Late Results of the Warm Heart Trial
The Influence of Nonfatal Cardiac Events on Late Survival

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Background—The Warm Heart Trial randomized 1732 CABG patients to receive warm or cold blood cardioplegia. In the warm cardioplegia patients, nonfatal perioperative cardiac events were significantly decreased and the mortality rate was nonsignificantly decreased (1.4% versus 2.5%, \( P = 0.12 \)). The purpose of the present study was to evaluate the late results of these trial patients.

Methods and Results—Randomization was stratified according to surgeon and urgency of the operation. Seven hundred sixty-two patients recruited from 1 of the centers were followed through the hospital clinic for late events. Late survival (including perioperative deaths) at 72 months was nonsignificantly greater in the warm cardioplegia patients (94.5 ± 1.7%, mean ± SEM) than in the cold cardioplegia patients (90.9 ± 2.6%). Independent predictors of mortality by Cox proportional hazards model were redo CABG, diabetes mellitus, renal insufficiency, and increasing age. The influence of nonfatal perioperative events (perioperative myocardial infarction according to computerized ECG readings or low output syndrome as determined by an outcome committee) on late survival was also analyzed. Late survival at 84 months was significantly reduced in the group who experienced nonfatal perioperative outcomes (94.5 ± 1.7% versus 84.9 ± 4.5%, \( P < 0.001 \)) and remained a significant predictor after adjustment for other important variables (risk ratio 6.4, 95% CI 1.87 to 8.73, \( P < 0.0001 \)).

Conclusions—Effective myocardial protection through either cold or warm blood cardioplegia is essential, because late survival is significantly reduced in patients with nonfatal perioperative cardiac outcomes. (Circulation. 2000;102[suppl III]:III-339-III-345.)

Key Words: bypass ■ cardioplegia ■ complications ■ survival ■ trials

In the Warm Heart Trial, 1732 patients who underwent isolated CABG were randomized to receive either normothermic or hypothermic blood cardioplegia. The results showed a nonsignificant decrease in mortality rates (1.4% versus 2.5%, relative risk 0.55, 95% CI, 0.28 to 1.11, \( P = 0.12 \)) in favor of the use of warm cardioplegia, similar rates of nonfatal myocardial infarction (MI) according to the computerized ECG readings (10.1% versus 11.1%), and a significant reduction in both low output syndrome (LOS) (6.1% versus 9.3%, relative risk 0.65, 95% CI 0.47 to 0.91, \( P = 0.01 \)) and MI determined with serial creatine kinase (CK)-MB sampling (12.3% versus 17.3%, relative risk 0.72, 95% CI 0.56 to 0.91, \( P < 0.01 \)). The difference in case-fatality rate was due to an increase in both cardiac (16 versus 10 deaths) and noncardiac (6 versus 2 deaths) mortality rates.

A sample size of 750 patients per group was calculated to provide 80% power to detect a 50% reduction in the combined end point of early death or nonfatal MI on computerized ECG analysis with the assumption of a control event rate of 9%. The difference in early mortality rates had emerged at the time of the planned interim analysis (750 patients). A sample of \( \approx 3000 \) patients would have been necessary to achieve statistical significance. Interestingly, the relative risks for death, LOS, and enzymatic MI were similar, suggesting that the difference in mortality rates may have been real and potentially related to myocardial protection rather than due to chance alone. On the other hand, the rates of Q-wave MI as determined on computerized ECG analysis were consistent in the 2 groups, suggesting that technical difficulties related to revascularization were primarily responsible for this end point rather than differences due to myocardial protection. (This conclusion was supported by the significant effect due to surgeon \( [P = 0.02] \) for the combined end point of death and nonfatal ECG MI.) We stopped the trial after 1732 patients were recruited rather than attempt to enroll \( 3000 \) patients because the projected sample size was exceeded, the budget was insufficient to continue, and the study investigators were experiencing “trial fatigue.”

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We postulated that the significantly increased incidence of nonfatal perioperative events in the group randomized to cold cardioplegia, specifically LOS and enzymatic MI, may be associated with increased late mortality rates (ie, leading to improved survival in the warm treatment group late after surgery). In support of this hypothesis is the well described (albeit inconsistent) decrement in the survival of patients after perioperative MI.\textsuperscript{2,3} The late effect of perioperative LOS or enzymatic (presumably non–Q-wave) MI for hospital survivors is less well described. Late survival is affected, however, in patients undergoing PTCA who have had non–Q-wave MI as determined on the basis of increased perioperative CK-MB levels.\textsuperscript{4}

The objective of the present study was to evaluate the late results of the Warm Heart Trial with respect to survival. Our underlying hypotheses were that (1) nonfatal perioperative cardiac events are associated with reduced late survival and (2) because nonfatal perioperative cardiac events and mortality rates were decreased in the warm cardioplegia treatment arm, late survival will therefore be enhanced in the warm cardioplegia patients. The Warm Heart Trial was designed to assess perioperative events rather than late survival. For this reason, the current study was completed through an evaluation of the late outcome of trial patients from 1 of the 3 participating centers through its follow-up clinic.

\section*{Methods}

\subsection*{Protocol}

The protocol of the Warm Heart Trial has been presented in detail previously.\textsuperscript{1} The study was conducted at the 3 adult centers of cardiac surgery at the University of Toronto from November 5, 1990, to December 31, 1992. Patients who underwent isolated CABG were eligible for inclusion in the study. Relative contraindications were hemodynamically significant cerebrovascular disease and renal insufficiency. Patients who proceeded directly from the catheterization laboratory to the operating room were ineligible. Each eligible patient signed a consent form approved by the institutional ethics review board. Randomization was stratified using an electronic random number generator. Patient assignment was made at the catheterization laboratory to the operating room and was performed by the cardiac anesthesiologist on duty. Treatment assignment was made with the sealed envelope method, which occurred after the patient’s arrival at the operating room. Of the 1732 patients enrolled into the study, 762 were recruited from the Sunnybrook site (warm cardioplegia n=378, cold cardioplegia n=384) and constitute the patient population for the present study.

The surgical techniques have been described in detail previously.\textsuperscript{1} Briefly, cardiopulmonary bypass was established with a single 2-staged right atrial cannula and ascending aortic perfusion cannula and an ascending aortic cardioplegic cannula/event line. Cardiopulmonary bypass management included membrane oxygenators, arterial line filters, nonpulsatile flows of 2.4 L \cdot min\textsuperscript{−1} \cdot m\textsuperscript{−2}, mean arterial pressure of 50 to 80 mm Hg, moderate hemodilution with a hematocrit of >20%, and \textit{α}-stat acid-base balance. In the warm cardioplegia treatment group, the systemic temperature was 33\textdegree to 37\textdegree C compared with 25\textdegree to 30\textdegree C by active cooling in the cold cardioplegia group. The blood cardioplegia for both groups was prepared by mixing oxygenated blood with a crystalloid additive (Fremes’ solution)\textsuperscript{1} in a 4:1 ratio, which was delivered in an intermittent, antegrade manner.\textsuperscript{5} In the warm cardioplegia group, cardioplegia was administered at 37\textdegree C, and in the cold cardioplegia group, it was delivered at 5\textdegree to 8\textdegree C.

Patients had serial ECGs taken before surgery, 1 day after surgery, and 5 days after surgery; the ECGs were digitized and transferred to the University of Alberta Cardiac Epidemiology Coordinating Research Center for computerized ECG analysis.\textsuperscript{6} Blood samples for CK-MB analysis were obtained at 0, 4, 8, 12, 20, and 28 hours after the patient’s arrival at the intensive care unit. Records of any patients who received an intra-aortic balloon pump or inotropic support in the intensive care unit were photocopied, stripped of patient identifiers, and reviewed by an adjudicating committee. All patients were contacted at 30 days after surgery by the research personnel.

\subsection*{Warm Heart Trial Outcome Measures}

The primary endpoints of the Warm Heart Trial were 30-day, all-cause mortality and nonfatal Q-wave MI according to computerized ECG analysis.\textsuperscript{1} Patients who were hospitalized for \textit{>}30 days but who subsequently died in hospital were counted as perioperative deaths consistent with the recommendations of the Society for Thoracic Surgeons.\textsuperscript{7} Secondary outcomes of the Warm Heart Trial were postoperative LOS and enzymatic MI according to the CK-MB area of the curve. LOS was defined as the requirement of inotropes or intra-aortic balloon pump support, or both, for \textit{>}60 minutes to maintain the cardiac index at >2.2 L \cdot min\textsuperscript{−1} \cdot m\textsuperscript{−2} and the systolic blood pressure at >90 mm Hg in association with a wedge pressure of \textit{≥}18 mm Hg. The diagnosis of LOS required a 2-of-3 decision by the LOS committee, which consisted of 3 intensivists. Enzymatic MI was defined from serial CK-MB sampling for an area under the curve of \textit{>}645 IU/h. This cut point had been validated from previously collected information regarding technetium pyrophosphate scans.\textsuperscript{8}

\subsection*{Sunnybrook Site Protocols and Late Follow-Up}

Data on >200 demographic, angiographic, operative, and outcome-related variables were collected prospectively by our research assistant. Patients were reviewed in the hospital clinic by the operating surgeon at 3 months after surgery. They were encouraged to return to the clinic for subsequent visits at 1, 3, 5, and 7.5 years after surgery. At each clinic visit, a data form was completed and entered into the computerized database. The patients’ follow-up records were also supplemented from the referring physicians’ correspondence.

\subsection*{Statistical Analysis}

The primary outcome measure of the present study was late death. The primary analysis compares late mortality rates between the 2 cardioplegia groups for all study patients recruited from the Sunnybrook site. Late mortality rates are also compared for the hospital survivors who did or did not experience a nonfatal perioperative cardiac event.

Data from the Warm Heart Trial concerning treatment assignment and perioperative outcomes as originally defined were merged with the data collected from Sunnybrook site concerning clinical characteristics, angiographic data, operative characteristics, and late mortality. Continuous data are summarized as mean±SD, categorical data are given as a frequency or percentage, and late survival data in the life tables are given as mean±SEM. Baseline between-group comparisons were performed with unpaired Student’s \textit{t} tests for continuous data and \textit{χ}\textsuperscript{2} or Fisher’s exact test for categorical data. Late survival rates were compared between groups by log-rank methods. Covariant adjustment was performed with Cox proportional hazards model. Probability values are provided for each comparison; statistical significance is assumed for \textit{P}<0.05. All statistical analyses were performed with SAS for PC, Version 6.12 (SAS Institute).

\subsection*{Results}

Clinical characteristics of the warm and cold cardioplegia patients recruited from the Sunnybrook site are summarized in Table 1. Apart from an excess of preoperative hypertension in the warm cardioplegia patients, the baseline variables were similar. Angiographic data are provided in Table 2. The groups were comparable in terms of angiographic findings. Operative results are listed in Table 3. There was an excess of coronary reoperations in the cold cardioplegia group compared with the warm cardioplegia group, but the incidence
in the warm cardioplegia versus the cold cardioplegia patients. An intra-aortic balloon pump was inserted in 8 of the 8 warm cardioplegia patients and in 14 of the 18 cold cardioplegia patients with LOS. The incidence of enzymatic MI was significantly reduced in the warm cardioplegia treatment arm.

Actuarial survival rates for the warm and cold cardioplegia patients are presented in Figure 1. Survival rates were nonsignificantly increased in the warm cardioplegia compared with the cold cardioplegia patients at 6 years after surgery ($P=0.56$). At 6 years, the survival rate was 94.9±1.6% versus 91.2±2.9% ($P=0.50$) when redo patients were excluded from the analysis. Results of the proportional hazards model are presented in Table 4. Redo CABG, diabetes mellitus, renal insufficiency, and increased age were associated with an increased risk of late death, whereas the use of the left internal thoracic artery and female sex were protective. The use of warm cardioplegia did not significantly influence the late survival rates in the multivariate analysis after adjustment for other covariates (risk ratio 0.86, 95% CI 0.40 to 1.84, $P=0.70$).

The predicted survival rate was calculated for each patient according to the significant risk variables from the proportional hazards model plus Canadian Cardiovascular Society class, left ventricular function, cerebrovascular and peripheral vascular disease, and urgency of operation. The individual patient results were ranked and then grouped into terciles. Actuarial survival stratified for estimated risk without adjustment for cardioplegic assignment is presented in Figure 2. Figure 3 shows the results in the highest risk tercile separately for warm cardioplegia and cold cardioplegia patients.

**Effect of Perioperative Events on Late Survival**
Late survival rates for hospital survivors are presented in Table 5. The linearized rate of late death for patients who had a benign perioperative course was ≈1.0%/y. Late survival rates were significantly reduced after ECG-defined MI and LOS. Figure 4 depicts the actuarial survival rates for patients with and without perioperative MI or LOS. Late survival rates were nonsignificantly reduced in patients who had a perioperative MI according to enzymatic criteria (89.9±3.8% versus 93.8±1.7%, Table 5, Figure 5). To adjust for differences in baseline risk profiles, separate individual Cox proportional hazards models were analyzed including the individual nonfatal perioperative cardiac events with other risk variables. The results are summarized in Table 6 and show that Q-wave MI, LOS, or both adversely affect late survival rates after adjustment for other important risk variables. Nonfatal enzymatic MI with a threshold value of 645 IU*h does not significantly influence late survival.

**Discussion**
“Warm heart surgery” was introduced in the late 1980s and involved the infusion of blood cardioplegia at normothermic temperatures. It was argued that cardiac arrest was the predominant factor that reduced myocardial oxygen consumption, with minimal additional benefit from hypothermia. The Warm Heart Trial was designed to test for a 50% reduction in the combined end point of death or Q-wave MI.

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### TABLE 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Warm Cardioplegia</th>
<th>Cold Cardioplegia</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>$61.4 \pm 8.7$</td>
<td>$60.5 \pm 9.4$</td>
<td>0.20</td>
</tr>
<tr>
<td>Age ≥70 y, %</td>
<td>13.5</td>
<td>15.6</td>
<td>0.41</td>
</tr>
<tr>
<td>Female, %</td>
<td>14.0</td>
<td>16.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Urgent, %</td>
<td>23.0</td>
<td>23.7</td>
<td>0.86</td>
</tr>
<tr>
<td>CCS class, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4.5</td>
<td>3.4</td>
<td>...</td>
</tr>
<tr>
<td>II</td>
<td>28.0</td>
<td>25.3</td>
<td>...</td>
</tr>
<tr>
<td>III</td>
<td>39.4</td>
<td>40.6</td>
<td>...</td>
</tr>
<tr>
<td>IV</td>
<td>28.0</td>
<td>30.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>19.6</td>
<td>22.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>53.9</td>
<td>46.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>2.1</td>
<td>1.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Vascular disease, %</td>
<td>11.1</td>
<td>12.5</td>
<td>0.58</td>
</tr>
<tr>
<td>Recent MI</td>
<td>7.1</td>
<td>5.7</td>
<td>0.46</td>
</tr>
<tr>
<td>Preoperative IABP</td>
<td>1.6</td>
<td>1.6</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society; IABP, intra-aortic balloon pump.

The 2 groups had similar preoperative clinical characteristics apart from an increase in the prevalence of hypertension in the patients who received warm cardioplegia.

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### TABLE 2. Angiographic and Operative Data

<table>
<thead>
<tr>
<th></th>
<th>Warm Cardioplegia</th>
<th>Cold Cardioplegia</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV grade, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>62.7</td>
<td>57.8</td>
<td>...</td>
</tr>
<tr>
<td>II</td>
<td>29.4</td>
<td>29.6</td>
<td>...</td>
</tr>
<tr>
<td>III</td>
<td>7.4</td>
<td>11.5</td>
<td>...</td>
</tr>
<tr>
<td>IV</td>
<td>0.5</td>
<td>1.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Left main stenosis, %</td>
<td>18.5</td>
<td>20.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Diseased vessels, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.1</td>
<td>5.5</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>22.0</td>
<td>20.0</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>70.9</td>
<td>74.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Redo CABG, %</td>
<td>0.8</td>
<td>3.1</td>
<td>0.03</td>
</tr>
<tr>
<td>LITA, %</td>
<td>84.4</td>
<td>83.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Coronary TEA, %</td>
<td>10.1</td>
<td>9.1</td>
<td>0.71</td>
</tr>
<tr>
<td>Distal anastomoses, n</td>
<td>$3.2 \pm 0.9$</td>
<td>$3.2 \pm 1.0$</td>
<td>0.71</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>$59.8 \pm 19.5$</td>
<td>$57.8 \pm 17.9$</td>
<td>0.14</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>$95.8 \pm 29.0$</td>
<td>$96.5 \pm 28.2$</td>
<td>0.73</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; LITA, left internal thoracic artery; TEA, thromboendarterectomy; and CPB, cardiopulmonary bypass.

The 2 groups had similar angiographic findings. Operative procedures were identical apart from a small but statistically significant excess in reoperative coronary surgery (Redo CABG) in the patients who received cold cardioplegia.
The study investigators expected a positive study result with an unbiased hard clinical end point to be very persuasive evidence for cardiac surgeons to adopt warm blood cardioplegia for CABG. Despite being one of the largest randomized clinical trials ever conducted in cardiac surgery, the Warm Heart Trial has had a smaller-than-expected impact, although enzymatic MI and LOS favored the use of warm cardioplegia, the primary outcomes did not differ between groups.

A systematic overview may also provide important clues regarding the relative benefit of warm versus cold blood cardioplegia. At least 17 trials that compared warm or tepid blood cardioplegia with cold blood or crystalloid cardioplegia have been published in peer-reviewed, English-language journals.1,11-26 Most of the studies enrolled <100 patients, whereas the Emory trial11 (which was stopped prematurely because of an excess of neurological events in the warm cardioplegia group) and the Toronto study1 each involved >1000 patients. Although the majority of the studies favored warm cardioplegia, smaller studies were generally powered only to detect differences in sensitive surrogate end points. Consistent with the Warm Heart Trial, 5 other studies demonstrated reduced cardiac enzyme release after surgery in the warm or tepid groups.12,14,20,22,26 Estimates of MI and LOS are more limited because of the small sample sizes of most of the studies and the lack of uniformity of definition; crude prevalence estimates by summing across trials were, however, reduced in the warm groups (MI 5.8% [125 of 2142 patients] versus 6.4% [138 of 2155 patients], LOS 9.7% [193 of 2142 patients] versus 12.1% [243 of 2155 patients]). The reporting of perioperative death is presumably more reliable from study to study and less subject to differences in definitions that may occur with nonfatal events. The aggregated data support a protective effect of warm cardioplegia regarding mortality; crude estimates were 1.3% (27 of 2095 patients) versus 1.9% (40 of 2074 patients). We recognized, however, that there are important limitations of overviews and that a single large study is generally stronger evidence.

The present study was conducted to determine whether any differences in late survival existed between the 2 groups, because a statistically significant improvement in late survival rates would also be very compelling evidence to support a particular method of myocardial protection. We postulated that patients who experienced a significant nonfatal perioperative cardiac event could be at an increased risk of subsequent death beyond the perioperative interval, especially if the perioperative event was associated with clinically important myocardial necrosis or ongoing congestive heart failure. Because all early fatal or nonfatal cardiac events favored the warm treatment arm (significantly or nonsignificantly), the warm cardioplegia group would therefore be expected to have a greater likelihood of late survival.

### Perioperative Myocardial Infarction

Perioperative myocardial injury after cardiac surgery has been detected with ECG criteria,2,3 various serum markers,27-32 infarct avid scans,33 and wall motion studies.34 ECG changes with or without CK-MB elevations are most commonly used. There are limitations of the diagnostic accuracy (both sensitivity and specificity) of each of these methods. The use of a combination of techniques may improve the

<table>
<thead>
<tr>
<th>TABLE 3. Early Results for the Sunnybrook Site</th>
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<tbody>
<tr>
<td><strong>Warm Cardioplegia</strong> (n=378)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Death, %</td>
</tr>
<tr>
<td>ECG MI, %</td>
</tr>
<tr>
<td>LOS, %</td>
</tr>
<tr>
<td>Enzymatic MI, %</td>
</tr>
</tbody>
</table>

The perioperative outcomes of the 2 groups from the Sunnybrook site. ECG MI indicates MI determined with computerized ECG analysis; enzymatic MI, MI according to serial CK-MB measurements.
specificity and identify the clinically more relevant infarctions. Chaitman et al 2 and Schaff et al 3 both published the early and late effects of perioperative MI from the Coronary Artery Surgery Study (CASS) Registry. On the basis of new Q waves, Chaitman et al reported that perioperative MI from data collected during a single year of the study (incidence 4.6%) was associated with a significant increase in early death but little subsequent decrement in survival thereafter. Conversely, Schaff et al used ECG and enzyme criteria (presumably both Q-wave and non–Q-wave MI, incidence 5.7%) and documented both an early and a late adverse effect on survival. More recently, the EAST study investigators concluded that perioperative Q waves, especially inferior Q waves, were of minimal prognostic significance.35 Svedjeholm et al 30 reported that early outcome was more dependent on the levels of serum markers than Q waves alone, whereas the worst results were observed in patients who had both elevated serum markers and new Q waves. The use of a combination of serum markers and ECG findings may underrepresent the true incidence of perioperative MI but presumably identifies the infarcts that are prognostically more important by reducing the number of false-positive results.

Late survival rates at our institution were influenced to a greater degree by Q-wave MI rather than by MI determined with CK-MB area under the curve measurements. It is probable that the CK-MB threshold was overly sensitive. Although useful for the computation of relative differences for studies of myocardial protection, both clinically significant and nonsignificant infarcts were captured with a cut point of 645 IU*h. The incidence of perioperative MI is routinely monitored in our institution according to the appearance of new Q waves or left bundle-branch block in association with a CK-MB of ≥50 IU/L, which represents ≥7% of the total CK. The rates of MI according to ECG plus enzyme criteria were 2.1% and 2.6% in the warm and cold cardioplegia patients, respectively, which were much lower than the estimates in these same patients according to ECG or enzyme criteria alone. Late survival rates after hospitalization were significantly decreased in patients with or without a clinically defined MI (83.6±10.8% versus 93.6±1.6% at 72 months), and perioperative MI remained a significant risk variable after adjustment for other covariates (risk ratio 3.80, 95% CI 2.83 to 14.45, P = 0.04). These point estimates for late survival are remarkably similar to values for patients discharged alive from the CASS Registry (85% versus 92% at 5 years).3 It is also noteworthy that the clinically defined infarcts were prognostically more relevant than the trial-defined MIs, although they were potentially more biased (Tables 5 and 6).

**TABLE 5. Actuarial Survival Rates (72 months) for Hospital Survivors**

<table>
<thead>
<tr>
<th>No Event</th>
<th>Event</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG MI, %</td>
<td>93.8±1.7</td>
<td>89.4±4.6</td>
</tr>
<tr>
<td>LOS, %</td>
<td>94.1±1.6</td>
<td>75.8±9.9</td>
</tr>
<tr>
<td>Enzymatic MI, %</td>
<td>93.8±1.7</td>
<td>89.9±5.8</td>
</tr>
<tr>
<td>ECG MI±LOS, %</td>
<td>94.5±1.7</td>
<td>84.9±4.5</td>
</tr>
</tbody>
</table>

Late survival (mean±SEM) rates are presented for hospital survivors (ie, early deaths are excluded in this analysis) for Sunnybrook site patients who did or did not experience a perioperative cardiac event. See Table 3 for abbreviations.

**LOS as Predictor**

LOS is a strong predictor of perioperative death.36 Less is known concerning the late consequences of perioperative

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**Figure 2.** Predicted survival rates for 762 patients calculated according to their risk profile and ranked. Actuarial survival rates are presented for low, medium, and high risk terciles. Both perioperative and late deaths were counted. Late survival was significantly depressed in high risk tercile.

**Figure 3.** Actuarial survival rates for high risk tercile presented according to assignment to warm or cold cardioplegia. Late survival rates were nonsignificantly greater in group randomized to warm cardioplegia.

**Figure 4.** Late survival rates for hospital survivors who did or did not experience a perioperative MI on basis of computerized ECG analysis or LOS adjudicated by an outcomes committee. Late survival was significantly reduced for patients who had a perioperative event.
LOS. For patients who had been treated with an intra-aortic balloon pump, Golding et al 37 noted that 2-year survival rates were excellent in hospital survivors (96%) on the basis of data collected in the 1970s. Both Naunheim et al 38 and Arafa et al 39 presented results for patients operated on in the 1980s. The 1-year mortality rate was very high in both groups; for patients surviving 1 year, the 5-year mortality rate was still ≈ 20%, compatible with the findings in our study.

The incidence of LOS is prospectively monitored in our institution with criteria similar to those of the Warm Heart Trial. This diagnosis of LOS is not vetted by an adjudication committee, only by chart review. The incidence of LOS was 13.2% and 12.5% in the warm and cold cardioplegia patients, respectively. It is important to recognize not only that these estimates are much higher than those numbers determined by the LOS committee (Table 4) but also that these estimates are mainly composed of patients who received inotropic support alone, not an intra-aortic balloon pump. Late survival rates after hospitalization were reduced in patients with and without clinically defined LOS (84.8 ± 4.9% versus 94.6 ± 1.7% at 72 months), and clinically defined LOS remained an important predictor of late death after the adjustment of other risk variables (risk ratio 4.5, 95% CI 2.15 to 9.42, P < 0.0001).

Study Limitations

There are several potential reasons why a significant late survival advantage was not identified for patients randomized to receive warm cardioplegia, despite confirmation of the first hypothesis (ie, that late mortality is dependent on nonfatal perioperative outcomes). The primary limitation of the current study is that follow-up information was obtained from only 1 of the participating sites rather than all 3 centers, strictly for logistical reasons. The Warm Heart Trial was designed and budgeted to study perioperative events, and therefore research personnel did not collect subsequent follow-up data. The Sunnybrook site maintains a comprehensive clinical data base that includes follow-up information that was not available from the other 2 centers. Complete follow-up of all 1732 patients would increase the power to detect a survival advantage, should one exist. In addition, there were important interinstitutional differences in the prevalence of the primary and secondary endpoints of the Warm Heart Trial. 1 Operative mortality rates were less in the cold cardioplegia patients from the Sunnybrook site (0.5% versus 2.5% overall), and nonfatal cardiac events were reduced in every instance. Such differences in event rates would minimize the probability of detecting a separation in survival curves from this single site; conversely, the chances of observing important differences in survival with data from all sites would be amplified. Finally, there was a difference in the prevalence of previous CABG between the warm and cold cardioplegia patients. Exclusion of these patients did not affect the warm cardioplegia–cold cardioplegia comparisons.

In the entire study, baseline characteristics were well balanced in the 2 treatment arms. 1

Conclusions

Surveillance for perioperative myocardial injury is important for quality assurance, postoperative management, and prognostication. The use of cardiospecific serum markers such as troponin I 30–32 may improve the diagnostic accuracy for the detection of perioperative MI, but additional follow-up of such patients is essential to identify appropriate threshold values to differentiate between clinically important and clinically insignificant necrosis in the surgical setting. In addition, future clinical trials of myocardial protection should consider extending the time horizon from 30 days to 12 to 24 months postoperatively, which would increase the numbers of events and potentially decrease the sample size.

We conclude that perioperative myocardial protection with warm or cold blood cardioplegia is essential as late mortality is increased, even in patients with nonfatal perioperative cardiac events. Furthermore, late survival should be assessed for the Warm Heart Trial patients from all 3 study sites. Power calculations have been performed for control event rates that vary between 0.08 to 0.12 (ie, compatible with the late mortality rates observed in the cold cardioplegia group from this center). The total study population would provide ≈ 80% power for a similar relative difference in late survival as observed from this single center.

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![Figure 5. Late survival rates for hospital survivors for patients who had a perioperative MI on basis of CK-MB area under the curve measurements were reduced nonsignificantly.](https://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.100.110491)

**Figure 5.** Late survival rates for hospital survivors for patients who had a perioperative MI on basis of CK-MB area under the curve measurements were reduced nonsignificantly.

**TABLE 6. Late Death Rates of Hospital Survivors in Cox Proportional Hazards Model**

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG MI</td>
<td>2.67</td>
<td>0.98–7.24</td>
</tr>
<tr>
<td>LOS</td>
<td>9.77</td>
<td>3.54–27.00</td>
</tr>
<tr>
<td>Enzymatic MI</td>
<td>1.53</td>
<td>0.51–4.52</td>
</tr>
<tr>
<td>ECG MI or LOS</td>
<td>6.40</td>
<td>1.87–8.73</td>
</tr>
</tbody>
</table>

Individual Cox proportional hazards models were performed to determine whether nonfatal perioperative cardiac events affected late survival rates after adjustment for other risk variables. ECG-defined MI and LOS significantly increased the risk of late death, whereas MI determined with serial enzymes did not.

See Table 3 for abbreviations.
References

Late Results of the Warm Heart Trial: The Influence of Nonfatal Cardiac Events on Late Survival

Stephen E. Fremes, Miguel G. Tamariz, Dan Abramov, George T. Christakis, Jeri Y. Sever, Kathy Sykora, Bernard S. Goldman, Christopher M. S. Feindel and Samuel V. Lichtenstein

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