Catecholamines in Coronary Sinus and Peripheral Plasma During Pacing-Induced Angina in Man


SUMMARY We measured aortic and coronary sinus dopamine (DA), epinephrine (E), and norepinephrine (NE) in eight patients with cardiac ischemia (I) and eight control subjects (C). Samples were taken at rest (73 ± 3 beats/min in C and 68 ± 3 beats/min in I) and during coronary sinus pacing to peak rates (144 ± 4 beats/min in C and 136 ± 6 beats/min in I). Arterial NE was higher in the ischemic patients at rest (254 ± 25 pg/ml in C and 324 ± 21 in I; p < 0.05). There were no differences in arterial E and DA. Neither pacing nor angina affected peripheral catecholamine concentrations. Resting myocardial NE flux was similar for both groups. With pacing, coronary sinus flux and net myocardial NE release increased significantly in both groups. The maximum relative increase in net myocardial NE release was less in the ischemic patients than in the controls (575 ± 145% in C and 255 ± 40% in I; p < 0.05). Thus, angina induced by pacing does not augment peripheral sympathetic activity. Furthermore, pacing-induced angina appears to be associated with a decrease in cardiac sympathetic tone compared with that found in paced controls.

AN INCREASE IN sympathetic activity has been postulated to be a significant determinant for some of the pathophysiological events associated with angina pectoris. With a compromise in regional myocardial blood flow, an increase in circulating catecholamines, by increasing myocardial oxygen consumption, would be expected to have deleterious effects on the jeopardized myocardium. Though an increase in peripheral plasma catecholamine concentration has been well-documented as a result of acute myocardial infarction,14 the plasma catecholamine response to angina is not clear.

The classic studies cited to support an association between an increase in circulating catecholamines and angina pectoris are those of Raab6 and Gazes.6 These studies, performed a generation ago, used techniques to measure plasma catecholamines which are now known to be imprecise. Raab could not differentiate between "cortical sterols" and "adrenalin," and the resting levels of plasma catecholamines reported by Gazes were greater than those now known to be valid. These early investigators based their conclusions on an increase in plasma catecholamines during exercise.
in their patients with angina. Their results are in contrast to those of Battock,7 who used a trihydroxyindole fluorometric technique and reported that plasma norepinephrine levels in patients suffering from exercise-induced angina did not differ from those observed in control patients exercised to the same pressure-rate index. Also, the former investigators failed to observe an increase in plasma catecholamines during exercise in their control patients, while modern radiometric techniques support a direct relationship between the level of exercise and circulating catecholamine concentration.8, 9

We have recently developed a precise, sensitive radiometric assay for the simultaneous measurement of norepinephrine, epinephrine and dopamine in small aliquots of plasma.10 This technique has permitted us to study both the myocardial and peripheral catecholamine response to the development of angina pectoris in man. Angina was induced by rapid right atrial (coronary sinus) pacing rather than by exercise to avoid obscuring any angina-induced catecholamine response that might be induced by exercise.

**Methods**

Sixteen patients undergoing cardiac catheterization for the investigation of chest pain were studied. No patient received propranolol or digitalis for 72 hours before the study. Patients fasted for 16 hours and were given 10 mg of intramuscular diazepam before catheterization; patients did not receive atropine. The biochemical studies were performed before left ventriculography and selective coronary arteriography by the Judkins technique. Informed consent was obtained from all patients. The protocol was approved by the human experimentation committee at the University of Toronto.

**Experimental Procedure**

A #7F coronary sinus thermodilution pacing catheter (Wilton Webster Laboratories, Altadena, California) was inserted, by cutdown, into a left antecubital vein, advanced to the right atrium and then passed into the mid-coronary sinus. Right and left heart catheterization was performed by percutaneous techniques from the right groin. The arterial catheter was left in the descending aorta; the right heart catheter, a Swan-Ganz thermodilution cardiac output catheter, was positioned in the main pulmonary artery.

The full protocol and sample code is illustrated in figure 1. After an undisturbed 10-minute period, coronary sinus flow measurements and arterial and coronary sinus blood samples for catecholamines, lactate and oxygen content were obtained in duplicate. Arterial pressure and cardiac output were measured. Coronary sinus pacing was then started at 100 beats/min and increased at 10 beats/min each minute to 120 beats/min. Data were collected at this heart rate, which took approximately 5 minutes. The pacing rate was then increased at 15 beats/min each minute to the fastest rate that atrioventricular conduction would permit or to a maximum heart rate of 150 beats/min. Pacing was maintained at this rate for 5 minutes for data collection. Pacing was then abruptly terminated and blood sampling repeated at 1 minute. If angina appeared during incremental pacing, data collection was immediately performed and pacing was then terminated without a further increase in pacing rate. An ECG lead V5 was recorded before, during, and immediately after the termination of pacing. Fluoroscopy was performed intermittently during pacing to ensure that the position of the coronary sinus catheter remained constant.

**Patient Groups**

The control group included eight patients (seven males and one female; mean age 52.1 years, range 49–56 years). The patients had atypical chest pain, a negative exercise ECG, normal coronary arteriograms and a normal left ventricular angiogram. They also had no evidence of valvular or congenital heart disease. Patients who were hypertensive (blood pressure ≥ 150/100 mm Hg) or who had previous heart surgery were excluded. They had a normal response to rapid atrial pacing — that is, no induced chest pain, ECG changes or myocardial lactate production. In three of these patients subsequent studies documented an esophageal etiology to their chest pain; the remaining five are undiagnosed. The ischemic group consisted of eight patients (seven male and one female); mean age 57.1 years, range 42–68 years. These patients all had significant stenosis of the left anterior descending coronary artery.
(50% in one and 75–90% in the others); six of these eight patients also had significant right and/or circumflex disease. All experienced angina with pacing and had objective evidence of anterior left ventricular wall ischemia, either reversible horizontal ST-segment depression ≥ 1 mm in V_{3} (seven of eight patients) and/or lactate production (four of eight patients). In five patients, ischemia appeared at pacing rates between 120–135 and in three, at rates between 135–150. No patient had ECG evidence of prior anterior wall infarction.

Coronary sinus blood flow (CSBF) was measured by the thermodilution technique. Normal saline solution at room temperature was injected into the coronary sinus using a Harvard pump at a rate of 38.2 ml/min for 30–40 seconds. CSBF was calculated using the following formula:

\[ \text{CSBF} = F_{1} \left( \frac{T_{b} - T_{i}}{T_{b} - T_{m}} - 1 \right) \times 1.08 \]

where \( F_{1} \) is the volume of normal saline injected (ml/min), \( T_{b} \), \( T_{i} \) and \( T_{m} \) are temperatures of blood, injectate and mixture of blood and injectate (°C) and 1.08 is a constant derived from the density and specific heat of the saline solution and blood.

The mean of the differences between the two resting measurements of CSBF in our patients was 3.6 ± 2.6%. Duplicate measurements for CSBF were obtained at peak pacing in 13 of 16 patients; the reproducibility of these results was 6.2 ± 1.6%.

**Biochemical Techniques**

Plasma norepinephrine, epinephrine and dopamine were assayed radioenzymatically as described by Sole and Hussain. Catechol-O-Methyl transferase (COMT) preparations may vary with each new preparation of COMT enzyme stock; therefore, we found it necessary to determine the optimum amount of enzyme and the corresponding amount of benzylxoyamine to include in the incubation medium. Either too little or too much of the latter caused the dopamine counts to soar.

Lactate was determined in blood filtrates.

Data are given as mean ± SEM. The statistical significance of differences between groups was determined by the Student's t test.

**Results**

The values for the concentrations of arterial and coronary sinus norepinephrine, coronary sinus flow and net myocardial norepinephrine flux for individual patients at rest and peak pacing (angina) are presented in table 1.

The grouped hemodynamic and metabolic data for the entire protocol are summarized in table 2. There were no differences in coronary sinus flow or myocardial oxygen consumption between the two groups. Systemic vascular resistance was greater and cardiac index less in the ischemic patients.

There were no differences in plasma dopamine and epinephrine either between the patient groups or between basal and pacing states in individual patients. The heart neither extracted nor produced either of these two catecholamines at rest or with pacing in any of the patients. Arterial norepinephrine concentrations were higher in the ischemic patients at all stages in the protocol; however, there was no change in arterial norepinephrine with pacing. Resting myocardial norepinephrine flux was similar for both groups of patients. With pacing, coronary sinus flow and the flux of norepinephrine across the myocardium increased significantly in both groups. A comparison of absolute values for net myocardial norepinephrine release between patients may be misleading for these data are directly related to the position of the coronary sinus catheter in each patient. A more valid comparison is the increase in norepinephrine flux during pacing (angina) relative to that at rest for each individual (table 1, fig. 2). The maximum increase in transmyocardial norepinephrine flux was significantly less in the ischemic patients compared with their controls. With the cessation of pacing,
norepinephrine flux promptly returned to resting levels in both groups.

Discussion

It is generally believed that myocardial ischemia produces an augmentation of sympathetic activity not only in the heart, but also systemically. Our findings do not substantiate, and may actually contradict, this belief.

Our values for the resting catecholamine concentration of peripheral plasma correspond closely to basal values reported by others. Arterial norepinephrine (but not epinephrine or dopamine) slightly but significantly increased in the ischemic group; this may be associated with the increase in systemic vascular resistance also found in these patients. A similar increase in 24-hour urinary catecholamine excretion in patients with coronary artery disease has been reported. We found no further increase in catecholamine concentration in the peripheral plasma during angina. The failure of plasma catecholamines to increase in response to the stress of the obvious discomfort felt by our patients during pacing-induced angina was surprising, since pain is a stimulus for sympathetic activation and catecholamine release. In a recent study, however, the urinary catecholamine excretion in patients suffering from acute myocardial ischemic pain was not different from control subjects, while excretion was significantly increased in

### Table 1. Norepinephrine Concentrations and Coronary Sinus Flows In Individual Patients at Rest and During Peak Pacing (Angina)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Protocol stage</th>
<th>NE Concentration (pg/ml)</th>
<th>Coronary sinus flow (ml/min)</th>
<th>Net myocardial NE release (flux) (pg/min)</th>
<th>% Basal flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>BN Basal</td>
<td>4</td>
<td>386 329 154</td>
<td>138 5374</td>
<td>275</td>
<td></td>
</tr>
<tr>
<td>RN Basal</td>
<td>4</td>
<td>334 298 150</td>
<td>153 2976</td>
<td>671</td>
<td></td>
</tr>
<tr>
<td>CE Basal</td>
<td>4</td>
<td>245 191 179</td>
<td>106 3475</td>
<td>464</td>
<td></td>
</tr>
<tr>
<td>KG Basal</td>
<td>4</td>
<td>374 352 22</td>
<td>96 1274</td>
<td>1,457</td>
<td></td>
</tr>
<tr>
<td>ZA Basal</td>
<td>4</td>
<td>262 168 87</td>
<td>82 4415</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>BN Basal</td>
<td>4</td>
<td>227 187 40</td>
<td>102 2436</td>
<td>822</td>
<td></td>
</tr>
<tr>
<td>SS Basal</td>
<td>4</td>
<td>298 227 71</td>
<td>71 3112</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>RP Basal</td>
<td>4</td>
<td>315 288 27</td>
<td>184 2916</td>
<td>356</td>
<td></td>
</tr>
<tr>
<td>EN Basal</td>
<td>4</td>
<td>326 290 36</td>
<td>152 3505</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td>PW Basal</td>
<td>4</td>
<td>393 351 42</td>
<td>309 8300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JN Basal</td>
<td>4</td>
<td>394 355 39</td>
<td>160 3484</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BN Basal</td>
<td>4</td>
<td>451 226 225</td>
<td>165 20765</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EL Basal</td>
<td>4</td>
<td>516 392 124</td>
<td>130 6276</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT Basal</td>
<td>4</td>
<td>444 321 123</td>
<td>120 7957</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HN Basal</td>
<td>4</td>
<td>474 305 169</td>
<td>225 20534</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SN Basal</td>
<td>4</td>
<td>494 342 92</td>
<td>102 5625</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Myocardial norepinephrine flux (pg/min) = [(CS-Ao)NE] x [CS Flow] x [1-hematocrit]. In the ischemic patients, protocol stage 4 represented angina. Abbreviations: NE = norepinephrine; CS = coronary sinus; Ao = arterial. 


TABLE 2. Hemodynamic and Metabolic Data During Pacing Protocol

<table>
<thead>
<tr>
<th>Protocol stage</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac index (l/min/m²)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Systemic vascular resistance (resistance units)</th>
<th>Coronary sinus flow (ml/min)</th>
<th>Myocardial oxygen consumption (ml/min)</th>
<th>Arterial catecholamine concentration (pg/ml)</th>
<th>Net myocardial NE release (pg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>73 ± 3</td>
<td>3.0 ± 1</td>
<td>95 ± 4</td>
<td>17 ± 0.9</td>
<td>116 ± 4</td>
<td>1580 ± 1</td>
<td>51 ± 5</td>
<td>96 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>120 ± 1</td>
<td>3.2 ± 1</td>
<td>103 ± 4</td>
<td>17 ± 1</td>
<td>164 ± 6</td>
<td>267 ± 10</td>
<td>55 ± 6</td>
<td>92 ± 10</td>
</tr>
<tr>
<td>4</td>
<td>144 ± 4</td>
<td>3.1 ± 1</td>
<td>104 ± 4</td>
<td>18 ± 1</td>
<td>191 ± 20</td>
<td>2398 ± 13</td>
<td>57 ± 5</td>
<td>98 ± 12</td>
</tr>
<tr>
<td>5</td>
<td>142 ± 6</td>
<td></td>
<td></td>
<td></td>
<td>187 ± 18</td>
<td>267 ± 14</td>
<td>59 ± 13</td>
<td>93 ± 16</td>
</tr>
<tr>
<td>6</td>
<td>70 ± 4</td>
<td></td>
<td></td>
<td></td>
<td>107 ± 13</td>
<td>93 ± 16</td>
<td>62 ± 16</td>
<td>93 ± 16</td>
</tr>
<tr>
<td>Ischemic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>68 ± 3</td>
<td>2.6 ± 0.1†</td>
<td>97 ± 3</td>
<td>20 ± 0.9†</td>
<td>110 ± 12</td>
<td>1498 ± 18</td>
<td>53 ± 12</td>
<td>94 ± 11</td>
</tr>
<tr>
<td>3</td>
<td>117 ± 4</td>
<td>2.7 ± 0.1†</td>
<td>104 ± 3</td>
<td>20 ± 1</td>
<td>150 ± 22</td>
<td>233 ± 22</td>
<td>52 ± 12</td>
<td>91 ± 12</td>
</tr>
<tr>
<td>Angina</td>
<td>136 ± 6</td>
<td>2.6 ± 0.2†</td>
<td>108 ± 4</td>
<td>23 ± 2†</td>
<td>180 ± 23</td>
<td>395 ± 22</td>
<td>54 ± 22</td>
<td>83 ± 22</td>
</tr>
<tr>
<td>4</td>
<td>140 ± 7</td>
<td>2.6 ± 0.2†</td>
<td>108 ± 4</td>
<td>23 ± 2†</td>
<td>196 ± 40</td>
<td>305 ± 22</td>
<td>66 ± 16</td>
<td>93 ± 14</td>
</tr>
<tr>
<td>5*</td>
<td>140 ± 7</td>
<td>2.6 ± 0.2†</td>
<td>108 ± 4</td>
<td>23 ± 2†</td>
<td>196 ± 40</td>
<td>305 ± 22</td>
<td>66 ± 16</td>
<td>93 ± 14</td>
</tr>
<tr>
<td>6</td>
<td>67 ± 4</td>
<td></td>
<td></td>
<td></td>
<td>125 ± 16</td>
<td>101 ± 14</td>
<td>54 ± 14</td>
<td>101 ± 14</td>
</tr>
</tbody>
</table>
| *Excludes three patients whose angina necessitated termination of pacing before the second set of angina samples could be collected.
†Diffs from control at P <0.05.
‡Diffs from control at P <0.01.
§Diffs from basal at P <0.05.
¶Diffs from basal at P <0.001.
Abbreviations: DA = dopamine; E = epinephrine; NE = norepinephrine.

those with actual myocardial infarction. An absence of an increase in both plasma norepinephrine and heart rate during dental pain also has been described and is attributed to overriding parasympathetic influences.17 Pain did induce an increase in plasma epinephrine in this latter study.

Both resting (and post-pacing) myocardial oxygen consumption and coronary sinus flow were similar in the two groups (table 2), supporting a corresponding group similarity in coronary sinus catheter position and in the amount of myocardium sampled. This similarity allowed comparison of the absolute catecholamine flux across the heart in the two groups, in addition to an examination of the relative changes between resting and pacing states in each individual. We found no increase in net myocardial norepinephrine release that could be attributed to angina; indeed, in the ischemic patients a relative decrease compared with control patients paced to the same rate was noted (fig. 2). The concentration of norepinephrine either in peripheral or coronary sinus plasma appears to serve as a reasonable index of sympathetic tone.18-20 However, before it can be concluded that pacing-induced angina may be associated with a relative decrease in cardiac sympathetic activity, other possible explanations for these findings should be considered.

The net overflow of norepinephrine into the circulation represents a balance between norepinephrine release and re-uptake or metabolism. We speculated that our observations could be due to an increase in norepinephrine re-uptake or metabolism rather than a decrease in release by the sympathetic nerve terminals of the heart. Inactivation of released norepinephrine in the heart occurs largely by re-uptake into the sympathetic nerve endings rather than metabolism.21-22 The conditions thought to exist in the ischemic zone (a decrease in oxygen availability, pH and ATP and an increase in extracellular potassium) act to inhibit rather than enhance norepinephrine re-uptake by the nerve endings.23-24 Furthermore, ischemic conditions would be unfavorable to monoamine oxidation.

We also considered the possibility that we failed to capture catecholamines produced in the ischemic area because of incorrect positioning of the coronary sinus catheter. However, we were careful to choose patients expected to manifest ischemia in a myocardial region.
which drained into the upper half of the coronary sinus. We had no difficulty in identifying alterations in lactate metabolism during angina, verifying our ability to obtain samples appropriate to the ischemic zones.

Finally, we considered a failure to capture a late washout of norepinephrine because of a reduced perfusion in the ischemic region. In five of eight ischemic patients, we obtained two pairs of plasma samples during pain; we also sampled all patients 1 minute post-pacing and post-pain to ensure capture of any washout. Figure 2 indicates that the second estimation of myocardial catecholamine flux at peak pacing rate showed no increase over the first in the control group; rather, the pattern suggests a fall. Similar results were obtained for the ischemic patients in whom two pairs of samples were collected during pain. Prolonged stimulation of cardiac sympathetic nerves in dogs also has been shown to result in an early peak followed by a reduction in norepinephrine overflow into the coronary venous effluent, suggesting a time-dependent loss of releasable norepinephrine stores.20

Thus, it appears that myocardial norepinephrine release in pacing-induced angina is not stimulated beyond that normally encountered during pacing; in some cases, relatively less augmented release may be observed. These results may reflect a permanent reduction of norepinephrine stores in ischemic myocardium in spite of our selection of patients with apparently normal function of the anterior left ventricular wall. It also appears reasonable to postulate an actual neural basis for our observations.

An increase in sympathetic nervous activity appears to accompany acute myocardial infarction in man.1-4 In these studies, however, the observations were made several hours after the insult, when secondary responses such as the baroreceptor reflex may have a dominant role.25 The early stages of myocardial ischemia and infarction have been examined in a variety of animal models. These paradigms suggest that cardio-cardiac reflex alterations in autonomic nerve traffic play an important role in the pathophysiology of myocardial ischemia.25-31 Afferent signals appear to arise in mechanoro- and/or chemoreceptors in the affected myocardium and travel through vagal fibers and sympathetic afferents to the central nervous system. Some of these afferent signals may be inhibitory, resulting in a reduction in efferent cardiac sympathetic tone.25-28 Perhaps a similar mechanism mediates the norepinephrine response to pacing-induced angina.

The interplay between efferent and afferent autonomic nerve traffic in the regulation of the cardiovascular system is complex. The level of cardiovascular efferent sympathetic tone during angina probably depends on associated circumstances. Stimulation of motor nerves,29, 30 or of the central nervous system34 modeling the neural events thought to be associated with exercise, has been shown to overcome the inhibition of cardiac sympathetic afferents mediated by other afferent pathways. Such factors may mask an attenuation of sympathetic tone by ischemia-induced cardio-cardiac reflexes when angina is induced by exercise. It is also possible that some cases of spontaneous angina35, 36 are precipitated by an increase in cardiac sympathetic tone.

In this study we have shown that angina induced by pacing does not augment peripheral sympathetic activity. Furthermore, pacing-induced angina may actually be associated with a decrease in cardiac sympathetic tone compared with that found in paced controls.

Acknowledgments
We thank Dr. Errol B. Marliess for the measurement of blood lactate and Dorothy Train, Molly Baine, Carol Szarga and Vicki Theman for nursing and technical help.

References
17. Taggart P, Hedworth-Whitty R, Carruthers M, Gordon PD:
Myocardial Release of Lactate, Inosine and Hypoxanthine During Atrial Pacing and Exercise-Induced Angina

GUNThER KUGLER, M.D.

SUMMARY The coronary venous efflux of lactate, inosine and hypoxanthine during pacing-induced angina has been compared with myocardial extraction of the catabolites during exercise-induced angina. Inosine and hypoxanthine were analyzed by enzyme assay after separation by column chromatography.

Myocardial lactate extraction at rest (15 ± 9%, mean ± SD) was converted to production levels (−34 ± 26%) during pacing-induced angina (p < 0.0005) and increased (24 ± 13%) during exercise (p < 0.005). The arterial values at rest (850 ± 330 μmol/l) were unchanged during pacing and increased fivefold during exercise (4380 ± 1860 μmol/l). The mean myocardial inosine extraction at rest (33 ± 10%) was transformed to release values (−41 ± 30%) during pacing (p < 0.0005) as well as during exercise (−20 ± 27%) (p < 0.0005). The hypoxanthine extraction at rest (25 ± 11%) decreased during pacing (−7.8 ± 29%) (p < 0.0025) and exercise (10 ± 25%) (NS). The slight increase of arterial inosine and hypoxanthine values was not significant.

Myocardially produced lactate, a sensitive marker of pacing-induced ischemia, was obscured by elevated arterial concentrations during exercise. However, inosine significantly correlated with lactate during pacing, and was useful in detecting ischemic myocardial energy deficiency during exercise-induced angina.

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Received February 23, 1978; revision accepted August 30, 1978.

MYOCARDIAL ISCHEMIA leads to anaerobic glycolysis with lactate release from the myocardium, in contrast to lactate utilization by the normally oxygenated heart.1-10 Lactate production, reported very frequently during pacing-induced angina, cannot be demonstrated during exercise-induced angina, since metabolic evidence of ischemia is obscured by elevated arterial lactate concentrations.11, 12 In relationship to anaerobic glycolysis, a decrease of myocardial tissue content of high-energy phosphates, ATP and CP, has been demonstrated.13, 14 An increase in myocardial tissue content15-17, 19 and a coronary venous release of the diffusible ATP catabolites adenosine, inosine and hypoxanthine, have been shown19, 20, 22, 23 in animals after temporary coronary occlusion.
Catecholamines in coronary sinus and peripheral plasma during pacing-induced angina in man.
L Schwartz, M J Sole, E F Vaughan-Neil and N M Hussain

Circulation. 1979;59:37-43
doi: 10.1161/01.CIR.59.1.37

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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