Intermittent Ischemia: An Alternative to Cardioplegic Arrest during Myocardial Revascularization Surgery

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Lancaster, PA

Abstract

Cardioplegic myocardial protection has become the standard for myocardial revascularization surgery (MRS). In contrast, our group performed 500 consecutive MRS with intermittent aortic cross-clamping for distal anastomoses, left ventricular venting, and systemic hypothermia. Average patient age was 62 years (range: 30–89 years). 194 patients (38.8%) had urgent or emergent MRS. 251 patients (50.2%) had unstable angina and 123 others (24.6%) had preinfarction angina (rest pain in the hospital); 27 (5.4%) had ejection fractions (EF) <0.50 including 75 patients (15.0%) with EFs <0.40; 16 patients (3.2%) had left ventricular aneurysms. Average number of grafts was 3.3 per patient and average ischemic time was 7.6 minutes per graft.

There were five hospital deaths (1.0%), none due to poor myocardial protection and low cardiac output. Only three survivors (0.6%) required an intra-aortic balloon pump (IABP) to wean from cardiopulmonary bypass (CPB): two had acute Mls preoperatively; the other had EF <0.30 and intractable atrial arrhythmias. Only two other patients (0.4%) received any inotropic infusions postoperatively. 18 patients (3.6%) had perioperative Mls.

These results, particularly the virtual absence of postoperative inotropic support, in unselected patients of whom 80% had acute coronary syndromes, indicate that intermittent ischemia (II) can provide excellent myocardial protection for MRS. Brief periods of II alleviate concerns about cardioplegic protection via occluded coronary arteries or internal mammary artery grafts. II provides a simple and safe alternative to cardioplegic arrest for myocardial protection during MRS.

Introduction

Profoundly hypothermic, hyperkalemic cardioplegic arrest of the heart has become the standard technique for myocardial protection during myocardial revascularization surgery (MRS). Since cardioplegia is utilized by virtually all cardiac surgical teams in the United States, the vast majority of perfusionists trained since the mid-1970s (when cardioplegia was successfully reintroduced into cardiac surgical practice) have never been exposed to other non-cardioplegic techniques of myocardial protection. It is the purpose of this paper to present to the perfusion community the physiological bases and specialized techniques of intermittent ischemia as an alternative to cardioplegic arrest during MRS. Cardioplegia is not the myocardial protection panacea of modern cardiac surgery. Randomized and non-randomized studies comparing cardioplegic with non-cardioplegic techniques have not demonstrated differences in clinical results.

Our rationale for using non-cardioplegic myocardial protection during myocardial revascularization surgery has three bases. First, it provides satisfactory clinical results even in patients with severe left ventricular dysfunction. Second, when executed properly a non-cardioplegic scheme is more versatile and allows the cardiac surgical team greater intraoperative flexibility. Third, we are concerned that cardioplegic myocardial protection is inherently ill-suited for patients with multiple occluded native coronary arteries, patent internal mammary artery grafts, or abundant non-coronary collateral blood supply.

Patient Population

500 consecutive patients underwent primary MRS at Lancaster General Hospital with intermittent ischemia from September 7, 1983, to April 5, 1985. All patients in this series were operated upon by two cardiac surgeons experienced in the technique of intermittent ischemia. Seven patients who underwent MRS during this time period were excluded from analysis because they had atherosclerotic aortic disease.
which precluded safe application of an aortic partial occlusion clamp for proximal vein graft anastomoses. MRS in six of these seven patients was therefore performed with a crystalloid cardioplegic technique of myocardial protection for proximal and distal anastomoses during a single prolonged period of aortic cross-clamping. The seventh patient had total calcification of the ascending aortic arch and transverse aorta, combined with bilateral femoral artery occlusion, that precluded safe cannulation for cardiopulmonary bypass. MRS was successfully performed in this patient utilizing a sequential left internal mammary artery graft to the left anterior descending and first diagonal coronary arteries with local vessel occlusion and without the aid of cardiopulmonary bypass. There were no deaths among these seven excluded patients. Patients were also excluded if they underwent concomitant valvular repair or replacement since we use cardioplegia and a topical hypothermia jacket for valve procedures. No patients were excluded from this study because of poor preoperative left ventricular function, ventricular aneurysm, emergency operation, etc. The clinical characteristics of the 500 patients studies are listed in Table 1.

The average age of all patients was 62 years, with a range of 30 to 89 years. 106 patients (21.2%) were 70 years old or greater. 130 patients (26.0%) were female. 94 patients (18.8%) were diabetic. Two hundred fifty-one (251) patients (50.2%) had unstable (progressive) angina, defined as anginal pain at rest while in the hospital. One hundred ninety-four (194) patients (38.8%) underwent urgent or emergent operations. An urgent operation was performed when the patient’s condition was determined to be too precarious to allow safe discharge from the hospital without MRS. An emergency operation was defined as any MRS performed within eight hours of cardiac catheterization.

One-half of the patient population studied had suffered a preoperative myocardial infarction (MI). In 27 patients (5.4%), the MI was evolving acutely, and in 11 others (2.2%), an MI had occurred within the preceding seven days. Twenty-six patients (5.2%) had received streptokinase thrombolytic therapy at the onset of MI symptoms, and 35 patients (7.0%) had undergone prior percutaneous transluminal coronary angioplasty (PTCA). In 10 patients (2.0%), PTCA had been performed less than 24 hours prior to MRS.

One hundred seventy-six (176) patients (35.2%) had left ventricular ejection fractions (EF) of 0.50 or less, including 100 patients (20.0%) with EF less than or equal to 0.40. Sixteen patients (3.2%) presented with ventricular aneurysms.

**Table 1**

<table>
<thead>
<tr>
<th>Preoperative Clinical Characteristics (500 Patients)</th>
<th>Number of Patients</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>SEX</td>
<td></td>
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<tr>
<td>Male</td>
<td>370</td>
<td>74.0</td>
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<tr>
<td>Female</td>
<td>130</td>
<td>26.0</td>
</tr>
<tr>
<td>AGE</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 70 Years</td>
<td>394</td>
<td>79.8</td>
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<tr>
<td>≥ 70 Years</td>
<td>106</td>
<td>21.2</td>
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<tr>
<td>ANGINA</td>
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<tr>
<td>Asymptomatic</td>
<td>14</td>
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<tr>
<td>Stable</td>
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<tr>
<td>Unstable&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Preinfarction&lt;sup&gt;2&lt;/sup&gt;</td>
<td>123</td>
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<tr>
<td>PRIOR MYOCARDIAL INFACTIONS</td>
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<tr>
<td>Total Patients</td>
<td>248</td>
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<tr>
<td>Evolving</td>
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<tr>
<td>Within 1–7 Days of MRS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>11</td>
<td>2.2</td>
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<tr>
<td>Within 1–6 Weeks of MRS</td>
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<td>Remote (more than 6 weeks)</td>
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<td>DIABETES MELLITUS</td>
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<td>PREOPERATIVE STREPTOKINASE THERAPY</td>
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<tr>
<td>PREOPERATIVE PTCA&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Total Patients</td>
<td>35</td>
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<tr>
<td>Within 24 Hrs of MRS</td>
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<td>VENTRICULAR FUNCTION (EF)&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>EF 0.41 to 0.50</td>
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<td>EF &lt; 0.30</td>
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<tr>
<td>VENTRICULAR ANEURYSM</td>
<td>16</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<sup>1</sup>Angina of recent onset or recent increase in frequency or severity
<sup>2</sup>Chest pain at rest while in hospital (New York Heart Association Class IV)
<sup>3</sup>Myocardial revascularization surgery
<sup>4</sup>Percutaneous transluminal coronary angioplasty
<sup>5</sup>Ejection fraction

**Perfusion Techniques**

The cardiopulmonary bypass (CPB) circuit employed by our group during this study consisted of either a bubble or membrane oxygenator, cardiotomy reservoir, and a 40-micron arterial filter. A variety of commercially available devices in each category were evaluated during the course of this study. An in-line arterial oxygen partial pressure (paO<sub>2</sub>) sensor with integral temperature monitor (CardioMet 1000 Model)<sup>a</sup> was also utilized during all perfusions. The CPB circuit prime consisted of lactated Ringer’s solution (2,200 ml +/− 200 ml), bovine lung heparin (5,000 units).

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<sup>a</sup> Orange Medical, Inc., Costa Mesa, CA 92626
sodium bicarbonate (50 mEq), mannitol (25 grams),
methylprednisolone sodium succinate (Solu-Medrol/500 milligrams), cefazolin (Kezol/1 gram), and tobramycin (Nebcin/80 milligrams). Tobramycin was omitted from the priming solution in patients with renal insufficiency due to the nephrotoxicity of aminoglycoside antibiotics. A 5.0-micron pre-bypass filter was inserted into the CPB circuit tubing and the priming solution was recirculated for at least 15 minutes through this filter. 8 If the anticipated hematocrit on CPB was calculated to be less than 25%, washed and packed red blood cells were added to the priming solution after removal of the pre-bypass filter from the extracorporeal circuit.

A DeBakey-type roller pump capable of generating pulsatile arterial flow (Model 7400) was used for all procedures. Pulsatile arterial flow was employed selectively at the discretion of the perfusionist to elevate peak systolic perfusion pressure in patients with impaired renal function to improve renal perfusion and/or in patients with cerebral vascular disease to augment cerebral perfusion. Arterial cannulation was accomplished with either a 22 Fr or 24 Fr aortic cannula for continuous arterial in-flow (Model 1869). For pulsatile arterial in-flow, either a 26 Fr or 28 Fr aortic cannula was used (Model 1869). Femoral artery cannulation was accomplished with a 5.4 mm beveled metal cannula; femoral arterial cannulation was considered to be a contraindication to pulsatile perfusion. Venous drainage by gravity was achieved using either a 40Fr/34Fr two-stage right atrial/inferior vena cava cannula (Model 1969) or a 51Fr/36Fr two-stage right atrial/inferior vena caval cannula (Model 12340). Anesthesia was maintained throughout CPB with a high-dose narcotic (fentanyl citrate), supplemented with either a benzodiazepine (diazepam or lorazepam) and/or an inhalational anesthetic (isoflurane only). Muscular paralysis was maintained with one of three non-depolarizing type muscle relaxants (atracurium, vecuronium, or pancuronium). Heparin derived from bovine lung was administered in sufficient quantity to contain external water heating and cooling device (Hemotherm Model). The perfusate temperature was reduced to 23°C to 2°C prior to the initial cross-clamping of the aorta with careful attention to the maintenance of a water-to-blood temperature gradient not in excess of 12°C. Upon initial cross-clamping of the aorta, the perfusate temperature was rewarmed to 29°C to 1°C to facilitate defibrillation of the heart during the initial reperfusion interval. All patients were cooled systematically to a rectal temperature of 30°C. Hypothermic perfusion flow rates were maintained at 2.0 L/min/M² +/- 0.2 L/min/M² and were adjusted by the perfusionist according to the adequacy of tissue perfusion as measured by the venous oxygen partial pressure (pO₂).

In order to maintain adequate oxygen carrying capacity, the patient’s hematocrit was held in the range of 25–28% during CPB. The type of volume added to the circuit during CPB was governed by this criteria. If the hematocrit was greater than 28%, isotonic intravenous crystalloid solution was added (lactated Ringer’s). If the hematocrit was less than 25%, packed red blood cells were added. Mean perfusion pressure during CPB was maintained in the range of 50 to 75 mmHg. If pharmacologic intervention was required, vasoconstriction was obtained with phenylephrine hydrochloride (Neo-synephrine). Vasodilitation was obtained with either sodium nitroprusside (Nipride) or intravenous nitroglycerin Tri-dil). The mean arterial perfusion pressure was always lowered transiently by reduction of the perfusion flow rate for application or removal of an aortic clamp.

An alpha-stat blood gas management scheme was maintained for all perfusions conducted during this study. Arterial and venous blood gas samples were drawn from the perfusion circuit after the first five minutes of CPB and every 30 minutes thereafter to corroborate the accuracy of the in-line pO₂ meter. A pO₂ of 100 to 125 mmHg was considered to be optimal in an attempt to limit the release of free oxygen radicals. Optimal ranges for all other blood gas parameters were defined as being in the usual normal range when measured at 37°C (pH = 7.40 +/- 0.2, pH = 40 mmHg +/- 2 mmHg, base excess = +2 to -2, pO₂ = 40 mmHg +/- 5 mm Hg).
Rewarming of the patient was initiated upon application of the final aortic cross-clamp. Again, a water-to-blood temperature gradient not in excess of 12°C was maintained during rewarming. Perfusion flow rates were gradually raised to the normothermic perfusion rates described earlier. Weaning of the patient from CPB was begun when the rectal temperature had risen to at least 34°C.

Surgical Techniques
Exposure of the left internal mammary artery (LIMA) was accomplished with a standard median sternotomy retractor opened eccentrically to elevate the left side of the chest. Dissection of the LIMA was performed with electrocautery. Saphenous veins were harvested through continuous incisions to avoid excessive traction, and they were distended with a pressure-limiting device. Generally, the aorta was cannulated for arterial inflow, although femoral arterial cannulation was utilized on occasion if the condition of the aorta precluded safe aortic cannulation. The right atrial appendage was cannulated with a single, two-stage right atrial/inferior vena cava cannula for gravity venous drainage. A flexible vent catheter was inserted into the left ventricle via the right superior pulmonary vein. The vent catheter was connected to the cardiotomy reservoir by closed gravity drainage. Systemic hypothermia to 30°C was induced in all patients, so that blood temperature (and presumably myocardial temperature) was considerably lower than 30°C during the initial stages of the operation. Each distal anastomosis was constructed with a single running suture during a brief period of aortic cross-clamping, followed by the respective proximal anastomosis with a partial occlusion clamp on the aorta. A global reperfusion interval was maintained during construction of the proximal anastomosis. Ventricular fibrillation occurred either spontaneously as the perfusate cooled or it was induced with a brief electrical stimulus as the aorta was cross-clamped. The heart was defibrillated with low energy levels (10 watt-seconds) during the reperfusion intervals whenever possible, although persistent fibrillation was considered preferable to repeated countershocks. A bolus dose of 100 milligrams of lidocaine hydrochloride (Xylocaine) was administered routinely by the perfusionist after the initial ischemic interval to facilitate defibrillation.

In patients with acute evolving Mls, failed PTCAs, or severe preoperative left ventricular dysfunction, the most ischemic zone of myocardium was revascularized first. With these exceptions, operations were performed according to our group’s established protocol. All procedures were carefully planned to ensure maximum reperfusion time between ischemic intervals without disrupting the progress of the surgery. Circumflex system grafts were performed first. The right coronary arterial system was not exposed until after the LIMA graft(s) was(were) completed, thus providing a reperfusion interval after the final distal LIMA anastomosis.

Two sequential coronary artery anastomoses to a single vein graft were often performed during one aortic cross-clamping period. However, if both distal anastomoses could not be comfortably performed in less than 12 to 14 minutes, the proximal anastomosis was done after the first sequential distal anastomosis. Vein grafts with more than two distal anastomoses were performed only rarely. Sequential anastomoses were confined to two branches of the same coronary arterial system. Both anastomoses of sequential LIMA grafts were occasionally performed during a single aortic cross-clamp interval, but usually the side-to-side anastomosis was performed first followed by a reperfusion interval. The LIMA’s distal end was prepared for grafting during such reperfusion intervals in lieu of the construction of a proximal anastomosis. Reperfusion times almost always exceeded the ischemic times and in no event were the reperfusion times less than five minutes in duration.

Systemic rewarming was initiated with the final application of the aortic cross-clamp. A left atrial pressure monitoring catheter was inserted in all patients through the right superior pulmonary vein after the left ventricular vent catheter had been removed. Right heart balloon flotation (Swan-Ganz type) catheters were only used in a very small number of patients with exceptional preoperative hemodynamic problems.

Results

The characteristics of the operations performed are summarized in Table 2. One thousand six hundred sixty-eight (1,668) distal anastomoses were constructed, an average of 3.3 grafts per patient (range: 1 to 6 grafts). Left internal mammary artery (LIMA) grafts were carried out with increasing frequency during the period of this study. Two hundred sixty-two (262) pedicled LIMA grafts and three free LIMA grafts were performed, six of which were done in the left coronary arterial system. There were 143 sequential grafts and 20 constructed “Y” grafts. The duration of CPB ranged from 24 to 166 minutes with an average of 86.7 minutes per patient. All proximal and distal anastomoses were carried out during CPB. Average total aortic cross-clamp time was 25.5 minutes per patient (range: 4 to 53 minutes), or 7.6 minutes per distal anastomosis.
is defined as death within the same hospitalization. All five deaths occurred in patients 68 years of age or older.

One 70-year-old male who had suffered an anterior MI and unstable renal failure. The second death was in a 78-year-old patient who underwent MRS due to intractable rest angina despite severe calcification throughout the entire coronary arterial system. The right coronary artery had no lumen and the obtuse marginal was not graftable because of severe calcification. The left anterior descending and second marginal coronary arteries were bypassed. As the chest incision was being closed, she became hypotensive with marked S-T segment elevation. CPB was resumed and she was treated with sublingual nifedipine for presumed coronary artery spasm, but she could not be weaned from CPB. Femoral insertion of an IABP catheter was attempted but was unsuccessful due to bilaterally occluded femoral arteries. A severely calcified aorta precluded trans-thoracic passage of the IABP catheter. She expired in the operating room upon termination of extracorporeal circulatory support.

There were five operative deaths (1.0%). Mortality is defined as death within 30 days of operation or within the same hospitalization. All five deaths occurred in patients 68 years of age or older. One death occurred in a 70-year-old male with occluded right, circumflex, and left anterior descending coronary arteries. This patient had an intra-aortic balloon pump (IABP) inserted at cardiac catheterization for cardiogenic shock and ventricular fibrillation. His leg became obviously ischemic and he was submitted for emergency MRS; immediate MRS was performed with a good hemodynamic result. The IABP catheter was removed in the surgical suite at the conclusion of the operation and the femoral artery was repaired. Nevertheless, his serum creatine phosphokinase (CPK) rose to 24,000 (with negative CPK-MB fraction) and he developed gross myoglobinuria with renal failure that was refractory to therapy. He expired three weeks later due to renal failure. The second death was in a 78-year-old male who had suffered an anterior MI and unstable angina after failed PTCA. His aorta was severely calcified. A sequential LIMA graft to the left anterior descending and first diagonal coronary arteries was performed during a single application of the aortic cross-clamp. This patient never regained full consciousness postoperatively, although he was able to move all extremities. Two weeks later he had a sudden cardiorespiratory arrest from which he was not resuscitated.

The third death was in a 69-year-old female with a massive preoperative MI (CPK = 8,400). Cardiac catheterization revealed occlusion of the left main coronary artery and an ostial stenosis of the right coronary artery. Streptokinase, PTCA, and IABP insertion were all utilized prior to emergent MRS. She expired 16 days postoperatively of renal failure and pneumonia. The fourth death occurred in a 68 year old female with persistent angina after an inferior MI due to right coronary artery occlusion. She underwent MRS to both terminal branches of the right coronary artery 12 days post-MI. This patient was being prepared for discharge one week after operation when she suffered a sudden cardiac arrest which was initially attributed to a pulmonary embolus or cardiac tamponade because of severe systemic venous congestion with a central venous pressure of 30 mmHg. At emergency re-operation, however, the right ventricle was found to be almost totally infarcted and akinetic. Despite patency of both grafts, the right coronary had thrombosed retrograde from the original site of distal occlusion, closing all of the major right ventricular coronary branches. She expired shortly after re-operation.

The fifth death was in a 75-year-old obese female who underwent MRS due to intractable rest angina despite severe calcification throughout the entire coronary arterial system. The right coronary artery had no lumen and the obtuse marginal was not graftable because of severe calcification. The left anterior descending and second marginal coronary arteries were bypassed. As the chest incision was being closed, she became hypotensive with marked S-T segment elevation. CPB was resumed and she was treated with sublingual nifedipine for presumed coronary artery spasm, but she could not be weaned from CPB. Femoral insertion of an IABP catheter was attempted but was unsuccessful due to bilaterally occluded femoral arteries. A severely calcified aorta precluded trans-thoracic passage of the IABP catheter. She expired in the operating room upon termination of extracorporeal circulatory support.

Major complications are listed in Table 3. Five patients (1.0%) required insertion of an IABP postoperatively that had not been inserted preoperatively. All of the patients who required IABP support were greater than 65 years old. Three of these IABP patients (0.6%) required IABP support to wean from CPB. Two patients had suffered acute myocardial infarctions at cardiac catheterization (one with PTCA). The third patient had a preoperative EF of 0.30 and intractable atrial arrhythmias. A fourth patient with severe rest angina and an ungraftable circumflex system deteriorated during sternal closure due presumably to coronary spasm. This patient improved with administration of calcium channel blocking drugs while the IABP was mobilized. Since the IABP catheter had already been inserted, it was decided to leave the IABP in place and support the patient. The IABP was utilized in this patient for less than 24 hours. The fifth patient developed coronary artery spasm eight hours postoperatively. An IABP was inserted to acutely stabilize the patient and calcium channel blocking therapy was begun. IABP support was maintained for less than 24

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### Table 2

**Operation Characteristics (500 Patients)**

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percent</th>
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<tbody>
<tr>
<td><strong>DISTAL ANASTOMOSES</strong></td>
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<tr>
<td>(average 3.3 per patient)</td>
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<td></td>
</tr>
<tr>
<td>Sequential vein grafts</td>
<td>143</td>
<td>28.6%</td>
</tr>
<tr>
<td>Constructed ‘Y’ grafts</td>
<td>20</td>
<td>4.0%</td>
</tr>
<tr>
<td>Internal mammary artery grafts</td>
<td>262</td>
<td>52.4%</td>
</tr>
<tr>
<td>Free internal mammary artery grafts</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Frozen homograft vein grafts</td>
<td>3</td>
<td>0.6%</td>
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<td><strong>CORONARY ENDARTERECTOMY</strong></td>
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<tr>
<td>Right coronary system</td>
<td>8</td>
<td>1.6%</td>
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<tr>
<td>Left coronary system</td>
<td>6</td>
<td>1.2%</td>
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</table>
hours. This fifth IABP patient underwent repeat (post-MRS) cardiac catheterization which revealed all three bypass grafts to be patent and normal left ventricular function. Two other patients (0.4%) received inotropic infusions without IABP support to wean from CPB. Inotropic support, defined as any inotropic drug infusion other than digoxin or calcium, was instituted whenever systemic arterial perfusion pressure was less than or equal to 90 mmHg and left atrial pressure was greater than or equal to 25 mmHg. The remaining 488 survivors received no inotropic infusions or mechanical circulatory support postoperatively.

Nine patients (1.8%) suffered neurologic insult (stroke). Eighteen patients (3.6%) had perioperative MI, defined as the appearance of new Q waves in the electrocardiogram or elevated CPK with greater than 10% CPK-MB fraction.

**Late Results**

Complete follow-up was obtained for all survivors by direct contact with the patient, the patient’s family, or the referring physician. There were six late deaths, at 1, 2, 3, 8, 9, and 18 months postoperatively. Five of these late deaths were due to non-cardiac causes. One patient died of colon cancer, one committed suicide, one patient on chronic hemodialysis preoperatively expired due to renal failure, one died of ruptured cerebral aneurysm, and one died of disseminated aspergillosis infection related to chronic steroid therapy for severe asthma. The only late cardiac death was attributable to congestive heart failure and renal failure two months postoperatively in a 76-year-old male with a preoperative EF of 0.28 and a left ventricular end diastolic pressure of 29 mmHg.

Twenty-three patients, with a total of 74 bypass grafts in place, underwent repeat coronary arteriography from 5 days to 21 months postoperatively (mean: 6.7 months). Only 2 patients were studied electively; the remaining 21 patients were studied to evaluate complaints of recurring chest pain. Overall, 65 of 74 grafts (88%) were patent in this adversely selected, non-randomized group of patients. Nine of nine (100%) LIMA grafts were patent (eight to the left anterior descending coronary artery and one to the second diagonal coronary artery). Fifty-six (56) of 65 reversed saphenous vein grafts (86%) were patent.

**Discussion**

Hypothermic, hyperkalemic cardioplegia (either crystalloid or blood) has virtually replaced all other techniques of myocardial protection during MRS. Most non-cardioplegic techniques, such as intermittent ischemia and local vessel occlusion, were generally abandoned during the mid- to late 1970s. Since that time, most reports in the literature have demonstrated the superiority of cardioplegia. We believe that this phenomenon has occurred for two reasons. First, a vast majority of practitioners in cardiac surgery and perfusion technology are generally unfamiliar with the inherent subtleties in the techniques that are required for successful implementation of non-cardioplegic methods of myocardial protection. Secondly, a vast expansion of knowledge regarding cardiac physiology and pathophysiology, surgical technology, and extracorporeal circulation, has occurred since the mid-1970s. Non-cardioplegic myocardial protection was abandoned before the advent of this body of knowledge.

These advances have enabled the relatively few remaining users of non-cardioplegic methods to “fine tune” their application of non-cardioplegic techniques. When the technique of cardioplegia was first introduced, it was dismissed due to inappropriate application of the technique although its fundamental bases were correct. Once the technique of cardioplegia was refined and implementation was performed correctly, cardioplegia reestablished itself as a useful method of myocardial protection.

The same analogy can be made for intermittent ischemia and other non-cardioplegic techniques of myocardial protection. Interestingly, the few contemporary randomized studies that directly compare hypothermic cardioplegia and correctly-performed intermittent ischemic techniques similar to ours have not demonstrated the clinical superiority of either technique. Such comparative studies are further complicated by the infinite variety of cardioplegic solutions and the differences among various strategies for non-cardioplegic myocardial protection.

Good clinical results are the most fundamental criterion of adequate myocardial protection. The results in this series of patients are quite satisfactory when compared to the results reported in other large series. The patients in this study had a high incidence of acute coronary syndromes requiring either urgent or emergent surgical intervention. The average patient age was 62 years, and all deaths were in patients greater

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**Table 3**

Major Complications (500 Patients)

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Death</td>
<td>5</td>
</tr>
<tr>
<td>IABP* (not present preoperatively)</td>
<td>5</td>
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<tr>
<td>Inotropic Support</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic Insult (Stroke)</td>
<td>9</td>
</tr>
<tr>
<td>Perioperative Infarction</td>
<td>18</td>
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*IABP = intra-aortic balloon pump*
than 68 years old. There was a high incidence of females (26%), who are known to have a higher operative mortality. The age and sex distribution of these patients and the large number with acute coronary syndromes accounts in part for the average of 3.3 grafts per patient.

The five operative deaths were unrelated to the technique of myocardial protection and only one was associated with perioperative low cardiac output. The use of an IABP in five other patients seemed likewise unrelated. Indeed, four of the five patients who received the IABP could probably have been managed with inotropic support alone. However, we believe that IABP counterpulsation provides better protection of the myocardium than prolonged administration of inotropic support and hence opted for the former therapeutic modality. The use of inotropic support for only two other patients in this series differs markedly from most reports of MRS performed with other techniques of myocardial protection. In a controlled study, Flameng, et al, compared intermittent ischemia at 32°C and 25°C with cold cardioplegia. They defined inotropic support as “more than 4 micrograms of dopamine per minute (sic) for at least 12 hours” and found such support necessary in 12.5%, 8.7%, and 8.0% respectively in the three patient groups. Pepper, et al, compared cardioplegia with intermittent ischemia and used inotropic support in 16% and 12% of the respective groups. These investigators’ higher incidence of inotropic drug administration in their intermittent ischemia groups than we experienced in our series may be related in part to their use of only mild (32°C) hypothermia in most patients and longer ischemic intervals (average 11.1 minutes for Flameng, et al; 10.0 minutes for Pepper, et al). Although the technique of Pepper, et al, resembles our own, it is unclear from Flameng’s report whether or not an adequate reperfusion interval was provided after each ischemic period.

The fundamental basis of the intermittent ischemic technique employed in this study is that myocardial oxygen consumption during ischemic arrest decreases markedly with hypothermia. The effects of ischemia for less than 20 minutes at 30°C are apparently rapidly reversible by adequate reperfusion. In addition, the oxygen debt incurred is repaid more rapidly in a decompressed heart. Although fibrillation was often induced with a brief electrical stimulus at the onset of the ischemic period, fibrillation continued spontaneously thereafter and the hearts usually became quiescent after a short period, further decreasing myocardial oxygen requirements. In studies conducted by Hottenrot, et al, electrical fibrillation had a detrimental effect on regional myocardial blood flow in experimental animal models, but this was not true in the case of spontaneous fibrillation. Spontaneous fibrillation was associated with preservation of myocardial blood supply, particularly to the subendocardium. Furthermore, the brief ischemic intervals realized in this analysis minimize concern about the reperfusion injury that has been demonstrated after prolonged periods of cardioplegic arrest.

Hottenrot, et al, and Buckberg have reported that ventricular fibrillation during CPB may result in increased myocardial wall tension, increased myocardial oxygen consumption, and impaired subendocardial blood flow. Some factors potentiating these deleterious effects include prolonged high-frequency electrical stimulation of the heart, ventricular distension, low myocardial perfusion pressure, coronary artery disease, and ventricular hypertrophy. Our perfusion techniques are specifically oriented to attenuate and/or eliminate these deleterious effects. The perfusionist can achieve this goal by increasing myocardial perfusion pressure during reperfusion intervals, maintaining an appropriate oxygen carrying capacity (hematocrit), optimizing perfusate temperature, pH, serum potassium, and physiologic oxygen content, as well as administration of an antiarrhythmic agent. In patients with severe preoperative left ventricular dysfunction or ventricular hypertrophy, myocardial protection can be further enhanced by employing pulsatile flow.

In contrast, cardioplegic solution may be unevenly distributed in hearts with severely stenotic or occluded coronary arteries. This fact has been emphasized repeatedly in the literature. Surgical strategies that first revascularize areas supplied by occluded arteries, in order to permit infusion of cardioplegic solution through these vein grafts, are compromised by the increasing use of left internal mammary arteries for critical bypasses. In addition, flow from non-coronary collateral circulation may wash out cardioplegic solution and lessen its effectiveness. In contrast, such non-coronary collateral perfusion is actually beneficial with intermittent ischemia since it decreases the accumulation of an oxygen debt during aortic cross-clamping. Cardioplegic myocardial protection is especially complicated during reoperation on a patient with a patent internal mammary artery graft. An arterial graft of this type represents an extreme example of myocardial non-coronary collateral blood supply.

Non-cardioplegic myocardial protection is particularly well suited for patients with multiple totally occluded coronary arteries, especially if the occlusions are acute (e.g. following PTCA). Collateral circulation is usually not well developed in the latter set of patients, and it is usually possible to construct the critical bypass graft or grafts without aortic cross-clamping. In a recent report, Horneffer, et al, demonstrated that regional
reperfusion before global ischemic arrest improved the salvage of infarcting myocardium in the swine model with experimental coronary artery occlusion. In contrast, cardioplegia administration in such patients is poorly distributed to the most vulnerable areas of myocardium and therefore severely limits the effectiveness of cardioplegic arrest.

Non-cardioplegic myocardial protection during MRS also minimizes concern about patients with high titers of cold agglutinins and eliminates the need for cumbersome management strategies that require wash out of coronary blood with crystalloid solutions before changing to blood cardioplegia in such patients. Our perfusion technique in positive cold agglutinin patients is to cool the perfusate more slowly, ensuring that the blood temperature does not fall below 28°C (most cold agglutinins are activated only below this temperature). Systemic patient temperature is then allowed to "drift" down to 30°C.

No single technique of myocardial protection is all-encompassing. For procedures wherein prolonged periods of ischemia are unavoidable, such as during valvular procedures or combined coronary/valve procedures, our group utilizes blood cardioplegia combined with a topical hypothermia jacket. However, during routine myocardial revascularization, the necessity for prolonged periods of ischemia is uncommon. As described earlier, MRS lends itself to the technique of intermittent ischemia due to the many separate proximal and distal anastomoses, each requiring 7 to 15 minutes for construction. However, in rare circumstances, a left anterior descending coronary endarterectomy with a long anastomosis is necessary. Such a long anastomosis is time-consuming and might strain the safe limits of non-cardioplegic ischemia. In situations where an ischemic interval greater than 15 minutes is anticipated, we employ hypothermic cardioplegia for myocardial protection. Such occasions arise very infrequently. In fact, six patients in this series of 500 (1.2%) had endarterectomies to the left coronary system with intermittent ischemic arrest and without untoward results.

Severe calcification of the aorta is another relative contraindication to the use of intermittent ischemia. In such circumstances, standard hypothermic cardioplegic arrest for myocardial protection during MRS is considered by our group to be the preferable alternative. Repeated clamping and unclamping of a severely calcified aorta could potentially cause numerous embolic showers due to dislodgement of atherosclerotic material. When the aorta is only moderately atherosclerotic, but retains normal strength and pliability, we utilize our standard intermittent ischemia technique. In such cases, the excluded cul-de-sac of aorta within the partial occlusion clamp is copiously irrigated prior to completing each proximal anastomosis to avoid the release of atherosclerotic emboli.

Repeated application of a partial occlusion clamp on such aortas can cause focal aortic injury. The use of intermittent ischemia requires continuous observation of the aorta by the surgeon in order to detect small intimal tears with intact overlying adventitia. Such intimal tears must be oversewn immediately; they can be prevented by using clamps with soft jaws and decreasing aortic pressure before applying or removing clamps. Decreasing aortic pressure during clamping and unclamping of the aorta is the responsibility of the perfusionist and is accomplished by lowering the perfusion flow rate momentarily (less than ten seconds) to decrease perfusion pressure. Usually, decreasing the flow rate to 1.0 L/min/M² is sufficient to decrease aortic pressure to a safe level. It is noteworthy that there were no early or late aortic dissections in our series of 500 patients. We believe this is due in part to the fact that when a patient’s aorta is heavily calcified and rigid, we utilize our hypothermic cardioplegic arrest technique for myocardial protection, with all proximal and distal anastomoses performed during a single prolonged period of aortic cross-clamping.

As noted earlier, no single technique of myocardial protection is all encompassing. There are various successful strategies for both cardioplegic and non-cardioplegic techniques. Akins has reported excellent results with elective ventricular fibrillation, local vessel occlusion for distal anastomoses, no aortic cross-clamping, systemic hypothermia, and left ventricular venting. In 500 patients in his series, there were only two deaths (0.4%). However, Akins’ series is not comparable to ours in that all of his patients had elective (non-emergency) procedures. Nevertheless, it is noteworthy that only 16 patients in Akins’ series (3.2%) required an IABP intraoperatively or postoperatively. The use of inotropic support and the overall incidence of low cardiac output were not specifically mentioned.

Conclusion

The technique of intermittent ischemia requires a completely different perfusion management strategy from that employed during cardioplegic arrest of the heart. Increased patient safety is achieved by the elimination of any cardioplegic delivery system incorporated into the perfusion console set-up and its attendant risks. However, successful implementation of intermittent ischemia for myocardial protection during MRS is dependent upon adequate substrate delivery during the reperfusion intervals. Adequate substrate delivery is achieved primarily by maintaining a physiologic arterial oxygen content at an appropriate
perfusion pressure. Both of these parameters are under the direct control of the clinical perfusionist. The perfusionist must remain constantly aware of the progress of the surgical procedure in order to make all of the necessary perfusion adjustments required during both the ischemic periods and the reperfusion intervals. The cardiac surgeon must carefully plan the sequence of anastomosis construction and other obligatory surgical tasks so that adequate restoration of myocardial energy and substrate stores can be achieved during the reperfusion interval without compromising the efficient progress of the surgery or compromising the "payback" (reperfusion) period itself.

Intermittent ischemia provides a simple and safe alternative to cardioplegic arrest during myocardial revascularization surgery. However, it is not the purpose of this paper to demonstrate the superiority of one technique of myocardial protection over another. As with virtually all aspects of cardiac surgery and clinical cardiovascular perfusion, that system and any related techniques which are most familiar to and skillfully applied by any given cardiac surgical team can generate good results. Instead, we have attempted to show that non-cardioplegic techniques, such as our technique of intermittent ischemia, can be applied successfully during MRS when performed expeditiously within a coordinated surgical/perfusion strategy, and with the full benefit of modern perioperative management of coronary artery disease.

References

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**Questions from the Audience**

**Question—Mike Harloff:** Do you have any trouble trying to get the heart to beat in the reperfusion time of 30 degrees?

**Answer:** We don’t. As I mentioned in the paper, when we initially cool, we take the perfusate down to 23 degrees so that the heart is optimally cool, initially. We then rewarmed the perfusate to 28 to 30 degrees, so that during the first reperfusion interval, the heart can be defibrillated with the administration of lidocaine. We give lidocaine after the first cross-clamp and then the heart is defibrillated. But the perfusates do have to be in the 28 to 30 range to do that successfully. Now there are times when the heart won’t defibrillate, and we believe that continued fibrillation with perfusion according to our protocol is preferable to repeated counter shocks. We will not try to shock the heart more than twice to establish beating.

**Question—Frank Hurley:** Relative to the blood usage on bypass, I noticed you maintaining your hematocrits in the 25–28 range. Could you give me an average blood utilization during a procedure?

**Answer:** Blood utilization during a procedure in our institution is 2.1 units per patient, and on bypass, it’s .8. We use fewer than 500 units of blood for all the patients in this series.

**Question—Frank Hurley:** Have you had occasion to alter your surgical technique due to sequential or jump graphing?

**Answer:** Absolutely. Fortunately, we have a very fast surgeon. Sometimes they will do two distals on a single aorta cross-clamp. The time ranges have been as low as 9 minutes, and an average 12 to 14 minutes. So when they do two sequentials on, for instance, a sequential mammary, when you don’t have time, you don’t have a need to construct a proximal anastomosis between distals. They will prolong the ischemic interval. As I said earlier, if we anticipate any kind of ischemic interval greater than 15 minutes, we will opt for cardioplegia. It’s what we consider the primary benefit of this whole scheme of things. We can literally customize the myocardial protection to the surgical requirements.

**Question—Mike Tam:** One of our surgeons spent a month with Dr. Carpentier in France, and we have begun using intermittent cross clamp for both mitral valve repairs and combined mitral valve repairs and coronaries. In our series we only keep the aorta cross-clamped during the valve repair procedure to a
maximum of 15 minutes and reperfused a maximum of five minutes, and that has worked quite nicely.

Answer: The technique can be applied during valve procedure. However, we feel that it adds unnecessary delay to the surgery. As you mentioned, the reperfusion rule of five minutes during or after a 15-minute cross-clamp seems to be adequate to restore myocardial energy stores. But during those five minutes, while you're reperfusing the heart, you have a bloody surgical field. It slows down the progress of the operation. Therefore, for valve procedures, we use blood cardioplegia and a topical hypothermia jacket.

Response—Mike Tam: With Dr. Carpentier's technique, the surgeon has to intermittently appreciate how the valve is collapsing during repairs.

Question—Phil Wagoner: Do you have any comparisons in overall pump time between your intermittent ischemic arrests and regular cardioplegic systems?

Answer: I don't have any specific data for you, but I can tell you from clinical experience that whenever we use cardioplegia, it requires from anywhere to 15 to 25 minutes additional pump time. And the reason for that is that we cool the patients to a greater degree of hypothermia. We usually go down to 26, increasing the rewarming time.

Question—Phil Wagoner: Do you have some means of quickly administering cardioplegia in the case of surgical complication or mishap—something that would unexpectedly prolong your ischemic time?

Answer: No, we don't. In the instances when we have opened up a patient and found a severely calcified aorta, and had to switch to a cardioplegic technique, we then had to scramble to set up a cardioplegic system. It usually takes anywhere from 10 to 15 minutes. The patients are not on bypass during that time. One thing that I will say about the intermittent ischemic technique: it does require a very fast surgeon. I'm not familiar with the average ischemic, or the average distal construction time, but ours was seven and a half minutes. Excellent surgical skills are necessary to execute this technique.