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Exercise-Induced Ischemic Arrhythmias in Patients With Previous Myocardial Infarction: Role of Perfusion and Tissue Viability

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Objectives. **This study sought to investigate whether residual viability of infarcted myocardium may play a role in the pathogenesis of exercise-induced ventricular arrhythmias.**

Background. **We previously showed that transient ischemia within partially infarcted areas often precipitates ventricular arrhythmias during exercise that are consistently obliterated by intravenous nitrates.**

Methods. **We studied 60 patients with chronic stable angina and a previous myocardial infarction. All underwent at least two consecutive exercise stress tests, coronary angiography and stress/rest myocardial perfusion tomography by Tc-99m 2-methoxy isobutyl isonitrile (MIBI). In the last 26 consecutive patients, residual viability was assessed by single-photon emission computed tomography (SPECT) using fluorine (F)-18 fluorodeoxyglucose. Perfusion and metabolic data were evaluated qualitatively by three independent observers in blinded manner.**

Results. **With exercise, 30 patients (group A) consistently developed ventricular arrhythmias (>10 ventricular ectopic beats/min, couplets, nonsustained ventricular tachycardia); the remaining 30 patients (group B) did not. The severity of coronary artery disease (Gensini score) was similar in the two groups. Postexercise SPECT showed partial reperfusion of an infarcted area in 28 of 30 patients of group A but in only 9 of 30 of group B ($p < 0.0001$). Uptake of F-18 fluorodeoxyglucose was observed within the infarcted zone in 10 of 13 and 1 of 13 patients in groups A and B, respectively ($p = 0.0003$).**

Conclusions. **In patients with myocardial infarction, exercise-induced ventricular arrhythmias appear to be triggered by transient ischemia occurring within a partially necrotic area containing large amounts of viable myocardium. Therefore, occurrence of arrhythmias during exercise may represent a clue to the presence of residual viability within a previously infarcted area.**

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Although relatively rare in patients with ischemic heart disease, frequent or repetitive ventricular arrhythmias induced by exercise stress testing, are associated with a 2- to 15-fold increase in mortality on long-term follow-up (1–5). Many factors have been suggested to contribute to the occurrence of these arrhythmias, but since intravenous nitrates are very effective in their prevention (6), myocardial ischemia is likely to play a major pathophysiologic role.

Although exercise-induced arrhythmias have been reported to be more frequent in patients with previous myocardial infarction (7), no studies have addressed the mechanisms responsible for their occurrence: specifically, the hypothesis that they might be caused by transient, exercise-induced myocardial ischemia arising from within-infarct viable tissue has not been investigated.

The aim of the present study was to characterize the anatomic and functional perfusion to the infarct area as well as the presence of residual tissue viability in a group of patients with previous myocardial infarction who consistently developed significant ventricular arrhythmias during exercise testing.

Methods

Patients. We evaluated 430 consecutive patients with a recent (generally 4 to 5 weeks old) myocardial infarction and angiographically proven coronary artery disease, admitted between March 1992 and September 1993. During the acute phase of the myocardial infarction, 50% of patients had undergone intravenous thrombolysis (either recombinant tissue-type plasminogen activator or streptokinase). In the remaining 50%, thrombolytics had not been administered either because of late arrival or because of contraindications.

Of the 430 patients studied, 30 consistently developed frequent (≥10 ectopic beats/min) and/or repetitive (couplets, nonsustained ventricular tachycardia) ventricular arrhythmias during repeat exercise stress testing and represented the study group. They were 28 men with a mean age of 61.1 ± 8.3 years,

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of whom 11 had had an anterior, 16 an inferior and 3 both an anterior and inferior myocardial infarction. To be considered, patients had to exhibit the same type of ventricular arrhythmias in at least two (range two to three) separate exercise test sessions with a variability <20% in the number of ventricular ectopic beats. Thirty consecutive patients (26 men, mean age 60.7 ± 8.1 years) with similar clinical and angiographic characteristics but no exercise-induced ventricular arrhythmias during repeat exercise (at least two) were recruited from the same cohort and constituted the control group. Ten had had an anterior, 17 an inferior and 3 both an anterior and inferior myocardial infarction. None of the subjects in the study had diabetes, hypertension, valvulopathy, primary cardiomyopathy or significant (more than Lown class 1B) arrhythmia on Holter monitoring.

The protocol was approved by the Ethics Committee of our institution, and each patient gave written informed consent to the study.

Study protocol. After 3 days of pharmacologic washout, all patients underwent a protocol, including the following investigations.

Exercise stress testing. All tests were maximal, symptom limited and performed on a motor-driven treadmill using the modified Bruce protocol. Twelve-lead electrocardiographic (ECG) and blood pressure measurements were obtained during control, at 1-min intervals during exercise and for 10 min during recovery. Six ECG leads (II, III, VF, V_2, V_5 and V_6) were continuously monitored before, during and after exercise. The level of the ST segment was calculated (Case 12, Marquette Electronics) in blinded manner by two independent observers in three selected leads (usually III, V_2 and V_5). Disagreement was resolved by consensus. Angina, fatigue, diagnostic ST segment depression and repetitive arrhythmia were considered reasons for discontinuing the exercise.

The number and type of arrhythmic events were assessed, both from analogue recordings (25 min s^{-1} paper speed) obtained automatically by the system whenever arrhythmia occurred and from the final arrhythmia report and printout, obtained by the manufacturer's proprietary algorithm (Case 12, Operator's Manual, Marquette Electronics Inc.). Furthermore, ventricular arrhythmias that were seen on the monitor screen by the supervising physician were also annotated.

Positron emission tomographic studies of myocardial glucose metabolism. This test was performed in only 26 patients, the last 13 of each group, as this technology became available to our institution only during the final part of the study. Regional myocardial glucose metabolism was assessed by positron emission tomography (PET), and F-18-fluorodeoxyglucose was synthesized according to the method described by Hamacher et al. (8) with a compact automated module connected to the cyclotron (CTI/Siemens RDS 112 cyclotron, Siemens/CPS). The labeled glucose analogue was used within 1 h of its preparation. The PET studies were carried out with an ECAT 931/04-12 tomograph (Siemens/CPS) equipped with Ge-68 retractable ring sources for transmission scans; transaxial and axial field of views were respectively 55.5 and 5.4 cm. Blood glucose and insulin levels were measured at the time of fluorodeoxyglucose injection. To enhance the detection of ischemic and yet viable tissue, patients fasted overnight (15 h). This method has been shown to be very sensitive for detecting areas of viable myocardium (9,10). To correct for photon attenuation, two transmission scans were performed in the region encompassing the heart, previously identified on a rectilinear scan; indelible ink lines that defined the upper limit of the PET field of view were drawn on the torso. Two consecutive emission scans, each lasting 10 min, were carried out between 40 and 60 min after the intravenous administration of approximately 250 MBq of F-18-fluorodeoxyglucose. The two emission scans were performed by sliding the bed axially to acquire two sets of seven tomographic images of radioactivity distribution. Fourteen contiguous slices, 6.75 mm thick, were reconstructed in the transaxial plane using the Hann filter (cutoff frequency 0.5 cycles/pixel) on a 64 × 64 matrix. Under these conditions, the spatial resolution in the transaxial plane was 0.8 cm full width at half-maximum.

Stress/rest myocardial perfusion scintigraphy. The exercise equipment and protocol were the same as described above. Imaging was performed within 90 min from exercise and again 48 h later. Regional myocardial perfusion was assessed by single-photon emission computed tomography (SPECT) on the day after the PET metabolic study. A dose of 740 MBq of Tc-99m 2-methoxy isobutyl isonitrile (MIBI) was injected intravenously 1 min before discontinuing the test. A standard cholecystokinetic fatty meal was given 30 min postinjection, and tomographic imaging was started within 90 min of tracer injection using a large-field of view, single-head rotating gamma camera (either a STARCAM 400 AC, General Electric, or a 7500 Orbiter, Siemens) equipped with a high-resolution, low-energy, parallel-hole collimator and interfaced with a dedicated computer. Radioactive external markers were placed, just before the SPECT studies, on the torso at the level of the indelible ink lines that defined the upper limit of the PET field of view. Sixty-four angular projections (64 × 64 matrix) were obtained in approximately 40 min over 360°. Transaxial slices 6.2 cm thick were reconstructed using a filtered back-projection algorithm with a Butterworth filter (cutoff frequency 0.4 cycles/pixel). No correction for attenuation was performed. Spatial resolution in the transaxial plane was 1.8 cm full width at half-maximum.

Combined PET and SPECT assessment. A semiquantitative analysis was carried out on tomographic images of resting perfusion and metabolism by dividing the left ventricle into six segments: anterior, apical, inferior, lateral, posterior and septal. The PET and SPECT data were transferred to a Sun workstation (Sun 4/330, Sun Microsystem) for image processing and integration through an Ethernet network connection. The reconstruction of the SPECT transaxial slices was started from the level defined by the radioactive markers, consistent with the upper limit of the PET field of view, to match corresponding transaxial slices in the SPECT and PET studies. Images were decoded and converted to a standard file format. The SPECT and PET transaxial slices were realigned along the

horizontal and vertical long and short axes with commercially available software (Image tool, Siemens).

Corresponding PET and SPECT images were displayed on a color TV screen in random order and analyzed in blinded manner by two experienced observers for the presence of fluorodeoxyglucose uptake within underperfused areas.

Each PET F-18-fluorodeoxyglucose image was displayed together with the matching perfusion slice, and circular regions of interest (ROIs) 1 cm in diameter were drawn in the areas of the left ventricular wall corresponding to the underperfused region. Counts/pixel were measured in each ROI, and values from two to five discrete ROIs from each segment were averaged to obtain a mean segmental value. A segmental index of F-18-fluorodeoxyglucose uptake was calculated by dividing the mean value of counts/pixel in each segment by the mean value of counts/pixel in the ventricular cavity. Underperfused tissue was defined viable when the F-18-fluorodeoxyglucose index was above the 95% confidence interval defined in six segments from five normal subjects studied in the fasting state.

Coronary angiography. All patients underwent left ventriculography and coronary angiography by the Judkins technique. Left ventriculography was performed in the 35° right anterior oblique and 60° left anterior oblique views. Selective angiograms of the left and right coronary arteries were performed in several views, both in the right and the left oblique position with craniocaudal angulations whenever appropriate. Coronary artery disease was considered significant if the diameter of at least one major coronary artery was reduced by 50% or more by quantitative coronary angiography. A global severity score of coronary artery disease was calculated for each patient using the Gensini (11) method. Collateral channels, if present, were graded according to the classification of Cohen and Rentrop (12). The studies were evaluated by two observers in a blinded manner.

Statistical analysis. Data are expressed as mean value ± SD unless otherwise stated. Differences in continuous variables between the two groups were assessed using a two-tailed Student *t* test. Comparisons of discrete variables were performed by the chi-square or the Fisher exact test as required. A p value of ≤0.05 was considered significant.

Results

Exercise stress testing. Exercise end points as well as type and frequency of arrhythmias were highly reproducible (within-patient variability < 10%) in both groups. Therefore, only data relative to the first exercise test are presented. In the patients with arrhythmias, total exercise duration was 502 ± 181 s, and in the control group it was 676 ± 266 s (p = 0.005); the rate–pressure product at peak exercise was, respectively, 20,760 ± 4,314 mm Hg × beats/min and 20,383 ± 5,491 mm Hg × beats/min (p = NS). Diagnostic ST segment depression was present in 24 and 19 patients, and time to 1 mm ST depression was, respectively, 411.8 ± 173 s and 494 ± 270 s in the two groups (p = NS). Rate–pressure product at the onset of ischemia, was also similar (18,731 ± 4,101 mm Hg × beats/min and 17,948 ± 5,551 mm Hg × beats/min; p = NS). In three control patients, exercise induced only T wave "pseudonormalization" without significant ST segment changes, and in one patient the appearance of left bundle block prevented the interpretation of the test. In the remaining seven control patients, exercise testing did not induce diagnostic ST segment changes. In the arrhythmia group, exercise was discontinued in 24 patients for the appearance of ST ischemic changes (accompanied by angina in 10 patients) and in six patients for the onset of frequent or repetitive arrythmias (nonsustained ventricular tachycardia), which were associated with angina in 1 patient. In the control group, appearance of diagnostic ST segment depression was the reason for termination in 19 patients, that was accompanied by angina in 6; in the remaining 11 exercise was discontinued because of physical exhaustion.

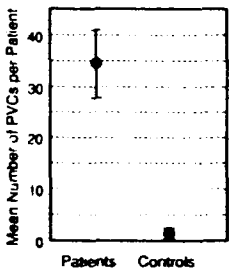


Figure 1. Central tendency with 95% confidence intervals of premature ventricular contractions (PVCs) during exercise in patients and control subjects.

Premature ventricular contractions totaled 1,039, of which 10% and 5%, respectively, were represented by couplets and nonsustained ventricular tachycardia: repetitive arrhythmias were seen in 23 patients. Figure 1 represents the central tendency of premature ventricular contractions during exercise in patients and control subjects.

Left ventriculography and coronary angiography. Left ventricular end-diastolic pressure (14.7 ± 2 and 12.8 ± 2 mm Hg, respectively) and ejection fraction (49 ± 9% and 51 ± 8%) were similar in the two groups. No patients had a true ventricular aneurysm.

Likewise, the distribution of patients with one-, two- and three-vessel disease (11, 9, 10 [mean 1.9 ± 0.8] and 11, 10, 9 patients [mean 1.9 ± 0.8], respectively) and the overall severity of coronary artery disease (37.8 ± 19 and 34.7 ± 17 points, respectively) were similar in the two groups.

The infarct-related artery was occluded in 20 and 22 patients of the two groups (p = NS): subtotal occlusion (≥90%, Thrombolysis in Myocardial Infarction [TIMI] flow grade 1) was present in 6 and 5 patients (p = NS). The remaining seven patients (four with arrhythmia and three control subjects) had significant residual stenosis (>50%).

Angiographically significant collateral channels to the necrotic area (TIMI flow grade 2 to 3), were seen in 22 patients with arrhythmia and 14 control subjects (p = 0.03). Of these, respectively, 20 and 14 had an occluded infarct-related artery.

Myocardial perfusion scintigraphy with Tc-99m MIBI. A fixed perfusion defect, indicative of previous myocardial necrosis, was present in all 60 patients on study. Exercise-induced

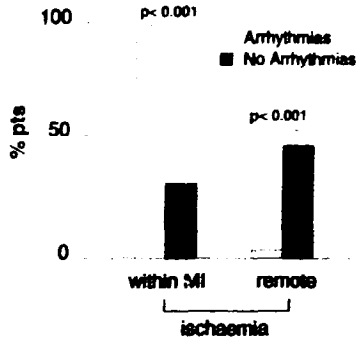


Figure 2. Percent prevalence of stress-induced ischemia within or remote from the infarcted area in patients (pts) with and without exertional arrhythmia. MI = myocardial infarction.

peri-infarction ischemia was evident in 28 patients with arrhythmias (92%) but in only 9 control subjects (30%, $p < 0.0001$) (Fig. 2).

Reversible myocardial ischemia remote from the infarcted area was present in 1 (3.3%) patient with arrhythmias and in 14 control subjects (46.6%) ($p = 0.0001$), 4 of whom also had periinfarction ischemia (Fig. 2).

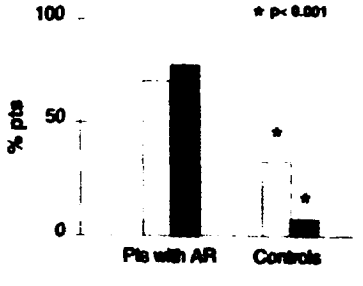
Myocardial metabolism assessed by F-18-fluorodeoxyglucose PET. Metabolic assessment of residual viability was obtained only in the last 13 patients of each group. Of these, respectively 9 and 4 had partial reperfusion within the infarcted area on MIBI SPECT. Myocardial uptake of F-18-fluorodeoxyglucose indicative of residual metabolic activity in the context of the infarcted area was evident in 10 of 13 patients showing exercise-induced arrhythmias (77%) and in only 1 control subject (7.7%, $p = 0.0003$) (Fig. 3).

Discussion

Although relatively rare, ventricular arrhythmias that occur in patients with ischemic heart disease (13–15) during exercise stress testing are associated with increased long-term mortality. This appears particularly true in patients with previous myocardial infarction (1–5,7).

Increased sympathetic tone and circulating catecholamines (16,17), decreased parasympathetic activity (18), changes in local pH and geometric factors (19) have all been considered to contribute to the development of exercise-induced ventricular arrhythmias. Occurrence of ischemia is also likely to play an important role, since the latter can influence the three main mechanisms of arrhythmogenesis: reentry, increased automaticity and triggered activity (16,17,20,21). In fact, suppression of ischemia by drug treatment (6), bypass grafting (22), and coronary angioplasty (23) has also been shown to obliterate exercise-induced arrhythmias.

Figure 3. Percent prevalence of transient ischemia and glucose uptake within the infarcted area in the 13 patients (pts) undergoing positron emission tomography (see text). **Open bars** = partial reperfusion within infarcted areas (MIBI); **solid bars** = F-18-fluorodeoxyglucose uptake within infarcted areas. AR = arrhythmias.



The results of our study demonstrate that patients with previous myocardial infarction, who exhibit ventricular arrhythmias on exercise testing, invariably show reversible perfusion abnormalities within the context of partially infarcted myocardium. Furthermore, despite the limited number of patients who underwent PET scanning, a great majority of them (77%) also showed residual metabolic activity within the infarct area, which is usually perfused by a patent artery or by angiographically visible collaterals. Therefore, in the post-myocardial infarction patients, occurrence of transient ischemia in the context of patchy necrosis seems to represent the prerequisite for the development of repetitive arrhythmias. Conversely, transient myocardial ischemia involving areas remote from the infarction site seems to have little arrhythmogenic potential. In fact, reversible perfusion defects in noninfarcted myocardium were significantly more common in the control group.

Approximately 73% of our patients had occlusion of the infarct-related artery. This rate is somewhat higher than that reported in various series after the introduction of the systematic use of thrombolysis in myocardial infarction. However, only 50% of our patients were treated with fibrinolytic therapy because of late arrival or contraindications: whether ischemia arises from an area perfused by an open but stenotic artery or by collaterals is unlikely to affect the likelihood of ventricular arrhythmias to develop.

Ventricular arrhythmias and transient myocardial ischemia. Previous studies exploring the relation between transient myocardial ischemia and exercise-induced arrhythmias have provided conflicting results (6,22–24). McHenry et al. (25) did not find a correlation in 197 patients with CAD. However, these authors only considered ST segment depression as a marker of ischemia, although transient perfusion abnormalities may well be present on myocardial scintigraphy even in the absence of ST segment changes (26–28). Moreover, the ST segment is unlikely to detect myocardial ischemia when the exercise is discontinued because of the appearance of repetitive arrhythmias. Other investigations (2,13,14,34,36) recruited patients both with and without previous myocardial infarction, but we specifically selected a cohort of patients all of whom had documented myocardial necrosis.

Experimental evidence suggests that the proarrhythmic effects of myocardial ischemia are more prominent when superimposed on a susceptible substrate like the one created by the nonuniformly anisotropic regions typical of myocardial infarction (29,30). In a cohort of patients with recent myocar-

dial infarction, Tsuji et al. (33) found a significant correlation between reversible perfusion defects on Tl-201 myocardial scintigraphy and repetitive ventricular arrhythmias recorded during ambulatory ECG monitoring. Although these authors did not analyze ambulatory recordings for the occurrence of ST-segment changes, they postulated that transient ischemia was not the cause of arrhythmias because the heart rate at which they occurred was low (between 56 and 70 beats/min). However, many studies have now shown that the great majority of ischemic episodes detected by Holter monitoring in patients with chronic stable coronary disease occur at low heart rate levels (32–34).

Ventricular arrhythmias and left ventricular function. Early studies conducted in patients with coronary artery disease found a frequent correlation between the degree of left ventricular dysfunction and the presence of ventricular arrhythmias (24,25,35). In agreement with more recent data (36–38), we could not find significant differences in the values of left ventricular end-diastolic pressure and ejection fraction recorded in patients with and without arrhythmias. In fact, the association between ventricular premature contractions and increased mortality persists even after adjusting for left ventricular ejection fraction (37).

The possibility that a different infarct size distribution in the two groups might have influenced our results needs considering, as we did not perform a quantitative evaluation of infarct size. However, none of our patients had, on angiography, a "true" aneurysm, which is a well-known cause of arrhythmias. Furthermore, patients with anterior and inferior myocardial infarctions were distributed equally in the two groups, suggesting that the extension of the necrotic area was also similar.

Clinical implications. We believe that our study carries important clinical implications because sudden cardiac death is significantly more frequent in patients with coronary artery disease and exercise-induced arrhythmias. In these patients, purely antiarrhythmic drugs are frequently ineffective and associated with serious side effects (39), and suppression of ischemia by surgery (22), angioplasty (23) or medical treatment (6) can obliterate arrhythmias. Our data call for randomized trials aimed at assessing whether aggressive antiischemic treatment by either drugs or revascularization procedures may be advisable to improve prognosis when exercise-induced arrhythmias occur in association with objective documentation of periinfarction ischemia.

Moreover, in the post–myocardial infarction patient, the occurrence of exercise-induced arrhythmias may, itself, represent a clue to the presence of residual viability within the infarct and suggest the use of more sophisticated tools when clinically indicated.

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