Preliminary experience with synchronized coronary sinus retroperfusion in humans

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ABSTRACT  Synchronized coronary sinus retroperfusion (SCSR) with arterial blood has been extensively tested in animals. This intervention offers temporary support to areas of ischemic myocardium while a method of definitive revascularization is being sought. The feasibility and safety of this procedure for patients with unstable angina was therefore tested. A No. 7F autoinflatable retroperfusion balloon catheter (USCI) was inserted percutaneously into the coronary sinus of the study patients. Arterial blood was obtained through a No. 8F catheter placed in the femoral artery. Arterial blood was infused in a retrograde fashion into the coronary venous system during cardiac diastole by means of a piston-driven pump that was electrocardiographically synchronized with the drainage of the venous system during systole. This procedure was performed in five patients with unstable angina refractory to maximum medical therapy. SCSR significantly decreased the frequency of anginal episodes and the requirement for antianginal medications. SCSR also provided time for patient stabilization before diagnostic cardiac catheterization or therapeutic intervention. This preliminary experience suggests that synchronized coronary sinus retroperfusion is a feasible and safe procedure. It can be performed at the bedside with no apparent adverse effects to the patient. Retroperfusion also appears to be effective in relieving ischemic symptoms as assessed by clinical parameters. Based on our preliminary experience, further delineation of its clinical applications is warranted.


THE CONCEPT OF perfusing the heart via the coronary sinus is based on the observation that the coronary venous system is not affected by the atherosclerotic process. It has been known since the late 1800s that myocardial viability in animals can be maintained through retrograde flow of oxygenated blood via the coronary sinus. In the late 1940s, Beck and his colleagues demonstrated that shunting of arterialized blood to the coronary venous system could relieve angina in patients with chronic coronary artery disease. The major limitation of surgical retroperfusion was the inadequacy of venous drainage, which led to engorgement of the coronary sinus, myocardial edema, and heart failure. Beck's operation was superceded by direct myocardial revascularization with saphenous vein grafts, a more physiologically appealing procedure since it directly reestablishes antegrade blood flow to the myocardium.

A nonsurgical approach to coronary sinus retroperfusion was reported by Meeraum et al. in 1976. This system was synchronized to the cardiac cycle to deliver blood into the coronary sinus during diastole and allow normal physiologic drainage during systole. Several reports in dogs and baboons have confirmed the beneficial effects and safety of synchronized retroperfusion. In our own laboratory, we have studied the safety and efficacy of synchronized retroperfusion for up to 24 hr in dogs. No significant change in blood pressure, pulse, cardiac output, or right-sided pressures were noted in the 38 animals studied. Myocardial damage, as documented by triphenyltetrazolium chloride staining, was limited to a small area in the subendocardial layer. Postmortem examination of animals revealed no histologic evidence of damage to the coronary sinus or surrounding structures. In addition, myocardial viability was maintained during left anterior descending coronary artery occlusion. Accordingly, we initiated an FDA-approved trial to evaluate the
feasibility and safety of this intervention in humans in a clinical setting that might also allow a preliminary assessment of efficacy. We selected critically ill patients with unstable angina who were unresponsive to "maximal" medical therapy.

Methods

Instrumentation. A synchronous retroperfusion system (USCI Model ECI) was developed to deliver pulsatile arterialized blood to the coronary sinus during diastole with venous drainage occurring during systole (figure 1). The system consists of a physiologic monitor, a pump controller, a piston-driven pump, and an extracorporeal circuit. The monitor is a two-channel unit capable of monitoring and displaying the electrocardiogram and pressure or pump timing. Information from the monitor is fed to and processed by the pump controller, which maintains pump flow and pump timing through feedback circuits that compensate for variations in the patient's heart rhythm and rate. The extracorporeal blood circuit consists of a disposable piston-driven pump chamber assembly; tubing connects the arterial blood supply and SRP balloon catheters once they have been positioned in the patient.

Catheter system. Retroperfusate (arterial blood) is obtained through a No. 8F, 40 cm supply catheter (USCI) placed through a No. 8F catheter introducer (USCI Hemaquet) inserted into the femoral artery. A No. 7F, 56 cm autoinflatable retroperfusion balloon catheter (USCI) is positioned in the great cardiac vein 2 to 3 cm proximal to the anterior interventricular vein (figure 2) via the coronary sinus with use of a No. 9F catheter introducer (USCI) with a diaphragm-occluded sidearm is positioned in the internal jugular vein. As arterial blood is delivered through the coronary sinus catheter during diastole, it inflates a balloon at the tip of the catheter. This retards efflux from the regional coronary veins and permits more effective retrograde delivery of arterial blood to the myocardium. On termination of retrograde catheter perfusion at end-diastole, the occluding balloon automatically deflates (as documented by fluoroscopy and contrast injection), thereby allowing prograde coronary sinus drainage of venous blood from the myocardium into the right atrium during systole (figure 3).

Patient selection. Patients in the coronary care unit with unstable angina were eligible for this intervention if they had not responded to "maximum" medical therapy and were believed to be at extremely high risk for a fatal cardiac event. Unstable angina during bed rest was defined as multiple episodes of pain lasting more than 5 min but not longer than 30 min that were associated with electrocardiographic ST segment elevation or depression in two consecutive leads of at least 1.5 mm that normalized as the pain subsided and with creatinine kinase elevation less than two times the upper limits of normal. Patients with the following conditions were excluded: persistent arterial hypertension (systolic blood pressure > 200 mm Hg) or hypotension (systolic blood pressure < 90 mm Hg), significant valvular heart disease, coagulation defects or thrombocytopenia, any contraindication to heparinization, advanced cardiac conduction abnormalities, and/or inability to give informed consent. All patients had received maximal medical therapy for unstable angina in the coronary care unit, including oxygen, morphine, intravenous nitroglycerin, sublingual nitroglycerin, β-blockers, and calcium-channel blockers.

This investigation was approved by the Committee on the Protection of Human Subjects in Research at the University of Massachusetts Medical Center. Each patient and at least one responsible family member provided written informed consent to this investigation.

Catheterization technique. With the patient in the supine position...
position, introducers were placed percutaneously in the internal jugular vein and femoral artery. The arterial supply catheter was positioned in the distal aorta. The coronary sinus catheter was then advanced through the right atrium and into the coronary sinus under fluoroscopic guidance. Position in the coronary sinus was verified when a blood oxygen saturation of less than 40% was observed and was checked after the injection, by hand, of contrast material (Renografin 76, Squibb) (figure 4). The coronary sinus catheter was then advanced over a wire such that its tip was positioned in the great cardiac vein. Unimpeded emptying of the coronary sinus was verified by free flow of contrast material into the right atrium during systole.

After arterial and venous cannulation each patient received 5000 units iv heparin in a bolus, followed by a constant heparin infusion to maintain the activated clotting time at 2 to 2 1/2 times control. During the period of synchronized coronary sinus retroperfusion, patients were maintained on the same cardiac medications and at the identical doses they had received over the 36 hr before intervention.

Pulmonary arterial flow-directed catheters were placed in four of the five patients. In all patients continuous arterial blood pressure was monitored through the sidearm of the femoral artery introducer. Retroperfusion was instituted at an arbitrarily predetermined flow rate of 0.5 ml/kg/min and increased every 10 min until relief of ischemic symptoms or a maximum flow rate of 2.2 ml/kg/min (or 150 ml/min, the maximum output of the system) had been achieved. The electrocardiogram was monitored continuously. All patients were maintained on synchronized coronary sinus retroperfusion until cardiac catheterization was performed. At that time a decision about definitive therapy, including the feasibility of coronary artery angioplasty or bypass surgery, was made. It was clearly understood that in some patients, because of the severity of their illness, no further mechanical intervention would be feasible.

Results

Feasibility

Coronary sinus retroperfusion. The procedure was successfully implemented in the five consecutive patients in which it was attempted. The patients ranged in age from 44 to 80 years; there were four men and one woman. All patients were critically ill and demonstrated significant ischemia of the anterior wall as docu-

FIGURE 2. Optimal placement of the retroperfusion catheter in the great cardiac vein and the catheter's relationship to the cardiac venous system.
the coronary sinus catheter was 5 min, with a range of 30 sec to 10 min. Within 3 to 5 min after the catheters had been positioned, patients were placed on the pump by connecting the pump chamber inlet tubing to the arterial catheter, displacing the heparinized saline from the tubing with the patient’s own oxygenated blood under arterial pressure, and connecting the outlet tubing to the coronary sinus catheter. Coronary sinus retroperfusion was arbitrarily instituted at 0.5 ml/kg/min in all patients. The mean coronary sinus retroperfusion flow was 103 ml/min, ranging from 55 to 135 ml/min, and the flow rate was adjusted to control each patient’s symptoms. Synchronized coronary sinus retroperfusion was used continuously for a mean of 28.2 hr (range 12 to 50 hr; table 1).

**Safety**

**Hemodynamic findings during retroperfusion.** There were no significant changes in right heart pressures during the insertion of the introducers or catheters or during synchronized coronary sinus retroperfusion. Arterial blood pressure, heart rate, right heart pressures, and cardiac output were not significantly affected by synchronized coronary sinus retroperfusion. There were no changes in the type and frequency of ventricular ectopic activity, nor were there serious ventricular arrhythmias.

**Hematologic data.** Despite up to 50 hr of retroperfusion, there were no clinically significant changes in any hematologic parameters (table 2). Group mean hemoglobin values were 12.0 g/dl before synchronized coronary sinus retroperfusion and decreased to 11.2 g/dl at 24 hr. Similar insignificant changes were observed for hematocrit. There was an insignificant decrease in platelet count from $155 \times 10^4$ to $127 \times 10^4$ at 24 hr. Plasma free hemoglobin, a measure of red blood cell breakdown (hemolysis), did show some minor fluctuations over the period of time that patients were retroperfused; it increased modestly from a preprocedure mean value of 4.1 to 5.0 mg/dl at 24 hr.

**Subsequent direct coronary sinus observation.** Three of these patients subsequently underwent bypass surgery. One other patient died and underwent an autopsy. Thus, direct coronary sinus observation was possible in four of five patients. In the three patients undergoing

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**TABLE 1**

Clinical profile of patients on synchronized coronary sinus retroperfusion (SCSR)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Time on SCSR (hr)</th>
<th>Cath findings</th>
<th>Subsequent intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>F</td>
<td>12</td>
<td>99% LAD</td>
<td>PTCA and CABG</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>50</td>
<td>99% proximal LAD, 90% distal LAD (2), 99% mid CIRC, 100% RCA</td>
<td>CABG</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>M</td>
<td>40</td>
<td>99% LAD, 100% RCA, 80% CIRC</td>
<td>Intra-aortic balloon/medical treatment — not a surgical candidate because of poor LV function</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>18</td>
<td>95% LAD, 75% CIRC, 75% RCA</td>
<td>CABG</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>21</td>
<td>75% left main, 100% CIRC, 75%–80% RCA</td>
<td>Intra-aortic balloon/medical treatment — not a surgical candidate because of ungraftable distal vessels</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; CIRC = circumflex artery; LAD = left anterior descending artery; PTCA = percutaneous transluminal coronary angiography; RCA = right coronary artery; LV = left ventricular.
TABLE 2
Hematologic parameters during retroperfusion (SCSR)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before SCSR</td>
<td>&lt;12 hr</td>
<td>12-24 hr</td>
<td>24-48 hr</td>
<td>&gt;48 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11.6</td>
<td>205</td>
<td>7.8</td>
<td>11.4</td>
<td>9.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12.6</td>
<td>134</td>
<td>2.0</td>
<td>12.3</td>
<td>142</td>
<td>3.9</td>
<td>12.1</td>
<td>133</td>
</tr>
<tr>
<td>3</td>
<td>10.4</td>
<td>102</td>
<td>4.1</td>
<td>9.9</td>
<td>101</td>
<td>4.2</td>
<td>11.1</td>
<td>103</td>
</tr>
<tr>
<td>4</td>
<td>15.6</td>
<td>122</td>
<td>-</td>
<td>14.3</td>
<td>124</td>
<td>9.2</td>
<td>13.6</td>
<td>125</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>212</td>
<td>2.3</td>
<td>9.0</td>
<td>202</td>
<td>4.8</td>
<td>10.3</td>
<td>173</td>
</tr>
<tr>
<td>Group mean</td>
<td>12.0</td>
<td>155</td>
<td>4.1</td>
<td>11.4</td>
<td>143</td>
<td>8.1</td>
<td>11.2</td>
<td>127</td>
</tr>
</tbody>
</table>

Hb = hemoglobin (g/dl); Pt = platelet count (thousands/min³); Plasma Hb = plasma free hemoglobin (mg/dl; normal 0.0 to 7.0).

bypass surgery, careful examination of the external surface of the heart was conducted at the time of pericardiotomy with particular attention to the coronary sinus. In two patients, there was no evidence of any traumatic injury to the external surface of the coronary sinus, great cardiac vein, or epicardium. In the third patient, ecchymoses were noted on the anterior surface of the heart in the distribution of the proximal left anterior descending coronary artery. It is not likely that these resulted from this intervention since the coronary sinus catheter was positioned in the posterior portion of the heart. The ecchymoses might have been due to increased pressure in regional myocardial veins.

An autopsy was performed on one of the patients who did not undergo bypass surgery or angioplasty because of diffuse distal coronary artery disease. The coronary arteries demonstrated severe distal atherosclerosis. There was a small hematoma in the posterior portion of the heart near the coronary sinus. A flat ½ mm × 3 mm thrombus was found at the orifice of the coronary sinus at the site of catheter contact. Microscopically, multiple sections of the coronary sinus revealed disappearance of the endothelial lining and replacement by a thin layer of fibrin. Myocytes in the vicinity of the coronary sinus were free of coagulation or contraction band necrosis. Occasional red blood cells were noted in the interstitium between the myocytes. Periadventitial hemorrhage around the coronary sinus was noted in some areas.

Clinical response

Short-term response to retroperfusion. Several clinical variables were followed to assess the efficacy of synchronized coronary sinus retroperfusion. In four of five patients there was reversal of ischemic electrocardiographic changes back to baseline within 10 min of instituting retroperfusion. In one patient, the anterior ischemic changes improved, but ST segment depression persisted despite relief of pain. This patient was found, on coronary angiography, to have a posterior infarction. Clinical conditions of the patients during a 36 hr control period before and during synchronized coronary sinus retroperfusion are compared in table 3. The average frequency of anginal episodes before retroperfusion was 0.7 ± 0.4 episodes per hour. This declined significantly to 0.01 ± 0.1 episodes per hour during retroperfusion (p < .05). Before synchronized coronary sinus retroperfusion the group mean intravenous nitroglycerin dose was 786 ± 130 µg; during synchronized coronary sinus retroperfusion it was 731 ± 160 µg (p = NS). No attempt was made to wean patients off intravenous nitroglycerin during retroperfusion. The medication requirement for control of anginal pain decreased significantly with retroperfusion: 0.74 ± 0.26 mg iv morphine/hr was required before retroperfusion and 0.17 ± 0.19 mg/hr was required during retroperfusion (p < .02). The mean sublingual nitroglycerin requirement of the patients also decreased significantly, from 0.23 ± 0.13 tablets/hr be-

TABLE 3
Comparison of clinical conditions before and during retroperfusion

<table>
<thead>
<tr>
<th></th>
<th>Before synchronized coronary sinus retroperfusion</th>
<th>During synchronized coronary sinus retroperfusion</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of anginal episodes (episodes per hour)</td>
<td>0.71 ± 0.4</td>
<td>0.01 ± 0.01</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Intravenous nitroglycerin (mg/min/hr)</td>
<td>0.786 ± 0.130</td>
<td>0.731 ± 0.160</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous morphine (mg/hr)</td>
<td>0.74 ± 0.26</td>
<td>0.17 ± 0.19</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Sublingual nitroglycerin (tablets/hr)</td>
<td>0.23 ± 0.13</td>
<td>0.0 ± 0</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

*During the 36 hr just before synchronized coronary sinus retroperfusion.
*There was no change in the amount or frequency of any oral antian-ginal medication during the 36 hr before and during retroperfusion.

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fore retroperfusion to 0.0 tablets during the procedure (p < .05).

Subsequent clinical course. Coronary angiography was performed 1 to 18 hr after the institution of retroperfusion. Cardiac catheterization and angiography was performed during retroperfusion. As shown in table 1, all five patients had significant coronary artery disease with marked coronary stenoses in the distribution of the left anterior descending artery. Three of the five patients underwent emergency coronary artery bypass surgery. Two patients were not considered candidates for bypass surgery because of diffuse distal disease; these individuals were treated with an intra-aortic balloon pump, as per our protocol, after synchronized coronary sinus retroperfusion was discontinued. These latter two patients died 48 and 72 hr after intra-aortic balloon counterpulsation had been terminated. Of the patients undergoing coronary artery bypass grafting, two had an uncomplicated hospital course and were discharged 1 week after bypass surgery. The third patient had a prolonged postoperative course with respiratory and renal failure secondary to sepsis that occurred on the seventh postoperative day. None of these complications were believed to be related to the use of synchronized coronary sinus retroperfusion in these patients. Rather, they represented the natural history and progression of the underlying disease.

Discussion

In animals, synchronized coronary sinus retroperfusion has been validated as a relatively simple technique for the maintenance of myocardial viability in an infarct preparation of coronary occlusion. In that study, synchronized coronary sinus retroperfusion was instituted 30 min after the onset of ischemia, and then maintained for 6 hr. However, concern about the safety and the feasibility of the technique has delayed its clinical application.8,13

Our study demonstrates the feasibility and safety of synchronized coronary sinus retroperfusion in five patients with unstable angina resistant to maximal medical therapy. The procedure can be performed expeditiously at the bedside and maintained for at least 50 hr with no apparent adverse hemodynamic, hematologic, pathologic, or clinical effects.

Feasibility of synchronized coronary sinus retroperfusion. A major concern about synchronized coronary sinus retroperfusion is related to the ease with which the coronary sinus catheter can be placed. The design of this catheter allows for relatively easy placement from the internal jugular or subclavian vein. In all patients in this study, the catheter was placed directly into the coronary sinus with the use of fluoroscopy. In two of the five patients, a guidewire was required to advance the catheter further into the great cardiac vein. Satisfactory positioning of the catheter must be confirmed by measurement of the coronary sinus blood oxygen saturation or by a hand-powered contrast injection and visualization of the coronary sinus angiographically. Synchronized coronary sinus retroperfusion was safely implemented and utilized to control myocardial ischemia in two patients in whom significant peripheral vascular disease precluded intra-aortic balloon counterpulsation.

Safety of synchronized coronary sinus retroperfusion. This system appears to be safe, since no untoward hemodynamic, hematologic, pathologic, or adverse clinical effects were noted in this small pilot series. There was a tendency for heart rate to decrease while blood pressure remained unchanged. Inspection of the heart at the time of coronary artery bypass surgery revealed ecchymosis on the anterior surface in one patient and a small hematoma in the area of the coronary sinus in another. These findings are in keeping with those of Drury et al.14 in animals. Pressure in the regional coronary veins may be a potential cause of the anterior ecchymosis, and the coronary sinus catheter was probably the cause of the periadventitial hemorrhage around the coronary sinus. Our patients experienced no discomfort during synchronized coronary sinus retroperfusion. Muffling of the retroperfusion pumping mechanism may make it less disturbing to patients and staff as compared with intra-aortic balloon pumping. In two patients synchronized coronary sinus retroperfusion was maintained beyond 24 hr because it was well tolerated and effective in relieving myocardial ischemia.

The institution of synchronized coronary sinus retroperfusion to augment blood flow to areas of jeopardized myocardium did not cause any detectable hemodynamic alteration. All patients tolerated the augmentation of coronary sinus blood flow from 0.5 to 1.5 ml/kg/min with minimal adverse effects.

Preliminary assessment of efficacy. The intent of this initial trial of synchronized coronary sinus retroperfusion was to determine if it could be safely used in critically ill humans. Patients selected were those presenting with multiple episodes of acute anterior ischemia as evidenced by reversible precordial electrocardiographic changes. Based on experience in animals, it was believed that patients deriving maximal benefit from this intervention would be those with ischemia in the distribution of the left anterior descending coronary artery. In choosing patients with little or no elevation
in total creatinine kinase, we hoped to select individuals with predominantly ischemic, and therefore potentially salvageable, myocardium. It must be emphasized that these five patients were not the usual unstable angina patients. Rather, they were all critically ill individuals whose disease was not controlled with maximal medical therapy and who required some further intervention for stabilization before catheterization, and synchronized coronary sinus retroperfusion was believed to be a reasonable alternative.

Although the primary purpose of these initial studies was to assess feasibility and safety in a clinical setting, patients with unstable angina were selected to permit a preliminary assessment of efficacy. In four of five patients there was improvement with respect to the electrocardiographic manifestations of ischemia within 10 min. In the only patient in whom there was no electrocardiographic improvement, a total occlusion of the circumflex artery and a posterior wall infarction were present.

With each patient serving as his own control, there was significant improvement in each individual’s clinical status during synchronized coronary sinus retroperfusion. Recognizing that unstable angina can vary on an hour-to-hour basis, clinical observations were made over a sufficiently long period (36 hr) before synchronized coronary sinus retroperfusion for comparison with similar variables observed during retroperfusion. Relief of symptoms within 10 min after the institution of retroperfusion therapy, recurrence of angina when the intervention was discontinued, and the attenuation of requirements for pain medication during retroperfusion suggest clinical benefit.

Technical limitations. Animal studies have verified that arterialized blood is required for retroperfusion to be effective since venous blood does not alleviate myocardial ischemia. Thus, cannulation of an artery as well as the coronary sinus is required. Although fluoroscopy is presently required to place the coronary sinus catheter, further advances in design may decrease the fluoroscopy time required for placement of the catheter in the coronary sinus.

To date, the effects of synchronized coronary sinus retroperfusion have only been studied over a relatively short time period. The potential effects on formed blood elements and/or the heart itself of longer exposure to retroperfusion are unknown.

Future directions with synchronized coronary sinus retroperfusion. There are numerous potential applications for synchronized coronary sinus retroperfusion. Although this treatment was initially evaluated in patients with unstable angina, we are presently assessing the potential of this technique to alleviate myocardial ischemia during coronary artery angioplasty procedures.

Retrograde infusion of pharmacologic agents via the coronary sinus is another area of potential application; for example, cold cardioplegic solution could be infused by this method during open heart surgery. Preliminary animal studies at our institution have shown that excellent myocardial cooling is achieved in dogs on cardiopulmonary bypass with continuous pulsatile coronary sinus cardioplegia.

Other potential clinical uses of synchronized coronary sinus retroperfusion that have been evaluated in animals but not yet in humans include instillation of thrombolytic agents, vasodilators, and antiarrhythmic drugs. Retrograde coronary sinus retroperfusion may also have an application in cardiac transplantation. Canine hearts have been preserved for 24 to 36 hr by retrograde perfusion through the coronary sinus, with functional recovery.

We thank Edward Winters and Kenneth Spector, who have been instrumental in the design, development, and clinical application of the system that was used; Steven P. Ball, R.N., and Jeanne Corrao, R.N., who assisted the authors in human trials; Drs. Eliot Corday, Samuel Meeraub, and Kevin Drury, who did the pioneering work with retroperfusion; the staff of the UMMC coronary care unit and cardiac catheterization laboratory, who have been understanding, patient, and supportive of this project; and Mary Larson for her assistance in preparing this manuscript.

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