Sodium Pump Reduction Correlates with Aortic Clamp Time in Pediatric Heart Surgery

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Myocardial depression after cardiac surgery is modulated by cardiopulmonary bypass (CPB) and the underlying heart disease. The sodium pump is a key component for myocardial function. We hypothesized that the change in sodium pump expression during CPB correlates with intraoperative and postoperative laboratory and clinical parameters in neonates and children with various congenital heart defects. Sodium pump isoforms alpha1 (ATP1A1) and alpha3 (ATP1A3) mRNA expression in right atrial myocardium, excised before and after CPB, was quantified. Groups were assigned according to presence (VO group, $n = 8$) or absence (NO group, $n = 8$) of right atrial volume overload. CPB and aortic clamp time correlated with postoperative troponin-I values and ICU stay. ATP1A1 ($P = 0.008$) and ATP1A3 ($P = 0.038$) mRNA expression were significantly reduced during CPB. Longer aortic clamp times were associated with lower postoperative ATP1A1 ($P = 0.045$) and ATP1A3 ($P = 0.002$) mRNA expression. Low postoperative ATP1A1 ($P = 0.043$) and ATP1A3 ($P = 0.002$) expressions were associated with high troponin-I values. These results were restricted to the VO group. No correlation of sodium pump mRNA expression was found with the duration of ICU stay or ventilation. The postoperative troponin-I and clinical parameters correlated with the length of CPB, regardless of volume overload. In contrast, only dilated right atrium seemed to be susceptible to CPB in terms of sodium pump expression, showing a reduction during the operation and a correlation of sodium pump with postoperative troponin-I values. Exp Biol Med 231:1300–1305, 2006

This study was supported by grant 32-64144.00 from the Swiss National Science Foundation, Berne, to M.P.

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Received January 18, 2006.
Accepted March 1, 2006.

1535-3702/06/2318-1300$15.00

Key words: sodium pump; cardiopulmonary bypass; pediatric; heart surgery

Introduction

Cardiopulmonary bypass (CPB) is known to induce clinically deleterious effects by activation of inflammation and coagulation pathways (1), potentially leading to myocardial failure. Apart from duration of aortic clamping time (2) and need for ventriculotomy (3), the cardiac troponin-I level, a parameter of myocardial injury, correlated with younger age of the patients (4), displaying the higher susceptibility of pediatric myocardium to the effects of ischemia, and reperfusion (5). The postoperative troponin-I values correlated with the extent of inotropic support, renal dysfunction, and ventilatory support (6). The basis for myocardial injury seems to be not only oxidative stress and free radical activation (7), as progressive myocardial dysfunction after CPB was found in pigs even without ischemia (8), suggesting other mechanisms than those of myocardial stunning.

The sarcolemmal Na,K-ATPase (sodium pump), a key component for myocardial function, is reduced in patients with heart failure and dilated cardiomyopathy (9, 10). The diminished Na,K-ATPase concentration correlated well with the decreased left ventricular ejection fraction (11), and after unloading the heart with an ventricular assist device the reduced expression was reversed in these patients (12). The gene expression of different isoforms of the sodium pump also was reduced during ischemia-reperfusion due to different cellular mechanisms (13). Significant differences in the expression of the sodium pump have been found between species (14), different experimental models (15), and different age groups (16).

To date, studies on the expression of the sodium pump in pediatric cardiac surgery are sparse. We recently have

shown that isoforms of the sodium pump are reduced during CPB (17). We hypothesized that the postoperative depression of myocardial function after cardiac surgery might be due to a reduction of the sodium pump, and that its expression might be correlated with intraoperative and postoperative parameters.

Materials and Methods

Samples. All parents of the patients gave written informed consent, and the study protocol was approved by the local ethics committee (request 168/2000). Myocardial tissue was collected from 16 patients undergoing corrective cardiac surgery just before initiation of and immediately after CPB. An echocardiography (Acuson Sequoia 512; Siemens, Mountain View, CA) was performed preoperatively, and the areas of the right and left atria were calculated in all patients. According to the atrial dimensions and the ratio between right and left atrial areas, the patients were assigned either to a group having a right atrial volume overload (VO, $n = 8$), or a group without volume overload (NO, $n = 8$) of the right atrium. In all patients the surgical procedure required a right atriotomy. In one patient with a complex cardiac anomaly (transposition of the great arteries, ventricular septal defect, dysplastic aortic valve, and hypoplastic aortic arch) an additional right ventriculotomy was performed. This patient died after the operation. After sternotomy and opening of the pericardium, a first sample of right atrial myocardium was taken. The ascending aorta and both caval veins were cannulated, patients were cooled to 32°C, aorta was clamped, and cold blood cardioplegia was given. At the end of the operation, after a warm reperfusion of blood cardioplegia, the aortic clamp was opened and reperfusion was started. After weaning from CPB again, about 20 mg myocardial tissue from the right atrial free wall was obtained. The tissue was snap-frozen in liquid nitrogen and stored at –80°C. For analysis of cardiac troponin-I a Microparticle Enzyme Immunoassay (MEIA; Abbott Laboratories, Abbott Park, IL) was used, and the reference value was <0.4 μg/l.

Quantitative Transcript Analysis. RNA extraction was performed with the RNeasy Mini-Kit (Qiagen, Hilden, Germany) using the protocol for heart tissue, including Proteinase K digestion. Quantitative one-step reverse transcription–polymerase chain reaction (RT-PCR) was performed with a OneStep RT-PCR Kit (Qiagen), using 2 μl (20 ng) total RNA as described elsewhere (17). The sodium pump isoform alpha1 (ATP1A1) forward primer was 5′ GAAGTGCTGGAATTAAGGTCATC 3′, and the reverse primer was 5′ CCTTTAGATCACTGCCGTGTAC 3′ (product length: 195 bp). The ATP1A3 forward primer was 5′ GCCAAGATGGGGGACAAGA 3′, and the reverse primer was 5′ GGATCTCCTGGGCTTTGCT 3′ (product length: 190 bp). RT-PCR products were analyzed by polyacrylamide gel electrophoresis (PAGE) and silver staining to ensure accurate amplification.

Statistical Analysis. The mRNA levels are expressed as median (range). Because of the small sample size and skewed data distribution, nonparametric exact methods were applied throughout using commercially available software (StatXact 6 and LogXact 6, both from Cytel Software Corp., Cambridge, MA). The 3 dichotomous clinical variables—sex, VO versus NO, and infants up to the age of 12 months versus older children—were used to form groups of patients. For univariate analyses evaluating differences of mRNA levels between these dichotomous groups, Hodges-Lehmann estimates and exact 95% confidence intervals (CIs) of the differences were calculated, and exact Wilcoxon/Mann-Whitney tests were applied. Exact Jonckheere-Terpstra tests were used to test associations between mRNA levels and CPB-related variables (18). For multivariate analyses of clinical and CPB-related variables that were significantly associated with the respective mRNA levels, exact polytomous regression applying the adjacent category logit model was used (19). Two-sided tests were used throughout; $P < 0.050$ was considered statistically significant.

Results

There was a significant difference regarding the ratio of right to left atrium between patients without shunt at the atrial level (NO group, median: 0.9; range: 0.5–1.4) compared with patients with a left-to-right shunt (VO group, median: 2.1; range: 1.5–2.9; $P < 0.0001$; Fig. 1).

Comparing VO and NO groups there was no difference regarding age and sex distribution, CPB variables, maximal troponin-I, and duration of postoperative care (Table 1). In the NO group five patients had a VSD, one had aortic regurgitation, one had a subaortic stenosis, and one had a double inlet left ventricle; none of them had a shunt at the atrial level. The VO group consisted mainly of patients with secundum atrial septal defect (ASD); two had a complete atrioventricular canal and one had a primum ASD. Postoperatively, one patient from each group had a junctional ectopic tachycardia, and one patient from the NO group had a complete atrioventricular block after closure of a large ventricular septal defect. Apart from the patient with a complex cardiac lesion who died, all patients recovered normally and had normal ventricular function on the postoperative echo.

CPB Variables and Clinical Course. The troponin-I levels correlated significantly with the duration of CPB ($P = 0.001$, $r^2 = 0.56$; Fig. 2A) and aortic clamp ($P = 0.0005$, $r^2 = 0.63$; Fig. 2B). Moreover, when one patient who died 16 hrs after the operation was excluded, the duration of CPB correlated with the length of the intensive care unit (ICU) stay ($P = 0.004$, $r^2 = 0.49$; Fig. 2C) and duration of ventilation ($P = 0.025$, $r^2 = 0.33$). The duration of the ICU stay ($P = 0.02$, $r^2 = 0.35$; Fig. 2D) and ventilation ($P = 0.01$, $r^2 = 0.41$) also correlated with aortic

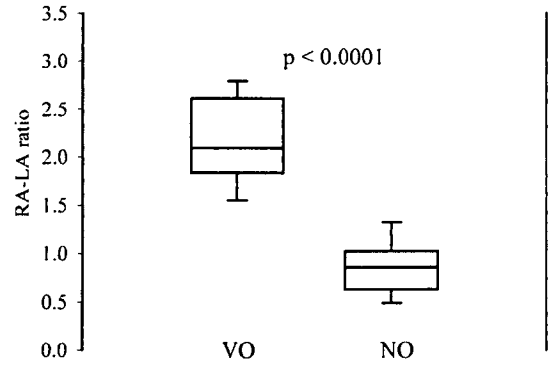

Figure 1. Ratio of right to left atrial area. Significant difference of right atrium–left atrium (RA/LA) ratio between patients without shunt at the atrial level (NO group, median: 0.9; range: 0.5–1.4) compared to patients with heart defects leading to a left-to-right shunt (VO group, median: 2.1; range: 1.5–2.9; $P < 0.0001$). NO, no overload; VO, volume overload.

clamp time. These associations were true, regardless of the volume overload status (NO or VO group).

CPB Variables and Sodium Pump Expression. The mRNA expression of both sodium pump isoforms decreased during CPB only in the VO group (17). We investigated the association of the CPB variables (duration of CPB, aortic clamp, and reperfusion time) with the postoperative mRNA levels of the isoforms and the extent of change from pre- to postoperative levels. As duration of the aortic clamp time increased, lower postoperative mRNA expressions of the ATP1A1 ($P = 0.045$) and the ATP1A3 ($P = 0.002$) isoforms were found (Table 2). Moreover, the longer the aortic clamp duration, the more severe the change from pre- to postoperative ATP1A3 mRNA levels (mean: –0.75; 95% CI: –1.00 to –0.11; $P = 0.028$). The durations of CPB and reperfusion were not associated with the sodium pump expression (data not shown).

Sodium Pump Expression and Postoperative Laboratory and Clinical Parameters. The postoperative ATP1A1 and ATP1A3 mRNA levels and the extent of change of the isoforms during the operation were compared with the maximal troponin-I values (Table 3), duration of milrinone therapy, ICU stay, and ventilation time. Low postoperative sodium pump levels were associated with high postoperative troponin-I values; this was true for the ATP1A1 (mean: –0.71; 95% CI: –1.00 to +0.54; $P = 0.043$) and the ATP1A3 (mean: –0.91; 95% CI: –1.00 to –0.62; $P = 0.002$; Fig. 3) isoform mRNA levels. Also, the extent of change from pre- to postoperative ATP1A3 mRNA levels was associated with higher postoperative troponin-I values (mean: –0.74; 95% CI: –0.98 to –0.11; $P = 0.030$; Fig. 4). All associations were restricted to patients from the VO group, and no significant association was found in the NO group.

There was no correlation between the pre- or postoperative ATP1A1 and ATP1A3 expressions or the extent of their changes during CPB with the duration of milrinone therapy, ICU stay, or ventilation time (data not shown).

Table 1. Patient Characteristics[a]

	VO group[b]	NO group[b]	*P* value
n	8	8	
Age, months	33 (1–133)	6.5 (2–183)	NS
Sex (male–female)	5:3	6:2	NS
CPB time, min	60 (17–358)	58 (50–97)	NS
Aortic clamp, min	36 (7–180)	38 (9–69)	NS
Reperfusion, min	19 (10–213)	23 (11–42)	NS
Troponin-I, μg/l	97 (9–358)	36 (9–94)	NS
Milrinone, hrs	11 (0–180)	5 (0–68)	NS
Ventilation, hrs	2 (1–384)	13 (2–120)	NS
ICU stay, hrs	48 (24–480)	96 (24–240)	NS

[a] CPB, cardiopulmonary bypass; ICU, intensive care unit; NO, no volume overload; VO, volume overload.
[b] Values expressed as median and range.

Discussion

Cardiac operations may lead to postoperative myocardial depression, particularly if performed on CPB. As the sodium pump is a key component for myocardial function, we aimed to study its expression during corrective cardiac surgery in children and its relation to CPB variables and postoperative data. We found that sodium pump reduction during CPB correlated with the duration of aortic clamp time and maximal postoperative troponin-I levels.

Cardiopulmonary bypass time and ischemic time are important factors that determine the duration of postoperative ICU stay (20). Moreover, it is accepted that the peak troponin-I release is a marker for myocardial damage after heart surgery (21). In our patients the length of postoperative ventilation and ICU stay and the maximal troponin-I levels were significantly associated with CPB and aortic clamp time. A correlation between troponin-I and duration of the CPB and aortic clamp time has been found previously (22); however, in that particular study patients with atrial septal defects showed no correlation between troponin-I and duration of the CPB and aortic clamp time, which is in contrast to our results. In neonates with transposition of the great arteries the troponin-I release did not correlate with the duration of CPB and aortic clamping (23).

During the CPB myocardial damage and cardiac dysfunction are not only related to the systemic inflammatory response and other cellular changes (24), but also to intracellular Na+ accumulation (25) and Ca^{2+} overload (26). It has been shown that components of the sarcoplasmic reticulum play an important role in preservation of myocardial function. A reduction of Na,K-ATPase has been found in myocardial ischemia (27) and during CPB (28). Previous studies suggested that changes in Na,K-ATPase gene expression by ischemia-reperfusion may be mediated by oxidative stress (29). In our patients there was a

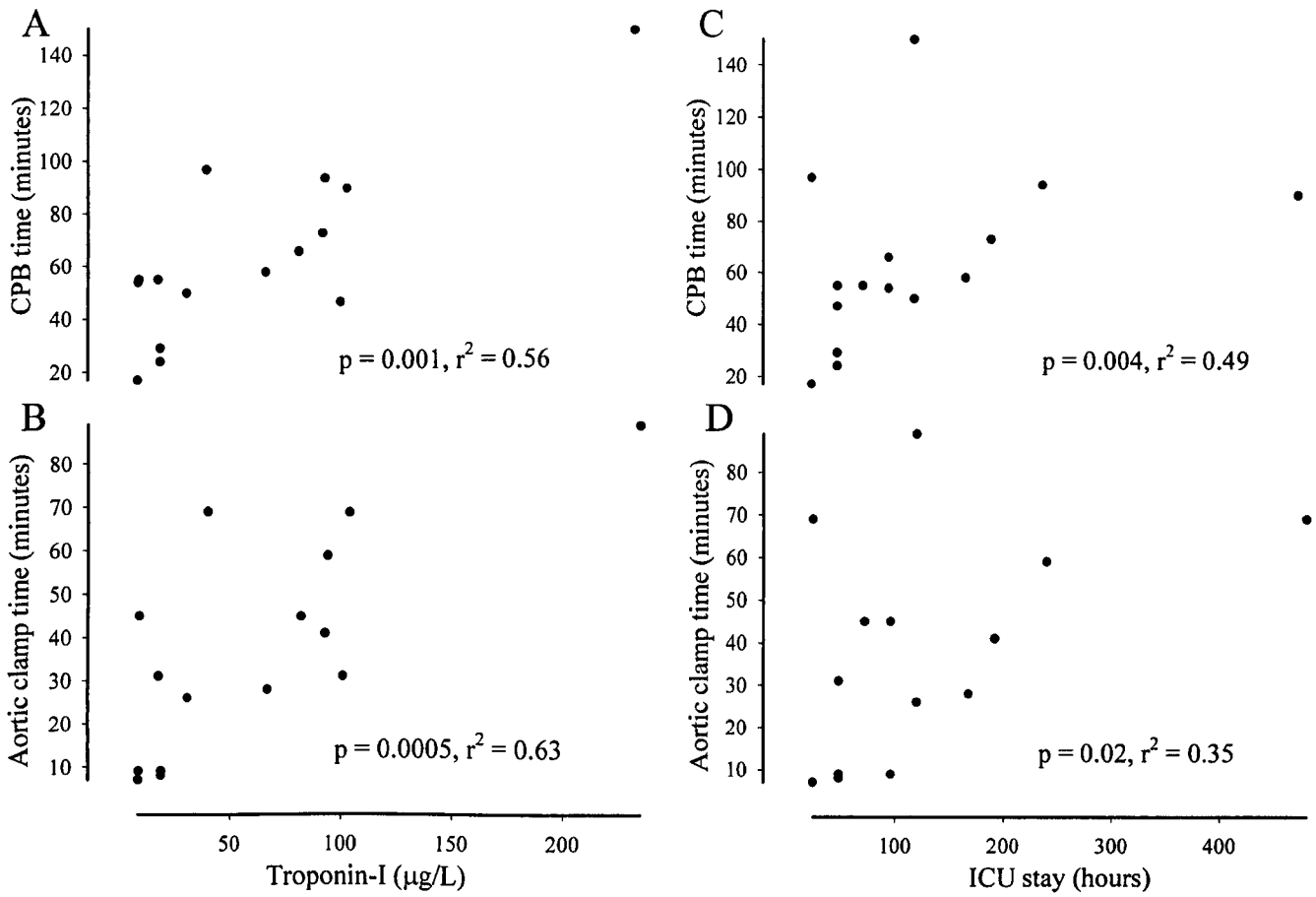

Figure 2. Postoperative laboratory and clinical parameters. (A) Significant correlation between troponin-I levels and the duration of CPB ($P = 0.001$; $r^2 = 0.56$). (B) Troponin-I levels correlated significantly with the aortic clamp ($P = 0.0005$; $r^2 = 0.63$). ICU stay correlated with (C) the duration of CPB ($P = 0.004$; $r^2 = 0.49$), and (D) aortic clamp time ($P = 0.02$; $r^2 = 0.35$). CPB, cardiopulmonary bypass; ICU, intensive care unit.

Table 2. Aortic Clamp Time and Sodium Pump Expression[a]

Group	Mean (95% CI)	*P* value
Aortic clamp versus ATP1A1		
All	−0.2 (−0.66 to +0.32)	0.42
NO	+0.21 (−0.82 to +0.92)	0.60
VO	−0.71 (−1.00 to +0.28)	0.045
Aortic clamp vs. ATP1A3		
All	−0.43 (−0.81 to +0.24)	0.086
NO	+0.40 (−0.82 to +1.00)	0.32
VO	−0.88 (−1.00 to −0.80)	0.002
Aortic clamp vs. A1A3 ratio		
All	−0.35 (−0.77 to +0.33)	0.14
NO	+0.44 (−0.74 to +0.97)	0.27
VO	−0.87 (−1.00 to −0.34)	0.004

[a] ATP1A1, sodium pump alpha1 isoform; ATP1A3, sodium pump alpha3 isoform; CPB, cardiopulmonary bypass; CI, confidence interval; ICU, intensive care unit; NO, no overload; VO, volume overload.

significant association between the postoperative ATP1A1 and ATP1A3 mRNA levels and the aortic clamp time. While the postoperative clinical course and troponin-I levels correlated with CPB variables regardless of atrial dilatation, the association between the molecular findings and both the aortic clamp time and troponin-I was restricted to patients with dilated myocardium. We have reported that preoperative mRNA expression of calcium-regulating proteins is reduced only in children with dilated right atria (30), and that only in volume-overloaded myocardium does CPB lead to a reduction of the sodium pump (17). Hence, compared with patients without right atrial dilatation, it seemed that the dilated myocardium was more prone to the negative effects of CPB. The reason for this phenomenon remains to be elucidated. Former studies have shown that diseased myocardium, such as that found in patients with coronary artery disease, is prone to more significant molecular changes during CPB than a healthy heart (31). Our patients had no signs of heart failure; however, even a dilatation of the atrial wall changed the susceptibility to the CPB in terms of mRNA expression of the Na,K-ATPase.

In conclusion, molecular changes in the course of myocardial disease and during cardiac surgery mainly have

Table 3. Sodium Pump Expression and Postoperative Laboratory and Clinical Parameters[a]

Group	Mean (95% CI)	*P* value
ATP1A1 vs. troponin-I		
All	−0.44 (−0.85 to +0.25)	0.077
NO	+0.02 (−0.85 to +0.92)	0.98
VO	−0.71 (−1.00 to +0.54)	0.043
ATP1A1 vs. ICU		
All	−0.29 (−0.74 to +0.22)	0.24
NO	−0.45 (−0.97 to +0.55)	0.25
VO	−0.44 (−0.96 to +0.53)	0.27
ATP1A3 vs. troponin-I		
All	−0.35 (−0.80 to +0.35)	0.17
NO	+0.30 (−0.60 to +0.92)	0.39
VO	−0.91 (−1.00 to −0.62)	0.002
ATP1A3 vs. ICU		
All	−0.25 (−0.70 to +0.33)	0.31
NO	+0.15 (−0.87 to +0.76)	0.73
VO	−0.46 (−0.93 to +0.36)	0.22

[a] ATP1A1, sodium pump alpha1 isoform; ATP1A3, sodium pump alpha3 isoform; CI, confidence interval; ICU, intensive care unit; NO, no overload; VO, volume overload.

been investigated in adult patients. Due to developmental differences of virtually all components of the cardiomyocyte, these results cannot be transferred to the situation in childhood. This study in children, which shows an association between Na,K-ATPase mRNA expression and both aortic clamp time and troponin-I levels, highlights the importance of the underlying heart defect for susceptibility to the effects of CPB. In our patients the Na,K-ATPase reduction seemed to be an early molecular event, as other than one patient with a complex heart defect who died on the second day after the operation, none of the patients had signs of heart failure.

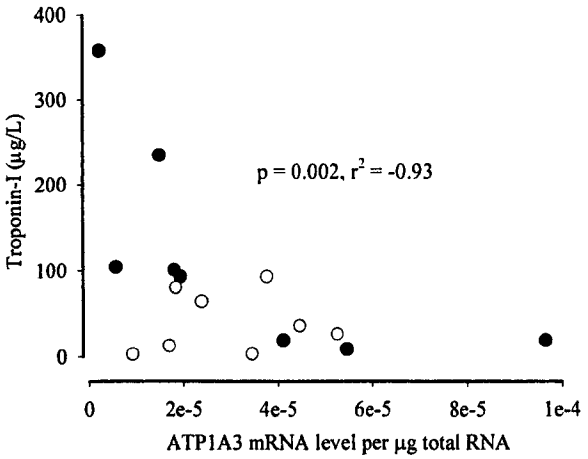

Figure 3. Maximal postoperative troponin-I values and postoperative sodium pump mRNA expression. A correlation between ATP1A3 mRNA expression and postoperative troponin-I values was found only in patients from the VO group (black dots; mean: −0.93; 95% CI: −1.00 to −0.62; $P = 0.002$) but not in patients from the NO group (white dots; mean: +0.30; 95% CI: −0.60 to +0.92; $P = 0.39$). ATP1A3, sodium pump alpha3 isoform.

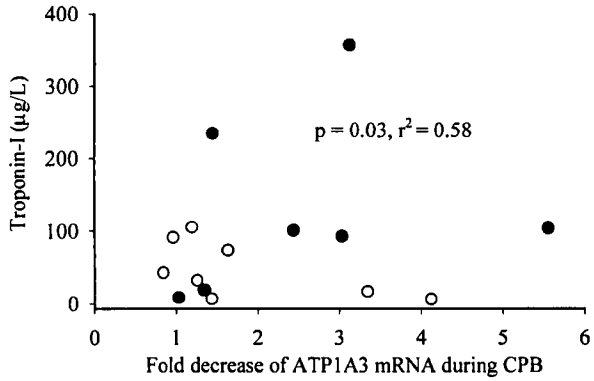

Figure 4. Association between the extent of the ATP1A3 mRNA change during the operation and maximal postoperative troponin-I values. The more severe the decrease of the ATP1A3 mRNA levels, the higher the maximal postoperative troponin-I values in patients from the VO group (black dots; mean: −0.74; 95% CI: −0.98 to −0.11; $P = 0.030$). No correlation was found in patients from the NO group (white dots; mean: +0.62; 95% CI: −0.14 to +1.00; $P = 0.083$). ATP1A3, sodium pump alpha3 isoform; CPB, cardiopulmonary bypass.

Due to the small amount of myocardial tissue and the need for informed consent, this paper had several limitations. First, the small sample number and the heterogeneity of patients regarding age distribution and diagnoses might mask some important results. We tried to take this into account by using accurate statistical methods. Second, we investigated mRNA expression. Although this might be an early molecular marker, it does not necessarily correspond to the protein expression or the physiologic actions within the cell. Moreover, the sodium pump expression in the ventricular myocardium would have been highly interesting; however, due to ethical reasons it was not accessible in most of the cases. In spite of these issues, we believe that this study provides new data in the field of molecular changes during pediatric heart surgery.

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