SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

IMPROVEMENT OF THE DETECTION OF MYOCARDIAL ISCHEMIA WITH NUCLEAR CARDIOLOGICAL EXAMINATIONS AND THE ROLE OF THE PATIENT'S POSITION IN THE QUANTITATIVE PARAMETERS PROVIDED BY THE MYOCARDIAL PERFUSION SPECT

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Live online access will be provided. If you wish to take part in the discussion, please send an e-mail to kracskobertalan@gmail.com not later, than 12 pm on the day before the discussion (January 11, 2021). After the deadline, for technical reasons, it is no longer possible to join in to the defense.

1. Introduction

1.1. Myocardial ischemia and its effect for the left ventricle

1.1.1. The development of myocardial ischemia

Left ventricular contractile function depends on some important physiological features: the coronary flow, the oxygen binding and transport capacity of the blood. Deterioration of the flow and blood supply, and the failure of oxygen delivering capacity cause deficiency in the myocardial oxygen supply resulting myocardial ischemia and angina pectoris (similarly, rise in oxygen demand will cause relative oxygen deficiency). After the admission of vasodilators, such as adenosine or adenosine reuptake inhibitor dipyridamole, altered myocardial perfusion can be observed in myocardial segments supplied by a stenotic vessel because of the coronary flow redistribution managed by segments with normal coronary flow. Reduced perfusion results in altered myocardial oxygen supply and myocardial ischemia can occur. Because of these mechanisms and insufficient oxygen supply, myocardial contractile system is also involved resulting systolic and diastolic dysfunction. Left and right ventricular volumetric parameters and ejection fraction are also affected in these circumstances. Thereby, proper quantification of the myocardial perfusion and volumetric parameters are especially important in coronary artery disease.

1.1.2. The detection of myocardial ischemia, the importance of quantitative parameters of left ventricle in coronary artery disease

According to the recent ESC guideline, a noninvasive cardiological imaging technique is suggested in intermediate pretest probability and angina symptoms (depends on feature of the angina: e.g. typical, atypical, noncardiac) to describe the probability of myocardial ischemia. The role of different cardiological imaging modalities is important in the ischemic risk stratification. High cardiovascular risk suggests significant myocardial ischemia. Diagnostic coronary angiography can prove the coronary artery stenosis in case of high cardiovascular risk detected by noninvasive imaging modalities (reversible perfusion abnormality more than 10 % of the left ventricle by nuclear cardiological imaging, myocardial ischemia in more than 3 left ventricular segments described by cardiac MR or echocardiography) or in case of uncertain noninvasive test. During coronary angiography invasive pressure monitoring can quantify the myocardial ischemia (PW technique and FFR measurement). Thereby, the noninvasive tests give the possibilities to measure left ventricular function both in stress and also in rest conditions, which is a relevant predictor of cardiovascular events. Reduced left ventricular ejection fraction can support the further invasive steps.

1.2. The role of nuclear cardiology in coronary artery disease

For years, one of the most sensitive diagnostic modalities for diagnosing coronary artery disease (CAD) was myocardial perfusion imaging (MPI). MPI is a well-established method for obtaining functional information of the myocardium. Furthermore, it is well known that stable angina patients with normal MPI study have a low risk of fatal cardiovascular event. The results can be improved by the usage of ECG gated acquisition. The ECG gated acquisition gives extra information about the function of the left ventricle, ventricular dimension can be calculated, ejection fraction can be measured and left ventricular wall motion abnormalities can be detected and finally more complex and accurate diagnosis can be achieved.

1.2.1. Tc^{99m} SestaMIBI myocardial perfusion SPECT

In the recent years, the most prevalent nuclear cardiological radiopharmaceutical is the metastable Technetium 99 labelled SestaMIBI. The radiopharmaceutical has lipophilic feature, it enters the cells by diffusion (controlled by the negative membrane potential of the intact myocardial cell), and then it accumulates only in the functional mitochondria in the vital and working myocardial cells. The injected pharmakon reflects the myocardial blood supply, the perfusion and the extent of viable myocardium. During physical or pharmacological stress test significant coronary stenosis will cause decreased cardiac perfusion in the distal segments because of altered coronary flow circumstances. Inadequate perfusion results in failure of O_2 supply and less functioning myocardium with heterogeneity of SestaMIBI distribution. Comparing the rest and stress condition different distribution caused by poor blood supply can be described.

The Tc^{99m} SestaMIBI has minimal redistribution, thus repeated injection is needed for the detection of reversible perfusion abnormality caused by myocardial ischemia. The stress test and the resting acquisition can take place on the same day or on two separate days. After the acquisition dedicated computer software processes the data, the relative and total perfusion defects can be visualized. We can represent and value the regional perfusion of the left ventricle on view and surface-projected images („bull's eye mapping). With ECG gated acquisition additional quantitative parameters can be explored such as end systolic, end diastolic volumes, ejection fraction, and left ventricular mass.

1.2.2. The role of acquisition in the calculation of quantitative parameters

SPECT images are usually acquired with the patient in supine position. The procedure itself lasts approximately 20 to 40 minutes. However, some patients are not able to lie flat on their back for an extended period of time because of a variety of medical or personal problems (e.g., orthopedic conditions, congestive heart failure, claustrophobia, etc.). In recent years, SPECT gamma cameras have been developed, which allow the imaging of the patient in sitting or upright position. The upright sitting position alters the position and shape of the heart, and consequently changes soft tissue attenuation.

Clinical stress SPECT imaging routinely incorporates commercial software for quantification of LV function and volumes and, most importantly, quantification of regional myocardial perfusion abnormalities relative to a normal reference database. These commercially available normal databases were created from images obtained in normal volunteers in supine position, or sometimes in prone position.

1.3. Myocardial ischemia detection by invasive pressure measurements – FFR

The reduced myocardial oxygen supply can be detected by invasive and non-invasive procedures.

Myocardial ischemia caused by coronary sclerosis can be quantified during diagnostic coronary angiography by pressure wire technique. This method was validated with PET in 1994. It is well documented that the manipulation of the wire into the coronary tree is easy and safe and the fractional flow reserve (FFR) was comparable with standard non-invasive tests for myocardial ischemia in invasive circumstances. FFR can be calculated from actually measured flow (in the stenotic vessel) and achievable maximal flow (in a normal vessel) in the relevant coronary artery. At maximal arteriolar vasodilatation, a close linear relationship can be found between coronary flow and pressure. The invasively measured FFR value calculated as a pressure ratio of the distal and proximal pressure (Pa/Pd) shows the fraction of the achievable flow through the stenotic coronary artery, indicating the functional severity of coronary lesion. The FFR value <0.75 implied significance and strongly correlated with non-invasive ischemia. The latest studies confirm the clinical relevance of FFR values in single-vessel (DEFER study) and multivessel disease (FAME study). When non-invasive stress imaging is unavailable, the measurement of FFR on coronary lesions with intermediate severity is helpful. According to the current ESC guideline, the indication of percutaneous coronary interventions is based on the determination of FFR when functional information of moderate coronary stenosis is lacking. It is a simple, reliable and reproducible method, but the FFR value itself does not reflect the localization of stenosis.

Based on previously reported studies, the invasively measured FFR and the quantitative parameters generated from two-day Tc99m SestaMIBI examinations have significant correlation.

2. Aims

The overall aim of our study was to analyze two main problems to improve the usefulness of the everyday nuclear cardiological examinations:

a. How can the invasively measured pressure wire technique provided functional information about coronary stenosis be optimized by stress-rest myocardial perfusion imaging technique?
b. Are the acquisition and the postprocessed quantitative and semi-quantitative parameters affected by the patient position during nuclear cardiological examination?

3. Patients and Methods

3.1. The relationship between the location of coronary stenosis and the supplied left ventricular segments

3.1.1. Patient's population

The coronary angiograms of 28 patients (male: 22, female: 6, age 62+7.6) were analyzed retrospectively by Holistic Coronary Care (HCC Coronart Ltd., Debrecen, Hungary). The software registered 23 epicardial coronary segments using the modified SYNTAX segmentation system. The supplied left ventricular segments on the standard 17- segment polar map was rendered to each coronary branch by an appropriate algorithm. All 28 patients had stress/rest SPECT acquisition followed by FFR measurements within six months. Regarding pressure wire measurements commonly one vessel was examined in one patient, however in 6 cases 2 vessels/patient and in one case 3 vessels/patient were measured, respectively. In every case one stenosis were studied in one vessel. Measurements were performed in all intermediate stenosis (40-60%) expect on the culprit vessels of prior myocardial infarctions. Thus, 36 vessels with 36 intermediate stenosis were compared with the myocardial perfusion SPECT studies.

3.1.2. Left Ventricular ischemic index, „Holistic Coronary Care"

According to or hypothesis FFR results are significantly influenced by the supplied left ventricular mass: the more extended the supplied left ventricular mass is, the higher FFR value will also cause myocardial perfusion abnormality. Thus, we introduced a new ischemic index by combining the FFR value with the number of the corresponding myocardial segments (N) determined by HCC software: left ventricular ischemic index [LVIi=N x (1-FFR)]. This index was correlated with the regional myocardial perfusion defects identified on the scintigrams. Regional perfusion reversibility score, which was calculated automatically from the regional summed stress and regional summed rest score, of 2 or above was considered as indicative of active ischemia (regional Difference Score: rDSc).Regional segments on scintigram were the same which was determined by HCC.

3.1.3. Coronary angiography and FFR measurement

Cardiac catheterization was performed in local anesthesia from femoral or radial approach. The image acquisition was executed by Axiom Artis (Siemens Medical Solutions of Siemens AG, Erlangen, Germany) X-ray machine at a speed of 15 frames/second. During cardiac catheterization, a 6 F guiding catheter without side-holes was positioned at the orifice of the left or right coronary artery to detect the proximal (aortic) pressure without damping. The distal pressure was recorded by a pressure-sensor guidewire (PressureWire Certus, Radi Medical, Uppsala, Sweden) advanced at about 3 cm distally from the stenosis. Maximal hyperemia was induced by intracoronary injection of 100 micrograms of adenosine. The aortic pressure at the guide tip (Pa) and distal coronary pressure (Pd) were simultaneously measured. The FFR value was calculated as the ratio of these pressures: Pa/Pd.

3.1.4. Stress/rest perfusion scintigraphy

A separate-day non-gated stress/rest perfusion scan protocol was performed before FFR-guided PCI in all cases. Patients had fasted overnight. Coffee and medication containing caffeine or aminophylline were withdrawn for at least 12 hours. Approximately 400-450 MBq technecium-99m SestaMIBI was injected intravenously for stress (3 minutes after the dipyridamole injection) and on another day the same doses for rest acquisition, respectively. Acquisition was initiated 60-90 minutes after the injections. Data acquisition was performed with a double-headed Cardio-C camera (Mediso Ltd., Budapest, Hungary). The energy discrimination was centered on 140 keV with a 20% window. 64 projections were acquired on 180° using a high-resolution collimator, with 64x64 matrices. Short-axis slices were reconstructed using InterviewXP (Mediso Ltd., Budapest, Hungary), and then the Emory Cardiac ToolBox 3.0 was applied for quantitative analysis, using 17 segments. A severity score was assigned to each segment by the software automatically, ranging from 0 (normal perfusion), to 4 (for a total perfusion defect). Significant reversible myocardial ischemia was defined if the summed difference score was at least two in the affected region.

3.1.5. Statistical considerations

Linear regression analysis (created by MedCalc software, Ostend, Belgium) as used for statistical analysis to compare the parameters of FFR, LVIi and rDSc and to find the correlations among these parameters. Receiver operating characteristic (ROC) curve analysis was used to test the relationship between sensitivity and specificity at different cut off values.

3.2. Validation of quantitative parameters provided by gated myocardial perfusion SPECT in the usage of different detector position.

3.2.1. Patients

Fifty-five patients were enrolled in this prospective study. All patients were referred for evaluation of exertional angina pectoris. The average BMI of the study cohort was 28.7 $\pm$ 4.1. Twenty-one patients (38%) were obese (BMI>30). This is consistent with the increasing incidence of overweight among the Hungarian population.

3.2.2. SPECT imaging

All patients had vasodilator stress SPECT myocardial perfusion imaging after an overnight fast. Coffee and caffeine-containing medication, aminophylline, nitrates or betablockers were withheld for at least 12 hours. Three min after completion of the dipyridamole infusion (0.56 mg/kg over 4 min) 400-450 MBq of technetium-99m SestaMIBI was administered. Patients with BMI > 30 received a dose of 650 MBq.

Supine SPECT imaging was always performed first with the Cardio-C (CC) camera (Mediso Ltd, Budapest, Hungary) starting at 60-90 min after radiotracer injection to avoid the significant influence of background activity. Moreover, to decrease high hepatic concentration and to avoid liver-dominant SPECT images a fatty meal or drink was commonly used to speed hepatobiliary clearance of the SestaMIBI. As soon as supine image acquisition was completed, the patients were moved to the CardioDesk (CD) camera (Mediso Ltd, Budapest, Hungary) for repeat imaging, now in sitting position. The mean time between the two acquisitions was 32.5± 5.26 min. The acquisition parameters for both cameras were the identical: low-energy high-resolution parallel-hole collimators; energy window (20%) symmetrically set over 140 keV; 64 projections acquired over a 180° arc with 27 sec per stop. The image matrix was 64x64. For ECG gating the R-R interval was divided into 8 frames. No attenuation correction was applied.

Both cameras have two large field-of-view high-resolution, rectangular detectors at a fixed 90^{o} angle. The only difference is the starting position of the detector heads: for the CC camera one crystal surface was positioned horizontally and the other vertically, whereas for the CD camera both crystal surfaces were in vertical position. The detector heads of both cameras rotated over a 90^{o} arc during image acquisition. The sizes of the NaI crystals were identical (430 x 244 mm with a thickness of 9.5 mm) and each detector head housed 33 photomultipliers. Same camera installation were used, pixel size was also the same in both cameras (pixel size: 6mm).

Interview XP software package (Mediso Ltd, Budapest, Hungary) was used for SPECT image reconstruction. Butterworth pre-filter was applied on each 2D projections, OSEM iterative reconstruction were used.

Reconstructed tomographic slices were imported into the Emory Cardiac Toolbox 3.2 (ECTb) software for quantitative analysis. During post-processing automatic contour detection was used to define the border of the myocardium. Image quantification was performed relative to the ECTb normal reference database. According to manufacturer's information, this normal database was generated from 30 healthy male and 30 healthy female volunteers with low likelihood of coronary artery disease. These volunteers had one-day stress-rest Tc-99m Sestamibi SPECT imaging in supine position. Quantitative image data were automatically generated: left ventricular (LV) ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), LV mass (MASS). After the assignment of the center of the imaged myocardium end-diastolic endocardial and epicardial borders can be estimated. Fourier analysis of the size-intensity relationship is used to compute the wall thickening throughout the cardiac cycle.

17-segment bull's eye display of summed stress scores (SSS) and total severity score (TSS) and wall motion score were also calculated automatically. The TSS reflects both the extent and severity of myocardial perfusion abnormality and is computed on the basis of regional relative variance of radiotracer uptake compared to normal limits.

3.2.3. Diagnostic Image Categorization

For the present study only stress SPECT images were used for analysis. Two experienced physicians, blinded to the patients' medical history and clinical image interpretations re-analyzed all image data independently. Thus, reconstructed tomographic slices, 17-segment bull's eye display of regional myocardial perfusion and wall motion were reviewed in static and dynamic cine mode, when available. Based on an integrated review of all available data on each camera, the studies were then categorized as either normal (no perfusion defect and normal regional and global function (0) or abnormal (1). The interpretive 0 or 1 scores were tabulated. The numerical differences of interpretive scores (difference score) between the two cameras were recorded. For further analysis the difference score of the two physicians was averaged. Thus, an average difference score of 0 meant identical categorization as either normal or abnormal by both readers on images generated by the two different cameras. An averaged difference of -0.5 or 0.5 indicated that one physician concluded that the two acquisitions were different (a difference of 1 or -1), whereas the other physician concluded they were similar (difference 0). Finally, an average difference score of -1 or 1 indicated that both readers agreed that the images of the two cameras were different. Since imaging with the CC camera was always done first, a negative score sign indicates that the CC study was normal, whereas the CD study was considered abnormal.

3.2.4. Statistical analysis

All data are presented as mean ± standard deviation, or as median and range when appropriate. GraphPad Prism 6.0 package was used for statistical analysis (GraphPad Software, San Diego California, USA, www.graphpad.com).

Differences of numerical data were analyzed for statistical significance using the paired t-test, Student t-test or Fisher’s exact test. For normally distributed data the paired t-test or Shapiro-Wilk test was used. For comparison of nonparametric categorical data, the Wilcoxon Signed Rank test was used. A p-value $\leq$ 0.05 was considered statistically significant.

The primary endpoints of our study were the automatically generated quantitative SPECT LV function and regional myocardial perfusion data. A secondary endpoint was the overall diagnosis by the two experienced readers: interpretive scores 0 or 1.

4. Results

4.1. The relationship between the location of coronary stenosis and the supplied left ventricular segments

13 lesions (6 lesions on the LAD, 3 lesions on the RCA, 4 lesions on the CX) supplied by 92 left ventricular segments proved to be significant based on intracoronary pressure measurements (FFR ≤0.75). 50 segments showed reversibility out of the 92 segments. The sum of reversible difference scores was 74. The remaining non-significant 23 FFR values (>0.75) (14 on the LAD, 7 on the RCA, 2 on the Cx) corresponded to 141 LV segments (sum of reversible difference scores was 21 in 18 segments). Out of these 23 lesions 6 (26%) lesions showed a 2- or- above reversibility score regionally after the process of SPECT images.

Stepwise linear regression analysis revealed that LVIi is a significant predictor of rDSC ($p<0.0001$), while adding FFR does not significantly improve the model ($p>0.1$). LVIi predicted active ischemia (>2 rDSc) on myocardial scintigraphy with 78% sensitivity and 94% specificity when the cut off value was set to 0.96. The FFR value alone predicted the ischemia on the scintigraphy with 72% sensitivity and 94% specificity at the best 0.8 cut off value. The odds ratios for active ischemia of FFR and LVIi are 121 and 80, with 95% confidence intervals 9.9-1485 and 7.5-859, respectively. The area under the ROC curve was significantly higher for LVIi than FFR (0.94 vs. 0.87; $p<0.05$).

4.2. Validation of quantitative parameters provided by gated myocardial perfusion SPECT in the usage of different detector position

All 55 patients had good diagnostic quality static SPECT images. In two patients, ECG-synchronized gating failed because of irregular heart rate and the gated SPECT studies were not of diagnostic quality. Thus, ECG-gated data were available in 53 patients.

4.2.1. LV function and volumes

In the entire patient cohort mean LVEF computed from gated SPECT images acquired on both cameras was not different (p=NS). However, mean EDV, ESV and LV mass were significantly ($p<0.0001$) lower in sitting position (CD) than in supine position (CC). The analysis results were similar in males and females. Women had significantly ($p<0.01$) smaller LV volumes than men.

When the patients were divided into those with BMI > 30 and BMI < 30, again LVEF was not different in the two imaging positions. Also, EDV and ESV were again significantly smaller in sitting position (CD) than in supine position. However, although in patients with BMI< 30 LV mass was significantly less in sitting position than in supine position, in patients with BMI >30 there was no such significant difference.

4.2.2. Regional myocardial perfusion

In the entire cohort of 55 patients SSS and TSS were significantly ($p<0.0001$) larger in sitting position than supine position. The same was found when males and female were analyzed separately. Patients with BMI <30 also had higher SSS and TSS in sitting position than in supine position. However, although patients with BMI>30 also had significantly higher SSS in sitting position, the TSS was not statistically different compared to supine position. By the analysis of vascular territories, higher amount of RCA and LAD defect were observed with CardioDesk (Physician #1: LAD - 7 vs.11 cases, RCA - 5 vs. 10 cases; Physician #2: LAD - 5 vs 9 cases, RCA - 6 vs. 8 cases, CC and CD respectively).

4.2.3. Overall interpretive score

The two readers were in complete agreement with each other in 40 (72%) of 55 paired patient studies. The distribution of disagreements in 15 paired SPECT studies is also shown in Table 3. Disagreements appeared to occur more often on SPECT images of women than on those of men. Based on all available imaging information, physician #1 interpreted 14 (25%) of 55 SPECT images acquired in supine position as abnormal, whereas he interpreted 22 (40%) of the SPECT images acquired in sitting position as abnormal. Similarly, physician #2 interpreted 13 (24%) of the images acquired in supine position as abnormal and 19 of the images acquired in sitting position (35%) as abnormal. Thus, overall, more SPECT studies acquired in sitting position were interpreted as abnormal than those acquired in supine position ($p<0.05$).

5. Discussion

5.1. The relationship between the location of coronary stenosis and the supplied left ventricular segments

We have developed an algorithm combining the FFR value and the number of supplied segments, characterizing the clinical significance of ischemia resulting from a stenosis. The HCC software provided a possibility for a direct comparison between the predicted ischemia on the generated coronary polar map and the ischemia detected on the SPECT images. We introduced a new ischemic index (LVIi) which correlated with the severity of regional myocardial perfusion defects identified on the scintigrams.

During FFR measurement the value <0.75 implies significance based on the suggestion of the recent European guidelines; lesions below 0.75 FFR value proved myocardial ischemia with the accuracy of 100%. Above 0.8 FFR value indicated lack of ischemia with the accuracy of 90%. According to the current ESC guideline the deferral of PCI or CABG surgery in patients with 0.80 FFR value is safe and the clinical outcome is excellent. Values between 0.75 and 0.80 are considered as a “gray zone” (none among our patients). In earlier studies some cases in the “gray zone” showed abnormalities on noninvasive tests especially on myocardial perfusion scintigraphy. Therefore, it raises the point that reversible ischemia can occur above 0.75 FFR values mainly in the case of proximal stenosis. In the FAME study, cut off point of intervention was raised to 0.80. Recently, in the clinical practice the interventional cardiologists decide about the intervention of close to 0.80 stenosis. In the clinical practice interventional cardiologists have agreed recently about the intervention of close to 0.8 stenosis.

While previous papers described a linear relationship between FFR and rDSc, we found that LVIi is a better linear predictor of rDSc. Furthermore, when we compared the predictive value of FFR alone with our combined parameter of the LVIi values, the ROC analysis revealed a bigger area under the latter curve, as well as higher sensitivity and specificity. An LVIi >0.96 indicates clinically significant stenotic lesion. This additive information may be especially helpful in the “gray zone” of pressure measurement.

It is important to note that FFR measurements obtained just distal to the lesion can have a higher value than the value detected with a sensor positioned as distally as possible. This common result has been explained in the literature by diffuse invisible disease of the distal epicardial segments, small vessel disease and left ventricular hypertrophy. However, since the distal segments in the lesion-associated region always exhibit a higher degree of perfusion abnormality than the proximal segments, we may hypothesize that the better-collateralized proximal part can show a higher FFR value just distal to the lesion than at a very distal position without real resistance of the distal segments of the epicardial artery. This hypothesis implies that an FFR measurement at a position not reaching the very distal part of the run-off will show a value characterizing the average drop in the perfusion pressure of the distal segments. Considering the inhomogeneous longitudinal perfusion, distal myocardial ischemia cannot be ruled out despite of an FFR value above the upper limit of significance (0.80). An LVIi>0.96 can be a helpful indicator revealing ischemia in these scenarios.

The other possible clinical relevance of LVIi is the functional assessment of relevance of lesion placed in the distal part of the coronary artery. An FFR value under 0.75 at a lesion with a small supplied region obviously has little clinical relevance. Unnecessary interventions can lead to increased risk. In that case an LVIi value <0.96 suggests deferring of intervention. In our approach, the LVIi should be taken into consideration in cases with borderline FFR values. It can help interventional cardiologists make the appropriate decision in uncertain cases.

Our results can be interpreted with some limitations. A small study group was analyzed especially in the case of FFR positive lesions. A larger population would be needed for further analysis.

Our SPECT results may be less accurate due to the lack of CT attenuation correction or using prone acquisition, which is useful to correct attenuation artifacts such as mamma and diaphragm resulting in false positive areas on SPECT. However, in clinical settings the stress/rest protocol without attenuation correction is generally accepted for detection of myocardial ischemia because it is assumed that the attenuation features cannot change significantly between two examinations, therefore the reversibility of the perfusion defects can be assessed reliably.

Myocardial PET examination is the most accepted method, the "gold standard" to quantitatively measure the severity of coronary perfusion abnormalities, with a better spatial resolution than SPECT. Thus, PET examinations may further confirm the real relevance of our results. We evaluated MPI using automated program (Emory Cardiac Tool Box). It is well known that all automated evaluations have limiting factors. Visual semi-quantitative approach would give additional information. We used intracoronary adenosine administration for FFR measurements, however some latest studies suggest that i.v. adenosine injection can produce different values. To examine this kind of correlation further examinations need to be performed.

5.2. Validation of quantitative parameters provided by gated myocardial perfusion SPECT in the usage of different detector position

This study demonstrates that patient positioning has a significant and quantifiable impact on semi-quantitative and quantitative parameters derived from ECG gated SPECT imaging. In the upright sitting position, regional myocardial perfusion abnormalities (SSS and TSS) were significantly larger than in the conventional supine position. On the other hand, EDV, ESV, and LV mass were significantly smaller in upright sitting position, whereas LVEF was not affected. Our analysis further showed that not only were there quantitative differences, but also significant differences in overall image interpretation by experienced readers.

It has long been recognized that myocardial perfusion images may be different when acquired in supine, prone or left-lateral position. The different image appearance is attributed to soft tissue attenuation. In some laboratories, this understanding is even used for identifying soft tissue attenuation artifacts by reviewing images acquired in both positions. Such artefactual different appearance may be altered using attenuation correction devices.

Several investigators also reported differences in LV dimensions in different positions. The smaller volumes of EDV and ESV in the sitting position can be readily explained by decreased LV preload. Since LVEF represents a ratio of volumes, and EDV and ESV are equally affected by a change in position, it should be no surprise that LVEF was unchanged.

Over the recent decades, important innovations have been introduced in SPECT gamma camera design, detector geometry, reconstructive software, and also by introducing imaging in different body positions. Traditionally, cardiac SPECT imaging was performed with the patient in supine position. This position may be uncomfortable for patients with orthopedic shoulder or back problems, congestive heart failure, obesity, debilitating illness, or simply claustrophobia. This may be especially problematic when imaging time is prolonged. Most patients, when given the choice, prefer imaging in sitting position rather than in supine position.

Thus far, published reports on differences of myocardial perfusion images acquired in supine or sitting position were based on subjective segmental scoring, although some reports describe differences in the quantitatively determined scores. Our analysis was based on computer-generated semi-quantitative SSS and TSS.

In many laboratories, quantitative software is routinely used to improve reproducibility of interpretation, which is suboptimal when limited to subjective visual analysis. Presently available commercial quantitative software packages incorporate normal reference databases derived from volunteers imaged in supine position. To the best of our knowledge, no commercial software offers normal databases for imaging in sitting position. Our quantitative analysis was done using a supine normal reference database.

The observation of significant quantitative differences in SSS and TSS in sitting position does not necessarily imply that imaging in sitting position is more accurate. Since the differences were independent of anatomic location, gender, and BMI, our findings cannot readily be explained by altered soft tissue attenuation in sitting position alone.

An important limitation of our study is that no attenuation correction was applied in either the supine or sitting position. Certain inferior diaphragmatic attenuation artifacts may be less in the sitting position, whereas anterior breast artifacts may be more pronounced while sitting. Accordingly, it is unclear why in our analysis, myocardial perfusion abnormalities were consistently larger in the sitting position, regardless of anatomic location, gender, and BMI. These issues may only be resolved by the use of position-specific normal reference databases and attenuation correction.

In our imaging protocol, each patient had supine imaging first, followed by imaging in sitting position. It is conceivable that, although unlikely, with the increasing time interval after stress, the effects of ischemia on radiotracer uptake and regional wall motion may have been different. All our patients underwent pharmacological stress, which generates flow heterogeneity, but rarely true myocardial ischemia. Nevertheless, it would have been preferable using a random sequence of imaging. The lack of rest acquisition analysis is an important limitation of our study; however, the expansion of our study population with rest acquisition would add a new parameter resulting in a slight heterogeneity in the statistical analysis and leading to further possibilities for discrepancies.

6. Summary

The nuclear cardiology and the Tc99m SestaMIBI myocardial perfusion SPECT have been taking an important part in noninvasive cardiology. However, its role restricts for the diagnosis of chronic ischemic heart disease and stabile angina due to its well-known limiting factors. Moreover, the data mirroring the perfusion (reversible or irreversible perfusion defect) are used in the clinical practice most frequently. Recent work is focusing on that data exported from the nuclear cardiological examinations which can be used in multiple ways, but the exact evaluation of the data is crucial.

Having data coming from the perfusion images, invasively measured parameters and its significance can be refined, what is more individualized, if exact coronary anatomy of the patient is known. Either stenosis which requires intervention or nonsignificant lesions, where intervention can be postponed, can be differentiated. This differentiation is critical in coronary stenosis where the significance is not evaluated by visual or numeric analysis.

Furthermore, ECG gating of the procedures gives additional information about left ventricular systolic function, left ventricular volumes, left ventricular mass and wall motions. These new parameters influence the procedures only in a minimal way (increase the time of the sampling time), but it gives a hand for the evaluation of the disease extension. Otherwise, proper knowledge of the physical and physiological background and quality assurance is also important for the accurate description of the parameters above.

During our investigations we made the following key observations: 1. Left ventricular ischemic index predicts significantly better the consequent left ventricular ischemia compared with the conventional fractional flow reserve, if supplied ventricular territory is taken into the consideration. 2. Modified acquisition does not influence significantly the ejection fraction of the left ventricle during myocardial perfusion imaging, however other quantitative parameters, such as left ventricular end systolic and end diastolic volumes, left ventricular mass can be affected. 3. Development of position specific database is suggested before the initiation of the everyday clinical examinations, if new cardiac camera using modified patient position is installed. These results are comparable, camera independent and reproducible data.

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List of publications related to the dissertation

1. **Kracskó, B.**, Barna, S., Sántha, O., Kiss, A., Varga, J., Forgács, A., Garai, I.: Effect of patient positioning on the evaluation of myocardial perfusion SPECT.
   J. Nucl. Cardiol. 25 (5), 1645-1654, 2018.
   DOI: http://dx.doi.org/10.1007/s12350-017-0865-4
   IF: 4.112

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Total IF of journals (all publications): 5,253
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