12.1; p<.001), post stress LVEF (χ^2–gain of 5.5; p=.019) and presence of ischemia (χ^2–gain of 4.3; p=.044) were independent predictors of MACE-HF. Diabetes mellitus (χ^2= 17.8; p< .001), presence of angina complaints (χ^2–gain of 6.8; p=.028) and post stress LVEF (χ^2–gain of 6.3; p=.008) were independent predictors of cardiac death or non-fatal myocardial infarction.

Conclusions: In patients with impaired LV function and CAD, post stress LVEF is an independent predictor of future cardiac events.

Introduction

Coronary artery disease (CAD) is the most common cause of heart failure in the Western world, accounting for 60-70 % of the cases [1]. Incidence and prevalence of congestive heart failure due to CAD are increasing worldwide as a result of increasing life expectancy in general and the longer survival of patients with CAD in particular [2]. Although rates of death from most cardiovascular diseases are stable or declining, mortality data from heart failure are less clear [3]. Patients with CAD and impaired left ventricular (LV) function are at very high risk for cardiac death and future cardiac events [4].

Myocardial ischemia assessed by nuclear myocardial perfusion imaging is a well-known risk factor for future cardiac events in patients with known or suspected CAD [5-9]. It is less clear whether ischemia is of prognostic importance in patients with depressed LV function. Revascularisation procedures have shown to improve prognosis in patients with CAD and a depressed LV function [10], but some studies suggest no prognostic value for the presence of ischemia in patients with a poor systolic LV function [11]. The favourable imaging characteristics of 99m-Tc bound ligands make it possible to perform ECG gated cardiac Single Photon Emission Computed Tomography (SPECT) during the acquisition of myocardial perfusion [12], which not only improves the specificity for detection of CAD [13] but also permits the assessment of global LV functional parameters, including LV ejection fraction (LVEF) and LV volumes [14-15]. The predictive value of global LV functional parameters can be assessed using different imaging modalities and have shown predictive value in patients with known or suspected CAD [16-21]. The aim of this study was to investigate the predictive value of combined perfusion and function assessment during gated SPECT in patients with CAD and impaired LV function for prediction of future cardiac events.

Methods

Study population

All patients with ischemic heart disease and a resting LVEF ≤ 40 % determined by gated SPECT were prospectively evaluated (n=285) among 2168 consecutive patients referred for a 2 day stress-rest gated myocardial perfusion SPECT imaging in the period from October 1998 until December 2001. The diagnosis of ischemic heart disease was based on a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting or angiographic significant CAD (at least one vessel with ≥ 75 % stenosis). Follow-up was achieved in 273 patients (95 %). Twelve patients were excluded because they had an early revascularisation procedure within 3 months following the myocardial SPECT [8]. Therefore 261 patients (231 males) formed the study population.

Stress testing

Bicycle stress testing was used in patients able to perform maximal physical stress (n= 130, 50%). Each subject underwent maximal exercise testing on a computer-driven bicycle ergometer (Ergoselect, Ergoline GmbH, Bitz, Germany) using a ramp protocol starting at 50 Watts with gradual increase of 25 or 10 Watts according to the general condition of the patient. A standard 12-lead ECG was continuously recorded and the heart rate was followed. Blood pressure was measured by means of a mercury sphygmomanometer at each stage and at the peak of exercise. Subjects were exercised to their self-determined maximal capacity or until the physician stopped the test because of significant symptoms, such as chest pain or dizziness, potential dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension.
When a patient was not able to perform maximal bicycle stress (n= 27, 10%), an additional intravenous infusion of dipyridamole was given (infusion over a 4 minute period, 0.142 mg/kg/min).
In patients who were not able to perform bicycle stress at all (n= 104, 40%), only dipyridamole was given (infusion over a 4 minute period, 0.142 mg/kg/min).
Patients were informed not to consume caffeine-containing products for 24 hours before testing. At peak stress 900 MegaBecquerel Technetium-99m tetrofosmin was injected.

Gated SPECT acquisition and reconstruction

Stress and rest studies were performed in a 2-day protocol as described previously [22]. In both stress and rest studies, 900 MegaBecquerel (25 milliCurie) of technetium-99m tetrofosmin was injected intravenously. Imaging was started between 30-60 minutes after injection in the resting state and 15-30 minutes after injection at peak stress. A gated SPECT acquisition was performed over 360° in step-and-shoot mode (120 sectors of 3°, 30 seconds/ step, matrix size 64 x64) using a triple-headed camera (Picker Prism 3000, Marconi, Philips, Cleveland, Ohio) equipped with low energy all-purpose collimators. Acquisitions were gated for 8 frames per cardiac cycle. There was a 20 % acceptance window around the 140 keV photon peak. Attenuation correction, background subtraction and beat rejection were not performed. The raw gated SPECT data were ungated and reconstructed using filtered back projection (ramp filter) and post-filtered using a low pass filter (order 5, cut-off frequency .21). The left ventricle was reoriented manually to obtain short axis gated and ungated images. The gated images were processed using Quantified Gated SPECT software (QGS®, Cedars-Sinai, Los Angeles, CA, USA) to obtain resting and post stress LVEF and LV volumes.

Scoring of the perfusion images

The ungated short axis images were used for semi-quantitative determination of myocardial defect extent on stress and rest myocardial perfusion images using 4D-MSPECT® software (University of Michigan, Ann Arbor, Mi, USA) by comparison with a gender specific normal perfusion database generated at our institution. These stress and rest normal database files were made out of patients with a low cardiac risk (< 5 %) [23]. Ischemia scoring was made visually by comparing short axis, vertical and horizontal long axis on stress and rest images.

Clinical data and follow-up

Demographic data at study entrance were collected by reviewing hospital records. Hypertension was defined as a blood pressure ≥ 140 / 90 mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level > 140 mg/ dl or the need for insulin or oral antidiabetic agents. Follow-up data were collected in 2003. One author (ODW) contacted patients' general practitioners and reviewed hospital records. The author was blinded to scanning results at the time of follow-up. A standard questionnaire was used for follow-up interviews. The following cardiac events were taken into account: non-fatal acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, the need for hospitalisation because of heart failure, death and cause of death. Cardiac death was defined as death caused by acute myocardial infarction, refractory congestive heart failure, clinically important cardiac

arrhythmias and sudden death without another explanation. The need for cardiac transplantation (n = 2) was also considered as cardiac death. Myocardial infarction was defined according to the Joint European Society of Cardiology/ American College of Cardiology Committee criteria [24]. Patients who died from non-cardiac causes were censored on the day of their death. The time of the last patient contact was used to determine the end of the follow-up period in patients without events. Follow-up was limited to 36 months.
Three combined cardiac end points were defined in advance and used for further analysis:

1) MACE: cardiac death, non-fatal myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting.
2) MACE-HF: MACE or the need for hospitalisation due to heart failure.
3) Cardiac death or non-fatal myocardial infarction.

If a patient died from a cardiac cause, only cardiac death was considered. If there were 2 or more non-fatal events in one patient, only the event that came first in time was considered.

The study was approved by the local Ethics Committee of the Ghent University Hospital.

Statistical analysis

Statistical analyses were performed using SPSS 11.0.1 statistical software (SPSS Inc., Chicago, USA). Data are shown as median (25^{th} – 75^{th} percentile) or number (%). Non-parametric Mann-Whitney U testing or Chi-square testing was used to assess differences in clinical and SPECT variables between patients with and without events. Kruskal-Wallis testing was used to investigate trends in event rates between groups. Cumulative event free survival rates as a function over time were obtained by the Kaplan-Meier method. Differences in survival were analysed by log-rank testing. Clinical parameters significant by univariate analysis were forced into a stepwise multivariate Cox proportional hazards regression model to identify SPECT variables (functional parameters at rest and post stress, stress and rest defect extent and presence of reversibility) predicting cardiac events independently and incrementally above clinical parameters. Significance was set at $< .05$.

Results

Clinical characteristics of patients with and without events

Patients' characteristics are summarized in table 1. Median age was 67 years. Of the 261 patients 231 (89 %) were male. At the time of myocardial SPECT imaging 174 patients (67 %) had a history of myocardial infarction, 45 patients (17 %) a history of percutaneous coronary intervention and 58 patients (22 %) previously underwent coronary artery bypass grafting. At the start of the follow-up period, 133 patients (51 %) were taking beta-blockers and 188 (72 %) angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers as medical treatment (see further table 1).

Gated SPECT variables in patients with and without events

During a median follow-up of 31 months (interquartile range 21-36 months), 52 patients (20 %) died of which 35 deaths (13 % of the total population) were considered cardiac. This means that 67 % of the death causes in this population were cardiac. There were 50 patients (19 %) who developed a MACE and 69 (26 %) a MACE-HF. In the whole population, the annual event rate was 8.4 % for MACE and 12.1 % for MACE-HF. Patients who developed a MACE during follow-up were more likely to be diabetic and to have angina complaints (table 1). When considering MACE-HF, the presence of diabetes mellitus was the only significant clinical variable in the univariate analysis ($p = < .001$). Table 2 shows the results of the gated SPECT variables in all patients and in patients with and without MACE. Patients who developed a MACE during follow-up had a lower post stress LVEF and more frequent presence of ischemia on perfusion imaging. Patients with a MACE-HF similarly showed more presence of ischemia (45% versus 30%; $p= .022$) and a lower post stress LVEF ($p= .027$) when compared to patients without a MACE-HF. Cardiac event rates were significantly higher in patients with ischemia on perfusion imaging (table 3). Kaplan-Meier survival analysis and log-rank testing showed that patients had significantly more MACE (figure 1) ($p= .003$) and MACE-HF (figure 2) ($p= .028$) during the follow-up period when they had ischemic myocardium visualised on myocardial perfusion imaging. Similary, Kaplan-Meier curves showed a significant shorter event free survival time for MACE (figure 3) ($p= .020$) and MACE-HF (figure 4) ($p= .044$) when patients had a lower post stress LVEF.

Multivariate predictors of cardiac events

With diabetes and the angina status as the major clinical variables included into the stepwise multivariate Cox regression model for MACE, adding of post stress LVEF provided a Chi-square gain of 6.4 (p= 0.008). When the ischemia detection was added to this model, there was an additional Chi-square gain of 5.8 (p = 0.018) (figure 5).
In the clinical model of MACE-HF, only diabetes was significant and was forced in the multivariate analysis. Adding of post stress LVEF provided a Chi-square gain of 5.5 (p= .019) and ischemia detection on perfusion imaging an additive Chi-square gain of 4.3 (p= .044) in this model (figure 5).

Uni- and multivariate predictors of cardiac death or non-fatal myocardial infarction

Univariate predictors of cardiac death or non-fatal myocardial infarction were diabetes mellitus (p < .001), presence of angina complaints (p = .005), a higher NYHA classification (p = .026), a lower resting and post stress LVEF (p= .013 and .017 respectively). Diabetes mellitus (Chi-square = 17.8; p< .001) and presence of angina complaints (Chi-square gain of 6.8; p= .028) were independent clinical predictors in the Cox regression analysis. Adding of post stress LVEF to the model provided an additive Chi-square gain of 6.3 (p = .008). Considering this end point, there was no significant predictive value for ischemia detection (p= .112).

Discussion

The results of this study indicate that the combined assessment of function and perfusion using technetium-99m tetrofosmin gated SPECT provide significant and independent predictive information regarding the subsequent risk of major cardiac events in patients with CAD and systolic LV dysfunction.

Prognostic value of myocardial perfusion assessment

Multiple studies investigated the prognostic value of myocardial perfusion imaging in subjects with known or suspected CAD for predicting cardiac events and mortality [7,9,25-29]. However, these prognostic data were all collected in patient populations with known or suspected CAD and only few data are available regarding the prognostic value of myocardial perfusion imaging in patients with impaired LV function and known CAD. The risk for subsequent cardiac events is much higher in this population than in the generally investigated populations [30]. Therefore, results and risk factors found in other populations may not be extrapolated [31].
Data on the prognostic value of myocardial perfusion imaging in patients with CAD and LV dysfunction are scarce. In concordance with our data, Miller et al. found a higher revascularisation rate, but no difference in survival between patients with large ischemic defects versus patients with large fixed defects in 214 patients with a LVEF <45 % [32]. In 156 patients with CAD and a LVEF < 30 %, Sharir et al. also did not find a difference in mortality in patients with fixed versus reversible defects [11]. As expected, ischemia was frequently detected in our study population. Thirty-four percent had ischemia on myocardial perfusion imaging. Patients with ischemia were at increased risk for MACE and MACE-HF but not for cardiac death or non-fatal myocardial infarction.

Prognostic value of LV functional parameters

One of the most powerful prognostic parameters in patients with CAD is the LVEF. Multiple studies have demonstrated the important prognostic value of this parameter assessed using planar radionuclide angiography [19-21] or using other imaging modalities [16-18] in patients with known or suspected CAD. Our data demonstrated that even in this population in which all patients had a depressed LVEF and the spreading of LVEF values was narrow, post stress LVEF was highly predictive for future cardiac events.

Importance of combined perfusion and function assessment in patients with CAD and poor LV function using gated SPECT

The addition of LV ventricular functional data to myocardial perfusion imaging has shown benefit in diagnostic settings by increasing specificity and decreasing the number of borderline interpretations [13,33,34]. Another potential diagnostic use is in identifying patients with multivessel disease who might be otherwise missed by myocardial perfusion imaging [35].

There are however limited data on the prognostic value of LVEF as assessed by gated SPECT in patients with impaired LV function. As part of a larger study, Sharir et al. [36] investigated a subgroup of 277 patients with suspected CAD and a LVEF < 45% using gated SPECT and followed these during 19 ± 5 months. They concluded that it is possible to further risk stratify patients these patients upon a post stress LV end systolic volume with 70 ml as cut-off value. Although the size of our study group was comparable and our follow-up was even longer, we did not find an important predictive value for cardiac volumes in our study. Only 20 patients (7.8 %) in our population had a post stress LV end systolic volume < 70 ml and these patients had no significant lower mortality than those with a LV end systolic volume ≥ 70 ml. In our study group, there was a trend towards a higher resting (p= .084) and post stress (p= .0100) LV end systolic volume in patients with a subsequent hard event (cardiac death or non-fatal myocardial infarction). However, once the post stress LVEF was added to the model, there was no further predictive value for LV volumes.

Since myocardial perfusion imaging is used in daily clinical practice for diagnosis and follow-up of patients with CAD and LV dysfunction and ECG gating during the acquisition of myocardial SPECT can be easily performed in daily practice, gated SPECT could be an ideal tool for risk stratification in this patient population.

Study limitations

Because only 130 (50 %) of the 261 patients were able to perform maximal bicycle exercise stress, a possible incremental prognostic value of nuclear imaging variables above parameters obtained during bicycle stress (stress electrocardiography changes, maximum workload or blood pressure change) could not be assessed.

Conclusions

This study showed the significant incremental power of nuclear imaging data over clinical data in predicting cardiac events in patients with a depressed systolic LV function due to CAD. A lower post stress LVEF is an independent predictor of future cardiac events in patients with CAD and impaired systolic LV function.

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Tables

Abbreviations in the tables

ACE-I: Angiotensin-Converting Enzyme Inhibitors
AT-IIA: Angiotensin-II antagonists
BMI: body mass index
CABG: coronary artery bypass grafting
ECG: electrocardiogram
ICD: implantable cardioverter defibrillator
LVEDV: left ventricular end diastolic volume
LVEF: left ventricular ejection fraction
LVESV: left ventricular end systolic volume
MACE: major cardiac event
MACE-HF: major cardiac event or hospitalisation due to heart failure.
MI: myocardial infarction
n: number
NYHA: New York Heart Association classification
PCI: percutaneous coronary intervention

Table 1

Clinical characteristics of all patients and comparison between patients with and without MACE.

Variables	All patients (n = 261)	Patients without MACE (n = 211)	Patients with MACE (n = 50)	P value
Demographics				
Age (year)	67 (59-73)	67 (59-73)	70 (58-75)	.253
Gender (males)	231 (89%)	188 (89%)	43 (86%)	.537
BMI (kg/m^2)	26.2 (23.6-28.7)	26.0 (23.5-28.7)	26.6 (23.9-28.2)	.887
Functional status				
NYHA I-II	242 (93%)	198 (94%)	44 (88%)	.144
NYHA III-IV	19 (7%)	13 (6%)	6 (12%)	.144
Angina	29 (11%)	18 (9%)	11 (23%)	.005
Risk factors				
Hypertension	121 (46%)	98 (46%)	23 (46%)	.887
Diabetes mellitus	58 (22%)	38 (18%)	20 (40%)	.001
Serum cholesterol (mg/dl)	198 (173-230)	198 (173-227)	197 (175-252)	.409
Cardiac history				
History of MI	174 (67%)	142 (67%)	32 (64%)	.657
History of PCI	45 (17%)	37 (18%)	8 (16%)	.796
History of CABG	58 (22%)	51 (24%)	7 (14%)	.121
ECG				
Resting heart rate (beats /')	69 (60-78)	68 (60-77)	70 (60-79)	.586
Atrial fibrillation/ flutter	19 (7%)	15 (7%)	4 (8%)	.828
ICD implanted	63 (24%)	54 (26%)	9 (18%)	.253
Medication				
Aspirin	166 (64%)	133 (63%)	33 (66%)	.671
Aspirin or coumarin	200 (77%)	163 (77%)	37 (74%°	.620
B-blockers	133 (51%)	109 (52%)	24 (48%)	.645
ACE-I or AT-IIA	187 (72%)	152 (72%)	35 (70%)	.780
ACE-I or AT-IIA or B-blockers	215 (82%)	175 (83%)	40 (80%)	.744
Diuretics	85 (33%)	69 (33%)	16 (32%)	.931
Spironolactone	9 (3%)	6 (3%)	3 (6%)	.271
Digitalis	43 (16%)	33 (16%)	10 (20%)	.450
Amiodarone	23 (9%)	19 (9%)	4 (8%)	.840

Data are presented as median (25^{th}-75^{th} percentile) or number (%)

Table 2

Gated SPECT variables of all patients and comparison between patients with and without major cardiac events.

	All patients (n = 261)	**Patients without MACE (n =211)**	**Patients with MACE (n = 50)**	**P value**
Left ventricular function				
Resting LVEF (%)	29 (23-35)	30 (24-36)	27 (22-34)	.054
Resting LVEDV (ml)	191 (147-241)	188 (147-238)	199 (153-256)	.217
Resting LVESV (ml)	132 (98-179)	128 (97-174)	144 (101-202)	.123
Post stress LVEF (%)	31 (24-37)	31 (25-38)	27 (21-33)	.014
Post stress LVEDV (ml)	193 (152-243)	191 (151-239)	200 (163-251)	.258
Post stress LVESV (ml)	133 (94-177)	130 (94-176)	146 (109-193)	.098
Perfusion				
Defect extent stress (%)	38 (22-50)	36 (22-49)	39 (22-55)	.349
Defect extent rest (%)	30 (17-46)	30 (17-46)	29 (16-45)	.854
Presence of ischemia (%)	88 (34%)	62 (29%)	26 (52%)	.002

Data are presented as median (25^{th} – 75^{th} percentile) or number (%)

Table 3

Annual cardiac event rate according to the presence of ischemia on myocardial perfusion imaging.

	MACE	**MACE-HF**
No ischemia (n = 173)	6.0 %	9.8 %
Ischemia (n = 88)	13.5 %	16.7 %
Overall p	p = .003	p = .022

Annual cardiac event rate= number events/ person years

Figures

Abbreviations in the figures

LVEF: left ventricular ejection fraction
MACE: major cardiac event
MACE-HF: major cardiac event or hospitalisation for heart failure

Figure 1

Kaplan-Meier curves for MACE free survival according to the presence or absence of ischemia detected by myocardial perfusion imaging

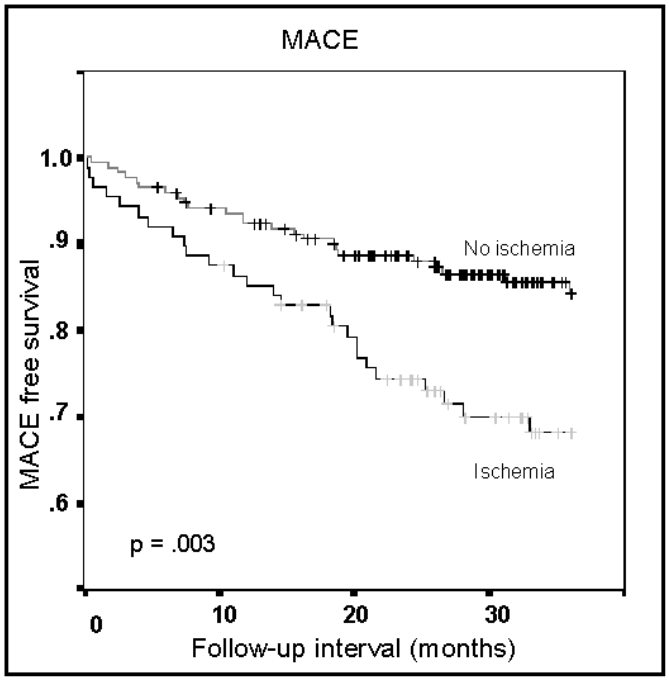


Figure 2

Kaplan-Meier curves for MACE-HF free survival according to the presence or absence of ischemia

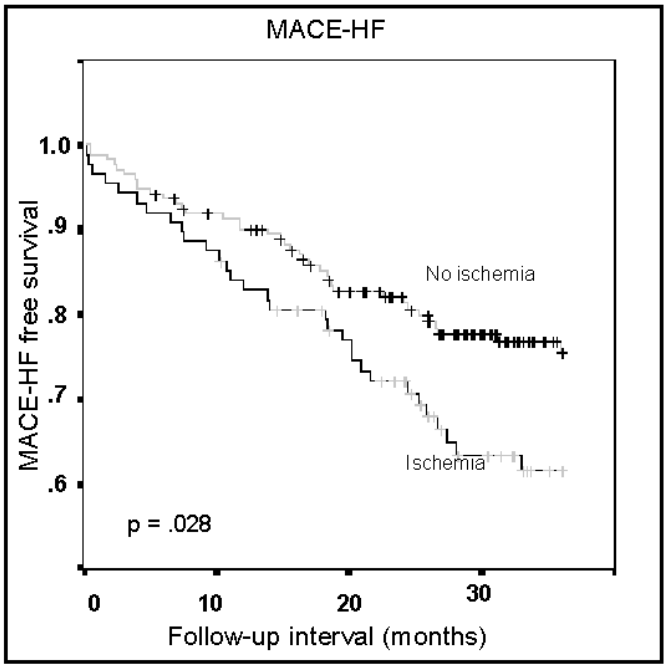


Figure 3

Kaplan-Meier curves for MACE free survival according to the post stress LVEF (in tertiles)

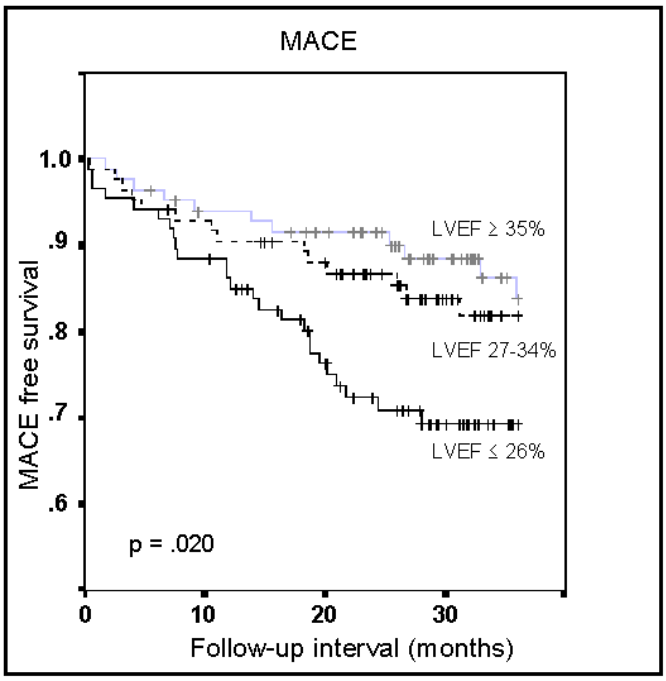


Figure 4

Kaplan-Meier curves for MACE-HF free survival according to the post stress LVEF (in tertiles)

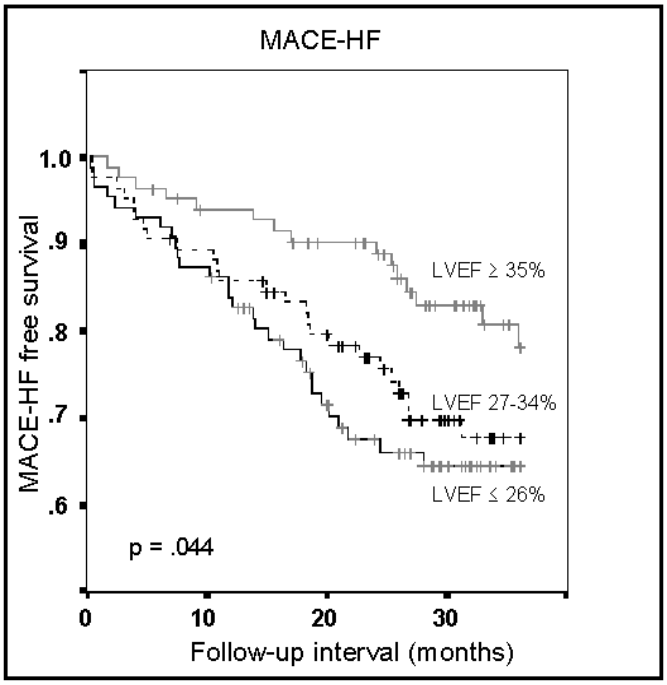
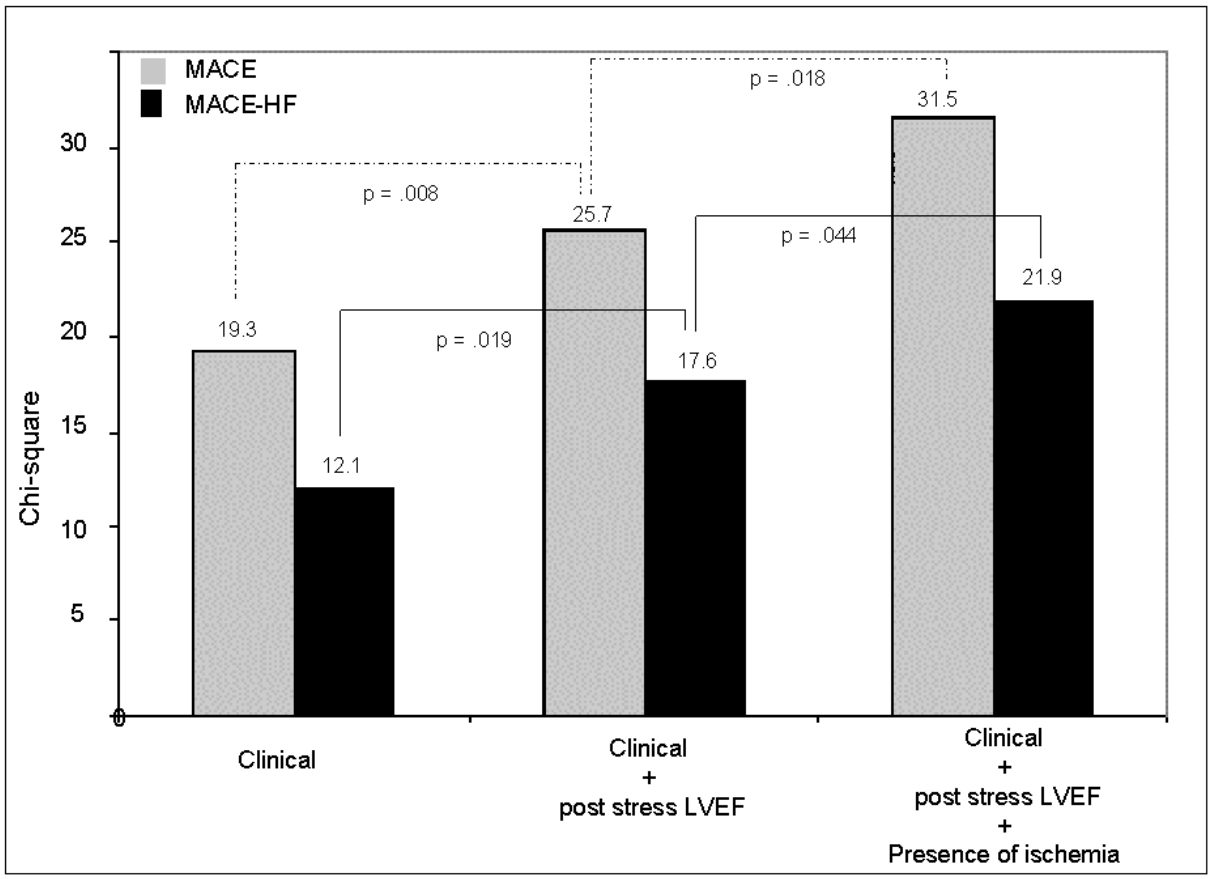


Figure 5

Chi-square found by stepwise multivariate analysis for the clinical model and when post stress LVEF and the amount of ischemic myocardium is added to the model.



2.3
Relationship between QRS duration, left ventricular volumes and prevalence of non-viability in patients with coronary artery disease and severe left ventricular dysfunction

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Abstract

Background: Patients with coronary artery disease (CAD), a QRS duration ≥120 ms and left ventricular ejection fraction (LVEF) ≤30% are potential candidates for cardiac resynchronisation therapy (CRT). Our aim was to investigate the relationship between QRS duration, left ventricular volumes and prevalence of nonviable tissue in this patient population.
Methods: We studied 132 patients (118 men, age 68±5 years) with CAD and LVEF ≤30% (mean LVEF 24±6 %). LV volumes and myocardial viability were determined by gated myocardial perfusion imaging.
Results: A QRS duration ≥ 120 ms was present in 91 patients (69%). Although there were no differences in LVEF, patients with longer QRS durations had significant larger end-diastolic and end-systolic volumes ($p<0.01$). Substantial non-viable tissue in the inferior or lateral wall was present in 29% of patients with a QRS duration ≥120 ms versus 7% of those with a QRS duration <120 ms ($p<0.01$).
Conclusions: An increased QRS duration is associated with more advanced remodeling in patients with CAD and poor LV function. Almost one third of these patients with a prolonged QRS duration have no viable tissue in the inferolateral wall, an area that is usually stimulated with CRT.

Background

Cardiac resynchronisation therapy (CRT) is considered as a potential therapeutic option in patients with heart failure, reduced left ventricular ejection fraction (LVEF) and an increased QRS duration. Although functional improvements and effects on morbidity and mortality have been reported, up to 30 % of CRT patients do not respond to this therapy and this percentage could be even higher in patients with underlying coronary artery disease (CAD) [1-3]. One of the reasons could be the presence of non-viable tissue in the inferolateral wall which is usually paced when the LV lead is placed transvenously via the coronary sinus.

Aims

Our study aims were to assess the relationship between QRS duration on the surface ECG, left ventricular volumes and the prevalence of nonviable tissue–in patients with CAD and poor LV function.

Methods

We studied 132 consecutive patients with CAD and a resting LVEF ≤ 30 %. The diagnosis of CAD was based on a history of myocardial infarction, coronary revascularisation or angiographic significant CAD (at least one vessel with ≥ 75 % stenosis). All patients were studied more than 3 months after myocardial infarction or revascularization and patients with ventricular pacing on the resting ECG were excluded. QRS duration was measured on a 12-lead surface ECG, at a speed of 25 mm/s, from the resting ECG.

All patients underwent a resting gated myocardial perfusion SPECT study using technetium-99m tetrofosmin as described previously [4]. Quantified Gated SPECT software (QGS®, Cedars-Sinai, Los Angeles, CA, USA) was used to obtain resting LV ejection fraction and volumes. For viability scoring, the myocardium was divided in 5 regions, anterior wall, lateral wall, inferior wall, septal wall and apex. The anterior, lateral, inferior and septal wall were subdivided in 3 regions (apical, mid and basal region), the apex was subdivided in 2 regions [5]. A myocardial wall was considered to contain substantial non-viable tissue if none of the segments had a mean myocardial uptake higher than 55% of the maximum uptake in the myocardium on the resting perfusion images [6].

Statistical analyses were performed using SPSS 11.0.1 statistical software (SPSS Inc., Chicago, USA). Spearman rank correlations, Mann-Whitney U and Kruskall-Wallis testing were used to investigate relations between QRS duration and LV volumes and prevalences of nonviable according to QRS duration.

The study was approved by the local Ethics Committee of the Ghent University Hospital.

Results

Mean age of the 132 patients was 68±5 years and mean LVEF was 24±6 %. Previous myocardial infarction was present in 86 (65%) and previous coronary revascularization in 63 (48%) patients. According to the SPECT findings, the anterior wall was infarcted in 21 (16 %), the septal wall in 19 (14 %) and the inferolateral in 73 (55 %) patients. Patients were treated with ACE-inhibitors or AT-2 receptor blockers (n=98, 74%), beta-blockers (n=59, 45%) and diuretics (n=48, 36%). Mean QRS duration was 131±32 ms and a QRS duration ≥ 120 ms was present in 91 patients (69%). For the whole group QRS duration correlated significantly with LV enddiastolic volumes ($r=0.31$, $p<0.001$) and LV endsystolic volumes ($r=0.30$, $p<0.001$). As compared to patients with small QRS, patients with QRS duration > 120 ms had significantly higher LV enddiastolic volumes (248±77 vs 205±73 ml, $p<0.01$) and LV endsystolic volumes (193±68 vs 159±60 ml, $p<0.01$). Figure 1 shows the mean LV enddiastolic and endsystolic volumes according to four classes of QRS duration. No significant relation was found between LVEF and QRS duration.
The inferior or lateral wall was nonviable in 26 patients with a QRS duration ≥ 120 ms (29%). This frequency was significantly higher than in patients with QRS duration < 120 ms (29% vs 7%, $p<0.01$). Prevalences of nonviable tissue in different regions for patients with QRS < 120 ms and QRS ≥ 120 ms are shown in figure 2.

Conclusion

Our results indicate that a prolonged QRS duration (≥120 ms) is frequent in patients with CAD and LVEF ≤ 30% with a prevalence of almost 70%. Similar to previous studies in patients with idiopathic dilated cardiomyopathy [7-9], this increase in QRS duration is clearly related to an increase in LV enddiastolic and endsystolic volumes, indicating more advanced remodeling in these patients. More importantly, absence of viable tissue in the inferolateral wall in CAD patients with poor LV function is frequent, with a prevalence of 29% when QRS duration is increased as compared to only 7% when QRS duration is < 120 ms. This implicates that almost 30% of potential candidates for CRT with CAD have non-viable tissue in the inferolateral wall. Since non-viable tissue is electromechanically non-functional [10] placement of the lead in the inferolateral region could lead to ineffective pacing in these patients [11]. This could therefore be one of the explanations why CRT is ineffective in a substantial number of patients with CAD. Further studies are however needed to determine whether viability assessment can help in the selection of candidates for CRT and in the determination of optimal lead localisation.

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Figures

Figure 1

Relationship between QRS duration and left ventricular volumes. A significant increase in LV endiastolic (EDV) and endsystolic (ESV) volumes is noted according to QRS duration.

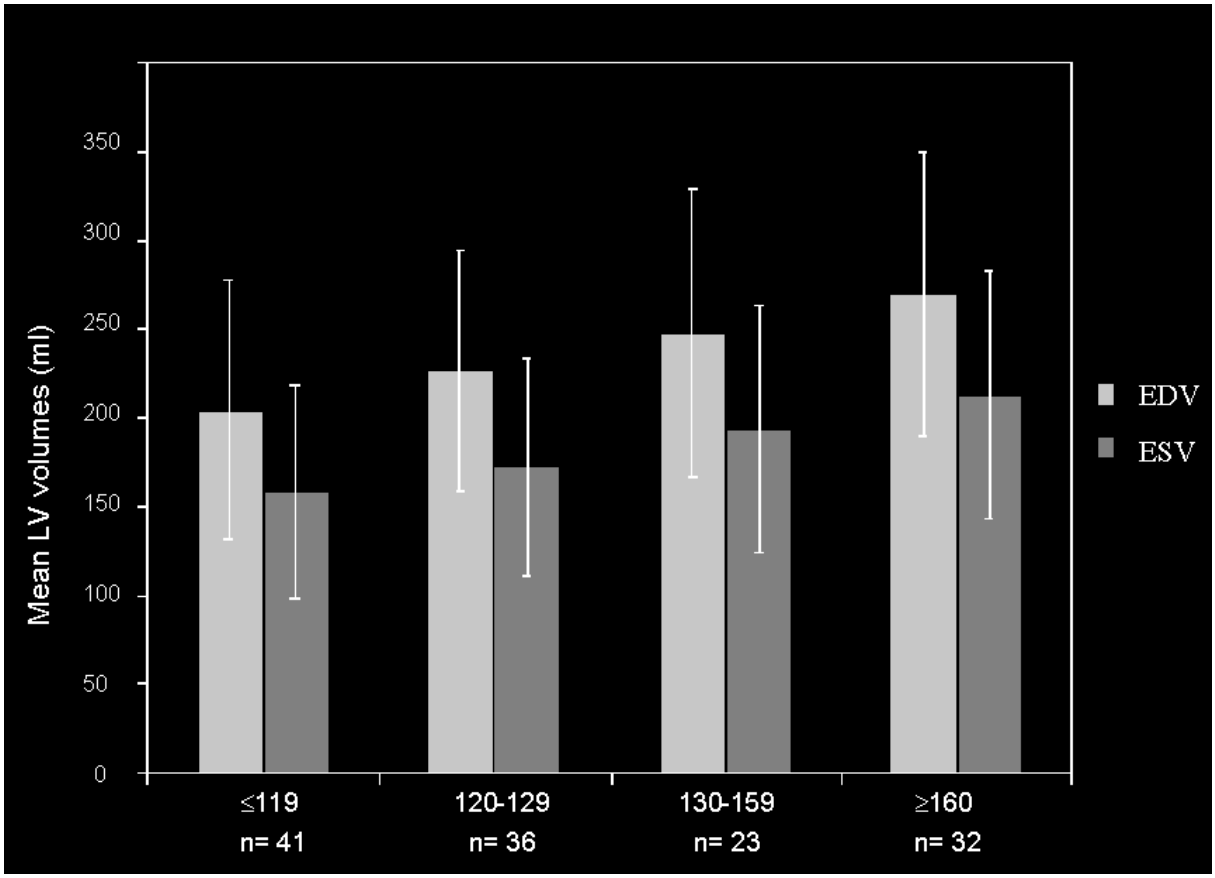
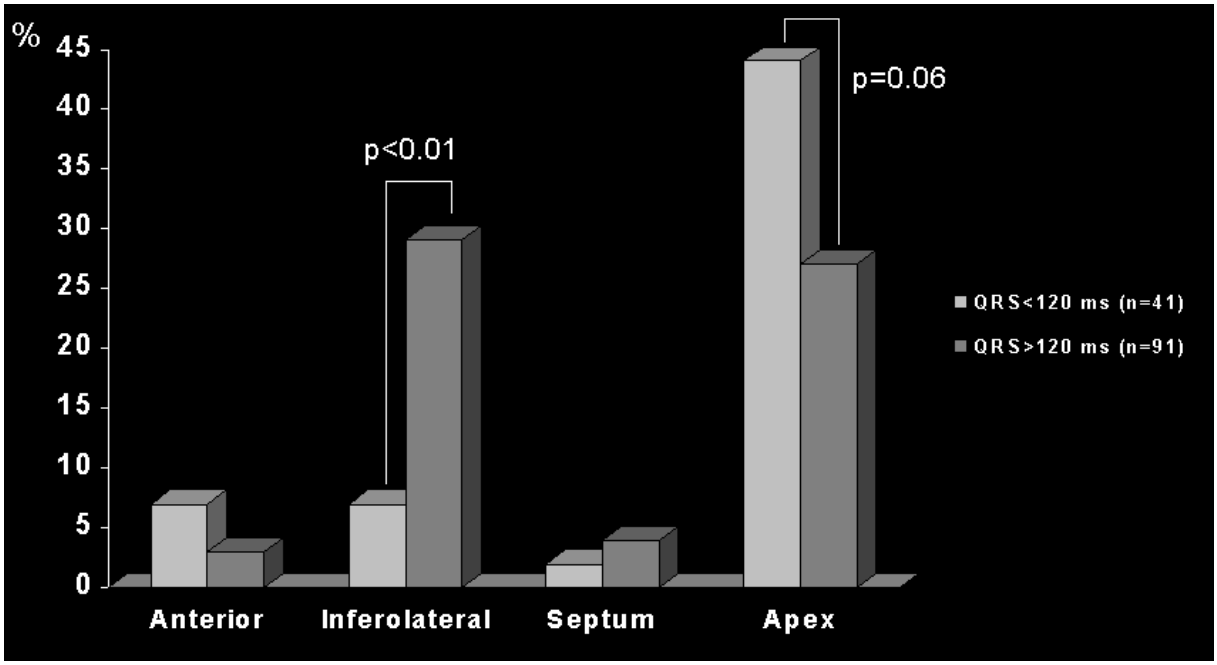


Figure 2

Prevalence of nonviable tissue in different myocardial regions in patients with QRS duration < 120 ms and patients with QRS duration ≥ 120 ms. A significantly higher prevalence of nonviable tissue in the inferolateral wall is noted in patients with QRS duration ≥ 120 ms.



Chapter 3

Human studies in the elderly patient population

3.1. Introduction
Myocardial perfusion imaging in the old: a review

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Abstract

Coronary artery disease (CAD) is the major cause of morbidity and mortality in the elderly population. Due to aging of the population and better medical, interventional and surgical treatment of patients with CAD, more and more elderly patients are referred to the cardiology department for diagnostic work-up. Stress testing in combination with myocardial perfusion imaging (MPI) is routinely used in elderly patients, a population where the diagnosis of significant CAD is often challenging because of atypical symptomatology. Since the introduction of technetium-99m ligands for MPI, it is possible to perform ECG gated perfusion imaging. This does not only improve the specificity of the test for CAD detection, it also enables the simultaneous assessment of left ventricular functional parameters. This article briefly overviews possible stress modalities, diagnostic accuracy and prognostic value of MPI in elderly patients.

I. Introduction

Coronary artery disease (CAD) is the major cause of morbidity and mortality in the elderly population [1-4]. Due to aging of the population and better medical, interventional and surgical treatment of patients with CAD, more and more elderly patients are referred to the cardiology department for diagnostic work-up. In the elderly patient population, the diagnosis of CAD is challenging because ischemic symptoms are often atypical. Also, the proportion of female patients is much higher in this population and it is known that by the age of 75, rates for coronary morbidity and mortality are similar in men and women [5].

Because of the high prevalence of CAD and the atypical symptomatology in the elderly, accurate non-invasive techniques are needed in this population to identify patients with significant CAD. Stress testing in combination with myocardial perfusion imaging (MPI) is routinely used in the elderly patient to assess CAD. Since the mid-nineties, there is an increased use of technetium-99m labelled perfusion agents, like sestamibi and tetrofosmin, with more favourable imaging characteristics compared to 201-thallium. This makes it possible to perform electrocardiogram gated single photon emission computed tomography (SPECT) during the acquisition of myocardial perfusion [6], which does not only improve the specificity for the detection of CAD [7], but also enables the assessment of left ventricular (LV) functional parameters including LV ejection fraction (LVEF) and LV volumes [8,9]. The LVEF is known as one of the most powerful prognostic parameters [10-12], but also cardiac volumes provide important prognostic information in middle-aged CAD patients [13-14]. Therefore, perfusional parameters [15-16] and functional data seem to be important for prognostic assessment in the elderly patient [17-18]. This article aims to overview briefly the use of MPI and gated MPI in the elderly patient population for diagnostic and prognostic purposes.

II. Coronary artery disease in the elderly

In contrast with the middle-aged CAD population, women significantly outnumber men in the age group 65 years and older. In the European Union, women represent 65 % of the population aged 75 years and older (data from EUROSTAT, 2003). Death rates due to CAD have increased in women because of a more sedentary lifestyle in the elderly age group and a higher prevalence of obesity, diabetes mellitus type 2 and hypercholesterolemia [19-20]. Data of the Framingham study revealed that women present with their first anginal symptoms 10 year later and sustain their first myocardial infarction 20 years later than men [21] and, by the age of 75, rates for coronary morbidity and mortality are similar in both sexes [5]. This makes that in contrast with the middle-aged CAD population (40-65 y) the proportion of women in the elderly population with suspected CAD is much higher. Also, the diagnosis of CAD is more difficult in elderly patients because of atypical symptomatology and a higher frequency of co-morbidity. For example, exertional angina pectoris is commonly the first manifestation of CAD in middle-aged persons, but many elderly patients will not experience any exertional angina because of limited physical exercise in daily life. Secondly, other disorder can mask or mimic the ischaemic cascade: shoulder pain is frequently diagnosed as degenerative disease and epigastric pain as peptic ulcer disease. It has been shown that 20-50 % of patients >65 years demonstrate silent myocardial ischemia upon stress testing [22]. The detection of this silent ischemia is important because coronary events are twice as common in patients with silent myocardial ischemia versus those without ischemia [23].

III. Stress testing in the elderly

a) Physical ECG stress testing in the elderly patient

Current ACC practice guidelines advise a simple treadmill test as first choice investigation in elderly patients. However, the frequent presence of resting abnormalities in the ECG of elderly patients and the high proportion of women lowers the value of ECG exercise stress testing in this population [24]. Secondly, the frequent presence of neurological, respiratory or orthopaedic disorders, makes it more challenging to perform adequate exertional stress testing and to achieve maximal heart rates. Moreover, left bundle branch block and ventricular-paced rhythm, frequently seen in older people, are also established indications for pharmacologic stress testing [25]. Therefore, ECG stress testing is less useful in elderly patients than in the middle-aged population.

b) Stress testing for MPI in the elderly

The high prevalence of asymptomatic multivessel disease in the elderly population and the fact that a high proportion of patients above 75 years are not able to perform adequate stress testing for MPI renders the application of other stress modalities in this patient population necessary. Iskandrian et al. reported that SPECT perfusion imaging after submaximal exercise is significantly less sensitive than after maximal exercise in detecting CAD and in correctly identifying patients with multivessel disease [26]. In these patients, it is possible to perform perfusion imaging after pharmacological stress using agents such as dipyridamole, adenosine or dobutamine. Dipyridamole and adenosine cause vasodilatation in the normal coronary arteries more than in stenotic vessels. This creates a coronary steal effect, resulting in a relative hypoperfusion of the diseased myocardial area, which is visualised by MPI.
Although achieving at least 85% of predicted maximal heart rate is quite difficult to obtain in the elderly due to chronotropic incompetence or the use of β- blockers, the majority of elderly patients are still able to perform low-level exercise. Therefore it is possible to combine physical and pharmacological stress: physical exercise stress is started until exhaustion and followed by infusion of pharmacological vasodilator stress agents (dipyridamole or adenosine). The addition of pharmacological vasodilators to submaximal stress testing does not only improve the diagnostic ability of the stress test [27], it also improves image quality and decreases the frequency of side effects compared to using the pharmacological stressors alone [28-30]. Although the use of vasodilators is relatively safe, it must be noted that the use of adenosine or dipyridamole is contraindicated in patients with active bronchospasm, acute coronary syndrome, hypotension, grade II-III atrioventricular block, sick sinus syndrome and sinus bradycardia, situations frequently seen in elderly [31]. It should be noted that one should not add low-level

exercise to patients with left bundle branch block, as they are susceptible to the same false positive findings in the interventricular septum as would be seen with exercise. As an alternative to vasodilator stress, it is possible to use dobutamine, a synthetic catecholamine, as stress agent. The infusion of dobutamine increases heart rate and myocardial contractility, resulting in an increased cardiac output. This causes an increase in myocardial oxygen demand and blood flow of the normal vessels [32]. The chronotropic effect of dobutamine is however suboptimal and therefore the target heart rate might not be reached [33]. In this case, atropine addition can increase the heart rate and the sensitivity for detection of ischemic heart disease without increasing the side-effects [34,35]. Contraindications for dobutamine infusion include severe hyper- and hypotension, a recent dissection of the aorta or coronary arteries, uncontrolled atrial fibrillation or atrial flutter and recurrent ventricular tachycardia. Dobutamine can not be used as a stress agent for MPI in patients with left bundle branch block because this may result in false positive findings in the interventricular septal wall.

IV. Diagnostic accuracy of stress MPI in the elderly

Radionuclide perfusion imaging combined with exercise or pharmacological stress testing demonstrated a high diagnostic accuracy in the detection of CAD in the middle-aged patient [36,37]. MPI has also been shown to have a good accuracy in the elderly. Lam et al. reported similar sensitivities and specificities for 201-thallium dipyridamole imaging in patients aged 70 years or above versus younger patients [38]. More recently, Gentile et al. investigated the accuracy of bicycle stress-rest MPI using 201-thallium in 132 patients aged >65 years who were hospitalised because of cardiac events (angina, dyspnoea, cardiac rhythm disturbances and atypical chest pain) using subsequent coronary angiography as a gold standard [39]. In this study a lesion on coronary angiography was considered significant if ≥ 60% of the lumen diameter was obstructed. The diagnostic accuracy of MPI in this study was 86.3% with a sensitivity of 93.5% and a specificity of 54.1%. The use of technetium-99m based myocardial imaging agents with more favourable imaging characteristics resulting in less attenuation and scatter, has improved the specificity and diagnostic value of SPECT imaging in women [40]. Wang et al. studied 75 consecutive patients aged >80 years who underwent a coronary angiography within 6 months of MPI using technetium labelled sestamibi. Overall sensitivity for detection of a >75% stenosis was 95% with a specificity of 75% and results were similar for pharmacological and exercise stress MPI [41].

V. Risk stratification by MPI in the elderly

a) Prognostic value of myocardial perfusion assessment

Multiple studies investigated the prognostic value of MPI in patients with known or suspected CAD for predicting cardiac events and cardiac mortality [42-47]. These studies demonstrated the prognostic or incremental prognostic value of MPI above clinical variables in middle-aged patient populations with known or suspected CAD. Exercise MPI has significant added value for risk stratification in CAD, but most studied patients have been middle-aged or younger [48,49]. Iskandrian et al. studied 499 patients with CAD aged 60 years or older using exercise thallium-201 planar imaging and found a prognostic value for MPI in the prediction of future cardiac death or non-fatal myocardial infarction [15]. Steingart et al. investigated 578 patients aged 65 years or older with interpretable electrocardiograms who were able to perform exercise testing with MPI (99m-technetium ligands and 201-thallium) [50]. During a 4.4±1.3 year follow-up, there were 39 deaths and 17 non-fatal myocardial infarctions. In this study population, the assessment of stress-induced ischemia provided only limited prognostic information above clinical parameters in the prediction of all-cause death and myocardial infarction.

More recently, Schinkel et al. investigated 272 patients aged > 65 years with limited exercise capacity using dobutamine tetrofosmin SPECT and found that the summed stress score and abnormal myocardial perfusion (fixed or reversible) provided incremental information over clinical data in the prediction of all-cause mortality, cardiac death and the combined end point of non-fatal myocardial infarction or cardiac death [51].

Due to aging of the general population, a patient population above 60 or 65 years cannot be considered a really elderly population. In a study by Shaw et al. investigating 348 patients aged older than 70 years who underwent dipyridamole planar thallium-201 perfusion imaging, an abnormal perfusion scan was the best predictor of cardiac events (cardiac death or non-fatal myocardial infarction) [16]. Similar findings were reported by the same group in 120 patients older than 70 undergoing exercise planar thallium-201 perfusion imaging [52].

The first study investigating the prognostic value of MPI in a large population (328 patients) aged 75 years or older with suspected CAD was performed by Lima et al. [53]. In this population, there were 24 cardiac deaths during a 34±15 months follow-up time. These authors found that an abnormal myocardial perfusion scan (either fixed or reversible) was an independent predictor of cardiac death.

More recently Valeti et al. reported on the prognostic value of thallium-201 perfusion imaging in 247 patients aged 75 years or older [54]. They found that a higher summed stress score provided incremental information above clinical parameters. A higher summed difference score, ventricular enlargement (graded subjectively as present or absent) and increased uptake of thallium-201 in the lungs were univariate predictors of cardiac death or myocardial infarction, but these

parameters did not prove any incremental value once the summed stress score was entered in the multivariate analysis.
One of the most striking aspects of using MPI as a prognostic tool is the extremely low risk in patients with normal scintigraphic images [45,55,56]. Many clinical studies have demonstrated that patients with normal myocardial perfusion images have a very low cardiac event rate (< 1% cardiac deaths/ year). Even when exercise ECG (ST depression) or angiographic (multivessel disease) markers of poor outcome are present the prognosis in patients with normal MPI is benign [57,58] and these findings seem to be similar in the elderly population [39,50]. In the study by Steingart et al. in 578 patients aged 65 years or older with interpretable electrocardiograms who underwent exercise testing with MPI, normal scan findings were associated with a good prognosis (97% 3-year event free survival rate) [50].

b) Prognostic value of LV dilatation at stress

The TID (transient ischemic dilatation ratio = ungated volume post stress/ ungated volume at rest imaging) ratio is a marker for the transient enlargement of the left ventricle after stress. It is most commonly known for its diagnostic power as a marker of ischemia [59]. However, also the prognostic value of a high TID ratio has been extensively investigated in middle-aged patient populations with CAD [59-61]. In the study by Steingart et al. which is already discussed above, ventricular dilatation post stress was strongly predictive of future death or non-fatal myocardial infarction [50]. These findings were confirmed by Valeti [54] and by our group [62].

c) Prognostic value of left ventricular functional parameters

Multiple studies demonstrated the prognostic value of LV functional parameters using gated radionuclide angiography [12,63,64], X-ray angiography [13], echocardiography [65-68] and even cardiac magnetic resonance [69] in the middle-aged population. Using gated SPECT, Sharir et al. found that post stress LVEF and post stress LV end-systolic volume assessed during gated SPECT had incremental value above clinical parameters in predicting cardiac death [70]. Functional data assessed during echocardiography have shown prognostic value in elderly patients [71,72]. However, there is only one report regarding the prognostic value of combined perfusion and function imaging assessed by myocardial gated SPECT in the elderly. Over the period 1998-2002, we evaluated 294 consecutive patients aged 75 years or more (mean age 78±3 years) with suspected or known CAD using stress-rest myocardial gated SPECT and followed these during a median follow-up of 25.9 months [62]. We found that LV functional data (LVEF and LV volumes) provided independent and incremental prognostic information above clinical and SPECT perfusion data for cardiac and all-cause mortality in these patients. More importantly, we found that LV functional measurements provided by gated SPECT provided a higher predictive value than myocardial perfusional parameters in the

prediction of future cardiac death or total mortality. The strongest predictor of total mortality in our population was a lower LVEF (X^2 = 16.9; p<.001) where a higher resting LV end systolic volume was the strongest predictor of cardiac mortality (X^2 = 24.4; p< .001). Additionally, when comparing post stress and resting functional parameters, we found that their prognostic values were comparable. This could be expected because the correlation between resting and post stress parameters was very high (.91 for LVEF's and .96 for LV end-systolic volumes). Therefore, when functional data are only obtained during stress imaging, these data can be used for prognostic stratification instead of the resting data.
A brief overview of these prognostic studies is provided in the table.

VI. Conclusions

The increasing number of elderly patients requiring diagnostic and prognostic assessment for coronary artery disease has necessitated accurate, non-invasive techniques applicable to this age group. Exercise testing, either alone or with perfusion imaging, remains a useful tool in elderly patients capable of performing vigorous treadmill or bicycle exercise. Fortunately, for the large elderly subset incapable of such exercise, pharmacologic stress testing with dipyramidole, adenosine, or dobutamine offers an excellent alternative. Furthermore, recent data support a prognostic approach to the management of middle-aged patients with coronary artery disease based on the results of gated myocardial perfusion SPECT imaging. Similar in the elderly, the assessment of LV function adds further to the diagnostic and prognostic relevance of this imaging modality. This further provides significant independent information in the prediction of future cardiac death or all-cause mortality, especially in a patient population with multiple co-morbidities.

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TABLE

Abbreviations in the table

ESV: end systolic volume
EDV: end diastolic volume
FU: follow-up
LV: left ventricular
MI: myocardial infarction
n: number
pts: patients
SDS: summed difference score
SRS: summed rest score
SSS: summed stress score
201-Tl: 201-thallium
99m-Tc: 99m-technetium
y: years

Table

Author	Age	N of pts	Tracer / protocol	Stress modality	Planar vs SPECT	Gated data	End points	Follow-up	Significant univariate MPI predictors	Significant multivariate MPI predictors
Iskandrian et al. (15)	> 60 y	499	201-Tl	treadmill	planar	No	cardiac death or MI	mean FU 25 months	abnormal MPI	abnormal MPI
Steingart et al. (50)	> 65 y	578	99m-Tc ligands and Tl-201	treadmill	SPECT	No	all-cause death or MI	mean FU 51 months	LV enlargement, ischemia on MPI	ischemia on MPI
Schinkel et al. (51)	> 65 y	272	99m-Tc tetrofosmin (2 day)	dobutamine	SPECT	No	cardiac death	mean FU 38 months	abnormal MPI	abnormal MPI
Shaw et al. (16)	> 70 y	348	201-Tl	dipyridamole	planar	No	cardiac death or MI	mean FU 23 months	abnormal MPI	abnormal MPI
Hilton et al. (52)	> 70 y	120	201-Tl	treadmill	planar	No	cardiac death or MI	mean FU 36 months	abnormal MPI	abnormal MPI
Lima et al. (53)	> 75 y	328	99m-Tc sestamibi (2 day)	dipyridamole and treadmill	SPECT	No	cardiac death or MI	mean FU 34 months	abnormal MPI	abnormal MPI
Valeti et al. (54)	> 75 y	247	201-Tl	treadmill	SPECT	No	cardiac death	median FU 76 months	SSS, SDS, LV enlargement	SSS
De Winter et al. (62)	> 75 y	294	99m-Tc tetrofosmin (2 day)	dipyridamole and bicycle	SPECT	Yes	cardiac death	median FU 26 months	SSS, SRS, abnormal MPI, LVEF, LV EDV and ESV	SRS and LV ESV

Note: the studies by Schinkel et al. and De Winter et al. also included an analysis of total mortality.

3.2
Determinants of Amino-terminal pro Brain Natriuretic Peptide (Nt-proBNP) in elderly patients with coronary artery disease.

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Abstract

Aim: Amino-terminal pro Brain Natriuretic Peptide (Nt-proBNP) is a valuable tool in the diagnosis of heart failure and has a prognostic value in coronary artery disease (CAD) patients. Clinical parameters, kidney function and parameters derived from gated myocardial perfusion imaging also have shown strong prognostic value in these patients. Our study aim was to assess independent determinants of Nt-proBNP in elderly patients with stable CAD.

Methods: We studied 247 consecutive patients (198 males and 49 females) with stable CAD referred for myocardial perfusion imaging aged ≥ 60 years (mean age 71±6 years). Left ventricular (LV) volumes were derived from myocardial gated SPECT data. Summed stress, rest and difference scores (as marker for myocardial ischemia) were calculated using semi-quantitative 4DM gated SPECT software (Michigan University). Glomerular filtration rate (GFR) was calculated with a validated equation based on serum creatinine level. A linear regression model was used to determine independent predictors of log Nt-proBNP.

Results: Univariate predictors of a higher Nt-proBNP in the study population were higher age ($p<.001$), lower body mass index ($p= .026$), lower resting systolic blood pressure ($p= .009$), longer QRS duration ($p= .024$), presence of a left bundle branch block on the ECG ($p=.005$), lower GFR ($p<.001$), higher resting and post-stress end-diastolic and end-systolic (ESV) volumes (all $p<.001$), lower resting and post stress ejection fractions (both $p< .001$), higher summed difference scores ($p= .026$) and higher summed stress and rest scores (all $p< .001$). A higher post stress LV end-systolic volume (ESV) ($F = 106.1$; $p< .001$), a lower GFR (F change= 40.3; $p<.001$) and a higher age (F change= 9.3; $p= .002$) were the only independent determinants of Nt-proBNP by multivariate regression analysis.

Conclusion: A higher post stress LV ESV, a worse kidney function (assessed by GFR), and increasing age are independent determinants of Nt-proBNP in elderly patients with stable CAD. In contrast, Nt-proBNP levels were not associated with myocardial ischemia in multivariate analysis.

Introduction

Coronary artery disease (CAD) is the most common cause of heart failure in the Western world, accounting for 60-70 % of the cases [1]. Incidence and prevalence of congestive heart failure due to CAD are increasing worldwide as a result of increasing life expectancy in general and the longer survival of patients with CAD in particular [2]. The increasing prevalence of congestive heart failure has resulted in the need for improved therapeutic agents together with simple diagnostic screening tools. Brain Natriuretic Peptides (BNP) are neurohormones synthesized by and released from cardiac myocytes in response to an increased wall stress. In patients with failing hearts, peptide production increases and becomes more generalized throughout the myocardium [3]. Amino-terminal pro Brain Natriuretic Peptide (Nt-proBNP), an inactive fragment of BNP, is a valuable tool in the diagnosis of heart failure [4,5] and has prognostic value in CAD patients [6,7]. Clinical parameters such as kidney function and data derived from gated SPECT have however also a strong prognostic value in this patient population [8-11]. Our study aim was to investigate which clinical and gated single photon emission computed tomography (SPECT) parameters independently determine Nt-proBNP levels in elderly patients with stable CAD.

Methods

Study population

The study population consisted of 247 consecutive Caucasian patients aged 60 years or older with documented CAD. All patients underwent a 2-day stress-rest myocardial gated SPECT investigation in the period October 2001- July 2005. The diagnosis of ischemic heart disease was based on a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting or angiographic significant CAD (at least one coronary artery with ≥ 75 % stenosis). There had to be at least 3 months between infarction or revascularisation and inclusion in the study.

Nt-proBNP

Patients came to the laboratory for venous blood samples between 8 and 9 AM and had been fasting for at least 12 hours. Venous blood was drawn from an antecubital vein into gel filled tubes at rest. The specimens were centrifuged within 1 hour and plasma was frozen at –80° C until analysis. Concentration of Nt-proBNP in serum was measured on an Elecsys^{TM} 2010 apparatus (Roche Diagnostics, Mannheim, Germany) with an automated electrochemiluminescence sandwich immunoassay that uses two polyclonal antibodies directed against residues 1-21 and 39-50 of the molecule.

Renal function

Serum creatinine was determined by a rate-blanked compensated Jaffé method using commercial reagents (Roche, Mannheim, Germany) on a Modular P analyzer (Hitachi, Tokyo, Japan). Renal function was assessed by entering this serum creatinine value in a validated equation to calculate the estimated glomerular filtration rate (GFR). For male patients we used the formula 186 x [(serum creatinine level (in mg/dl)] $^{-1.154}$ x [age (in years)] $^{-0.203}$. For female patients a correction was made by multiplication with 0.742 [12,13].

Clinical data

Demographic data were collected at study entrance. All the investigated clinical variables are shown in table 1. Blood pressure was measured at rest with a calibrated mercury sphygmomanometer. Diabetes mellitus was defined as a fasting blood glucose level > 126 mg/ dl and/or the need for insulin or oral antidiabetic agents. Body mass index was calculated by the formula: weight (kg)/ square length (m^2).

Gated SPECT acquisition

Stress and rest studies were performed in a 2-day protocol. In both stress and rest studies, 900 MegaBecquerel (25 milliCurie) of 99m-technetium sestamibi was injected intravenously. Imaging was started between 30-60 minutes after injection in the resting state and 15-30 minutes after injection at peak stress. A gated SPECT acquisition was performed over 360° in step-and-shoot mode (120 sectors of 3°, 30 seconds/ step, matrix size 64 x64) using a triple-headed camera (Picker Prism 3000, Marconi, Philips, Cleveland, Ohio) equipped with low energy all-purpose collimators. Acquisitions were gated for 16 frames per cardiac cycle.

Calculation of global LV parameters

The raw gated SPECT data were reconstructed using filtered back projection (ramp filter) over 180° and post-filtered using a low pass filter (order 5, cut-off frequency .21). The left ventricle was reoriented manually to obtain short axis images, which were processed using Quantified Gated SPECT software (QGS®, Cedars-Sinai, Los Angeles, CA, USA) to obtain resting LV ejection fraction and LV volumes. The automatic myocardial border detection by QGS® was visually inspected and corrected if necessary.

Scoring of the perfusion images

For perfusion scoring, the raw gated SPECT data were ungated and reconstructed using filtered back projection (ramp filter) and post-filtered using a low pass filter (order 5, cut-off frequency .21). The left ventricle was reoriented manually to obtain short axis images. These ungated short axis images were used for semi-quantitative analysis of myocardial perfusion using 4D-MSPECT® software (University of Michigan, Ann Arbor, Mi, USA). Myocardial perfusion in stress and rest were compared to a gender specific normal perfusion database generated at our institution. Stress and rest normal database files were made out of patients with a low cardiac risk (< 5 %) [14]. Summed stress, summed rest and summed difference scores were automatically generated by the software. Summed stress and rest scores can be considered as global myocardial perfusion scores in stress and rest respectively. The summed difference score is calculated by subtracting the summed stress from the summed rest score and is a marker of myocardial ischemia. Automatic myocardial border detection by the software was visually inspected and corrected if necessary. Semi-quantitative scoring was used instead of visual scoring because this makes perfusion scoring more reproducible and less dependent on the experience of the observers.

The study was approved by the local Ethics Committee of the Ghent University Hospital. All included patients gave informed consent prior to the study.

Statistical analysis

Statistical analyses were performed using SPSS 11.0.1 statistical software (SPSS Inc., Chicago, USA). As Nt-proBNP values were not normally distributed, they were logaritmised for further statistical analysis. Patients were categorized in quartiles according to the Nt-proBNP value. Univariate clinical and SPECT predictors of log Nt-proBNP were analysed using non-parametric Kruskal-Wallis testing. Univariate determinants of log Nt-proBNP significant at the 0.05 level were inserted in a forward stepwise multivariate regression model to determine independent determinants of log Nt-proBNP. Data are shown as mean ± standard deviation or percentage.

Results

Clinical characteristics and univariate determinants of Nt-proBNP

Clinical characteristics (table 1) and gated SPECT parameters (table 2) for the whole group are given in the tables. Patients were divided in 4 groups according to Nt-proBNP quartiles. In this population of elderly patients with stable CAD, 134 had a history of myocardial infarction, 91 a history of percutaneous coronary intervention and 127 a history of coronary artery bypass grafting. Cardiac medications included aspirin (n= 183), beta-blockers (n= 181), angiotensin-converting enzyme inhibitors or angiotensin-II antagonists (n= 159) and statins (n=152).
A higher age ($p<.001$), a lower body mass index ($p= .026$), a lower resting systolic blood pressure ($p= .009$), a longer QRS duration ($p= .024$), the presence of a left bundle branch block on the ECG ($p=.005$), a lower GFR ($p<.001$), higher resting and post-stress end-diastolic and end-systolic (ESV) volumes (all $p<.001$), lower resting and post stress ejection fractions (both $p< .001$), higher summed difference scores ($p= .026$) and higher summed stress and rest score (all $p< .001$) were univariate determinants of higher Nt-proBNP (see tables).

Multivariate regression analysis

A higher post stress LV ESV ($F = 106.1$; $p< .001$), a lower GFR (F change= 40.3; $p<.001$) and a higher age (F change= 9.3; $p= .002$) showed to be independent determinants of log Nt-proBNP in a multivariate regression analysis model. The figure shows mean log Nt-proBNP levels in function of GFR (divided on the median= 72 ml/ min) and post stress LV ESV (divided in tertiles: tertile 1: ≤ 37 ml, tertile 2: 38- 69 ml, tertile 3 ≥ 70 ml). Summed difference scores did not appear to be multivariate determinants of log Nt-proBNP levels.

Discussion

The present study shows that renal function, post stress LV ESV and age are independent determinants of Nt-proBNP in CAD patients aged 60 years or above. Therefore, these parameters must be taken into account when interpreting Nt-proBNP values in this population. No significant relationship was found between summed difference scores and Nt-proBNP levels.

Determinants of BNP in healthy people

In healthy people, increasing age, female gender and a lower heart rate have been shown to be associated with higher serum BNP levels [15,16] and Nt-proBNP levels [17,18]. Even in our study population, focused on the elderly, there was a clear relation between increasing age and higher Nt-proBNP levels. However, we did not find a significant relation to gender and heart rate.

Relationship between extent of CAD and Nt-proBNP values.

In a younger patient population, other groups showed a significant relation between Nt-proBNP levels and the extent of CAD [19-21]. Because of the invasiveness of the procedure, a coronary angiography was not performed routinely in our study population. However, we found also a strong univariate relation between the extent of CAD (determined by the summed perfusion scores) and Nt-proBNP with worse myocardial perfusion scores in patients in the upper Nt-proBNP quartiles. Left ventricular functional and perfusion parameters are however closely related in CAD patients and our data suggest that once LV functional variables are inserted in the multivariate regression model, there is no additional value for myocardial perfusion scores for the prediction of Nt-proBNP values in the elderly patient population.
In contrast, since brain natriuretic hormones are synthesized by and released from cardiac myocytes and because there is an increased peptide production in failing hearts, higher cardiac volumes are intrinsically related to higher serum Nt-proBNP values [4,5,22,23]. This is in concordance with data by Sharir et al. where cardiac volumes are associated with a worse prognosis [10]. In this study there was however no BNP or Nt-proBNP determined.

Relationship between myocardial ischemia and Nt-proBNP values

In a younger patient population, Weber et al. found a significant univariate association between resting Nt-proBNP values and ischemia detection [19]. Bibbins-Domingo et al. showed in a multivariate analysis that resting BNP values were higher in CAD patients with inducible ischemia versus those without [24].
However, in our population aged > 60 years, there was only a relationship between ischemia detection and Nt-proBNP levels in univariate analysis (higher summed difference scores in patients with a higher Nt-proBNP). Once age, LV ESV and GFR were known, there was no significant relationship between the summed difference scores and Nt-proBNP values. Our data therefore suggest that ischemia as determined by myocardial perfusion imaging is not an independent determinant of Nt-proBNP in elderly patients with CAD.
In the recent literature there is more and more evidence that myocardial ischemia can cause an increase of BNP values at stress [25]. The specificity of an increased BNP in stress for the detection of ischemia is however questionable since physical stress can increase BNP values even in the absence of myocardial ischemia [26]. Since our measurements of Nt-proBNP, like in most large studies investigating the diagnostic value of BNP measurements, were made at rest, it is not possible to make a comparison with studies where stress BNP values were taken.

BNP or Nt-proBNP and renal failure

Impaired renal function is one of the major risk factors in CAD patients [12] and in the elderly patient population [27]. It is known that BNP levels increase in patients with impaired renal function [28,29]. Nt-proBNP is predominantly excreted by the kidneys and impaired renal function is common in CAD patients aged 60 years or above [30]. Therefore it is especially in these patients of importance to determine renal function when interpreting BNP values.

Prognostic value of BNP or Nt-proBNP in the elderly population

Nt-proBNP levels increase with age in the general population Therefore, higher cut-off values for Nt-proBNP levels are needed in elderly patients. Wendelboe et al. showed that even in patients aged > 75 years, high Nt-proBNP plasma levels are predictive of major adverse cardiac events when a higher threshold is used [31]. By ROC curve analysis, a 3-fold higher cut point had to be used in elderly patients than in patients under the age of 75 years. Even in patients aged > 80 years [32] and > 85 years [33], BNP has shown predictive value for major cardiac events. In a recent article, Galasko et al. determined normal values and cut-off values for the detection of CAD and heart failure [34]. Based on Nt-proBNP levels in healthy people aged ≥ 60 years, cut-off values of 172 pg/ ml for men and 225 pg/ ml for women are proposed in this article. We found however 'normal' Nt-proBNP values following the criteria of Galasko et al. in as much as 29 % of the men and 43 % of the women in an elderly patient population with known CAD and a mean age of 71 years. Therefore, in the knowledge that CAD is frequently present in the elderly, our data suggest that the negative predictive value of 'normal' Nt-proBNP levels for the detection of CAD is rather low in this population.

Conclusions

The present study shows that renal function (assessed by GFR), post stress LV ESV and age are independent determinants of Nt-proBNP in CAD patients aged 60 years or above. However no significant relationship was found between myocardial ischemia and Nt-proBNP levels.

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Tables

Abbreviations in the tables

DBP: diastolic blood pressure
GFR: glomerular filtration rate
HR: heart rate
LBBB: left bundle branch block
LVEDV: left ventricular end diastolic volume
LVEF: left ventricular ejection fraction
LVESV: left ventricular end systolic volume
n: number
Nt-proBNP: amino-terminal pro brain natriuretic peptide
RBBB: right bundle branch block
SBP: systolic blood pressure
SDS: summed difference score
SRS: summed rest score
SSS: summed stress score
y: years

Table 1

Clinical Characteristics according to Nt-pro BNP levels

	All patients n= 247	**Quartile 1 n= 61**	**Quartile 2 n= 62**	**Quartile 3 n= 62**	**Quartile 4 n= 62**	**P**
range Nt-proBNP	**26-7775**	**26-153**	**156-319**	**321-706**	**713-7775**	
mean Nt-proBNP (pg/ ml)	**646±958**	**92±34**	**222±47**	**494±108**	**1767±1377**	<.001
mean Log Nt-proBNP (pg/ ml)	**2.53±0.48**	**1.93±.19**	**2.34±.90**	**2.68±.95**	**3.16±.26**	<.001
Age (y)	71 ± 6	68 ± 6	71 ± 6	70 ± 5	73 ± 5	<.001
Male gender	80 %	79 %	79 %	81 %	82 %	.958
BMI (kg/ m^2)	27.6±5.1	29.1±4.7	27.9±4.4	27.0±4.2	26.8±4.7	.026
Diabetes	30%	30%	35%	27%	29%	.784
resting HR (beats/ min)	63±13	62±11	61±11	62±14	65±15	.534
Resting SBP (mm Hg)	145±24	145±23	152±22	139±23	144±25	.009
Resting DBP (mm Hg)	78±13	78±14	78±11	77±12	77±15	.782
QRS duration (ms)	100±32	94±26	95±27	95±26	115±41	.024
LBBB	5%	0%	2%	5%	13%	.005
RBBB	5%	5%	3%	6%	6%	.831
GFR (ml/ min 1.73 m^2 body surface area)	73±17	78±5	78±14	73±18	61±16	<.001

Data are expressed as mean ± standard deviation or %.

Univariate clinical predictors of log Nt-proBNP were analysed using ANOVA for continuous and using Kruskal-Wallis testing for categorical variables.

Table 2

Gated SPECT parameters according to Nt-pro BNP levels

	All patients n= 247	**Quartile 1 n= 61**	**Quartile 2 n= 62**	**Quartile 3 n= 62**	**Quartile 4 n= 62**	**P**
resting LVEDV (ml)	126±60	97±30	119±46	125±51	160±84	<.001
resting LVESV (ml)	65±53	38±18	55±39	64±39	101±78	<.001
resting LVEF (%)	53.7±14.5	61.9±9.6	57.1±13.3	52.7±12.6	43.2±15.2	<.001
Post stress LVEDV (ml)	132±67	100±30	124±53	138±58	171±91	<.001
Post stress LVESV (ml)	68±60	37±19	56±41	64±39	109±85	<.001
post stress LVEF (%)	54.7±15.1	64.2±10.4	58.4±11.7	52.5±14.2	43.5±15.4	<.001
SSS	9.1±10.0	4.4±6.2	5.8±7.2	11.6±9.9	15.4±12.1	<.001
SRS	7.4±9.1	3.4±5.7	4.7±6.8	8.6±8.8	13.5±11.2	<.001
SDS	2.2±3.3	1.6±2.6	1.6±2.6	3.2±4.3	2.5±3.4	.026

Data are expressed as mean ± standard deviation.

Univariate SPECT predictors of log Nt-proBNP were analysed using ANOVA.

Figure

Abbreviations

ESV: left ventricular end systolic volume
GFR: glomerular filtration rate
ESV: end systolic volume
Nt-proBNP: amino-terminal pro Brain Natriuretic Peptide

Figure

Relationship between mean log NT-proBNP, GFR and post stress LV ESV

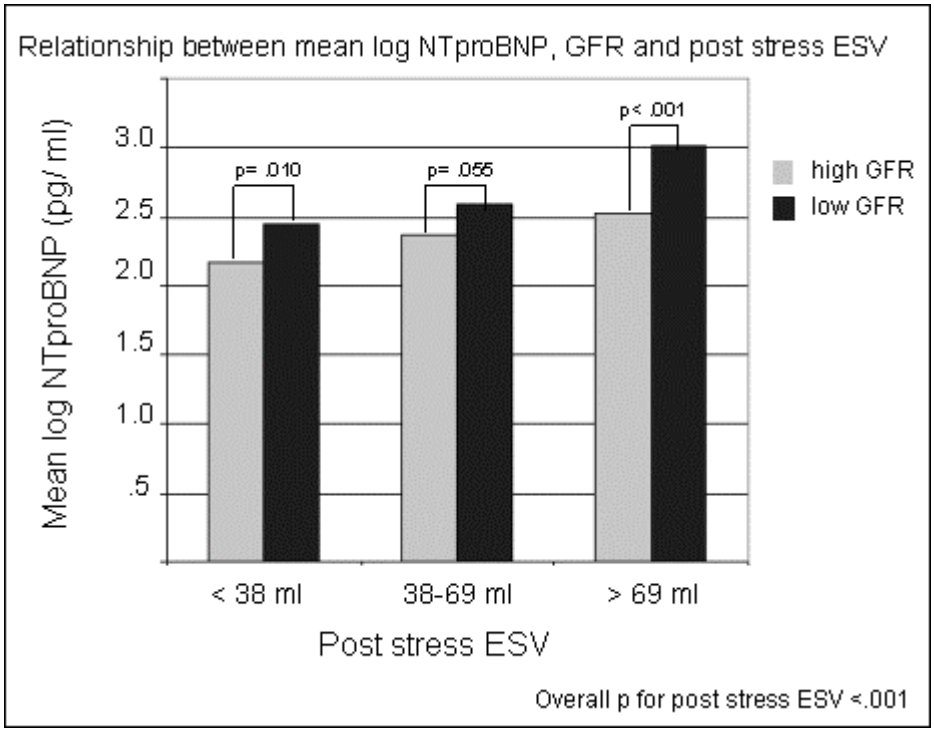

Figure legend

GFR is divided on the median (=72 ml/ min); post stress LV ESV is divided in tertiles.
Overall p for the relation between Nt-proBNP values and post stress left ventricular ESV is:

- < .001 in the whole population
- < .001 in patients with GFR below the median
- < .001 in patients with GFR above the median

3.3
Incremental prognostic value of combined perfusion and function assessment during myocardial gated SPECT in patients aged 75 years or older

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Abstract

Background: Perfusion and functional data obtained during gated SPECT have proven prognostic value in the middle-aged patient population. The aim of this study was to investigate if perfusion and functional cardiac gated SPECT data have prognostic value in patients aged 75 years or older.
Methods: We studied clinical and gated SPECT predictors of cardiac and all-cause mortality in 294 patients with known or suspected coronary artery disease aged 75 years or older referred for tetrofosmin cardiac gated SPECT imaging. Summed perfusion scores were calculated in a 17-segment model using commercially available software (4D-MSPECT). Left ventricular functional data were calculated using QGS gated SPECT software.
Results: Median age of the study population was 78 years (range 75-91 years). There were 160 males (54%) and 134 females (46%). During a median follow-up of 25.9 months (range 1.8-36), 47 patients (16%) died (27 cardiac deaths). In a multivariate Cox proportional hazard regression analysis, the summed rest score (X^2-gain= 8.0, p=.009), transient ischemic dilatation index (χ^2-gain= 6.3, p=.012) and resting left ventricular ejection fraction (X^2-gain= 7.0, p=.030) were independent predictors of all-cause mortality. Summed rest score (X^2-gain= 8.2, p=.004) and resting end-systolic volume (X^2-gain= 13.7, p=.005) were independent predictors of cardiac death.
Conclusions: This study showed that gated SPECT left ventricular functional data assessed during myocardial gated SPECT provide independent and incremental information above clinical and perfusion SPECT data for the prediction of cardiac and all-cause mortality in patients aged 75 years or older referred for myocardial SPECT imaging.

Introduction

Due to aging of the population and better medical and revascularisation treatment of patients with coronary artery disease (CAD), more and more elderly patients are referred to the cardiology department for diagnostic work-up. Perfusion and functional parameters assessed by myocardial gated single photon emission computed tomography (SPECT) have incremental prognostic value above clinical parameters in patients with known or suspected CAD [1-6]. However, these findings are based on middle-aged populations and may therefore not be applicable to the elderly patient population. The aim of this study was to investigate if perfusion and functional data obtained by myocardial gated SPECT are predictive of all-cause and cardiac mortality in patients aged 75 years or older.

Methods

Study population

Among 2701 patients referred for a 2 day stress-rest gated myocardial perfusion SPECT imaging in the period October 1998 until June 2002, all patients aged 75 years or above were considered for further prospective prognostic follow-up (n= 307). Follow-up was successful in 294 patients (96 %) and they formed the study population.

Stress testing

Bicycle stress testing was used in patients able to perform physical stress (n= 103, 35%). When a patient was not able to perform maximal bicycle stress, an additional intravenous infusion of dipyridamole was given (n= 48, 16%). In patients unable to perform physical stress, only intravenous dipyridamole stress testing was used (n= 143, 49%). Patients were informed not to consume caffeine-containing products for 24 hours before testing. Technetium-99m tetrofosmin was injected at peak stress.

Gated SPECT Acquisition and reconstruction

The stress and rest studies were performed in a 2-day protocol as described previously [7]. In both stress and rest studies, 900 MegaBecquerel (25 milliCurie) of technetium-99m tetrofosmin was injected intravenously. Imaging was started between 30-60 minutes after injection in the resting state and 15-30 minutes after injection at peak stress. An ECG-gated SPECT acquisition was performed over 360° using a triple-headed camera (Picker Prism 3000, Marconi, Philips, Cleveland, Ohio) equipped with a low energy all-purpose collimator. The gated images were processed using Quantified Gated SPECT software (QGS®, Cedars-Sinai, Los Angeles, CA, USA) to obtain resting and post stress left ventricular ejection fraction (LVEF) and left ventricular (LV) volumes. QGS® gated SPECT software was used to determine LV functional data because this software has been extensively validated for this purpose [8-9].
The transient ischemic dilatation (TID) ratio was calculated as the ratio of left ventricular volumes at stress and rest using the formula: ungated cardiac volume post stress/ ungated cardiac volume at rest [10].

Scoring of the perfusion images

The raw gated SPECT data were ungated and reconstructed (using filtered back projection and a low pass filter of order 5 and cut-off frequency .21). Myocardial perfusion was scored semi-quantitatively in a 17-segment model by 4D-MSPECT® software (University of Michigan, Ann Arbor, Mi, USA) using the ungated short axis images. This software package was used for perfusion analysis because it allows to score perfusion data in a standardized 17-segment model corresponding to the AHA/ ACC guidelines [11]. Summed stress (SSS), summed rest (SRS), summed difference scores (SDS) were automatically generated by comparison with a gender specific normal perfusion database generated at our institution. These scores can be considered global perfusion scores of the left ventricular myocardium during stress (SSS) and in resting condition (SRS). The SDS is calculated by subtracting the SRS from the SSS and this score reflects the amount of myocardial ischemia. Higher scores indicate a worse perfusion. Ischemia was considered significant if the SDS score was ≥ 4. The stress and rest normal database files were made of patients with a low cardiac risk (< 5 %) [12]. Semi-quantitative scoring was used because this makes perfusion scoring more reproducible and less dependent on the experience of the observers. The prognostic value of semi-quantitative perfusion scoring has been shown to be similar to expert visual analysis [13-14].
Additionally, myocardial perfusion studies were scored visually as normal (= no defect or ischemia) or abnormal (fixed or reversible defect). Visual scoring was added to allow comparison of our data with previous studies using visual perfusion scoring.

Clinical data and follow-up

Demographic data were collected at study entrance (October 1998 until June 2002). Hypertension was defined as a blood pressure ≥ 140 / 90 mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level > 128 mg/ dl or the need for insulin or oral hypoglycaemic agents.
Clinical parameters, perfusion and function myocardial SPECT data were collected prospectively for their potential to predict both cardiac and all-cause mortality.
Follow-up data were collected in the second half of 2003. The investigator was blinded to scanning results at the time of follow-up. Information on mortality and cause of mortality were obtained by contacting patients' general practitioners and reviewing hospital records. Cardiac death was defined as death caused by acute myocardial infarction, refractory congestive heart failure, clinically important cardiac arrhythmias and sudden death without another explanation. A standard questionnaire was used for follow-up interviews. Follow-up was limited to 36 months.
The study was approved by the local Ethics Committee of the Ghent University Hospital.

Statistical analysis

All statistical analyses were performed using SPSS 11.0.1 statistical software (SPSS Inc., Chicago, USA). Data are shown as median (25-75th percentile) or number (%). Mann-Whitney U testing or Chi-square testing was used to assess differences in clinical and SPECT variables between survivors and non-survivors. Cumulative survival rates as a function over time were obtained by the Kaplan-Meier method. Differences in survival were analysed by log-rank testing.
Clinical predictors of mortality, including age, gender, body mass index, cardiac history, cardiac risk factors, cardiac medication and presence of diabetes mellitus were tested by univariate analysis. Significant clinical parameters were forced into a stepwise multivariate Cox proportional hazards regression model followed by perfusion SPECT variables and gated SPECT variables to determine independent predictors of both cardiac and all-cause mortality above clinical parameters. Significance was set at < .05.

Results

At the time of myocardial SPECT imaging 111 patients (38 %) had a history of prior myocardial infarction, 44 patients (15 %) a history of a percutaneous coronary intervention and 87 patients (30 %) previously underwent coronary artery bypass grafting.
During a median follow-up period of 25.9 months (range 1.8-36), 47 patients (16 %) died of which 27 deaths were considered of cardiac origin. In this period, 21 patients underwent coronary artery bypass grafting and 8 patients had a percutaneous coronary intervention. Non cardiac causes (total n= 20) of death were infectious diseases (pneumonia or septic shock) (n= 7), malignancies (n= 4), cerebro-vascular attacks (n= 3), renal failure (n= 2) and other causes (n= 4).

a) All-cause mortality

Clinical characteristics in survivors and non-survivors

Patients' characteristics are summarized in table 1. The median age of the study population was 78 years (range 75-91 years) and 160 (54 %) of the 294 patients were male. Patients who died during the follow-up period were significantly more of male gender (p= .018) and had a higher resting heart rate (p= .001). There were no significant differences in survival between patients who underwent a different modality of stress testing.

Medical treatment in survivors and non-survivors

At the start of the follow-up period, 152 patients (52 %) were taking beta-blockers and 136 (46%) Angiotensin-Converting Enzyme inhibitors or Angiotensin-II antagonists as medical treatment (table 2). Survivors were more often taking beta-blocker treatment (p= .020) than non-survivors.

Gated SPECT variables in survivors and non-survivors

Resting myocardial perfusion was significantly worse in patients who died during the follow-up period. Non-survivors also had a significant worse global left ventricular function compared to survivors, which is reflected in lower resting and post stress left ventricular ejection fractions and larger cardiac volumes (table 3). There was however no significant difference in median SDS score or in presence of ischemia in survivors versus non-survivors.

Multivariate predictors of all-cause mortality

In a multivariate Cox proportional hazard model, a higher resting heart rate and absence of beta-blocker treatment were independent clinical predictors of all-cause mortality (X^2 = 13.9, p <.001). After forcing the resting heart rate and the knowledge of beta-blocker treatment into the multivariate Cox regression model, additional predictive information was provided by the SRS (X^2-gain of 8.0, p=.009) and the TID ratio (additional X^2-gain of 6.3, p=.012).
In a final step, functional information was added to the model. This showed that the resting LVEF provided an additional X^2 -gain of 7.0 (p=.030) above the clinical and perfusion SPECT parameters for the prediction of all-cause mortality.
All-cause mortality curves for SRS, TID index and resting LVEF are shown in figures 1-3. For the SRS curve, patients were divided in normal (SRS 0-3), mildly abnormal (SRS 4-8) and moderately-severely abnormal (SRS > 8). For the TID index, patients were divided on the median. To obtain the resting LVEF curve, patients were grouped as followed: normal (LVEF > 45%) mildly depressed LV (LVEF 30-45%) and severely depressed function (LVEF < 30%). Annual mortality rates were 17.4%, 11.1% and 5.1% in patients with a resting LVEF < 30%, 30-45% and > 45% respectively (p< .0001). This results in a hazard ratio of 3.5 for patients with a LVEF < 30% versus those with a LVEF > 45%.
In fact, the prognostic value of the resting LVEF had a higher predictive value for all-cause mortality than either perfusion SPECT or clinical parameters (table 4).

b) Cardiac mortality

Univariate predictors of cardiac mortality

The only univariate clinical predictor of cardiac death was a higher age (p= .048). Considering function and perfusion SPECT data, univariate predictors of cardiac death were a higher SSS, a higher SRS, an abnormal perfusion scan, a lower resting and post stress LVEF and larger resting and post stress cardiac volumes (table 5). Similar as for all-cause mortality, there was no higher SDS score or more frequent presence of ischemia in patients who died from a cardiac cause.

Multivariate predictors of cardiac mortality

In the multivariate Cox proportional hazard model, the SRS (X^2-gain of 10.3, p=.001) and the resting left ventricular end systolic volume (additional X^2-gain of 8.9, p=.003) were independent predictors of cardiac death above clinical parameters (= higher age, $X^2 = 4.7$; $p = .031$).
Cardiac mortality curves for SRS and left ventricular end systolic volume are shown in figure 4 and 5. For the SRS curve, patients were grouped as discussed above. To obtain the end systolic volume curves (figure 5), a cut-off was made on ≤ 70 versus > 70 ml based on previous prognostic data (1). In a sensitivity analysis (ROC-analysis) performed on our data we found that a cut-off point of 60 and 70 ml gave similar sensitivities. A cut-off of 70 ml resulted however in a better specificity than 60 ml (79% versus 73%). The annual cardiac mortality rate was 10.4% in patients with a resting end systolic volume > 70ml versus 2.3% in those with an end systolic volume ≤ 70 ml (p= .002), resulting in a hazard ratio of 4.5.
The predictive value of the resting left ventricular end systolic volume was clearly more predictive of cardiac death than clinical and perfusion SPECT parameters (table 6).

Discussion

Our data show that functional parameters obtained by gated SPECT provide incremental and independent prognostic value above clinical and perfusion SPECT parameters in patients aged 75 years or above.

Prognostic value of myocardial perfusion imaging in the elderly patient population

Multiple studies investigated the prognostic value of myocardial perfusion imaging in patients with known or suspected CAD for predicting cardiac events and cardiac mortality [4,6,15-18]. These studies demonstrated the prognostic or incremental prognostic value of myocardial perfusion imaging above clinical variables in middle-aged patient populations with known or suspected CAD.
Iskandrian et al. found a prognostic value for exercise thallium-201 planar imaging in 499 patients aged 60 years or older for the prediction of future cardiac death or non-fatal myocardial infarction [19]. Steingart et al. investigated 578 patients aged 65 years or older with interpretable electrocardiograms who were able to perform exercise testing with myocardial perfusion imaging (technetium-99m ligands and thallium-201) [20]. There were 39 deaths and 17 non-fatal myocardial infarctions during a 4.4±1.3 year follow-up. They found that ischemia on perfusion imaging provided only limited prognostic information above clinical parameters in this population. More recently, Schinkel et al. investigated 272 patients aged > 65 years and a limited exercise capacity using dobutamine tetrofosmin SPECT [21]. In concordance with our findings in patients aged > 75 years, the summed stress score and an abnormal perfusion scan (fixed or reversible) provided incremental information over clinical data in the prediction of all-cause mortality, cardiac death and cardiac death or non-fatal myocardial infarction.
However, due to aging of the general population, a patient population above 60 or 65 years cannot be considered a really elderly population. Shaw et al. found that an abnormal perfusion scan was the best predictor of cardiac events in 348 patients older than 70 years who underwent dipyridamole planar thallium-201 perfusion imaging [22]. Similar findings were reported by the same group in 120 patients older than 70 undergoing exercise planar thallium-201 perfusion imaging [23].
The first study investigating the prognostic value of perfusion imaging a large population (328 patients) aged 75 years or older was performed by Lima et al. [24]. In this study, there were 24 cardiac deaths during a 34±15 months follow-up time. Similar to our findings, the authors found that an abnormal myocardial perfusion imaging (fixed or reversible defect) was an independent predictor of cardiac death.
Recently Valeti et al. reported on the prognostic value of thallium-201 perfusion imaging in 247 patients aged 75 years or older [25]. In concordance with our findings, they found that a higher summed stress score provided incremental information above clinical parameters. A higher summed difference score, ventricular enlargement (graded subjectively as present or absent) and increased uptake of

thallium-201 in the lungs were univariate predictors of cardiac death or myocardial infarction, but these parameters did not prove any incremental value once the summed stress score was entered in the model.
Gated SPECT imaging was however not performed by any of these previous prognostic studies in the elderly. Therefore, our study is unique in the fact that it showed that further prognostic stratification is possible by implementing left ventricular functional data.

Prognostic value of left ventricular functional parameters

Multiple studies demonstrated the prognostic value of left ventricular functional parameters using gated radionuclide angiography [26-28], X-ray angiography [29], echocardiography [30-33] and even cardiac magnetic resonance [34] in the middle-aged population. Using gated SPECT, Sharir et al. found that post stress LVEF and post stress LV end-systolic volume assessed during gated SPECT had incremental predictive value above clinical parameters in predicting cardiac death [1]. In our study post stress LVEF provided similar prognostic information as resting LVEF and post stress end-systolic volume similar information as resting end-systolic volume. This could be expected because correlation between resting and post stress parameters is very high (.91 for LVEF's and .96 for LV end-systolic volumes). Therefore, when functional data are only obtained during stress imaging, these data can be used for prognostic stratification instead of the resting data.
Our study is the first showing that left ventricular functional data obtained by gated SPECT provide significant incremental value above clinical and SPECT perfusion parameters in predicting all-cause and cardiac mortality in an elderly patient population.

Prognostic value of LV dilatation at stress

The TID ratio is a marker for the transient enlargement of the left ventricle after stress. It is most commonly known for its diagnostic power [10]. However, also the prognostic value of a high TID ratio has been extensively investigated in middle-aged patient populations with CAD [10,35,36]. We found similar prognostic value for TID in patients aged 75 years or above.

Study limitations

Related to the high age, only 103 (35 %) of the 294 patients were able to perform maximal bicycle exercise stress. Therefore, a possible prognostic value of nuclear imaging variables incremental to parameters obtained during bicycle stress (stress electrocardiography changes, maximum workload or blood pressure change) could not be assessed. The relative low percentage of patients who underwent maximal stress testing in this study might also explain the reason why post stress functional parameters provided similar prognostic information as resting functional parameters.
A possible prognostic value of regional wall motion analysis was not performed since there is no well-validated software available for this purpose and because variability of visual wall motion analysis is high.

Conclusions

This study showed that left ventricular functional data assessed during myocardial gated SPECT provide independent and incremental information above clinical and perfusion SPECT data for the prediction of cardiac and all-cause mortality in patients aged 75 years or older referred for myocardial SPECT imaging.

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Tables

Abbreviations in the tables

ACE-I: Angiotensin converting enzyme inhibitors
AT-IIA: angiotensine-II antagonists
BMI: body mass index
CABG: coronary artery bypass grafting
ECG: electrocardiography
LVEDV: left ventricular end diastolic volume
LVEF: left ventricular ejection fraction
LVESV: left ventricular end systolic volume
MI: myocardial infarction
MPI: myocardial perfusion imaging
n: number
PCI: percutaneous coronary intervention
pts: patients
SRS: summed rest score
TID: transient ischemic dilatation ratio
y: years

Table 1

Clinical backgrounds of all patients and comparison between survivors and non-survivors.

	Demographics	All pts (n=294)	Non-survivors (n= 47)	Survivors (n= 247)	P
	Age (y)	78 (76-80)	78 (76-80)	78 (76-79)	.255
	Male gender (%)	160 (54%)	33 (70%)	127 (51%)	.018
	BMI (kg/m^2)	25.5 (23.4-27.9)	25.4 (22.8-28.0)	25.5 (23.4-27.9)	.499
	Known ischemic heart disease	237 (81%)	39 (83%)	198 (80%)	.655
	Clinical angina	52 (18%)	7 (15%)	45 (18%)	.585
	Hypertension	175 (60%)	26 (55%)	149 (61)	.462
	Systolic blood pressure (mm Hg)	140 (122-160)	140 (120-160)	140 (125-160)	.452
	Diastolic blood pressure (mm Hg)	80 (70-89)	80 (70-89)	80 (72-88)	.769
	Diabetes mellitus	63 (21%)	14 (29%)	49 (20%)	.142
Cardiac history	History of MI	111 (38%)	20 (43%)	91 (37%)	.460
	History of PCI	44 (15%)	5 (11%)	39 (16%)	.365
	History of CABG	87 (30%)	12 (26%)	75 (30%)	.507
ECG	Resting heart rate (beats /')	65 (58-72)	70 (61-80)	63 (56-71)	.001
	Atrial fibrillation/ flutter	37 (11%)	7 (15%)	24 (10%)	.290

Data are expressed as median (25-75th percentile) or number (%).

Table 2

Medical therapy in survivors and non-survivors

	All pts (n=294)	Non-survivors (n= 47)	Survivors (n= 247)	p
Aspirin	176 (60%)	27 (57%)	149 (60%)	.713
Aspirin or warfarin	201 (68%)	31 (66%)	170 (69%)	.699
beta-blockers	152 (52%)	17 (36%)	135 (53%)	.020
ACE-I	120 (41%)	21(45%)	99 (40%)	.572
AT-IIA	18 (6%)	2 (4%)	16 (6%)	.561
ACE-I or AT-IIA	136 (46%)	23 (49%)	113 (46%)	.688
ACE-I or AT-IIA or beta-blockers	209 (71%)	32 (68%)	177 (72%)	.621
Diuretics	79 (27%)	17 (36%)	62 (25%)	.117
Spironolactone	34 (12%)	5 (11%)	29 (12%)	.829
Statine	35 (12%)	4 (9%)	31 (13%)	.434
Fibrate	22 (7%)	3 (6%)	19 (8%)	.755
Nitrates	118 (40%)	22 (47%)	96 (39%)	.309

Data are expressed as number (%).

Table 3

Gated SPECT variables of all patients and comparison between survivors and non-survivors.

	All pts (n=294)	Non-survivors (n= 47)	Survivors (n= 247)	P
Myocardial perfusion				
Summed stress score	4 (0-12)	5 (1-16)	4 (0-11)	.112
Summed rest score	4 (0-10)	7 (3-16)	3 (0-9)	.004
Summed difference score	0 (0-2)	0 (0-1)	0 (0-2)	.063
Ischemia on MPI	46 (16%)	4 (9%)	42 (17%)	.142
Abnormal MPI	165 (56%)	34 (72%)	131 (53%)	.015
TID	1.00 (.93-1.11)	1.06 (.98-1.13)	1.00 (.91-1.10)	.015
Global left ventricular function				
Resting LVEF (%)	56 (43-66)	45 (28-56)	57 (45-68)	<.001
Resting LVEDV (ml)	93 (64-131)	117 (66-169)	90 (63-126)	.011
Resting LVESV (ml)	41 (23-71)	56 (32-127)	39 (22-68)	.001
Post stress LVEF (%)	58 (44-69)	47 (31-62)	60 (48-70)	<.001
Post stress LVEDV (ml)	95 (68-136)	122 (75-179)	89 (65-126)	.002
Post stress LVESV (ml)	39 (21-75)	66 (35-136)	37 (19-64)	<.001

Data are expressed as median (25-75th percentile) or number (%).

Table 4

Comparison of the predictive value for all-cause mortality of clinical, SPECT perfusion and functional parameters.

	Parameters	X^2	P
Clinical model		13.9	< .001
Myocardial perfusion	SRS	7.0	.008
	TID	4.1	.037
Functional data	Resting LVEF	16.9	< .001
	Post stress LVEF	16.1	< .001

Table 5

Gated SPECT variables in patients who died from a cardiac cause versus those who did not.

	Cardiac death (n= 27)	No cardiac death (n= 267)	P
Defect extent			
Summed stress score	8 (2-17)	4 (0-11)	.030
Summed rest score	8 (4-17)	4 (0-11)	.007
Summed difference score	0 (0-1)	0 (0-2)	.464
Ischemia on MPI	2 (7%)	44 (16%)	.217
Abnormal MPI	21 (78%)	144 (54%)	.018
TID	1.06 (.98-1.10)	1.00 (.92-1.11)	.087
Global left ventricular function			
Resting LVEF (%)	36 (24-56)	56 (45-67)	<.001
Resting LVEDV (ml)	141 (76-233)	90 (63-126)	.002
Resting LVESV (ml)	82 (31-176)	40 (23-68)	.001
Post stress LVEF (%)	35 (28-55)	59 (47-70)	<.001
Post stress LVEDV (ml)	137 (79-232)	90 (67-126)	.001
Post stress LVESV (ml)	87 (35-156)	38 (20-65)	<.001

Data are expressed as median (25-75th percentile) or number (%)

Table 6

Comparison of the predictive value for cardiac death of clinical, SPECT perfusion and functional parameters.

	Parameters	X^2	P
Clinical model		4.7	.031
Myocardial perfusion	SRS	10.9	.001
Functional data	Resting LVESV	24.4	< .001
	Post stress LVESV	20.4	< .001

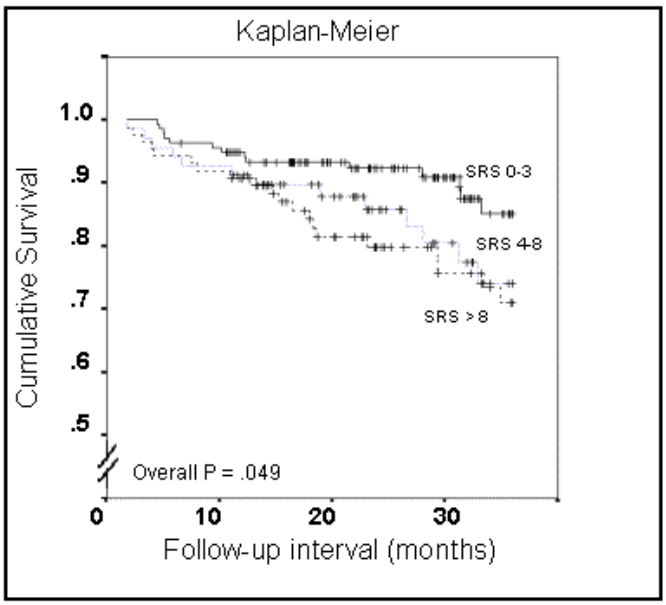
Figures

Abbreviations in the figures

ESV: end systolic volume
LVEF: left ventricular ejection fraction
SRS: summed rest score
TID ratio: transient ischemic dilatation ratio

Figure 1

All-cause mortality in function of the summed rest score.

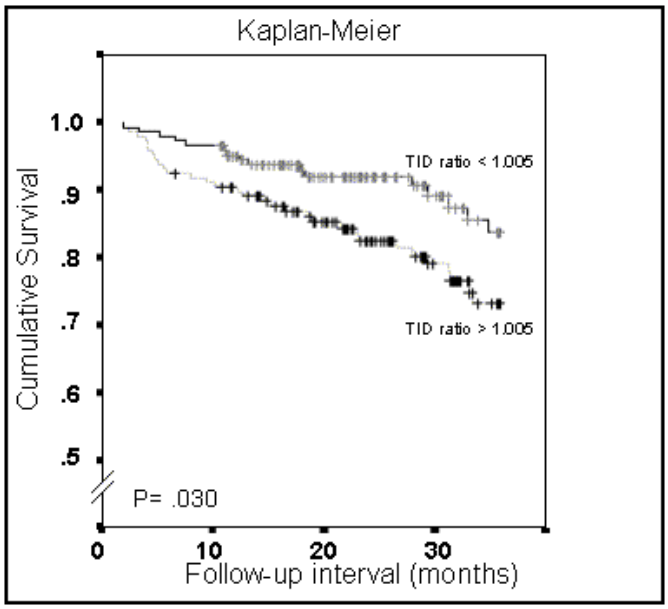


Kaplan-Meier survival curves according the resting LVEF group:

a) SRS 0-3 (n= 138, 14 deaths)
b) SRS 4-8 (n= 69, 13 deaths)
c) SRS > 8 (n=87, 20 deaths)

Figure 2

All-cause mortality according to the TID ratio.

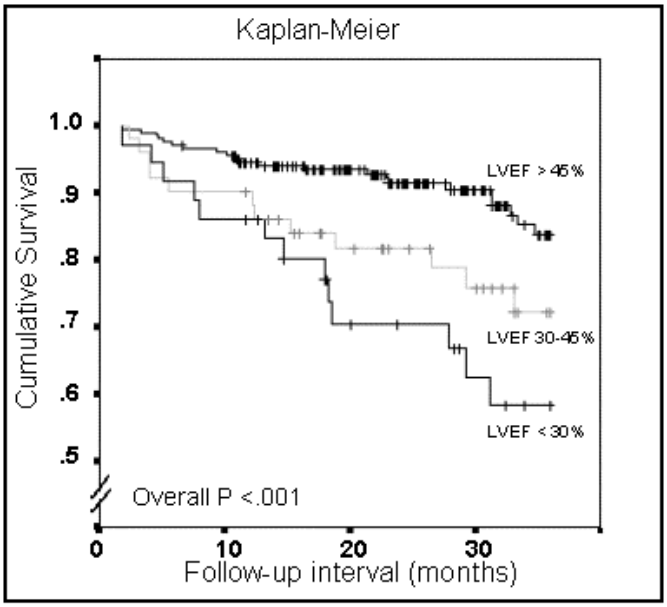


Kaplan-Meier survival curves according the TID divided on the median:

a) TID ratio < 1.005 (n= 147, 16 deaths)
b) TID ratio > 1.005 (n= 147, 31 deaths)

Figure 3

All-cause mortality in function of the resting left ventricular ejection fraction.

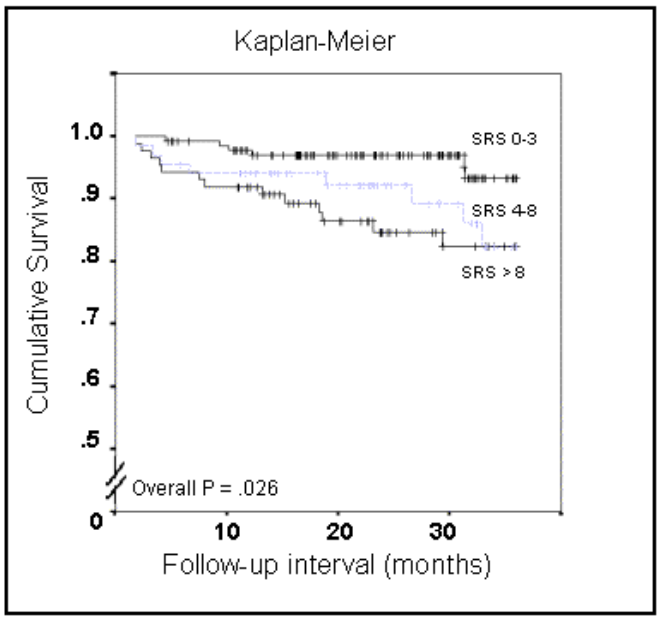


Kaplan-Meier survival curves according the resting LVEF group:

a) LVEF > 45% (n= 207, 22 deaths)
b) LVEF 30-45% (n= 51, 12 deaths)
c) LVEF <30% (n=36, 13 deaths)

Figure 4

Cardiac mortality in function of the summed rest score.

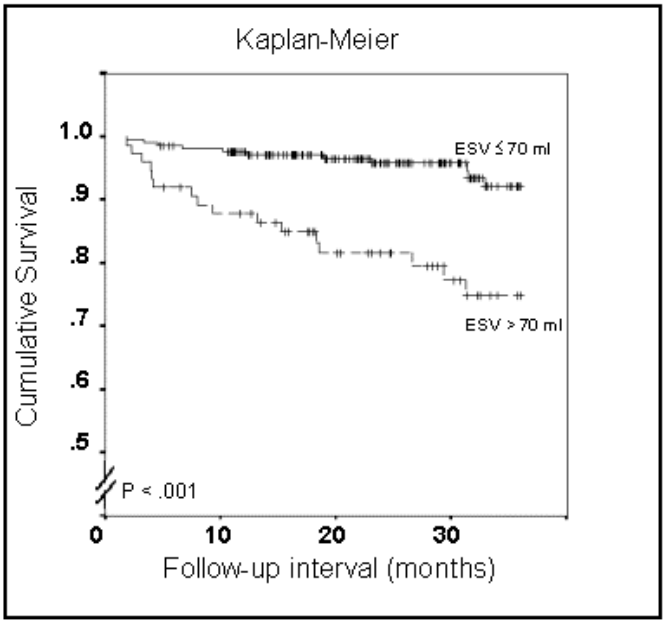


Kaplan-Meier survival curves according the SRS group:

a) SRS 0-3 (n= 138, 6 cardiac deaths)
b) SRS 4-8 (n= 69, 8 cardiac deaths)
c) SRS > 8 (n=87, 13 cardiac deaths)

Figure 5

Cardiac mortality in function of the resting left ventricular end systolic volume.



Kaplan-Meier survival curves according the resting ESV:

a) ESV ≤ 70 ml (n= 219, 11 cardiac deaths)
b) ESV > 70 ml (n= 75, 16 cardiac deaths)

General discussion and future prospects

In this discussion, main results of the study findings in this thesis are summarised and placed in perspective to findings by other groups. Also future prospects are given.

Chapter 1

In the first chapter, we investigated relevant technical issues regarding myocardial and bloodpool gated single photon emission computed tomography (SPECT) imaging.

First, we investigated the day-to day variability of perfusion and global left ventricular (LV) measurements assessed by Quantitative Gated SPECT (QGS®, Cedars-Sinai, Los Angeles, California, USA) using 99m-technetium tetrofosmin in patients with coronary artery disease (CAD) and LV dysfunction. This imaging technique is routinely used in these patients for follow-up of myocardial perfusion and function over time. The knowledge of the day-to day variability of this technique is important since myocardial gated SPECT is routinely used for follow-up of changes in LV perfusion and function in these patients. We showed that variability of these global indices of cardiac function assessed during gated myocardial SPECT is fairly small in this patient population and is comparable to other techniques such as cardiac MRI (magnetic resonance imaging). Therefore, this imaging technique can be used for the detection of changes global LV functional parameters (LV ejection fraction or volumes) in these patients.

Secondly, we investigated the agreement between four software algorithms for the calculation of left and right ventricular functional data obtained during gated bloodpool SPECT imaging. For LV ejection fraction (LVEF), tomographic radionuclide ventriculography techniques were compared with the well-validated planar gated bloodpool technique. We found that the LVEF calculated by the four algorithms correlated well with planar radionuclide ventriculography (correlation coefficients between .71 and .81) and Bland-Altman plotting showed no significant trends across the range of LVEF values. Therefore, these algorithms can be applied in clinical practice for the determination of LVEF. However, LVEF values are not interchangeable between planar and tomographic techniques or between different tomographic algorithms. Volume calculations, especially from the right ventricle need further validation, mainly with other techniques, such as cardiac magnetic resonance before they can be applied in clinical practice.

Chapter 2

In chapter 2, we investigated the clinical value of myocardial gated SPECT imaging in patients with CAD and LV dysfunction.

First, we investigated the prognostic value of combined perfusion and functional imaging using myocardial gated SPECT in these patients. Due to an increased survival of CAD patients, the prevalence of congestive heart failure is increasing in the general population and in the cardiologist's practice. Multiple studies have investigated the prognostic value of myocardial perfusion imaging (MPI) in subjects with known or suspected CAD for predicting future cardiac events and mortality [1-6]. However, these prognostic data were all collected in patient populations with known or suspected CAD and only few data are available regarding the prognostic value of MPI in patients with impaired LV function and known CAD. The risk for subsequent cardiac events is much higher in this population than in the generally investigated populations [7]. Therefore, results and risk factors found in other populations may not be extrapolated [8]. Data on the prognostic value of MPI in patients with CAD and LV dysfunction are scarce. We found that the combined assessment of function and perfusion using 99m-technetium tetrofosmin gated SPECT provided significant and independent predictive information regarding the subsequent risk of major cardiac events in 261 patients with CAD and systolic LV dysfunction (LVEF ≤40%). The detection of ischemia on MPI was predictive of future major cardiac events, however it was not a significant predictor of future cardiac death. In concordance with our data, Miller et al. found a higher revascularisation rate, but no difference in survival between patients with large ischemic defects versus patients with large fixed defects in 214 patients with a LVEF <45 % [9]. In 156 patients with CAD and a LVEF < 30 %, Sharir et al. also did not find a difference in mortality in patients with fixed versus reversible defects [10]. The unique aspect of our study compared to previous prognostic data are the fact that we included resting and post stress gated functional data in our analysis in a patient population with CAD and impaired systolic LV function. Our data demonstrate that even in this population in which all patients had a depressed LVEF and the spreading of LVEF values was narrow, post stress LVEF was highly predictive for future cardiac events and provided incremental value in the prediction of future cardiac death. As part of a larger study, Sharir et al. investigated a subgroup of 277 patients with suspected CAD and a LVEF < 45% using gated SPECT and followed these during 19 ± 5 months [11]. They concluded that it is possible to further risk stratify these patients upon a post stress LV end systolic volume with 70 ml as cut-off value. Although the size of our study group was comparable and our follow-up was even longer, we did not find an important predictive value for cardiac volumes in our study. Only 20 patients (7.8 %) in our population with CAD and a LVEF < 40% had a post stress LV end systolic volume < 70 ml and these patients had no significant lower mortality than those with a LV

end systolic volume ≥ 70 ml. In our study group, there was a trend towards a higher resting (p= .084) and post stress (p= .010) LV end systolic volume in patients with a subsequent hard event (cardiac death or non-fatal myocardial infarction). However, once the post stress LVEF was added to the model, there was no further predictive value for LV volumes.

Secondly, we investigated the relation between QRS duration, LV volumes and localisation of non-viable tissue in patients with CAD and severe systolic LV dysfunction (LVEF ≤30%). We found that a prolonged QRS duration (>120 milliseconds) is present in almost 70% of these patients. This increase in QRS duration is clearly related to an increase in LV end diastolic and end systolic volumes, indicating more advanced remodelling in these patients. Patients with CAD, an increased QRS duration and severe LV dysfunction are possible candidates for cardiac resynchronisation therapy. We found however that 30% of these patients had substantial non-viable tissue in the inferolateral wall, the region were the LV pacing lead is usually placed. Since non-viable tissue is electromechanically non-functional, lead placement on non-viable LV wall tissue could lead to ineffective pacing in these patients. The high prevalence of non-viable tissue in these patients could be one of the explanations why cardiac resynchronisation therapy is ineffective in a substantial number of patients with CAD. Further prospective studies are however needed to determine whether viability assessment can help in the selection of candidates for cardiac resynchronisation treatment and in the determination of the optimal lead localisation.

Chapter 3

In chapter 3, we performed studies in the elderly population using myocardial gated SPECT imaging.

First, we investigated the determinants of amino-terminal pro Brain Natriuretic Peptide (Nt-proBNP) in 247 patients with stable CAD aged 60 years or above. Brain natriuretic peptides are neurohormones synthesized by and released from cardiac myocytes in response to an increased wall stress. In patients with failing hearts, peptide production increases and becomes more generalised throughout the myocardium [12]. Nt-proBNP is a valuable tool in the diagnosis of heart failure [13,14] and has prognostic value in CAD patients [15,16]. In healthy people, increasing age, female gender and a lower heart rate have been shown to be associated with higher Nt-proBNP values [17,18]. We found that a higher post stress LV end systolic volume, a worse kidney function (lower glomerular filtration rate) and a higher age were independent predictors of a higher Nt-proBNP in our investigated population of CAD patients aged 60 years or above. We found however no significant relationship between myocardial ischemia and Nt-proBNP levels.

Secondly, we investigated the prognostic value of combined gated SPECT perfusion and function imaging in 294 patients aged 75 years or above referred for MPI. We showed that LV functional parameters obtained during gated SPECT provide significant incremental value above clinical and perfusion SPECT parameters for the prediction of cardiac death and all-cause mortality. In fact, functional data assessed during gated SPECT had a higher predictive value for cardiac death and all-cause mortality than either perfusion SPECT or clinical parameters. Multiple previous studies investigated the prognostic value of MPI in elderly patients [19-25]. Gated SPECT imaging was however not performed by any of these previous prognostic studies in the elderly. Therefore, our study was unique in the fact that it showed that further prognostic stratification in the elderly is possible by implementing LV functional data.

Future prospects

The number of patients with CAD and LV dysfunction will further increase during the next decade due to aging of the population and better medical and revascularisation strategies. Similarly, the proportion of elderly patients referred to the cardiology department will continue to grow. This will result in a higher demand for non-invasive imaging techniques. These techniques should be accurate, cost-effective, patient friendly and preferably with low or no radiation burden.
Gated SPECT imaging has proven diagnostic and prognostic abilities for the detection of significant CAD and may prove in the future to be an ideal tool in these patients because it allows both the detection of perfusion and functional abnormalities and it gives additional prognostic information. Myocardial perfusion imaging has proven to be a cost-effective gatekeeper in the management of patients with suspected CAD [26]. However, due to the aging of the population, healthcare demands will continue to rise. Therefore it is necessary that large cost effectiveness studies of diagnostic strategies using gated SPECT are compared against other imaging modalities in selected patient populations. In the mean time, imaging modalities of the heart are improving fast:

-Technical advances in the echo equipment have improved image quality of contrast echocardiography (perfusion imaging). Using 3-dimensional echocardiography, it is now possible to measure accurate LV volumes without the assumption of an ideal ellipsoid structure. Stress echocardiography is a radiation free alternative for cardiac imaging of myocardial ischemia and is based on the visualisation of wall motion abnormal wall motion during or after stress (stunning).
-Due to its high resolution and because it is free of radiation burden, cardiac magnetic resonance has several advantages above other imaging techniques. Although it is technically possible to perform both perfusion imaging and functional imaging of the left ventricle, cardiac MRI is still time consuming. Similar as in stress echocardiography, ischemia imaging by this technique is indirect by showing wall motion abnormalities during or after stress.
-Since the development of multislice CT-scanners, CT-angiography is new promising tool in clinical cardiology. It allows to visualise the coronary anatomy and makes it possible to diagnose CAD in a non-invasive manner. Therefore, this tool could become important in risk stratification of asymptomatic patients. However, at present time, it does not give information on myocardial function or perfusion.

-With the increasing availability of positron emission tomography (PET), an increasing number of centres are able to perform fluorodeoxyglucose (FDG) PET for viability imaging. However, PET perfusion imaging is also becoming more available. Previously, PET perfusion studies could only be performed in centres with an in-house cyclotron to provide ammonia (13-NH3) or O-labelled water. Recently, generator based 82-rubidium has been commerialised, and this results in an increase in the number of centres performing PET perfusion imaging in daily routine. The use of 82-rubidium PET is still very expensive (costs of the PET camera and the isotope); however, the favourable imaging characteristics, high possible throughput (stress and rest imaging possible in 40 min) and the very low radiation burden to the patients (only 2.75 mSv) [27] means that this technique has possibilities in the next few years .

-PET/CT opens possibilities towards a 'one-stop-shop' in cardiac imaging; however, the complexity of data acquisition, reconstruction and analysis, together with the unsolved item of cost effectiveness and radiation exposure, need further proof and validation before it can be used in clinical practice.

-In SPECT imaging, attenuation correction of the images is made easier in the daily clinical practice because of the introduction of dedicated cardiac SPECT scanners with transmission sources. Also the recent development of hybrid SPECT/CT makes attenuation correction easier in the clinical routine and offers possibilities for combined visualisation of myocardial perfusion (by SPECT) and coronary artery stenosis (by CT angiography).

Recently, new biochemical parameters, such as Nt-proBNP, have also shown prognostic value in selected patient populations [15,16]. Future studies are needed to determine the clinical utility of natriuretic hormones and other biochemical markers as compared to different imaging modalities.

Finally, non-invasive cardiac imaging will continue to grow and the true challenge will be to establish the added value of the different techniques in different patient populations in a cost-effective manner.

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Summary

Prognosis in patients with coronary artery disease (CAD) is determined by clinical and biochemical factors, the extent and severity of the CAD and the degree of left ventricular dysfunction.
The major goal of this thesis was to assess the prognostic value of combined perfusion and function imaging using myocardial gated single photon emission computed tomography (SPECT) in two subgroups of the cardiac population: patients with CAD and left ventricular dysfunction and the elderly.

There were three aims: 1) to investigate the variability of gated SPECT techniques 2) to assess the prognostic value of gated myocardial perfusion imaging in patients with CAD and left ventricular dysfunction 3) to assess the prognostic value of gated myocardial SPECT in the elderly.

In the first chapter of this thesis, we investigated relevant technical issues regarding cardiac gated SPECT imaging.
First, we investigated the day-to day variability of myocardial perfusion and global left ventricular measurements assessed by Quantitative Gated SPECT (QGS®, Cedars Sinai, Los Angeles) using 99m-technetium tetrofosmin in patients with CAD and left ventricular dysfunction. We showed that variability of global indices of left ventricular function (ejection fraction, end systolic and end diastolic volumes) is fairly small in this patient population. Therefore, this imaging technique can be used for the detection of left ventricular functional changes in these patients.
Secondly, we investigated the agreement between four software algorithms for the calculation of left and right ventricular ejection fraction and volumes obtained during bloodpool gated SPECT imaging. We found that the left ventricular ejection fraction (LVEF) calculated by these four algorithms correlated well with planar radionuclide ventriculography and that there were no significant trends across the range of LVEF values. We concluded that, although results from these algorithms are not interchangeable, they can be used in clinical practice for calculation of the LVEF. Calculation of the right ventricular ejection fraction and volume assessment need however further validation before they can be implemented in clinical practice.

In the second chapter, we investigated the clinical value of myocardial gated SPECT in patients with CAD and left ventricular dysfunction.
First, we investigated the prognostic value of combined perfusion and function imaging in this population. We found that the combined assessment of perfusion and function provides significant independent predictive information regarding the subsequent risk of major cardiac events in these patients. Our data demonstrated that, even in this population where all patients had a depressed left ventricular function and the spreading of the LVEF's was narrow, post stress LVEF had a high predictive value for future cardiac events and provided incremental predictive value for future cardiac death.

Secondly, we investigated the relation between QRS duration, left ventricular volumes and the localisation of non-viable tissue in patients with CAD and severe systolic left ventricular dysfunction (LVEF ≤ 30%). We found that the increase in QRS duration is clearly related to the increase in left ventricular end diastolic and end systolic volumes, indicating a more advanced remodelling in these patients. We also found that 30% of the patients with a LVEF ≤ 30% and an increased QRS duration have substantial non-viable tissue in the inferolateral wall. This may be important since these patients are possible candidates for cardiac resynchronisation treatment and because lead placement on non-viable tissue may lead to ineffective cardiac pacing.

In the third chapter, we investigated clinical, biochemical, myocardial perfusion and function SPECT determinants of amino-terminal brain natriuretic peptide (NT-proBNP) in the elderly. We found that a higher post stress end systolic volume, a worse kidney function and a higher age were independent predictors of a higher NT-proBNP in patients with CAD aged 60 years or above. We found however no significant relationship between myocardial ischemia and Nt-proBNP levels.
Secondly, we investigated the prognostic value of combined perfusion and function imaging using myocardial gated SPECT in patients aged 75 years or above referred for MPI. We showed that left ventricular functional data obtained during gated SPECT provide significant incremental predictive value above clinical and SPECT perfusion parameters. In fact, functional data had a higher predictive value for cardiac death and all-cause mortality than either clinical or perfusion SPECT data. Therefore, further prognostic stratification is possible by implementing left ventricular functional information in elderly patients undergoing MPI.

Samenvatting

De prognose bij patiënten met ischemisch hart lijden (IHL) wordt bepaald door klinische en biochemische factoren, de uitgebreidheid en de ernst van het IHL en de graad van de linker ventrikel dysfunctie.
Het belangrijkste doel van deze thesis was het onderzoeken van de prognostische waarde van gecombineerde beeldvorming van de doorbloeding (perfusie) en functie van de hartspier met behulp van gated SPECT in twee populaties van hartpatiënten:

1) patiënten met IHL en linker kamer dysfunctie
2) oudere patiënten

Er waren drie vooropgezette doelstellingen 1) het onderzoeken van de variabiliteit van gated SPECT technieken 2) het onderzoeken van de prognostische waarde van gated myocardperfusie SPECT bij patiënten met IHL en linker ventrikel dysfunctie 3) het onderzoeken van de prognostische waarde van gated myocardperfusie SPECT in de oudere patiënten populatie.

In hoofdstuk 1 onderzochten we de relevante technische vraagstellingen in cardiale gated SPECT beeldvorming.
Vooreerst onderzochten we de dag- tot dag variabiliteit van de meting van de myocard doorbloeding en linker ventrikel functie gemeten met behulp van Quantitative gated SPECT software (QGS®, Cedars-Sinai, Los Angeles) voor 99m-technetium tetrofosmin bij patiënten met IHL en linker ventrikel dysfunctie. We toonden aan dat de variabiliteit van de globale linker ventrikel functie metingen (ejectiefractie, eind-systolische en eind-diastolische volumes) relatief klein is bij deze patiënten en dat daarom deze beeldvorming kan gebruikt worden voor het opsporen van linker ventrikel functionele veranderingen bij deze patiënten.
Ten tweede onderzochten we de overeenkomst tussen 4 software algoritmes welke gebruikt worden voor de berekening van de linker en rechter ventrikel ejectiefractie en volumes tijdens bloodpool gated SPECT beeldvorming. We vonden dat de linker ventrikel ejectiefractie (LVEF) berekend met behulp van deze 4 algoritmes goed overeenkomt met de planaire isotopen ventrikelbeeldvorming en dat er geen significante trends waren over de spreiding van de LVEF waarden. We concludeerden hierbij dat deze algoritmes in de klinische praktijk kunnen gebruikt worden voor de berekening van de LVEF, maar dat de waarden van de verschillende algoritmes niet onderling uitwisselbaar zijn. De berekening van de rechter ventrikel ejectiefractie en van volumes moet verder gevalideerd worden vooraleer deze in de klinische praktijk toegepast kan worden.

In het tweede hoofdstuk onderzochten we de klinische waarde van myocardperfusie SPECT bij patiënten met IHL en een linker ventrikel functie stoornis.
Ten eerste onderzochten we de prognostische waarde van gecombineerde perfusie en functie beeldvorming bij deze patiënten. We vonden hierbij dat gecombineerde meting van perfusie en functie significante voorspellende informatie oplevert met betrekking tot toekomstige cardiale events bij deze patiënten. Onze data toonden aan dat de LVEF na stress, niettegenstaande de smalle spreiding bij deze patiënten, een hoge voorspellende waarde had voor toekomstige cardiale events naast een toegevoegde voorspellende waarde voor toekomstige cardiale dood.
Ten tweede onderzochten we het verband tussen de QRS duur, linker ventrikel volumes en lokalisatie van niet-leefbaar weefsel bij patiënten met IHL en een ernstige systolische linker ventrikel functie stoornis (LVEF ≤ 30%). We vonden dat de toename van de QRS duur duidelijk verband houdt met de toename in de linker ventrikel einddiastolische en eindsystolische volumes, wat wijst op een verder gevorderde remodellering van het hart bij deze patiënten. We vonden tevens dat 30% van de patiënten met een LVEF < 30% en een verlengde QRS duur een substantiële hoeveelheid niet-leefbaar weefsel hebben ter hoogte van de inferolaterale wand. Dit kan van belang zijn bij deze patiënten aangezien ze mogelijke kandidaten zijn voor cardiale resynchronisatie behandeling en omdat de positionering van de electrodes op niet-viabel weefsel kan leiden tot niet-effectieve cardiale stimulatie.

In hoofdstuk 3, onderzochten we klinische, biochemische, myocardperfusie en myocardiale functie variabelen welke amino-terminaal brain natriuretic peptide (NT-proBNP) bepalen in een oudere patiënten populatie. We vonden hierbij dat een hoger eind systolisch volume na stress, een verminderde nierfunctie en een hogere leeftijd onafhankelijke voorspellende factoren zijn van een hoger NT-proBNP bij patiënten ouder dan 60 jaar. Deze factoren moeten dus in rekening gebracht worden wanneer NT-proBNP in deze populatie geïnterpreteerd wordt voor diagnostische of prognostische doeleinden.
Ten tweede onderzochten we de prognostische waarde van gecombineerde perfusie en functie beeldvorming met behulp van myocardiale gated SPECT bij patiënten ouder dan 75 jaar welke verwezen werden voor myocardperfusie beeldvorming. We toonden hierbij aan dat de functionele linker ventrikel data welke gemeten werden tijdens gated SPECT een significante toegevoegde waarde hadden, boven de klinische en myocardperfusie data, voor de voorspelling van cardiale en totale mortaliteit. De functionele data in se hadden zelfs een grotere voorspellende waarde voor cardiale en totale sterfte dan de klinische of myocardperfusie SPECT data. Verdere prognostische stratificatie met behulp van de functionele data van het linker ventrikel is dus mogelijk bij deze oudere patiënten welke een myocardperfusie scintigrafie ondergaan.

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Addendum

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