β-Blockade as an Alternative to Cardioplegic Arrest During Cardiopulmonary Bypass

R. David Warters, Steven J. Allen, Karen L. Davis, Hans J. Geissler, Irene Bischoff, Ernst Mutschler and Uwe Mehlhorn

*Ann Thorac Surg* 1998;65:961-966

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

http://ats.ctsnetjournals.org/cgi/content/full/65/4/961
β-Blockade as an Alternative to Cardioplegic Arrest During Cardiopulmonary Bypass

R. David Warters, MD, Steven J. Allen, MD, Karen L. Davis, BS, Hans J. Geissler, MD, Irene Bischoff, PhD, Ernst Mutschler, PhD, MD, and Uwe Mehlhorn, MD

Center for Microvascular and Lymphatic Studies, Department Of Anesthesiology, University of Texas-Houston Medical School, Houston, Texas

**Background.** As an alternative to cardioplegic arrest, cardiac surgical conditions have been produced using β-blocker–induced minimal myocardial contraction (MMC) during cardiopulmonary bypass. The technique of MMC involves the use of high-dose intravenous esmolol to suppress myocardial chronotropy and inotropy sufficiently to produce cardiac surgical conditions. The purpose of this study was to compare conventional crystalloid cardioplegic arrest with MMC in terms of ischemia avoidance, myocardial edema formation, and cardiac function.

**Methods.** Twelve dogs were placed on cardiopulmonary bypass. Six dogs were subjected to crystalloid cardioplegic arrest for 2 hours. Surgical conditions were produced in the other 6 dogs for 2 hours using intravenous esmolol without aortic clamping or cardioplegia. Arterial and coronary sinus lactate concentrations were determined as a gauge of myocardial ischemia. Myocardial water content was determined using microgravimetry and preload recruitable stroke work was determined using sonomicrometry.

**Results.** Significant lactate washout was demonstrated after cardioplegic arrest but not after MMC. Myocardial water content was significantly less during and after MMC compared with cardioplegic arrest ($p < 0.05$). Preload recruitable stroke work was decreased compared with baseline values in both groups ($p < 0.05$).

**Conclusions.** In contrast to a previous study that involved 1 hour of MMC, in this study, ventricular function was decreased to the same extent as with cardioplegic arrest after 2 hours of MMC. This was attributed to the accumulation of ASL-8123, the primary metabolite of esmolol, which possesses β-blocker properties. Although postbypass ventricular function is similar in both groups, MMC appears to be superior in terms of ischemia avoidance and myocardial edema formation.


Cardioplegia-induced cardiac arrest is used routinely to provide myocardial protection as well as a flaccid heart during cardiac operations. However, numerous studies have shown that conventional hypothermic cardioplegic arrest (CA) is associated with myocardial ischemia and interstitial myocardial edema, both of which impair postbypass cardiac function [1–6]. Thus, conventional hypothermic cardioplegia does not protect the myocardium completely.

Cardioplegia-induced myocardial edema results from an imbalance between fluid flux out of the myocardial microvasculature and its subsequent removal through myocardial lymphatics [6–8]. Edema accumulates secondary to increased fluid filtration, decreased lymph flow, or both. We have shown in previous studies that the absence of organized myocardial contractions causes the cessation of myocardial lymph flow; thus, decreased myocardial lymph removal is at least partially responsible for myocardial edema formation during CA [6, 7]. Further, these data suggest that both ischemic and non-ischemic cardioplegia techniques lead to myocardial edema by depressing myocardial lymphatic function [7].

An alternative to CA for myocardial protection has been described in high-risk patients undergoing coronary artery bypass grafting [9]. The investigators produced surgical conditions during circulatory support by suppressing myocardial chronotropy and inotropy with high intravenous doses of the ultra–short-acting β-blocker esmolol, avoiding aortic cross-clamping and cardioplegia [9]. Subsequently, we investigated this technique in dogs and showed that myocardial lymphatic function is maintained, resulting in less myocardial edema formation associated with normal left ventricular function after circulatory support [10]. The maintenance of myocardial lymphatic function was attributed to the presence of minimal myocardial contraction (MMC), in contrast to CA, during which no organized cardiac activity exists.

Conventional cold crystalloid CA remains one of the most commonly used regimens for myocardial protection. Therefore, the purpose of this study was to compare directly cold crystalloid CA with maintenance of MMC.
using high-dose esmolol in terms of avoidance of ischemia, myocardial edema formation, and postbypass cardiac function. In addition, the duration of CA and esmolol-induced cardiac surgical conditions was extended to 2 hours.

Material and Methods
Animal Preparation
All procedures were approved by the University of Texas Animal Welfare Committee and were consistent with the National Institutes of Health “Guide for the Care and Use of Laboratory Animals.” Six conditioned mongrel dogs of either sex (28.6 ± 1.5 kg) were used for the cardioplegia experiments and 6 (26.7 ± 0.9 kg) for the esmolol experiments. The dogs were anesthetized through the intravenous administration of 25 mg/kg of thiopental sodium (Pentothal; Abbot Laboratories, North Chicago, IL), intubated, and mechanically ventilated with 100% oxygen using a volume-cycled ventilator (Siemens-Elema AB, Sweden). Anesthesia was maintained with the intravenous infusion of 1% thiopental sodium in Ringer’s solution.

Subcutaneous needle electrodes were used to monitor the heart rate. Fluid-filled catheters were placed in the left femoral artery and vein for mean arterial pressure monitoring, arterial blood sampling, and fluid administration. A 7F Swan-Ganz thermodilution catheter was inserted into the pulmonary artery through the left jugular vein for central venous pressure, pulmonary artery pressure, and cardiac output determination. A 5F catheter was introduced through the right jugular vein into the coronary sinus for coronary sinus blood sampling. The right femoral artery then was exposed for subsequent cardiopulmonary bypass (CPB) cannulation. After median sternotomy, the pericardium was incised and a micromanometer-tipped pressure transducer (Millar Instruments Inc, Houston, TX) was introduced into the left ventricular cavity through the apex of the left ventricle. A snare then was placed around the inferior vena cava for cardiac preload manipulation. Sonomicrometry crystals (5 MHz; Triton Technology Inc, San Diego, CA) were placed into the left ventricular subendocardium across the septum/free-wall axis of the left ventricle.

Left Ventricular Function Parameters
Left ventricular pressure was measured with a micromanometer and the left ventricular septum/free-wall diameter was obtained with the use of a sonomicrometer (Triton Technology Inc). These data were recorded at a frequency of 200 Hz during 15 seconds of inferior vena cava occlusion (MacLab; World Precision Instruments Inc, Sarasota, FL). The following left ventricular function parameters were derived as previously described [6, 7, 11, 12]: preload recruitable stroke work, maximum pressure, and end-diastolic pressure.

Myocardial Fluid Balance Parameters
Myocardial water content was derived using a microgravimetric technique as previously described [7, 13]. A biopsy forceps (Cordis Corporation, Miami, FL) was introduced transapically into the left ventricle and endomyocardial samples were collected [7]. The specific density of these myocardial biopsies was measured in a linear density gradient consisting of bromobenzene and kerosene [7]. With the knowledge of myocardial specific density, the grams of water per grams of tissue, or myocardial water content, can be calculated using the following equation [7, 13]:

\[
\text{MWC} = \left(1 - \frac{([\text{SG}_{\text{myo}}] - 1)}{(1 - \frac{1}{\text{SG}_{\text{dry}}}) \cdot \text{SG}_{\text{myo}}}\right) \cdot 100\% \quad (1)
\]

where MWC is myocardial water content and SG_{myo} and SG_{dry} are the specific gravities of the myocardial sample and of dry myocardium, respectively. Because changes in myocardial density are linearly related to changes in myocardial water content, serial myocardial density determinations allow the measurement of myocardial water content changes over time [7]. At the end of the experiment, a last myocardial density measurement was performed. The dogs were euthanized with an intravenous overdose of pentothal and saturated potassium chloride and the hearts were excised rapidly. Both ventricles were weighed and then dried to a constant weight at 60°C. The specific gravity of the dry myocardium was calculated using the following equation [7, 13]:

\[
\text{SG}_{\text{dry}} = 1/\left(1 - \frac{([\text{SG}_{\text{myo}}] - 1) \cdot W}{D \cdot \text{SG}_{\text{myo}}}\right) \quad (2)
\]

where W and D are the wet and dry weights of both ventricles, respectively. We assumed that SG_{dry} did not change over the experimental period. We performed all myocardial water content measurements in duplicate.

Cardiopulmonary Bypass
After preparation, heparin (250 IU/kg) was given intravenously for systemic anticoagulation. Additional doses of 100 IU/kg were administered every 60 minutes throughout the experiment. A 14F arterial perfusion cannula was introduced into the prepared right femoral artery. A two-stage (34F/38F) venous cannula (model TAC2; DLP Inc, Grand Rapids, MI) was placed into the right atrium/inferior vena cava. The left ventricle was vented with a 12F catheter inserted through the left atrium. Cardiopulmonary bypass was performed using three roller pumps for extracorporeal circulation, left ventricular drainage, and suction, respectively. The extracorporeal circuit and the membrane oxygenator (Monolyth M2; Sorin Biomedical Inc, Irvine, CA) were primed with 800 mL of Ringer’s solution and 1,000 IU of heparin. A rectal temperature probe was placed and the body temperature was manipulated using a heat exchanger. Cardiopulmonary bypass flow was maintained between 70 and 90 mL·kg⁻¹·min⁻¹ and systemic perfusion pressure was maintained above 50 mm Hg.

Maintenance of Minimal Myocardial Contraction During Circulatory Support
To provide acceptable surgical conditions on CPB, myocardial inotropy and chronotropy were suppressed using the ultra-short-acting β-blocker esmolol (Brevibloc; Ohmeda Pharmaceutical Products Division Inc, Liberty Corner, NJ) as suggested by Sweeney and Frazier [9].

Downloaded from ats.ctsnetjournals.org by on October 5, 2009
Accordingly, an esmolol bolus of 10 mg/kg was administered initially, followed by an intravenous esmolol infusion of 500 μg · kg⁻¹ · min⁻¹. The aorta was not cross-clamped and no cardioplegia was given. Additional esmolol boluses were given when the maximum left ventricular pressure exceeded 10 mm Hg during circulatory support. The body temperature was maintained at 37°C.

Maintenance of Cardioplegic Arrest During Circulatory Support
In the CA group, the aorta was cross-clamped and 10 mL/kg of iced (4°C) crystalloid cardioplegia (26 mEq/L potassium, 32 mEq/L magnesium, 304 mOsmol/L, pH 7.8; Plegisol; Abbot Laboratories) was infused into the aortic root at a pressure of 100 cm H₂O (74 mm Hg). An additional dose of 100 mL of cardioplegia was given when electrical or mechanical cardiac activity was observed. The body temperature was reduced to 28°C by the heat exchanger. Rewarming to 37°C was initiated 20 minutes before aortic cross-clamp removal.

Experimental Protocol
After instrumentation, baseline measurements of all parameters were recorded. Arterial and coronary sinus plasma samples were frozen at −20°C for later lactate quantification using an enzymatic test (Sigma Diagnostics, St. Louis, MO). Circulatory support then was initiated with CPB, and MMC or CA was induced for 120 minutes as described previously. Measurements of all parameters were repeated at 10, 60, and 110 minutes of MMC or CA during CPB. After cessation of the esmolol infusion or removal of the aortic clamp, coronary sinus and arterial lactate and blood gases were drawn at 3, 9, and 15 minutes. Circulatory support then was maintained for an additional 60 minutes. Thereafter, the dogs were weaned from circulatory support, all cannulas were removed, and measurements were repeated at 30, 60, and 120 minutes after separation from CPB. Plasma concentrations of esmolol and its metabolite ASL-8123 were determined using high-performance liquid chromatography as described by Achari and colleagues [14].

All data presented are mean plus or minus standard error. To examine the data for changes over time and differences between CA and MMC, we used a two-way analysis of variance for repeated measures. Post-hoc comparisons were performed using Student’s t test with Bonferroni correction for multiple comparisons. A value of p less than 0.05 was considered statistically significant.

Results
Data from 12 dogs are presented. Animals in the MMC group received 2.6 ± 0.2 mg/kg of infused esmolol, in addition to 24.5 ± 6.7 mg/kg of bolus esmolol. Animals in the CA group received 607 ± 20 mL of cardioplegia.

Tables 1 and 2 provide all the data on hemodynamics, left ventricular function, and hematocrit values. Left ventricular contractility, as reflected by preload recruitable stroke work, was decreased significantly compared with baseline values in both groups at 30, 60, and 120 minutes after bypass.

Figure 1 shows the arterial–coronary sinus lactate difference at various points throughout the protocol. Significant lactate washout is seen in the CA group at 3 and 9 minutes after cross-clamp removal compared with the esmolol group at 3 and 9 minutes after esmolol cessation. Table 3 shows that during esmolol infusion, the coronary sinus oxygen saturation was elevated compared with baseline.

Figure 2 shows myocardial water content at various points throughout the protocol. The hearts of the dogs in the esmolol group accumulated significantly less water at 60 and 110 minutes of esmolol infusion compared with the hearts of the dogs in the CA group at 60 and 110 minutes of CA. After separation from CPB, myocardial edema was partially resolved in both groups. However,
myocardial water content at 60 and 120 minutes after CPB was significantly higher in the CA group compared with the esmolol group. Table 4 provides the arterial plasma concentrations of esmolol and ASL-8123, the major metabolite of esmolol.

**Comment**

Our data show that the maintenance of MMC during circulatory support is an effective alternative to CA. We previously demonstrated that myocardial ischemia is avoided and myocardial water content is minimized compared with CA. However, in contrast to our previous models involving 1 hour of MMC, 2 hours of MMC resulted in no significant difference in postbypass ventricular function compared with CA.

**Avoidance of Ischemia**

The role of cardioplegia in cardiac operations is not only to provide immobility of the heart to facilitate the surgical procedure, but also to provide myocardial protection while the heart is arrested. Conventional hypothermic crystalloid cardioplegia primarily provides myocardial protection through hypothermia, which prolongs the myocyte’s ischemia tolerance. However, studies have shown that hypothermic crystalloid cardioplegia is still associated with myocardial ischemia [1–6].

We used the arterial–coronary sinus lactate difference as an indicator of anaerobic myocardial metabolism (Fig 1). The negative arterial–coronary sinus lactate difference after CA demonstrates lactate production by the myocardium and suggests ischemia. In contrast, lactate production is not observed during MMC, demonstrating that anaerobic myocardial metabolism is avoided. Thus, we conclude that ischemia avoidance is superior with MMC than with CA.

We also measured oxygen saturation in the coronary sinus, as shown in Table 3. Because arterial oxygen saturation is 100% throughout, coronary sinus oxygen saturation is a useful indicator of the adequacy of myocardial oxygen delivery. During MMC, coronary sinus oxygen saturation increased significantly above baseline, indicating decreased oxygen consumption. This is consistent with what we would expect from both mechanical workload reduction on CPB and negative inotropic effects of β-blockade. After cessation of MMC, coronary sinus oxygen saturation returned to baseline more slowly than after CA. The gradual return to baseline after MMC may reflect esmolol metabolism and return of normal cardiac function.
Myocardial Water Content

Our data show that maintenance of MMC during normothermic circulatory support minimizes the accumulation of myocardial edema compared with hypothermic CA. This is consistent with our previous findings concerning the primary role of organized myocardial contraction in myocardial lymphatic function [6]. In a previous model of normothermic blood cardioplegia, myocardial lymph flow essentially ceased when cardiac contraction stopped despite continuous coronary perfusion, leading to significant increases in myocardial water content [7]. In another study, the modest degree of contraction that persisted during MMC was sufficient to maintain myocardial lymph flow at or above baseline values during circulatory support [10]. Thus, the preservation of organized cardiac activity during MMC maintains lymph flow and is at least partially responsible for the lower myocardial water content in this group.

Another factor that contributes to the effectiveness of MMC in minimizing edema accumulation is the higher colloid osmotic pressure to which the capillaries are exposed compared with crystalloid cardioplegia. The plasma colloid osmotic pressure is decreased during MMC as a result of hemodilution with the crystalloid

![Figure 2. Myocardial water content in the minimal myocardial contraction group (MMC; circles; n = 6) and the cardioplegic arrest group (CA; squares; n = 6) at baseline (BL), 10, 60, and 110 minutes during MMC or CA, and 30, 60, and 120 minutes after cardiopulmonary bypass (CPB). (*p < 0.05 MMC versus CA.)](image)

**Table 3. Coronary Sinus Oxygen Saturation**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Baseline Value</th>
<th>Value During MMC</th>
<th>Value After MMC</th>
<th>Value After CA</th>
<th>Value After CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC (n = 6)</td>
<td>42 ± 0.8</td>
<td>41.6 ± 3.9</td>
<td>96.7 ± 1.2bc</td>
<td>95.5 ± 2.1bc</td>
<td>96.7 ± 1.2bc</td>
</tr>
</tbody>
</table>

Values are mean plus or minus standard error and are given as percentages. *p < 0.05 compared with baseline value.

**Table 4. Arterial Plasma Concentrations of Esmolol and Its Metabolite ASL-8123**

<table>
<thead>
<tr>
<th>Substance Measured</th>
<th>No. of Animals Tested</th>
<th>Value After Cardiopulmonary Bypass (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol</td>
<td>6</td>
<td>246.8 ± 37.2 220.1 ± 27.6 230.2 ± 40.6</td>
</tr>
<tr>
<td>ASL-8123</td>
<td>6</td>
<td>246.8 ± 37.2 220.1 ± 27.6 230.2 ± 40.6</td>
</tr>
</tbody>
</table>
bypass prime, explaining the increase in myocardial water content over baseline values. However, colloid osmotic pressure during MMC is still significantly higher than with pure crystalloid cardioplegia (0 mm Hg). Thus, fluid filtration out of the myocardial capillaries into the interstitium is less favorable with MMC than with CA.

Ventricular Function

Ventricular function, as reflected by preload recruitable stroke work, was not significantly different after circulatory support between the MMC and CA groups. However, preload recruitable stroke work was decreased in both groups compared with baseline values. This finding contradicts our previous work, which showed no decrease in preload recruitable stroke work compared with baseline values after 1 hour of MMC [10]. We previously showed that maintenance of organized cardiac activity with 1 hour of MMC maintained lymph flow, resulting in minimal accumulation of myocardial edema and preservation of cardiac function [10]. However, in the present study, we maintained MMC for 2 hours, and although myocardial water content was significantly lower than with CA, preload recruitable stroke work was decreased to the same extent after circulatory support. Thus, the depressed myocardial function apparently was not related to myocardial edema.

Because the MMC group in the present study received substantially more esmolol than the MMC group in our previous study (336.5 ± 30.7 mg/kg versus 170.6 ± 15 mg/kg, respectively), we analyzed plasma samples (stored at −20°C) for possible residual esmolol at 30, 60, and 120 minutes after CPB. No esmolol (half-life, 9 to 11 hours), the primary acid metabolite of esmolol, were detected in any of the samples. However, significant concentrations of ASL-8123 (half-life, 4 to 6 minutes) was detected in any of the samples. However, plasma samples (stored at −20°C) for possible residual esmolol at 30, 60, and 120 minutes after CPB. No esmolol (half-life, 9 to 11 hours), the primary acid metabolite of esmolol, were detected in any of the samples. However, significant concentrations of ASL-8123 (half-life, 4 to 6 hours), the primary acid metabolite of esmolol, were detected in the samples (Table 4). ASL-8123 has been shown to possess β-blocking properties, but it is approximately 1,580-fold less potent than esmolol [15]. β-Blockade has been demonstrated in vitro and in vivo with ASL-8123 concentrations in the range that we detected [15]. Shaffer and associates [15] showed that ASL-8123 levels of 293 ± 65 µg/mL were associated with a 50% reduction in isoproterenol-induced tachycardia. Thus, we believe that the depressed cardiac function after 2 hours of MMC is secondary to the accumulation of clinically significant concentrations of ASL-8123.

We would expect the heart rate to be lower after CPB in the presence of significant levels of ASL-8123. However, we do not believe that meaningful conclusions can be drawn from the heart rate data because they are influenced by many other factors.

How could the high ASL-8123 concentrations and associated negative inotropic effects seen with the MMC technique be avoided? Rather than systemic infusion of esmolol, the aorta could be clamped and warm oxygenated blood with esmolol infused into the aortic root to expose the myocardium selectively to high levels of esmolol. Although there are disadvantages to clamping the aorta, the cumulative dose of esmolol should be reduced significantly. We currently are investigating this modality in an animal model.

Conclusion

In conclusion, we have demonstrated that the MMC technique is superior to cold crystalloid cardioplegia in terms of ischemia avoidance and myocardial edema minimization. However, prolonged surgical times may lead to the accumulation of esmolol metabolites, which may limit the utility of MMC for longer cases. A modification of the MMC technique that will reduce the esmolol requirement currently is being investigated. The MMC technique may represent a useful alternative to conventional cardioplegic arrest.

References

β-Blockade as an Alternative to Cardioplegic Arrest During Cardiopulmonary Bypass
R. David Warters, Steven J. Allen, Karen L. Davis, Hans J. Geissler, Irene Bischoff, Ernst Mutschler and Uwe Mehlhorn