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Serial assessment of left ventricular performance at rest and during bicycle exercise by ECG-gated myocardial perfusion SPECT

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The present study evaluates left ventricular performance during exercise by ECG-gated myocardial perfusion SPECT with short-time data collection. ***Methods:*** The study population consisted of 10 healthy volunteers (Group N) and 9 patients with ischemic heart disease (Group I). Seven patients in Group I had a history of prior myocardial infarction. Rest ECG-gated SPECT was performed 40 min after an injection of Tc-99m-tetrofosmin (555–740 MBq). After resting data acquisition, Group N underwent up to two 5-min stages of exercise (75 and 125 watts) on a detachable bicycle ergometer. The Group I patients all underwent symptom-limited, maximal testing on the ergometer. ECG-gated SPECT data were acquired from both groups for 3 min at rest and during the last 3 min of each exercise stage. ***Results:*** Significant increases occurred in LVEF from rest to peak stress in both groups (from 55.4 ± 5.8 to 66.6 ± 4.1% in group N, $p < 0.0001$; from 49.0 ± 12.8 to 56.7 ± 13.8% in Group I, $p < 0.001$). The LVESV values significantly decreased to peak stress in Group N (from 49.9 ± 13.1 to 37.8 ± 10.0 m*l*, $p < 0.0001$), whereas LVEDV did not change (from 110.6 ± 18.9 to 112.0 ± 19.0 m*l*). In contrast, the LVESV values at rest and under peak stress were similar in Group I (from 52.6 ± 23.9 to 51.7 ± 31.4 m*l*) and LVEDV in Group I at peak exercise tended to increase (from 102.8 ± 36.7 to 111.3 ± 39.0 m*l*). The changes in LVESV from rest to peak stress were significantly different between Groups N and I (–12.1 ± 6.3 vs. –0.9 ± 11.6 m*l*, $p < 0.02$). ***Conclusion:*** ECG-gated SPECT with short-time data collection can assess left ventricular function during exercise and may offer useful information for evaluating patients with ischemic heart disease.

Key words: ^{99m}Tc-tetrofosmin, ECG-gated SPECT, bicycle exercise, ischemic heart disease

INTRODUCTION

EXERCISE RADIONUCLIDE ANGIOGRAPHY (RNA) is an important technique that can noninvasively evaluate cardiovascular disease. Ischemic heart disease is diagnosed by RNA on the basis of an abnormal wall motion and left ventricular ejection fraction (LVEF) responses during exercise.[1–9] Technetium-labeled myocardial perfusion tracers, such as Tc-99m-ethylenebis [bis(2-ethoxyethyl) phosphine] (Tc-99m-tetrofosmin), now allow simultaneous assessment of myocardial perfusion and left ventricular function by ECG-gated single-photon emission computed tomography (SPECT).[9–13] The present study evaluated left ventricular performance during exercise by means of ECG-gated myocardial perfusion SPECT using short-time data collection.[14]

MATERIALS AND METHODS

Study Population

The study population consisted of 10 healthy male volunteers (Group N; mean age, 34 ± 7 yr; range, 27 to 49 yr) and 1 female and 8 male patients with ischemic heart disease (Group I; mean age, 64 ± 11 yr; range, 43 to 77 yr).

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Seven patients in Group I had a history of myocardial infarction. The diagnosis of infarction was established on the basis of clinical, enzymatic and ECG criteria. All patients in Group I had undergone coronary angiography within one month (mean interval, 15.8 ± 12.2 days) from the SPECT data acquisition. Coronary angiography was performed according to Judkins' technique, and significant coronary stenosis was defined as at least 70% luminal diameter narrowing. None of the participants were considered to be trained athletes. Informed consent was obtained from all participants before the start of the study.

Exercise Protocol

A detachable bicycle ergometer (Exometer™, ADAC, Milpitas, CA)[15] was installed on the table of a VERTEX gamma camera system (ADAC, Milpitas, CA), and exercise was performed in the supine position. Thirty to 40 min after an intravenous injection of Tc-99m-tetrofosmin (555–740 MBq), base-line rest ECG-gated myocardial perfusion SPECT data, blood pressure, heart rate and resting ECG were recorded while the subject remained supine with legs resting on the ergometer pedals. After resting data acquisition, Group N performed up to 75 and 125 watts of exercise, each stage being of 5-min duration. All Group I patients underwent symptom-limited, maximal testing on the detachable bicycle ergometer. The stress workload was 25 or 50 watts with subsequent stepwise increments of 25 or 50 watts every 5 min. Exercise was continued until the conventional guidelines for exercise termination (fatigue, angina, ECG changes, and blood pressure changes) were achieved. In both groups ECG-gated myocardial SPECT data were acquired for 3 min at rest and during the last 3 min of each exercise stage. Heart rate, blood pressure and standard 12-lead ECG traces were recorded every min during each stage of exercise and post-exercise until these values were stabilized. To minimize motion artifact under stress, each participant lay supine on the gamma camera bed with arms lifted to hold a grip bar, and the chest was firmly fixed to the bed with a breast band.

ECG-gated Myocardial Perfusion SPECT Data Acquisition

Data from ECG-gated myocardial perfusion SPECT were acquired with a two-detector gamma camera (VERTEX, ADAC, Milpitas, CA) equipped with low-energy, general-purpose collimators, and with the detectors set up to form a 90-degree angle (L-shape). Sixteen frames per R-R interval were acquired during 180° rotation in a 64 × 64 matrix from the 45° right anterior oblique to the 45° left posterior oblique projection, with each head performing a 90° rotation. Rapid ECG-gated data were acquired for 12 sec per step at 6° angular steps in the continuous acquisition mode to avoid rotational dead time. The total acquisition period was 3 min.

ECG-gated SPECT Data Analysis

The ECG-gated SPECT data for each stage were preprocessed with a Butterworth filter (order = 10, critical frequency = 0.2 cycles/pixel, slice thickness = 6.5 mm), and were reconstructed by filtered back-projection (ramp filter). The AMC (automatic motion correction) program[15,16] corrected the vertical and horizontal motions of the myocardial SPECT image. A Pegasys™ processing computer and function analysis software QGS program™ (Cedars-Sinai Medical Center)[17,18] automatically calculated the left ventricular end-diastolic volume (LVEDV, m*l*), end-systolic volume (LVESV, m*l*) and LVEF (%) based on the SPECT data. Cardiac output (CO, *l*/min) was also calculated as stroke volume, (LVEDV − LVESV) × heart rate, where heart rate is defined as the mean number of cycles/min during a 3-min collection period, at each stage. With the QGS program the left ventricular endocardial surface and volume were determined for each gating interval in the cardiac cycle. A 3D-cine mode display was then created with the QGS program. To visually assess left ventricular regional wall motion, mobile images of the left anterior oblique and left lateral views for each patient were recorded on video tape. The regional wall motion of each stage was qualitatively assessed according to the three major coronary regions by two experienced observers. The anterior and septal walls were considered to be in the left anterior descending coronary artery segment (LAD), the lateral wall in the left circumflex coronary artery segment (LCX) and the inferior wall in the right coronary artery segment (RCA). The attribution of apical abnormalities depended on coexistent abnormalities in adjacent regions. We classified regional wall motion changes as follows: (1) improvement, (2) no change, (3) worsening, and (4) biphasic response, which was defined as improvement at low workload followed by worsening at high workload. In the myocardial segments, (3) worsening and (4) biphasic response were considered as abnormal responses during the bicycle exercise.

Statistical Analysis

All data are expressed as the means ± one standard deviation. Paired and unpaired Student's t-tests, as well as the chi-squared analysis determined differences between proportions. A p value of <0.05 was considered significant.

RESULTS

Nineteen subjects completed 19 data acquisitions at rest and 41 data acquisitions during exercise. Although motion-correction was carried out, left ventricular function analyses revealed endocardial irregularity in 4 of 41 stages (9.8%) during the bicycle exercise.

Coronary Angiographic Findings

Coronary angiography revealed significant coronary stenoses (≥70%) in all in Group I. Two patients had

Table 1 Hemodynamic parameters at rest and peak exercise in normal subjects (Group N) and patients with ischemic heart disease (Group I)

	Group N (n = 10)	Group I (n = 9)	p
Age (yr)	34 ± 7	64 ± 11	< 0.001
Sex (M/F)	10/0	8/1	NS
Maximal workload (watts)	125.0 ± 0.0	97.2 ± 36.3	< 0.05
Heart rate (beats/min)			
Rest	67.4 ± 5.8	62.2 ± 4.6	< 0.05
Peak exercise	101.3 ± 8.7	102.0 ± 19.2	NS
Systolic blood pressure (mmHg)			
Rest	124.6 ± 6.8	122.6 ± 24.8	NS
Peak exercise	143.3 ± 14.7	161.6 ± 27.5	NS
Double product (K mmHg beats/min)	14.5 ± 2.2	17.2 ± 4.5	NS

Table 2 Left ventricular performance at rest and peak exercise in normal sujects (Group N) and patients with ischemic heart disease (Group I)

	Group N (n = 10)	Group I (n = 9)	p
LVEF (%)			
Rest	55.4 ± 5.8	49.0 ± 12.8	NS
Peak exercise	66.6 ± 4.1	56.7 ± 13.8	< 0.05
Change from rest to peak EX	11.2 ± 4.3	7.7 ± 3.4	NS
LVEDV (m*l*)			
Rest	110.6 ± 18.9	102.8 ± 36.7	NS
Peak exercise	112.0 ± 19.0	111.3 ± 39.0	NS
Change from rest to peak EX	1.4 ± 6.5	8.6 ± 12.7	NS
LVESV (m*l*)			
Rest	49.9 ± 13.1	52.6 ± 23.9	NS
Peak exercise	37.8 ± 10.0	51.7 ± 31.4	NS
Change from rest to peak EX	–12.1 ± 6.3	–0.9 ± 11.6	< 0.05
Cardiac output (*l*/min)			
Rest	4.1 ± 0.8	3.1 ± 1.1	< 0.05
Peak exercise	7.5 ± 1.0	5.9 ± 1.9	< 0.05
Change from rest to peak EX	3.4 ± 0.6	2.8 ± 1.2	NS

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EX, exercise.

one-vessel disease, four had two-vessel disease, and three had three-vessel disease (total 19 vessels: 8 LAD, 6 LCX and 5 RCA). Of 9 vascular territories with prior myocardial infarction, the infarct-related artery was patent in one infarct site and occluded in 8.

Hemodynamic Changes under Bicycle Exercise

Various parameters at rest and under peak stress are shown in Table 1. Group N completed two stages (up to 125 watts) of exercise, and the peak workload of Group I was 97.2 ± 36.3 watts (50–150 watts). Systolic blood pressure and heart rate increased progressively in both groups during the various stages of exercise, and peak double product values (systolic blood pressure × heart rate) were 14.5 ± 2.2 K and 17.2 ± 4.5 K, respectively. At peak stress, heart rate, blood pressure and double product were similar in the two groups, so that their exercise efforts appear to have been comparable.

Ejection Fraction and Ventricular Volume Changes

Tables 2 and 3 show the changes in left ventricular parameters from rest to peak exercise. Significant increases occurred in LVEF from rest to peak stress in both groups (from 55.4 ± 5.8 to 66.6 ± 4.1% in Group N, $p < 0.0001$; from 49.0 ± 12.8 to 56.7 ± 13.8% in Group I, $p < 0.001$), but the left ventricular volume changes from rest to peak exercise in the two groups differed. In Group N, LVESV significantly decreased to peak stress (from 49.9 ± 13.1 to 37.8 ± 10.0 m*l*, $p < 0.0001$), whereas LVEDV did not change (from 110.6 ± 18.9 to 112.0 ± 19.0 m*l*, $p = 0.5$). In contrast, Group I had similar LVESV values at rest and under peak stress (from 52.6 ± 23.9 to 51.7 ± 31.4 m*l*, $p = 0.8$). The LVEDV values in Group I at peak exercise tended to increase (from 102.8 ± 36.7 to 111.3 ± 39.0 m*l*), although the difference was not statistically significant ($p = 0.08$). Table 2 shows that changes in LVESV from rest to peak stress for Groups N and I significantly differed (–12.1 ± 6.3 vs. –0.9 ± 11.6 m*l*, $p < 0.02$).

Table 3 Coronary angiographic findings and left ventricular performance in patients with ischemic heart disease (Group I)

Patient No.	Infarct site	Coronary stenosis	Maximal workload (watts)	LVEF (%)		LVEDV (m*l*)		LVESV (m*l*)	
				Rest	Peak EX	Rest	Peak EX	Rest	Peak EX
1	(–)	LAD, RCA	125	66	74	102	94	34	25
2	(–)	LAD, LCX	125	60	65	94	115	38	40
3	LAD	LAD	100	58	67	72	72	31	23
4	RCA	LCX	75	51	63	73	88	36	33
5	LAD	LAD, LCX	75	40	50	52	59	31	29
6	LAD	LAD, RCA	125	26	34	122	132	81	98
7	LAD	LAD, LCX, RCA	150	55	66	114	109	55	37
8	RCA	LAD, LCX, RCA	50	49	53	177	182	90	86
9	LAD, LCX, RCA	LAD, LCX, RCA	50	36	38	119	151	77	94

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 4 Regional wall motion obtained from ECG-gated SPECT during exercise in patients with ischemic heart disease (Group I)

Myocardial segments		Regional wall motion during exercise			
		Improvement	No change	Worsening	Biphasic
MI (+), stenosis (+)	(n = 8)	1	2	4	1
MI (+), stenosis (–)	(n = 1)	1	0	0	0
MI (–), stenosis (+)	(n = 11)	7	1	3	0
MI (–), stenosis (–)	(n = 7)	6	1	0	0

MI, myocardial infarction; stenosis, coronary arterial stenosis more than 70%.

Regional Wall Motion Changes during Exercise

The regional wall motion changes grouped by the presence of myocardial infarction and significant coronary arterial stenosis (≥70%), in the 9 patients (27 coronary arterial territories) with ischemic heart disease (Group I) are shown in Table 4. ECG-gated SPECT revealed regional wall motion abnormalities (worsening or biphasic response) in 8 (42.1%) of 19 segments with significant coronary arterial stenosis. All of the 8 segments with wall motion abnormalities had significant coronary arterial stenoses. In other words, no segments without coronary stenoses had wall motion abnormalities during exercise. Figure 1 shows a patient with myocardial infarction who developed regional wall motion abnormalities during bicycle exercise.

DISCUSSION

With the use of technetium-labeled myocardial perfusion tracers, left ventricular function and regional wall motion can be determined by means of ECG-gated myocardial perfusion SPECT. This technique can assess myocardial perfusion and left ventricular function simultaneously. With the QGS program, ECG-gated SPECT provides high-quality data regarding left ventricular function that are operator-independent and therefore reproducible.[17,18] To assess left ventricular function during exercise by means of ECG-gated myocardial perfusion SPECT, the data acquisition time must be as short as possible. Twenty-five patients with cardiac disease were imaged twice in our previous study.[14] ECG-gated SPECT data were acquired at a standard acquisition time of 15 min and rapid data collection of 3 min, and LVEFs were measured automatically with the QGS program. An excellent correlation ($r = 0.98$, $p < 0.01$) was shown between the LVEFs obtained with the two acquisition protocols.[14] As a clinical application of the rapid gated SPECT data acquisition technique, we serially assessed left ventricular function during bicycle exercise in eight healthy volunteers.[15] The LVEF and cardiac output values increased during supine bicycle exercise. That was a finding similar to that which was found in almost all previous studies by first-pass and equilibrium RNA.

The only currently available method that can evaluate exercise ventricular function with technetium-labeled perfusion tracer is exercise first-pass RNA.[2,6,7,19,20] This procedure can record and analyze the transit of a radionuclide bolus through the central circulation, and it is suitable for evaluating ventricular function at peak stress. But exercise gated SPECT in the present study required about 3 min of steady state during exercise to obtain adequate SPECT data (that is, exercise gated SPECT can only assess submaximal stress data). In contrast, the assessment of left ventricular function by conventional exercise first-pass RNA is limited because of the non-tomographic format (usually with only one piece of projection data)

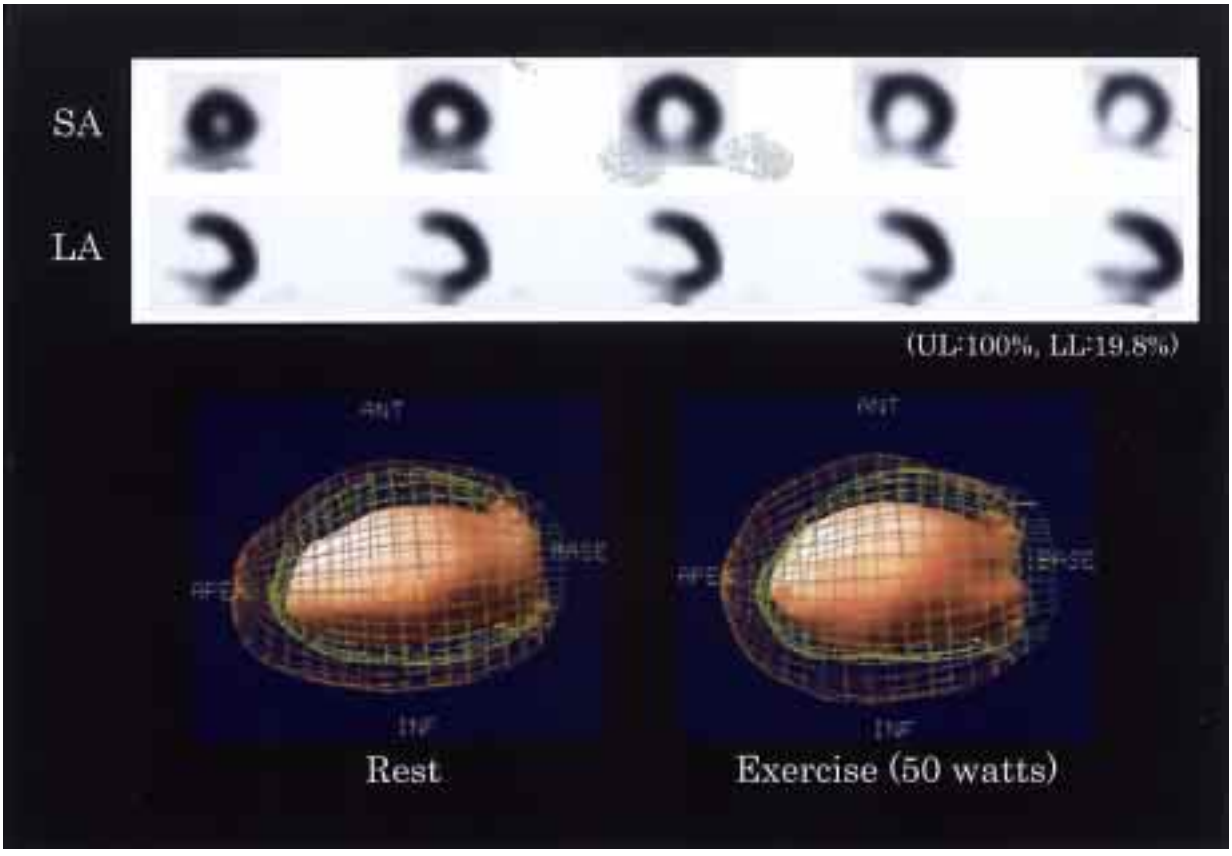

Fig. 1 Non-gated (summed) myocardial perfusion SPECT (*upper*) and left ventricular functional images (*lower*) obtained from ECG-gated data in a 69-year-old male with inferior myocardial infarction. Short-axis (SA) and vertical long-axis (LA) SPECT scans demonstrate moderate hypoperfusion in the inferoposterior wall. The function image (left lateral view) at rest demonstrates moderate hypokinesis in the inferoposterior wall. The function image during bicycle exercise (50 watts) shows severe hypokinesis in the inferior wall. In addition, anterior wall motion abnormality is depicted on the stress image. Based on these findings, coronary angiography was performed, and this revealed three-vessel disease. In the function images, the inner wire cage and the solid surface represent the endocardial surfaces at end-diastole and end-systole, respectively. UL, upper level; LL, lower level at image display.

and the exclusive number of data acquisitions. One advantage of short-time gated SPECT is that tomographic data can be acquired at any stage. Acquired tomographic data could more accurately measure left ventricular volume and more sensitively detect regional wall motion abnormalities. Calculating left ventricular volumes revealed the differences between the volume changes during exercise in Groups N and I. The changes from rest to peak stress were significantly different, especially in LVESV between the two groups.

ECG-gated SPECT revealed regional wall motion abnormalities in 8 (42.1%) of 19 segments with significant coronary arterial stenoses in 9 patients (27 segments) with ischemic heart disease (Group I). In contrast, the wall motion response of the remaining 8 segments without coronary stenosis was normal (improvement or no change) during exercise. These results indicated that assessment of regional wall motion in the present study could be considered as a specific marker (specificity 100%) for detection of affected coronary arterial stenosis. This marker based on regional wall motion abnormalities (worsening or biphasic response) was, however, less sensitive (sensitivity 42.1%) in detecting stenosed vessels. In 6 LCX segments with coronary stenoses, wall motion was abnormal in only one (16.7%) during exercise. This wall motion response in the LCX territory potentially lowered the sensitivity of short-time gated SPECT in detecting affected coronary arteries in the present study. In the visual segmental analysis, declines in the regional wall motion in a small ischemic area in the LCX territory are likely to be underestimated due to interference by neighboring normal myocardium. To overcome this, additional assessments of regional wall motion (e.g., regional wall thickening based on myocardial count intensity) are required.

Recently, several investigators have reported the utility

of post-stress ECG-gated myocardial perfusion SPECT, since calculated left ventricular function values influenced "post stress stunning"[21,22] and/or clinical prognosis.[23,24] Although the myocardial perfusion tracer is administered during stress and the perfusion images represent relative myocardial distribution during stress, the measurement of left ventricular function reflects function at the time of image acquisition itself, which may take place 30 to 60 min after stress. Therefore, it is a fact that in only some of the cases there is a function decline due to myocardial ischemia. In patients with ischemia, stress myocardial distribution is certainly different from rest images. It is possible that this difference causes endocardial border misregistration in the left ventricular function analysis. On the other hand, our protocol in the present study is favorable in the function analysis, since the same myocardial distribution is being used at rest and stress, but the influence of body movement is a disadvantage of our method. As mentioned before, 4 of 41 function images (9.8%) under exercise revealed endocardial irregularity due to motion artifact. This motion artifact will remain one of the major problems in this protocol until a reliable correction method is devised for it.

CONCLUSION

ECG-gated myocardial perfusion SPECT with short-time data acquisition can assess left ventricular function and volumes at rest and during exercise. This technique may therefore offer useful information with which to evaluate patients with ischemic heart disease.

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