Detecting Abnormalities in Left Ventricular Function During Exercise Before Angina and ST-segment Depression

MARK T. UPTON, M.D., STEPHEN K. RERYCH, M.D., GLENN E. NEWMAN, M.D., STEVEN PORT, M.D., FREDERICK R. COBB, M.D., AND ROBERT H. JONES, M.D.

SUMMARY To determine if abnormalities in left ventricular function precede angina pectoris and electrocardiographic evidence of myocardial ischemia, we used radionuclide angiocardiography to measure left ventricular ejection fraction, volumes, cardiac output and wall motion in 10 normal subjects and 25 patients with coronary artery disease at rest and during two levels of upright bicycle exercise. In the patients with coronary artery disease, the first radionuclide study during exercise was performed before and the second after the onset of ST-segment depression.

In all normal subjects, the ejection fraction increased more than 5%, the end-diastolic volume increased less than 25% and the end-systolic volume decreased from rest to both levels of exercise. Wall motion was normal at rest and increased with exercise. No patient with coronary artery disease had chest pain or ST-segment depression during the first level of exercise. The ejection fraction either decreased or increased less than 5% in 18 patients, the end-diastolic volume increased more than 25% in nine, the end-systolic volume increased in 19 and a segmental contraction abnormality developed in 14. Hemodynamic and wall motion abnormalities occurred in all patients during the second level of exercise when ST-segment depression was present. During exercise in patients with coronary artery disease, abnormalities in left ventricular function frequently develop before angina pectoris and electrocardiographic evidence of myocardial ischemia.

TENNANT AND WIGGERS first showed in 1935 that the contraction pattern of the left ventricle was altered after ligation of a coronary artery. More recently, segmental contraction abnormalities were detected within 5 seconds of coronary artery occlusion by Theroux et al. using ultrasonic dimension gauges. Other investigators have shown that these wall motion abnormalities usually precede epicardial electrocardiographic ST-segment shifts. Myocardial ischemia in these animal studies was produced by abrupt total occlusion of a normal coronary artery. In man, transient myocardial ischemia usually occurs as a consequence of increased myocardial demand in the face of a fixed, partial occlusion that limits the increase in blood flow. Whether regional abnormalities of myocardial contraction and a global deterioration of left ventricular function precede, coincide with or follow pain and electrocardiographic changes is uncertain.

Accordingly, we sought to determine whether exercise-induced myocardial ischemia in patients with stable coronary artery disease produces abnormalities in left ventricular function that can be detected by radionuclide angiocardiography before the onset of angina pectoris and ST-segment depression on the ECG.

Methods

Subjects

Twenty-five male patients with stable coronary artery disease constituted the study population. The mean age of this group was 51 years (range 37–69 years). Ten of the patients had a history of previous myocardial infarction and eight had pathologic Q waves on their 12-lead ECG. None had a history of congestive heart failure or resting chest pain. All were in sinus rhythm and had angiographic evidence of 75% or greater stenosis in one or more coronary arteries. No patient received nitrates within 4 hours of the exercise tests, but five patients were on other cardiac medications. Each of the 25 patients had a positive 12-lead ECG treadmill stress test (standard Bruce protocol) manifested by at least 1 mm of ST-segment depression in the anterolateral leads. One patient was excluded from study because he developed frequent ventricular ectopy during exercise.

Ten male subjects with a mean age of 32 years (range 25–42 years) served as controls. Each had a normal cardiovascular history, physical examination, resting ECG and exercise tolerance test. None was taking medications at the time of study.

Study Design

After a resting radionuclide angiocardiogram was performed, exercise was begun on an isokinetic bicycle ergometer (Fitron) with the subject in the sitting position. The work load was started at 400 kilopounds (kpm)/min and increased by 100 kpm/min every 2 minutes. A single bipolar CM_{34} electrocardiographic lead was continuously monitored by telemetry, and blood pressure was recorded by sphyg-
momanometer at 1-minute intervals during exercise and the recovery period.

In the patients with coronary artery disease, the first exercise radionuclide angiogram was performed at approximately 50% of the change in heart rate that occurred during the preliminary treadmill stress test. All patients were asymptomatic and without ST-segment depression at this time. The work load was then progressively increased, and a second exercise radionuclide angiogram was performed when the ECG showed either 1 mm of ST-segment depression if the patient had angina pectoris or 2 mm of ST-segment depression if chest pain did not occur.

All normal subjects were exercised to 85% of their age-predicted maximal heart rates. In these control subjects, the first radionuclide angiogram during exercise was performed at approximately 50% of the anticipated increase in heart rate and the second at the target heart rate.

Radionuclide Procedure

First-pass radionuclide angiography uses data recorded during the initial transit of a radionuclide bolus through the heart to assess left ventricular performance. A 20-gauge polyethylene catheter was inserted into either an antecubital or external jugular vein, and 10 mCi of technetium-99m pertechnetate was rapidly injected intravenously and flushed with 10 ml of normal saline. A multicrystal gamma camera (Baird System Seventy-seven) equipped with a 1-inch, parallel-hole collimator was used for imaging, and anterior precordial counts were recorded in binary form at 50-msec intervals for 1 minute. The two exercise studies were done in the same manner as the resting study except that background counts were collected over the precor-
dium before each additional injection. The subject's chest was stabilized against the collimator to prevent excessive motion during the exercise injections. Each subject received three injections, or a total of 30 mCi of technetium-99m pertechnetate.

Data Processing

The radionuclide angiograms were analyzed as previously described.7-10 Each study was first corrected for field nonuniformity and dead time; the two exercise studies were also corrected for preexisting background counts in each crystal.

A high-frequency time-activity curve was obtained from the left ventricular region of interest, and individual ventricular beats were identified. After subtracting background activity, an average cardiac cycle was derived by summing counts from four to six of these beats. Regional wall motion was assessed by inspecting both dynamic and static images of the representative cardiac cycle (figs. 1-4). The left ventricular outline was divided into three segments: anterolateral, inferoapical and inferobasal. Two observers graded each segment on a scale of 2 to −1, where 2 = normal, 1 = hypokinetic, 0 = akinetic and −1 = dyskinetic wall motion. After the observers reached a consensus, scores from each segment were summed, and a wall motion index was assigned to each ventricle, ranging from 6 (normal) to −3 (severely dyskinetic).

The left ventricular ejection fraction (EF) was determined from the representative cardiac cycle:

\[
EF = \frac{ED \text{ counts} - ES \text{ counts}}{ED \text{ counts}} \times 100
\]

where ED and ES represent end-diastole and end-

**Figure 1.** Composite images of the left ventricle at rest, exercise 1 and exercise 2 in a normal subject. The computer-generated end-diastolic perimeter is superimposed on the end-systolic image above and on the end-systolic perimeter and aortic valve plane below. Tracer activity is color-coded, ranging from black (lowest counts per crystal) through shades of green, blue, purple, red, yellow and white (highest counts per crystal). The ejection fraction (EF) progressively increased with heart rate (HR). Also, end-diastolic volume (EDV) increased slightly during exercise. The regional wall motion index (WMI) was normal in all three studies.
LV FUNCTION DURING EXERCISE / Upton et al.

Figure 2. Images from a patient with two-vessel coronary artery disease (left anterior descending and circumflex coronary arteries). The ejection fraction (EF) decreased and the end-diastolic volume (EDV) increased dramatically from exercise 1 to exercise 2. Also, anteropapical hypokinesia developed during exercise 2. HR = heart rate; WMI = wall motion index.

Figure 3. The ejection fraction (EF) decreased and the end-diastolic volume (EDV) increased progressively during exercise in this patient with two-vessel coronary artery disease (left anterior descending and right coronary arteries). Wall motion was normal at rest, but apical hypokinesia developed during exercise 1 and progressed to akinesia during exercise 2. WMI = wall motion index; HR = heart rate.

Figure 4. Left ventricular function was normal at rest in this patient with three-vessel coronary artery disease. The ejection fraction (EF) decreased, and the end-diastolic volume (EDV) increased progressively during exercise. Global wall motion abnormalities were present during both levels of exercise. HR = heart rate; WMI = wall motion index.
systole, respectively. Left ventricular end-diastolic volume (EDV) was calculated in milliliters by the area-length method of Dodge and associates:

$$EDV = \frac{0.85 A^2}{L}$$

where A is the planimetered area of the left ventricle and L is the maximal length. Time-activity curves were generated over the pulmonary artery and left atrium, and the pulmonary transit time (PTT) in seconds was defined as $PTT = atrium_{MTT} - pulmonary \ artery_{MTT}$, where MTT represents the mean transit time of the curves from each chamber.

Stroke volume (SV), end-systolic volume (ESV), cardiac output (CO), pulmonary blood volume (PBV) and stroke work (SW) were derived from the measured EF, EDV and PTT by the following equations: $SV (ml) = EDV (ml) \times EF$; $ESV (ml) = EDV (ml) - SV (ml)$; $CO (l/min) = SV (ml) \times HR$ (beats/min); $PBV (ml) = CO (l/sec) \times PTT (sec)$; and $SW (g-m) = 0.0136 \times mean \ BP (mm \ Hg) \times SV (ml)$.

**Critique of Methods**

The radionuclide measurements used in this study have been validated in our laboratory. In 33 patients with coronary artery disease, supine radionuclide angiograms were performed immediately before cardiac catheterization. The radionuclide measurements of ejection fraction and end-diastolic volume were compared with those made by contrast ventriculography, and the correlation coefficient was 0.89 for both sets of measurements. In 18 healthy young adults, stroke volume and cardiac output were simultaneously measured by radionuclide and dye-dilution methods at rest and during various levels of exercise. A close correlation was observed between the duplicate measurements of stroke volume ($r = 0.89$) and cardiac output ($r = 0.94$). A comparison of minor-axis dimensions at end-diastole measured by implanted sonar crystals and radionuclide angiography in 20 dogs revealed a correlation coefficient of 0.82.

The mean variability (± sd) in ejection fraction was 4 ± 4% at rest and 3 ± 2% during exercise in 10 normal subjects studied on two different days. In the same study, the mean variability in end-diastolic volume was less than 10 ml both at rest and during exercise.

**Results**

**Heart Rate and Blood Pressure**

The 25 patients with coronary artery disease and the 10 normal subjects had comparable mean heart rates and blood pressures at rest. During both levels of exercise, heart rate was significantly faster in the normal subjects (table 1).

In the patients with coronary artery disease, the first radionuclide angiogram during exercise was performed at a mean heart rate of 105 ± 13 beats/min, the onset of ST-segment depression occurred at 123 ± 16 beats/min, and the second radionuclide angiogram during exercise was performed at 132 ± 16 beats/min. No patient had angina pectoris before the onset of ST-segment depression. In 16 patients (64%) who had chest pain, exercise was stopped when the ECG showed 1 mm of ST-segment depression. The nine other patients did not experience angina, and exercise was discontinued when the ECG showed 2 mm of ST-segment depression. All normal subjects completed both levels of ex-

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic Measurements at Rest and During Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
</tr>
<tr>
<td>EF (%)</td>
</tr>
<tr>
<td>EDV (ml)</td>
</tr>
<tr>
<td>ESV (ml)</td>
</tr>
<tr>
<td>SV (ml)</td>
</tr>
<tr>
<td>SW (g-m)</td>
</tr>
<tr>
<td>CO (l/min)</td>
</tr>
<tr>
<td>PTT (sec)</td>
</tr>
<tr>
<td>PBV (ml)</td>
</tr>
<tr>
<td>WMI</td>
</tr>
</tbody>
</table>

*p* values compare the two groups at rest, exercise level 1 and exercise level 2.

**Abbreviations:** HR = heart rate; BP = blood pressure; EF = ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; SW = stroke work; CO = cardiac output; PTT = pulmonary transit time; PBV = pulmonary blood volume; WMI = wall motion index; CAD = coronary artery disease.
Exercise without developing severe fatigue, chest pain, hypotension, ST-segment depression or significant arrhythmias.

Ejection Fraction

The mean resting ejection fraction was similar in the normal subjects and in the patients with coronary artery disease (66 ± 7% vs 61 ± 8%, p = NS) (table 1). Although 10 of the patients had previous myocardial infarctions, only two had resting ejection fractions less than 50%.

During the first level of exercise, the mean ejection fraction increased to 76 ± 5% in the normal subjects but remained unchanged at 60 ± 9% in the patients with coronary artery disease. In each normal subject, the ejection fraction increased greater than 5%. The response of ejection fraction varied in the patients with coronary artery disease (fig. 5). However, in only seven patients (28%) did ejection fraction increase 5% or more at the first level of exercise before ST-segment depression was noted on the ECG.

At the second level of exercise, the ejection fraction for the control group increased further, to 82 ± 7%, with only one subject failing to achieve his highest ejection fraction at this time (fig. 5). In the coronary disease group, the mean ejection fraction decreased to 52 ± 8% at the second level of exercise. In each patient the ejection fraction either decreased or increased less than 5% above the resting value.

End-diastolic Volume

End-diastolic volume was comparable in both groups at rest (126 ± 14 vs 133 ± 15 ml, p = NS) (table 1). The largest end-diastolic volume (161 ml) occurred in a patient who had suffered a myocardial infarction.

The mean end-diastolic volume increased slightly but significantly in the normal subjects, to 133 ± 17 ml (p < 0.01), during the first level of exercise but did not increase further during the second level of exercise. The increase in end-diastolic volume was less than 25% in each normal subject at both levels of exercise (fig. 6). In contrast, in the group with coronary artery disease, end-diastolic volume increased to 160 ± 26 ml during the first level of exercise and to 193 ± 35 ml during the second level of exercise. An increase greater than 25% in end-diastolic volume occurred in nine of the patients (36%) at the first level of exercise.
exercise and in 19 (76%) at the second level of exercise; an increase greater than 50% in end-diastolic volume occurred in 14 patients (56%) at the second level of exercise.

**End-systolic Volume**

The mean end-systolic volume was slightly but insignificantly smaller at rest in the normal subjects than in the coronary patients (43 ± 9 vs 52 ± 13 ml, $p = \text{NS}$) (table 1). In each normal subject, end-systolic volume decreased at both levels of exercise. In contrast, it increased in 19 of the coronary patients (76%) at the first level of exercise and in 24 (96%) at the second level of exercise (fig. 7). The end-systolic volume was more than threefold larger in the coronary group than in the control group at the higher level of exercise ($25 \pm 11$ vs $93 \pm 25$ ml, $p < 0.01$) (table 1).

**Stroke Volume, Stroke Work and Cardiac Output**

Although the mean stroke volume and stroke work progressively increased in both groups during exercise (fig. 8), six patients with coronary artery disease had an actual decrease in stroke volume from rest to the second level of exercise. Stroke volume and stroke work were not significantly different in the two groups at rest or during the first levels of exercise (table 1). However, the mean stroke volume was slightly higher in the normal subjects at the second level of exercise ($119 \pm 13$ vs $100 \pm 23$ ml, $p < 0.05$). When stroke work was plotted as a function of end-diastolic volume, the slope of the resultant ventricular function curve was steeper in the control group than in the coronary artery disease group (fig. 9).

The resting cardiac outputs were approximately the same for the two groups (table 1). However, during both levels of exercise, the cardiac output was significantly higher in the control group than in the coronary group, primarily because of the faster heart rates achieved by the normal subjects.

**Pulmonary Transit Time and Blood Volume**

Although the mean pulmonary transit time was significantly shorter in the normal subjects than in the coronary patients at rest and during the two levels of exercise, considerable overlap occurred among individuals in both groups. At the second level of exercise, the pulmonary transit time was twice as long in the coronary artery disease group as in the control group ($5.3 \pm 1.5 \text{ vs } 2.4 \pm 0.6 \text{ seconds}; p < 0.01$) (table 1). In seven of the patients with coronary artery disease (28%), pulmonary transit time increased 1 second or more from the first to the second level of exercise. No increase of similar magnitude occurred in any of the normal subjects. Pulmonary blood volumes varied greatly among individuals in both groups at rest and during exercise. However, at the second level of exercise, pulmonary blood volumes remained less than 1000 ml in each normal subject but increased to

![Figure 7](image_url) **Figure 7.** Changes in end-systolic volume (ESV) from rest to exercise 1 and exercise 2. CAD = coronary artery disease.

![Figure 8](image_url) **Figure 8.** Hemodynamic responses to exercise in 10 normal subjects (solid line) and 25 patients with coronary artery disease (dashed line). Mean values and standard deviations are presented at rest, exercise 1 and exercise 2. HR = heart rate.
greater than 1000 ml in 17 of the patients with coronary artery disease (68%).

Wall Motion

The contraction pattern of the left ventricle was normal at rest and increased during both levels of exercise in the normal subjects (fig. 1). Wall motion was also normal in 20 (80%) of the patients with coronary artery disease at rest. The other five patients had either hypokinesia or akinesia involving only one of the three segments of the left ventricle analyzed in the anterior projection (fig. 10). At the first level of exercise, 14 of the coronary patients (56%) developed a new wall motion abnormality or demonstrated progression in a pre-existing defect at rest (figs. 3 and 4). At the second level of exercise, wall motion was abnormal in all patients (figs. 2, 3 and 4).

The mean regional wall motion index for the coronary group was 5.7 ± 0.7 at rest, 4.8 ± 1.3 at the first level of exercise and 3.0 ± 1.2 at the second level of exercise (fig. 10).

Discussion

The present study was designed to determine if abnormalities in left ventricular function precede angina pectoris and electrocardiographic evidence of myocardial ischemia. Left ventricular function was assessed by radionuclide angiocardiography at rest and during two levels of exercise in patients with coronary artery disease, selected on the basis of electrocardiographic evidence of myocardial ischemia during treadmill stress tests. The first radionuclide angiocardiogram during exercise was performed before and the second after the onset of ST-segment depression.

First-pass radionuclide angiocardiography is a simple, noninvasive method for evaluating global and regional left ventricular function. Radionuclide measurements of left ventricular ejection fraction, volumes, cardiac output and regional wall motion are highly reproducible and correlate well with measurements made by contrast ventriculography and indicator dilution techniques. Because studies can easily be performed during upright exercise, the radionuclide method is ideal for assessing the effect of exercise on left ventricular function.

A single bipolar CMs lead was used to monitor the ECG during exercise. Although it is possible that ST-segment depression may have occurred in some other anatomic location of the heart before it was manifest in the CMs lead, this possibility seems unlikely because we excluded patients who had ST-segment depression only in the inferior leads during the preliminary 12-lead ECG stress test. The CMs lead has been reported to be almost as sensitive as the 12-lead ECG in detecting exercise-induced ST-segment changes.

The cardiac response to exercise of the 10 normal subjects in this study was similar to that previously reported from this laboratory. In each control subject, ejection fraction increased more than 5%, end-diastolic volume increased less than 25%, end-systolic volume decreased and wall motion was normal during both levels of exercise. In 22 of the 25 patients with coronary artery disease, abnormalities in left ventricular function were present at the first level of exercise before angina pectoris and electrocardiographic evidence of myocardial ischemia were noted. The first exercise radionuclide angiogram was performed an average of 18 beats/min below the heart rate at which ST-segment depression was first observed on the ECG. The ejection fraction either decreased or increased less than 5% in 18 patients (72%), the end-diastolic volume increased more than 25% in nine (36%), the end-systolic volume increased in 19 (76%) and a new wall motion abnormality developed in 14 (56%).

Three patients had completely normal left ventricular responses at the first level of exercise but developed significant hemodynamic and wall motion abnormalities at the second level of exercise. Left ventricular dysfunction may also have occurred in these patients before ST-segment depression but after the first exercise study. Alternatively, abnormalities in left...
ventricular function may have coincided with ST-segment depression in these patients or the radionuclide technique may not be sensitive enough to detect early myocardial ischemia in all patients. Nine patients did not experience chest pain during exercise, confirming earlier clinical studies that showed myocardial ischemia can occur in the absence of angina pectoris. In eight of the patients in this study, hemodynamic abnormalities occurred at the first level of exercise when wall motion appeared normal. Wall motion data were gathered from the anterior projection, which does not permit adequate assessment of septal and lateral wall motion. Thus, it is possible that contraction abnormalities were present in a region of the left ventricle that was not visualized. At the second level of exercise, all patients had segmental contraction abnormalities indicating more severe myocardial ischemia.

Because end-diastolic volume increased substantially in most patients at the second level of exercise, stroke volume was maintained despite the decrease in ejection fraction. This pathologic but protective increase in end-diastolic volume is probably related to a reduction in contractility and passive stretch of the ischemic myocardial fibers during diastole. End-diastolic volume may occasionally increase greater than 25% in trained athletes during maximal effort. In such subjects, the increase is related to enhanced venous return and associated with an increase rather than a decrease in ejection fraction. When stroke work was plotted against end-diastolic volume, the slope of the resultant ventricular function curve was depressed in the coronary artery disease group compared with the control group. Further, seven patients had a decrease in stroke work associated with an increase in end-diastolic volume when exercise was increased from the first to the second level. This observation suggests that these patients might be functioning on the descending limb of the Starling curve. However, changes in the relationship between stroke work and end-diastolic volume are difficult to interpret clinically because a shift from one ventricular function curve to another can be produced by many factors, including changes in contractility, compliance, afterload and heart rate.

Although all patients in this study developed dramatic hemodynamic and wall motion abnormalities during the second level of exercise, this investigation was not designed to determine the sensitivity of radionuclide angiocardiography in diagnosing coronary artery disease. Only male patients with angiographically proved coronary artery disease and electrocardiographic evidence of myocardial ischemia during stress were studied. Occasionally, patients with significant coronary artery disease documented by coronary angiocardiography have completely normal radionuclide angiograms during exercise. These observations suggest that significant anatomic disease does not necessarily indicate that significant functional myocardial ischemia will occur during exercise. In addition, all patients in this study had normal or only slightly depressed left ventricular function at rest. In patients with previous myocardial infarctions and significant resting abnormalities, detection of exercise-induced myocardial ischemia is considerably more difficult. The control subjects were all young men in good physical condition in whom the diagnosis of coronary artery disease was not entertained. Occasionally, the ejection fraction will decrease during exercise in older patients, especially women, who have chest pain but no detectable coronary artery disease at cardiac catheterization. However, wall motion abnormalities do not develop in these women.

Because exercise-induced left ventricular dysfunction was detected in most patients before the onset of ST-segment depression, radionuclide angiography may prove particularly useful in diagnosing significant coronary artery disease in patients who develop fatigue at low heart rates. Approximately one-third of exercise stress tests are inadequate because ST-segment depression does not occur before the target heart rate is reached. These findings may explain why preliminary studies from this institution indicate that radionuclide angiography is more sensitive than stress electrocardiography in diagnosing coronary artery disease. Radionuclide angiography may prove helpful in diagnosing coronary artery disease in patients in whom the stress ECG cannot be meaningfully interpreted because their resting ECG is abnormal, as in left bundle branch block, left ventricular hypertrophy, digitalis administration or electrolyte imbalance.

The significant abnormalities in left ventricular function that were detected by radionuclide angiography occurred in the majority of patients before clinical symptoms or electrocardiographic evidence of myocardial ischemia. By the time the ECG showed ST-segment depression, all patients had developed wall motion abnormalities and significant hemodynamic alterations, including a decrease or less than 5% increase in ejection fraction, an increase greater than 25% in end-diastolic volume and an increase in end-systolic volume. This study shows that angina pectoris and ST-segment shifts on the ECG are frequently late manifestations of myocardial ischemia and supports the use of this noninvasive, radionuclide technique to detect myocardial ischemia in patients suspected of having coronary artery disease.

References
5. Waters DD, Da Luz P, Wyatt HL, Swan HJC, Forrester JS: Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. Am
LV FUNCTION DURING EXERCISE/Upoton et al.

J Cardiol 39: 537, 1977


Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression.
M T Upton, S K Rerych, G E Newman, S Port, F R Cobb and R H Jones

_Circulation._ 1980;62:341-349
doi: 10.1161/01.CIR.62.2.341

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/2/341

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/