The Correlation of Coronary Angiography and the Electrocardiographic Response to Maximal Treadmill Testing in 76 Asymptomatic Men


SUMMARY
This report presents the results of coronary angiography in 76 asymptomatic aircrewmen with exercise testing responses suggestive of coronary artery disease. There were two subgroups: 18 men with normal resting electrocardiograms; and 58 men with a history of repolarization changes on their resting electrocardiogram after at least one normal ECG. Of the 76 men, 53% had angiographically demonstrated coronary artery disease, and many of them had high risk lesions. Forty-seven percent had no angiographic evidence of lesions and were recommended for return to flying status. Those individuals with normal angiograms will be closely followed at the USAF School of Aerospace Medicine in an effort to determine their natural history and prognosis. The findings in this study, the lack of significant complications resulting from coronary angiography, the concern for public safety, and the economics of maintaining a flying force all support the continued use of elective coronary angiography in selected asymptomatic aircrewmen.

Additional Indexing Words:
Coronary angiography Asymptomatic population Maximal exercise testing
Repolarization abnormalities Silent coronary heart disease Double Master’s tests

In 1957, the electrocardiogram (ECG) was made a requirement for each applicant for entry into flying training and also for all periodic physical examinations in United States Air Force flying personnel. The USAF Central ECG Library was established in 1957 to serve as a research repository for ECGs of flyers. From the ECG data bank, studies have been reported on such abnormalities as hypertrophy, arrhythmias, myocardial infarction patterns, bundle branch block, and early repolarization. At the same time the USAF School of Aerospace Medicine (USAFSAM), the consultation referral center for aircrewmen with flying safety and health problems, began performing extensive cardiovascular evaluations on all referrals including those referred for noncardiovascular reasons.

Epidemiological studies and clinical experience have demonstrated that an abnormal ECG response to exercise testing, as well as resting repolarization changes (ST-depression or T wave abnormalities), are statistically associated with the future development of coronary heart disease events. Approximately 25% of the first episodes in the natural history of this disease are sudden death. Since even nonfatal myocardial infarctions can be incapacitating, the cardiovascular status of aircrewmen with these electrocardiographic abnormalities must be clarified in the interest of public safety. Also, because of the large investment in aircrew training and the personal interests of each aircrewman pursuing a flying career, it is economically desirable to maintain aircrewmen on flying...
status if possible. For these reasons, the USAFSAM has since February, 1971, been performing elective cardiac catheterizations and coronary angiography on aircrewmen with abnormal electrocardiographic findings or other cardiovascular abnormalities. One hundred and seventy catheterizations have been performed at the USAFSAM and no major complications have occurred in asymptomatic individuals. These catheterizations were performed for diagnosis of suspected cardiomyopathy and mild valvular lesions as well as for coronary atherosclerosis.

This report deals with the USAFSAM experience in completely asymptomatic individuals who have had normal ECGs and subsequently developed repolarization changes and/or abnormal exercise ECG responses. Although these electrocardiographic findings have been statistically associated with later development of coronary artery disease, in any given patient they are not specific. Exercise testing results can be especially misleading in individuals with pre-existing repolarization abnormalities. Individuals taking certain medications and those with cardiomyopathies, ventricular hypertrophy, valvular disease, anemia, vasoregulatory asthenia, or electrolyte abnormalities can also have abnormal resting ECGs and ECG exercise tests without having coronary heart disease. Patients with these disease entities or on medications have been carefully excluded from the group of subjects studied here. Also excluded were individuals having a history compatible with angina, myocardial infarction, pericarditis, or myocarditis and those with ECG evidence of transmural myocardial infarction or bundle branch block. The correlation between coronary angiographic findings and cardiovascular symptoms has been presented in other reports, and the USAFSAM experience with detection of bundle branch block has also been recently reported.

Methods

The periodic ECGs given all USAF flying personnel are reviewed at the USAFSAM. Approximately 4,000 ECGs are reviewed each month. Repolarization abnormalities representing a change from a previously normal ECG are found in approximately 1% of all the periodic ECGs. These changes include mild degrees of ST-segment depression and low amplitude or inverted T waves in leads II, aVF, or the lateral precordial leads. Individuals whose ECGs show these changes are requested to have repeat ECGs and double Master’s exercise tests at their Air Force bases. If the changes are persistent or if the double Master’s test is borderline or abnormal, the individual is referred to the USAFSAM. At the USAFSAM a chest X-ray, blood chemistry profile, resting ECG, vectorcardiogram, avionics monitoring, double Master’s test, and maximal treadmill test are performed on all referrals.

The study group underwent maximal treadmill exercise testing using a constant treadmill speed of 3.3 mph (90 m/min) and an increasing incline of one percent each minute. Simple bipolar leads were used to approximate an orthogonal lead orientation with the following sites of lead attachment: lead X connecting the right and left V5 positions; lead Y connecting the second intercostal space on the sternum and the sixth intercostal space on the left anterior axillary line; lead Z connecting the fourth intercostal space on the sternum and a position directly opposite on the spine. In addition to the bipolar XYZ leads, standard leads I, II, aVF, V2 and V5 were recorded during the resting baseline period and at one minute intervals during recovery. The orthogonal ECG data were recorded continuously during exercise on a conventional strip chart recorder, displayed on a multi-channel oscilloscope and recorded on analog tape for permanent storage and subsequent computer analysis.

The baseline ECG was recorded with the patient resting in the supine position, and then with the subject standing for several minutes prior to exercise. A physician was in attendance at all times to monitor both the patient’s condition and his ECG data. The patient exercised to his maximal effort unless the test was prematurely terminated by order of the physician according to standard exercise testing guidelines. During the final minutes of exercise the patient’s expired air was collected by the Douglas bag method and analyzed for maximal oxygen consumption and carbon dioxide production using Beckman gas analyzers. At the termination of exercise, the immediate recovery period was recorded for 45 sec in the upright position and then for at least 8 min in the supine position. Indirect cuff blood pressures were obtained each minute throughout the entire procedure.

One millimeter or more of horizontal or downward sloping ST-segment depression in relation to the P-R segment in X, Y, or the standard leads observed during exercise and/or recovery was interpreted as an “abnormal” ECG response to exercise stress testing. This interpretation was made regardless of the degree of baseline ST-segment depression.

Individuals with abnormal exercise tests were offered the opportunity to undergo cardiac catheterization. If the results of this procedure showed no abnormalities, the airman was returned to flying status. All the risks and possible complications were explained and informed consent obtained from those who elected to have the procedure.

Cardiac catheterization was performed via a right brachial arteriotomy. Left ventricular end diastolic pressure and dP/dT were measured utilizing a #7 Eppendorf catheter, P-23 Statham pressure transducer, and an Electronics-for-Medicine DR-8 recorder. Left ventricular angiography was accomplished in the 20° right anterior oblique (RAO) position using 50cc of contrast media injected at the rate of 15 cc per second. Selective coronary angiography was done using the
Table 1

Coronary Angiographic Findings in the Total Group of Asymptomatic Aircrewmen with an Abnormal ECG Response to Maximal Treadmill Testing

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Subjects</th>
<th>No angiographic coronary artery disease</th>
<th>Angiographic coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Less than 50% lesions 50% or greater</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>35-44</td>
<td>40</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>45-55</td>
<td>30</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>36 (47.4%)</td>
<td>7 (9.2%) 33 (43.4%)</td>
</tr>
<tr>
<td>Total No.</td>
<td>40 (52.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sones technique. Multiple injections of both the right and left coronaries were done in the left anterior oblique (LAO), anteroposterior (AP), and RAO positions, and recorded on 35 mm cine film. Nitroglycerine was given before coronary injections to reduce the possibility of coronary spasm.

The results of the radiographic and ECG studies were reviewed by the authors and a consensus interpretation was agreed upon. Individuals with inadequate studies have not been included in the report.

Results

Approximately 3% of the noncardiovascular referrals to the USAFSAM have an abnormal ECG response to maximal treadmill exercise, and 40% of the referrals with a history of a change from normal to repolarization abnormalities on their routine ECGs have an abnormal electrocardiographic response to maximal treadmill exercise. Over six thousand maximal treadmill tests have been performed without complication and the data stored for analysis and prospective follow-up.

Table 1 shows the results of coronary angiography in the 76 asymptomatic men with abnormal electrocardiographic responses to maximal treadmill exercise. Of these 76 asymptomatic men, 43% had significant coronary artery disease detected by coronary angiography (lesions causing lumen narrowing by 50% or greater). An additional 9% had minimal disease (less than 50% lesions) detected angiographically. The absence of significant disease as determined by angiography in the younger age group in spite of abnormal exercise testing is obvious as is the higher incidence of coronary artery disease in the older age group.

Table 2 shows the mean age and age-adjusted serum cholesterol percentiles for the subjects grouped by findings on coronary angiography. The cholesterol percentile groups were based on several thousand cholesterol determinations performed on referrals to the USAFSAM who had normal electrocardiographic responses to maximal exercise.

Tables 3 and 4 give the detailed angiographic findings in the 33 men with significant disease. Table 3 shows the severity of the angiographic lesions and table 4 shows their sites. Nearly one-third of the men had 75% or greater lesions, two had diseased left main coronary arteries, and three had collateral vessels visualized.

Table 5 separates out the coronary angiographic findings in the subgroup of 18 individuals who had normal serial resting ECGs and an abnormal ECG response to maximal exercise. Eleven of the 18 individuals did not show significant coronary artery disease. Thus 61% had an unexplained abnormal response. Table 6 relates the treadmill ECG response and occurrence of positional changes to the angiographic findings. Of the 18, seven were abnormal only in the orthogonal Y lead and these seven men did not have significant angiographic lesions. Prior to exercise, all seven men had ECGs

Table 2

Age and Age-Adjusted Cholesterol Percentiles

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
<th>All subjects (N = 76)</th>
<th>No angiographic CAD (N = 36)</th>
<th>&lt; 50% lesions (N = 2)</th>
<th>50% or &gt; (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Range</td>
<td>26-55</td>
<td>27-50</td>
<td>26-54</td>
<td>35-55</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>43</td>
<td>40</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Age-adj. cholesterol percentiles</td>
<td>Range</td>
<td>14-100</td>
<td>14-99</td>
<td>24-97</td>
<td>27-100</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>67</td>
<td>55</td>
<td>70</td>
<td>76</td>
</tr>
</tbody>
</table>

*CAD = Coronary Artery Disease
with minor Y lead ST-segment depression despite normal ECG recordings in II and aVF, and four had ECGs with orthostatic T wave changes in Y.

The results of double Master’s testing at the USAFSAM in this subgroup of 18 were as follows: Two individuals with three vessel disease and three individuals with two vessel disease had normal double Master’s tests. One individual without angiographic coronary artery disease had an abnormal response and one had a borderline response to double Master’s testing.

Table 7 shows the incidence and severity of coronary artery disease in the subgroup of 58 men with an abnormal ECG response to maximal treadmill exercise and serial ECGs showing repolarization abnormalities after at least one normal ECG. Some showed progressive changes or had borderline or abnormal double Master’s tests performed at their referring facilities. Twenty-six or 45% had significant disease manifest and an additional six had minimal but evident coronary artery disease for a total of 55% with any angiographically demonstrated lesions.

Table 8 shows the patterns of exercise electrocar-

### Table 3

**Severity and Extent of the Coronary Artery Lesions in the 33 Asymptomatic Men Found to Have Significant Coronary Artery Disease by Angiography**

<table>
<thead>
<tr>
<th>Age</th>
<th>Subjects</th>
<th>Individuals with 50% or greater lesions</th>
<th>Individuals with 75 to less than 90% lesions</th>
<th>Individuals with 90% or greater lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>1 vessel</td>
<td>2 vessels</td>
<td>3 vessels</td>
</tr>
<tr>
<td>35-44</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>45-55</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>15</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

diographic response in this subgroup of 58 men. The second column represents the vasoregulatory pattern described by Friesinger et al.22 It has been proposed that this pattern is inconsistent with coronary artery disease; however, two of the six subjects in our study with this ECG pattern had significant disease. One of these individuals had three vessel disease with involvement of the left main coronary artery and the other had two vessel disease. The third and fourth columns of table 8 show that the arbitrary criteria used by some investigators requiring one millimeter of ST-segment depression in the ECG in addition to the pre-exercise ST-segment depression for an abnormal response does not differentiate those with significant disease from those without disease. The fifth column of table 8 shows that the presence of positional ECG changes does not preclude the existence of significant coronary artery disease.

Table 9 delineates occurrence of and leads demonstrating ST-segment depression in the subgroup of 58 subjects with resting repolarization abnormalities. No particular time course or lead involvement differentiates those with coronary artery disease from those without disease.

Table 10 represents the results of double Master’s testing at the USAFSAM in the subgroup with repolarization abnormalities on their ECGs. The double Master’s tests performed at the referring facilities were reviewed at USAFSAM but the results are not considered here because many of the tests were technically inadequate and the results often differed from the test done at the USAFSAM.

### Discussion

The subjects in this study constitute a highly selected group of individuals, both by their acceptance into a flight training program and continuation on flying duties, and by referral to the USAFSAM. Because of the selection process, these men represent a unique population of apparently healthy individuals who came to medical attention only because of ECG findings, in contrast to
CORRELATION OF ANGIOGRAM AND ECG

Table 5
Angiographic Findings in the Subgroup of 18 Men with Normal Resting Electrocardiograms and Abnormal Exercise Tests

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No angiographic coronary artery disease</th>
<th>&lt; 50% lesions</th>
<th>Angiographic coronary artery disease</th>
<th>1 vessel</th>
<th>50% or greater lesions</th>
<th>2 vessels</th>
<th>3 vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35-44</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45-55</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total No.</td>
<td>18</td>
<td>10 (55.6%)</td>
<td>1 (5.6%)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6
Exercise Electrocardiographic Response and Positional Changes in the Subgroup of 18 Men with Normal Resting ECGs

<table>
<thead>
<tr>
<th>Time and lead occurrence of one millimeter or more of horizontal or downward sloping ST-segment depression</th>
<th>Angiographically significant coronary artery disease</th>
<th>No angiographically significant coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>X, Y &amp; V5 or aVF</td>
<td>XY only</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

individuals who are medically evaluated because of symptoms.

This report involves only a small number of asymptomatic individuals with abnormal maximal exercise tests who have had coronary angiography. However, the alarming incidence of significant high risk coronary artery lesions in many of them is important and hopefully will stimulate further studies. The USAFSAM electrocardiographic methods for detecting silent coronary artery disease are supported especially when the results are compared with the angiographic findings of asymptomatic individuals reported by other investigators.14, 17, 23 These investigators have reported clinical findings in individuals referred for cardiac catheterization who were judged not to have symptomatic coronary artery disease. They reported finding an approximate 5 to 7% incidence of significant coronary artery disease determined by angiography and a 15 to 20% incidence of some degree of coronary artery disease revealed on angiography. Our figures of 43% and 53% respectively contrast sharply. The mean age of our asymptomatic individuals was about five years less than the mean age of the “control groups” in these earlier studies, yet we found a much higher incidence of angiographic coronary artery disease.

The etiology of resting electrocardiographic repolarization abnormalities (nonspecific ST-T

Table 7
Angiographic Findings in the Subgroup of 58 Men with Repolarization Abnormalities in Their Resting Electrocardiograms

<table>
<thead>
<tr>
<th>Age</th>
<th>Subjects</th>
<th>No.</th>
<th>No angiographic coronary artery disease</th>
<th>&lt; 50%</th>
<th>Angiographic coronary artery disease</th>
<th>1 vessel</th>
<th>50% or greater lesions</th>
<th>2 vessels</th>
<th>3 vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35-44</td>
<td>23</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>45-55</td>
<td>24</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total No.</td>
<td>58</td>
<td>26 (45%)</td>
<td>6</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Total No. = 26 (45%)

Total No. = 32 (55%)

Circulation, Volume XLVIII, September 1973
Abnormalities in their ECGs and myocarditis can persist for years. These repolarization changes may worsen during exercise testing in spite of a lack of symptoms and normal functional capacity.

The analysis of age and age-adjusted serum cholesterol values in relation to the severity of angiographically demonstrated coronary artery disease reflected the known influence the factor of age and cholesterol levels have in the atherosclerotic disease process. However, the values range too widely to be useful in deciding whether an individual should undergo coronary angiography.

An analysis of the maximal oxygen consumption of the subjects grouped according to their angio-
graphic findings did not differ significantly from that of normal subjects of their own age (data to be published).

The Y axis or vertical ECG lead has been more labile than the other leads.24 However, its importance for detecting ischemia in the inferior-posterior myocardial wall, as suggested by other investigators,25 has been considered. Changes in Y only were associated with lesions in the right coronary artery or left circumflex coronary artery, which supply the inferior-posterior myocardial wall, in approximately one-half of the instances when Y changes correlated with significant coronary artery disease.

Analysis of the time course, lead appearances, and degree of ST-segment depression failed to differentiate those with angiographic coronary artery disease from those without disease. Six individuals with the vasoregulatory abnormality pattern described by Friesinger et al.26 have been included in this study. In this group, two individuals had significant coronary artery disease. Orthostatic or positional changes also occurred in our coronary artery disease group.

A disappointing result was the poor specificity of an abnormal electrocardiographic response to maximal treadmill exercise for diagnosis of coronary artery disease shown on angiography. This could be anticipated in the subjects with repolarization abnormalities in their ECGs since it has been reported by other investigators.14 However, poor specificity of maximal exercise testing was not expected in those with a normal resting ECG. The strong specificity of exercise testing for coronary artery disease demonstrated by other investigators26-28 may be explained by the populations they studied. Individuals in the populations of these other studies were selected for study because they had symptoms of coronary artery disease and so the results would be expected to be biased toward a higher disease prevalence.

None of the individuals under 34 years of age with abnormal exercise responses had angiographically significant disease. On the basis of what we know of the natural history of atherosclerosis, younger individuals would benefit most from a good screening test that would be sensitive enough to detect those who should adopt preventive measures to slow the atherosclerotic process.

A number of possibilities exist for resolving the lack of sensitivity and specificity of maximal treadmill testing. First, it may be that methods of analyzing the exercise ECG need to be improved. Vector analysis of the ST-segment using computer methods may separate the abnormal response of those with coronary artery disease from individuals with other reasons for an abnormal response.26 Secondly, further investigation of positional and hyperventilation changes as well as the lead appearance and pattern of ST-segment depression may make the test more specific. Some abnormal responses may be due to abnormal sympathetic tone. However, there is no assurance yet that the modification of an abnormal ECG response by administration of drugs rules out the possibility of a diagnosis of coronary artery disease.

Another explanation for the poor correlation of abnormal maximal treadmill tests with angiographically demonstrated coronary artery disease in this study is that the criteria of 50% or greater lesions may be too strict. Possibly, even intimal disease resulting in arterial stiffness and limited coronary dilation during exercise can result in some degree of myocardial ischemia. Further studies are needed to clarify the relationship of anatomic coronary artery lesions to myocardial ischemia. Because of this possibility and the recognition that atherosclerotic lesions can progress rapidly,17,29 the USAFSAM policy has been to recommend grounding of aircrewmens with any angiographically demonstrated lesions. This policy has still allowed approximately 50% of aircrewmens studied here, who would otherwise have been grounded on the basis of their ECG and exercise testing results, to return to flying status.

The aim of the USAFSAM electrocardiographic screening methods was to improve flying safety but these methods are equally applicable to preventive cardiology. Since a mass modification of the American life style as a means of reducing the incidence of coronary heart disease seems unlikely, identification of individuals with silent coronary artery disease should be emphasized. Efforts could then be concentrated on these individuals to encourage them to adopt a healthier life style to slow the progression of disease. Because of the lack of sensitivity, screening for silent coronary artery disease by serial resting ECGs is inadequate. Maximal exercise stress testing has a greater sensitivity, but suffers because of its lack of specificity, as illustrated by this report, and because of its expense. Technical advances in exercise electrocardiography may improve its specificity for silent coronary artery disease, but until that time the USAFSAM has proposed that the United States Air Force incorporate the double Master's tests as a required part of each periodic examination of flying
personnel. We have also proposed a multiple risk factor screening protocol.30

Acknowledgment

The authors acknowledge the work of Dr. Robert C. Touchon in beginning the USAFSAM Cardiac Catheterization Laboratory, and express their thanks to Mrs. Anne Breaux and Mrs. Julie Froelicher for typing the manuscript.

References

The Correlation of Coronary Angiography and the Electrocardiographic Response to Maximal Treadmill Testing in 76 Asymptomatic Men
VICTOR F. FROELICHER, JR., MAJOR, FRANK G. YANOWITZ, MAJOR, A. J. THOMPSON, MAJOR and MALCOLM C. LANCASTER, COLONEL

_Circulation_. 1973;48:597-604
doi: 10.1161/01.CIR.48.3.597
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 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/48/3/597

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/