

Does troponin-I measurement predict low cardiac output syndrome following cardiac surgery in children?

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Low cardiac output syndrome (LCOS) caused by impaired myocardial function is a leading cause of perioperative organ dysfunction and excess morbidity following surgical correction of congenital heart defects in children.¹ Myocardial dysfunction may be due to ischaemia, reperfusion injury, inflammation or direct surgical trauma. Regardless of the aetiology, early postoperative identification of children destined to develop LCOS after cardiac surgery may allow timely institution of appropriate therapies aimed at optimising cardiac output, and offers an opportunity to minimise postoperative complications.

An early predictor of LCOS would therefore be useful. Cardiac troponin I (TnI), an intracellular protein unique to myocardial cells, may fulfil this role. Elevation of TnI is a reliable and specific marker of myocardial injury in many adult and paediatric settings. In acute coronary syndromes, measurement of serum TnI level has emerged as the preferred means of diagnosing and quantifying ischaemic myocardial injury.² In paediatric cardiac surgery, elevated early postoperative serum TnI levels have been shown to be associated with postoperative complications, including prolonged intubation, high inotrope requirements and death.³⁻⁵ By identifying and quantifying myocardial injury, early postoperative measurement of TnI is expected to be an important predictor of postoperative LCOS.

The objective of our study was to prospectively evaluate TnI as a predictor of LCOS. We hypothesised that measurement of serum TnI levels 4 hours after cardiac surgery is clinically useful in identifying children who go on to develop LCOS.

Methods

This prospective, observational study was conducted at British Columbia's Children's Hospital, Vancouver, Canada, after approval by the University of British Columbia Clinical Research Ethics Board and the British Columbia Children's Hospital Research Review Committee. Informed consent was obtained from all participants or their families.

Consecutive eligible patients (aged 16 years or younger and admitted to the paediatric intensive care unit after cardiopulmonary bypass for congenital heart surgery from 1 June 2003) were enrolled. Exclusion criteria included: elevated preoperative serum TnI level, preoperative respiratory

ABSTRACT

Objective: To determine whether serum troponin I (TnI), measured 4 hours after surgery for congenital heart disease, is a predictor of myocardial dysfunction and low cardiac output syndrome (LCOS).

Design: Prospective, observational study.

Setting: Paediatric intensive care unit in a tertiary care academic children's hospital, 1 June 2003 to 12 May 2004.

Patients: 99 consecutive eligible children who underwent a variety of surgical procedures for congenital heart disease, using cardiopulmonary bypass. All patients were cared for by a consistent perioperative care team.

Interventions: Measurement of TnI preoperatively, and at 0, 4, 8, 12, 24 and 36 hours after ICU admission.

Results: Patient demographics and outcome (as median and 25th–75th percentile) were as follows: age, 23.9 (4.6–65.9) months; cardiopulmonary bypass time, 135 (98–178) minutes; aortic cross-clamp time, 65 (28–85) minutes; preoperative TnI level, 0.02 (0.01–0.03) ng/mL; 4h TnI, 10.6 (3.0–23.4) ng/mL; highest 24 h TnI, 11.7 (3.9–29.5) ng/mL; time to discontinuation of inotropes, 43.9 (18.7–92.9) hours; maximal inotrope score, 10.0 (5.0–16.3); time to extubation, 42.4 (19.8–137.5) hours; and time to ICU discharge 91.8 (45.7–169.7) hours. Twenty-three patients developed LCOS. A 4h TnI level > 13 ng/mL predicted LCOS with a sensitivity of 0.78 (95% CI, 0.56–0.93), and a specificity of 0.72 (95% CI, 0.61–0.82). The area under the receiver operating characteristic curve for TnI as a predictor of LCOS was 0.75 (95% CI, 0.63–0.88). TnI was the only predictive variable associated with LCOS in multivariate logistic regression analysis, with an odds ratio of 1.45 (95% CI, 1.05–2.01) for developing LCOS with each 10 ng/mL increase in 4h TnI. Linear regression analysis showed TnI to be significantly correlated with increased time to discontinuation of inotropes, maximal inotrope administration, time to extubation, and time to ICU discharge.

Conclusions: Measurement of early postoperative levels of TnI may aid in the early identification of children who will develop LCOS.

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failure requiring mechanical ventilation, preoperative infusions of intravenous inotropes and preoperative extracorporeal cardiopulmonary life support (ECLS).

Surgical procedures were carried out in a single institution by one of two cardiac surgeons and a consistent intraoperative and postoperative care team. All participants had an arterial catheter placed after induction of anaesthesia and before skin incision. Central venous lines were also placed after induction of anaesthesia. Myocardial protection during aortic cross-clamp application was achieved with cold blood cardioplegia. Inotropic support during and after separation from cardiopulmonary bypass was initiated at the discretion of the attending surgeon and anaesthetist.

All patients were transferred directly to the PICU after surgery. All ICU management, including adjustments to inotropic support, institution of ECLS, weaning and withdrawal of mechanical ventilatory support, and discharge from the ICU, was at the discretion of the attending paediatric critical care staff. Sedation was achieved with continuous morphine infusions.

Patient age, duration of cardiopulmonary bypass and duration of aortic cross-clamp application were recorded for each participant. Each surgical procedure was classified on the Risk Adjusted Classification of Congenital Heart Surgery (RACHS-1) scale (range, 1–6) by the method of Jenkins et al.⁶ If multiple procedures were performed, the most complex procedure was used for classification. All inotropes administered were recorded until discontinuation. Total inotropic support was quantified by an inotrope score comprising the sum of all inotrope administration rates ($\mu\text{g}/\text{kg}/\text{min}$), corrected for potency (dopamine and dobutamine, $\times 1$; milrinone, $\times 15$; and epinephrine, $\times 100$).¹ Tracheal extubation was defined as tracheal extubation without reintubation for at least 24 hours.

Blood samples for measurement of TnI were obtained from the existing arterial catheter before cardiopulmonary bypass. Further TnI samples were obtained at 0, 4, 8, 12, 24 and 36 hours after admission to the PICU. As knowledge of TnI levels could influence medical decision-making, all personnel caring for participants were blinded to TnI results. Any instances of the PICU team obtaining serum TnI levels as part of clinical care were noted.

Blood for TnI analysis was collected into non-additive serum tubes and allowed to clot at room temperature. After centrifugation, the serum was transferred to polypropylene tubes and stored at -80°C until analysis. Batch analysis for TnI was performed in our hospital laboratory using the Beckman Access AcuTnI assay (Beckman Coulter, Fullerton, Calif, USA) with a reported within-run coefficient of variation of less than 4%.

Table 1. Procedures classified by operation performed, and by risk category (n = 99)

	No.
Operation performed	
Ventricular septal defect repair	21
Atrioventricular septal defect repair	13
Atrial septal defect repair	11
Right ventricle to pulmonary artery conduit	9
Fontan procedure	8
Subaortic stenosis resection	5
Bidirectional superior cavopulmonary anastomosis	4
Tetralogy of Fallot repair	3
Other	25
RACHS-1 category	
1	12
2	42
3	42
4	3
5	0
6	0

RACHS-1 = Risk Adjusted Classification of Congenital Heart Surgery.⁶

Table 2. Patient demographics and outcome (n = 99)

	Median (25th–75th percentile)
Age (months)	23.9 (4.6–65.9)
Cardiopulmonary bypass time (min)	135 (98–178)
Aortic cross-clamp time (min)	65 (28–85)
TnI concentration (ng/mL)	
Preoperative	0.02 (0.01–0.03)
4 h after ICU admission	10.6 (3.0–23.4)
Maximum	11.7 (3.9–29.5)
Maximal inotrope score	10.0 (5.0–16.25)
Duration of inotropes* (h)	43.9 (18.7–92.9)
Duration of intubation*† (h)	42.4 (19.8–137.5)
Time to ICU discharge*† (h)	91.8 (45.7–169.7)

TnI = troponin I. * One patient died while ventilated and receiving inotropes and was not included.

† One patient was transferred to another ICU while ventilated and was not included.

Data analysis

The primary outcome variable for this study was a composite variable comprising either death or the development of LCOS within the first 36 hours of admission. LCOS was defined as per Hoffman et al.⁷ This definition requires the

presence of clinical signs of low cardiac output (eg, tachycardia, oliguria and decreased capillary refill), and either the introduction of ECLS, the addition of a new positive inotropic agent, or the need for an increase in dose of an existing inotropic medication of 100% or more above the baseline inotropic support on admission to the PICU. The performance of the variable TnI level at 4 hours after cardiac surgery (4h TnI) as a predictor of LCOS was evaluated by calculating the area under the receiver operating characteristic (ROC) curve.

Secondary outcome variables were time to withdrawal of mechanical ventilation, time to discharge from the PICU, maximal inotrope score, and time to discontinuation of inotropes. The association of 4hTnI and secondary continuous outcome variables was examined using linear regression analysis.

In addition to 4hTnI, the following variables were analysed as potential predictors of primary outcome: age, cardiopulmonary bypass time, aortic cross-clamp time and RACHS-1 score. Multivariate logistic regression analysis was used to describe the association of these potential predictors of outcome with LCOS.

All statistical calculations were performed using the StatsDirect statistical software package version 2.4.5 (StatsDirect, Cheshire, UK). A sample size goal of 100 participants was calculated to allow 10 participants for each variable potentially predictive of LCOS (four continuous variables and six RACHS-1 classification categories).

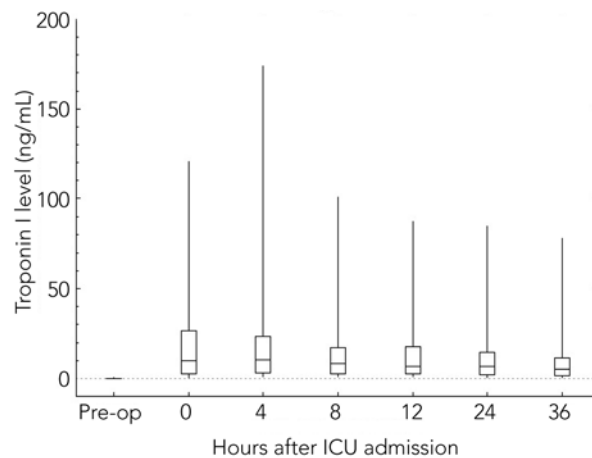
Results

Between 1 June 2003 and 12 May 2004, 116 surgical procedures for congenital heart disease using cardiopulmonary bypass were performed in patients aged 16 years or younger. Seventeen of these procedures were excluded from this study for the following reasons: consent not obtained (10), preoperative inotropes or ventilation (5), and protocol violations (2: one with no preoperative TnI level, and another with no TnI levels). This left 99 participants in the analysis. Surgical procedures are described in Table 1, and demographic and outcome data in Table 2.

Figure 1 illustrates TnI levels at all time intervals after cardiac surgery. Twenty-three participants fulfilled the definition for LCOS within the first 36 hours of admission to the PICU. The area under the ROC curve for 4hTnI as a predictor of LCOS was 0.75 (95% CI, 0.63–0.88) (Figure 2). Four-hour TnI levels above 13 ng/mL predicted LCOS with:

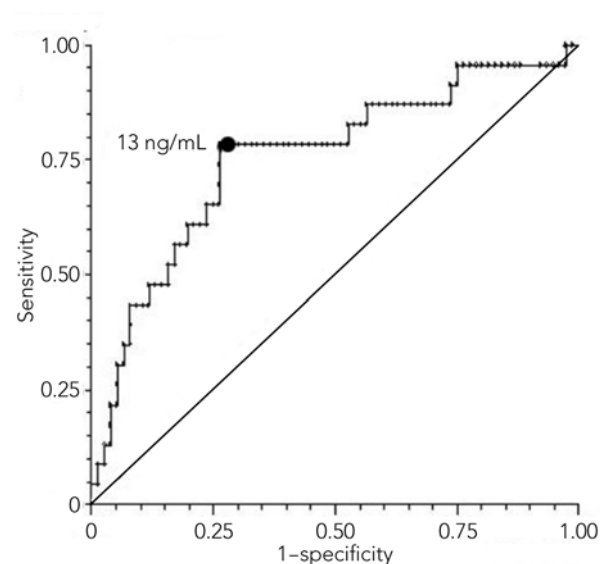
- a sensitivity of 0.78 (95% CI, 0.56–0.93);
- a specificity of 0.72 (95% CI, 0.61–0.82);
- a positive predictive value of 0.47 (95% CI, 0.31–0.64); and

Figure 1. Serial troponin-I levels in 99 children who underwent cardiac surgery*



* Boxes represent 25th–75th percentile range (intersected by the 50th percentile), and lines represent the maximum to minimum range. Pre-op = preoperative.

Figure 2. Receiver operating characteristic curve for 4-hour troponin I level as a predictor of low cardiac output syndrome



Area under the ROC curve = 0.75 (95% CI, 0.63–0.88).

- a negative predictive value of 0.92 (95% CI, 0.82–0.97).
- In multivariate logistic regression analysis, 4h TnI was the only variable significantly predictive of LCOS (exp B = 0.037, $P = 0.03$, odds ratio of developing LCOS for each 10 ng/mL increase in TnI = 1.45; 95% CI, 1.05–2.01). None of the other variables included in the analysis (age, cardiopul-

Figure 3. Linear regression analysis of secondary outcomes versus 4-hour troponin I levels

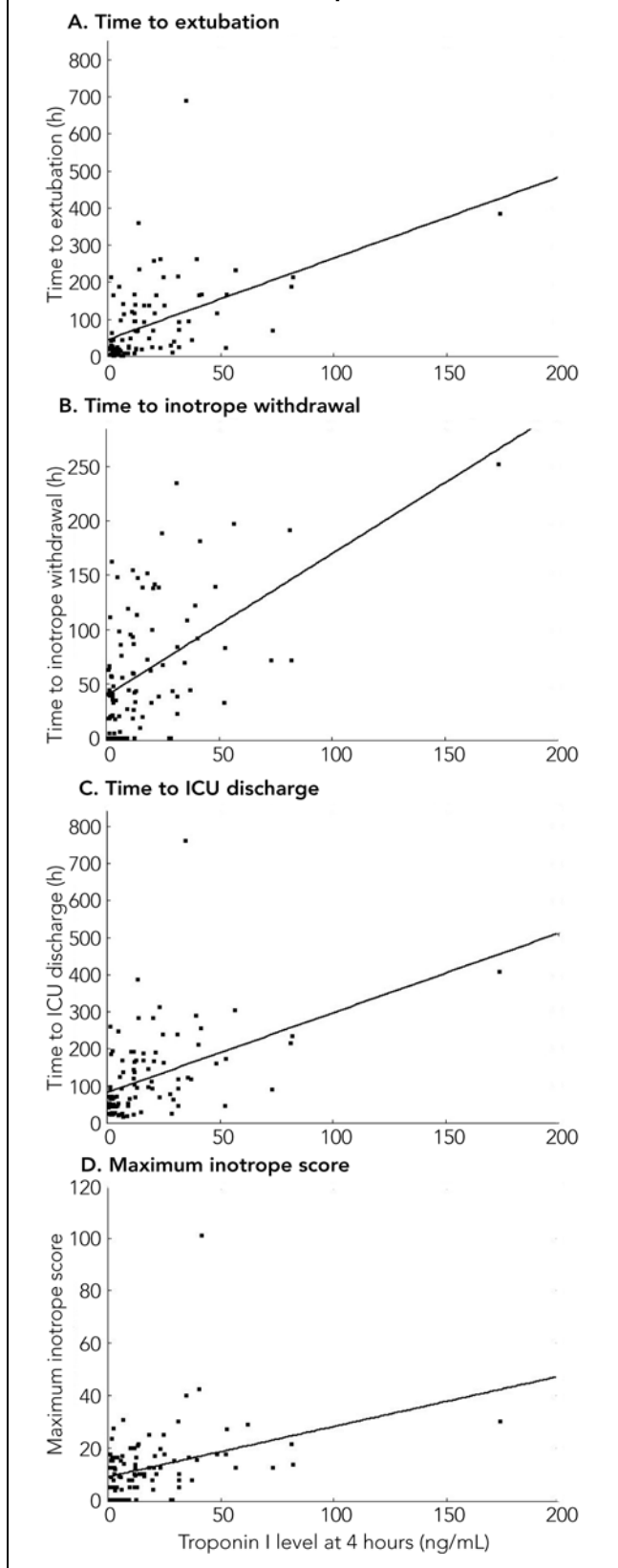
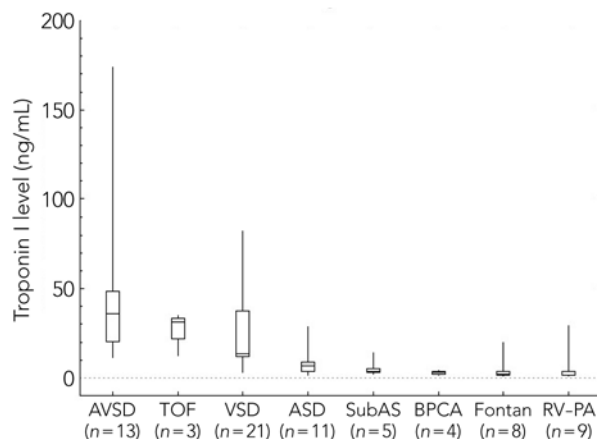


Figure 4. Four-hour troponin-I levels for all procedures with a sample size over 2*



AVSD = atrioventricular septal defect repair.

TOF = tetralogy of Fallot repair. VSD = ventricular septal defect repair. ASD = atrial septal defect repair.

SubAS = subaortic stenosis resection.

BPCA = bidirectional superior cavopulmonary anastomosis.

RV-PA = right ventricle to pulmonary artery conduit.

* Boxes represent 25th–75th percentile range (intersected by the 50th percentile) and lines represent the maximum to minimum range.

monary bypass time, aortic cross-clamp time and RACHS-1 score) improved the predictive performance of the multivariate model.

The association between 4h TnI and secondary outcome variables is shown in Figure 3. Linear regression analysis revealed the following r^2 values for the association between 4h TnI levels and:

- time to tracheal extubation, $r^2 = 0.25$ (95% CI, 0.11–0.40);
- time to discontinuation of all inotropes, $r^2 = 0.28$ (95% CI, 0.13–0.43);
- time to ICU discharge, $r^2 = 0.21$ (95% CI, 0.08–0.37); and
- variability in maximum inotrope score, $r^2 = 0.13$ (95% CI, 0.03–0.27).

When the analysis was repeated using the highest TnI level in the first 24 hours as the potential predictor of outcome in place of 4h TnI, results were unchanged (including area under ROC curve for LCOS, and r^2 for time to discontinuation of inotropes, time to tracheal extubation, time to ICU discharge and maximum inotrope score).

In five participants, early postoperative TnI levels were ordered by, and thus available to, the clinical caregivers. Analysis excluding these participants did not alter the findings.

Troponin-I levels varied with surgical procedures, as shown in Figure 4.

There was one death in our series, occurring 40 hours after admission to PICU. This child underwent repair of an atrioventricular septal defect, and met clinical and inotrope criteria for LCOS within the first 36 hours. The 4h TnI level and maximum TnI level were 62 and 63 ng/mL, respectively.

Discussion

We conducted this prospective study to determine the clinical utility of TnI measurement 4 hours after cardiac surgery in predicting the development of LCOS in the first 36 hours of ICU admission. Consistent with previous studies of the relationship between early postoperative TnI levels and other postoperative outcomes, we found an independent association between TnI levels and the development of LCOS. The clinical utility of early postoperative TnI measurement is determined by the strength of this association. Our results suggest that early TnI measurement in cardiac surgery has clinical value as a predictor of LCOS, but that there are limitations to its usefulness. An area under the ROC curve of 0.75, as was observed in our study, is typically interpreted as indicating fair performance of a diagnostic test. Given an overall prevalence of LCOS in our population of 0.23, our result of a positive predictive value of 0.47 for a 4hTnI result greater than our optimal threshold value of 13 ng/mL in predicting LCOS means that the post-test likelihood of developing LCOS is increased by 24%. This result can be interpreted as indicating early 4hTnI measurement to be a moderately useful test. In multivariate analysis, a relatively substantial increase in 4hTnI of 10 ng/mL increased the likelihood of developing LCOS 1.5 times, again indicating real but modest utility of 4hTnI measurement.

Low cardiac output syndrome in children after cardiac surgery has multifactorial causes. In addition to myocardial injury, these include abnormalities in pulmonary and systemic vascular resistance, as well as residual obstructive, regurgitant and shunt lesions. The limitation of TnI measurement in predicting LCOS observed in our study may be explained by the fact that TnI is a marker specific to myocardial injury.

Similar to our findings for LCOS, 4hTnI was associated with time to discontinuation of inotropic medications, maximum inotrope administration, time to extubation and time to ICU discharge, with a high degree of statistical significance but generally poor strength of association.

Our results are consistent with previous findings. Mildh et al found that first-day troponin T and admission lactate concentrations were the only variables independently predictive of 30-day mortality, and reported an area under the ROC curve of 0.77 for troponin predicting mortality.⁸ In participants undergoing ventricular septal defect repair,

Modi et al reported an association of peak TnI with duration of inotropic support ($r^2 = 0.47$), time to extubation ($r^2 = 0.41$) and time to ICU discharge ($r^2 = 0.36$).⁹

We used a clinical definition of LCOS in our study, as cardiac output was not measured. We chose the clinically derived, previously validated definition introduced by Hoffman et al.⁷ There is no "gold standard" for the diagnosis of LCOS, and, as for all definitions of LCOS based on clinical criteria, the definition we used has limitations. For example, it may fail to classify a patient as suffering from LCOS, despite high inotropic medication requirements, if inotropic therapy is not sufficiently escalated from the therapy in place on ICU admission. Because of the limitation of our LCOS definition, we prospectively chose to assess 4hTnI as a predictor of other outcomes related to myocardial performance simultaneously with LCOS.

The relationship between postoperative troponin and surgical procedure found in our study, as well as in previous research,^{5,8-10} is partly related to procedural variation in surgical myocardial incision trauma and myocardial incision-related troponin release. Examination of Figure 4 reveals higher 4hTnI levels following procedures involving more significant myocardial incision (atrioventricular septal defect, tetralogy of Fallot and ventricular septal defect repairs) as compared with extracardiac procedures (bidirectional superior cavopulmonary anastomosis and Fontan procedures). Limiting the variation of surgical incision-related troponin release would be expected to strengthen the association between early troponin measurement and global myocardial injury, and thus outcome. This hypothesis is supported by the increased strength of association between troponin and duration of inotrope administration, ventilation and ICU stay found by Modi et al in a procedure-specific study population, as compared with ours.⁹

We chose to study a single measurement of TnI as opposed to the highest result of serial TnI measurements because a single measurement would have practical value for clinicians. Peak values can only be ascertained post hoc and are therefore less useful in guiding therapy. Our choice to measure TnI 4 hours after ICU admission was based on previous research showing that TnI levels were highest at this time.^{3,5} The results of our serial TnI analysis confirmed this finding (Figure 1). The highest 24h TnI level did not have a better predictive capacity than the 4h level, suggesting that, for use as a predictor of outcome, a single postoperative TnI measurement is adequate.

Our study suffers from the lack of a defined treatment protocol for inotrope manipulation, tracheal extubation and ICU discharge. However, we believe our findings can be generalised, as postoperative care was provided by a consistent critical care team, who were blinded to study troponin levels.

Conclusions

Elevated Tnl levels following paediatric cardiac surgery, measured 4 hours after admission to the ICU, are associated with an increased risk of developing LCOS. Routine measurement of early postoperative Tnl decreases, but does not eliminate, uncertainty in identifying children destined to develop low cardiac output.

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