Gut permeability and myocardial damage in paediatric cardiac surgery

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CHAPTER 6

Effect of three different anaesthetic agents on the postoperative production of cardiac troponin T in paediatric cardiac surgery.

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Background: Paediatric cardiac surgery is associated with some degree of myocardial injury. Ischaemic preconditioning (IP) has been widely investigated in the adult population. Volatile agents have been shown to simulate IP providing extra protection to the myocardium during adult cardiopulmonary bypass while propofol seems to act through different mechanisms. IP has not been investigated in the paediatric population to the same extent. Cardiac troponin T (cTnT) is a reliable marker of myocardial injury in neonates and children. We have investigated the relationship between three anaesthetic agents, midazolam, propofol and sevoflurane, and postoperative production of cTnT.

Methods: Ninety patients undergoing repair of congenital heart defect with cardiopulmonary bypass were investigated in a prospective randomized study. cTnT was measured four times during the first 24 hours following admission to the paediatric intensive care unit. Other parameters measured included arterial blood gases, lactate, fluid balance, use of inotropic drugs, PaO_2/FiO_2 ratio and ventilator hours.

Results: cTnT was elevated in all three groups throughout the study period. The differences between the three groups were not statistically significant. Eight hours after admission to the intensive care unit cTnT concentrations tended to be higher in the midazolam group (mean (95% confidence intervals)); 2.7 (1.9 – 3.5) ng ml^{-1} . Patients receiving a propofol based anaesthesia had similar concentrations 2.6 (1.7 – 3.5) ng ml^{-1} while those receiving sevoflurane tended to have a lower cTnT production 1.7 (1.3 – 2.2) ng ml^{-1}.

Conclusions: Midazolam, propofol and sevoflurane seem to provide equal myocardial protection in paediatric cardiac surgery when using cTnT as a marker of myocardial damage.

During repair of a congenital heart defect the child is exposed to myocardial hypoxia. Exposing the adult myocardium to brief periods of ischaemia and reperfusion induces greater tolerance to a subsequent more prolonged ischaemic insult, a phenomenon known as ischaemic preconditioning (IP).

Animal experiments have shown that the effects of ischaemic preconditioning are mimicked by inhalational anaesthetics[1], morphine[2], and possibly other opioids. This is often referred to as anaesthetic preconditioning. The use of inhalational anaesthetics improves clinical and biochemical parameters after coronary artery bypass surgery.[3,4] The subject has been reviewed extensively.[5,6] There is little available information as to whether IP also occurs in paediatric patients. IP is absent in rats at birth and only develops in the second week of postnatal life.[7] Preconditioning can be induced in isolated perfused immature rabbit hearts.[8] It has been suggested that the normoxic paediatric heart is less likely than the adult heart to undergo injury with bypass or surgical ischaemia.[9] Recent studies, however, have suggested that the paediatric myocardium is more sensitive to hypoxia and cardioplegic arrest than the adult one.[10] On the other hand cyanotic patients are exposed to high concentrations of oxygen when bypass starts (similar to reperfusion injury).

The effect of halogenated agents and propofol on ischaemia and reperfusion injury has been widely investigated in adults. Midazolam has not been investigated to the same extent and information about its potential benefits or lack thereof is scarce. Midazolam, sevoflurane and propofol are three anaesthetic agents commonly used in paediatric practice.

Cardiac troponin T (cTnT) is a specific marker of myocardial infarction.[11] It is also a reliable marker of myocardial injury in the paediatric population.[12] There is no information in the literature about the relationship between postoperative production of cTnT in children and the anaesthetic agents, midazolam, propofol and sevoflurane. In this study we investigated whether midazolam, propofol or sevoflurane afford equal myocardial protection during paediatric cardiac surgery, as assessed by postoperative cTnT production.

Materials and Methods

After approval by the hospital ethics committee and parental consent 90 patients were prospectively investigated. cTnT was measured four times during the first 24 h following admission to the paediatric intensive care unit. This is standard practice in our institution.

Patients were randomized using standard randomization tables to receive either midazolam, propofol or sevoflurane as the main anaesthetic agent. We used a process of minimization to achieve similar number of patients for each surgical procedure. The first patient for each operation is allocated at random. For each subsequent patient we determined which treatment would lead to a better balance between the groups with respect to the type of operation. The patient is then randomized using a weighting system in favour of the treatment which will minimize the imbalance.[13] Measurement of cTnT was done by the hospital clinical chemistry laboratory, and the analysts were unaware of the conduct of this study.

Patients received premedication consisting of oral atropine (0.02 mg kg^{-1}) and midazolam (0.5 mg kg^{-1}) 30 min before induction of anaesthesia. Anaesthesia was induced with sevoflurane followed by a bolus of sufentanil (1 μg kg^{-1}) and pancuronium (0.2 mg kg^{-1}). For maintenance of anaesthesia, (30 patients in each group) patients received either a continuous infusion of midazolam (0.2 mg kg^{-1} h^{-1}), a continuous infusion of propofol (6 to 8 mg kg^{-1} h^{-1}), or an end tidal concentration of sevoflurane of 2 to 3% throughout the operation.

Each patient received a continuous infusion of sufentanil (2 μg kg^{-1} h^{-1}) throughout the operation. The lungs of the patients were mechanically ventilated with a mixture of oxygen and air. Mechanical ventilation was maintained until the start of cardiopulmonary bypass (CPB). After heparin administration (3 mg kg^{-1}) and aorta cannulation, CPB was instituted with a Dideco hollow fibre oxygenator with a blood flow between 200 and 300 ml kg^{-1} min^{-1}.

The prime volume 325 to 750 ml according to the patient's weight, contained lactate free Ringer's solution, albumin, mannitol, blood and heparin. Body temperature during bypass was maintained at 28 °C except for patients undergoing circulatory arrest who were cooled to 20 °C during the period of circulatory arrest. Patients underwent modified ultrafiltration at the end of the bypass.

Blood samples (0.5 ml) were taken immediately after admission, and 8, 15 and 24 h after admission to the paediatric intensive care unit. Samples were collected in a Gel-Microtainer tube and immediately analysed by the hospital clinical chemistry department using the Elecsys Modular E170 immunochemistry analyzer (Cardiac Troponin T, Roche Diagnostics, Mannheim).

Briefly, this immunoassay employs two monoclonal antibodies specifically directed against human cardiac troponin T. The antibodies recognize two epitopes located in the central part of the cardiac troponin T protein. The lower detection limit is 0.01 ng ml^{-1}. Ten patients admitted to the paediatric intensive care unit before surgery had cTnT levels measured as part of standard clinical practice.

Arterial oxygen tension (PaO_2), pH, base excess (BE), bicarbonate and lactate were measured immediately after admission to the intensive care unit and 24 h later (Chiron 865, Bayer, Mijdrecht, The Netherlands). Fluid balance in the 36 h following admission, and ventilator hours were also recorded.

The type of vasoactive drugs and their amount were recorded after admission to the intensive care unit and 24 h later. To quantify inotropic support, inotrope scores were calculated as the sum of all inotrope doses correcting for potency (dopamine, dobutamine = 1, milrinone = 15, epinephrine = 100).[14,15] Fluid intake (including crystalloids, colloids and blood products), output (urine, blood and serous fluid loss) and fluid balance were recorded over a 36 h period following admission to the intensive care unit.

Statistical analysis

In a retrospective analysis of fifteen patients the mean (SD) cTnT postoperatively was 1.92 (2.13) ng ml^{-1}. A power analysis based on these findings showed that we would need 90 patients to detect a difference in cTnT of 2 ng ml^{-1} with = 0.05 and a power of 95%.

Data were analysed with the statistical package SPSS v10, and are summarized as mean and 95% confidence intervals. Patient's characteristics (age, weight, surgery times and ventilator hours) and fluid balance were analyzed with ANOVA Bonferroni correction for post-hoc analysis. Because cTnT concentrations were not normally distributed, the data were first subjected to a natural logarithmic transformation before analysis by repeated measures ANOVA with the Greenhouse-Geisser correction. Differences (T8) from baseline values were analysed with ANOVA Bonferroni correction for pos-thoc analysis. Blood gas variables were also analyzed with repeated measures ANOVA. Categorical data were analysed using the Chi-squared test. Correlation coefficients between variables were calculated using Pearson test for normally distributed data and Spearman test for non normally distributed data. Values of $P < 0.05$ were considered statistically significant.

Results

The groups were comparable with respect to sex, age, weight, type of surgery, and cardiopulmonary bypass, aortic cross clamp and circulatory arrest times (Table 1). The number of cyanotic patients and those undergoing a ventriculotomy were well matched in each group. Table 2 shows the type of operations performed in each group. In the 10 patients from whom blood samples were obtained preoperatively (midazolam = 3, propofol = 4 and sevoflurane = 3), cTnT concentrations were less than 0.02 ng ml^{-1}. These patients were admitted to the intensive care unit preoperatively for logistical reasons the day before surgery. Table 3 shows cTnT concentrations throughout the study period in the three groups. Figure 1 shows the changes in cTnT in the three groups throughout the study period. Although the cTnT concentrations in the midazolam group tended to be higher at T8 than in the other two groups, the differences were not significant.

	Midazolam	Propofol	Sevoflurane
N	30	30	30
Age (months)	6 (0.9 – 11)	14 (2.9 – 26)	13 (5.4 – 21)
Sex (M/F)	17/13	20/10	15/15
Weight (kg)	5 (3.8 – 6.2)	7.5 (4.8 – 10)	6.8 (5.3 – 8.4)
Surgery time (min)	183 (159 – 208)	190 (166 – 215)	194 (172 – 216)
Bypass time (min)	114 (90 – 137)	122 (99 – 144)	120 (102 – 138)
Clamp time (min)	77 (56 – 98)	74 (53 – 96)	67 (50 – 85)
Arrest time (min)	9 (0 – 19)	9 (0 – 18)	7 (0 – 13)
Ventriculotomy (Y/N)	9/21	7/23	10/20
Cyanotic (Y/N)	14/16	17/13	16/14
Ventilator hours	87 (60 – 115)	106 (59 – 153)	84 (48 – 120)

Table 1: Patient characteristics. Values are expressed as mean (95% confidence intervals).

The differences of cTnT concentrations between T8 (maximum peak) and baseline for the three groups were (mean (95% Confidence Intervals)) 0.85 (1.2 – 1.49) ng ml^{-1} for midazolam, 0.7 (0.13 – 1.27) ng ml^{-1} for propofol and 0.05 (0 – 0.38) ng ml^{-1} for sevoflurane. Between groups variations were not statistically significant ($p < 0.49$) either.

There were no significant differences in PaO_2, pH, base excess, bicarbonate or lactate between the groups. The differences in fluid balance, PaO_2/FiO_2 ratios and ventilator hours in the 36 h following admission to the PICU also were not significantly different. There were no differences between the groups in the use of inotropic drugs on admission to the intensive care or 24 hours later. One patient in the sevoflurane group died 30 days after readmission to the intensive care unit due to irreversible cardiac failure.

	Midazolam	Propofol	Sevoflurane
VSD	8	8	6
ToF	3	3	6
TAPVC	2	1	2
Arterial switch	6	6	3
Norwood stage I	2	3	2
IAA	1	0	1
Pulmonary homograft	2	1	2
Fontan	1	2	2
AVSD	2	3	3
Aortic stenosis	2	1	0
Glenn	1	2	2
MVR	0	0	1
Total	30	30	30

Table 2: Surgical procedures. Ventricular septal defect (VSD), Tetralogy of Fallot (ToF), Total anomalous pulmonary venous connection (TAPVC), Interrupted aortic arch (IAA), Atrioventricular septal defect (AVSD), mitral valve replacement (MVR).

	T0	T8	T15	T24
Midazolam	1.9 (1.5 – 2.3)	2.7 (1.9 – 3.5)	2.4 (1.8 – 2.9)	1.9 (1.5 – 2.3)
Propofol	1.9 (1.4 – 2.4)	2.6 (1.7 – 3.5)	2.3 (1.5 – 3.1)	2.1 (1.3 – 2.8)
Sevoflurane	1.7 (1.3 – 2.1)	1.7 (1.3 – 2.2)	1.6 (1.2 – 1.9)	1.5 (1.2 – 1.8)

Table 3: Cardiac troponin T concentrations (ng ml^{-1}) in blood immediately after admission to PICU and at 8, 15 and 24 h after admission. Values are expressed as mean (95% confidence intervals).

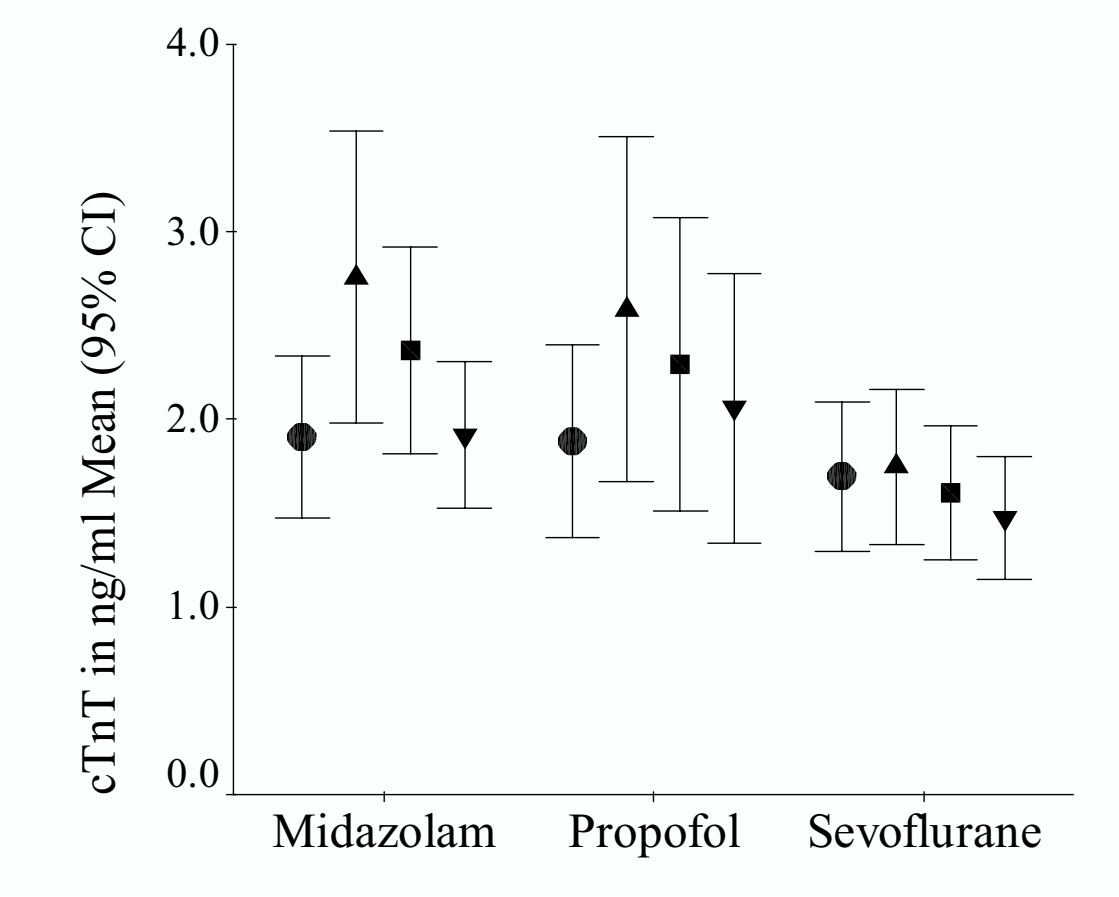

Fig 1: cTnT concentrations in the three groups at the four different time points. Values are expressed as mean (95% confidence intervals).T0 (●), T8 (▲), T15 (■) and T24 (▼).

Concentrations of cTnT peaked at T8 in all three groups. Univariate analysis of variance showed that cTnT concentrations at this time point were not related to sedation, cyanosis or the use of ventriculotomy. At T8 acyanotic patients had lower concentrations of cTnT than cyanotic patients in all groups although the differences were not significantly different. The values for acyanotic patients were 2.68 (1.8 – 3.5) ng ml^{-1} for midazolam, 2.28 (1.3 – 3.3) ng ml^{-1} for propofol and 1.67 (1.2 – 2.2) ng ml^{-1} for sevoflurane. The corresponding values for cyanotic patients were 2.84 (1.4 – 4.3) ng ml^{-1} for midazolam, 2.82 (1.3 – 4.3) ng ml^{-1} for propofol and 1.81 (1.1 – 2.5) ng ml^{-1} for sevoflurane.

There was a significant correlation between ventilator hours and cTnT concentrations at T8 in the sevoflurane group (r = 0.45) and midazolam group (r = 0.50), but not in the propofol group. There was no correlation between cTnT concentrations and the inotropic score on admission to the PICU.

Discussion

Our study shows that the postoperative production of cTnT in paediatric patients undergoing cardiac surgery is similar with midazolam, propofol or sevoflurane anaesthesia. To our knowledge this is the first time this has been reported. Peak concentrations of cTnT 2.7 (1.9 – 3.5) ng ml^{-1} (mean (95 % Confidence Intervals)) are similar to those reported in other studies. Immer and colleagues[12,16] reported mean cTnT concentrations of 4.06 ng ml^{-1} and 5.5 ng ml^{-1} in two consecutive studies with a patient population similar to ours. Unfortunately they failed to mention the type of anaesthetic technique used by them.

Hovels-Gurich and colleagues[17] reported a mean value of 5 ng ml^{-1} in neonates with transposition of the great arteries undergoing arterial switch operation. However all these patients underwent surgery with circulatory arrest. Seven patients in our study underwent a similar period of circulatory arrest, with a maximum cTnT concentration at T8 of 3.9 ng ml^{-1}.

IP has been little investigated in children. Classical IP in rats is not present at birth, and the enhanced recovery of contractile function develops only at the end of the first postnatal week.[7] Baker and colleagues found that preconditioning can be induced in isolated perfused normoxic immature rabbit hearts.[8] In the same study they found that isolated immature rabbit hearts that were chronically hypoxic from birth could not be preconditioned, even when the number of occlusion periods was increased. In an animal study,[18] pregnant rats were exposed chronically to intermittent periods of hypoxia. Their new born offsprings underwent periods of IP immediately after birth. Neither procedure in isolation increased tolerance to subsequent periods of hypoxia, while the combination increased cardiac tolerance.

A phenomenon similar to reperfusion injury happens at the start of CPB in cyanotic patients. Allen and colleagues[19] took biopsies of myocardial tissue in acyanotic and cyanotic patients before and 10 minutes after initiating bypass to measure antioxidant reserve capacity. In contrast to acyanotic patients, abrupt reoxygenation of cyanotic patients resulted in a significant depletion of endogenous tissue antioxidants. The effect of cyanosis on cTnT production was not our primary end point. Univariate analysis demonstrates that cyanosis did not have any influence in our results. cTnT concentrations were consistently higher in cyanotic patients in all three groups.

The differences however were not statistically significant. This is in contrast with two other studies[20,21] where unfortunately there is no description of the anaesthetic technique.Preliminary data indicate that cTnT values shortly after surgery for congenital heart disease are potentially useful prognostic indicators of postoperative recovery.[12,17] Once again those studies did not mention the type of anaesthetic agent used perioperatively.

We have demonstrated in our study that only ventilator hours correlates with cTnT production, and this was limited to the midazolam and sevoflurane group. Although statistically significant the correlations are weak.

Both cardiac troponin I (cTnI) and cTnT seem to evolve in a similar way after paediatric cardiac surgery.[16] Reported baseline values for cTnT remain below the standard cutoff point of 0.1 ng ml^{-1}. False pathological values of cTnT in patients with renal failure make cTnI theoretically a better choice. None of our patients developed renal failure during their admission to intensive care. However cTnI also has its limitations. Sasse and colleagues[22] showed that for up to nine months after birth in healthy infants, and for up to two years in infants with congenital heart disease, cTnI is not expressed solely in the myocardium. Slow twitch skeletal muscle troponin I is expressed in variable amounts in these infants.

Propofol decreases postischaemic myocardial mechanical dysfunction, infarct size and histological degeneration. It also suppresses the activity of neutrophils, and may therefore produce its beneficial effects by reducing free radicals, Ca^{2+} influx and neutrophil activity.[23] Other studies have failed to demonstrate a protective effect of propofol on myocardial function during ischaemia and reperfusion, and it does not appear to act as a preconditioning agent.[24]

Volatile anaesthetics improve recovery of contractile function of the stunned myocardium. Sevoflurane mimics ischaemic preconditioning, with an improvement of postischaemic contractility in isolated guinea pig hearts.[25] It also appears to reduce myocardial infarct size and to decrease the time threshold for ischaemic preconditioning in dogs, through activation of adenosine triphosphate-regulated potassium (K_{ATP}) channels.[26,27] The cardioprotective effect was independent of changes in coronary blood flow or a reduction in cardiac work. In addition to its preconditioning effects, sevoflurane also appears to exhibit cardioprotective effects against reperfusion injury. This effect has been attributed to its radical scavenging properties and the reduction of postischaemic adhesion of neutrophils.[28]

It has been suggested that sevoflurane may preserve myocardial function better than propofol in patients undergoing coronary artery bypass surgery.[29] Troponin I concentrations were significantly lower in the sevoflurane group than in the propofol group.[29] Compared to propofol, anaesthesia with either sevoflurane or desflurane resulted in a shorter length of stay in the ICU in adults after coronary artery surgery.[30] In our study the type of anaesthesia did not influence length of stay in the paediatric intensive care unit.

Benzodiazepines have not been investigated extensively in the adult population, and we could find no references in the literature to their myocardial effects in paediatric cardiac surgical patients. In isolated perfused guinea pig hearts subjected to ischaemia midazolam reduced neutrophil adhesion to non-ischaemic control levels.[31] Adhesion of polymorphonuclear neutrophils (PMN) to the coronary endothelium is a crucial step in the development of ischemic myocardial injury. In this study ketamine and thiopental behaved in a similar way. Midazolam may interfere with Ca^{2+} influx and free radical production but the data is contradictory in this respect.[32,33]

If IP occurs in children, sevoflurane seems to lack the IP-like effect demonstrated in the adult population.[30] Propofol and sevoflurane may provide protection to the adult myocardium by different mechanisms. However, they both appear equally effective in our study.

In conclusion we have demonstrated that midazolam, propofol and sevoflurane produce similar concentrations of cTnT postoperatively in paediatric cardiac surgery. Contrary to what has been published in adult patients undergoing coronary bypass surgery, sevoflurane did not reduce significantly cTnT production when compared to propofol.

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