Quantitative Assessment of Ventricular Performance in Unstable Ischemic Heart Disease by Dextran Function Curves

LAWRENCE D. RAPHAEL, M.D., JOHN A. MANTLE, M.D., ROGER E. MORASKI, M.D., WILLIAM J. ROGERS, M.D., RICHARD O. RUSSELL, JR., M.D., and CHARLES E. RACKLEY, M.D.

SUMMARY The ability to quantify the amount of permanent left ventricular dysfunction in patients with unstable ischemic heart disease would have important clinical value. Left ventricular function curves were constructed in sixteen patients with acute myocardial infarctions and five patients with unstable angina pectoris syndrome at an average of 66 hours (±8) after the onset of symptoms. Fifty ml increments of low molecular weight dextran were rapidly infused into the right atrium during constant monitoring of the pulmonary artery end-diastolic pressure (PAEDP) via a Swan-Ganz thermodilution catheter. An average of 400 ml (range 200-800) was infused to produce a significant change in the PAEDP (range 3-13 mm Hg). The cardiac index was measured before and after the dextran infusion. The slope of the left ventricular function curve was calculated by dividing the change in the cardiac index by the change in the PAEDP. The sixteen patients with acute myocardial infarction underwent left heart catheterization and left ventricular biplane angiography an average of six months later. The five patients with unstable angina pectoris were studied within one month. The slope value of the left ventricular function curve was compared to angiographic ejection fraction by linear regression analysis and the correlation coefficient was 0.80. These data demonstrate 1) the slope of the left ventricular function curve in patients with acute myocardial infarction or unstable angina correlates well with the angiographically calculated ejection fraction; 2) as early as two days post myocardial infarction, the residual impairment of left ventricular function can be estimated.

THE PROGNOSIS OF PATIENTS WITH ISCHEMIC HEART DISEASE has been shown to be influenced by the extent of anatomical coronary artery disease and impairment of left ventricular function. In recent years, angiographic ejection fraction has become an accepted technique for quantitating left ventricular function in patients undergoing cardiac catheterization and angiography. Although the construction of left ventricular function curves has been described as a qualitative method for assessing myocardial reserve in patients with myocardial infarction, the function curves have not been used in a quantitative manner nor related to other objective methods of evaluating ventricular function. Prediction of the amount of permanent left ventricular dysfunction accompanying an episode of acute ischemic injury would contribute to the prognosis and treatment of the patient. In this study of patients with acute myocardial infarction or unstable angina, left ventricular function curves were constructed during the initial three days of hospitalization. The slopes of the function curve during the acute phase were then compared to the angiographic ejection fraction obtained an average of six months later in order to develop a quantitative technique for assessing left ventricular performance in ischemic heart disease.

Materials and Methods

Patients

Twenty-one patients with acute chest pain were admitted to the Myocardial Infarction Research Unit of the University of Alabama in Birmingham. Sixteen of the 21 patients had a documented myocardial infarction established by the clinical presentation of severe chest pain, development of new Q-waves in either the anterior or inferior electrocardiographic leads, and a characteristic rise and fall of serum cardiac enzymes. The remaining five patients exhibited typical ischemic pain at rest and associated transient ST-T changes on the electrocardiogram during the episodes of pain but did not develop a characteristic rise and fall in the serum enzymes or acute Q-waves on the electrocardiogram.

Hemodynamic Studies

Shortly after admission, all 21 patients were instrumented with a #7 Swan-Ganz pulmonary arterial thermostor catheter which was positioned under fluoroscopic control in the pulmonary artery. The midpoint of the anterior-posterior diameter of the chest was used for the zero pressure level. Statham (P 23 DB) pressure transducers were used for pressure measurements. The pulmonary artery pressures and electrocardiographic signals were sampled for nine seconds, and a median cardiac cycle was calculated. The systolic and diastolic pressures and heart rates were determined by an on-line computer system as previously described. To reduce variability in sampling, thermodilution cardiac outputs were obtained in triplicate. Blood pressure was measured by sphygmomanometer.

The cardiac index (CI) was calculated as cardiac output/body surface area in liters per meter; stroke work index (SWI) was calculated as SI × (MSP-LVFP) × 0.0136 in g·m/beat/m² where SI (stroke index) = CI/heart rate; MSP (mean systolic pressure) = 0.8 × systolic + diastolic + diastolic aortic pressure (reference 3); and LVFP (left ventricular filling pressure) = pulmonary arterial end-diastolic pressure. The pulmonary arterial wedge pressure obtained by inflation of the balloon was recorded to insure

Received June 11, 1976; revision accepted January 7, 1977.
accurate measurements of the left ventricular filling pressure. The mean blood pressure (BP) was calculated as (systolic blood pressure + twice diastolic blood pressure)/3 (reference 5).

Informed consent according to the Declaration of Helsinki was obtained from all patients.6

Protocol

The median cardiac index, baseline pulmonary arterial end-diastolic pressure (PAEDP), heart rate, and blood pressure were recorded with the patient at bed rest and free of pain. Only those patients with a baseline PAEDP less than 22 mm Hg were included in the study. Low molecular weight dextran (Rheomacrodex) in 50 ml increments was infused manually as rapidly as possible through the right atrial lumen of the thermistor catheter during continuous monitoring until a significant change of at least 3 mm Hg rise (range 3–12) in the PAEDP was obtained.7 An average of 400 ml of colloid was infused (range 200–800) in each patient. After the rise in the PAEDP had occurred, heart rate, blood pressure, PAEDP, and cardiac output measurements were repeated.

The slope of the left ventricular function curve was calculated by dividing the change in the CI and the SWI by the change in PAEDP, i.e.,

\[
\text{SCI} = \frac{\Delta CI}{\Delta \text{PAEDP}}
\]

\[
\text{SSWI} = \frac{\Delta \text{SWI}}{\Delta \text{PAEDP}}
\]

Where SCI = the slope of the cardiac index function curve; SSWI = the slope of the stroke work index function curve; \(\Delta CI\) = change in cardiac index; \(\Delta \text{SWI}\) = the change in stroke work index; and \(\Delta \text{PAEDP}\) = the change in PAEDP.

All 21 patients underwent right and left heart catheterization with coronary arteriography and quantitative left ventricular biplane angiography from three weeks to one year (average six months) after the acute studies. Left ventricular volumes were calculated according to the method of Dodge et al.8 Ejection fraction was calculated as angiographic left ventricular stroke volume (end-diastolic volume minus end-systolic volume) divided by left ventricular end-diastolic volume.9

The ejection fraction in each patient was compared to the baseline hemodynamic measurements obtained during the acute studies and to the slope of the function curve. The relationships were analyzed by linear regression analysis. In addition, the presence or absence of an S3 gallop sound on admission was noted by at least one of the authors. This finding was evaluated in light of the slope of the individual cardiac index function curve.

Results

Table 1 lists the hemodynamic data obtained during the acute studies and subsequent ejection fraction obtained at follow-up angiography.

Ventricular Function Curves

Figure 1 shows representative examples of different left ventricular function curves. The patient, shown as a closed circle, has a normal slope of 0.23. The initial PAEDP was 6 mm Hg and cardiac index = 2.4 L/min/m². With the infusion of dextran, the PAEDP increased to 12 mm Hg and the CI increased to 3.9 L/min/m². By dividing the changes in the CI by the changes in the PAEDP (\(\Delta CI/\Delta \text{PAEDP}\)), the value of 0.23 is obtained.

The second patient, shown as closed squares, reveals a depressed curve with a corresponding slope of only 0.04. The

### Table 1. Acute Hemodynamic Determinations and Follow-up Ejection Fractions

<table>
<thead>
<tr>
<th>Event</th>
<th>PAEDP (mm Hg)</th>
<th>BP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CI (L/min/m²)</th>
<th>SWI (g-m/beats/m²)</th>
<th>SCI (L/min/m²/mm Hg)</th>
<th>SSWI (g-m/beats/m²/mm Hg)</th>
<th>EF (%)</th>
<th># Cor. vessels involved</th>
<th>DEX (ml) total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MI</td>
<td>14 22</td>
<td>85 92</td>
<td>81 82</td>
<td>2.8 3.3</td>
<td>43 49</td>
<td>.06</td>
<td>0.8</td>
<td>N 35</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>2 MI</td>
<td>11 19</td>
<td>60 100</td>
<td>101 95</td>
<td>3.7 4.2</td>
<td>36 63</td>
<td>.06</td>
<td>0.9</td>
<td>N 35</td>
<td>2 800</td>
<td></td>
</tr>
<tr>
<td>3 MI</td>
<td>4 17</td>
<td>73 120</td>
<td>70 80</td>
<td>2.9 3.7</td>
<td>83 90</td>
<td>.06</td>
<td>0.6</td>
<td>N 35</td>
<td>2 400</td>
<td></td>
</tr>
<tr>
<td>4 MI</td>
<td>16 19</td>
<td>109 97</td>
<td>103 104</td>
<td>2.2 2.4</td>
<td>30 29</td>
<td>.06</td>
<td>-0.4</td>
<td>P 35</td>
<td>2 200</td>
<td></td>
</tr>
<tr>
<td>5 MI</td>
<td>8 20</td>
<td>70 113</td>
<td>109 99</td>
<td>2.3 2.4</td>
<td>24 24</td>
<td>.01</td>
<td>-0.0</td>
<td>P 28</td>
<td>2 200</td>
<td></td>
</tr>
<tr>
<td>6 MI</td>
<td>11 23</td>
<td>93 102</td>
<td>98 102</td>
<td>2.1 3.0</td>
<td>36 49</td>
<td>.08</td>
<td>1.0</td>
<td>N 42</td>
<td>1 500</td>
<td></td>
</tr>
<tr>
<td>7 MI</td>
<td>11 19</td>
<td>75 81</td>
<td>80 80</td>
<td>2.7 4.1</td>
<td>39 62</td>
<td>.18</td>
<td>3.0</td>
<td>N 69</td>
<td>1 700</td>
<td></td>
</tr>
<tr>
<td>8 MI</td>
<td>15 20</td>
<td>—</td>
<td>92 88</td>
<td>3.6 3.6</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
<td>P 33</td>
<td>1 200</td>
<td></td>
</tr>
<tr>
<td>9 MI</td>
<td>12 16</td>
<td>87 86</td>
<td>105 107</td>
<td>4.0 4.3</td>
<td>47 46</td>
<td>.08</td>
<td>-0.3</td>
<td>P 23</td>
<td>2 300</td>
<td></td>
</tr>
<tr>
<td>10 MI</td>
<td>10 17</td>
<td>44 55</td>
<td>76 80</td>
<td>2.3 2.6</td>
<td>20 25</td>
<td>.04</td>
<td>0.7</td>
<td>N 22</td>
<td>2 600</td>
<td></td>
</tr>
<tr>
<td>11 MI</td>
<td>14 21</td>
<td>83 87</td>
<td>76 79</td>
<td>2.2 3.0</td>
<td>35 46</td>
<td>.11</td>
<td>1.6</td>
<td>N 64</td>
<td>1 200</td>
<td></td>
</tr>
<tr>
<td>12 MI</td>
<td>11 31</td>
<td>100 94</td>
<td>93 96</td>
<td>2.3 3.1</td>
<td>36 40</td>
<td>.08</td>
<td>0.4</td>
<td>N 20</td>
<td>2 600</td>
<td></td>
</tr>
<tr>
<td>13 MI</td>
<td>13 21</td>
<td>78 84</td>
<td>69 71</td>
<td>3.2 4.0</td>
<td>37 60</td>
<td>.10</td>
<td>1.5</td>
<td>N 44</td>
<td>3 600</td>
<td></td>
</tr>
<tr>
<td>14 MI</td>
<td>13 23</td>
<td>79 81</td>
<td>86 90</td>
<td>2.4 2.7</td>
<td>32 79</td>
<td>.03</td>
<td>-0.3</td>
<td>P 35</td>
<td>2 350</td>
<td></td>
</tr>
<tr>
<td>15 MI</td>
<td>2 6</td>
<td>—</td>
<td>80 90</td>
<td>3.7 4.3</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
<td>N 50</td>
<td>0 300</td>
<td></td>
</tr>
<tr>
<td>16 MI</td>
<td>7 16</td>
<td>70 71</td>
<td>76 75</td>
<td>2.5 3.2</td>
<td>34 41</td>
<td>.08</td>
<td>0.8</td>
<td>N 28</td>
<td>1 300</td>
<td></td>
</tr>
<tr>
<td>17 UA</td>
<td>4 9</td>
<td>111 109</td>
<td>68 65</td>
<td>2.4 3.2</td>
<td>38 79</td>
<td>.16</td>
<td>4.1</td>
<td>N 59</td>
<td>1 300</td>
<td></td>
</tr>
<tr>
<td>18 UA</td>
<td>6 12</td>
<td>86 86</td>
<td>76 75</td>
<td>2.4 3.8</td>
<td>40 65</td>
<td>.23</td>
<td>4.7</td>
<td>N 53</td>
<td>3 400</td>
<td></td>
</tr>
<tr>
<td>19 UA</td>
<td>6 11</td>
<td>—</td>
<td>103 95</td>
<td>3.4 5.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>N 63</td>
<td>3 400</td>
<td></td>
</tr>
<tr>
<td>20 UA</td>
<td>2 6</td>
<td>80 81</td>
<td>92 88</td>
<td>2.7 3.8</td>
<td>37 55</td>
<td>.27</td>
<td>4.6</td>
<td>N 61</td>
<td>2 400</td>
<td></td>
</tr>
<tr>
<td>21 UA</td>
<td>2 16</td>
<td>80 82</td>
<td>63 57</td>
<td>2.5 2.6</td>
<td>44 52</td>
<td>.03</td>
<td>1.9</td>
<td>N 31</td>
<td>2 300</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; UA = unstable angina; C = Control; D = post dextran infusion; BP = mean systemic arterial blood pressure; PAEDP = pulmonary arterial end-diastolic pressure; HR = heart rate; CI = cardiac index; SWI = stroke work index; SCI = slope of cardiac index function curve; SSWI = slope of stroke work index function curve; S3 gallop = ventricular gallop sound; N = not present; P = present; EF = ejection fraction; # Cor. vessels = number of coronary arteries with >70% stenosis; DEX = dextran.
former patient had unstable angina and no evidence of myocardial necrosis. The function curve slope, as expected, appears quite normal. The latter patient sustained an acute myocardial infarction and had significantly impaired left ventricular function.

Control PAEDP, CI, SWI vs Ejection Fraction

There was no significant relationship between control values for PAEDP, CI, and SWI and the ejection fraction.

Left Ventricular Function Curves vs Ejection Fraction

In figure 2 the slopes of the CI dextran curves (SCI) obtained during the initial studies have been compared to the angiographic ejection fractions obtained an average of six months after the acute ischemic event. Fourteen of the 16 patients with acute myocardial infarction had ejection fractions of less than 50% and all 14 had slope values less than 0.15. Eleven of the patients studied had ejection fractions of less than 40% including one patient with unstable angina who had sustained a prior myocardial infarction. All 11 had further depressed slopes of less than 0.10. Linear regression analysis of the total sample revealed a correlation coefficient of 0.80, see ± 9%. The regression equation for the relationship between ejection fraction (EF) and slope (ΔCI/ΔPAEDP) as shown in figure 3 was

\[ \text{EF} = 0.28 + 1.34 \times \text{(slope ΔCI/ΔPAEDP)} \]

The correlation coefficient for the myocardial infarction group alone was the same, \( r = 0.80 \), see ± 9%. In patients with myocardial infarction the relationship between ejection fraction and slope of the function curve was

\[ \text{EF} = 0.22 + 2.20 \times \text{(slope ΔCI/ΔPAEDP)} \]

In figure 3, similar analysis was made comparing the slope of the stroke work index curve (SSWI) to the ejection fraction. Appropriate data were available on 14 patients with AMI and four patients with unstable angina. Thirteen patients had ejection fractions of less than 50% and all 13 had SWI slopes of less than 1.5. The five patients with ejec-
tion fractions above 50% had SWI slopes of greater than 1.5. As noted with the CI function curves, there was a correlation between the slope value for the SWI curve and the ejection fraction with \( r = 0.80, \text{ SEE} \pm 9\% \). The regression for the relationship between ejection fraction and slope (\( \Delta \text{SWI}/\Delta \text{PAEDP} \)) in all patients in figure 3 was

\[
\text{EF} = 0.31 + 0.07 (\Delta \text{SWI}/\Delta \text{PAEDP}).
\]

The relationship in patients with myocardial infarction between ejection fraction and slope of the SWI function curve was

\[
\text{EF} = 0.30 + 0.12 (\Delta \text{SWI}/\Delta \text{PAEDP}).
\]

Clinical Correlation

In an effort to relate these hemodynamic data to clinical observations, the presence or absence of an audible \( S_3 \) gallop sound on admission was related to the slopes of the cardiac index left ventricular function curve, and the results are illustrated in figure 4. Six patients with acute myocardial infarction were noted to have an \( S_3 \) gallop sound, and all six had considerably depressed slopes (<0.10; range 0.00–0.08). Fifteen patients did not reveal a detectable \( S_3 \). The slopes of the cardiac index curve ranged widely from 0.04 to 0.32. Although the absence of an \( S_3 \) gallop sound provided no information on ventricular function, the presence of the protodiastolic \( S_3 \) was found in a significant number of patients with a depressed slope (\( P = 0.03; \) Student's paired \( t \)-test).

Discussion

The prognosis in ischemic heart disease is affected by anatomical abnormalities in the coronary arteries and myocardial dysfunction.\(^1\) Construction of ventricular function curves has been used for assessing myocardial reserve, but this method of evaluating cardiac performance has been an investigative technique. Furthermore, ventricular function curves have been neither quantitated nor related to other expressions of the mechanical state of the heart.

Two clinical methods for constructing these curves have involved either blood volume expansion with the infusion of blood, saline, or dextran, or afterload augmentation with agents like angiotension. Interpretation of these curves has been empirical, without quantitation or comparison to objective measurements such as the ejection fraction. Early investigators reported variable responses between dextran induced alterations in cardiac output and pulmonary arterial pressure.\(^10\)\(^-\)\(^12\) Schnabel and associates were the first to demonstrate a relationship between volume-induced elevations of the pulmonary arterial pressures and corresponding increases in cardiac output in normal subjects.\(^15\) Frye and Braunwald could only produce significant increases in cardiac output, stroke volume, and stroke work after blood transfusion when sympathetic blockade was effected prior to volume expansion.\(^14\)

Subsequently, Ross and Braunwald used angiotension to construct left ventricular function curves by relating the changes in stroke work index and LVEDP before and after infusion of the drug.\(^18\) They divided their patients into three groups based upon whether the curves were steep, flat, or

![Figure 3. The slopes of the stroke work index function curves (\( \Delta \text{SWI}/\Delta \text{PAEDP} \)) are related to the angiographic ejection fraction.](image)

![Figure 4. The presence or absence of an \( S_3 \) gallop sound on admission is compared to the slope of the cardiac index-left ventricular function curve in the patients with unstable angina and acute myocardial infarction. Six patients (all with AMI) had an \( S_3 \), and each patient demonstrated a depressed slope of less than 0.10.](image)
descending. The steep curves were felt to indicate normal myocardial function, while the flat and descending curves were considered to represent moderate and severe impairment of left ventricular function, respectively. These investigators concluded that the angiotensin test could be useful for detecting impairment of myocardial function and for expressing the severity in a quantitative form. These function curves were not related to other objective determinations of left ventricular function.

Linhart and his group corroborated these findings in a study of 19 patients with documented coronary artery disease and compared their angiotensin function curves to left ventricular angiograms. Rating the angiograms as normal or abnormal, these investigators demonstrated that patients with abnormal angiograms exhibited flat or descending curves; however, neither the function curves nor the ventriculograms were quantitated.

Only a few reports have described ventricular function curves in patients with coronary artery disease. Russell et al. demonstrated that elevation of the left ventricular filling pressure during acute myocardial infarction could significantly increase the cardiac index. However, in patients with acute infarction an optimal filling pressure was identified above which ventricular function declined. Greene and colleagues observed an abnormal response to plasma volume expansion within 15 hours after uncomplicated myocardial infarction. Khaja et al. showed that in the absence of ischemia left ventricular function curves in patients with coronary disease and no prior infarction were identical to those of normal patients. Loeb et al. suggested that, in patients with prior infarction, volume expansion with dextran could distinguish a higher risk population.

In response to dextran infusion, one group in this study increased the cardiac index by an average greater than 20% while the other population raised this index less than 20%. This latter group of patients was considered to have greater impairment of left ventricular function and was noted to have an increased mortality at six months.

The design of the present study allowed evaluation of the ventricular function curve in further clinical situations. Left ventricular function was assessed in patients with documented coronary artery disease who were experiencing either an acute myocardial infarction or unstable angina. By the method of volume expansion with low molecular weight dextran infusion, left ventricular function curves were obtained, and the slopes calculated and expressed as a numerical value. At a six-month follow-up evaluation, left ventricular angiography was performed and ejection fractions determined. The slopes of the ventricular function curves were compared to these ejection fractions and a linear relationship was established. Therefore, we found that the slope of the dextran ventricular function curve obtained during acute ischemia could predict the ejection fraction obtained after recovery from the acute event. Both stroke work index and cardiac index function curves were equally useful in the assessment of myocardial function. However, single hemodynamic measurements like the PAEDP or cardiac index did not correlate with the ejection fraction.

Function curves in patients with acute myocardial infarction were different from those in unstable angina. Four of the five patients with unstable angina had function curve slope values greater than 0.15, while 15 of the 16 patients with acute infarction had slope values less than 0.15. These data demonstrate a significant relationship between hemodynamic and angiographic expressions of the mechanical performance of the left ventricle. One patient with unstable angina revealed a slope value less than 0.15, but he had sustained a prior MI with residual myocardial dysfunction damage. Fourteen of the 15 patients with ventricular function curve slopes less than 0.15 were ultimately shown to have ejection fractions less than 50%. Riley et al. reported that the S2 gallop sound in AMI was associated with a left ventricular filling pressure (expressed as PAEDP) ranging from 7–60 mm Hg. Six patients with acute infarction had a S2 gallop sound on admission, and all six were demonstrated slope values for the function curves of less than 0.10.

Several comments should be made regarding the technique employed in the current study. Function curves were constructed at not less than 48 hours after hospitalization because earlier investigations have revealed that ventricular function begins to improve between one through three days following myocardial infarction. Patients were not evaluated with volume expansion when the PAEDP was greater than 22 mm Hg since these patients have flat or descending curves and are likely to develop pulmonary edema if the PAEDP is elevated above 24 mm Hg. Mantle et al. have recently demonstrated that these patients may be assessed using isosorbide dinitrate to lower the PAEDP and produce a ventricular function curve in a reverse manner.

This investigation has demonstrated a relationship between two independent methods for assessing ventricular function in patients with unstable coronary artery disease. The slope of the left ventricular function curve was calculated two days after myocardial infarction or during unstable angina and correlated with the angiographic ejection fraction determined several months later. The clinical exclusion of patients with a PAEDP greater than 22 mm Hg eliminated subjects whose measurements probably would have strengthened the statistical relationship between the slope of the function curve and ejection fraction. The method for producing a ventricular function curve is only applicable to patients who often appear clinically uncomplicated. Although the left ventricular filling pressure may be abnormally elevated in 66% of patients with uncomplicated infarctions, the clinical indications for the insertion of a Swan-Ganz catheter should probably be based on therapeutic considerations.

Both echocardiography and radionuclear scintigrams appear to be promising noninvasive techniques for estimating chamber dimensions volume and ejection fraction. Since left ventricular function two days postinfarction can be quantitatively related to the mechanical performance in the recovery period, a noninvasive estimate of cardiac reserve would be useful for patients in the coronary care unit.

References

2. Strand EM, Wissner SE, Russell RO Jr, Rackley CE: The computer as
Quantitative assessment of ventricular performance in unstable ischemic heart disease by dextran function curves.
L D Raphael, J A Mantle, R E Moraski, W J Rogers, R O Russell, Jr and C E Rackley

Circulation. 1977;55:858-863
doi: 10.1161/01.CIR.55.6.858
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 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/55/6/858

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/