The immediate effects of iohexol on coronary blood flow and myocardial function in vivo

Harold Z. Friedman, M.D., Scott F. DeBoe, B.S., Mark J. McGillem, B.S., and G. B. John Mancini, M.D., F.R.C.P.(C)

ABSTRACT Radiographic techniques used to quantify coronary blood flow all require bolus injection of contrast material, which markedly alters the flow being measured. Newer nonionic contrast agents have been shown to have fewer adverse hemodynamic, inotropic, and rheologic effects compared with ionic media and it has been suggested that they might not substantially affect coronary blood flow. Six dogs were instrumented with electromagnetic flow probes and subendocardial ultrasonic crystals. Intracoronary injections of iohexol (300 mg/ml iodine) were administered to establish a relationship between the dose and rate of contrast injection and the effect on flow and regional myocardial function. Two and 4 ml volumes of iohexol were injected at 3 ml/sec; 4 ml volumes were administered at 1 and 4 ml/sec. The 2 and 4 ml volumes decreased coronary flow by a mean of 31% (p < .01) and 77% (p < .001). The 4 ml injection at 1 and 4 ml/sec decreased coronary flow by a mean of 77% (p < .001) and 69% (p < .001). The magnitude of the fall in flow was directly related to the dose, and the rate at which the flow nadir was attained was directly related to the rate of injection. Decrements in fractional shortening were temporally delayed by several beats compared with the flow changes and showed mean decrements of 19% to 29%. The effects on regional myocardial function were independent of contrast volume. However, the degree of dysfunction was more profound with slower infusion rates, suggesting that prolongation of contrast-induced ischemia was a major modulating factor. These precipitous changes in blood flow and regional myocardial function produced even by nonionic agents in this canine preparation may be important to consider in the clinical application of functional cardiac imaging. Meticulous attention to flow rates and contrast dosage are required to maintain predictable, systematic effects of contrast on parametric coronary digital images.

Circulation 74, No. 6, 1416-1423, 1986

Radiographic techniques that quantify coronary blood flow are now used in patients with cardiac diseases. These techniques measure the appearance, transit, and washout times of contrast material by digital subtraction, videodensitometry, and other computer processing algorithms. However, all of these methods require intracoronary bolus injections of contrast material, which can result in dramatic fluctuations in coronary blood flow itself. In particular, it is the immediate decrease in coronary flow after injection that is most relevant because the time-sequenced radiographic images necessary for analysis are acquired within the first 10 sec. Despite its importance, the immediate reduction in coronary flow has only recently been carefully measured in one study using the ionic agent sodium meglumine diatrizoate (Renograin).

Nonionic contrast agents now in clinical use were formulated to improve patient safety and have been shown to reduce negative hemodynamic and electrophysiologic effects related to the ionic media. Furthermore, investigations of the rheologic effects of different contrast media have demonstrated that the nonionic agents, especially iohexol, have relatively little influence on erythrocyte morphology and blood fluidity in vitro. This suggests the possibility of different or fewer fluctuations in coronary blood flow immediately after intracoronary bolus injection of iohexol and suggests that such agents may be preferable for quantitative coronary flow studies. Therefore the purpose of this study was to determine the
Methods

Trials were performed with an electromagnetic flowmeter to exclude possible causes of artifactual blood flow measurements. Studies included the injection of normal saline, 5% dextrose in water, heparinized arterial blood, and nonionic and ionic contrast media through a No. 3F Rentrop catheter (USCI, Billerica, MA) encircled by a grounded electromagnetic flow probe (Carolina Medical, King, NC) immersed in a normal saline bath and attached to a flowmeter (Carolina Medical, Model FM 501). Baseline flow measurements were then performed on coronary arteries in vivo, before and after intraarterial insertion of the No. 3F catheter through an extravascular flow probe. Intracoronary infusions with saline, 5% dextrose in water, and arterial blood were made with the catheter tip distal to the flow probe at the rates and volumes selected for study of contrast injections. To further corroborate that blood flow changes induced by contrast media were not artifactual, regional function measurements were recorded during all injections in the canine preparation.

Seven mongrel dogs (mean weight 29.8 kg, range 24.5 to 34 kg) were anesthetized with 35 mg/kg intravenous pentobarbital and ventilated with room air (15 ml/kg) by a Harvard respirator. A left carotid arteriotomy and internal jugular venotomy were performed and sheaths were inserted for vascular access. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. The proximal left anterior descending and circumflex coronary artery was dissected free and carefully encircled with both an electromagnetic flow probe of appropriate size and a distal ligature. The flow probe was calibrated by previous timed collections of blood, in vivo, with differing hematocrits to establish a probe factor–hematocrit relationship. Probe sensitivity was then set according to the hematocrit of each animal. Accuracy of the zero flow measurements was determined between injections during brief coronary occlusion. A No. 5F micromanometer (Millar Instruments, Houston) was inserted in the left ventricle via an apical stab wound. Subendocardial ultrasonic crystals were placed within the myocardial perfusion bed of interest in the midequatorial plane and parallel to the midmyocardial fibers. The crystals were connected to a sonomicrometer (Triton Technology, San Diego, Model 120). Correct subendocardial position was confirmed by oscilloscopic display (Tektronix, Model 2213A, Beaverton, OR) of the crystal signals, by documenting prompt dyskinesis during brief coronary artery occlusion, and by postmortem dissection.

Three thousand units of heparin were administered intravenously, and cannulation of the left main coronary artery, under fluoroscopic guidance, was performed with a No. 7F Amplatz or Multipurpose catheter (USCI) from the carotid approach. Intracoronary injections with minimal amounts of contrast were made to identify the coronary anatomy. A 0.018 gauge angioplasty guidewire was advanced through the catheter and into the designated artery. A No. 3F Rentrop catheter was then exchanged over the wire and positioned approximately 2 cm beyond the arterial flow probe. The guidewire was removed and subselective injections of contrast media were administered with a mechanical injector (MEDRAD, Pittsburgh, Model Mark IV). An electrical signal identified the exact onset and duration of injection. Room temperature (25°C) iohexol (Sterling-Winthrop, Rensselaer, NY) containing 300 mg/ml iode was used. A 4 ml volume of contrast was injected at rates of 1 and 4 ml/sec, whereas volumes of 2 and 4 ml were injected at a constant rate of 3 ml/sec. The order of injections was varied randomly, from dog to dog. Coronary blood flow, hemodynamics, and regional function were allowed to return to baseline between successive injections. All injections were monitored under fluoroscopic guidance by two or more observers. When contrast reflux through the probe was seen, the experiments were eliminated from the results. One animal was eliminated from the study because of reflux.

The mean and phasic coronary blood flow, myocardial segment lengths, left ventricular pressure, differentiated left ventricular pressure (dP/dt), limb lead electrocardiogram, and the injector pulse were continuously inscribed with a recorder (Gould Electronics, Cleveland, Model 2800S) at 200 mm/sec paper speed. Measurements were performed at baseline and at 0.5 sec intervals after injection for 10 sec. The following variables were assessed: heart rate, peak systolic left ventricular pressure, left ventricular end-diastolic pressure, peak positive and negative dP/dt, mean and diastolic coronary blood flow, percent myocardial fraction shortening, and the time at which the maximal and minimal values of these variables occurred during the 10 sec observation period. Left ventricular end-diastolic pressure and end-diastolic segment length (EDL) were assessed at the beginning of ventricular contraction when dP/dt became positive. End-systolic segment length (ESL) was determined 20 msec before peak negative dP/dt. Percent myocardial fractional shortening was defined as $(EDL - ESL)/EDL \times 100%$.

Repeated measures analysis of variance was performed for each variable to determine the presence of any perturbations from control after injections. If a statistically significant difference was indicated, a Bonferroni multiple comparisons method was used to establish the time at which each variable was significantly different from control (time = 0). If results from this analysis differed between rates or volumes, a similar analysis was carried out to allow precise determination of statistically different effects with respect to time between the rates or volumes. Results were considered statistically significant at $p < .05$.

Results

Injection of blood, saline, 5% dextrose in water, and iohexol through an electromagnetic flow probe immersed in saline did not disturb the zero flow reading. Similarly, subselective introduction of the No. 3F Rentrop catheter into the coronary artery did not produce a detectable change in baseline coronary blood flow. Moreover, subselective intracoronary injections with saline, arterial blood, and 5% dextrose in water, distal to the flow probe, did not significantly alter coronary blood flow.

Hemodynamic effects. Heart rate was unchanged after injection except with 4 ml injected at 3 ml/sec. With that dose, heart rate rose from $155 \pm 14$ (mean $\pm$ SD) to $158 \pm 12$ beats/min ($p < .05$) at 9.5 sec. No significant changes in peak systolic left ventricular pressure were noted except for a small rise seen with 4 ml infused at 3 ml/sec, 10 sec after injection ($135 \pm 13$ to $140 \pm 12$ mm Hg; $p < .001$). Left ventricular end-diastolic pressure did not change after any injection.

The 4 ml infusions of iohexol all increased peak positive dP/dt after 7 sec. Injectate rates of 1, 3, and 4 ml/sec increased peak positive dP/dt from $2100 \pm 380$ to $2800 \pm 418$ mm Hg.
to 2300 ± 480 mm Hg/sec (p < .001), 2200 ± 500 to 2350 ± 510 mm Hg/sec (p < .001), and 2210 ± 510 to 2310 ± 510 mm Hg/sec (p < .001), respectively. Peak negative dP/dt declined below baseline values between 5 and 10 sec for all of the 4 ml doses. Infusion rates of 1, 3, and 4 ml/sec reduced peak negative dP/dt from 1950 ± 400 to 1700 ± 260 mm Hg/sec (p < .01), 2120 ± 490 to 1940 ± 420 mm Hg/sec (p < .01), and 2080 ± 490 to 1930 ± 420 mm Hg/sec (p < .05), respectively. The 2 ml dose (3 ml/sec rate) increased peak positive dP/dt and reduced peak negative dP/dt, but not significantly.

Effects on coronary flow. Larger volumes of contrast medium increased the degree of flow perturbation observed but not its time of occurrence (figure 1). Mean coronary blood flow remained relatively stable for 0.5 to 1 sec then decreased rapidly. The 2 and 4 ml volumes administered at 3 ml/sec reduced mean coronary blood flow from 65 ± 14 to 45 ± 16 ml/min (p < .01) and 62 ± 16 to 14 ± 13 ml/min (p < .001), respectively. The flow nadir occurred 1.5 sec after the onset of both infusions, and the difference between the two flow nadirs was statistically significant (p < .001). Hyperemic levels of flow developed 5 to 6 sec after each infusion.

Variable injection rate with a fixed injection volume of 4 ml significantly affected the timing but not the magnitude of fall in mean coronary flow (figure 2). Iohexol injected at 1 and 4 ml/sec decreased early flow from 64 ± 14 to 16 ± 10 ml/min (p < .001) and 64 ± 14 to 20 ± 11 ml/min (p < .001), respectively. The nadirs of flow appeared at 1 and 2.5 sec with the 4 and 1 ml/sec rates.

Deterioration in percent regional shortening corroborated changes in blood flow. The overall average degree of functional impairment was minimal and similar for both 2 and 4 ml injections (figure 3). Effects were generally more profound with slower injection rates (figure 4). Four milliliters infused at 1 and 4 ml/sec reduced shortening from 16.3 ± 8.6% to 11.3 ± 8.4% (p < .01) and 16.4 ± 9.5% to 13.6 ± 9.0% (p < .001). The 2 and 4 ml doses (3 ml/sec rate) decreased shortening from 16.1 ± 9.4% to 12.9 ± 8.8% (NS) and 15.9 ± 8.5% to 12.8 ± 8.7% (p < .05). Reduced percent fractional shortening was maximal after the coronary flow nadir, improved gradually during hyperemic flow, and remained below baseline level at 10 sec. Table 1 summarizes the maximal flow and shortening decrements in individual animals. Maximal regional dysfunction always occurred after the flow nadir.

Discussion

Contrast-induced hyperemic coronary blood flow has been well recognized and quantified,20-24 but similarly detailed studies on early blood flow changes are

![FIGURE 1](http://circ.ahajournals.org/)

**FIGURE 1.** Coronary blood flow during intracoronary injection of iohexol with injection rate fixed at 3 ml/sec and volume varied between 2 and 4 ml. Blood flow was reduced from control by both doses but was significantly greater for 4 ml. There was no statistical difference in the time of occurrence of the flow nadir. Values shown are mean ± SEM.

1418
FIGURE 2. Coronary blood flow with volume fixed at 4 ml and rate varied between 1 and 4 ml/sec. The flow nadir occurred significantly earlier with the fastest injection rate. Blood flow reduction was significantly different from control but not between rates. Values shown are mean ± SEM.

Few.10,25 Only one study has closely examined the significance of early coronary flow reduction with respect to the amount and rate of intracoronary contrast medium injected.10 Yet flow changes after intracoronary injection of contrast are of considerable importance because they may interfere with several current digital and densitometric techniques used to assess coronary blood flow.9 Furthermore, fluctuations in coronary

FIGURE 3. Percent fractional shortening with injection rate fixed at 3 ml/sec and volume varied between 2 and 4 ml. Shortening was reduced significantly from control with 4 ml at 5.5 sec only. There was no statistical difference between rates. Values shown are mean ± SEM.
flow that appear within 10 sec are the most critical because they occur during a period when time-sequenced images necessary for analysis are acquired. Any contrast-induced reduction in early coronary blood flow would create a potential source of systematic measurement error.

The current study considers an alternative nonionic contrast agent, iohexol. Clinically, nonionic agents possess fewer negative hemodynamic and electrophysiologic side effects yet achieve an imaging quality similar to standard ionic agents.\textsuperscript{11-14} Moreover, studies in vitro have shown that nonionic media have significantly fewer effects on human red blood cell morphology, deformability, and aggregation when compared with ionic and other nonionic agents.\textsuperscript{26, 27} Iohexol can minimize these abnormalities, which affect the rheologic properties of blood.\textsuperscript{15-17} Therefore the medium was selected because it might potentially reduce post-injection coronary flow fluctuations in vivo.

This study demonstrates (1) a precipitous fall in early coronary blood flow after all doses of iohexol, (2) an increase in peak positive dP/dt within 10 sec, a period rarely assessed, and (3) transient reductions in regional myocardial function that paralleled changes in regional coronary blood flow.

The gross hemodynamic effects of iohexol adminis-

<table>
<thead>
<tr>
<th>Dose</th>
<th>% Flow reduction</th>
<th>Time (sec)</th>
<th>% Shortening reduction</th>
<th>Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml at 3 ml/sec</td>
<td>12.7</td>
<td>2.0</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>37.8</td>
<td>1.5</td>
<td>68.7</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>51.9</td>
<td>2.0</td>
<td>59.9</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>14.7</td>
<td>2.5</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>25.9</td>
<td>1.5</td>
<td>34.1</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>48.4</td>
<td>2.0</td>
<td>6.0</td>
<td>10.0</td>
</tr>
<tr>
<td>4 ml at 3 ml/sec</td>
<td>56.3</td>
<td>2.0</td>
<td>5.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>87.0</td>
<td>2.0</td>
<td>100</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>91.7</td>
<td>2.0</td>
<td>41.7</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>79.1</td>
<td>1.5</td>
<td>5.5</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>80.4</td>
<td>2.0</td>
<td>20.0</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>85.7</td>
<td>2.0</td>
<td>11.5</td>
<td>4.5</td>
</tr>
<tr>
<td>4 ml at 4 ml/sec</td>
<td>59.0</td>
<td>2.0</td>
<td>15.0</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>90.5</td>
<td>2.0</td>
<td>82.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>81.3</td>
<td>2.0</td>
<td>22.7</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>54.9</td>
<td>2.0</td>
<td>6.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>66.7</td>
<td>2.0</td>
<td>25.4</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>84.6</td>
<td>1.5</td>
<td>20.0</td>
<td>5.0</td>
</tr>
<tr>
<td>4 ml at 1 ml/sec</td>
<td>70.7</td>
<td>4.5</td>
<td>16.3</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5.0</td>
<td>133.3</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>89.2</td>
<td>4.5</td>
<td>52.5</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>68.6</td>
<td>4.5</td>
<td>17.0</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>72.2</td>
<td>4.0</td>
<td>57.0</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>76.7</td>
<td>4.0</td>
<td>16.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>
tered via central venous, left ventricular, and intracoronary injection techniques are well known.12, 23, 24, 28
The results of this study, in which the medium was injected via a subselective intracoronary method, were consistent with previous findings. Peak left ventricular systolic pressure and heart rate remained stable or increased after each intracoronary infusion. The 4 ml dose injected at 3 ml/sec was the only infusion to significantly elevate heart rate or systolic pressure. Although statistically significant, the relative increases in heart rate and systolic pressure were only 2% and 4%, respectively.

A significant increase in peak positive and a decrease in peak negative left ventricular dP/dt followed each infusion. Only the 2 ml dose of iohexol failed to exert a statistically significant positive inotropic effect. Diastolic dysfunction appeared early, whereas the positive inotropic effects were manifested later, after recovery from contrast-induced flow depression and regional dysfunction.

Direct measurement with electromagnetic flowmeters allowed immediate and precise assessment of coronary blood flow. The initial studies excluded artifactual signal shifts by the subselective catheter and injection method. Furthermore, iohexol was injected distal to the flow probe to avoid reflux, which would invalidate the flow signal.

After a brief period of stable flow there was an immediate and significant reduction in coronary blood flow (figures 1 and 2). The flow nadir appeared after injection and was followed by a sharp rise to hyperemic levels within 10 sec. The magnitude, direction, and temporal changes were identical for mean and peak diastolic flow measurements. The 2 ml dose of contrast failed to reach a statistically significant fall in coronary blood flow (31%). All 4 ml volumes caused much greater falls in coronary blood flow (69%, 75%, and 77% for 4, 3, and 1 ml/sec rates), which were statistically significant. The dose-related response of coronary flow also appeared to include the hyperemic phase (figure 1). Because the characteristics of iohexol-induced hyperemia are known,22-24 further evaluation of this phase was not performed.

The flow nadir appeared earlier after more rapid injection rates, whereas the rate did not influence the magnitude of the flow depression (figure 2). It is probable that the 4 ml bolus, injected subselectively, displaced most coronary blood even at the slowest rate. An increase in injection rate would not be expected to raise the arterial concentration of iohexol further or alter coronary blood flow differently.

The contrast-induced changes in early coronary blood flow in this investigation were similar to those in studies that used Renografin alone or in conjunction with the highest osmolar concentration of iohexol available.10, 25 Using a left coronary ostial injection technique, Hodgson et al.10 found that the degree of flow reduction was related to contrast volume for amounts less than 2 ml and that slower injection rates delayed flow nadirs and maximized flow depression. The relative changes in flow were less than those in the present study, which is contrary to what would be anticipated recognizing the greater hyperosmolarity (1680 mOsm/kg) and toxicity of Renografin. These results likely reflect the influence of the subselective injection technique in the current study. Moreover, a preliminary study25 showed that there were no differences between flow changes induced by subselective injection of Renografin compared with iohexol (350 mg/ml iodine, 844 mOsm/kg). The current study, using the least viscous and least hyperosmolar preparation of iohexol suitable for coronary angiography,20 continued to demonstrate a similar degree of coronary flow reduction.

Reversible alterations in red blood cell morphology and flexibility occur instantaneously after contact with contrast media and other hyperosmolar solutions.30 These effects on erythrocytes increase in proportion to the contrast/blood volume ratio or to the hyperosmolarity of the contrast solution. It has been estimated that adverse effects on erythrocyte flow may begin to appear when the osmolarity of blood exceeds 350 mOsm/kg (125% of normal).31 Although contrast media can affect blood flow by altering plasma viscosity,12, 32 it is the loss of red blood cell flexibility due to the effects of hyperosmolarity that appears to profoundly increase whole blood viscosity and resistance to flow.27, 33, 34 Flow rates of red cell suspensions after contact with iohexol are reduced in vitro.17, 31 Based on hyperosmolarity, iohexol and other nonionic agents should impede coronary blood flow less than ionic media. However, evidence in vitro with isosmolar dilutions of iohexol (300 mOsm/kg, 140 mg/ml iodine) indicates that additional mechanisms may exist in vivo to deform and increase the rigidity of human red cells and thereby impair microcirculatory flow.11, 15, 17, 31 Aspelin26 has hypothesized that the iohexol molecule has a direct chemotoxic effect on the erythrocyte membrane. Protein binding by iohexol and other nonionic media on the cell surface has also been suggested.11, 31 These factors may account for the similar effects of even the lowest osmolar preparation of iohexol compared with more hyperosmolar contrast media, whether ionic or nonionic.
Measurement of fractional shortening allowed assessment of myocardial function within the region exposed to contrast. Comparisons of flow and fractional shortening revealed that reductions in coronary blood flow were paralleled by a delayed reduction in myocardial function (figures 1 and 3, 2 and 4). Functional impairment was related to injection rate (figure 4) and independent of volume (figure 3). The 4 ml dose injected at the slowest rate, 1 ml/sec (figure 4), produced maximal impairment in shortening, suggesting that the mechanism of this effect may be contrast-mediated myocardial hypoxia. Slower intracoronary injections prolonged the duration of myocardial hypoperfusion, produced a larger cumulative ischemic effect, and retarded recovery of myocardial dysfunction. Although the magnitude of flow depression was greater with larger volumes, the duration of hypoperfusion was much shorter so that the larger volume caused only a slightly larger net ischemic effect. Direct myocardial toxicity of iohexol would be an unlikely cause of the observed dysfunction in light of its positive effect on global and regional contractility.

A precipitous reduction of coronary blood flow developed immediately after intracoronary injection of iohexol. This phenomenon may be due to the ability of iohexol to deform and reduce the flexibility of red blood cells thereby impeding flow at the microcirculatory level. Although these rheologic abnormalities are primarily a function of hyperosmolarity, blood flow perturbations with iohexol were quite similar to those reported for Renografin despite a 60% reduction in osmolarity. This suggests that the local intra-arterial concentrations of iohexol are sufficiently hyperosmolar to impair red cell deformability, thereby slowing blood flow through the capillaries. Deterioration of regional myocardial function corroborated the regional blood flow reductions, suggesting that ischemia caused by iohexol was the cause of this rather than a direct chemotoxic effect.

Iohexol and other nonionic contrast media possess a variety of beneficial clinical properties relative to ionic agents, but they still create the potential for measurement errors when attempting to quantify coronary blood flow and these errors are similar to those reported for ionic agents. Although it is always difficult to extrapolate results from an experimental, anesthetized, canine preparation to the clinical situation, the reported findings suggest that it is probably wise to pay strict attention to the constant dose of contrast medium and to the delivery rate even with nonionic contrast agents so that if similar flow perturbations do occur in man, they will remain systematic in nature and should not dramatically influence clinical measures of relative blood flow such as coronary flow reserve.

References
23. Gerber KH, Higgins CB: Comparative effects of ionic and nonionic
contrast material on coronary and peripheral blood flow. Invest Radiol 17: 292, 1982
The immediate effects of iohexol on coronary blood flow and myocardial function in vivo.
H Z Friedman, S F DeBoe, M J McGillem and G B Mancini

Circulation. 1986;74:1416-1423
doi: 10.1161/01.CIR.74.6.1416

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/74/6/1416

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/