原著

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ORIGINAL

# Cardiac troponin I and perioperative factors in pediatric open heart surgery

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**ABSTRACT**

**Background: Troponin I (TnI) are highly specific to the myocardium, and measurement of the plasma TnI levels has been widely used to evaluate myocardial damage. This study was performed to ascertain the pathologic or perioperative variables that are significantly associated with the plasma cardiac TnI level. We also intended to provide reference range of TnI elevation after uncomplicated pediatric open heart surgery.**

**Methods: One hundred fifty-one patients undergoing repair of atrial septal defects (ASDs) (n = 61), ventricular septal defects (VSDs) (n = 71), tetralogy of Fallot (TOF) (n = 14), or complete atrioventricular septal defects (CAVSDs) (n = 5) were included. The plasma TnI level was measured prior to surgery, on days 1 and 7 postoperatively. We analyzed the relationship between the TnI level and pathology, cardiopulmonary bypass, and other perioperative factors.**

**Results: All patients underwent uncomplicated surgery and postoperative course. With all pathologies, the plasma TnI level peaked on postoperative day 1 and rapidly declined. The TnI level on postoperative day 1 was higher in VSD than ASD, and there was a further rise in TOF and CAVSD but no significant difference between them. The TnI level on postoperative day 1 was strongly correlated with the operative time, cardiopulmonary bypass time, and aortic cross-clamp (ACC) time. Multiple linear regression analysis showed that the operative time, ACC time, lowest rectal temperature, TOF lesion, and inotropic support period could influence the TnI level.**

**Conclusions: Elevation of plasma TnI after pediatric open heart surgery for various congenital heart diseases is mainly associated with the condition of cardiopulmonary bypass (operative and ACC times) and is not affected with surgical procedures expect for ventricular muscle resection during repair of TOF. Level of TnI elevation confirmed in the study could provide reference range in uncomplicated open heart surgery for each four pathologies. (298 words)**

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**Key words:** aortic cross-clamp, cardiopulmonary bypass, congenital heart disease, open heart surgery, troponin

## 1. Introduction

Intraoperative myocardial damage during cardiac surgery is a major determinant of postoperative cardiac dysfunction-related morbidity and mortality. The degree of perioperative myocardial injury is determined not only by the duration of intraoperative ischemia but also by the pathology and preoperative state of the heart. Troponin is a complex of three regulatory proteins (I, C, and T). It is integral to muscle contraction in skeletal and cardiac muscle and is released into the bloodstream even with minor myocardial damage. Troponin I (TnI) and T (TnT) are highly specific to the myocardium; therefore, measurement of the blood cardiac TnI and TnT levels has been widely used to evaluate myocardial damage in routine pediatric medical care. However, TnI has the advantage of being uninfluenced by impaired renal

function.[1]

Unfortunately, the currently available reference data for TnI were obtained mainly from adult heart diseases such as myocardial infarction.[2)-5)] In terms of heart surgery, the TnI level has been examined mainly at the time of coronary artery bypass surgery or valvular disease repair.[6)-8)] Although a few reports have addressed structural congenital heart disease in children, the clinical significance of the TnI level in pediatric heart diseases has not been fully evaluated.[9)]

In this prospective study, we consecutively examined the plasma TnI level in 151 children undergoing open heart surgery for common congenital heart defects. Using multiple linear regression analysis, we specified the possible perioperative factors or pathologies that can influence the TnI level.

## 2. Material and methods

### 2.1 Patient characteristics

Three hundred thirty patients underwent open heart surgery at Hokkaido Medical Center for Child Health and Rehabilitation from April 2013 to December 2016. We recruited prospectively 151 patients with atrial septal defect (ASD) (n = 61), ventricular septal defect (VSD) (n = 71), tetralogy of Fallot (TOF) (n = 14), or complete atrioventricular septal defect (CAVSD) (n = 5). Patients within their first month of life were excluded because the plasma TnI level is thought to be generally high within the first month of life and to stabilize thereafter.[10)] Patients with other concurrent diseases and residual lesions were also excluded (Fig. 1). The study was approved by the ethics committee of the institute, and informed consent was obtained for all patients.

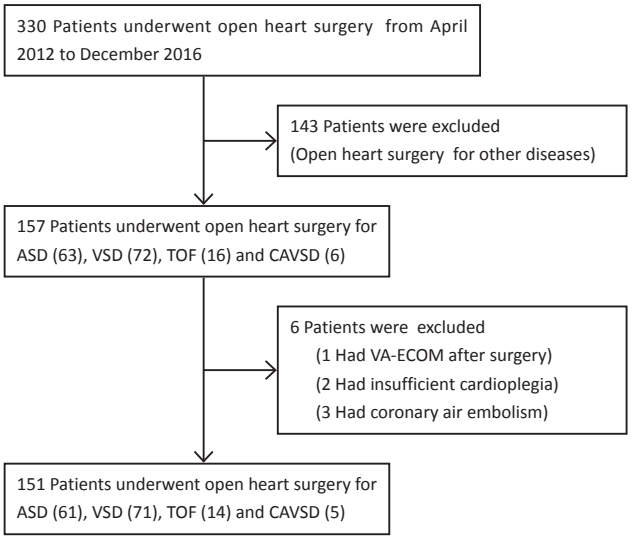


**Figure 1.** Flow chart of patient selection for analysis
ASD: atrial septal defect, VSD: ventricular septal defect, TOF: tetralogy of Fallot, CAVSD: complete atrioventricular defect, VA-ECMO: Venoarterial extracorporeal membrane oxygenation

### 2.2 Anesthesia

General anesthesia was induced and maintained with sevoflurane, and propofol was added as needed. Fentanyl and remifentanil were used as analgesics. Rocuronium bromide was used as a muscle relaxant.

### 2.3 Artificial cardiopulmonary device

High- and continuous-flow extracorporeal circulation was generally used. Roller pumps and centrifugal pumps were employed for younger and older children, respectively. The rectal temperature was maintained at 32℃ to 36℃ for patients with ASD or VSD and at 28℃ to 32℃ for those with TOF or CAVSD. For myocardial protection, antegrade cold intermittent blood cardioplegia was employed using a Mitotector® (Mochida Pharmaceutical, Tokyo, Japan).

### 2.4 Surgical technique

*ASD*

ASDs were closed directly via a right atrial incision.

*VSD*

VSDs were patched with Gore-Tex through the tricuspid valve after a right atrial incision. For subarterial VSDs, pulmonary arteiotomy was employed. No patients had muscular VSDs. The cases who underwent concomitant tricuspid and/or mitral valvuloplasty were included.

*TOF*

After incision of the right atrium and main pulmonary artery, the defect was closed with a Gore-Tex patch. The obstructive myocardium in the right ventricular outflow tract was excised via the atrium and tricuspid valve. The pulmonary valve underwent commissurotomy and was skeletonized as needed and preserved when possible. Main and bilateral pulmonary angioplasty was added as necessary.

*CAVSD*

After incising the right atrium, the defect was closed by the two-patch method, and common atrioventricular valvuloplasty was added. In addition, the main pulmonary

artery was debanded in previously banded patients.

### 2.5 Preoperative, intraoperative, and postoperative parameters

Height and weight were assessed as preoperative factors. Intraoperative parameters included the cardiopulmonary bypass (CPB) time, aortic cross-clamp (ACC) time, lowest rectal temperature, and operative time. Postoperative parameters included the inotropic support period, ventilation period, duration of intensive care unit (ICU) stay, and duration of hospital stay.

### 2.6 Measurement of cardiac TnI

The blood concentration of TnI was determined prior to surgery, on days 1 and 7 postoperatively using a chemiluminescence enzyme immunoassay that included the ARCHITECT · high-sensitivity troponin I® component (Abbott Japan, Tokyo, Japan).

### 2.7 Statistics

Results are expressed as mean ± standard error (SE). Intergroup analysis was performed using one-way analysis of variance or two-way repeated measures analysis of variance. Pearson's correlation coefficient was used to determine the strength of the correlation. Multiple linear regression analysis with a stepwise method was used to determine the variables that influenced TnI release. Statistical significance was determined by P values of $< 0.05$. All data were analyzed using StatMate IV for Windows (ATMS, Tokyo, Japan) and SAS ver.9.4 (SAS Institute, Cary, NC).

## 3. Results

### 3.1 Patient characteristics

The characteristics of patients with each disease and of all 151 patients are summarized in Table 1. Patients with VSD, TOF, and CAVSD were younger and had a lower height and weight than patients with ASD. The operative, CPB, and ACC times of patients with VSD were longer than those of patients with ASD; those of patients with TOF and CAVSD were even more prolonged. The CPB and ACC times of patients with CAVSD were longer than those of patients in the other three groups. The lowest rectal temperature of patients with VSD was lower than that of patients with ASD; that of patients with TOF and CAVSD was even lower than that of patients with VSD. The ventilation time of patients with CAVSD was longer than that in the other three patient groups. The inotropic support period of patients with VSD was longer than that of patients with ASD; that of patients with TOF and CAVSD was more prolonged than that of patients with VSD. The ICU stay of patients with VSD and TOF was longer than that of patients with ASD; that of patients with CAVSD was more prolonged than that of patients in the other three groups. The hospital stay of patients with TOF and CAVSD was longer than that of patients with ASD and VSD. Statistical significance of all of the above were as $P < 0.05$.

### 3.2 Perioperative cardiac troponin I release

In 84 cases, that is 30, 38, 7 and 4 cases with ASD, VSD, FOT and CAVSD, respectively, the TnI

**Table 1.** Patient characteristics

| | | Types of congenital heart disease | | | |
|---|---|---|---|---|---|
| | Total (n = 151) | ASD (n = 61) | VSD (n = 71) | TOF (n = 14) | CAVSD (n = 5) |
| Age (months) | 46.9 ± 44.5 | 87.9 ± 58.6 | 20.3 ± 33.4$^{*A}$ | 15.1 ± 6.0$^{*A}$ | 13.4 ± 5.9$^{*A}$ |
| Height (cm) | 91.0 ± 30.6 | 114.8 ± 27.8 | 75.3 ± 22.6$^{*A}$ | 73.6 ± 4.5$^{*A}$ | 70.9 ± 6.9$^{*A}$ |
| Weight (kg) | 15.4 ± 12.9 | 24.0 ± 14.1 | 10.0 ± 8.8$^{*A}$ | 8.2 ± 1.0$^{*A}$ | 7.6 ± 1.7$^{*A}$ |
| Operative time (min) | 187.5 ± 66.1 | 161.0 ± 40.3 | 179.2 ± 42.2$^{*A}$ | 285.9 ± 84.0$^{*A\,*V}$ | 347.2 ± 89.8$^{*A\,*V}$ |
| CPB Time (min) | 78.2 ± 52.7 | 45.0 ± 17.9 | 78.8 ± 26.5$^{*A}$ | 170.6 ± 62.4$^{*A\,*V}$ | 216.6 ± 60.0$^{*A\,*V\,*T}$ |
| ACC time (min) | 43.7 ± 35.3 | 36.0 ± 0.8 | 46.2 ± 12.6$^{*A}$ | 112.1 ± 31.5$^{*A\,*V}$ | 136.6 ± 31.6$^{*A\,*V\,*T}$ |
| Lowest rectal temp. (℃) | 35.2 ± 1.7 | 36.0 ± 0.8 | 35.4 ± 1.0$^{*A}$ | 32.5 ± 2.4$^{*A\,*V}$ | 31.0 ± 1.4$^{*A\,*V}$ |
| Ventilation (days) | 0.3 ± 0.8 | 0.1 ± 0.2 | 0.3 ± 0.8 | 0.3 ± 0.6 | 2.4 ± 2.6$^{*A\,*V\,*T}$ |
| Inotropes (days) | 1.7 ± 1.3 | 1.1 ± 0.4 | 1.7 ± 1.1$^{*A}$ | 3.6 ± 1.6$^{*A\,*V}$ | 4.0 ± 2.3$^{*A\,*V}$ |
| ICU stay (days) | 2.9 ± 1.8 | 2.0 ± 0.9 | 3.2 ± 1.6$^{*A}$ | 4.2 ± 1.7$^{*A}$ | 6.8 ± 3.5$^{*A\,*V\,*T}$ |
| Hospital stay (days) | 11.7 ± 4.9 | 10.4 ± 3.8 | 11.6 ± 4.7 | 15.7 ± 6.1$^{*A\,*V}$ | 17.2 ± 7.7$^{*A\,*V}$ |

CPB : cardiopulmonary bypass, ACC : aortic cross clamp, ASD : atrial septal defect,
VSD : ventricular septal defect, TOF : tetralogy of Fallot, CAVSD : complete atrioventricular defect
$^{*A}$ $P < 0.05$ versus ASD, $^{*V}$ $P < 0.05$ versus VSD, $^{*T}$ $P < 0.05$ versus TOF

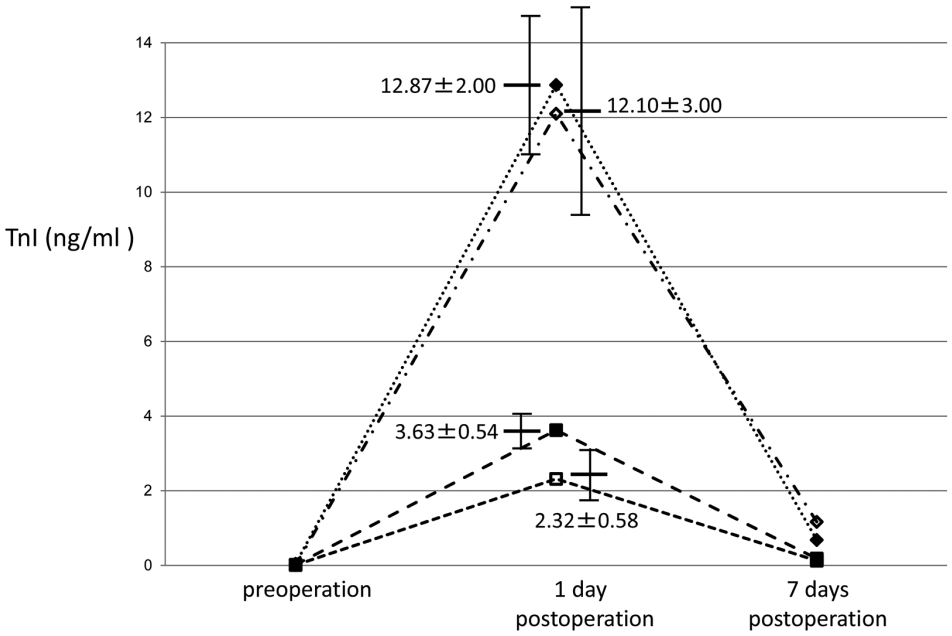


**Figure 2.** Time-dependent release of troponin I (TnI)
Results are expressed as mean ± standard error (SE). Three time-series TnI levels were completely measured in 84 cases, that is 30, 38, 7, 4 cases with ASD, VSD, FOT and CAVSD, respectively. Two-way repeated measures ANOVA and multiple comparison test with the Shecffe's procedure were performed. In all groups, the TnI levels on postoperative day 1 were higher than those on preoperative and postoperative day 7 days ($P < 0.05$). ASD (□), VSD (■), TOF (◇), CAVSD (◆).

levels could be measured for three time-series at preoperative, postoperative 1 and 7 days completely. Two-way repeated measures ANOVA with multiple comparison test by the Scheffe's procedure was applied. All preoperative TnI levels were within normal limits. The TnI levels in all groups peaked on postoperative day 1 and declined during the following 7 days after surgery ($P < 0.05$) (Fig. 2).

For all 151 cases, TnI level of postoperative day 1 could be recorded, and one way ANOVA was performed for intergroup comparison. The TnI level of patients with VSD (3.66 ± 0.29 ng/mL) was higher than that of patients with ASD (2.21 ± 0.29 ng/mL) ($P < 0.01$). The TnI level of patients with TOF (10.78 ± 1.75 ng/mL) and CAVSD (11.65 ± 1.97 ng/mL) increased more than that of patients with VSD (both, $P < 0.01$). There was no significant difference in the TnI level between patients with TOF and CAVSD.

### 3.3 TnI level on postoperative day 1 and perioperative parameters

The correlation between the TnI level on postoperative day 1 and each perioperative parameter was analyzed in all 151 patients. The TnI level on postoperative day 1 was strongly correlated with the operative time ($r = 0.66$, $P < 0.001$), CPB time ($r = 0.70$, $P < 0.001$), and ACC time ($r = 0.70$, $P < 0.001$); however, it was poorly correlated with the inotropic support period ($r = 0.59$, $P < 0.001$) and ICU stay ($r = 0.51$, $P < 0.001$). The TnI level on postoperative day 1 was poorly and negatively correlated with the lowest rectal temperature ($r = -0.41$, $P < 0.001$) (Fig. 3).

### 3.4 Multiple linear regression analysis for factors associated with the TnI level

We used multiple linear regression analysis to identify factors most highly associated with the TnI level on postoperative day 1 in all 151 cases. The explanatory variables included the 11 perioperative variables listed in Table 1 and all 4 pathologies (ASD, VSD, TOF, and CAVSD). Dummy variables (1 or 0) were applied for the four pathologies. As a result, five significant variables emerged. These five variables and their standardized regression coefficient were as follows: ACC time, 0.337 ($P < 0.01$); operative time, 0.281 ($P < 0.01$); inotropic support period, 0.217 ($P < 0.01$); lowest rectal temperature, -0.164 ($P < 0.05$); and TOF, 0.162 ($P < 0.01$) (Table 2). The multiple correlation coefficient and adjusted R-square were high at 0.753 ($P < 0.001$) and 0.552 ($P < 0.001$), respectively. Akaike's information criterion was 316.2.

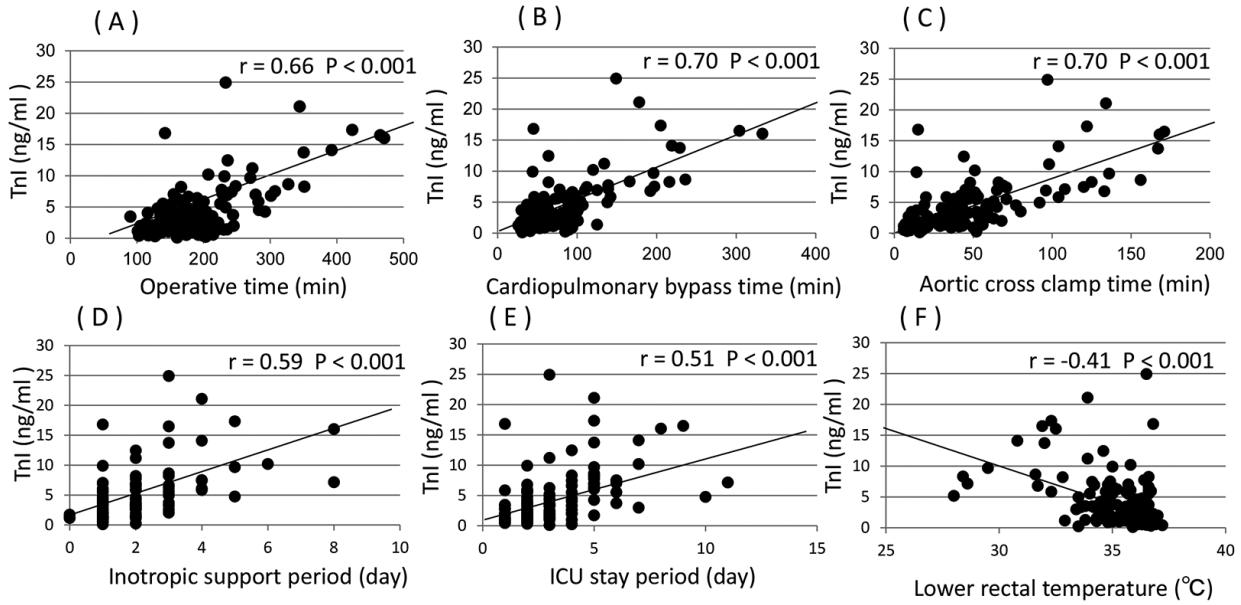


**Figure 3.** Correlation of plasma troponin I (TnI) level on postoperative day 1 and perioperative factors
Correlation between the TnI level on postoperative day 1 and each perioperative parameter was analyzed in all 151 patients. The TnI level was significantly correlated with the (A) operative time ($r = 0.66$, $P < 0.001$), (B) cardiopulmonary bypass time ($r = 0.70$, $P < 0.001$), and (C) aortic cross-clamp time ($r = 0.70$, $P < 0.001$). The TnI level was poorly correlated with the (D) inotropic support period ($r = 0.59$, $P < 0.001$) and (E) intensive care unit stay ($r = 0.51$, $P < 0.001$). (F) The TnI level was poorly and negatively correlated with the lowest rectal temperature ($r = -0.41$, $P < 0.001$).

**Table 2.** Multiple linear regression analysis for variables affecting troponin I levels at postoperative day 1

| Variables | Coefficient | Standard error | Standard coefficient | t value | p value |
|---|---|---|---|---|---|
| Operative time (days) | 0.0176 | 0.00588 | 0.281 | 2.997 | P < 0.01 |
| ACC time (min) | 0.0396 | 0.0141 | 0.337 | 2.813 | P < 0.01 |
| Lowest rectal temp. (℃) | −0.404 | 0.187 | −0.164 | −2.165 | P < 0.05 |
| TOF | 2.31 | 1.02 | 0.162 | 2.268 | P < 0.05 |
| Inotropes (days) | 0.704 | 0.241 | 0.217 | 2.913 | P < 0.01 |

Adjusted R-square = 0.753, analysis of variance for the full regression P < 0.001.
ACC : aortic cross clamp, TOF : tetralogy of Fallot

## 4. Discussion

In the present study, we examined the daily change in the plasma TnI level in 151 children undergoing open heart surgery for common congenital heart defects (ASD, VSD, TOF, and CAVSD). The TnI level peaked on postoperative day 1 and rapidly declined in patients with all pathologies. Using multiple linear regression analysis, we found that the operative time, ACC time, low rectal temperature, TOF pathology, inotropic support, and inotropic support duration significantly influenced the postoperative TnI level.

Kawamura[11] studied the kinetics of TnI release after open heart surgery in pediatric patients and reported that TnI peaked just after CPB and decreased to half from 12 hours to 2 days after surgery. Modi et al.[12] also reported that the TnI level peaked at 4 hours and dropped by half 24 hours after surgery. In the present study, we standardized the measurement of TnI release on postoperative day 1 in all 151 pediatric patients. Although the TnI level on postoperative day 1 was not the peak value, we considered that it might be close to half of the peak value for each patient, representative of the overall clinical picture, and valid for comparative studies.

Few reports to date have focused on the impact of pathology-specific or operation-specific TnI release in pediatric open heart surgery. Modi et al.[12] reported that the highest TnI level was observed in patients with TOF, followed by patients with VSD and ASD

in this order at 4 hours postoperatively. In their retrospective study, Mildh et al.[13] also reported that the TnI level on postoperative day 1 or 2 was highest in patients with TOF, followed by patients with CAVSD, VSD, and ASD in this order. We found no significant difference between patients with TOF and CAVSD, although their levels were higher than in patients with VSD and ASD.

With regard to the correlation of blood troponin levels after pediatric open heart surgery and associated factors, Kawamura[11] found a positive correlation between the peak TnT level and CPB/ACC times in 52 children with various congenital heart diseases. Imura et al.[14] also evaluated 58 patients with various cardiac pathologies and found that the peak TnI level was correlated with the ACC time, ICU stay, hospital stay, and inotropic support period. Modi et al.[12] examined patients with VSD and TOF separately and showed that the peak TnI level in both patient groups was correlated with the ACC time, inotropic support period, ventilation time, and duration of ICU stay. In the present study, the correlations between the postoperative TnI level and perioperative variables were examined in all 151 patients. Similar to the above-mentioned studies, a strong correlation between the TnI level and operative and CPB/ACC times was observed. Apart from these factors, the lowest rectal temperature was a negatively correlated factor.

However, few studies have applied multiple regression analysis to investigation of the explanatory variables for TnI release. Kawamura[11] is the only researcher to have conducted a multiple regression analysis of 38 pediatric patients who underwent open heart surgery for various pathologies; the significant positive variables in that study were the ACC time and patient height, and the significant negative variable was the lowest body/rectal temperature. In the present study, we examined 151 patients complicated by various pathologies and employed 15 variables. As a result, we identified five significant variables. Interestingly, in addition to perioperative conditions such as the operative/ACC time and inotropic support period, TOF but no other pathology was identified as a significant positive factor for TnI release. Among the operative procedures for the four pathologies, only that for TOF involved myocardial excision. Therefore, the factor TOF could be replaced with myocardial excision. Our results reinforce those of the study by Kawamura[11] as a whole and could add a new information about TOF.

Few studies assessed the usefulness of Troponin level for predictors of complications and prognosis after open heart surgery. Mildh et al.[13] reported that TnT level measured on the first postoperative day was independent predictor of death at 30 days. Immer et al[15] reported that serum Cardiac TnI levels after pediatric open heart surgery 4 h after admission to the ICU allowed anticipation of the postoperative course and correlated with the incidence of significant postoperative complications.

On the other hand, all our 151 patients underwent uncomplicated surgery and postoperative course. In addition, they all presented good function prognosis during chronic phase. Therefore, the level of TnI observed in the present study could be reference range of uncomplicated open heart surgery for each pathology. Especially, data of VSD or ASD cases were abundant and would be reliable. When the cases present very higher TnI level after 1 day of open heart surgery compared to our present data, we could suppose the occurrence of some complications and start careful examination in the future.

MB isozyme of creatine kinase (CK-MB) has been the conventional biochemical standards for quantifying myocardial damage after cardiac surgery.[16] On the other hand, Immer et al.[17] reported that TnI showed a higher specificity than CK-MB activity for detection of myocardial damage after pediatric cardiac surgery. Januzzi et al.[18] also showed that TnT was superior to CK-MB for the sensitivity and could predict impending complication after adult cardiac surgery. Hasegawa et al.[19] reported that heart fatty acid-binding protein, i.e. HFABF was superior to TnI and CK-MB as a rapid indicator for assessment of myocardial damage in pediatric cardiac surgery. In the present study, CK-MB and other biochemical maker of myocardial injury could not be measured. The comparison study of these biochemical makers for assessment of myocardial damage in pediatric open heart surgery should be considered to be an issue in future.

In conclusion, elevation of the plasma TnI level after pediatric open heart surgery for various congenital heart diseases is associated with several variables that reflect myocardial damages, such as the operative/ACC time, inotropic support period, and ventricular muscle excision for the TOF operation. Level of TnI elevation confirmed in the study could

provide reference range in uncomplicated pediatric open heart surgery for each four pathologies.

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**Disclosure**

The authors declare no conflict of interest.

**Author contributions**

T.W., M.Y. and J.O. designed the study; T.W., M.Y., M.T., D.A., N.E. and T.T. collected data; T.W, M.Y. and M.M. analyzed date statistically. T.W. M.Y. and H.T. wrote the manuscript. All authors read and approved the final manuscript.

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# 心臓トロポニンIと小児期開心術の周術期因子の検討

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**目的**：トロポニンは心筋障害を示すマーカーとして日常診療に使用されているが，小児期心疾患を対象に検討された報告は少ない．本研究の目的は小児期開心術におけるトロポニンI（TnI）の変動とそれに影響を与える周術期因子を検討することである．

**方法**：心房中隔欠損（ASD）61例，心室中隔欠損（VSD）71例，ファロー四徴（TOF）14例，完全型房室中隔欠損（CAVSD）5例の151例を前方視的に検討した．血漿TnIは術前，術後1日，術後7日に測定した．血漿TnIに影響を及ぼすと考えられる術前因子として年齢，身長，体重を，術中因子として人工心肺時間，大動脈遮断時間，最低直腸温，手術時間を，術後因子として心作動薬投与時間，人工呼吸器装着期間，集中治療室滞在期間，入院期間を選択した．術後1日のTnIと4術式および11の周術期因子が与える影響について検討した．

**結果**：重篤な合併症例，死亡例はなかった．すべての疾患群でTnIは術後1日に速やかに上昇し術後7日には下降した．術後1日のTnIはASD群よりVSD群で有意に高く，VSD群よりTOF群とCAVSD群で有意に高かったが，TOF群とCAVSD群に有意差は認めなかった．術後1日のTnIと手術時間，人工心肺時間，大動脈遮断時間に強い正の相関関係を認めた．重回帰分析では，大動脈遮断時間，手術時間，心作動薬投与期間，最低直腸温，TOFが有意な因子として選ばれた．

**結論**：小児期開心術においてTnIは術後速やかに上昇し下降する．術後1日のTnIの上昇は人工心肺時間，大動脈遮断時間，手術時間に大きく影響され，心筋切除以外の手術手技の影響は少ない．予後良好である術後TnIの正常域を設定することは可能と考えられ，人工心肺時間や手術操作を加味して評価することで，周術期の心筋障害，予後を的確に把握できると考える