Exercise and Human Collateralization: An Angiographic and Scintigraphic Assessment

PETER A. RECHNITZER, M.D., F.R.C.P.(C), F.A.C.C., AND DAVID A. CUNNINGHAM, PH.D.

SUMMARY The effect of exercise on the development of intercoronary collaterals and on left ventricular function is controversial. Twenty male patients (mean age 48 years, range 36–54 years) who had suffered an acute myocardial infarction were randomly allocated to an exercise group (10 patients) and a control group (10 patients). Both groups underwent coronary angiography, left ventricular function studies and myocardial perfusion studies with labeled microspheres, before and after the 7-month experimental period. Both groups had similar extent of disease as measured angiographically and both had mild progression of disease. Neither group showed changes in extent of collateralization, myocardial perfusion or left ventricular function. The exercise group had a significant increase in anginal threshold and a significant \( (p < 0.01) \) decrease in heart rate at a given work load. Exercise, therefore, does not appear to affect progression of disease, myocardial perfusion, extent of collateralization, or left ventricular function in patients with coronary artery disease.

IN 1957, Ekstein\(^1\) showed that significant coronary artery narrowing in dogs stimulated the formation of an effective collateral circulation, and that the addition of exercise resulted in even further collateralization. He also showed that while minimal stenosis alone would not initiate collateralization, the addition of exercise resulted in numerous, large, collateral channels that were sufficient to protect the myocardium against infarction. More recently, Redwood\(^2\) and his colleagues showed that an exercise program allowed patients with coronary artery disease to reach a higher triple product before the onset of angina, suggesting an improvement in myocardial oxygen delivery. Other studies,\(^3\) however, have not shown any change in the double product, although a higher anginal threshold was achieved after training. Clausen et al.\(^4,5\) hypothesized a peripheral effect in the skeletal muscle, resulting in decreased myocardial oxygen consumption rather than a primary improvement in myocardial oxygen delivery.

The theory that exercise promotes collateralization in humans is responsible for the observed improvements, although intuitively attractive, has not been substantiated in several uncontrolled studies.\(^6,7\) This study was undertaken to examine if exercise initiates or improves collateralization in patients with coronary artery disease.

Materials and Methods

Patient Selection

The study population consisted of 20 males, ages 36–54 years (mean 48 years), who had sustained a first documented myocardial infarction within the preceding 3–6 months. Twenty-two patients originally entered the study, but two dropped out after the initial testing. Eleven patients had had inferior infarctions and nine had had anterior infarctions. Ten patients had postinfarction angina pectoris which required medical treatment, seven with propranolol and four with isosorbide dinitrate. Four patients were class II and six were class III by the New York Heart Association Classification.\(^8,9\) One patient had had postinfarction congestive failure and was maintained on digoxin, while three patients had had rhythm disturbances which required treatment with quinidine sulfate. Seventeen patients smoked more than one package of cigarettes per day before their infarction. Four patients had long-standing hypertension which was treated medically and four patients had a positive family history for premature coronary artery disease. Ten patients had lipid abnormalities, six Fredrickson\(^10\) type IV and four type II (table 1).

Data Base

After obtaining an informed consent, we assessed all the patients by both noninvasive and invasive techniques. In addition to a complete history and physical examination, the noninvasive assessment included a resting and a stress ECG using a modified Bruce protocol with serial 12-lead ECGs taken both during and after exercise. Horizontal or down sloping ST-segment depression \( \geq 1 \) mm for at least 0.08 second after the J point was considered a positive response. We determined \( VO_2 \) by testing the patients at three work loads (approximately 25–80% of the patient's maximum aerobic capacity) on a constant work load bicycle ergometer at 55–60 rpm. The patient was maintained at each work load until a steady state was reached (< 5 beats/min difference between minute 3 and 4 of exercise), or 6-minute total if a steady state was not attained.

During the test, the patients breathed through a Koegel valve. The inspired ventilation was recorded from a dry gas meter, and the expired gas was
Table 1.  **Patient Profile at Entrance into Study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Infarct</th>
<th>Angina</th>
<th>Risk factors</th>
<th>Stress test</th>
<th>Grade score</th>
<th>Collaterals</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-1</td>
<td>54</td>
<td>Inferior</td>
<td>+</td>
<td>FH, S</td>
<td>±</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>E-2</td>
<td>52</td>
<td>Inferior</td>
<td>+</td>
<td>S, H</td>
<td>+</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>E-3</td>
<td>36</td>
<td>Inferior</td>
<td>+</td>
<td>FH, S</td>
<td>+</td>
<td>17</td>
<td>3+ (R→L)</td>
</tr>
<tr>
<td>E-4</td>
<td>42</td>
<td>Inferior</td>
<td>−</td>
<td>FH, S</td>
<td>+</td>
<td>41</td>
<td>2+ (L→R)</td>
</tr>
<tr>
<td>E-5</td>
<td>52</td>
<td>Anterior</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>E-6</td>
<td>52</td>
<td>Inferior</td>
<td>−</td>
<td>FH</td>
<td>+</td>
<td>27</td>
<td>2+ (L→R)</td>
</tr>
<tr>
<td>E-7</td>
<td>54</td>
<td>Anterior</td>
<td>−</td>
<td>H, S</td>
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<td>36</td>
<td>2+ (R→L)</td>
</tr>
<tr>
<td>E-8</td>
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<td>Anterior</td>
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<td>None</td>
<td>+</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>E-9</td>
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<td>Inferior</td>
<td>−</td>
<td>S</td>
<td>+</td>
<td>13</td>
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</tr>
<tr>
<td>E-10</td>
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<td>Anterior</td>
<td>−</td>
<td>None</td>
<td>+</td>
<td>20</td>
<td>2+ (R→L)</td>
</tr>
</tbody>
</table>

28.4 ± 10.3 (mean ± SD)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Infarct</th>
<th>Angina</th>
<th>Risk factors</th>
<th>Stress test</th>
<th>Grade score</th>
<th>Collaterals</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>39</td>
<td>Inferior</td>
<td>+</td>
<td>S, H</td>
<td>−</td>
<td>35</td>
<td>3+ (L→R)</td>
</tr>
<tr>
<td>C-2</td>
<td>36</td>
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<td>+</td>
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<td>3+ (L→R)</td>
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<tr>
<td>C-3</td>
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<td>Anterior</td>
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<td>S</td>
<td>±</td>
<td>29</td>
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<tr>
<td>C-4</td>
<td>38</td>
<td>Anterior</td>
<td>−</td>
<td>S</td>
<td>+</td>
<td>27</td>
<td>1+ (L→R)</td>
</tr>
<tr>
<td>C-5</td>
<td>48</td>
<td>Anterior</td>
<td>+</td>
<td>S</td>
<td>−</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>C-6</td>
<td>50</td>
<td>Inferior</td>
<td>+</td>
<td>S, H</td>
<td>+</td>
<td>48</td>
<td>1+</td>
</tr>
<tr>
<td>C-7</td>
<td>54</td>
<td>Inferior</td>
<td>−</td>
<td>S</td>
<td>+</td>
<td>19</td>
<td>1+ (R→L)</td>
</tr>
<tr>
<td>C-8</td>
<td>49</td>
<td>Anterior</td>
<td>−</td>
<td>S</td>
<td>+</td>
<td>16</td>
<td>3+ (R→L)</td>
</tr>
<tr>
<td>C-9</td>
<td>48</td>
<td>Inferior</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>30</td>
<td>2+ (L→R)</td>
</tr>
<tr>
<td>C-10</td>
<td>51</td>
<td>Anterior</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

28.3 ± 10.0 (mean ± SD)

Abbreviations: E = exercise; C = control; H = hypertension; angio = angiogram; FH = family history; + = positive; − = negative; ± = equivocal; CAP = coronary artery perfusion scan; S = smoker.

collected in a 350-liter Tissot spirometer during the final minute of each work load. We used an infrared \( CO_2 \) analyzer and a paramagnetic \( O_2 \) analyzer previously calibrated to analyze the expired gases.

To determine maximum oxygen uptake, inspired minute ventilation and the expired percentages of oxygen and carbon dioxide were continuously recorded in an 8-liter Plexiglas mixing box. Maximal oxygen uptake was calculated by analyzing the polygraph tracings for each of the last 3 minutes of work.

Left-heart catheterization was performed using the percutaneous Seldinger technique; selective coronary arteriograms were obtained with Judkins catheters. We assessed left ventricular function by measuring the end-diastolic pressure before and after angiography, end-diastolic volume and ejection fraction. We used the right anterior oblique (RAO) left ventriculogram to calculate the end-diastolic volume and the ejection fraction by the method described by Sandler and Dodge.\(^{13,14}\) Regional segmental contraction was evaluated using the chord technique described by Carroll\(^{15,16}\) et al. Using only sinus beats, we determined a percent shortening from the end-diastolic and endsystolic outline in the RAO projection. The plane of the aortic valve was bisected with the long axis to the apex. The axis was divided equally by three perpendicular lines creating six chords. The difference between the diastolic and systolic chord divided by the diastolic chord and multiplied by 100 gave a percent shortening for each chord. The chord shortening data was plotted in relation to infarct location. To obtain normal values for our laboratory, we measured the chords of 30 patients who were evaluated for chest pain and found to have normal coronary arteries and left ventricular function.

The three major coronary arteries were visualized in multiple projections using a 6-inch image intensifier (Siemens-Sirecon, 17 and 23-unit), and recorded on 35-mm film at 40 frames/sec. The selective coronary arteriograms were graded to permit assessment of both extent of disease and collateralization. Each coronary artery was divided into three segments — proximal, middle and distal; the left main was kept separate. The degree of narrowing was assessed numerically from 1 to 5: 1, 25% occlusion; 2, 25–50%; 3, 50–75%; 4, 75–99%; 5, total occlusion. This in turn was multiplied by a location factor, i.e., left main, 4; proximal, 3; middle, 2, and distal, 1. The total grade for coronary artery disease was then added to the score obtained for the left ventricular dysfunction. Using the RAO and left anterior oblique (LAO) ventriculogram, we divided the left ventricle into seven segments. Each segment received a multiplication factor of 2, except for the apex, which received 1. This
factor was multiplied by the degree of dysfunction, i.e., normal, 0; hypokinetic, 1; akinetic, 2; dyskinetic, 3; and aneurysmal, 4. The grading was done blindly before and after the experimental period.

The degree of collateralization was graded separately: 0, no collaterals visible; 1, collaterals faintly seen; 2, collaterals well-visualized, but the occluded vessel remained small; and 3, occluded vessel reconstituted to normal size.

After performing the selective coronary arteriograms, we selectively infused labeled macroaggregated albumin iodine-131 (131I) into the right coronary artery (dose 150 mCi) and albumin-labeled technetium-99m (99mTc) infused into the left coronary artery (dose 300 mCi). Within 1 hour of the procedure, the patients were scanned with a retinlinear scanner (General Electric maxi scan, interphased with the VDP2, a dedicated computer). The 45° LAO and anterior projections were obtained using 2-mm line spacing with the high-energy, medium-resolution, 5-inch focusing collimator with one discrimination setting centered on 140 keV for the 99mTc injection, the other discriminator setting centered on 364 keV for the 131I injection. The presence of collaterals was visually assessed as either absent, right to left or left to right.

Protocol

The patients were randomly allocated into an exercise group and a control group. The 10 patients in the exercise group participated in an individualized, supervised exercise program designed to produce a training effect. Their exercise prescription was based on their performance on the bicycle ergometer and was calculated by the method described by Cunningham and Rechnitzer, using 60-70% of their maximum achieved heart rate. The patients met as a group twice a week and exercised for 1 hour under supervision in a gymnasium. Individual, supervised exercise sessions were carried out on two out of the three remaining days, leaving only one day for individual, unsupervised training at home. We considered a training effect to have occurred if the heart rate dropped at least 10 beats/min at a standard VO2 of 1.2 l/min.

The 10 patients allocated to the control group participated in a supervised exercise program centered on recreational activities and shown by Ogirimah et al. not to produce a training effect. These patients also met twice a week in a gymnasium setting. The first 30 minutes consisted of light calisthenics to increase flexibility. The rest of the hour was spent playing volleyball. The rules were adjusted to allow limited, controlled exercise. The heart rates were closely monitored and recorded. The other supervised session consisted of relaxation exercises.

Statistical Analysis

We used the t test to test the significance of changes in the exercise performance and hemodynamic variables measured.

Results

Coronary Anatomy

Angiography showed significant single-vessel disease in four patients (20%), double-vessel disease in six (30%), and triple-vessel disease in 10 (50%). The extent of disease was similar in both groups, as shown by the grading score (exercise group 28.4 ± 10.3 vs control group, 28.3 ± 10.9 (mean ± sd)). Both groups showed a tendency toward progression of their disease at the end of the study, but the differences were not significant (the exercise group increased to 38.7 ± 11.5, the control group to 33.1 ± 12.0).

Stress Testing Results

Table 1 shows the results of the exercise stress tests performed at entrance into the study. Nine patients in the exercise group had a positive result and one had an equivocal result, while in the control group, seven were positive, two negative and one was equivocal. Table 2 shows the exercise stress test results after the experimental period for both groups. There were no changes in either group. At matched levels of exercise, the exercise group as a whole developed the ST-segment changes at a higher work load, while the patients in the control group developed the ischemic ST-segment response at a similar work load.

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Patient Data After Experimental Period</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Angina</td>
</tr>
<tr>
<td>E-1</td>
<td>+</td>
</tr>
<tr>
<td>E-2</td>
<td>+</td>
</tr>
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<td>E-3</td>
<td>+</td>
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<td>E-4</td>
<td>−</td>
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<td>E-9</td>
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<tr>
<td>E-10</td>
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</tr>
</tbody>
</table>

Abbreviations: Angio = angiogram; CAP = coronary artery perfusion scan.
Effect of Training

Figure 1 shows the effects of exercise on heart rate at a standard VO₂ of 1.2 l/min. The control group had no change in heart rate, but the exercise group showed a significant drop of 14 beats/min (p < 0.01) in their mean heart rate.

Angina

Each of the four exertional angina patients in the exercise group had a significant increase in his anginal threshold as evidenced by an increase in treadmill time from 4 to 10 minutes (p < 0.01) (fig. 2). The double product (heart rate × blood pressure) at the onset of angina, however, remained unchanged — 20,100 vs 20,450. The six patients in the control group showed no change in their anginal threshold and their double product at the onset of angina also remained unchanged — 19,560 vs 20,120 (fig. 3).

Left Ventricular Function

Neither group showed any improvement in left ventricular function (table 3). The end-diastolic pressure both at rest and after angiography did not change after the experimental period. Both groups did show a significant increase in end-diastolic pressure after angiography. The end-diastolic volume remained unchanged after training in both groups. Likewise, the ejection fraction was similar both before and after the experimental period in each group (table 3).

The percent contraction of each of the six chords was compared in relationship to infarct location (figs. 4A and B). There was no improvement in chord shortening, implying no change in left ventricular function.

Collateralization

Both the angiographic and scintigraphic assessment of collateral flow is tabulated before (table 1) and after
(table 2) the experimental period for both groups. Although collaterals were seen only in patients with arterial luminal stenosis > 80%, not all patients with such disease had collaterals. We could not, therefore, predict the presence of collaterals using severity of disease or degree of left ventricular dysfunction as criteria. After the experimental period there was no increase in the number, size or extent of collateral channels seen on the coronary arteriograms. Similarly, the extent of collateral perfusion as assessed by scintigraphy did not change during the experimental period.

Discussion

This study shows that patients can be safely and adequately trained after myocardial infarction. This form of cardiac rehabilitation has several advantages. As observed in our study and reported by others, the anginal threshold was greatly improved and the psychological well-being of the cardiac patient was enhanced.

The physiological basis of the observed improvements has yet to be clarified. Sim and Redwood observed an increase in the double and triple products at the onset of angina, which would suggest an increase in myocardial oxygen delivery. However, not all of Redwood's seven anginal patients had an increased triple product; in fact, three of the seven did not have a significant increase. We and others have found that although the anginal threshold increased substantially, the double product measured at the onset of angina remained unchanged. A major problem with our study is the small sample size. If we include Redwood's and Sim's data with our own, we find that 12 of 19 anginal patients had increased double or triple products at the onset of angina, while seven had no change. Because patients with ischemic heart disease are not a homogenous population, the response to exercise may be quite variable, and further study is warranted.

Another theory is that the observed changes may be due, in part, to peripheral factors and that although the amount of external work accomplished is increased, the myocardial oxygen delivery is unchanged. This coincides with Clausen et al., who argue that the improvements are based on changes in the oxygen utilization of the peripheral skeletal muscles, resulting in decreased demands placed on the myocardium at

![Figure 3. The double product (heart rate (HR) × systolic blood pressure (SBP)) at onset of angina. Open circles represent the mean. The double product is unchanged in both groups.](image)

<table>
<thead>
<tr>
<th>Table 3. Results of Left Ventricular Function Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise group</strong></td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>(24.6 ± 8.4)</td>
</tr>
<tr>
<td>End-diastolic volume (ml/m³)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
</tbody>
</table>

Values in parentheses represent change in pressure after ventriculography which is significant at the p < 0.005 level.

Abbreviations: T1 = entrance into study; T2 = after experimental period.
any given work load. Detry et al. also support this premise, and showed an increase in arteriovenous oxygen difference in exercising muscles after conditioning.

Several animal experiments showed enhanced collateralization after exercise and increased myocardial perfusion as evidenced by scintigraphy, but we could not show any improvements either in the number, size or extent of existing collaterals or the formation of new channels. The scintigraphic assessment of myocardial perfusion also failed to show any change after a vigorous 7-month exercise program.
Ashburn et al. and Weller et al. were the first to inject macroaggregated serum albumin microspheres labeled with $^{131}$I and $^{99m}$Tc into the coronary arteries of patients undergoing coronary angiography. The distribution of particles could then be assessed with a scintillation camera. The distribution of particles parallels the coronary artery distribution into which the particles are injected. The density of radioactivity is thought to mirror capillary perfusion. It has so far been impossible to quantitate the density of particles. The particle distribution does not accurately reflect the regional rates of myocardial capillary flow. However, keeping these limitations in mind we used this technique to assess gross collateral flow at rest in this select group of patients.

Left ventricular performance, which primarily reflects myocardial perfusion, measured hemodynamically (left ventricular end-diastolic pressure) and functionally (ejection fraction, end-diastolic volume and chord assessment) also remained unchanged. Using echocardiographic techniques to assess normal subjects before and after training, DeMaria et al. showed some marginal improvement in left ventricular function, the significance of which remains unclear.

All of our measurements were taken at rest. It is possible that during rest the stimulus for collateral flow would be minimal and one would not expect to see collaterals; if these measurements were taken during exercise, however, one might see evidence of improved ventricular function and collateral supply. Recently, Borer showed that normal subjects showed an increase in their ejection fractions (measured by radionuclide techniques) during exercise. Patients with ischemic heart disease had a decrease in ejection fraction. It is possible that if these patients are trained they may maintain the normal ejection fraction response to exercise.

The only stimulus for human collateralization appears to be severe coronary artery disease and this may be modified genetically. The genetic component seems to be important, as not all patients with severe disease develop intercoronary anastomotic channels. Both groups tended toward progression of their disease. This tendency might suggest that once the atherosclerotic cycle starts, it is a malignant, unremitting process. However, because of the small sample size and the heterogeneous nature of the disease itself, we can draw no valid conclusions. It is also possible that the experimental period may have been too brief; had we continued the study for a longer period, a change in progression of disease might have become evident.

It can also be argued that the experimental period was too brief to demonstrate adequate collateralization. One must be cautious in extrapolating these findings to people who stay trained throughout their lives. Paffenbarger et al. demonstrated that vigorous, continuous exercise seemed to protect longshoremen against sudden death secondary to coronary artery disease. The mechanism for protection is unclear.

The negative results of this study should not detract from the important positive effects of exercise. Although exercise did not appear to affect progression of disease or improve myocardial perfusion or left ventricular function, it definitely increased the efficiency of the cardiovascular system, as shown by an improved exercise tolerance. This, along with improved muscular tone and the positive mood changes resulting from the program, can enrich the quality of life.

Acknowledgment

We thank D. Deatrich for her expert technical assistance and J. Belanger for her help in preparing this manuscript.

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Effect of Acute Ischemia, Nitroglycerin and Nitroprusside on Regional Myocardial Thickening, Stress and Perfusion
Experimental Echocardiographic Studies

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with the technical assistance of Margaret Schrader, Gilbert Koenigsaecker, B.S., and Oscar Lim, M.S.

SUMMARY The purposes of this study were to demonstrate that echocardiography can be used to demonstrate the systolic wall thinning of acutely ischemic myocardium, and to compare the effects of nitroglycerin and nitroprusside on systolic thinning, wall stress and perfusion of ischemic myocardium. In 37 dogs, the ratio of end-systolic-to-end-diastolic posterior wall thickness fell from 1.30 ± 0.02 to 0.88 ± 0.01 ($p < 0.001$) after circumflex coronary occlusion; perfusions of the area supplied by the occluded artery fell from 98.2 ± 7.5 ml/100 g/min to 36.5 ± 2.9 ml/100 g/min ($p < 0.001$). Nitroglycerin and nitroprusside were given to lower mean arterial pressure by 7% and 15%. Despite the reduction in coronary perfusion pressure, transmural perfusion, endocardial/epicardial perfusion ratio and systolic thinning remained constant. Both drugs reduced the ischemic "wall stress index" (ventricular pressure × ventricular diameter/wall thickness) by almost 50%. Thus, both nitroglycerin and nitroprusside were equally beneficial in this model of acute myocardial ischemia.

EXPERIMENTAL STUDIES using a variety of techniques\textsuperscript{1-3} have shown that changes in dynamic wall thickness occur after coronary occlusion. Sassayama et al.,\textsuperscript{4} using implanted ultrasonic sonomicrometers, showed that wall thickness changes paralleled the shortening characteristics of adjacent subendocardial segments in response to alterations in heart rate and loading. Thus, wall thickness could be useful for characterizing regional function of ischemic myocardium. Based on these sonomicrometer studies, Ross and Franklin\textsuperscript{5} suggested that echocardiography could reveal changes in wall thickness that might be useful for assessing the effects of acute interventions on the regional dysfunction of acutely ischemic myocardium. This suggestion has not yet been validated in an experimental echocardiographic study.

The use of vasodilator agents is one important intervention which might be assessed by echocardiographic evaluation of wall thickness changes.
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A J Nolewajka, W J Kostuk, P A Rechnitzer and D A Cunningham

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