Vulnerability of paediatric myocardium to cardiac surgery

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Abstract
Objective—Myocardial injury is an important cause of mortality and morbidity after paediatric cardiac surgery. Data obtained from studies in animals imply that juvenile myocardium is more resistant to the effects of ischaemia and reperfusion than adult myocardium but there is little confirmatory evidence in the clinical setting.

Design—Prospective observational study of biochemical markers of myocardial injury in a paediatric population undergoing cardiac surgery.

Setting—Tertiary referral centre for paediatric cardiac surgery.

Patients—Forty patients undergoing paediatric cardiac surgery of varying complexity including closure of atrial and ventricular septal defects and arterial switch for simple transposition. A control group included patients undergoing thoracotomy for closure of a patent ductus arteriosus or repair of a coarctation.

Interventions—Serial measurements of myoglobin, the MB isoenzyme of creatine kinase (CK-MB), and the highly specific markers of myocardial damage cardiac troponin T (cTnT) and I (cTnI) were made before and 1, 6, 24, and 48 to 72 hours after operation.

Results—There were significant increases in myoglobin and CK-MB, but not cTnT or cTnI, in the control group. There were significant increases in the four biochemical markers in all the cardiac operations but especially in the ventricular septal defect and transposition group. Increases in CK-MB and cTnT were about five times greater than those previously reported in adult patients.

Conclusions—(i) Cardiac troponins are more specific markers of myocardial injury in paediatric cardiac surgery than myoglobin and CK-MB. (ii) Paediatric myocardium seems to be more vulnerable to injury during cardiac surgery than adult myocardium.

Keywords: cardiac surgery; paediatric patients; myocardial injury

Low cardiac output caused by perioperative myocardial injury remains an important cause of morbidity and mortality after paediatric cardiac operations. In recent years there has been a trend towards earlier repair of congenital cardiac defects in neonates and infants. The susceptibility of the human paediatric heart to ischaemia and reperfusion has not been adequately studied although most of the available evidence, derived almost exclusively from studies in animals, implies that the juvenile heart is more resistant to ischaemia and reperfusion than its adult counterpart. Smolenski and colleagues on the basis of release of purines, lactate, and phosphate from the coronary sinus, however, suggested that the hearts of children two to 10 years of age were more metabolically vulnerable to cardioplegic arrest.

Myoglobin and the MB isoenzyme of creatine kinase are the conventional biochemical standards for quantifying myocardial injury after cardiac surgery although neither is exclusive to myocardium. Cardiac troponin T and I are tissue specific isoforms of the respective subunits of the troponin regulatory complex whose systemic release implies myocardial damage. After surgical injury concentrations of myoglobin and CK-MB reach a peak earlier than those of the cardiac troponins, reflecting differences in molecular weights, cellular distribution, and plasma clearance. We have confirmed the value of cardiac troponin T in quantifying perioperative myocardial injury in adults undergoing cardiac surgery.

Patients and methods
The study was approved by the hospital ethics committee.

Serum concentrations of myoglobin, CK-MB, and cardiac troponin T and I (cTnT; cTnI) were measured serially (before and 1, 6, 24, and 48 to 72 hours after operation) in 40 patients undergoing paediatric cardiac surgery.

PATIENTS
The 40 patients comprised four groups undergoing surgery of varying complexity (table 1).

Group 1—Ten control patients undergoing extracardiac operations (for example, ligation of patent ductus arteriosus or repair of coarctation)

Group 2—Six undergoing closure of atrial septal defects (ASD)

Group 3—Sixteen undergoing closure of ventricular septal defects (VSD)
Group 4—Eight undergoing arterial switch operation for transposition of the great arteries

SURGERY
The control patients required a thoracotomy but no direct cardiac procedure. In patients in Groups 2–4 corrective surgery was performed with cardiopulmonary bypass (CPB) and myocardial protection was obtained with St Thomas’s cardioplegia (30 ml/kg) at 4°C, administered under gravity through the aortic root every 30 minutes. Group 2 patients were cooled to 32°C, group 3 patients to between 15°C and 28°C, and group 4 patients to between 15°C and 18°C. All patients in group 4 underwent a period of total circulatory arrest as did most patients in group 3.

BIOCHEMICAL ANALYSIS
Biochemical analyses has been described previously.11 Myoglobin was measured with a double antibody radioimmunoassay technique (Myoglobin RIA Test Kit, Biogenesis, Bournemouth); CK-MB was directly measured by microparticle enzyme immunoassay with the Abbott IMX CKMB kit (Abbott Diagnostics Division, Maidenhead); cTnT and cTnI were measured by enzyme linked immunosorbent assays (Elisa Troponin T kit, Boehringer Mannheim, UK, and Troponin I Pasteur kit, Sanofi Diagnostics Pasteur).

STATISTICAL ANALYSIS
Serial changes in the biochemical markers, within and between groups, were compared by Kruskal-Wallis one way analysis of variance. Differences were regarded as significant at the probability level of \( P < 0.05 \). Results were expressed as mean (SE) or medians and inter-quartile ranges

Results
Patient data are summarised in table 1. The mean (SD) age of the control group was 28 (0-8) months compared with 4 (1) years in the ASD group, 4 (1) months in the VSD group, and 15 (4) days in the arterial switch group. The mean (SD) ischaemic time increased from 19 (6) minutes in the ASD group to 36 (11) minutes in the VSD group and 92 (17) minutes in the TGA group.

Serial changes in myoglobin, CK-MB, cTnT, and cTnI are shown in figs 1–4. For the sake of clarity only median values are shown and the inter-quartile ranges are presented in table 2. The control group showed a highly significant (\( P < 0.01 \)) increase in myoglobin and CK-MB but no increase in either cTnI or cTnT. For groups 2–4 peak values of myoglobin (fig 1) and CK-MB (fig 2) were reached one hour after the end of the ischaemic period (\( P < 0.05 \)) while those of cTnT (fig 3) and cTnI (fig 4) were reached six hours after the end of the ischaemic period (\( P < 0.05 \)). The largest increases in CK-MB and cTnT
were seen in the VSD and arterial switch groups with peak concentrations about five times higher than those previously reported in adults undergoing myocardial revascularisation\textsuperscript{10\textendash}11 or aortic valve replacement (unpublished observations). The ASD group showed increases in CK-MB and cTnT similar to those previously reported in adults\textsuperscript{10\textendash}11 and considerably less than those of the VSD and arterial switch groups. Changes in cTnI (which we have not previously measured in adults) were broadly similar to those of cTnT.

**CLINICAL OUTCOME**

Three patients died in the postoperative period (one from the VSD group and two from the arterial switch group). The serum concentration of cTnI exceeded 12 µg/l between three and six hours in these three patients (42 µg/l, 17 µg/l, and 12 µg/l respectively) compared with only one of the 27 survivors of paediatric cardiac operations.

**Discussion**

This study supports the cardiac specificity of cTnT and cTnI as markers of myocardial injury during paediatric cardiac surgery. Whereas myoglobin, and to a lesser extent CK-MB, increased significantly in all groups, including the control group who were not subjected to direct myocardial injury, the increases in cTnT and cTnI occurred only in the cardiac surgery groups.

Our results do not support the contention\textsuperscript{4\textendash}6 that paediatric myocardium is more resistant to ischaemia and reperfusion than its adult counterpart. The peak concentrations of CK-MB and cTnT in our VSD and arterial switch patients were about five times higher than those observed in adult patients undergoing myocardial revascularisation\textsuperscript{10\textendash}11 or complex aortic valve surgery (unpublished observations) with comparable ischaemic times and similar myocardial preservation techniques. These differences are even more impressive when we bear in mind that the heart forms a smaller proportion of the body mass in infants than it does in adolescents and adults.\textsuperscript{12}

The discrepancy between our observations and those from studies in animals\textsuperscript{5\textendash}8 might be explained in the differing models of myocardial injury. The vulnerability of paediatric myocardium to ischaemia and reperfusion has been determined almost exclusively in studies of the hearts of healthy young animals which

![Graph showing serial changes in serum cTnT in the four paediatric groups.](image_url)

**Table 2** Interquartile range for the biochemical markers at various time points

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
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<tbody>
<tr>
<td></td>
<td>Myoglobin</td>
<td>CK-MB</td>
<td>cTnI</td>
<td>Myoglobin</td>
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<tr>
<td>Proop</td>
<td>199</td>
<td>2</td>
<td>0.4</td>
<td>25</td>
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<tr>
<td>1 h</td>
<td>195</td>
<td>21</td>
<td>0.5</td>
<td>25</td>
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<tr>
<td>6 h</td>
<td>80</td>
<td>21</td>
<td>0.2</td>
<td>0.2</td>
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<td>24 h</td>
<td>11</td>
<td>25</td>
<td>0.4</td>
<td>0.4</td>
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<tr>
<td>72 h</td>
<td>13</td>
<td>8</td>
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are not comparable to the volume and pressure overloaded hearts associated with congenital cardiac abnormalities. In addition to differences in myocardial metabolic function between human and other species, important differences in myocardial metabolic response to cardioplegic arrest has been demonstrated between adults and children. Smolenski et al reported a much greater release of lactate, phosphate, and purines in coronary sinus effluent in children aged two to 10 years undergoing cardiac surgery than in adults: this implies a much more severe metabolic injury.

While congenital abnormalities may result in abnormal cardiac function the normal serum concentrations of myoglobin, CKMB, cTnT, and cTnI before operation suggest that there was no ongoing structural damage. On the other hand these dilated, hypertrophied, and hypoxic hearts may be more sensitive to the effects of ischaemia and reperfusion. Our results are consistent with our own clinical experience and that of others that inadequate myocardial preservation may contribute to cardiac morbidity and/or mortality after paediatric cardiac surgery. Indeed, one study of 400 paediatric patients suggested that half of the postoperative deaths were attributable to inadequate myocardial preservation despite crystalloid cardioplegia.

The heterogeneous nature of the patients in the current study in terms of age, operations, and ischaemic times complicates interpretation of the results. The temporal pattern of myocyte transition from immaturity to mature biochemical and physiological function has not been elucidated but is probably not completed within the first few years of life and may well result in variations in the vulnerability of paediatric myocardium to ischaemia and reperfusion at different ages. The varied nature of the operations in our study, involving different anatomical approaches and incisions, is further complicated by differing ischaemic times for the various operations; though the ischaemic time for any particular operation was fairly constant. The least severe degree of myocardial injury was seen in the ASD patients who were considerably older than patients in the VSD and arterial switch groups (four years, four months and 15 days respectively) and whose ischaemic period was significantly shorter. The degree of biochemical myocardial injury seemed greater in the VSD group (whether repaired through an atriotomy or ventriculotomy) than the arterial switch group, despite significantly greater ischaemic periods in the latter group. This is unlikely to be due to ventriculotomy because there was no difference in biochemical injury whether the VSD was repaired through an atriotomy or ventriculotomy and might indicate that patch closure of the septum predisposed to increased release of biochemical markers.

Our study raises the possibility that the serum concentration of cTnT between three and six hours after operation might be of some prognostic value. The three patients who died had a serum concentration of cTnT in excess of 12 μg/l compared with only one of 27 survivors. Confirmation that the postoperative cTnT concentration is of prognostic value would, however, require a larger study and a correlation between biochemical markers of myocardial damage and echocardiographic or a more invasive assessment of ventricular function.

We hope that our findings will stimulate the search for more effective and specific methods of myocardial protection in the neonatal heart which could help to optimise the early and long term results in these patients.