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Quantitation of left ventricular ejection fraction reserve from early gated regadenoson stress Tc-99m high efficiency SPECT

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Abstract

Background—Ejection fraction (EF) reserve has been found to be a useful adjunct for identifying high risk coronary artery disease in cardiac positron emission tomography (PET). We aimed to evaluate EF reserve obtained from technetium-99m sestamibi (Tc-99m) high-efficiency (HE) SPECT.

Methods—Fifty patients (mean age 69 y) undergoing regadenoson same-day rest (8–11 mCi)/ stress (32–42mCi) Tc-99m gated HE SPECT were enrolled. Stress imaging was started one min after sequential intravenous regadenoson 0.4mg and Tc-99m injection, and was composed of five 2 min supine gated acquisitions followed by two 4 min supine and upright images. Ischemic total perfusion deficit (ITPD) ≥ 5 % was considered as significant ischemia.

Results—Significantly lower mean EF reserve was obtained in the 5th and 9th min after regadenoson bolus in patients with significant ischemia versus patients without (5th min: −4.2 ± 4.6% *vs.* 1.3 ± 6.6%, p = 0.006; 9th min: −2.7 ± 4.8% *vs.* 2.0 ± 6.6%, p = 0.03).

Conclusions—Negative EF reserve obtained between 5th and 9th min of regadenoson stress demonstrated best concordance with significant ischemia and may be a promising tool for detection of myocardial stunning with Tc-99m HE-SPECT.

Keywords

regadenoson Tc-99m high efficiency SPECT; early stress imaging; left ventricular ejection fraction reserve; image quality

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INTRODUCTION

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a well-established noninvasive procedure for evaluation and risk stratification of patients with coronary artery disease (CAD) (1). However, it has been recognized that with certain patients, SPECT MPI does not allow to detect the presence nor to estimate the extent of CAD. Indeed, the moderate to severe perfusion defects are revealed in less than half of the patients with significant left main disease (2). A number of studies have been conducted to improve the sensitivity of SPECT MPI, through the analysis of post-stress left ventricular (LV) ejection fraction (EF) (3, 4), post-stress wall motion abnormalities (5), and transient LV dilation (6), but these investigations have been made using conventional Anger cameras with waiting periods after stress tracer injection as long as 60 minutes. Such delayed EF measurements seem to be relatively ineffective for the detection of significant CAD, as a result of their transient nature. The ability of PET MPI to measure EF and to determine EF reserve during peak of stress using highly sensitive detectors and high dose short-lived tracers has been reported (7). Recently, a novel high efficiency (HE) SPECT camera with solid state cardiac-focused detectors has shown to be significantly more sensitive for the detection of cardiac activity than the conventional Anger scintillation camera (8–10), giving SPECT a “PET-like” ability to image rapidly during a peak of stress. The aim of this study was to explore the feasibility of evaluating EF reserve using HE SPECT.

METHODS

Study population

The patients of the study were selected from consecutive subjects who were referred to clinically indicated regadenoson pharmacologic stress MPI to the Nuclear Medicine Department, Sacred Heart Medical Center, Springfield, Oregon, between August, 2012 and August, 2013. The selection of the patient depended on the limitations related to the scheduling of a non-routine imaging protocol, in particular the availability of the stress lab staff and nurse during the entire procedure. Fifty consecutive patients were selected for the protocol. None had any significant respiratory problems that would preclude the use of regadenoson. The study was approved by the hospital’s institutional review board, which included a waiver of informed consent.

Regadenoson stress protocol and image acquisition sequence

Patients were instructed to discontinue any caffeine-containing products for 24 hours. Whenever possible, beta blockers and calcium-channel antagonists were terminated 48 hours before testing and nitrates at least 6 hours before testing. During the pre-imaging stress-lab evaluation and procedures, standard 12 leads for ECG monitoring and leads for image gating were applied, and a venous catheter was inserted into an antecubital vein through which the patient received a rest injection of 296–407 MBq (8–11 mCi) 99mTc-sestamibi, according to a body mass index related dose schedule (8mCi for BMI<25 9mCi for BMI range of 26–32, 10 mCi for BMI range of 33–38 and 11 mCi for BMI >40). Within 20 minutes, the patient was brought to the imaging room, equipped with an ECG/physiologic monitor, emergency cart, and oxygen source. The patient was placed in supine position in the HE-SPECT cardiac

camera (D-SPECT, Spectrum-Dynamics, Caesarea, Israel). Using the rest injected activity, the detector was positioned to include the entire heart image, as well as to isolate the heart from extra-cardiac activity, and a standard 6 min rest supine image was acquired. Approximately 30 min post rest injection and after obtaining baseline heart rate, blood pressure, and a 12 lead ECG, the patient, while remaining in supine position, received 0.4 mg of regadenoson bolus (11) over 30 seconds, immediately followed by an IV bolus of 1143–1806 MBq (32–42mCi) 99mTc-sestamibi, according to a body mass index related dose schedule (32 mCi for BMI < 25, 36 mCi for BMI range of 26–32, 40mCi for BMI range of 33–38 and 42 mCi for BMI >40). Imaging started at 1-minute post stress injection.

A series of five 2 min gated acquisitions were carried out. Between each subsequent acquisition, approximately 2 min delay was observed, which corresponds to the technical time currently required for the system to fully complete one acquisition and start the next one. These 2 min acquisitions are denoted by their starting time after injection in the following: 2 min, 5 min, 9 min, 13 min and 17 min. After the last 2 min acquisition, a standard supine 4 min acquisition (at 21^{s} min) followed by a standard 4 min upright acquisition was completed (Figure 1). There was no repositioning of the patient or camera detector during the entire sequence of supine imaging. Heart rate, blood pressure, and ECG were monitored and recorded during the imaging protocol and 10 minutes after. The entire clinical stress protocol was performed in a standard manner by the stress laboratory staff that could terminate the study at any time if deemed necessary.

High-efficiency SPECT scanner, scanning methods and image processing

The HE-SPECT system (D-SPECT, Spectrum Dynamics, Caesarea, Israel) uses 9 collimated, pixilated cadmium-zinc-telluride (CZT) detector columns, mounted vertically in 90° geometry (12, 13). Each of the columns consists of 1,024 (16 × 64), 5-mm thick CZT elements (2.46 × 2.46 mm). Square-hole tungsten collimators are fitted to each of the detectors, with the size of the collimator holes matching the dimensions of the detector elements. Scintigraphic data is acquired by the detector columns rotating in synchrony, focusing on the region of interest (the heart), and is saved in list-mode along with R-wave markers. Before imaging, the detector was positioned parallel to the patient’s chest, and care was taken to align the heart to the center of the field of view. Each image set was acquired with 120 projections per detector. Transaxial images were then generated by using proprietary Broadview reconstruction algorithm (Spectrum Dynamics), based on the maximum likelihood expectation maximization method (12). Images were reoriented into short-axis and vertical and horizontal long-axis slices using standard software (QPS/QGS, Cedars-Sinai Medical Center, Los Angeles, California).

All image contours were reviewed by experienced technologist and nuclear cardiologist and were individually adjusted if required. Since manual correction resulted in a fixed valve plane contour, it was then necessary to correct all gated images including the standard rest and stress images for purpose of comparison. This approach prevented us from a possible bias, which could occur if uncorrected contours were compared to user-corrected contours. Therefore, the correction rates for stress and rest scans and for early and delayed scans were

approximately the same. The contour correction was kept as similar as possible for all the standard and serial 2 min images within a patient study.

Automated quantification of perfusion and function and visual assessment

QPS software computed total perfusion deficit (TPD) score by integrating the hypoperfusion severities below normal limits in polar map coordinates (14). Normal limits threshold was defined as 3.0 mean absolute deviations (approximately equivalent to 2.5 standard deviations) for each polar map sample. Ischemic TPD (ITPD) was calculated as the absolute difference between TPD at stress, taken from the last 2 min supine acquisition (at 17th min) and rest TPD (15, 16), and was expressed as a percentage (%). Stress EF and rest EF were quantified separately for each acquisition using standard QGS software with 16 frames per cardiac cycle. EF reserve was calculated as the absolute difference between stress EF and rest EF for each acquisition. For further analysis, the patients were categorized retrospectively into 2 groups depending on their ITPD (5% cut-off). Significant ischemia was considered as ITPD ≥ 5%. Image quality was assessed by experienced imaging cardiologists and was scored using 4 categories (excellent/good, fair, poor, uninterpretable). Extracardiac activity was scored using 3 categories (none, low, high).

Statistical Analysis

Statistical analyses were performed using STATA software (version 12, StataCorp LP). All continuous variables were described as mean ± SD. Student two-sample t tests were used to compare differences for continuous variables. Chi-square test was used to compare differences across subgroups for categorical variables. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare differences between the ischemic and non-ischemic patient groups (as defined below). A 2-tailed $p<0.05$ was considered statistically significant.

RESULTS

Baseline clinical characteristics of studied patients are presented in Table 1. Overall, 22 patients (44%) had stress TPD = 0 %; stress TPD > 0 % was seen in 28 patients. 40 patients did not have significant ischemia (ITPD < 5%) and 10 patients had significant ischemia (ITPD ≥ 5%). Gated resting EF < 50% was recorded in 14 patients (28%).

Assessment of image quality

Low myocardial tracer activity, residual ventricular blood pool activity, and high interfering hepatic activity in the initial 2 min acquisition started 1 minute after tracer injection were noticed. Such poor quality precluded the use of this acquisition for further accurate quantitative perfusion and functional analysis. Thus, the images from 2nd min acquisition have been discarded.

However, the subsequent 2 min early acquisitions and the 4 min standard supine acquisition showed improved (at least a fair) image quality, except for only two early stress acquisitions where an excess of extracardiac (abdominal) activity was observed. Namely, the acquisitions taken at 5th, 9th, 13th, 17th and 21st min have been considered for analysis, as shown in

Figures 1 and 2. The grades of quality of stress and rest acquisitions are shown in Table 2. It is noteworthy that, despite beginning stress imaging 5 min after regadenoson/tracer injection, 96% of the stress images demonstrated good, excellent or fair quality, allowing a confident clinical reading. Clinical example of poor quality 1st min stress acquisition is depicted in Figure 3A. The examples of good image quality in 5th and 9th min stress acquisitions are presented in Figures 3B and 3C, respectively, but some mild degree of residual extra-cardiac activity is still seen. Similarly, to the standard rest acquisitions, 98% of early stress images demonstrated none or low grades of extracardiac activity (Table 2). The overall image quality and level of extracardiac activity were similar in both analyzed subgroups.

Quantitative results

Overall, in this study, the manual correction for all acquisitions was required in approximately 48% of the patients. Per patient, it was applied in 7/10 of abnormal (ITPD ≥ 5%) and 18/40 of normal (ITPD < 5%) patients. This is a much higher rate than in usual practice; however, in this study, if just one file required correction for a given patient, all studies had to be corrected for that patient. No difference in mean rest TPD in ITPD ≥ 5% group *vs.* ITPD < 5% group (5.1 ± 6.4 *vs.* 4.8 ± 6.0, p = 0.9) was observed. However, significantly higher mean values of stress TPD in ITPD ≥ 5% group *vs.* ITPD < 5% group (13.9 ± 4.6% *vs.* 5.1 ± 6.4%, p = 0.0002), were seen. Similarly, significantly higher mean ITPD values in ITPD ≥ 5% group *vs.* ITPD < 5% group (9.5 ± 2.6% *vs.* 1.2 ± 1.5%, p < 0.0001) were monitored.

Comparison of stress EF between the subgroups is shown in Table 3. The trend for lower mean EF values in the first two acquisitions (5th and 9th min) was seen. Comparison of mean EF reserve between the two groups during all consecutive acquisitions is depicted in Figure 2. In the ITPD ≥ 5% group, mean EF reserve was negative through all acquisitions (from −4.2% in 5th min to −1.5% in 21st min). In contrast, the ITPD < 5% group demonstrated positive mean EF reserve through all acquisitions. Moreover, in the ITPD < 5% group, mean EF reserve was higher during the first two acquisitions (5th and 9th min) as compared to the three later ones (Figure 2). In the first two early acquisitions (5th and 9th min), significantly lower mean EF reserve (p = 0.006 and p = 0.03) was observed in the ITPD ≥ 5% group as compared to the ITPD < 5% group (Figure 2). Regarding the later acquisitions (13th, 17th and 21st min), the ITPD ≥ 5% group showed lower mean EF reserve, but these results were not statistically significant as compared to second subgroup. Individual per-patient EF reserve responses at 5th and 21st min are depicted in Figure 4. In the group with ITPD ≥ 5%, 7 patients out of 10 patients demonstrated a negative EF reserve at both 5th and 21st min. In the group with ITPD < 5%, 33 out of 40 patients had a positive EF reserve at both 5th and 21st min.

DISCUSSION

To the best of our knowledge, this is the first study evaluating feasibility of EF reserve quantification obtained from early gated acquisitions using Tc-99m HE SPECT MPI. The main discovery in our study is that the EF reserve obtained from early gated acquisitions (5th

and 9th min) showed concordance with significant myocardial ischemia, while later acquisitions (13th, 17th and 21st min) or standard HE-SPECT gated acquisitions did not. According to our findings, the time range period (5th to 9th min) should be considered in further studies for the detection of early ischemic stunning secondary to regadenoson stress. This timing appears to be in accordance with regadenoson pharmacodynamics (11) where the vasodilatation effect starts 3 min after injection, peaking at 5 min and fading slowly during the next 10 minutes. Another important finding needs to be noted: the later acquisitions (13th, 17th and 21st min) failed to show significant correlation between ischemia and EF reserve. Based on our observations, we considered the practical inexpediency of performing multiple 2 min-long gated acquisitions as it was done in the present study. We would therefore recommend performing a single 2 min-long gated acquisition at 5th min or potentially even earlier after regadenoson bolus covering the peak of activity.

Another noteworthy finding was the good image quality with low or no extra-cardiac tracer activity as early as 5 min after Tc-99m injection as well as in later subsequent gated acquisitions. This observation appeared to be in accordance with a previous study (17) with the same HE SPECT camera but with a different (dual isotope) MPI protocol. This was explained by the fact that early post-injection imaging with HE SPECT camera may be completed rapidly before extra-cardiac radioactivity has reached maximum. However, our observations contradict another study (18), where different types of CZT camera were used, that showed that resting Tc-99m images acquired in the 0 to 8th min range period were predominantly uninterpretable due to either increased blood pool uptake or perfusion defects. In that study, the images acquired in the 8th to 12th min range were interpretable and compared to the conventional 60 min images. This discrepancy might be explained by differences in designs between CZT cameras.

Despite the fact that the mean body mass index of the studied population was 31 kg/m^2, which means mild to moderate obesity, the image quality for early gated images in obese patients was also found to be good. High diagnostic accuracy and image quality of HE SPECT in obese population has been recently reported (19).

First attempts to detect early ischemic stunning in nuclear cardiology were done with 82-Rb PET, when the usefulness of EF reserve assessment was demonstrated (7, 20 and 21). High EF reserve was shown to have excellent negative predictive value in exclusion of severe CAD during dipyridamole stress 82-Rb PET MPI (7). In a study of EF reserve during regadenoson 82-Rb PET, MPI is inversely related to the magnitude of reversibility and myocardial jeopardy, increasing from rest to stress in the normal MPI but not in the abnormal studies (20). The prognostic value of negative EF reserve to predict cardiac events and all-cause mortality has also been suggested (21). Due to i) high cost and unavailability of PET in many nuclear labs and ii) growing availability of new generation SPECT cameras (22), our study of HE SPECT might have significant practical repercussions. In particular, it is in agreement with results of PET studies (7, 20), showing that severe ischemia is associated with negative EF reserve. According to our results, HE SPECT appears to be a useful diagnostic tool for the evaluation of peak stress functional gated parameters similar to ^{82}Rb PET MPI. Furthermore, as it is routinely done with PET, the feasibility of myocardial blood flow measurements with HE-SPECT has been recently shown (23).

Therefore, it is possible that the same early imaging could be used to measure both myocardial flow and EF reserve.

This feasibility study has several limitations. The data was obtained in a single center and with one particular type of equipment. The study sample was small, especially for patients with significant ischemia, but nevertheless the results were shown to be statistically significant. Due to these limitations, we were not able to perform separate analysis for female or obese patients. No angiographic or clinical end-points correlation of negative EF reserve was evaluated. The timing of the acquisition was perhaps not optimal and could explain a modest EF decrease. It is possible that a slightly earlier acquisition, as compared to the 5^{th} min post stress acquisition used in this study, would allow an even better differentiation of ejection fraction reserves. However, image quality may be an issue and thus, further studies are required to determine the optimal imaging time. Additionally, in current implementation of the software, any manual correction of the valve constraints resulted in a user-defined fixed valve plane position. It was therefore necessary to correct all gated images including the rest and stress (at all time points) images for purposes of serial comparison for patients in which some correction was required in even one study. This approach, however, prevented us from a possible bias where uncorrected contours were compared to user-corrected contours (with no valve motion). Further studies are likely warranted with alternative segmentation approaches. Currently, cardiac ^{82}Rb PET MPI stress acquisitions start as early as 30 secs after regadenoson stress bolus (21). Larger studies with coronary angiographic correlation and comparison to cardiac PET imaging are needed for further evaluation of the usefulness of EF reserve with HE-SPECT.

New Knowledge Gained

It is feasible to evaluate EF reserve using HE SPECT during peak of regadenoson stress as early as 5 min after Tc-99m injection. Since the negative EF reserve correlated with significant ischemia, it would be helpful to acquire the gated images as early as 5 minutes in order to exclude ischemic myocardial stunning.

CONCLUSIONS

We have demonstrated the feasibility of early EF reserve measurement with HE SPECT. Negative EF reserve obtained between 5^{th} and 9^{th} minutes of regadenoson stress demonstrated best concordance with significant ischemia and could be a promising clinical tool for detection of early myocardial stunning with Tc-99m HE-SPECT.

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Yafim Brodov, MD, PhD is a Michael Kogan Save a Heart Foundation fellow in Cardiac Imaging and Nuclear Cardiology, Cedars Sinai Medical Center, Los Angeles, California.

List of Abbreviations

SPECT	single photon emission computed tomography
MPI	myocardial perfusion imaging
CAD	coronary artery disease
LV	left ventricular
EF	ejection fraction
PET	positron emission tomography
HE	high efficiency
CZT	cadmium-zinc-telluride
TPD	total perfusion deficit
ITPD	ischemic total perfusion deficit
SD	standard deviation
Min	minute

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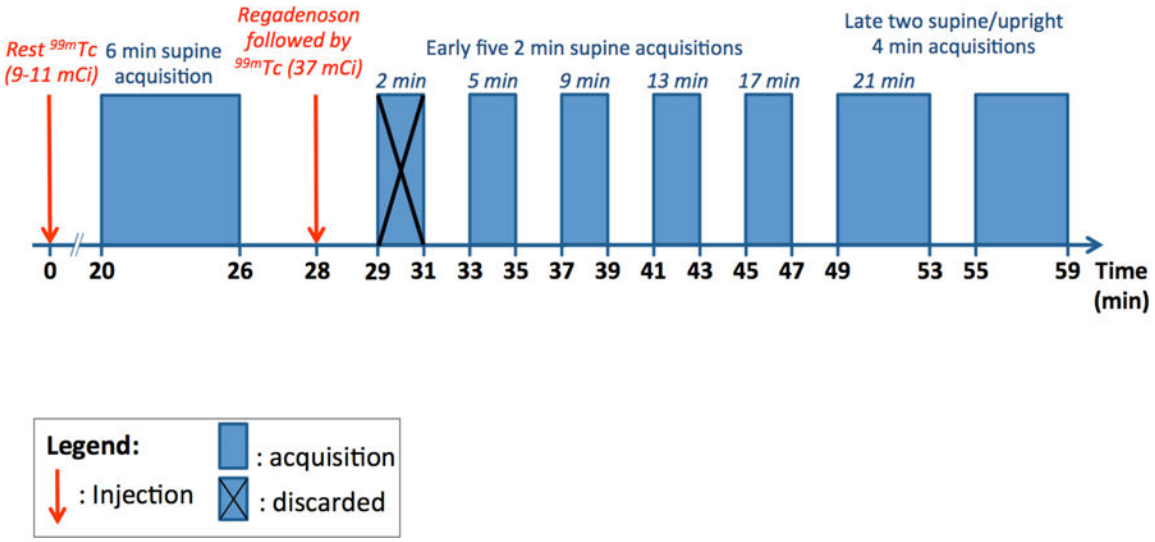


Figure 1.

Technetium-99m sestamibi rest - early/late stress protocol. Red arrows show timing of rest and stress tracer and regadenoson injection. Blue boxes show timing of rest and consecutive early and late stress acquisitions. Note that the first 2 min acquisition (2nd minute post-injection) has been discarded for further analysis due to poor image quality.

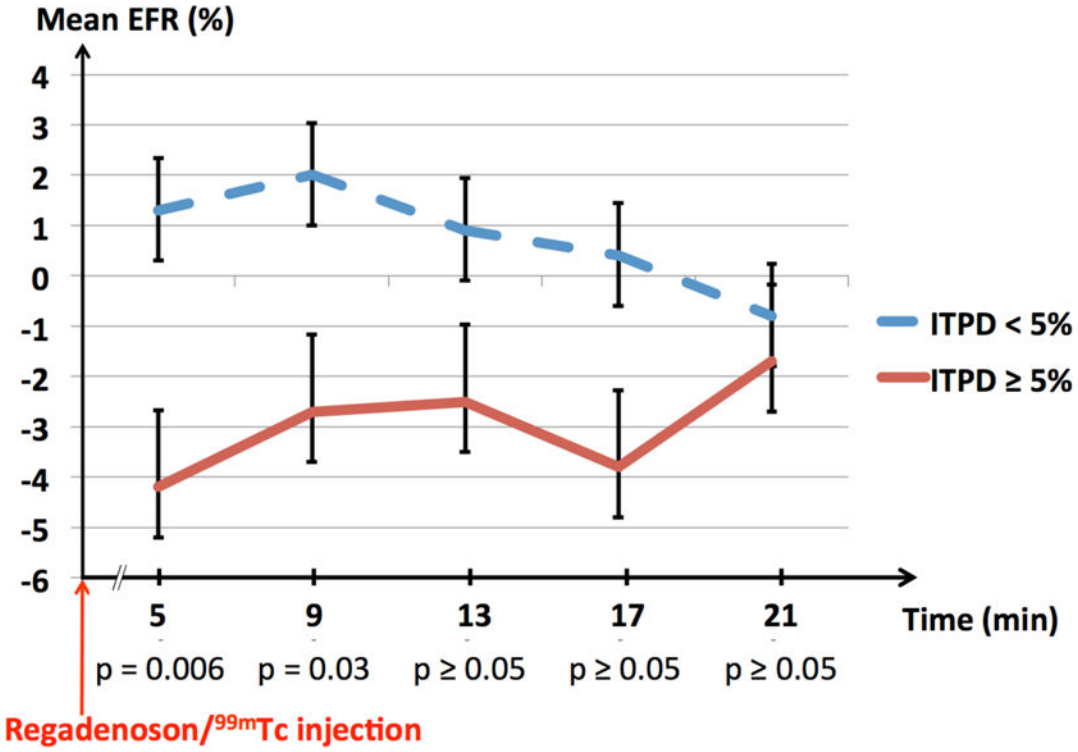
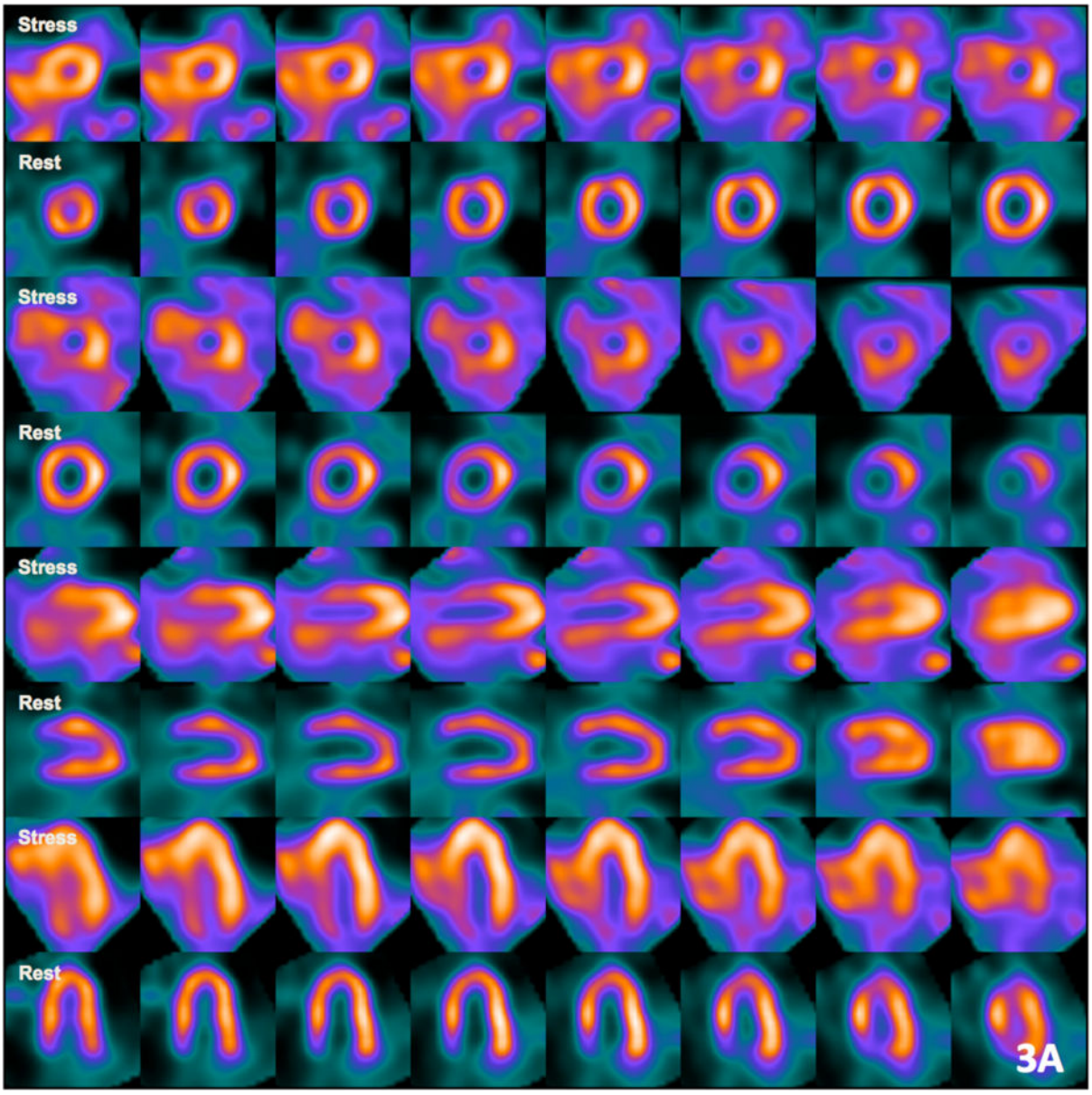
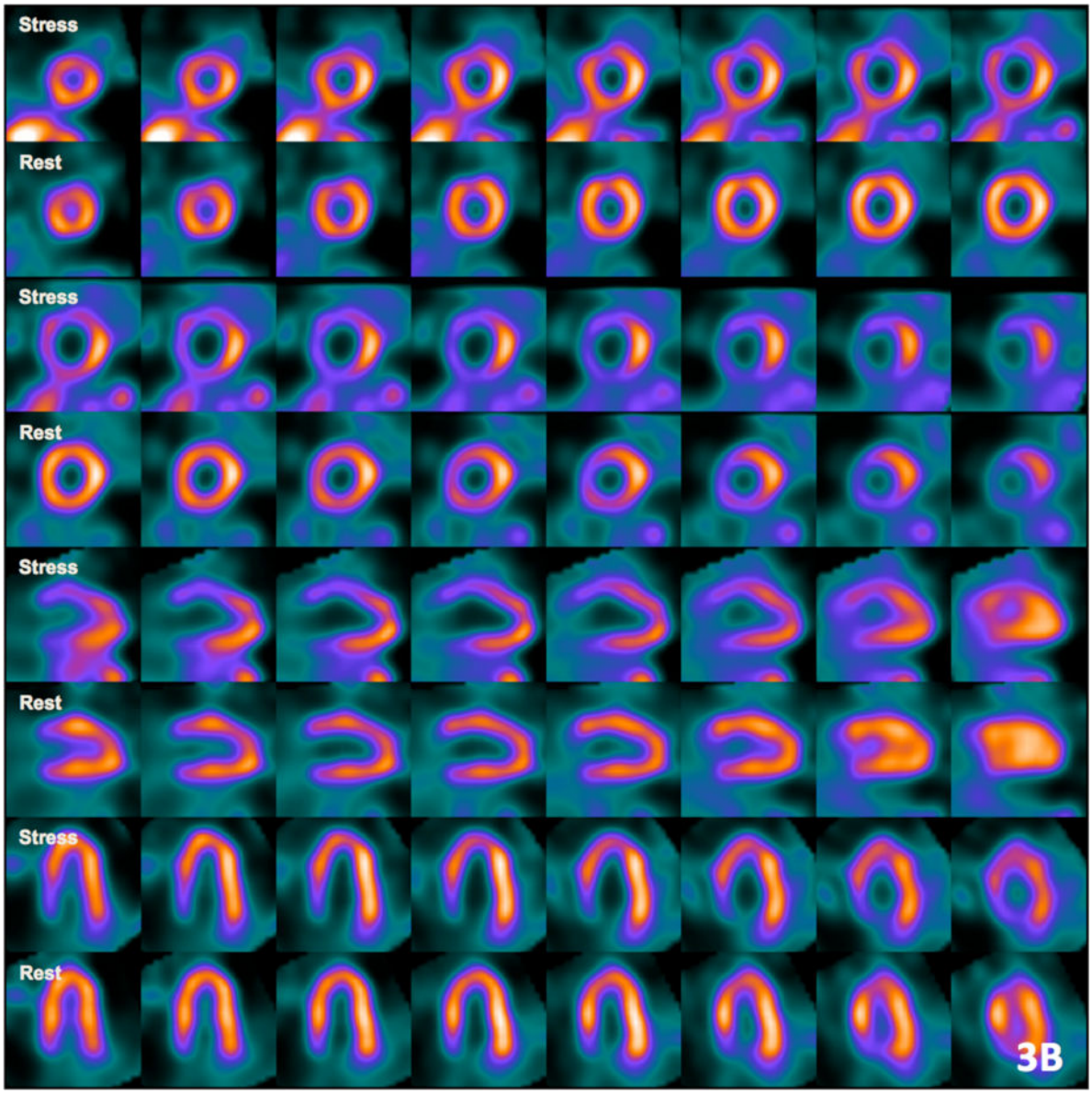


Figure 2.

Comparison of mean ejection fraction reserve (EFR) obtained from early and late consecutive acquisitions between ITPD ≥ 5% group (red line) and ITPD < 5% group (blue dotted line). Significant difference at 5th and 9th min between the 2 subgroups was observed. Small bars indicate standard deviation. ITPD = ischemic total perfusion deficit.





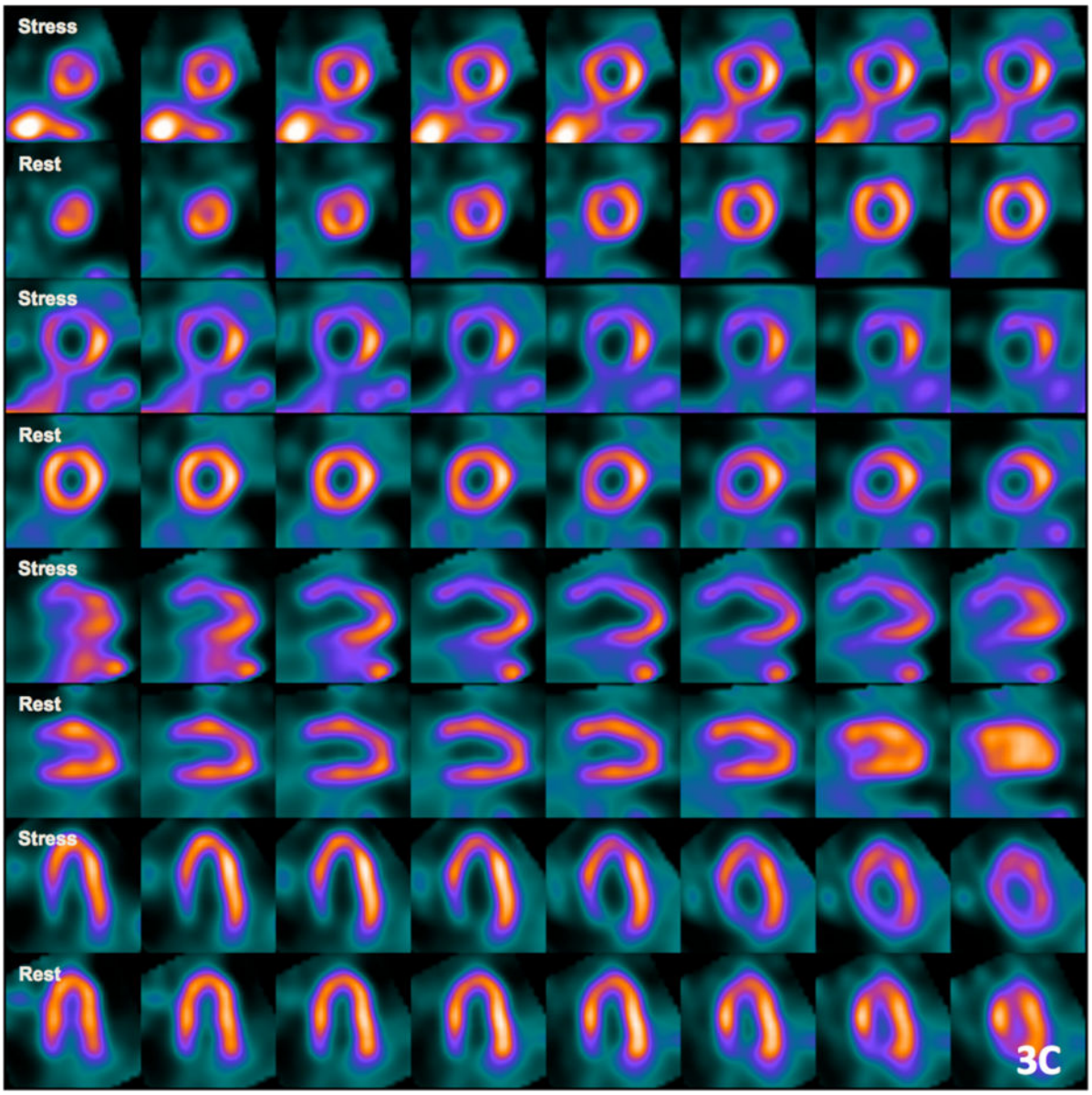


Figure 3.

Stress and rest gated images (short axis, vertical long axis and horizontal long axis) in the same patient at different acquisition times. **Panel A**. 2nd minute gated acquisition: increased right ventricular uptake and extra-cardiac activity in early 2nd minute gated stress acquisition and no right ventricular uptake/extra-cardiac activity in standard gated rest acquisition were noted. **Panel B**. Good quality early 5th minute gated stress acquisition and standard rest acquisition with no longer increased right ventricular uptake/extra-cardiac activity in stress images was noted. Anterior and septal reversible perfusion defects are clearly seen at that time, but were not seen in the 2nd minute acquisition shown in panel A. **Panel C**. Good quality 9th minute gated stress acquisition and standard rest acquisition with no increased right ventricular uptake/extra-cardiac activity in stress images. Anterior and septal reversible

perfusion defects are clearly seen similar to panel B. Some degree of residual extra-cardiac activity is still seen at the 5^{th} and 9^{th} minute images.

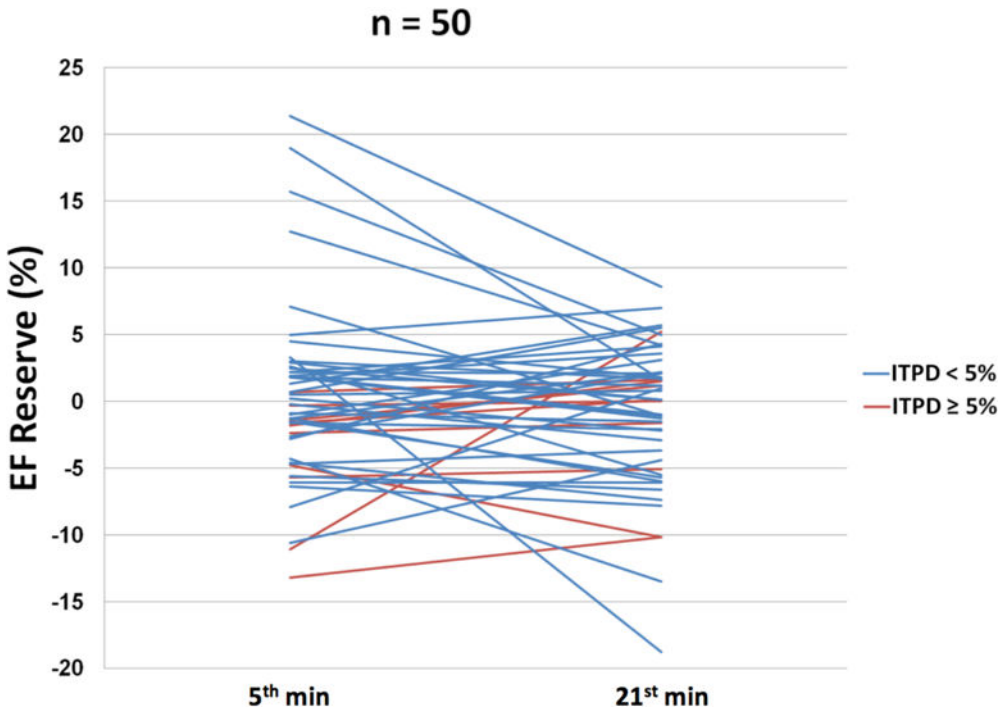


Figure 4.

Individual EF reserve responses for the 50 patients, corresponding to the 5th and 21st min acquisitions. Red lines correspond to the ITPD ≥ 5% group (n = 10). Blue lines correspond to ITPD < 5% group (n = 40).

Table 1

Demographic and clinical characteristics.

Variables	ITPD < 5% (n = 40)	ITPD ≥ 5% (n = 10)
Age [years], mean ± SD	68 ± 15	70 + 16
Female	16 (40%)	5 (50%)
Body mass index, kg/m^2	32 ± 7	29 ± 6
Diabetes	19 (48)	4 (40)
Hypertension	27 (68)	6 (60)
Hyperlipidemia	28 (70)	6 (60)
Smoking	5 (13)	1 (10)
Typical angina	6 (15)	5 (50) *
Shortness of breath	12 (30)	3 (30)
ST changes	9 (23)	2 (20)
Prior MI/PCI/CABG	15 (38)	4 (40)

Values are expressed as number of cases (%), except for age, which is expressed as (mean± SD); MI: myocardial infarction; PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft,

* < p 0.05 vs. ITPD < 5% group.

Table 2

Quality of gated images and extra cardiac activity during early stress and standard resting acquisitions.

	Stress image quality, n (%)	Rest image quality, n(%)
Good/excellent	38 (76)	48 (96)
Fair	10 (20)	2 (4)
Poor	2 (4)	0
Uninterpretable	0	0
	Stress extracardiac activity, n/%	**Rest extracardiac activity, n/%**
None	35 (70)	45 (90)
Low	14 (28)	5 (10)
High	1 (2)	0

All variables are expressed as number (%).

Table 3

Comparison of stress ejection fraction between the subgroups.

Variables	(ITPD < 5%, n = 40)	(ITPD ≥ 5%, n = 10)	*p* value
5th min EF	62 ± 15	52 ± 18	0.07
9th min EF	63 ± 14	54 ± 19	0.09
13th min EF	62 ± 14	54 ± 20	0.16
17th min EF	61 ± 14	52 ± 21	0.11
21st min EF	60 ± 14	55 ± 19	0.31

All variables are expressed in % as mean ± SD; nth min – starting times of consecutive acquisitions; EF = ejection fraction. ITPD = ischemic total perfusion deficit.