Coronary Perfusion Versus Cold Ischemic Arrest During Aortic Valve Surgery

A Randomized Study

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SUMMARY

Sixty-four randomized patients undergoing primary, isolated, scheduled, prosthetic aortic valve replacement were studied to determine the safety of coronary perfusion and mild hypothermia (31 patients) and of cold ischemic arrest (33 patients). Cardiac performance, metabolism, and isoenzyme release and the electrocardiogram were studied early postoperatively. No differences greater than expected by chance were found between the two groups; however, the difference between group means of several hemodynamic variables was significantly larger than experimental error. Combined abnormalities of creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) heart-specific isoenzymes, indicative of myocardial necrosis, were found in 33 of 48 patients (68.7%) so studied. The incidence was similar in both study groups. In 14 of 52 (27%) patients with electrocardiographic studies, changes indicative of new infarction or ischemia were demonstrated, but no differences in incidence between the two groups of patients were found. In both groups the transmyocardial excess lactate immediately postoperatively was elevated, falling to near normal over the next 24 hours. Aortic crossclamp and cardiopulmonary bypass times were less by 27% and 21% respectively when cold ischemic arrest was used.

Additional Indexing Words:
Cardiopulmonary bypass  Isoenzymes  Myocardial preservation
Micromanometers

During open intracardiac operations the myocardium should be as fully protected against damage as is compatible with adequate surgical exposure. For aortic valve replacement, this has been attempted by a variety of methods, including direct coronary arterial perfusion and ischemic arrest with varying myocardial temperatures. The mortality and morbidity reported with most methods are low but real. The causes of the residual morbidity and mortality are not clear, and there is disagreement as to what method is the best. We wished to study this matter and to determine the comparative safety of the two methods we had been employing clinically, coronary perfusion with mild hypothermia and a beating heart, and cold ischemic arrest.

Materials and Methods

Study Groups

Sixty-four patients undergoing primary, isolated, scheduled, prosthetic aortic valve replacement were studied in a five month period beginning 2 February 1973. Thirty-one patients (48.4%) were randomized to the coronary perfusion group and 33 (51.6%) to the cold ischemic arrest group. One patient died; he succumbed in the operating room of intractable ventricular fibrillation after being managed by coronary perfusion.

Technique of Randomization

Consecutive patients were randomized by pairs separately for each faculty surgeon using a random digit table.¹ At operation the surgeon decided to abort the randomization in the patient’s best interests in six instances. In each case the surgeon’s next patient was done by the method previously assigned to the excluded patient.

1190 Circulation, Volume XLIX, June 1974
Surgical Management

For coronary perfusion both coronary arteries were cannulated and perfused at a temperature of 32° C soon after the aorta was crossclamped (in one patient, only the left was perfused). Mean flow to the left coronary artery was 138 ± 6.5 ml/min at a mean pressure in the coronary perfusion line of 111 ± 2.7 mm Hg and to the right 109 ± 7.1 ml/min at 109 ± 3.3 mm Hg. Occasionally coronary perfusion was interrupted briefly to improve exposure. Near the end of the perfusion the temperature of the perfusate was elevated to 39° to rewarm the patient. Spontaneous ventricular fibrillation, when it occurred, was promptly reversed by electroversion.

For cold ischemic arrest, bypass was initiated and maintained for about 4 min at a perfuse temperature of 25°C after which the temperature was lowered for about 2 min to 12°. The aorta was then crossclamped and the perfusate temperature raised to 28° until near the end of the perfusion when it was elevated to 39°C for rewarming the patient. A bubble oxygenator was used. The pump oxygenator was primed with 500 ml ACD blood drawn the day prior to surgery, 7.5 ml heparin, 60 ml 1.4% NaHCO₃, 1500 ml 5% dextrose in 0.45% saline, and 5 ml 10% CaCl₂. A Starr-Edwards cloth-covered, composite seat prosthesis was used for valve replacement in 57 of the 64 patients (80.1%), a Bjork-Shiley in three (4.7%), a Braunwald-Cutter in three (4.7%), and a valvulotomy was performed in one (1.6%).

Postoperatively all patients were managed by our usual patient management programs. Drug administration included isoproterenol and/or epinephrine when cardiac index was less than about 1.8 L min⁻¹ m⁻² (ten patients), trimethaphan camsylate (Arfonad) for reducing afterload (six patients) and lidocaine for arrhythmias (three patients).

Instrumentation

Left ventricular (LV) wall thickness was measured with a 22 gauge needle introduced into the LV just until blood flowed back from the LV cavity. LV transverse diameter was measured using a caliper. LV subepicardial temperature was measured using a needle thermistor.

A high fidelity pressure micromanometer was introduced into the right superior pulmonary vein and advanced into the LV. A 14 gauge catheter, with 4 side holes was inserted through the right atrial wall and advanced into the coronary sinus and its position reconfirmed at each study period. Routine pressure monitoring catheters were placed in the left and right atria, and the pulmonary and radial arteries.

Postoperative Studies

 Hemodynamic, enzyme, and metabolic data were obtained at study periods which averaged 4, 9, 21, 26, 31, and 46 hours after initiation of cardiopulmonary bypass. In addition, blood for enzyme analyses was obtained 30 min prior to bypass (control sample) and again at 52 hours. Cardiac index was derived by computer from triplicate measurements of cardiac output (coefficient of variation (CV) = 6.94%) by the indicator dilution technique using indocyanine green as the indicator. Peak (dp/dt)-p was derived from triplicate measurements of LV pressure derivative (CV = 4.72%) divided by the difference between LV pressure at peak dp/dt and LV end-diastolic pressure. Other derived variables were obtained in the usual fashion.

Total creatine phosphokinase (CPK) and its isoenzymes, MM, MB, and BB, and total lactate dehydrogenase (LDH) and its five numbered isoenzymes were obtained in blood drawn from the coronary sinus, but on occasion from the right atrium; the final sample was always from a peripheral vein. Heart-specific CPK-MB isoenzyme, as analyzed by the method cited, is consistently absent in normal serum; in nonsurgical patients sustaining documented myocardial infarction it remains detectable for no less than 24 hours after its initial appearance; and in patients undergoing intracardiac operations it has been absent despite left ventricular venting and multiple defibrillation attempts. Thus, the detection of CPK-MB in serum was considered abnormal and indicative of myocardial damage. Haptoglobin levels were determined in three patients early in the study to ascertain the level of hemolysis.

Arterial and coronary sinus lactate and pyruvate concentrations were determined in duplicate enzymatically (CV = 2.7%, departure from standard = 5.82 ± 2.865%, n = 78; pyruvate CV = 3.3%, departure from standard = 3.96 ± 3.149%, n = 56). Arterial—coronary sinus excess lactate and percent lactate extracted were calculated.

Electrocardiogram Studies

A 12 lead electrocardiogram was recorded for each patient 2 to 3 days preoperatively and again 7 to 10 days postoperatively. These were assessed for the presence of myocardial infarction, or of ischemic changes (mutually exclusive diagnoses).

Data Analysis

Each hemodynamic, isoenzyme, and metabolic variable was tested in three separate ways against the hypothesis that the mean value for all patients done by coronary perfusion was the same as that for cold ischemic arrest. 1) The difference between the two group means at each study period was tested by student’s t test. 2) The difference between the two group means averaged over all study periods, obtained by least squares analysis, was tested by the F ratio of variation between groups to the variation between patients in the groups. 3) The difference between the two group means was tested against experimental error as in 2) using as experimental error the variability within patients in each group. For 2) and 3) a least squares rather than an standard analysis of variance was employed because of unequal group sizes and incomplete data for some patients. Averag- ing over periods to obtain a best unbiased estimate of popula- tion means was permitted because the group • period in- teraction term used in the analysis was never significantly different from zero.

Interrelations among certain variables were examined by correlation and regression. The following variables were

*We are indebted to Dr. Brian Maurer for the scoring of the electrocardiograms.
studied for correlation of each with all others in the patient population as a whole: cardiac index (time intercept and slope obtained by least squares), CPK-MB and LDH₁/LDH₂ (magnitude and rates of rise and disappearance fit with a gamma function), excess lactate (intercept and rate of return to zero), cardiothoracic ratio, LV diameter and wall thickness, the two myocardial temperatures, and crossclamp and bypass times. Cardiac index, CPK-MB, LDH₁/LDH₂ and excess lactate were regressed against age, sex, race, diagnosis of stenosis or incompetence at the aortic valve, orthopnea, angina, syncope, cardiothoracic ratio, LV diameter and wall thickness, macroscopic coronary artery disease, crossclamp and bypass times; additionally, for the coronary perfusion group, against average flows and pressures in the right and left perfusion cannulae. A forward stepwise regression procedure was used both for the patient population as a whole, using "group" as a regression variable, and separately by groups. Only those variables which had a P≤ 0.1 remained in the model.

When departures from the normal distribution were encountered, data transformations were selected to equalize as nearly as possible the variation within each group. All enzyme data were log transformed, and the reciprocal of \((\text{dp/dt}) \cdot \text{p}^{-1}\) was employed. Qualitative variables were tested by Chi Square for a 2-way contingency table. As an estimate of reproducibility for hemodynamic and metabolic variables, the ratio of the stan-

Figure 1a

Hemodynamic variables plotted against time in hours after starting bypass. The group means ± one standard error are plotted at the average time of observation for each study period. The X's connected by the solid line are for the coronary perfusion group and the open squares connected by the dotted line for the cold ischemic arrest group.
standard deviation of repeated measurements at each study period to the over-all mean was calculated using a nested analysis of variance and expressing it as a coefficient of variation. Trends over the five month study were examined by regressing each variable against the order in which patients were treated, and surgeon to surgeon differences by regressing against each surgeon. Each variable was also regressed against the interaction term, surgeon * group, to test for differences between group means which were significantly different from surgeon to surgeon.

The term "not significant" refers to the $P \geq 0.05$ significance level.

**Results**

**Hemodynamics**

The two group means at each study period for cardiac index, heart rate, stroke index, stroke work index, arterial mean pressure, systemic resistance, right and left atrial mean pressures, $(dp/dt) \cdot p^{-1}$, and coronary blood flow index were not significantly different at any period with two exceptions (fig. 1). Heart rate at 31 hours was lower in the cold ischemic arrest group than in the coronary perfusion group ($P < 0.04$). Arterial mean pressure in the cold ischemic arrest group at 26 hours was higher than in the coronary perfusion group ($P < 0.03$). It is of interest that five of the six patients in whom afterload was reduced pharmacologically early postoperatively were in the cold ischemic arrest group.

There were no significant differences between the two group means averaged over all study periods (table 1). However, differences between the two group means significantly greater than experimental error were found. Cardiac output and heart rate were higher, and arterial mean pressure, systemic resistance, right atrial pressure and coronary blood flow index lower in the coronary perfusion than in the cold ischemic arrest group.

None of the variables studied for interrelations with cardiac index (see Methods) for the study population as a whole and for each study group separately was found to influence it except three. For the study population as a whole the intercept of cardiac index (roughly equivalent to the first postoperative measurement) was negatively correlated with cardiothoracic ratio ($r = -0.336$), and older patients had lower cardiac indices (intercept regression coefficient for age = $-0.025 \pm 0.0061$, $P < 0.001$; slope regression coefficient for age = $1.00045 \pm 0.000199$, $P < 0.05$). When the two study groups were examined

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

*Circulation, Volume XLIX, June 1974*
separately, these same two influencing variables were found. In the cold ischemic arrest group no other influencing variable was found. In the coronary perfusion group one additional influencing variable was found: the intercept of cardiac index was higher when average flow to the left coronary artery had been higher (regression coefficient for left coronary flow = 0.0125 ± 0.00470, \( P < 0.05 \)).

Isoenzymes

Matched coronary sinus and right atrial levels of the isoenzymes were not significantly different. In the early patients tested, hemolysis sufficient to interfere with enzyme analysis was not present. CPK-MB ranged from 0 to 1522 International Units (IU). No significant differences between the group means of the two patient groups at each study period were found in CPK-MB and LDH1/LDH2 isoenzymes (fig. 2). The group mean averaged over all study periods for CPK-MB was 3.29 IU for the coronary perfusion group and 4.23 IU for the cold ischemic arrest group. The group mean averaged over all study periods for LDH1/LDH2 was 0.929 for the coronary perfusion group and 0.924 for the cold ischemic arrest group. No
significant difference between these two group means was found for either isoenzyme, nor was a difference found significantly greater than experimental error.

None of the variables studied for interrelations with the magnitude of CPK-MB (see Methods) for the study population as a whole nor for the cold ischemic arrest group was found to influence it. In the coronary perfusion group CPK-MB magnitude was higher when left ventricular wall thickness was greater (regression coefficient for LV wall thickness = 1.68 ± 0.752, P < 0.05).

A qualitative summary of the isoenzyme data in terms of evidence of myocardial necrosis revealed no significant difference between the two groups (table 2). The table does indicate, however, that 69% of the patients who had enzyme studies had combined enzyme abnormalities indicative of myocardial necrosis, and another 27% had single enzyme changes.

**Electrocardiogram**

Electrocardiographic evidence of myocardial injury was not significantly different between the two groups (table 3). Thirteen percent of the patients with these studies developed electrocardiographic evidence of myocardial infarction early postoperatively and an additional 13%, of new ischemic changes. The incidence of these changes was not significantly different for patients with stenosis as opposed to insufficiency at the aortic valve. All patients with these changes had combined CPK-MB and LDH₁/LDH₂ isoenzyme abnormalities. However, the isoenzyme magnitudes were not significantly greater in these patients versus those without detectable electrocardiographic changes.

**Myocardial Metabolism**

No significant differences were found between the two group means at each study period for arterial – coronary sinus excess lactate or lactate extraction (fig. 3). The group mean averaged over all study periods for excess lactate was 0.183 mM · L⁻¹ for the coronary perfusion group and 0.134 mM · L⁻¹ for the cold ischemic arrest group. The mean group mean averaged over all study periods for lactate extraction was 19.7% for the coronary perfusion group and 20.4% for the cold ischemic arrest group. No significant difference between these two group means was found for either metabolic variable, nor was a difference found significantly greater than experimental error.

None of the variables studied for interrelations with the excess lactate (see Methods) for the study population as a whole nor for the cold ischemic arrest group was found to influence it. In the coronary perfusion group the intercept of excess lactate was higher when average flow to the left coronary artery had been lower and when left ventricular diameter was smaller (excess lactate intercept = 3.4285 - 0.0055 ± 0.00183 · left coronary flow - 0.227 ± 0.0739 · LV diameter, P < 0.01).

**Surgical Events**

Aortic crossclamping and cardiopulmonary bypass times were significantly less by 27 and 21 percent respectively in the cold ischemic arrest group (table 4). Myocardial temperatures were significantly different as expected. The myocardial temperature at aortic crossclamping for each group was not statistically different for patients with stenosis as opposed to insufficiency at the aortic valve. In the coronary perfusion group average flow to the left coronary artery was significantly less for those patients with thicker left ventricular walls (regression

### Table 2

**Myocardial Necrosis Assessed by Isoenzymes of CPK and LDH**

<table>
<thead>
<tr>
<th></th>
<th>No CPK-MB</th>
<th>CPK-MB and</th>
<th>No CPK-MB</th>
<th>CPK-MB and</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDH₁ &lt; LDH₂</td>
<td>LDH₁ &gt; LDH₂</td>
<td>LDH₁ &lt; LDH₂</td>
<td>LDH₁ &gt; LDH₂</td>
</tr>
<tr>
<td>Coronary perfusion</td>
<td>1</td>
<td>14</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic arrest</td>
<td>1</td>
<td>19</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>2 (4.2%)</td>
<td>33 (68.7%)</td>
<td>6 (12.5%)</td>
<td>7 (14.6%)</td>
</tr>
<tr>
<td>Interpretation</td>
<td>None</td>
<td>Diagnostic</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

\[ P \text{ for table by } \chi^2 \text{ test is not significant.} \]

### Table 3

**Electrocardiographic Evidence of Myocardial Injury (7-10 Days Postoperatively)**

<table>
<thead>
<tr>
<th></th>
<th>Coronary perfusion</th>
<th>Ischemic arrest</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ischemic changes</td>
<td>2</td>
<td>5</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>New myocardial infarctions</td>
<td>5</td>
<td>2</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>No changes</td>
<td>20</td>
<td>18</td>
<td>38 (73.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>25</td>
<td>52</td>
</tr>
</tbody>
</table>

\[ P \text{ for table by } \chi^2 \text{ is not significant.} \]
Coefficient for left coronary flow = $-281 \pm 10.4$, $P < 0.025$.

Patient Population Variables

No significant differences between the two groups were found for certain vital statistics, diagnostic category, and cardiac symptoms (table 5), nor for certain preoperative quantitative variables (table 6). No significant difference between the groups was found with respect to the preoperative electrocardiogram. One patient in the coronary perfusion group had the electrocardiographic findings of an old myocardial infarction preoperatively.

Apropos of the Randomization Technique

No significant trend of any variable over the five month study period was found. Six significant individual surgeon differences were found and are presented as a departure from the mean of the other three surgeons: a higher cardiac index intercept (0.44 L · min$^{-1}$ · m$^{-2}$ · hr$^{-1}$, $P < 0.005$); a slower return of excess lactate to zero ($-2.83$ mM · L$^{-1}$ · hr$^{-1}$, $P < 0.03$); a lower myocardial temperature at aortic crossclamping time ($-4.32^\circ$C, $P < 0.0006$); a higher temperature at the time of crossclamp release ($4.55^\circ$C, $P < 0.0001$); a shorter aortic crossclamping time ($-7.04$ min, $P < 0.04$); and a longer bypass time ($9.27$ min, $P < 0.05$). No significant interaction of a surgeon with the two groups was found.

Discussion

Methods

The randomization was done separately for each faculty surgeon since significant surgeon to surgeon

Table 4

<table>
<thead>
<tr>
<th>Surgical Variables</th>
<th>Range</th>
<th>Mean ± SE</th>
<th>N</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary perfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic crossclamp time (min)</td>
<td>42-100</td>
<td>68.3 ± 2.54</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>58-119</td>
<td>82.4 ± 2.71</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Myocardial temperature at aortic crossclamping (°C)</td>
<td>28.1-34.4</td>
<td>31.4 ± 0.33</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Myocardial temperature at crossclamp release (°C)</td>
<td>24.7-35.6</td>
<td>29.6 ± 0.46</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Cold ischemic arrest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic crossclamp time (min)</td>
<td>31-74</td>
<td>49.7 ± 1.58</td>
<td>33</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>45-100</td>
<td>65.1 ± 2.13</td>
<td>33</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Myocardial temperature at aortic crossclamping (°C)</td>
<td>15.7-28.1</td>
<td>22.4 ± 0.64</td>
<td>26</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Myocardial temperature at crossclamp release (°C)</td>
<td>16.1-28.8</td>
<td>24.6 ± 0.71</td>
<td>26</td>
<td>$P &lt; 0.0001$</td>
</tr>
</tbody>
</table>
differences were expected and would have to be removed so that all patients treated by each method could be examined in combined groups. The results demonstrate that this was a necessary precaution. An uncontrolled factor was that some operations were done by a senior resident with the personal supervision of the faculty surgeon to whom the case was assigned. The paired randomization which assured an approximately equal number of patients in each group throughout the study was a protection against trends over the five month study. This precaution was not needed as shown in the results. The third precaution, randomization of all eligible patients for all surgeons, was taken to preclude the argument of patient selection since the study was consecutive. However, this resulted in an unequal number of patients done by each surgeon. The lack of significant differences in patient population variables between the two groups indicates the effectiveness of the randomization procedure. The exclusion of six patients from the study population detracts from complete randomization. The necessity of allowing for such exclusions in therapeutic surgical trials is evident. The method used for handling these exclusions did not involve removing data from the study, so the data set is gapless and completely random. All abortions of randomization consisted of a switch from coronary perfusion to another form of myocardial preservation, thus possibly introducing an unmeasurable bias into the study.

The early postoperative hemodynamic, isoenzyme, electrocardiographic, and metabolic states were chosen for the comparison since mortality and morbidity alone are insensitive parameters and are of such low incidence that an unacceptably large study would have had to have been done to document significant differences. The hemodynamic state was not specifically stressed to demonstrate differences in cardiac reserve, nor were preoperative hemodynamic data available as control measurements for most patients.

The appearance of CPK-MB, with the techniques

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**Table 5**

<table>
<thead>
<tr>
<th>Qualitative Population Variables</th>
<th>Coronary perfusion</th>
<th>Cold ischemic arrest</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
<td>83.9%</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>16.1%</td>
<td>9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28</td>
<td>90.4%</td>
<td>29</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>9.6%</td>
<td>4</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stenosis</td>
<td>21</td>
<td>67.7%</td>
<td>25</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>10</td>
<td>32.3%</td>
<td>8</td>
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<tr>
<td>Orthopnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive history</td>
<td>6</td>
<td>19.4%</td>
<td>12</td>
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<tr>
<td>Negative history</td>
<td>25</td>
<td>80.6%</td>
<td>21</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
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<tr>
<td>Positive history</td>
<td>17</td>
<td>54.8%</td>
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<tr>
<td>Negative history</td>
<td>14</td>
<td>45.2%</td>
<td>19</td>
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<tr>
<td>Syncope</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive history</td>
<td>12</td>
<td>38.7%</td>
<td>10</td>
</tr>
<tr>
<td>Negative history</td>
<td>19</td>
<td>61.3%</td>
<td>23</td>
</tr>
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</table>

**Table 6**

<table>
<thead>
<tr>
<th>Quantitative Population Variables</th>
<th>Coronary perfusion</th>
<th>Cold ischemic arrest</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± SE</td>
<td>N</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24-77</td>
<td>50.5 ± 2.46</td>
<td>31</td>
</tr>
<tr>
<td>LV diameter (cm)</td>
<td>7.5-13.0</td>
<td>9.6 ± 0.25</td>
<td>29</td>
</tr>
<tr>
<td>LV wall thickness (cm)</td>
<td>2.3-4.8</td>
<td>3.1 ± 0.11</td>
<td>30</td>
</tr>
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<td>Cardiac index*</td>
<td>0.40-0.66</td>
<td>0.50 ± 0.014</td>
<td>25</td>
</tr>
<tr>
<td>Cardiac index*</td>
<td>1.4-3.6</td>
<td>2.36 ± 0.190</td>
<td>12</td>
</tr>
<tr>
<td>Left atrial mean pressure*</td>
<td>4-45</td>
<td>13.5 ± 3.04</td>
<td>14</td>
</tr>
<tr>
<td>LV end-diastolic pressure*</td>
<td>5-37</td>
<td>21.9 ± 3.09</td>
<td>10</td>
</tr>
</tbody>
</table>

LV = left ventricular.

*Obtained at cardiac catheterization preoperatively.
used in this study, has been shown to be specific for myocardial necrosis. In the absence of hemolysis, as was so in this study, the finding of LDH$_1 >$ LDH$_2$ is also considered indicative of myocardial necrosis. When both these are present in patients with acute myocardial infarction from coronary artery disease, myocardial necrosis has clearly developed.

Data

The hemodynamic state of patients in whom coronary perfusion was utilized has not been shown with confidence to be different from that of patients in whom cold ischemic arrest was employed. The occurrence of significant differences in 2 of 60 tests from study period to study period was no greater than expected by chance alone. However, differences between the groups with respect to cardiac index, heart rate, arterial mean pressure, systemic resistance, right atrial mean pressure, and coronary blood flow index, while not significant due to large patient to patient variability, were significantly larger than experimental error. Therefore the evidence from this study is insufficient to draw a conclusive inference that there is no difference in these variables between the two groups. Since stroke volume was practically identical in the two groups, the difference in cardiac index resulted from a difference in heart rate. The latter, and differences in arterial pressure and resistance, may result from differing extrinsic autoregulatory effects upon the circulation resulting from differing cardiac and whole body temperatures during cardiopulmonary bypass in the two patient populations.

We failed to demonstrate a relation between cardiac output early postoperatively and the myocardial temperatures or aortic crossclamp time in the cold ischemic arrest group. Since the mean aortic crossclamp time plus two standard deviations was 68 min, we know nothing from this study of the effects of longer periods of cold ischemia. Some of the variability in myocardial temperature around the mean of 22.4°C at aortic crossclamping and 24.6°C at release may have resulted from variability in depth or location of the thermistor tip. We do not know the effect of lower or higher myocardial temperatures during cold ischemic arrest. The duration of direct coronary perfusion (about 10 min less than aortic crossclamp time) did not relate to the cardiac output early postoperatively, although the average flow to the left coronary artery did, either as a direct factor or as part of a mechanism which resulted in decreased coronary flow.

The lack of interrelation between cardiac output early postoperatively and isoenzyme changes indicating myocardial necrosis is noteworthy. The

hemodynamic function of the rat heart under some circumstances has been shown to be unaltered in spite of enzyme release. However, cardiac reserve may be limited by such events and by electrocardiographically demonstrable myocardial infarctions, and patients more seriously ill and with less cardiac reserve initially than most of the ones in this study might have been more affected by them.

Important findings in this study are that 13% of the patients developed electrocardiographic evidence of myocardial infarction early postoperatively, and another 13% of new ischemic changes; that 69% of the patients developed isoenzyme abnormalities indicative of myocardial necrosis; and that in this setting neither coronary perfusion nor cold ischemic arrest was superior to the other in minimizing these occurrences. Again, the lack of interrelation between isoenzyme changes and length of aortic crossclamping or myocardial temperature in the cold ischemic arrest group, duration of direct coronary artery perfusion in the other group, and duration of cardiopulmonary bypass in both groups, is noteworthy. We have no evidence that larger hearts in either group had a greater tendency to develop these changes, nor that aortic stenosis versus incompetence predisposed to them. However, thicker hearts in the coronary perfusion group did have higher CPK-MB. The incidence of these events in our patients is similar to that reported in patients undergoing coronary bypass grafting for ischemic heart disease. This all suggests that factors common to both study groups and to patients undergoing coronary bypass grafting (and probably other procedures as well) are responsible for these serious developments. These may include exposure of the heart at the start of cardiopulmonary bypass to the perfusate from the pump oxygenator with its denatured protein, microaggregates of platelets and fibrin, and microemboli of air. The strength of these common factors may be so great as to mask in our study the additive effects of myocardial ischemia with its depletion of intracellular glycogen and high energy phosphate reserves.

Abnormal cardiac metabolism reflected by lactate concentration differences across the heart has been reported previously for both coronary perfusion and ischemic arrest intraoperatively. The finding in the coronary perfusion group that higher early postoperative excess lactate concentrations were associated with lower intraoperative perfusion to the left coronary artery was not unexpected, but we are not able to offer a clear explanation for the inverse relationship observed in this group between left coronary flow rate and left ventricular diameter.

The 27% reduction in aortic crossclamping time
and 21% reduction in total cardiopulmonary bypass time when cold ischemic arrest was employed is of practical significance. In view of this and the failure of this study to show any conclusive difference in the effects of coronary perfusion and cold ischemic arrest on the parameters studied, cold ischemic arrest seems preferable for isolated aortic valve replacement when the crossclamping time can be kept less than 68 minutes and the myocardial temperature between 22° and 24°C.

Acknowledgment

We wish to acknowledge the technical assistance of Mrs. R. Johnson (Duke), and W. Tracy, R. Brown, M. Barbaree, N. Roberson and D. Pappas (UAB). We also thank Mrs. Anne McLeod for her editorial assistance.

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Circulation. 1974;49:1190-1199
doi: 10.1161/01.CIR.49.6.1190

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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