Effects of Acute Cellular Injury on Coronary Vascular Reactivity in Awake Dogs

FREDERICK R. COBB, M.D., PHILIP A. MCHALE, PH.D., AND JUDITH C. REMBERT, PH.D.

SUMMARY The study was designed to examine effects of acute cellular injury on regional myocardial blood flow (RMBF) and coronary vascular reactivity. Before myocardial infarction in 14 dogs, RMBF was measured using 7-10 μm microspheres during the hyperemic response following a 60 sec transient ischemic stimulation (TIS). Myocardial infarction was induced by complete occlusion for two hours and then inflow to the injured area was re-established. RMBF was measured four hours later during basal conditions, following a 60 sec TIS and during infusion of adenosine, 1.0 mg/kg/min. Effects of acute cellular injury were examined by measuring RMBF in multiple myocardial samples, grouped according to extent of histologic necrosis.

Four hours after reperfusion, RMBF was decreased when infarction exceeded 50%. The decrements in flow were directly proportional to the extent of infarction. The vascular bed was capable of delivering additional flow to the injured area since both TIS and adenosine infusion affected increases in RMBF in excess of 100% in each region of the ischemic zone. Blood flow responses to these stimuli, however, fell in proportion to the extent of infarction. RMBF responses to TIS and adenosine infusion were comparable, indicating ischemia which effects irreversible myocardial injury also directly alters vasomotor properties of the intramural vasculature.

ISCHEMIA OF THE MYOCARDIUM sufficient to initiate acute cellular injury effects local responses in the zone of ischemia which directly alter tissue perfusion.1-8 Studies from this laboratory4 have demonstrated that the alterations in regional myocardial perfusion which result from acute cellular injury are directly proportional to the extent of eventual histologic myocardial necrosis.

The objectives of the present study were to determine 1) whether factors which effect reduction in blood flow to an acutely injured area also prevent increases in blood flow in response to the metabolic stimuli resulting from transient ischemia, and 2) whether ischemia sufficient to effect irreversible myocardial injury also directly alters the vasomotor properties of the intramural vasculature. Regional myocardial blood flow was measured after re-establishing inflow to an area subjected to two hours of ischemia. Regional myocardial blood flow was measured during basal conditions, immediately following the metabolic stimulation resulting from transient ischemia, and during direct vascular stimulation effected by intravenous adenosine. Effects of acute cellular injury on myocardial perfusion during these interventions were assessed by determining regional blood flow in multiple myocardial samples grouped according to subsequent histologic myocardial infarction. The study was performed in awake, chronically prepared animals to avoid variables introduced by general anesthesia and acute surgery.

Methods

Complete studies were performed in 14 mongrel dogs weighing 25–34 kg. The dogs were anesthetized with thi-amyal sodium (30–40 mg/kg, i.v.) and underwent a left thoracotomy. The proximal 1 cm of the left circumflex coronary artery was dissected free and a pneumatic cuff occluder was placed around the vessel. Heparin-filled catheters were inserted into the left atrial cavity and the aortic root. The catheters and snare were tunneled to a subcutaneous pouch at the base of the neck.

Studies were performed 7–10 days after the surgical procedure with the dogs lying quietly on a laboratory table as previously described.6,7 The mean hematocrit at the time of study was 42%, range 38–52%. To assure proper function of
the coronary oculder, electrocardiographic and hemodynamic responses to a 45-60 sec occlusion were observed. Proper function of the pneumatic oculder was verified by absence of abnormal Q waves before occlusion, elevation of ST segment, and an increase in heart rate and left atrial pressure within 30 sec after occlusion, and returned to pre-occlusion values of each parameter within approximately 15 sec after release of the occlusion. If the above responses were not observed, the animals were not included in the study. Coronary occlusion was then performed over a 15 min interval by gradually increasing the pressure in the oculder tubing. Coronary occlusion was maintained for 2 hours. Blood flow was then re-established to the ischemic area by completely deflating the oculder. Lidocaine, 2 mg/kg, was administered intravenously before the occlusion and at 15 min intervals for 1 hour after occlusion to reduce early arrhythmias. Morphine sulfate, 10 mg, was injected intravenously as the snare was inflated to minimize any discomfort resulting from the coronary occlusion. Antiarrhythmic or analgesic agents were not administered after the first hour of the study. Using the procedure, three dogs developed ventricular fibrillation after the occlusion and were excluded from the study.

Measurements of myocardial blood flow were made by serial injections of carbonized microspheres, 7-10 μm in diameter, labeled with gamma-emitting nuclides 51Cr, 14Ce, 85Sr, and 46Sc as previously described. The initial myocardial blood flow measurement was made to assess the response of the normal coronary vasculature to the metabolic stimulus resulting from transient ischemic stimulation. Microspheres were injected over a 10-15 sec interval beginning 10 sec after release of a 60 sec complete circumflex occlusion. Studies performed in this laboratory using awake dogs with chronic implanted electromagnetic flow probes demonstrated that a 60 sec transient occlusion effects a reactive hyperemic response characterized by sustained maximum increase in blood flow measurements. Subsequent blood flow measurements were made 4 hours following release of the 2 hour occlusion. At this point blood flow was measured during basal conditions, following release of a 60 sec complete occlusion as described above and during a constant intravenous infusion of adenosine 1.0 mg/kg/min. In previous studies in this laboratory this dose of adenosine produced maximum increases in phasic coronary flow and 4-5 fold increases in transmural myocardial blood flow.

Six days after the initial study the animals were anesthetized with thiopental sodium and the hearts fibrillated with concentrated potassium chloride. The mean left ventricular weight was 104 ± 5 g (SEM). As illustrated in figure 1 and described in previous studies, the left ventricle was sectioned into four transverse sections, circumferential regions and finally into four transmural layers of approximately equal thickness, samples size 1-2 g. Ten percent buffered formalin was added to the vials to preserve the tissue for histological sections after measurement of the tissue radioactivity.

**FIGURE 1.** This schematic diagram illustrates the technique for sectioning the left ventricle. The atrial tissue and right ventricle were removed as indicated by the stippled and lined area. The left ventricle was sectioned into four transverse sections. Each ring was sectioned into circumferential regions, i.e., anterior (A), septal (S), posterior (P), posterior papillary (PP), lateral (L), and anterior papillary (AP). Each circumferential region in rings 1, 2, and 3 was divided into four equal transmural layers. Regions in ring 4 were divided into equal epicardial and endocardial layers.
The radioactivity in each myocardial sample and reference blood sample was determined in a gamma spectrometer (Model 167776, Beckman Instruments Inc.), using window settings selected to correspond to the peak energies of each radioactive nuclide. Blood flow to each myocardial sample in milliliters per minute per gram was calculated as previously described.6,7

After measurement of tissue radioactivity and calculation of blood flow to each myocardial sample, the samples were prepared for histological sectioning and the percentage of infarcted myocardium in each small myocardial sample was determined as previously described.6 Thus, blood flow and the extent of myocardial infarction were determined in multiple small tissue samples of the entire region subjected to ischemia. Since the effects of acute cellular injury on myocardial perfusion are a function of the extent of eventual necrosis6 and the extent of necrosis varies between animals, myocardial perfusion was analyzed in multiple myocardial samples grouped according to comparable degrees of histologic myocardial necrosis, i.e., 0–5, 6–25, 26–50, 51–75, 76–89, 90–100, and 100%.

The Student's t-test for paired data was used to compare blood flow measurements in the same myocardial samples. Student's t-test for nonpaired data was used to compare flow in regions subjected to prolonged ischemia to flow in regions not subjected to ischemia.

### Results

The results of hemodynamic measurements during control resting conditions and at each measurement of regional myocardial blood flow are tabulated in table 1. Average resting hemodynamics were as follows: heart rate 82 beats per minute; mean arterial pressure 100 mm Hg; and mean left atrial pressure 5 mm Hg. The initial blood flow measurement was carried out immediately following transient ischemic stimulation produced by a 60 sec occlusion of the circumflex coronary artery. During the occlusion the heart rate and mean arterial and left atrial pressures increased. Ten to fifteen seconds following deflation of the cuff, during the maximum reactive hyperemic response, heart rate, arterial and left atrial pressures were 91 beats/min, 103 and 7 mm Hg. The predominant rhythm during the 2 hour circumflex artery occlusion was sinus tachycardia with occasional premature ventricular contractions. Approximately 20 seconds after release of the two hour occlusion, the

### Table 1. Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Before occlusion</th>
<th>Four hours after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Reactive hyperemia</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>SEM</td>
<td>±3</td>
<td>±4</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>SEM</td>
<td>±3</td>
<td>±3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>SEM</td>
<td>±1</td>
<td>±1</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Measurement of mean heart rate (HR), arterial pressure (AP), and left atrial pressure (LAP) before occlusion and 4 hr after release of 2 hr occlusion. The P values associated with the reactive hyperemia response before occlusion and control after reperfusion compare the hemodynamic responses to the control before occlusion. The P values associated with the reactive hyperemia and adenosine responses after reperfusion compare the responses to the control after reperfusion. Values are mean ± sem.

### Table 2. Relationship Between Infarcted Myocardium and Blood Flow (ml/g/min)

<table>
<thead>
<tr>
<th></th>
<th>Anterior region</th>
<th>Left circumflex coronary artery region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>0-5%</td>
</tr>
<tr>
<td>A. Before infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Reactive hyperemia</td>
<td>1.16</td>
<td>5.33</td>
</tr>
<tr>
<td></td>
<td>±0.09</td>
<td>±0.73</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>B. Four hours after reperfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Control</td>
<td>1.23</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>±0.10</td>
<td>±0.13</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2. Reactive hyperemia</td>
<td>1.35</td>
<td>3.38</td>
</tr>
<tr>
<td></td>
<td>±0.16</td>
<td>±0.58</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3. Adenosine</td>
<td>4.13</td>
<td>4.37</td>
</tr>
<tr>
<td></td>
<td>±0.31</td>
<td>±0.43</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Myocardial blood flow, ml/min/g, before infarction during the reactive hyperemic response and 4 hr after release of a 2 hr occlusion during control, the reactive hyperemic response and infusion of adenosine 1.0 mg/kg/min. Blood flow in the left circumflex coronary artery region is grouped according to the percent of infarcted myocardium in each sample. Values are mean ± sem. P values compare blood flow in the anterior to that in the circumflex region.

NS = P >0.05.
rhythm was interrupted by ventricular tachycardia which lasted 10-15 min. Four hours after reperfusion the mean heart rate was 125 beats per minute and the mean arterial and mean left atrial pressures were 95 and 9 mm Hg, respectively. At this time the rhythm was predominantly ventricular in 9 animals. Fours hours after reperfusion, 60 second occlusion of the circumflex coronary artery did not produce significant changes in heart rate or arterial or left atrial pressure. At this time adenosine infusion increased heart rate to 143 beats/min and decreased arterial and left atrial pressure to 70 and 6 mm Hg, respectively.

The relationship between acute cellular injury and perfusion during each intervention was measured by determining mean blood flow in myocardial samples grouped according to the extent of histologic myocardial infarction, 0-6, 6-25, 26-50, 51-75, 76-89, 90-100 and 100% (table 2, figs. 2-6). Four hours after reperfusion blood flow to the acutely injured area was decreased in regions in which the subsequent extent of histologic myocardial infarction was greater than 50% (fig. 2). The decrements in flow were proportional to the extent of myocardial infarction. Significant levels of blood flow, however, remained in regions in which the extent of infarcted myocardium was 100%.

Four hours after reperfusion transient ischemic stimulation produced by a 60 second occlusion effected an increase in blood flow in all regions in the ischemic zone (fig. 3). Thus, even in regions which eventually developed complete infarction, the vasculature was capable of augmenting blood flow in response to the metabolic stimulus effected by transient ischemia. The response to transient ischemic stimulation, however, was significantly different from that recorded prior to the two hour occlusion (fig. 4). Prior to the two hour occlusion transient ischemic stimulation resulted in 4.5-5.0 fold increases in blood flow in all regions supplied by the circumflex coronary artery. Although a reactive hyperemic response could be elicited in all regions four hours after reperfusion, the response was decreased in each infarct range. The magnitude of reactive hyperemic response was reduced in direct proportion to the extent of subsequent myocardial infarction.

Four hours after reperfusion intravenous adenosine infu-
tion effected an increase in blood flow to all regions in the ischemic zone (fig. 5). Although blood flow increased in each infarct range, the magnitude of the blood flow response was inversely related to the extent of subsequent myocardial infarction. The response during adenosine infusion was significantly different in the region supplied by the nonoccluded anterior descending coronary artery and in the infarcted regions. In figure 6 blood flow to the infarcted regions is expressed as the ratio of infarct to anterior nonischemic region flow. As compared to blood flow in the anterior region which increased during the adenosine infusion, blood flow to the infarcted region during adenosine infusion was less in regions with greater than 25% infarction. The relative reductions in the response to adenosine were directly proportional to the extent of infarcted myocardium. The magnitude of blood flow response in the infarcted regions following transient ischemic stimulation and during adenosine infusion was not significantly different in regions with greater than 5% myocardial infarction. However, in regions with 5% or less myocardial infarction, the blood flow response during adenosine infusion was significantly greater than that following transient ischemic stimulation.

Discussion

Several previous studies have demonstrated that prolonged myocardial ischemia may initiate local responses in the zone of acute cellular injury which alter perfusion of the myocardium. In previous studies from this laboratory, regional perfusion was measured immediately, 15 minutes, 4 hours, and 3 days after re-establishing blood flow to an area subjected to prolonged ischemia and related to the extent of eventual histologic infarction. Immediately following reperfusion, blood flow was increased in each region of the zone subjected to prolonged ischemia, but the magnitude of the hyperemic response in a given region was reduced in direct proportion to the extent of eventual histologic myocardial infarction. Fifteen minutes after reperfusion, the hyperemic response had subsided and blood flow to the acutely injured zone was equal to or slightly in excess of flow to noninjured areas. Four hours and 3 days after reperfusion blood flow was decreased in regions with greater than 50% infarcted myocardium. The decrements in flow were proportional to the extent of histologic myocardial infarction. The reductions in blood flow 4 hours and 3 days after reperfusion were comparable indicating that local tissue responses which effected reductions in blood flow were completed within 4 hours of reperfusion.

In the present study, four hours after reperfusion blood flow was reduced in myocardial regions which subsequently demonstrated greater than 50% histologic myocardial infarction. The decrements in flow were proportional to the extent of myocardial infarction. Similar relationships were observed in a previous study. Although blood flow was reduced in areas of extensive myocardial injury, transient ischemic stimulation elicited a residual vasodilator response with blood flow, increasing in excess of 100% in each region of the acutely injured zone. Thus, even in regions which subsequently demonstrated complete histologic myocardial infarction, the vasculature was capable of delivering additional blood flow to the injured area in response to the metabolic stimulation elicited by transient ischemia. As compared to the response to transient ischemic stimulation prior to acute infarction, the magnitude of the response 4 hours after reperfusion was reduced in direct proportion to the extent of myocardial infarction.

Basal myocardial blood flow and the blood flow response which follows transient ischemic stimulation, the reactive hyperemic response, are coupled to the metabolic activity of the myocardium. The precise factors which link vascular tone and thus blood flow to metabolic activity remain controversial. Rubio et al. have presented evidence that adenosine, a potent vasodilator, is continuously released by the normal myocardium and is released in increased quantities in response to myocardial ischemia. These investigators concluded that adenosine provides the link between coronary vascular tone and metabolic activity of the myocardium and is the mediator of the vascular response to ischemia. ATP, a high energy product of aerobic metabolism and precursor of adenosine, is rapidly depleted during ischemia. Acute cellular injury resulting from prolonged ischemia would be expected to severely reduce metabolic capabilities, including the ability to synthesize vasoactive metabolites. It may thus be reasoned that the reductions in basal blood flow and the blood flow response to transient ischemic stimulation may represent simply the loss of metabolic stimulus to blood flow and/or inability to synthesize vasoactive compounds which link blood flow to myocardial metabolic needs. The hyperemic response which follows transient ischemia is also dependent on a vasculature capable of vasodilating when appropriately stimulated. Factors which directly alter vascular reactivity or the ability of the vasculature to vasodilate may reduce basal blood flow and/or the blood flow response to ischemic stimulation independent of myocardial injury.

The reactivity of the vasculature to direct stimulation was tested by measuring the blood flow response during an intravenous infusion of adenosine. In previous studies from the laboratory, intravenous infusion of adenosine in awake animals resulted in a four to five fold increase in transmural blood flow. The vasodilator response to adenosine appears to be mediated by a direct effect on the intramural coronary vasculature. It was thus reasoned that the vasodilator response to adenosine should remain intact if the alteration in perfusion to an acutely injured area resulted from loss of metabolically active myocardium surrounding an intact and reactive intramural vasculature. In the present study adeno-

**Figure 6.** Myocardial blood flow 4 hours after release of a 2 hour occlusion during intravenous adenosine 1.0 mg/kg/min. Blood flow is expressed as the ratio of flow in samples from the anterior region. Values are mean ± SEM.
sine infusion effected an increase in blood flow in each region of the acutely injured zone. As compared to blood flow to the anterior nonischemic region, the response to adenosine was reduced when the extent of myocardial infarction exceeded 25%. The magnitude of the blood flow response to adenosine in the ischemic regions was decreased in direct proportion to the extent of myocardial infarction. Prolonged ischemia sufficient to initiate irreversible myocardial injury directly altered the vasomotor properties of the intramural vasculature. The blood flow response to adenosine exceeded that to transient ischemic stimulation only in areas with less than 5% myocardial infarction. Thus, the blood flow response to adenosine and ischemic stimulation were essentially comparable. During the adenosine infusion heart rate increased and arterial pressure decreased significantly. Both of these hemodynamic changes would tend to reduce myocardial perfusion during maximum vasodilation. Temporary coronary occlusion did not produce significant hemodynamic changes 4 hours after reperfusion. It is thus likely that had heart rate and arterial pressure remained unchanged that blood flow during the adenosine infusion would have exceeded blood flow following ischemic stimulation in other areas of the acutely injured region. Greater blood flow response to direct vascular stimulation as compared to transient ischemic stimulation in regions of less myocardial necrosis, i.e., regions from the periphery of the infarct zone, suggests that ischemic injury affects the myocardial cells disproportionately. As discussed in the following section, Kloner et al. concluded that capillary damage occurred after irreversible injury to the myocardial cell. It is possible that vascular injury follows but never matches the extent of myocardial cell injury. In the present study, interstitial hemorrhage, a hallmark of vascular injury, was marked in the center of the infarct zone but minimal at the periphery.

A variety of factors including direct vascular injury, vascular or myocardial cellular swelling, and/or release of vasoactive compounds, may alter vasomotor properties of the coronary vasculature. Kloner et al. observed that following reperfusion of an area subjected to 40–90 min of ischemia, rapid and explosive swelling of myocardial cells occurred. Microvascular damage did not occur after 40 min of occlusion, but did occur after 90 min of occlusion. Willerson et al., using isolated perfused canine hearts, observed that 40 min of ischemia followed by reperfusion resulted in significant increases in heart weight, interstitial edema, focal vascular congestion, and swelling of muscle cells. These investigators observed that 1–20 min following reperfusion nitroglycerin plus adenosine infusion increased total flow to the heart 2.5 times control flow and concluded that the tissue responses to 40 min of ischemia did not alter the vascular response to these agents. Regional blood flow to the area of injury was not measured. Recently Powell et al. have reported that hypertonic mannitol reduced cell swelling produced by a transient period of myocardial ischemia in anesthetized animals. Leaf has hypothesized that ischemia may initiate cell swelling which results in a self-perpetuating vicious cycle which progressively reduced perfusion and ultimately results in cell death. Whether these local tissue responses to prolonged ischemia play a role in the processes leading to irreversible injury, or represent a result of irreversible injury, remains controversial.

Recent reports have indicated that following permanent coronary artery occlusion there is significant loss of microspheres from the infarcting myocardium. Approximately 25% of the microspheres injected prior to infarction were lost from the infarcted region at 24 hours. No further loss occurred at 41 or 8 days. In the present study the three blood flow measurements made after infarction were performed during a period of 20–30 min. Since the microspheres in a given tissue region should be lost randomly, the relationships between blood flow measured at the same interval after infarction should not change but each of the actual blood flow values may have been 20–30% higher than the values measured. Loss of microspheres after infarction would also be expected to reduce the blood flow measurements made during the reactive hyperemic response before infarction. Blood flow during the hyperemic response before infarction was increased five fold in samples from each infarct range indicating that microsphere loss in this model of infarction was not a function of the amount of infarction in the tissue samples and/or microsphere loss was minimal.

In the present study acute cellular injury which resulted in subsequent histologic myocardial necrosis reduced basal blood flow and reduced but did not entirely eliminate the vasodilator response to transient ischemic and direct vascular stimulation. Even in areas which eventually developed 100% histologic infarction, significant levels of basal blood flow were present and the vasculature was capable of delivering additional blood flow in response to direct vascular stimulation or the metabolic stimulus elicited by transient ischemia. This study was not designed to examine the specific factors, i.e., cell swelling, release of vasoactive compounds, or interstitial hemorrhage, which may have affected the alterations in perfusion. However, since prolonged ischemia altered the vasodilation response to direct and indirect vascular stimulation in a comparable fashion, the data indicate that ischemia sufficient to effect irreversible myocardial injury also directly alters the vascular reactivity of the intramural vasculature in the regions of irreversible myocardial injury.

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References

Unexplained In-Hospital Fever Following Cardiac Surgery

Natural History, Relationship to Postpericardiotomy Syndrome, and a Prospective Study of Therapy with Indomethacin versus Placebo

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SUMMARY In Part I of this study, the in-hospital course of 219 patients who had undergone a cardiac operation was analyzed. Fever (≥37.8°C, rectal) was present after postoperative day 6 in 159 patients (73%) and was of unexplained cause in 118. Fever decay in the population of unexplained fever patients was exponential. All patients with unexplained postoperative fever were afebrile by postoperative day 19. In-hospital pericardial rub and pleuritic chest pain, widening of the mediastinum on chest film, and pleural effusion were not specifically associated with unexplained postoperative fever. In Part II, 67 patients with unexplained postoperative fever were given indomethacin (100 mg per day) or placebo for 7 days by a randomized, double-blind protocol. Indomethacin resulted in a shorter duration of fever (2.4 vs 3.5 days, P < 0.01) and in a shorter duration of chest pain, malaise, and myalgias compared to placebo. Sixty-seven percent of the patients in Part I and all of the patients in Part II were contacted 2-8 months following hospital discharge. Five percent had experienced an illness that we considered to be acute pericarditis, but its occurrence was unrelated to whether the patient had had in-hospital unexplained postoperative fever, in-hospital rub or chest pain, or in-hospital administration of indomethacin.

FEVER AND CLINICAL SIGNS of a pleuropericardial process sometimes develop days to months after cardiac surgery, a combination of events widely referred to as the "postpericardiotomy syndrome."1-2 Opinions about what constitutes postpericardiotomy syndrome — when it begins, its relationship to the more general problem of unexplained postoperative fever, and its clinical importance and natural history — are extremely diverse. The incidence of the syndrome has been reported to be as low as 1% and as high as 64%,4-10 and recommendations for therapy have differed widely.4-8,11-13 Cardiologists and cardiac surgeons in our institution have frequently administered indomethacin to such patients when fever has been accompanied by pleuropericardial pain, by a pericardial rub, or by malaise. Standards of practice have varied widely, however, because of uncertainty about the significance and course of unexplained postoperative fever and because the risk-benefit ratio of indomethacin administration under these circumstances has not been established.

The present study consists of two parts. In the first, we examine 1) the incidence and natural history of the unexplained fever that frequently occurs during the in-hospital postoperative period following a cardiac operation and the relationship of fever during this period to the clinical signs that have been used to diagnose the postpericardiotomy syndrome; 2) whether either unexplained fever or the clinical signs that have been used to diagnose the postpericardiotomy syndrome, when they occur during the in-hospital postoperative period, are related to the later development of pericarditis following hospital discharge. The second part of the investigation is a prospective, randomized study of the effectiveness of indomethacin compared to placebo in the therapy of unexplained in-hospital postoperative fever and its associated symptoms.

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