Contrasting Influences of Alterations in Ventricular Preload and Afterload Upon Systemic Hemodynamics, Function, and Metabolism of Ischemic Myocardium

H. L. Wyatt, Ph.D., Protasio L. da Luz, M.D., David D. Waters, M.D., H. J. C. Swan, M.D., Ph.D., and James S. Forrester, M.D.

SUMMARY This study of anesthetized, open-chest dogs compares the effects of primary increases in left ventricular preload and afterload upon global and regional myocardial function and metabolism in the presence of a left anterior descending coronary artery stenosis (LAD). When LAD flow was reduced to 40–50% of control, regional systolic shortening declined by 20 to 25% and regional lactate extraction changed to production. In seven control dogs the mechanical abnormalities persisted during the 30 min of observation, but lactate production was reduced spontaneously. In ten dogs, increases in left ventricular end-diastolic pressure (LVEDP) during dextran infusion were associated with increases in cardiac output and regional systolic shortening; however, regional lactate production also increased (P < 0.05) despite an augmentation in LAD flow. In seven dogs mean arterial pressure increased by an average of 32 mm Hg during angiotensin infusion (0.2 to 0.4 μg/kg/min); LVEDP did not change but cardiac output decreased significantly. LAD artery flow improved markedly and lactate extraction shifted to extraction (P < 0.05) while systolic shortening remained unchanged. When angiotensin was discontinued, lactate extraction worsened again.

Thus, in the presence of a severe coronary stenosis, a primary increase in preload improves cardiac output but at the expense of aggravated ischemia. In contrast, a primary increase in afterload reduces cardiac output but may improve perfusion and lactate uptake of the ischemic myocardium.

Methods

Studies were carried out in 18 mongrel dogs weighing from 25 to 45 kg. The animals received 2.2 mg/kg of morphine sulphate intramuscularly 30 min prior to anesthesia with 100 mg/kg of intravenous chloralose. After endotracheal intubation, respiration was maintained with a Harvard ventilator. A left thoracotomy was performed through the fifth intercostal space and the heart was supported in a pericardial cradle. Systemic arterial pressure was monitored continuously with a P23Db pressure transducer (Statham Instruments) attached to a 25.0 cm 8F catheter advanced through a carotid artery to the ascending aorta. Left ventricular pressure was measured through a stiff 6.0 cm 10F catheter inserted into the left ventricle at the apex and connected directly to a pressure transducer (Model BT-70, Bio-Tech). Left ventricular end-diastolic pressure was manipulated by the use of a large left atrial catheter connected to a variable height reservoir. In 15 dogs, cardiac output was measured as ascending aortic flow via electromagnetic flowmeter (Model RC1000, Micron Instruments). Left ventricular stroke work was calculated from the formula: \[ SW = SV \times (AP - LVEDP) \times 0.0136, \] where \[ SW = \text{stroke work}; \ SV = \text{stroke volume}; \ AP = \text{mean arterial pressure}; \ LVEDP = \text{left ventricular end-diastolic pressure}. \]

Left anterior descending coronary artery flow was determined by electromagnetic flowmeter (Micron RC1000, Micron Instruments) using a 1.8 or 2.0 mm probe encircling the proximal left anterior descending coronary artery.

For assessment of the regional function, a 1.0 cm mercury-in-silastic length gauge (0.31 mm inner diameter; 0.62 mm outer diameter) (Parks Electronics) was sutured to the epicardial surface of the left ventricle parallel to the fibers in the region perfused by the left anterior descending coronary artery. Previous studies have demonstrated that the stiffness of the gauge is 1 g force/5% elongation. The
length gauge was prestressed for 30 min before each experiment; calibration was performed by attaching the ends of the gauge to the jaws of a vernier caliper and extending the gauge by fixed increments. Resting length of the gauge was 10.0 mm; when in use this length varied from 10.0 to 20.0 mm. Previous studies from this laboratory have demonstrated that within such a range, the calibration of the gauge is linear (±5% for up to 8 hours). Regional myocardial performance was assessed from measurements of segmental shortening during the ejection period. All pressures, flow, and length signals were recorded both on paper (Visicorder Model 1505, Honeywell Inc.) and magnetic tape (Model GR-2900, Consolidated Electrodynamic Corporation).

For studies of transmyocardial lactate uptake the anterior interventricular vein was cannulated with a 6.0 cm, 20 gauge, thin-walled Teflon catheter (Becton-Dickinson and Company). Regional venous flow was measured by free drainage of the cannulated vein into a graduated cylinder. Special care was taken to avoid obstruction of the vein by the catheter; intermittent heparinization was also carried out with 1000 I.U. of heparin every hour. Blood samples for calculation of lactate uptake were obtained simultaneously from the femoral artery and the anterior interventricular vein. To avoid spurious sampling, regional venous blood was withdrawn through a Y system, allowing continuous visualization of the aspirating pressure, which was not allowed to exceed 1.0 cm of water. Samples for lactate determinations were prepared immediately and analyzed in duplicate for lactate concentration by a modification of the enzymatic method of Marbach and Weil, using a semi-automated Gilford spectrophotometer (Model 300N). Regional myocardial lactate balance was expressed as \( A - V \times 100 \), where \( A \) = arterial lactate concentration and \( V \) = regional venous lactate concentration. Lactate uptake (LU), expressed in \( \mu \)g/min, was calculated as the product of the difference between arterial and venous lactate concentrations and the regional venous flow.

**Experimental Procedure**

For reduction of coronary flow a screw clamp was placed around the left anterior descending coronary artery just distal to the flowmeter. Particular care was taken that no coronary branches were present between the clamp and flowmeter. After control measurements were obtained during the preischemic period, coronary flow was reduced (ischemic period) to 40–50% of the control level. After 10 min of hemodynamic stabilization, measurements were repeated and one of the following procedures was carried out:

1) LAD coronary flow was maintained at the same reduced level for an additional 20 min (control experiments, 7 dogs).

2) Dextran was infused in two phases:
   a) LVEDP was increased from 5 to 11 mm Hg and maintained at this level for 10 min (10 dogs).
   b) LVEDP was then increased from 11 to 17 mm Hg and maintained at this level for 10 min (8 dogs).

3) Angiotensin (0.2–0.4 \( \mu \)g/kg/min) was administered to augment mean arterial pressure by approximately 30 mm Hg; arterial pressure was then maintained at this level for 20 min (7 dogs). Next, the mean arterial pressure was allowed to fall to the initial level by discontinuing the angiotensin infusion. This lower level was then maintained for 20 min (6 dogs).

**Results**

**Effects of Coronary Flow Reduction**

Reduction of LAD flow to 40 to 50% of control was associated with 5 to 10% reduction in cardiac output, stroke volume, and mean arterial pressure, as well as 10 to 20% reduction in stroke work in all dogs. In the ischemic zone the magnitude of systolic shortening also declined significantly in all three groups of dogs (tables 1 and 2). During the period before reduction of flow (pre-ischemic period), regional lactate balance was 32% in the control group, 29% in the volume-loading dogs and 30% in angiotensin-treated dogs. Lactate uptake varied from +134 to +170 \( \mu \)g/min. Following reduction of LAD flow (ischemic period), lactate extraction shifted to production. In the seven control dogs, although mechanical abnormalities persisted over a period of 30 min following reduction of flow, the magnitude of regional lactate production declined spontaneously from −200 ± 49.1 \( \mu \)g/min at 10 min after reduction of flow to −63 ± 39.2 \( \mu \)g/min at 30 min. Lactate balance also shifted to a significantly less negative value during this period.

**Effects of Volume Loading**

In 10 dogs, LVEDP was increased from an average 4.6 ± 0.5 to 10.6 ± 0.4 mm Hg by volume loading with dextran. This increase in preload was associated with a 27% increase in cardiac output and a 16% increase in mean arterial pressure (fig. 1A) with no change in systemic vascular resistance (table 1). Heart rate decreased slightly in most dogs. When LVEDP was further increased to a mean of 17.1 ± 0.5 mm Hg, however, cardiac output increased by only 5% and mean arterial pressure by 11%. To exclude the possibility that prior depression of left ventricular function was responsible for this result, volume loading was performed in 5 of the 10 dogs during the pre-ischemic period as well as the ischemic period. A comparison of the effects of volume loading upon cardiac output before and during ischemia is shown in figure 2. With an increase in LVEDP from 5 to 11 mm Hg, the increase in cardiac output was similar during both periods; however, with an increase in LVEDP from 11 to 17 mm Hg, cardiac output increased substantially (about 0.7 L/min) during the pre-ischemic period but very little (about 0.1 L/min) during the period with reduced LAD coronary flow.

During the initial phase of volume loading, LAD coronary flow increased significantly, from an average of 18.6 ± 2.2 to 27.6 ± 3.9 ml/min (table 1). Concomitantly, enddiastolic length and systolic shortening in the ischemic segment increased significantly (fig. 1B). However, regional lactate production also increased in eight of ten dogs, the mean value increasing from −110.7 ± 49.9 to −207.6 ± 32.5 \( \mu \)g/min (\( P < 0.05 \)). This value is significantly different from the finding of lactate production in the control study at the same time. Further increase in LVEDP, from 11 to 17 mm Hg, was accompanied by increasing lactate production in seven of eight dogs, the mean value increasing to
Table 1. Effects of Increasing Preload during Coronary Flow Reduction

<table>
<thead>
<tr>
<th>Increased Preload (N = 10)</th>
<th>LAD Coronary Flow Reduction - Control</th>
<th>LAD coronary stenosis (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEDP (mm Hg)</td>
<td>CO (L/min)</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
<tr>
<td>Pre-ischemic</td>
<td>110 ± 0.5</td>
<td>1.54 ± 0.08</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard error of the mean.

-320.0 ± 56.6 µg/min (P < 0.05). Left anterior descending coronary flow and the magnitude of systolic shortening did not change significantly (fig. 1B).

Effects of Angiotensin

Figure 3 illustrates the effects of coronary flow reduction and angiotensin II infusion upon systolic shortening of the ischemic segment in a typical experiment. Although angiotensin II infusion was accompanied by an increase in arterial and ventricular systolic pressures and little change in LVEDP, systolic shortening of the ischemic segment increased slightly along with an increase in LAD coronary flow.

In contrast to the effects of volume loading, in the seven dogs that were treated with angiotensin, an increase in mean arterial pressure of 32 mm Hg was associated with a 100% increase in systemic vascular resistance (table 2) but little change in LVEDP. Concomitantly, cardiac output decreased by 20% (P < 0.05) (fig. 4A) and heart rate also decreased slightly.

The increase in mean arterial pressure was also associated with increment in coronary flow from 13.1 ± 3.1 to 21.0 ± 4.4 ml/min (P < 0.05) but the magnitude of systolic shortening of the ischemic segment did not change significantly. In parallel with the increase in coronary perfusion, regional lactate production (−244.4 ± 89.0 µg/min) shifted to extraction (+32.6 ± 55.3 µg/min; P < 0.05) (fig. 4B). This change was also reflected in the lactate balance. Figure 5 shows the individual changes in lactate production during angiotensin infusion. In six dogs, when angiotensin was stopped for 20 min, the hemodynamic conditions returned to the pre-angiotensin level (table 2); during this period, lactate metabolism deteriorated slightly in all six dogs.

Discussion

This study demonstrates that in the presence of a flow-limiting coronary stenosis, left ventricular volume loading and pressure loading may have directionally opposite effects upon the performance and metabolism of both ischemic muscle and the left ventricle.

Influences of Volume Loading during Regional Myocardial Ischemia

Moderate volume loading (LVEDP 4.6 to 11 mm Hg) caused a substantial increase in cardiac output and a moderate increase in mean arterial pressure in both the control state and during regional myocardial ischemia. Further volume loading (from 11 to 17 mm Hg), however, increased cardiac output minimally in the ischemic heart as compared to a substantial increase in the nonischemic ventricle. Thus, although the initial response to volume loading is similar in the two states, the Starling function curve apparently exhibits an earlier plateau in the presence of severe ischemia. This observation is generally consistent with previous studies in patients with acute myocardial infarction that have demonstrated that although volume loading is an effective means of enhancing cardiac output, it is limited by the mass of remaining infarcted muscle.4,8 Because of differences in ventricular compliance between animals and man, specific
levels of ventricular end-diastolic pressure in these studies cannot be compared accurately.

Although the improvement in total left ventricular performance following volume loading is well documented, the influence of increases in ventricular preload upon the function and metabolism of the ischemic myocardium is relatively unknown. In this study, volume loading was associated with an augmentation in LAD coronary flow distal to the stenosis, concomitant with an increase in arterial pressure proximal to the stenosis. When LVEDP was increased to a

**TABLE 2. Effects of Increasing Afterload during LAD Coronary Flow Reduction**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Istemic</th>
<th>Stenosis 10 min</th>
<th>Angiotensin 30 min</th>
<th>Stop Angiotensin 50 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4.7 ± 0.5</td>
<td>5.3 ± 1.1</td>
<td>6.3 ± 1.2</td>
<td>4.7 ± 1.3</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>102 ± 8</td>
<td>95 ± 4</td>
<td>127 ± 3*</td>
<td>102 ± 11†</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>2.36 ± 0.33</td>
<td>2.09 ± 0.25</td>
<td>1.67 ± 0.34*</td>
<td>1.95 ± 0.35</td>
</tr>
<tr>
<td>SV (ml/beat)</td>
<td>18.7 ± 3.0</td>
<td>18.0 ± 2.2</td>
<td>15.9 ± 3.2</td>
<td>16.6 ± 2.5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>132 ± 10</td>
<td>128 ± 12</td>
<td>121 ± 12*</td>
<td>128 ± 14</td>
</tr>
<tr>
<td>SW (g/m/beat)</td>
<td>24.2 ± 4.2</td>
<td>21.6 ± 3.5</td>
<td>26.2 ± 5.8</td>
<td>22.6 ± 4.3</td>
</tr>
<tr>
<td>TPR (µ)</td>
<td>49.0 ± 6.7</td>
<td>47.4 ± 6.4</td>
<td>53.2 ± 20.3*</td>
<td>57.8 ± 7.6</td>
</tr>
<tr>
<td>LAD Flow (ml/min)</td>
<td>34.1 ± 5.6</td>
<td>13.1 ± 3.1†</td>
<td>21.0 ± 4.4*</td>
<td>14.4 ± 3.6†</td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>12.5 ± 0.6</td>
<td>12.9 ± 0.5</td>
<td>13.2 ± 0.6</td>
<td>13.3 ± 1.0</td>
</tr>
<tr>
<td>SS (mm)</td>
<td>1.99 ± 0.26</td>
<td>1.55 ± 0.33†</td>
<td>1.82 ± 0.32</td>
<td>1.76 ± 0.14</td>
</tr>
<tr>
<td>LAC Bal (%a)</td>
<td>30.1 ± 5.4</td>
<td>-72.8 ± 19.2‡</td>
<td>5.1 ± 12.4*</td>
<td>-12.5 ± 20.0</td>
</tr>
<tr>
<td>RVF (ml/min)</td>
<td>3.1 ± 0.4</td>
<td>2.7 ± 0.7</td>
<td>3.3 ± 0.6</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>LU (µg/min)</td>
<td>134.0 ± 29.7</td>
<td>-244.4 ± 89.0†</td>
<td>+32.6 ± 55.3*</td>
<td>-49.5 ± 70.8†</td>
</tr>
</tbody>
</table>

N = 7
Values are given as mean ± standard error of the mean.
*P < 0.05, compared to 10 min stenosis value.
†P < 0.05, compared to pre-ischemic.
‡P < 0.05, compared to angiotensin-treated.
Abbreviations: see table 1.

**Figure 1.** A) Hemodynamic response to ventricular volume loading during coronary stenosis in 10 dogs. Points are plotted at control, 10, 20, and 30 min after coronary stenosis. Abbreviations: CO = cardiac output; AP = mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; M = mean values; (N) = number of dogs for last point. *P < 0.05 compared to 10' stenosis value. (8) = number of dogs for last point. B) Functional and metabolic response of regional ischemic myocardium to ventricular volume loading during coronary stenosis in 10 dogs. Points are plotted at control, 10, 20, and 30 min after coronary stenosis. Abbreviations: SS = systolic shortening of ischemic segment; M = mean values; (N) = number of dogs for last point. *P < 0.05 compared to 10' stenosis value. (8) = number of dogs for last point.
mean of 11 mm Hg, systolic shortening in the ischemic segment also increased substantially, suggesting that the ischemic muscle responded according to the Starling mechanism. Even though coronary flow increased substantially, however, regional lactate production also increased, indicating aggravation of ischemia. When LVEDP was further increased from 11 to 17 mm Hg, an additional increase in lactate production was observed, but this occurred without an increase in regional function. The absence of mechanical response may have been responsible for the con-

comitant abnormally small increment in total cardiac output.

These results indicate two apparent paradoxes: an increase in lactate production despite increased regional flow and an improvement in function despite increased lactate production. The increase in lactate production may be explained by an increase in oxygen demand, secondary to increased wall tension, which exceeded the increase in oxygen supply, secondary to increased perfusion pressure. Improved function despite increased ischemia has been
observed to occur with inotropic agents as well as volume loading. Since our measurement of function represented only epicardial performance, whereas lactate balance represented blood from both epicardium and endocardium, it is possible that altered distribution of flow to endocardium and epicardium may also have occurred with volume loading.

Influences of Pressure Loading during Regional Myocardial Ischemia

A primary increase in afterload, as opposed to volume loading, reduced cardiac output and stroke volume but improved regional lactate metabolism without a change in regional function. The effects of increasing afterload upon total left ventricular performance found in this study are consistent with previous studies in the normal canine heart, and in the ischemic canine heart in ischemia and in clinical heart failure. The regional metabolic findings are consistent with the results of other investigators, who found a reduction of ischemic injury by the ST-segment mapping technique when arterial pressure was increased in dogs with coronary occlusion but without left ventricular failure. In contrast, the observed absence of effect on regional myocardial function differs from the results of others who have found that an increase in afterload in the presence of mild regional ischemia results in decreased regional systolic shortening. The mechanisms responsible for the alleviation in ischemia following afterloading are probably related to alterations in the determinants of oxygen supply and demand. Since ischemia was induced by means of a coronary stenosis rather than coronary occlusion, an increase in aortic pressure increased LAD coronary flow distal to the stenosis, thus increasing oxygen supply directly to the ischemic zone. Further increase in blood supply may also have occurred through collateral vessels from the circumflex to the distal LAD, as suggested by previous studies, demonstrating that in the presence of ischemia coronary collateral flow is dependent upon coronary perfusion pressure. Thus, although myocardial oxygen demand may have increased with increasing afterload, the increase in oxygen supply to the ischemic region was sufficient to improve the regional balance between supply and demand of oxygen. This hypothesis is consistent with previous observations that elevation of arterial pressure can increase coronary flow proportionately more than myocardial oxygen consumption.

The extent to which our findings are applicable to man is yet undefined. Coronary stenosis is fairly common in clinical myocardial infarction and in this respect, the experimental preparation is clinically relevant. However, since human coronary atherosclerosis usually involves more than one coronary artery, blood flow may be reduced in several different regions of myocardium simultaneously while in the experimental dog reduction of blood flow probably occurs only in the specific region of myocardium under study. In addition, the collateral vasculature is extensively developed in the dog but may be poorly developed in patients. Nevertheless, this study indicates that volume loading in the presence of coronary stenosis may increase cardiac output and regional ischemic function but at the expense of an aggravation of ischemia. In contrast, an increase in arterial pressure with no change in preload reduces ischemic injury, but at the expense of a decrease in cardiac output.

Acknowledgment

The authors are grateful for the technical assistance of Mark Chag, Gary Toten, Tanya Genov, Willie Davis, Lance LaForteza and the editorial assistance of Betty Garrigues and Deborah Austin.

References

10. Forrester JS, Tyberg JV, Wyatt HL, Goldner S, Parmley WW, Swan...
Variability in the Analysis of Coronary Arteriograms

TIMOTHY A. DE ROUEN, PH.D., JOHN A. MURRAY, M.D., AND WILLIAM OWEN, A.B.

SUMMARY Variability in coronary arteriogram readings was studied by having cine films from ten patients read by eleven readers. Three of the eleven subsequently met as an expert panel to provide a joint evaluation which could serve as a standard. Considerable variability was found between individual readers and between readers and the panel. The average standard deviation for estimation of any segmental stenosis by any single reader was 18%. Disagreement about

THE PROGNOSIS OF PATIENTS with atherosclerotic heart disease managed medically or surgically is markedly influenced by the extent of coronary artery disease and left ventricular dysfunction.1-3 These factors are two among several assessed in patients enrolled in the Seattle Heart Watch, a community based project which is attempting to assess quantitatively the predictors of sudden cardiac death and myocardial infarction in patients studied within the community.

Since cardiac catheterization was performed and qualitative analysis was done by cooperating physicians in five participating Seattle hospitals (Providence, Swedish, University, Virginia Mason, and Veterans), it was necessary to assess the variability arising from reading coronary and ventricular angiograms in the different institutions.

This report presents the analysis of variability within a panel of eleven readers who read studies from ten patients. Sources of variability are reviewed and remedies proposed.

Materials and Methods

Cine films from ten patients examined at a single site, University Hospital, were selected. Filming was made in multiple views in the coronal plane, with efforts made to provide views at 90° angles to one another. No hemiational views were taken. A stratified random sampling scheme was used to ensure selection of a representative spectrum of coronary disease groups, as categorized by the number of major vessels with at least 70% stenosis and by normal or abnormal left ventricular function. Only films estimated to be of adequate technical quality were eligible for this study.

Eleven physicians, representing the Seattle Heart Watch cooperating facilities, individually reviewed these ten films in a pre-assigned random order and completed the standard Heart Watch arteriography forms. Three of the eleven subsequently met to resolve differences of opinion and provide a joint reading which could serve as a standard from an “expert panel.”

Raw observations collected were: the estimated amount of stenosis (percent narrowing in the diameters) of each of the ten vessel segments, the presence or absence of collaterals, the degree of left ventricular contraction according to a qualitative five-division grading, as well as a film quality rating, and an overall assessment of the presence of coronary artery disease.

The statistical approach taken for all entirely numerical variables was to use the standard deviation of the responses as a measure of the amount of variability and thus of the amount of agreement. When considering the amount of agreement on variables that were at least partially nominal in nature, standard deviations were not always applicable. For example, each reader was asked to estimate the amount of narrowing (to the nearest 10%) in the diameters of each of the ten vessel segments from each patient. However, when the vessel segment was not sufficiently visible to allow an assess-
Contrasting influences of alterations in ventricular preload and afterload upon systemic hemodynamics, function, and metabolism of ischemic myocardium.

H L Wyatt, P L Da Luz, D D Waters, H J Swan and J S Forrester

Circulation. 1977;55:318-324
doi: 10.1161/01.CIR.55.2.318

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/55/2/318