

## Early elevation of cardiac troponin I is predictive of short-term outcome in neonates and infants with coronary anomalies or reduced ventricular mass undergoing cardiac surgery

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**Objective:** The present study aimed to assess the usefulness of routine monitoring of cardiac troponin I concentrations within 24 hours of surgery (cTn-I<24h) in neonates and infants undergoing cardiac surgery.

**Methods:** The added predictive ability of a high peak cTn-I<24h (within the upper quintile per procedure) for a composite outcome, including 30-day mortality and severe morbidity, was assessed retrospectively. The predicted risk for the composite outcome was estimated from a logistic regression model including preoperative and intraoperative variables. Adding a high peak cTn-I<24h to the risk model resulted in reclassification of the predicted risk. It also allowed quantification of the improvement in reclassification and discrimination by the difference between c-indexes, the Net Reclassification and the Integrated Discrimination Indexes (NRI and IDI).

**Results:** Overall, 1023 consecutive patients were included. Adding a high peak cTn-I<24h to the model resulted in no improvement in reclassification or discrimination in the overall population (difference between c-indexes: 0.011 [-0.004 to 0.029], NRI = 0.06,  $P = .22$ , IDI = 0.02,  $P = .06$ ), except in a subgroup of patients undergoing the arterial switch operation with or without ventricular septal defect closure and/or aortic arc repair, anomalous origin of the left coronary artery from the pulmonary artery repair, truncus arteriosus repair, Norwood procedure, and Sano modification, in whom NRI = 0.23 ( $P = .005$ ) and IDI = 0.05 ( $P < .001$ ).

**Conclusions:** Patients with coronary anomalies and patients with reduced ventricular mass should benefit from the routine monitoring of cTn-I concentrations after surgery for congenital cardiac disease. (*J Thorac Cardiovasc Surg* 2012;144:1436-44)

Myocardial damage is a major determinant of postoperative cardiac dysfunction associated with morbidity and mortality after cardiac surgery. Cardiac troponins are highly sensitive and specific markers of myocardial damage and have evolved as the gold standard for the diagnosis of myocardial infarction.<sup>1</sup> They are well documented to predict clinical outcome after cardiac surgery in adults.<sup>2-7</sup> Several authors have suggested prognostic implications of troponin concentrations measured early in children undergoing cardiac surgery.<sup>8-17</sup> However, troponin release after surgery for congenital cardiac disease is multifactorial and depends on the type of procedure being performed. Overall, pediatric literature on this topic has included small samples and various case mixes, rendering conclusions difficult to draw. The present study aimed to

assess the predictive ability of cardiac troponin I (cTn-I) for short-term outcome in a large cohort of consecutive neonates and infants undergoing cardiac surgery in a tertiary referral cardiothoracic surgical center and to identify procedures in which serial measurements of cTn-I provide clinical usefulness.

### PATIENTS AND METHODS

The project was reviewed and approved by the Ethics Committee of the French Society of Thoracic and Cardiovascular Surgery, Paris, France, which waived the need for parental consent to the use of records made anonymous for this research.

### Study Population

This retrospective study included all consecutive neonates and infants who underwent surgery for congenital heart disease from January 2007 through June 2010 at the Necker-Enfants Malades University Hospital, Paris, France, and relied on a database storing all of their preoperative, intraoperative, and postoperative data. Owing to an extensive French policy of prenatal detection and abortion in cases of hypoplastic left heart syndrome (HLHS), few patients had HLHS procedures during the study period. Surgical complexity was accounted for by the Aristotle Basic Complexity score.<sup>18</sup>

### Surgical Management

Patients underwent surgery with normothermic or mildly hypothermic cardiopulmonary bypass (CPB) or deep hypothermic circulatory arrest with selective cerebral perfusion when requiring aortic arch repair. Myocardial protection was achieved with intermittent blood cardioplegia at

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### Abbreviations and Acronyms

ALCAPA	= anomalous origin of the left coronary artery from the pulmonary artery
ASO	= arterial switch operation
cTn-I	= cardiac troponin I
cTn-I<24h	= cardiac troponin I concentrations within 24 hours of surgery
CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenation
HLHS	= hypoplastic left heart syndrome
ICU	= intensive care unit
IDI	= Integrated Discrimination Improvement
LOS	= length of stay
NRI	= Net Reclassification Improvement
TAPVC	= total anomalous pulmonary vein connection
VSD	= ventricular septal defect

the same temperature as the CPB perfusate, as described previously.<sup>19</sup> When the aorta was not opened, the cardioplegic solution was administered in the ascending aorta and repeated every 10 minutes in normothermia. When aortic opening was necessary, such as during the arterial switch operation (ASO), repair of the anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), or repair of truncus arteriosus, cardioplegic solution was first delivered into the ascending aorta and subsequently directly into the coronary ostia.

Surgical procedures were performed with standard or previously described techniques.<sup>20-22</sup> Most ventricular septal defects (VSDs) were closed through the right atrium. Repair of tetralogy of Fallot used a transatrial-transpulmonary approach. The ASO was performed using the Lecompte maneuver and standard coronary transfer. Complete atrioventricular canal was repaired with the 2-patch technique. During truncus arteriosus repair, the pulmonary outflow tract was reconstructed with either a valved conduit or autologous tissue. Patients with ALCAPA underwent aortic reimplantation of the anomalous artery. Coarctation was repaired with extended end-to-end anastomosis. Few patients with severe hemodynamic instability, requiring the modified Blalock-Taussig shunt, underwent the procedure with CPB. Only few bidirectional cavopulmonary shunts were performed with an inert shunt, and most of them were performed with CPB. The classic Norwood procedure or Sano modification was performed for palliation of HLHS.

### Troponin Concentration Measurement

Only cTn-I concentrations were measured during the study period, as independent of renal function.<sup>11</sup> The cTn-I concentrations were measured before surgery, at 20 minutes after unclamping, at admittance in the intensive care unit (ICU), every 6 hours on day 0, and every 6 to 12 hours thereafter. Blood samples were assayed for cTn-I with an immunometric technique on the Vitros ECI Immunodiagnosics System (Ortho-Clinical Diagnostics, Rochester, NY). The detection limit was  $0.01 \mu\text{g} \cdot \text{L}^{-1}$ .

### Short-Term Outcome

Because of the low mortality rate, a composite variable was defined as the occurrence of death within 30 days of surgery and/or severe postoperative morbidity. Severe morbidity was accounted for by events that have

been shown previously to be associated with early mortality: an extremely low cardiac output necessitating extracorporeal membrane oxygenation (ECMO)<sup>23</sup> and/or leading to severe renal injury necessitating dialysis (peritoneal in the present population)<sup>24</sup> and/or a very long length of stay (LOS) in the ICU.<sup>25</sup> Because LOS depends on surgical complexity, and in an attempt to standardize the LOS of all patients on the same scale, a specific threshold for a very long LOS was defined in each procedure by its 95th percentile.<sup>26</sup>

### Statistical Analysis

Concentrations of cTn-I measured within 6 to 24 hours of surgery have been shown to provide the best predictive ability for short-term outcome in both children and adults.<sup>4,5,16</sup> The ability of the peak cTn-I within 24 hours of surgery (cTn-I<24h) to predict the composite outcome was assessed visually by plotting all of the cTn-I concentrations recorded during the first week in patients meeting the composite outcome and in the others (Figures 1 and 2) and then by comparing the mean peak cTn-I<24h concentrations with the Wilcoxon rank test (Table 1). To standardize all measurements on the same scale and according to a previous publication,<sup>2</sup> we defined a high peak cTn-I<24h by the upper quintile of all peak cTn-I<24h concentrations measured in similar procedures, and then we calculated its sensitivity, specificity, and likelihood ratio for the composite outcome. The likelihood ratio of a screening test summarizes how many times more likely patients with disease are to have a positive result; it is considered to provide strong evidence to rule in diagnoses when greater than 10 and to rule out diagnoses when less than 0.1.<sup>27</sup>

Preoperative and intraoperative characteristics available in the database were compared between patients meeting the composite outcome and the others. These characteristics were used as predictors of the composite outcome in a logistic regression model (the non-T model) if a significant difference was noted ( $P < .10$ ). The predicted risk was further estimated from a second model, including in addition the high peak cTn-I<24h as a predictor (the T model). Discrimination of each model was assessed by the c-index, and the improvement in discrimination was quantified by the difference between c-indexes, with 95% confidence interval estimated from bootstrapping with 1000 resamples.

New indexes have been shown to provide information about the usefulness of a biomarker: the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI).<sup>28</sup> For this purpose, the predicted risk was estimated according to each model and stratified into 4 risk categories: less than 5%, 5% to 15%, 15% to 30%, and more than 30%. It allowed us to cross-classify the predicted risks, to compare the predicted versus observed risks, and to identify subjects who changed their risk category after adding the high peak cTn-I<24h to the model.<sup>29</sup> The NRI is the difference in the proportion of improvements in reclassification (when a patient meeting the outcome moves up a risk category and a patient not meeting the outcome moves down) and the proportion of worse reclassification (when a patient meeting the outcome moves down a risk category and a patient not meeting the outcome moves up). This index has been criticized because it requires and may be affected by the choice of predefined risk categories<sup>28</sup>; therefore, the IDI, which has been proposed as a continuous version of NRI, was also calculated. The R statistical package ([www.r-project.org](http://www.r-project.org)) was used for all analyses.

### RESULTS

Overall, 1269 patients less than 1 year old underwent cardiac surgery from January 1, 2007, through June 30, 2010, and were enrolled retrospectively. They had undergone 65 different procedures. Overall, 995 (78.4%) patients underwent surgery with CPB; the mean duration of CPB was  $102.5 \pm 65.8$  minutes and ranged between  $49.5 \pm 14.5$  minutes in aortic valvuloplasty and  $199.9 \pm 89.9$  minutes in

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