Effect of Two Different Bypass Techniques on the Serum Troponin-T Levels in Newborns and Children

Does pH-Stat Provide Better Protection?

Zsolt L. Nagy, PhD; Mike Collins, MSc; Tracy Sharpe; Saeed Mirsadraee, MRCS; Rafael R. Guerrero, MD; John Gibbs, MRCP; Kevin G. Watterson, FRACS

Background—Cardiac troponin-T is a sensitive marker of myocardial damage. In a prospective study, the effect of 2 different pH strategies during cardiopulmonary bypass on ischemic myocardial injury and clinical outcome was measured in a pediatric population.

Methods and Results—One hundred one patients (31 neonates 13.2±8.3 days and 70 children 34.5±44.1 months of age) undergoing open-heart surgery were selected to either α-stat (n=51) or pH-stat (n=50) acid-based management protocol. Serum troponin-T levels were measured before and 30 minutes after bypass and then 4 and 24 hours postoperatively. Surgical procedure, bypass details, inotropic support requirement, and postoperative recovery were recorded. Baseline troponin-T level was higher in neonates than in children (0.18±0.22 versus 0.04±0.05 μg/L, P=0.02). Also, a higher baseline level was found in patients with pulmonary hypertension (0.13±0.21 versus 0.04±0.05 μg/L, P=0.04). Cyanotic children showed a higher peak troponin-T level (3.76±3.11 versus 1.67±1.33 μg/L, P=0.04). Peak troponin levels showed a correlation with the length of circulatory arrest and aortic cross-clamp time. Postoperative levels remained high at 24 hours in patients requiring inotropic support. Peak troponin-T levels were significantly lower in the pH-stat group in patients with pulmonary hypertension (P=0.03) and in cases where circulatory arrest (P=0.01) or inotropic support (P=0.01) was necessary during operation than in those with α-stat technique. Postoperative ventilation time and length of intensive care unit stay were also significantly longer with α-stat than with pH-stat technique (P=0.005 and P=0.006, respectively).

Conclusions—Cardiac troponin-T sensitively reflects myocardial damage in children. Our results suggest that pH-stat acid-based management protocol may provide better protection against ischemic myocardial damage than α-stat technique. (Circulation. 2003;108:577-582.)

Key Words: pediatrics ■ cardiopulmonary bypass ■ myocardium ■ ischemia

Progressive development in surgical, anesthetic, and perfusion techniques has allowed the repair of most congenital heart defects either in infancy or early childhood in one stage. These repairs can be time consuming; therefore, the immature, often volume- or pressure-loaded heart can be exposed to longer periods of ischemia. Despite the fact that overall results are improving, little is known about the vulnerability of the pediatric myocardium to ischemia and reperfusion injury.

The immature myocardium has traditionally been considered to be more resistant to hypoxia than its adult counterpart based on the results of experiments on healthy young animals. However, more recent studies on children have suggested that the congenitally abnormal pediatric heart is more sensitive to cardioplegic arrest; furthermore, most of the postoperative morbidity and mortality has been attributed to inadequate myocardial protection.

The technique of extracorporeal perfusion and quality of cardioplegia are essential in protecting the myocardium from reperfusion injury. Presently there are 2 acid-based management protocols used during cardiopulmonary bypass (CPB). In the α-stat strategy, the pH and pCO₂ of the arterial blood are measured at 37°C and maintained at 7.40 and 40 mm Hg, respectively, regardless the patient’s actual temperature. In pH-stat management, the in vivo pH of the arterial blood is maintained at 7.40 by adjusting the pCO₂ to 40 mm Hg at the actual hypothermic temperature. In adult patients operated on using mild hypothermia, the α-stat strategy is commonly used because of the superior neurologic outcome compared with the pH-stat technique. However, in the pediatric population, when deep hypothermia and circulatory arrest are sometimes necessary, both animal studies and clinical trials suggest better myocardial recovery and early clinical outcome using the pH-stat acid-based management protocol.

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Despite clinical evidence of myocardial cell damage during cardiac surgery, until recent years there was no specific marker to measure sensitively the extent of myocardial injury. Cardiac troponin-T (cTnT), a thin filament contractile protein present at high concentrations in the myocardium, was found to be a sensitive and specific marker of myocardial infarction.11,12 After developing a more cardiac-specific and -sensitive new 1-step immunoassay for cTnT, it was selected to be a sensitive and specific marker of myocardial infarction.11,12 After developing a more cardiac-specific and -sensitive new 1-step immunoassay for cTnT,13 it was adapted as a marker of myocardial cell damage during CPB.14 Recent studies have demonstrated that cTnT is a reliable marker of myocardial injury even in the pediatric population.4,6,15

We designed a protocol to demonstrate the effect of 2 different acid-based management protocols on perioperative myocardial injury. In our study, serial measurements of serum cardiac troponin-T were performed in 101 randomly selected neonates and children undergoing open-heart operation for congenital heart disease.

**Methods**

The study was approved by the local ethical committee of the Leeds Teaching Hospitals, and informed consent was obtained from the parents of the patients.

**Patient Population**

One hundred one consecutive pediatric patients (31 infants and 70 children) undergoing elective open-heart surgery for congenital heart disease performed by the same 2 surgeons at the Yorkshire Heart Centre between January 1998 and December 1999 were enrolled prospectively in the present study. All patients younger than 14 years of age were included whose parents consented to the study regardless of the clinical diagnosis. In the first part of the study, the patients were selected to be part of the clinical diagnosis; patients with right-to-left shunt were considered cyanotic patients, whereas left-to-right shunt with volume-loaded right ventricle and elevated pulmonary pressures was considered pulmonary hypertension.

The preoperative characteristics and operative data are summarized in Table 1. There were more neonates in the α-stat group; therefore, the mean age was higher in the pH-stat group, although it did not reach the level of significance. However, the aortic cross-clamp and CPB times were significantly longer in the pH-stat group. No other major differences were observed between the 2 groups regarding the preoperative and intraoperative variables.

**Surgical Technique**

CPB with ascending aortic and right atrial or bivacual cannulation was used for all operations. Aprotinin (10 mL/kg) was routinely administered to the pump prime in all pediatric cardiac operations. Myocardial protection was provided by either cold crystalloid (below 10 kg of weight) or by cold blood cardioplegia (above 10 kg of weight). Diastolic arrest was achieved by an antegrade infusion of the cardioplegic solution. A single dose (30 mL/kg) was used in neonates. In older patients, the dose was repeated at 30 to 40 minutes. The number of patients receiving one or another cardioplegia solution was not significantly different in the 2 groups. If circulatory arrest was necessary, the core temperature was lowered to 18°C, adjusting the hematocrit to 18% in the cooling phase and 30% during rewarming. In all other cases, systemic hypothermia of 28 to 32°C was used, maintaining the hematocrit at approximately 30%. The surgical procedures for the 2 groups are listed in Table 2.

**Postoperative Care**

All patients were transferred to the pediatric intensive care unit (ICU). Routine postoperative management was given to all patients. Inotropic support and all other medication were given on the basis of hemodynamic and clinical conditions. The physicians involved in patient treatment were blinded to the serum cTnT levels.

**Blood Samples and Biochemical Analysis**

Two milliliters of native blood samples were collected from the patients at skin incision, 30 minutes after termination of CPB, and 4 and 24 hours postoperatively. The blood samples were centrifuged at 2000g for 10 minutes and stored at −70°C, thawed once, and analyzed in batches. Cardiac troponin-T levels were determined by an electrochemiluminescence immunoassay (Elecsys 1010, Boehringer Mannheim) using 2 highly specific monoclonal antibodies directed against 2 different epitopes of the cardiac troponin-T molecule.13 All of the samples were analyzed by a single operator who was unaware of the patient’s clinical condition.

**Data Collection and Analysis**

Intraoperative variables (length of CPB, aortic cross-clamp time, and circulatory arrest time) and postoperative data (inotropic support requirement, hemodynamic status, renal function, major complications, length of mechanical ventilation, and length of ICU stay) were collected prospectively for all patients. Two neonates who developed...
renal failure early postoperatively in the α-stat group were excluded from the study.

Clinical and biochemical data are expressed as mean±SD. Statistical intragroup analysis was performed by use of paired t test; for intergroup analysis, unpaired t test was used. One-way ANOVA was used for testing the significance of the differences between preoperative and postoperative troponin T levels. Multivariate linear regression was used to study the correlation of independent variables with postoperative troponin T levels at 30 minutes and 4 and 24 hours. The following independent variables were included: age, aortic x-clamp time, circulatory arrest time, cyanosis, pulmonary hypertension, inotropic support requirement, and acid-based management protocol. Significance was determined by P<0.05. Statistical analysis was performed using SPSS version 10 for Windows statistical software (SPSS Inc).

Results
The overall hospital mortality was 3% in the whole series (2 patients in the α-stat, 1 patient in the pH-stat group). There was no major difference between the 2 pH strategies regarding the postoperative cardiac complications (2 patients developed severe low cardiac output syndrome in each group, 2 patients in the pH-stat and 1 in the α-stat group had cardiac arrest requiring resuscitation, and 1 patient in each group developed supraventricular tachycardia). However the ventilation time and the length of the ICU stay were significantly longer with the α-stat than with the pH-stat technique (55.9±50.5 versus 35.6±22.1 hours, P=0.005, and 4.03±3.09 days versus 2.75±1.52 days, P=0.006, respectively).

The data of the 99 patients remaining in the study were analyzed. The pattern of the troponin-T levels in neonates and children for the different bypass techniques is shown in Figure 1. Results of the Tukey honest significance difference multiple comparisons showed that postoperative troponin-T levels were significantly higher than the preoperative levels at all times (P<0.001). However, there were no significant differences between troponin-T levels at 30 minutes, 4 hours, and 24 hours. The baseline level of cTnT was higher in neonates than in children (0.18±0.22 versus 0.04±0.05 µg/L, P=0.02). The levels at 30 minutes and 4 and 24 hours in neonates were significantly higher in the α-stat group than those in the pH-stat group (P=0.01, P=0.02, and P=0.01, respectively). No significant difference was found between the different bypass techniques in children at the above times (P=0.11, P=0.40, and P=0.27, respectively).

A correlation was found between the length of circulatory arrest and aortic cross-clamp times and the postoperative troponin-T levels (Figure 2). The longer the ischemic time, the higher the cTnT levels, regardless of bypass technique. The cTnT levels were significantly higher in the α-stat group for the longest circulatory arrest and aortic x-clamp times (P=0.03 and P=0.04, respectively) compared with the pH-stat technique.

Cyanotic children showed a higher peak level of cTnT than the acyanotic children (P=0.02). In addition, the peak cTnT level for cyanotic children was higher in the α-stat than in the pH-stat group (P=0.04). No significant difference was found in cTnT levels between the cyanotic and acyanotic neonates (Table 3).

Patients with elevated right ventricular and pulmonary pressures also showed a higher baseline troponin-T level. The peak level of cTnT for patients with pulmonary hypertension was higher with the α-stat technique than with pH-stat. No significant difference was found in patients with normal pulmonary pressures regarding the acid-based management protocol (Table 4).

Figure 3 shows the pattern of cardiac troponin-T levels in the patients requiring inotropic support for termination of CPB against those who did not. The peak level in the α-stat group was significantly higher than that in the pH-stat group (5.19±4.47 versus 1.93±1.68 µg/L, P=0.01). The cTnT levels remained high at 24 hours in patients requiring inotropic support in the postoperative period (3.02±2.29 versus 1.21±1.05 µg/L, P=0.01).
TABLE 3. Postoperative Troponin T Levels (µg/L) in Neonates and Children With and Without Cyanosis Using 2 Different Acid-Based Management Protocols

<table>
<thead>
<tr>
<th></th>
<th>Cyanotic Stat</th>
<th>Cyanotic Stat</th>
<th>pH-Stat</th>
<th>pH-Stat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>30 min</td>
<td>4 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Neoneates</td>
<td>n=9</td>
<td>n=9</td>
<td>n=9</td>
<td>n=9</td>
</tr>
<tr>
<td>Preop</td>
<td>0.12±0.11</td>
<td>0.19±0.15</td>
<td>0.22±0.26</td>
<td>0.11±0.12</td>
</tr>
<tr>
<td>30 min</td>
<td>3.12±3.21</td>
<td>4.08±4.29</td>
<td>1.97±1.71</td>
<td>1.95±1.63</td>
</tr>
<tr>
<td>4 h</td>
<td>2.08±1.97</td>
<td>2.88±2.99</td>
<td>1.42±0.97</td>
<td>1.46±1.14</td>
</tr>
<tr>
<td>24 h</td>
<td>1.66±1.48</td>
<td>2.13±2.41</td>
<td>1.16±0.99</td>
<td>1.26±1.21</td>
</tr>
<tr>
<td>Children</td>
<td>n=9</td>
<td>n=23</td>
<td>n=12</td>
<td>n=26</td>
</tr>
<tr>
<td>Preop</td>
<td>0.05±0.06</td>
<td>0.08±0.12</td>
<td>0.02±0.02</td>
<td>0.03±0.03</td>
</tr>
<tr>
<td>30 min</td>
<td>5.24±3.91†</td>
<td>2.11±1.86</td>
<td>2.98±2.39*</td>
<td>1.19±0.94</td>
</tr>
<tr>
<td>4 h</td>
<td>3.19±1.49*</td>
<td>1.40±1.19</td>
<td>2.52±1.57</td>
<td>1.28±0.88</td>
</tr>
<tr>
<td>24 h</td>
<td>2.22±2.51</td>
<td>1.23±1.06</td>
<td>2.82±2.26</td>
<td>1.39±1.18</td>
</tr>
</tbody>
</table>

Preop indicates preoperative.
*P<0.05 vs acyanotic patients in the same group; †P<0.05 vs pH-stat acid-based management protocol.

The results of the multivariate linear regression analysis showed that the use of pH-stat strategy resulted in significantly lower peak troponin-T level at 30 minutes after termination of CPB (F=4.327, P=0.041). However, the troponin levels were not significantly different at 4 and 24 hours postoperatively between the 2 different acid-based management protocols. Patients who required inotropic support for termination of CPB and in the early postoperative period had significantly higher serum troponin-T levels at 24 hours postoperatively with both pH strategies (F=10.173, P=0.002). None of the other independent variables showed significant correlation with postoperative troponin-T levels based on the results of multivariate regression analysis, although the effect of aortic x-clamp time and circulatory arrest time on the peak troponin-T level was approaching the level of significance (Table 5).

Discussion
The usefulness of cardiac troponins in detection of myocardial cell damage in the pediatric population has been extensively reported.6,15–17 Cardiac troponin-T is a thin filament contractile protein with high specificity to the myocardial cell. However, several reports have found elevated levels in patients with renal insufficiency.18,19 Therefore, 2 neonates who developed renal failure early after the operation were excluded from the study.

Our results confirm previous findings that the baseline level of cTnT in children is around the analytical limit of detection.20 However, the preoperative levels of cTnT in

TABLE 5. Results of Multivariate Linear Regression Analysis

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dependent Variable</th>
<th>Mean Square</th>
<th>F Value</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>30 min</td>
<td>14.099</td>
<td>1.480</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>1.845</td>
<td>0.580</td>
<td>0.449</td>
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<td>4.507E-05</td>
<td>0.000</td>
<td>0.997</td>
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<tr>
<td>X-clamp time</td>
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<td>33.227</td>
<td>3.493</td>
<td>0.065</td>
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<td></td>
<td>4 h</td>
<td>10.552</td>
<td>3.317</td>
<td>0.072</td>
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<td></td>
<td>24 h</td>
<td>8.012</td>
<td>2.985</td>
<td>0.088</td>
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<tr>
<td>Arrest time</td>
<td>30 min</td>
<td>32.003</td>
<td>3.360</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>4.250</td>
<td>1.336</td>
<td>0.251</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>1.595</td>
<td>0.594</td>
<td>0.443</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>30 min</td>
<td>0.897</td>
<td>0.094</td>
<td>0.760</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>1.832</td>
<td>0.576</td>
<td>0.450</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>2.870</td>
<td>1.069</td>
<td>0.304</td>
</tr>
<tr>
<td>PHT</td>
<td>30 min</td>
<td>0.280</td>
<td>0.029</td>
<td>0.864</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>1.228</td>
<td>0.386</td>
<td>0.536</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>4.903</td>
<td>1.827</td>
<td>0.180</td>
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<tr>
<td>Inotropic support</td>
<td>30 min</td>
<td>8.535</td>
<td>0.896</td>
<td>0.347</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>2.514</td>
<td>0.790</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>27.303</td>
<td>10.173</td>
<td>0.002</td>
</tr>
<tr>
<td>pH management</td>
<td>30 min</td>
<td>41.219</td>
<td>4.327</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
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<td>3.785</td>
<td>1.190</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>4.612E-05</td>
<td>0.000</td>
<td>0.997</td>
</tr>
</tbody>
</table>

*P<0.05 vs the patients without pulmonary hypertension in the same group; †P<0.05 vs pH-stat acid-based management protocol.
neonates (younger than 1 month of age) was found to be significantly higher, although still in the normal range. The possible explanation is that neonatal patients undergoing surgery are in a more compromised cardiac situation from a cardiac viewpoint, with detectable myocardial damage even before surgery. This is also supported by the finding that patients with pulmonary hypertension and volume- and pressure-loaded hypertrophied right heart showed higher preoperative cTnT levels as well.

In a previous pilot study, the pattern of cTnT concentration in the serum was analyzed by postoperative serial measurements every 2 hours. The results showed that the peak concentration reached 30 minutes after termination of CPB and then in uncomplicated cases showed a steady decrease, reaching the baseline level 4 to 5 days after surgery. The most considerable changes were detected in the first 24 hours. The same pattern was found in the study patients. The postoperative levels were slightly lower in our series than reported by others.6,15,17 The possible explanation for this difference could be the routinely administered aprotinin, which has been reported to improve myocardial protection both in animals and humans.21,22

Imura et al23 have recently demonstrated an age-dependent and hypoxia-related difference in myocardial injury during CPB in the pediatric population. We also found a higher peak level of cTnT in the serum of cyanotic children than in their acyanotic counterparts. There was no significant difference between the cyanotic and acyanotic neonates in terms of the cTnT levels. These results might confirm that the chronically hypoxemic human myocardium is more sensitive to ischemia and requires more sophisticated protection during complex cardiac surgery.

Our results also support previous findings that there is a correlation between the length of myocardial ischemia and the extent of myocardial damage.24 The cTnT levels were significantly higher in the circulatory arrest group compared with the CPB group. The longer aortic cross-clamp or circulatory arrest time resulted in more myocardial cell injury. The serum troponin-T levels sensitively reflected the extent of myocardial damage.

In uncomplicated cases, the cTnT concentration started decreasing 4 hours postoperatively. In those cases when inotropic support was required for termination of CPB or early postoperatively, the cTnT levels remained higher than in patients without inotropic support, as was also shown by Siaplaouras et al.25 The elevated cardiac troponin levels 24 hours after surgery may be related to ongoing myocardial cell damage and might predict poorer outcome.

We found a major difference in myocardial cell damage and postoperative recovery between the different acid-based management protocols in favor of the pH-stat technique. In a previous clinical study by du Plessis et al.,10 a lower mortality rate, better myocardial recovery, and shorter ventilation period and ICU stay were found using the pH-stat strategy. In our series, patients with the α-stat protocol showed a higher level of cTnT in all subgroups. The difference was significant in patients with cyanosis and pulmonary hypertension and in cases when circulatory arrest or inotropic support was necessary. In other words, the results suggest that the pH-stat strategy might provide better protection against ischemic myocardial damage in those cases when the pediatric heart is compromised. The better myocardial protection with the pH-stat technique was reflected in a faster recovery after surgery, as indicated by the shorter ventilation time and ICU stay. There have been several publications that have found better neurological protection with the pH-stat bypass technique in patients undergoing cardiac surgery using deep hypothermia and circulatory arrest.26–28 To our knowledge, there has been no report demonstrating better myocardial protection using pH-stat acid-based management protocol based on measurement of cardiac troponin levels. Theoretically, the vasodilatation caused by the higher carbon dioxide levels with the pH-stat technique will result in more even myocardial temperature during the cooling phase. Also, the pH-stat strategy improves oxygen delivery during hypothermia by shifting the oxygen-hemoglobin dissociation curve to the right because of the elevated carbon dioxide levels. Hypercapnia also decreases lactate production by inhibiting pyruvate dehydrogenase. All of these elements might improve the myocardial metabolism during the cooling and rewarming phase and result in a better myocardial protection and superior clinical outcome with the pH-stat acid-base management protocol.

There are a few important limitations of our study. First, it was not a truly randomized study, although there was no significant difference in the preoperative variables. Also, there was a great variation of clinical conditions and surgical procedures, but to make a sufficient number of measurements on a single pathology in a small unit would take too long. At least 2 different cardioplegia solutions were used in the study population. Our preference is the blood cardioplegia, but unfortunately at the time of the study there was no device available for using blood cardioplegia in patients below 10 kg of weight.

Conclusion
Cardiac troponin-T sensitively reflects the ischemic myocardial damage caused by cardiac surgery in children. In cases where the pediatric heart is overloaded or hypoxic before surgery and where a complex operation requires circulatory arrest or long ischemic time, pH-stat acid-based management technique may provide better protection against ischemic myocardial damage than α-stat technique.

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References
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