Improvement of Resting Myocardial Asynergy with Cessation of Upright Bicycle Exercise

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SUMMARY Exercise generally aggravates ischemic myocardial dysfunction, presumably by increasing tissue oxygen demand out of proportion to the increase in supply. Nevertheless, resting left ventricular (LV) wall motion abnormalities can improve dramatically after upright exercise. To investigate this "paradoxical" phenomenon, we performed upright bicycle exercise equilibrium radionuclide ventriculography in 93 patients with angiographic coronary artery disease. Immediately after exercise, LV end-diastolic volume was similar to the resting level (1 ± 22% of rest value), but end-systolic volume (ESV) was significantly below (p < 0.05) that at rest (−11 ± 32%) and LV ejection fraction increased significantly compared with rest (0.57 ± 0.16 vs 0.51 ± 0.13, p < 0.05). Improvement in resting myocardial asynergy was frequent (115 of 330 abnormal segments), and was observed more commonly in patients without pathologic Q waves and in segments manifesting mild rather than severe asynergy. In 60 additional patients with resting asynergy who were also studied after nitroglycerin (NTG), there was 89% concordance of wall motion response in asynergic segments after exercise and NTG: 71 of 85 segments manifesting improvement with NTG also improved after exercise, and 157 of 172 segments without improvement with NTG also failed to improve after exercise.

Despite similar wall motion response, the mechanism of improvement is probably different from that produced by NTG. With NTG, preload (end-diastolic volume) and afterload (systolic blood pressure) were significantly lower than their resting control levels (p < 0.05). These changes did not occur after exercise. Instead, an isolated, significant reduction in ESV was noted. These data support the hypothesis that catecholamine support is responsible for paradoxical wall motion improvement after upright exercise.

DETERIORATION of normal left ventricular (LV) function has been observed after exercise in patients with coronary artery disease (CAD) by a variety of techniques, including apexcardiography,1 cardiokymography,2 and echocardiography.3 With each method, the measurements have been recorded with the patient supine after upright exercise. Hemodynamic responses, however, are highly dependent on body position.4,7 Thus, although cardiac dimensions usually increase in the supine position after exercise,8–10 they characteristically decrease in the upright position.11 Because cardiac volume is a major determinant of myocardial oxygen demand,12 these positional differences could materially influence regional LV function in patients with ischemic heart disease. To evaluate this hypothesis, we studied a group of patients with angiographically documented CAD during and after upright bicycle exercise with equilibrium radionuclide ventriculography.

Methods

Patient Population

The patient population consisted of 93 patients with angiographically documented CAD (≥50% stenosis in at least one coronary artery) undergoing exercise equilibrium radionuclide ventriculography. Forty-eight patients had three-, 27 two- and 18 one-vessel CAD. All patients underwent contrast angiographic and radionuclide studies within 3 months. None had an intervening myocardial infarction, valvular heart disease or nonischemic cardiomyopathy. The mean age of this population, which included 80 males, was 60 ± 13 years (± SD).

Sixty additional patients with resting scintigraphic wall motion abnormalities also underwent resting radionuclide ventriculography after nitroglycerin. This population, 55 of whom were male (mean age 60 ± 9 years), included 27 patients with documented myocardial infarction and 33 with a history of stable angina pectoris but no previous infarction.

Exercise Scintigraphy

Each patient underwent maximal exercise testing on a bicycle ergometer after 3–4 hours of fasting. Beta-blocking drugs were withheld for 24–48 hours before testing and nitrates were withheld on the day of study. After an i.v. injection of 25 mCi of autologous red blood cells labeled in vitro with technetium-99m, the patients were positioned on an upright, constant-load bicycle ergometer, calibrated in kiloponds. A mobile gamma camera equipped with a 1/4" NaI crystal and an all-purpose collimator was then positioned in the 40–45° left anterior oblique (LAO) projection; the exact degree of obliquity was determined by the position providing the best separation of the LV and right ventricular blood pools. R-wave-synchronized, multiple-gated equilibrium cardiac blood pool scintigraphy was performed at rest and during exercise by acquisition of 20 frames distributed uniformly over the entire RR interval. Scintigraphic images were acquired over 2 minutes, resulting in approximately 100,000 counts/
frame, and were collected using a 25% energy window centered on the 140-keV photopeak of technetium-99m.

All patients underwent two periods of exercise, with the gamma camera first in the 45° LAO projection and then in the anterior projection. For the anterior projection, a 5–10° caudal tilt was used when it provided a better separation of the left and right ventricles. Two resting control images were first obtained. Graded exercise was begun at a work load of 200 kilopond-meters/min (kpm/min) and increased by 200 kpm/min every 3 minutes. Unless exertional hypotension or serious ventricular arrhythmia intervened, patients exercised to exhaustion or marked chest pain. Scintigraphy was performed during the last 2 minutes of each stage of exercise, and then again in the first 2 minutes after exercise, with the patients remaining upright on the bicycle.

After 20–30 minutes of supine rest, while patient heart rate and blood pressure were allowed to return to control levels, exercise was repeated in the anterior projection.

Cardiac rhythm, ST segments and heart rate were continuously monitored before, during and after exercise. Blood pressure was recorded at rest, during the third minute of each exercise level and during each minute after exercise.

**Nitroglycerin Scintigraphy**

Patients undergoing radionuclide ventriculography with nitroglycerin were allowed to rest supine after the double exercise period. After heart rate and blood pressure returned to preexercise levels, repeat resting scintigraphy was performed upright in the 45° LAO and anterior views, but the anterior view was not obtained in patients with resting wall motion abnormalities visible only in the LAO projection. Nitroglycerin (0.4 mg) was administered sublingually and radionuclide imaging was repeated after systolic pressure fell by at least 10 mm Hg or heart rate increased by at least 10 beats/min.

**Analysis of Scintigraphic Data**

**Global Function**

The LV ejection fraction was determined by light pen assignment of LV end-diastolic and end-systolic regions of interest and light-pen assignment of a left paraventricular background region of interest. Ejection fraction was calculated by dividing stroke counts (end-diastolic minus end-systolic counts) by background-corrected end-diastolic counts. Relative LV volume changes were assessed from end-diastolic and end-systolic counts in each state (rest, exercise, postexercise and nitroglycerin). All counts were corrected for heart rate by dividing the raw counts by the product of the number of cycles processed and the frame duration. In our laboratory, there is a high correlation ($r = 0.92$) for duplicate count determinations so corrected.

**Regional Function**

After image enhancement by space-time smoothing, LV segmental wall motion was assessed by viewing the scintigraphic data in a closed-loop format on the computer's video display. Rest, peak exercise and postexercise wall motion was evaluated by two experienced observers who were unaware of the patient's clinical data. Pre- and postnitroglycerin images were analyzed independently. For each scintigraphic projection, the left ventricle was divided into five segments. The wall motion of each segment was graded on a five-point scale, where $3 = $ normal wall motion; $2 = $ mild hypokinesis; $1 = $ severe hypokinesis; $0 = $ akinesis; and $-1 = $ dyskinesis. LV inferior wall segments that could not be clearly visualized without overlap of the right ventricle in the anterior projection were excluded from analysis. Differences in scoring by the two observers were resolved by consensus.15

Segmental asynergy was defined as any resting wall motion abnormality (score $\leq 2$). Improvement in wall motion was considered present when postexercise or postnitroglycerin wall motion became normal (score $= 3$) or increased by two scores from the associated resting value.

**Electrocardiographic Data**

Q waves lasting 0.04 second or longer were considered pathologic. Anterior and inferior Q waves were correlated with the corresponding anterior and inferior segments on the radionuclide ventriculograms.

**Statistics**

The hemodynamic data at rest, peak exercise and after exercise were compared by analysis of variance with repeated measures. When the analysis of variance demonstrated a significant result, the Tukey test for pairwise multiple comparisons was used to determine which values were significantly different from one another. The significance level for the Tukey test was 0.05. Hemodynamic changes after exercise and nitroglycerin were compared by paired $t$ test. Wall motion changes after exercise and nitroglycerin were compared with the kappa statistic,16 which provides an estimate of chance-corrected agreement. The kappa statistic ranges from $-1$ to $+1$: a kappa of zero reflects only chance agreement, negative values reflect less-than-chance agreement, and positive values reflect more than chance-corrected agreement. When divided by its standard error, kappa provides a test statistic that allows one to determine if chance-corrected agreement is significantly different from zero.

**Results**

**Hemodynamic Data at Rest, Peak Exercise and Postexercise**

Heart rate (mean $\pm$ sd) increased from 75 $\pm$ 13 beats/min at rest to 140 $\pm$ 20 beats/min at peak exercise ($p < 0.05$). Systolic blood pressure also increased, from 131 $\pm$ 19 to 188 $\pm$ 31 mm Hg ($p < 0.05$). Two minutes after exercise, heart rate (103 $\pm$ 20 beats/min) and systolic blood pressure (162 $\pm$ 25 mm Hg) were still significantly increased ($p < 0.05$) above the resting values (fig. 1).
LV ejection fraction decreased with exercise from 0.51 ± 0.13 to 0.48 ± 0.16 (p < 0.05). In contrast, ejection fraction increased after exercise to 0.57 ± 0.16 (p < 0.05 compared with both the rest and exercise value).

LV end-diastolic volume increased by 19 ± 25% (p < 0.05) and end-systolic volume increased by 28 ± 43% (p < 0.05) during exercise. After exercise, end-diastolic volume returned to resting levels (1 ± 22%, p > 0.05), but end-systolic volume fell below the resting level (−11 ± 32%, p < 0.05). The postexercise increase in LV ejection fraction, therefore, was associated with an isolated fall in end-systolic volume.

Segmental Wall Motion at Rest and After Exercise

Of the 920 LV segments that were assessed, 330 (36%) were asynergic at rest. (Ten inferior segments were excluded because of right ventricular overlap.) Wall motion improved after upright exercise in 115 of these 330 segments (35%), including one (4%) of 27 dyskinetic segments, five (10%) of 52 akinetic segments, 36 (28%) of 128 severely hypokinetic segments, and 73 (59%) of 123 mildly hypokinetic segments (fig. 2). All segments with normal wall motion at rest and peak exercise were also normal after exercise.

Of the 34 patients with pathologic Q waves, 27 (79%) had persistence of wall motion abnormalities after exercise in a corresponding segment. In contrast, only 13 (24%) of the 54 patients without pathologic Q waves were similarly abnormal. This association between the presence or absence of pathologic Q waves and postexercise asynchrony of corresponding segments was statistically significant (p < 0.001 by chi-square test). Five patients with left bundle branch block at rest were excluded from this analysis.

Segmental Wall Motion After Exercise and Nitroglycerin

In the 60 patients who were studied after nitroglycerin, eight inferior segments were excluded from analysis because of right ventricular overlap and 15 other segments were excluded because resting asynergy was noted in one of the resting images before exercise or nitroglycerin. An additional 40 anterior segments were not assessed in eight patients imaged solely in the LAO view. Thus, 537 segments were analyzed and 257 (48%) were asynergic at rest.

Scintigrams from a patient with wall motion improvement after exercise and nitroglycerin are shown in figure 3. Scintigrams from a patient with no wall motion improvement after exercise and nitroglycerin are shown in figure 4. Two hundred twenty-eight of the 257 resting asynergic segments (89%) demonstrated the same wall motion response after exercise and nitroglycerin: 71 of 85 segments (84%) that improved after nitroglycerin also improved after exercise, and 157 of 172 segments (91%) that did not improve after nitroglycerin did not improve after exercise (fig. 5).

The chance-corrected region-by-region percent agreement between the response of asynergic segments after exercise and nitroglycerin was 57.0-
nitroglycerin, the rise after exercise occurred without a fall in end-diastolic volume. Thus, despite the similarity in wall motion response of asynergic segments, the hemodynamic response of the left ventricle after exercise was different from that after nitroglycerin.

**Discussion**

During upright bicycle exercise in patients with coronary artery disease, LV end-diastolic and end-systolic volumes usually increase, and ejection fraction often falls. In this study, stopping exercise and maintaining the upright position provoked a dynamic reversal of these hemodynamic changes: LV end-diastolic volume returned to resting levels and end-systolic volume decreased significantly below that at rest. These changes were accompanied by a significant rise in LV ejection fraction.

In addition to these hemodynamic changes, myocardial segments that were asynergic at rest before exercise frequently improved (and even normalized) after exercise. This postexercise improvement in resting asynergy was more common in patients without pathologic Q waves and in segments manifesting mild rather than severe abnormalities. Hence, reversible asynergy after exercise occurred more frequently in segments suspected to be functionally viable.

To confirm this hypothesis, we compared the post-exercise response with that of nitroglycerin in the same asynergic segments. Improvement in myocardial asynergy with nitroglycerin identifies viable myocardium, as substantiated by the relatively normal histology, presence of normal thallium uptake in the redistribution phase, and correlation with sustained improvement after coronary artery bypass surgery in these abnormal zones. Thus, it is notable that there was a high degree of agreement between the wall motion response of asynergic segments after exercise and after nitroglycerin in this study. Segments that improved after exercise also improved after nitroglycerin, and
segments that did not improve after exercise did not improve after nitroglycerin.

**Mechanisms for Reversible Asynergy**

Despite the similarity of this wall motion response, the mechanism of reversible asynergy after exercise and nitroglycerin may not be the same. Reversal of myocardial asynergy follows three basic types of interventions: the diminution of myocardial oxygen demand, as mediated by preload reduction; direct inotropic stimulation of hypokinetically abnormal segments, as noted with postextrasystolic potentiation or catecholamines; and improvement of myocardial blood flow, as seen with coronary artery bypass surgery. In this study, improvement in wall motion after nitroglycerin was associated with a significant decrease in systolic blood pressure, as well as diminutions in both end-diastolic and end-systolic volumes. Because such changes diminish myocardial wall stress and myocardial oxygen consumption, improvement in wall motion abnormalities after nitroglycerin was possible. The mechanism of wall motion improvement after exercise appears to be different. Although the decrease in peak exercise end-diastolic and end-systolic volumes after exercise would be expected to result in a reduction in LV wall stress and relief of exercise-induced ischemic abnormalities, these hemodynamic changes probably do not account for the observed improvement of resting wall motion abnormalities. This conclusion is based on the observation that postexercise end-diastolic volume was not lower than resting end-diastolic volume, which suggests that LV preload after exercise was not diminished from rest. Further, systolic arterial blood pressure, an important determinant of afterload, decreased from peak exercise levels but remained persistently elevated above resting levels after exercise, as did the heart rate. Because there was no evidence that postexercise myocardial oxygen demand had fallen below resting levels, other mechanisms must have been operative in the reversal of resting asynergy.

The cause of reversible asynergy after exercise could be inotropic stimulation, caused by endogenous catecholamines. The hemodynamic changes in this study support this hypothesis. First, there was an isolated decrease in end-diastolic volume after exercise, especially in the face of a continued elevation of systolic blood pressure. Second, the increase in LV ejection fraction after exercise is not readily explained by the observed changes in ventricular loading. Pfisterer and co-workers observed that the postexercise rise in LV ejection fraction is attenuated by β blockers.

**Why Improvement Postexercise, Not During?**

The effect of catecholamine stimulation on myocardial function varies, depending on the presence or absence of myocardial ischemia at the time of stimulation. Mercier et al. for example, noted that dopamine can both intensify contractile abnormalities in regions rendered ischemic by CAD occlusion and normalize segmental contraction in these same segments after subsequent reperfusion. Since resting asynergic zones usually occur within the distribution of high-grade vascular obstruction, myocardial oxygen supply during exercise may not increase in these regions in proportion to the demand. In the face of the resultant local ischemia, a “masking” of the potential effect of catecholamine stimulation upon regional contractile function might occur. With the cessation of exercise, however, systolic blood pressure and end-diastolic volume fall from their peak values, and a favorable change in the myocardial oxygen supply/demand ratio ensues. This may result in an “unmasking” of the effects of catecholamine stimulation. Such potentiation of contractile function might also be aided by a favorable redistribution of coronary blood flow to previously ischemic regions after exercise, but this is not known. A redistribution of coronary blood flow has also been proposed as a mechanism for the action of nitroglycerin.

**Upright or Supine?**

LV ejection fraction also increases after supine exercise, but this global improvement does not necessarily imply that reversible asynergy occurs as frequently as in the upright position. LV ejection fraction...
increases after exercise both in patients with reversible and in those with nonreversible asynergy; this increase predicts neither regional nor global postoperative improvement.33 In patients who exercised both upright and supine, we have found that the ejection fraction response after exercise is similar for both postures.32 Still, in our preliminary observations, regional wall motion improvement after upright stress was at times not observed after supine stress. We do not know, however, whether such responses are typical, that is, whether there is a real tendency for a "blunted" augmentation of wall motion after supine exercise.

Methodologic Limitations

Two methodologic considerations are important. First, a stable heart rate is considered essential for performing gated equilibrium blood pool scintigraphy, and the rapid decline in heart rate after exercise may limit imaging at this time. However, this factor did not significantly influence our observations. Variations in sinus rhythm have been reported to cause less inaccuracy in systolic measurements than do ectopic beats,34 and it has been suggested that gated measurements are accurate even during atrial fibrillation.35 Second, the decrease in heart rate that occurs as a consequence of lengthening of diastole36 should not artifically affect systolic measurements. Whatever error is introduced by a lengthening of systole would tend only to reduce systolic measurements (e.g., ejection fraction and wall motion) from their true values, for averaging the varying minima would increase the observed counts at end-systole.35 Despite this potential underestimation of systolic function, improvement in wall motion immediately after exercise correlated strongly with that after nitroglycerin or coronary bypass surgery.33 Others have also observed similar improvement in ejection fraction (wall motion changes were not reported) when the onset of image acquisition is delayed for 1–2 minutes after exercise.27,37 Greater delays (3–6 minutes), however, appear to result in a decrease in the observed frequency of reversible asynergy.38

The actual time of onset of postexercise wall motion improvement cannot be determined by gated equilibrium blood pool scintigraphy, which requires the integration of data collected over a 2-minute period after exercise. Other techniques, however, can provide some insight into this question. For example, when LV function is measured by first-pass radionuclide ventriculography, improvement in LV function has been noted within 1 minute after peak stress.39 These observations, combined with those of the present study, should interest other investigators who have used first-pass radionuclide imaging 5–10 seconds after peak stress40 or postexercise echocardiography3 to assess "peak exercise" LV function.

Clinical Implications

The demonstration of reversible myocardial asynergy after upright bicycle exercise and the strong correlation between wall motion improvement after exercise and after nitroglycerin suggest that the value of exercise radionuclide ventriculography might be enhanced by extension of radionuclide imaging to the postexercise period. In this fashion, this procedure may be used both to detect the presence of hemodynamically significant CAD (during exercise) and to assess the functional viability of regions with resting myocardial asynergy (after exercise).33 In candidates for coronary artery bypass surgery, this knowledge of anatomy and functional viability should be helpful in choosing appropriate vessels for bypass.

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