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The additive prognostic value of gated myocardial perfusion scintigraphy in patients with coronary artery disease

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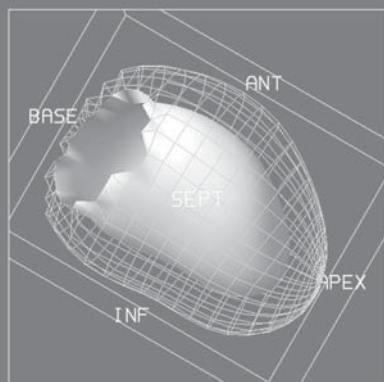
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Chapter 3



Comparison of left ventricular function at rest and post stress in patients with a myocardial infarction: evaluation with gated SPECT

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ABSTRACT

Background. Quantitative electrocardiogram-gated single photon emission computed tomography (SPECT) myocardial imaging (QGS) is a means of providing functional information about the left ventricle and myocardial perfusion. However, the functional information derived 30 minutes post-stress may be different from the left ventricular (LV) function determined at rest. This study determined whether LV function post-stress would be different from LV function at rest in patients with an earlier myocardial infarction.

Methods and Results. LV perfusion and ejection fraction (LVEF), were determined by means of both the rest and post-stress acquisition in 58 patients with an earlier myocardial infarction and in 23 patients with a low likelihood of coronary artery disease by using technetium-99m tetrofosmin and the QGS program. The interobserver and intraobserver variability of LVEF was excellent, within a margin of 2%. No significant differences in LVEF were observed between post-stress and rest in the 23 patients with a low likelihood of disease ($\Delta\text{LVEF } 0.04 \pm 3.2\%$, $p = \text{not significant}$). Conversely, the patients with an earlier myocardial infarction showed a significantly lower LVEF post-stress, compared with that at rest ($\Delta\text{LVEF } -1.9 \pm 4.2\%$, $p=0.002$). In 33 patients (57%), the LVEF post-stress was 2% or more lower than the LVEF at rest. Furthermore, reversible ischemia, which was present in 16 patients (28%), did not interact with the ΔLVEF post-stress, compared with the ΔLVEF at rest ($p=\text{not significant}$). Parameters such as the stress modality (adenosine stress or exercise), the number of stenosed vessels, or the perfusion defect severity score did not influence the ΔLVEF post-stress, compared to ΔLVEF at rest.

Conclusions. In patients with an earlier myocardial infarction, LV function post-stress may not represent true resting LV function. Consequently, this result justifies the stratification of patients before starting the gated SPECT study. In patients with an earlier myocardial infarction, the gated acquisition should be performed during the rest study.

INTRODUCTION

Because left ventricular ejection fraction (LVEF) is a major determinant of prognosis in patients with coronary artery disease, it is important to assess LVEF in addition to myocardial perfusion [1]. The recently developed quantitative gated single photon emission computed tomography (SPECT) program (QGS) provides reliable information on LVEF, LV wall thickening, LV wall motion, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) in addition to myocardial perfusion [2-4]. Gated acquisition of the stress myocardial perfusion images 30 minutes post-stress is generally considered myocardial perfusion at maximal stress where LV function is the resting situation. However, post-stress LV dysfunction may develop in patients with stress-induced ischemia, probably because of myocardial stunning [5-8]. This implies that when gated SPECT is obtained 30 to 45 minutes post-stress, LVEF and LV volumes may not represent the true resting LV function. Furthermore, the influence on LV function obtained by using pharmacological stress (adenosine, dipyridamole or dobutamine), as compared with that obtained by using exercise stress, is not fully elucidated [9-14]. The recently developed QGS program is applied routinely in an increasing amount of nuclear imaging departments worldwide [2-4]. So far, no studies involving pretest stratification of patients have been published. The aim of this study was to determine whether LV function post-stress would be different from basal LV function at rest in patients with a previously sustained myocardial infarction and whether there was a different influence on LV function between pharmacological stress and conventional exercise stress. This information may facilitate the stratification of patients before they undergo a gated SPECT study.

METHODS

Patients

We studied 58 consecutive patients with an earlier myocardial infarction. There were 10 women and 48 men (mean age, 61.8 ± 11.6 years; range 50 to 80 years). In all patients, a persistent defect in at least 3 of 18 LV segments was shown with gated SPECT myocardial perfusion imaging. Exclusion criteria were left bundle branch block, irregular heart rhythm, and reconstruction artifacts caused by tracer activity in intestines lying next to the heart. The baseline characteristics of the 58 patients are listed in table 1. A control group of 23 patients, who had a low pretest likelihood of coronary artery disease and normal results on a myocardial perfusion scintigram (Table 1), was selected.

Stress protocols

All patients underwent a 2-day imaging stress/rest protocol, in which the gating was done during both the rest and the stress myocardial perfusion SPECT acquisition. In 24 patients (41%), a symptom-limited exercise stress test was performed in the upright position with a bicycle ergometer. In all patients undergoing physical exercise, beta-blocking agents were discontinued at least 48 hours before the test. The exercise stress protocol included a stepwise increase in workload depending on gender, age, weight and height. This protocol is routinely applied in our institution. When the prespecified maximum workload (depending on gender, age, weight

Table 1. Patients characteristics and stress modalities used.

	Myocardial infarction (N =58)	Control Subjects (N=23)
Q-wave on ECG	51	n.a
Elevated enzymes (CK,CK-MB) with no Q-wave on ECG	7	n.a
Age (y)*	61.8 ± 11.6 (range 50-80)	58.5 ±10.4 (range 47-85)
Men*	48	13
Women	10	10
Stress modality -Ergometry	24	13
-Adenosine	27	9
-Dobutamine	7	1
1-vessel disease	17	n.a.
2-vessel disease	14	n.a.
3-vessel disease	12	n.a.
No angiogram	15	n.a.

* P <0.05 for difference in age and gender between patients and control subjects. Controls subjects were defined as patients with a low pre-test likelihood of coronary artery disease and normal results on a myocardial perfusion scintigram. n.a.=not applicable

and height) is achieved, the physical validity is considered to be at least 100%. Exercise stress endpoints were severe angina, physical exhaustion, dyspnoea, sustained tachyarrhythmias, exertional hypotension, or ischemic sinus tachycardia (ST)-T segment depression of at least 0.2 mV with a duration of 80 ms. Exercise was considered inadequate when the physical validity of the patient was less than 80% of the predicted validity (workload) in the absence of angina or an ischemic ST depression. Pharmacological stress with 0.14mg/kg/min adenosine during 6 minutes was used in 27 patients (47%) who were not able to exercise adequately. All these patients withheld caffeine-containing beverages for 12 hours before the test. A dose of 300 µg/kg dobutamine in 15 minutes was used in 7 patients (12%) who where not able to exercise adequately and who also had a contraindication to the use of adenosine. Before and every minute during stress, 12-lead electrocardiography (ECG) was performed. In case of ST-T-segment abnormalities, registration of the stress ECG was continued until normalization of the electrocardiogram was seen.

Exercise versus pharmacological stress

To assess the influence of different stress modalities on the change in LVEF, LVEDV, and LVESV, we analyzed baseline and post-stress LVEF, LVEDV and LVESV both in the patients who received pharmacological stress agents and the patients who underwent ergometry stress. For the purpose of this study, we only compared adenosine stress with conventional exercise.

Image acquisition protocol

A dose of 500 MBq (13.5mCi) technetium-99m tetrofosmin (Myoview, Cygne-Amersham) was administered 45 to 60 minutes before rest image acquisition and 30 minutes before to stress image acquisition. Imaging was performed with the patient in prone position with a Toshiba GC-9300 triple-head camera equipped with high-resolution collimators and connected to a

Toshiba GMS 5500 computer. A 360-degree rotation with a noncircular orbit as close to the patient as possible was obtained with 90 steps of 4 degrees, 30 seconds per step, and a 64-by-64 matrix size. A 20% symmetric energy window centered on the 140 keV peak was used. Sixteen frames per cardiac cycle were gated. The data were prefiltered with a Butterworth filter power 9, order 8, and a cut-off frequency of 0.32, and they were reconstructed with the filtered back-projected algorithm and a Ramp filter. The data were reoriented to obtain oblique-angle tomograms parallel to the long axis and short axis of the left ventricle. The reconstructed data were projected as tomographic slices in short, vertical, and horizontal axis views in a side-by-side display. In addition, the images were displayed as polar plots (bull's-eye maps). Numerical values of LV volumes and LVEF were calculated by using a commercially available software package (QGS), yielding a dynamic 3-dimensional LV image developed by Germano et al. [2-4,15,16]

Static image analysis

On the static perfusion images, semiquantitative analysis of myocardial perfusion was performed for 18 LV segments. There were 6 segments on a preapical and mid-short-axis slice, 4 segments on the basal short-axis slice, (the septal part was left out because of the presence of the membranous part of the interventricular septum), and 2 apical segments on the vertical long-axis slice. This segment scheme is a modification of the scheme used by Germano et al.[3]. The analysis was done in both rest and stress perfusion images. All segments were scored using a 4-point scale: no uptake; less than 30% of normal perfusion (score 0), severely diminished uptake; 30% to 55% of normal perfusion (score 1), slightly diminished uptake; 56% to 80% of normal perfusion (score 2); and 80% to 100% of normal perfusion (score 3), normal uptake. The percentages were judged by using a hot-metal square color scale. The scoring was done by 2 experienced observers in consensus (CB, MS). Defects were characterized as fixed or reversible. A defect was considered to be fixed when there was no change between the stress and the rest image. A defect was considered to be reversible when there was an improvement in tracer uptake of at least 1 grade between stress and rest images. A perfusion defect severity score was calculated by summing the scores of 18 segments in the rest study. A lower score implies a more extensive perfusion defect. The severity of the reversibility was judged by calculating the numerical difference in perfusion score between the rest and stress study. Based on the stress-rest images, patients were divided into groups: patients with only fixed defects (n=42) and patients with additional reversible defects (n=16). Additional ischemia was defined as reversible ischemia in 2 or more LV segments in addition to the fixed perfusion defect.

Coronary Angiography

Coronary angiography was performed according to the standard Judkins technique. An obstruction of 50% or more in 1 or more of the major 3 coronary arteries seen by means of a visual examination was considered to be significant.

Statistical analysis

To determine interobserver variability, 3 technicians reconstructed the raw data of 19 patients to analyze LVEF. The standard deviation (SD) of the LVEF was expressed in LVEF units. The intraobserver variability was determined by 1 technician reconstructing the raw data twice,

with an 11 day-interval between processing instances in all 19 patients. The outside limits for variability of the measurements were determined to be 2 SD beyond the mean value. Significant differences of changes in LVEF, LVESV, and LVEDV between patients with and without reversible ischemia was tested by using the unpaired Student's *t* test. The same test was applied as a means of calculating the significance of differences in differences in changes of LVEF, LVEDV and LVESV between patients undergoing adenosine and ergometry stress. The paired Student *t* test was used as a means of calculating the significance in change between post-stress and rest of LVEF, LVESV, and LVEDV within patients and control subjects. Analysis of variance (ANOVA) was applied as a means of analyzing the influence of reversible ischemia on the changes in LVEF, LVESV, and LVEDV post-stress versus rest in the whole group. ANOVA was also used as a means of determining the influence of the amount of stenosed vessels on changes in LVEF, LVEDV, and LVESV post-stress versus rest. Covariance analysis was used as a means of adjusting the confounding effects of age and gender. Values are shown as the mean plus or minus SD, unless indicated otherwise. A *p* value of 0.05 or less was considered to be significant.

RESULTS

Serial reproducibility

For the interobserver variability, a SD of the mean LVEF of 0.77% was found (range 0.5 to 1%) expressed in LVEF units. For the intraobserver (P.D.) variability, a SD of 0.89% was found. The limits for serial reproducibility of the measurements were thus determined to be 2x0.89=1.8%. The Bland Altman plot showed that the differences in LVEF measurements between 2 technologists in this reproducibility study were independent of the LVEF level. Because the QGS only provides integer values for LVEF, we used a cutoff value of 2% to distinguish real LVEF changes from LVEF changes that might be caused by imperfect reproducibility.

Control group

The resting LVEF, LVESV, and LVEDV are shown in table 2. The mean LVEF, LVESV, and LVEDV in the group of patients with a low likelihood of coronary artery disease were not significantly different between post-stress and resting condition (Table 3).

Table 2. Rest LVEF, LVESV and LVEDV in the control group (n=23) and in 58 patients with an earlier myocardial infarction.

	LVEF (%)	LVEDV (ml)	LVESV (ml)
Controls (n=23)	54.8 ± 4.5	99.7 ± 17.6	45.3 ± 10.9
All patients (n=58)	39.5 ± 12.4*	158.2 ± 57.2*	101.2 ± 54.0*
Isch + (n=16)	35.6 ± 14.8	160.3 ± 60.0	109.7 ± 60.0
Isch - (n=42)	41.0 ± 11.2	157.4 ± 56.9	98.0 ± 51.7

LVEF: Left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; Isch+: reversible ischemia in addition to a fixed defect; Isch-: only a fixed defect. Values represent mean ± SD. **p*<0.001, difference in rest LVEF, LVEDV, and LVESV between controls subjects and patients. *p*= not significant between patients with and without reversible ischemia. *P* value obtained with the unpaired Student's *t* test.

Table 3. Changes in LVEF, LVESV and LVEDV post-stress compared with rest in the 23 control patients and in patients with previous myocardial infarction.

	Δ LVEF (%)	Δ LVEDV (ml)	Δ LVESV (ml)
Control patients (n=23)	$0.04 \pm 3.2^*$	$-1.3 \pm 7.6^*$	$-0.7 \pm 5.1^*$
Patients with earlier MI (n=58)	-1.9 ± 4.2^a	7.9 ± 17.6^b	6.5 ± 18.7^c

Δ : Difference post-stress compared with rest; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MI: myocardial infarction. Values represent mean $\pm$ SD. *: p=not significant; Patients: ^ap=0.002 for Δ LVEF; ^bp= 0.001 for Δ LVEDV and ^cp=0.002 for Δ LVESV. P values obtained with the paired Student's t-test.

Myocardial infarction group

The mean resting LVEF, LVEDV and LVESV in patients with an earlier myocardial infarction are listed in Table 2. There was a significant difference in rest LVEF, LVEDV, and LVESV between the patient and control group (Table 2). In contrast, there were no significant differences in rest LV parameters between patients with and without reversible ischemia (Table 2). Within the total group of 58, we found a significant average change in LVEF, LVEDV and LVESV post-stress versus the resting condition (Table 3). Conversely, the difference in change of LVEF, LVESV and LVEDV between the rest and the stress acquisition was not different between patients with and patients without reversible ischemia [LVEF(%), 0.94 ± 1.1 (p=0.5), LVEDV(ml), -4.7 ± 4.6 (p=0.4); LVESV(ml), -4.4 ± 4.2 (p=0.4)]. Thus, it was demonstrated by means of ANOVA that the presence of reversible ischemia, which occurred in 16 patients (28%), did not influence the differences in LVEF, LVEDV and LVESV post-stress, as compared with the resting condition (p=0.4). By using the cutoff value of 2% to define a true change, we found a decrease ($\geq 2\%$) in LVEF in 33 patients (57%), an increase ($\geq 2\%$) in LVEF in 12 patients (22%), and no change in LVEF in 13 patients (21%; Figure 1). The amount and severity of the perfusion defects were not predictive of changes in LVEF post-stress compared with rest LVEF ($r=0.05$).

Figure 1. Percentage of patients with myocardial infarction with 1: decrease ($> 2\%$), 2: unchanged ($-2\% < x < 2\%$) or 3: increase ($> 2\%$) of left ventricular ejection fraction post-stress compared to rest. SEE for 1: 6.5%, SEE for 2: 5.3% and SEE for 3: 5.4%.

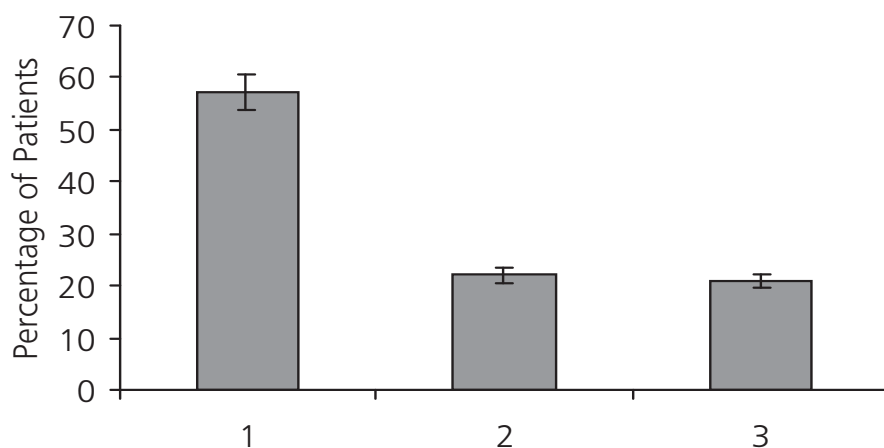


Table 4. Influence of the number of stenosed vessels on changes in LV functional parameters post-stress compared with rest. In 43 of 58 patients (74%), a coronary angiogram was available.

	1-vessel disease (n=17, LAD 12, RCA 4, LCX 1)	2-vessel disease (n= 14, LAD 12, RCA 6, LCX 10)	3-vessel disease (n=12)	P value by means of ANOVA
Rest LVEDV (ml)	163.1 ± 59.5	145.7 ± 62.5	173.1 ± 43.6	NS
Rest LVESV (ml)	102.3 ± 57.0	94.8 ± 58.8	114.8 ± 46.0	NS
Rest LVEF (%)	40.8 ± 13.2	39.3 ± 14.8	36 ± 11.8	NS
ΔLVEDV (ml)	7.5 ± 20.8	4.36 ± 14.8	5.6 ± 18.9	NS
ΔLVESV (ml)	8.6 ± 14.8	4.9 ± 15.5	8.25 ± 21.9	NS
ΔLVEF (%)	-2.1 ± 3.9	-1.3 ± 3.3	-1.9 ± 5.5	NS

LAD: Left coronary artery; RCA: right coronary artery; LCX: left circumflex artery; ΔLVEF: change in left ventricular ejection fraction post-stress compared with rest; ΔLVEDV: change in left ventricular end-diastolic volume post-stress compared with rest; ΔLVESV: change in left ventricular end-systolic volume post-stress compared with rest; NS: not significant. ANOVA, analysis of variance.

Coronary Angiography

In 43 patients (74%), coronary angiography data were available. The changes in LVEF, LVEDV, and LVESV post-stress between patients with 1, 2, or 3 stenosed vessels were not statistically significant (Table 4).

Stress modality

In the group of patients with an earlier myocardial infarction, there were no significant differences in resting LV function between the patients who underwent adenosine stress and the patients who underwent conventional exercise (Table 5). Also the changes in LVEF and LVESV post-stress compared with those at rest were not significantly different between groups. There was a marginally significant increase in LVEDV for the adenosine group (p=0.04). However, when applying the Bonferroni correction, the differences in change of LVEDV between both stress modalities were no longer statistically significant (p=0.08; Table 5).

Table 5. Mean LV function parameters in patients with different stress modalities. Because there were only 7 patients with dobutamine stress, we only calculated the P values between adenosine and conventional exercise.

	Ergometry (n=24)	Adenosine (n=27)	P Ergometry vs Adenosine
Rest LVEDV (ml)	169.4 ± 110.7	150.0 ± 51.6	NS
Rest LVESV (ml)	110.7 ± 57.8	92.0 ± 48.0	NS
Rest LVEF (%)	37.6 ± 11.5	41.8 ± 12.1	NS
ΔLVEF (%)	-1.2 ± 4.6	-2.6 ± 4.2	NS
ΔLVEDV (ml)	1.0 ± 18.4	11.9 ± 17.9	0.04, Bonferroni: 0.08
ΔLVESV (ml)	4.1 ± 20.4	11.7 ± 15.6	NS

LVEDV: Rest left ventricular end-diastolic volume; LVESV: rest left ventricular end-systolic volume; LVEF: rest left ventricular ejection fraction; ΔLVEF: change in left ventricular ejection fraction post-stress compared to rest; ΔLVEDV: change in left ventricular end-diastolic volume post-stress compared to rest; ΔLVESV: change in left ventricular end-systolic volume post-stress compared to rest; NS: not significant. Values represent mean ± SD.

Discussion

Gated SPECT myocardial imaging is routinely performed in many nuclear imaging departments. Because of logistics, the gating may be done during the acquisition of either the rest or the stress study. Several studies have shown a transient deterioration of LV function in patients with exercise-induced ischemia that persists long after cessation of exercise [5,6,8,17]. Therefore, when gated acquisition is only done during the acquisition of the stress perfusion study, LV function 30 minutes post-stress may not represent true LV function at rest. However, it is not known beforehand which category of patients will show reversible ischemia. Therefore, it is not possible to decide ahead of time whether the gated acquisition has to be done at rest. In our study, taking into concern the interobserver and intraobserver variability, we calculated a decrease of 2 or more LVEF points to be significant. The average decrease in LVEF for the whole patient group with a myocardial infarction was 1.9%, which was statistically significant. The highest LVEF decrease in this study was 13%. Although an average decrease of 1.9 LVEF points post-stress compared with rest is not clinically important, it is not fully known which patient will show a clinically significant or insignificant change when the rest study is non-gated. In our study we found that 33 of 58 patients (57%) with a previously sustained myocardial infarction showed a statistically significant deterioration of LV function ($\geq 2\%$) that persisted as long as 30 minutes after stress, even in patients without concomitant reversible ischemia. This finding allows the stratification of patients before starting the gated SPECT study. In all patients with definitive evidence of a previously sustained myocardial infarction, gating should be performed during the acquisition of the resting study to determine the true LV function at rest. Subsequently, in these patients, we found a similar change of LV function between post-stress and rest for patients who had adenosine stress and patients who underwent bicycle exercise.

Previous studies

Several studies have shown a transient deterioration of LV function in patients with exercise-induced ischemia that persisted long after cessation of exercise [5,6,8,17,18]. This phenomenon may be attributed to myocardial stunning, which has been defined as spontaneous reversible post-ischemic dysfunction in the presence of normalized perfusion [19]. This implies that patients with ischemia shown by means of the perfusion image may have a decreased LV function when gating is done during the post-stress study. Several pathophysiological mechanisms of myocardial stunning have been put forward, such as the oxygen-radical hypothesis and the calcium-overload hypothesis [19-22].

To date, only a few articles have been published on the evaluation of LV function at least 30 minutes post-stress analyzed with ^{99m}Tc labeled agents in combination with the QGS program [7,17,18]. Johnson et al.[7] analyzed 22 patients in whom a significant decrease in LVEF post-stress was shown. All 22 patients had reversible ischemia, and 10 of the patients (50%) had a history of myocardial infarction. In another group of patients ($n=20$), in whom only a fixed defect was shown, the average change in LVEF post-stress was not significant. In this group, 14 patients (70%) had sustained an earlier myocardial infarction. Because 6 of the patients (30%) were not known to have an earlier myocardial infarction, these results are not comparable with our results. Our findings are discordant with the findings of Paul et al.[17] who could not find a deterioration in LV function in 18 patients with a myocardial infarction. However, these patients were defined by means of the presence of fixed perfusion defects,

without additional historical or enzymatic evidence of earlier myocardial infarction. Because a fixed perfusion defect may be caused by an attenuation artifact, the perfusion abnormality might not necessarily represent infarcted tissue. In a recent study by Hashimoto et al.[18], a significant depression of post-stress LVEF relative to resting LVEF was shown in 11 patients with severe reversible ischemia. However, the authors did not explicitly describe whether their patient population (n=47) consisted of patients with an earlier myocardial infarction. As a result, it is not possible to compare their findings with ours.

Theoretical explanation

An explanation for the prolonged dysfunction after exercise in patients with myocardial infarction is the relative imbalance between oxygen supply and demand. In the presence of a flow-limiting coronary artery stenosis, exercise results in an alteration of the transmural distribution of myocardial perfusion in a manner such that flow is distributed preferentially to the subepicardium, while the subendocardium is most severely hypoperfused [23,24]. Moreover, it is known that the oxygen consumption per gram of tissue is usually higher in the subendocardium than in the subepicardium, and transmural thickening occurs primarily in the endocardial layer [25]. During stress, a relative high imbalance between oxygen supply and demand in the subendocardial layers subtended by stenosed vessels may develop without significant changes in overall blood supply. This may, in turn, lead to stunning and, hence, a decrease in LV function without signs of reversible ischemia on the myocardial perfusion images. In the QGS software program, an asymmetric Gaussian is fitted to each profile, and the inner and outer standard deviations of the Gaussian are noted [2]. A thinner perfused myocardium would decrease the count activity in the myocardial wall (partial volume effect), but probably would not shrink the width of the Gaussian count distribution across the wall much. Thus, in our opinion, a technical factor such as endocardial count loss is not an explanation for the fall in LVEF post-stress. Another factor leading to a relative high need for oxygen is the higher wall stress which occurs in large ventricles subjected to a previous myocardial infarction. This high oxygen need is further augmented during stress. When the blood supply is not adequate, this may also result in a relative deprivation of oxygen and, hence, may lead to myocardial stunning.

It is known that neurons are more sensitive to ischemia than myocytes. Therefore, LV dysfunction post-stress leading to a fall in LVEF could also be caused by neuronal dysfunction that is exaggerated during stress because of ischemia [26-28]. Because imaging with iodine-123-metaiodobenzylguanidine (a radio labeled norepinephrine analogue reflecting cardiac sympathetic activity) was not performed in our studied population, this neuronal involvement is only hypothetical.

Influence of the amount of stenosed vessels

We found no statistically significant differences between patients with 1-vessel, 2-vessel or 3-vessel coronary artery disease in the post-stress changes in LV function. This implies that there is probably no linear relationship between the extent of stenosed vessels and the level of LV function 30 minutes post-stress. The infarcted myocardium is probably the major determinant of global LV function. Although the number of patients in the 3 groups was not high (n=17, n=14, n=12) our findings were confirmed by Johnson et al.[7] who found that the number of diseased vessels was not a dependent variable that correlated significantly with LVEF

changes. In addition, Marcassa et al.[29] found that the extent of coronary artery disease was similar among patients with and without transient LV dilatation post-stress. Conversely, several studies have reported that the degree of LV dysfunction is related to angiographically assessed severity of coronary artery disease [12,13]. However, these studies are not comparable with our study, because dipyridamole radionuclide angiography was used as a means of assessing LV function, and thallium-201 dipyridamole images were used as a means of measuring the LV cavity. In addition, functional information was obtained during stress and not 30 minutes post-stress [12,13].

Influence of the severity of the perfusion defect

There was no significant correlation between the severity of the fixed perfusion defects and the change of LVEF post-stress, compared with rest. This could be explained by the extent of damaged neurons, which exceeds the extent of tissue necrosis defined by means of rest blood flow abnormalities. Because neurons are more sensitive to ischemia than myocytes [26-28], we tentatively conclude that the damaged tissue may be more extensive than one would judge from the number of perfusion defects.

Influence of stress modality on post-stress LV function

In our group, 47% of the patients had adenosine as stress modality, 41% of the patients had ergometry, and 12% of the patients had dobutamine. The resting LV functional parameters and the change in LVEF and LVESV post-stress were not different between the patients who had adenosine stress and the patients who underwent conventional exercise. In the adenosine group, there was a marginally significant higher difference in change in EDV post-stress, compared with rest. However, when we applied the Bonferroni correction, this significance did not hold. Moreover, because the number of patients in the subgroups (adenosine, n=27; conventional exercise, n=24) was relative low, we think it is preferable to conclude that there was a trend towards a higher change in LVEDV in the adenosine group than that in the conventional exercise and not a significant difference in increase of LVEDV between both stress modalities. In accordance with our study, Nallamothu et al.[30] found more patients with LV cavity dilatation in the adenosine group than patient who underwent bicycle exercise, although no explanation was provided. Several studies reported a significant increase in pulmonary capillary wedge pressure in patients with coronary artery disease, compared with healthy subjects, when adenosine was used [11,31,32]. The increase in pulmonary wedge pressure is probably initiated by a change in vascular loading, higher LVED pressure, or diastolic dysfunction, which in turn leads to a higher EDV. In our opinion, it is not unlikely that this phenomenon may persist long after cessation of the infusion.

Controversial opinions exist about the influence of adenosine or dipyridamole on LV function [9,13,29]. Pennell et al.[9] found that the site of wall motion deterioration found by using magnetic resonance imaging was always the site of a reversible thallium-201 defect. In a later study analyzing the influence of dobutamine on LV function by using magnetic resonance imaging, Pennell et al.[10] suggested that dobutamine is more effective in eliciting wall motion abnormalities in patients with coronary artery disease than dipyridamole. Ogilby et al.[11], who used adenosine in patients with coronary artery disease, observed perfusion defects without a decrease in global and regional systolic function. Conversely, the authors found a higher pulmonary capillary wedge pressure, probably caused by diastolic left ventricular dysfunction.

Takeishi et al.[12] stated that dilatation of the LV cavity on dipyridamole TI-201 imaging reflected relative subendocardial hypoperfusion induced by dipyridamole, rather than actual chamber enlargement. The cavity area increased, but the ventricular area did not change. In contrast, Klein et al.[13] concluded that dipyridamole induces ischemia that is sufficiently significant to be detected by means of radionuclide ventriculography such as LV dilatation and dysfunction. Marcassa et al.[29], who studied 234 patients, 130 of whom sustained a previous myocardial infarction, reported a similar incidence of transient LV dilatation after exercise and during pharmacologic stress testing (37% and 36%, respectively). However, the authors found LV dilatation in 86 patients (37%) of whom only 19 (22%) showed epicardial transient dilation. The remaining 67 patients showed endocardial transient dilation without concomitant epicardial dilation, probably caused by diffuse subendocardial hypoperfusion simulating an increase in LV cavity dimension. None of these studies used a QGS program similar to that applied in the present study, which could lead to different results.

Study limitations

Johnson et al.[7] analyzed the reproducibility of the test by applying the same gated SPECT approach as used in this study in 15 patients 24 hours later. They found a reproducibility of 5.2%. Because it was not allowed because of ethics in our institution to repeat the total myocardial perfusion test 1 day later, we tested the reproducibility of LVEF measurements by analyzing the interobserver and intraobserver variability by reconstructing the raw data. The reproducibility showed a mean standard deviation of 0.89%. Patients were studied in prone position during the acquisition of both the rest and stress study, eliminating the variability of LVEF caused by a difference in positioning [33]. In our study, only patient studies without gating problems or acquisition problems were used. Furthermore, the same technologist reconstructed the acquisition data for the rest and the stress study in 1 patient according to a standard protocol. Although a circumstantial variation cannot be excluded, we do not assume that the reproducibility would have been less accurate.

CONCLUSIONS

Most patients with an earlier myocardial infarction who undergo gated SPECT show a significant decrease in LVEF lasting at least until 30 minutes post-stress. This phenomenon occurs irrespective of the presence of demonstrable reversible ischemia or the stress modality used. To obtain true LVEF and LV volumes at rest in patients with an earlier myocardial infarction, it is preferable to perform the gating during the rest acquisition.

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