Biomarkers in Pediatric Cardiac Critical Care

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Objectives: In this review, we discuss the physiology, pathophysiology, and clinical role of troponin, lactate, and B-type natriuretic peptide in the assessment and management of children with critical cardiac disease.

Data Source: MEDLINE, PubMed.

Conclusion: Lactate, troponin, and B-type natriuretic peptide continue to be valuable biomarkers in the assessment and management of critically ill children with cardiac disease. However, the use of these markers as a single measurement is handicapped by the wide variety of clinical scenarios in which they may be increased. The overall trend may be more useful than any single level with a persistent or rising value of more importance than an elevated initial value. (*Pediatr Crit Care Med* 2016; 17:S215–S221)

Key Words: biomarkers; monitoring; myocardial injury; outcomes; pediatrics

LACTATE

Measured on arterial or venous blood gases, whole-blood lactate is the most commonly used point-of-care biomarker in the cardiac ICU (CICU). Serial measurements of lactate are frequently used in conjunction with venous oximetry as an indirect measure of the adequacy of tissue oxygenation, for the identification of high-risk patients and to monitor the responses to treatment. Lactate is constantly being produced (glycolysis) and consumed (oxidation/gluconeogenesis) by cells in the body. Under normal conditions, generation and consumption are equivalent, with plasma lactate concentrations equaling less than 1.5 mmol/L in a well infant/child and less than 2 mmol/L in a critically ill infant/child.

LACTIC ACIDOSIS

Lactic acidosis occurs when lactate production exceeds consumption and clearance and has been previously classified into two types: hyperlactemia secondary to tissue hypoxia (type A) and hyperlactemia with no evidence of inadequate tissue oxygen delivery (type B) (**Table 1**) (2). Production of lactate by glycolysis is accompanied by the release of an equivalent number of hydrogen ions. Elevated levels of lactate produce an anion gap metabolic acidosis. Pediatric critical care patients will frequently have multiple contributing factors to their hyperlactemia, and thus it is not specific for cellular hypoxia (Table 1) (3, 4). Lactate homeostasis can be further unbalanced by reduced liver metabolism of lactate (5).

Many studies have shown an association between admission plasma lactate levels and mortality in critically ill adults, children, and neonates (6–11). However, the value of a single lactate concentration as a predictor of mortality following pediatric cardiac surgery has not been demonstrated (12). Initial lactate concentrations following pediatric cardiac surgery probably reflect intraoperative factors including complexity of surgery, ongoing anaerobic metabolism of the myocardium (lactate levels in the coronary sinus can rise for 30 min following release of the aortic cross-clamp), and washout of lactate from regional tissues following restoration of perfusion. Although low levels of lactate are highly predictive of survival (predictive value [PV] 97%), high levels are only modestly predictive of nonsurvival (PV 43%) (10, 13). Due to significant overlap between survivors and nonsurvivors, admission lactate cannot reliably predict nonsurvivors (10, 14). Several studies have shown a relationship between hyperlactemia and adverse outcomes after cardiac surgery (10, 15). In a single-center study of 90 infants and children, a lactate level more than 5 mmol/L at 4 hours following admission was associated with a 44% chance of a major adverse event including cardiac arrest, chest opening, multiple organ failure or death. Interestingly, lactate levels in older children who have a bloodless prime do not carry the same prognostic significance (16). In the adult literature, failure of lactate to normalize during critical illness has been shown to be a better predictor of morbidity and mortality than

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Dr. Domico's institution received grant support from ELSO Registry Grant (ELSO grant is not related in any way to submitted work). Dr. Allen disclosed that she does not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000778

TABLE 1. Common Causes of Elevated Lactate in the Pediatric Cardiac ICU

Inadequate Tissue Oxygen Delivery	Adequate Tissue Oxygen Delivery
Tissue hypoxia	Drugs/toxins
Cardiac arrest	β_2 agonist stimulation
Septic shock	Propofol
Cardiogenic shock	Sodium nitroprusside
Hypovolemic shock	Cyanide
Hypotension	Lactate containing solutions
Regional hypoperfusion	
Reduced oxygen delivery or utilization	Associated with underlying disease
Hypoxemia	Sepsis
Severe anemia	Acute respiratory distress syndrome
Carbon monoxide poisoning	Pancreatitis
Excessive muscular activity	Reduced lactate clearance
Extreme exercise	Liver
Prolonged seizure	Kidney
	Inborn errors of metabolism

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admission levels (17–19). A retrospective case review by Kalyanaraman et al (20) in 2008 demonstrated that a persistently elevated lactate (> 2 mmol/L for 24–48 ht), also known as "lactime," following cardiac surgery was superior to initial lactate or peak lactate as a predictor of mortality in infants and children.

Lactate is an important biomarker used in the management of pediatric cardiac intensive care patients. High lactate levels are sensitive, but not specific for increased risk of mortality and serious adverse events following cardiac surgery. In critically ill patients, increased production and decreased elimination may coexist. Persistently elevated lactate or lactate that continues to increase over the initial 6–12 hours has been associated with an increased risk of major adverse events.

TROPONIN

The specific origin from the cardiomyocyte enables troponin to perform with high sensitivity and nearly absolute specificity for myocardial injury. The cardiac troponin (cTn) complex is made of three proteins (cTnC, cTnI, and cTnT), but only subtypes cTnI and cTnT have a unique N-terminal amino acid chain rendering them immunologically different from their skeletal muscle forms. The American College of Cardiology and the Joint European Society of Cardiology in conjunction with The National Academy of Clinical Biochemistry Laboratory Medicine declared cTn (cTnI or cTnT) the preferred biomarker for myocardial damage (21, 22). cTn levels rise during the first few days of life in healthy newborns, peaking on day 3 (23). The 99th percentile of cTnI has been reported at 0.183 ng/mL in neonates, which is double the upper limit of normal in adults (24). Serum cTnI levels in normal children are higher in the first year of life, and gradually decrease to adult concentrations by adolescence (25).

THE PREVIOUSLY HEALTHY CHILD WITH ELEVATED TROPONIN LEVELS

Myocardial injury in previously well children is rare, yet troponin measurements are increasingly used during the evaluation of cardiorespiratory symptoms in children. Healthy children presenting with chest pain and elevated troponin levels were most commonly diagnosed with myocarditis or pericarditis (about 50% of patients), followed by drug use, cardiac contusion, and sepsis (26, 27). In teenagers, cTnI elevation due to coronary vasospasm from drug use (particularly cannabis) is not uncommon (27).

TROPONIN LEVELS IN SEPTIC SHOCK

cTn elevation in septic shock has been well established and may correlate with sepsis-induced myocardial dysfunction (28, 29). Over 50% of children with septic shock have increased cTnI at the time of admission, which is associated with myocardial depression and disease severity (30, 31).

BASELINE TROPONIN LEVELS IN CHILDREN WITH HEART DISEASE

Children with symptomatic and asymptomatic congenital heart disease (CHD) have baseline troponin levels ranging from normal to an eight-fold elevation (32–34). Nearly

one-third of patients with chronic heart failure from various etiologies will have increased cTn levels (35). In general, congenital heart defects that are volume loaded have higher cTnI values than lesions that are pressure loaded (33, 36). Without evidence for necrosis, troponin elevations in children with CHD may be due to a mismatch between myocardial oxygen supply and demand (37, 38). A list of ischemic and nonischemic conditions associated with cTn release is noted in **Table 2**.

TROPONIN IN THE PERIOPERATIVE CARDIAC SURGICAL PATIENT

Irrespective of the impetus for troponin release, an elevated cTn level in the critically ill is associated with an adverse prognosis (39, 40). Increased troponin is observed after almost every cardiac surgery, even in the absence of postoperative complications. There is convincing evidence that early postoperative cTnI levels can identify increased morbidity and mortality in adult cardiac surgical and nonsurgical patients (41–43). Concentrations generally peak at 24 hours postoperatively and can remain elevated for 7–10 days (40, 41). Release of cTn in the postoperative period may be related not only to acute myocardial infarction but also to myocardial cell injury, reperfusion techniques, and unavoidable surgical trauma. The degree of troponin elevation in pediatric cardiac surgery has been shown to correlate with cardiopulmonary bypass duration, cross clamp time, cardioplegia techniques, surgical severity, ventriculotomy, and delayed sternal closure (44, 45). In a retrospective review of 1,001 children after open-heart surgery, Mildh et al (46) reported that a cTnT value above 5.9 ng/mL was a strong independent predictor of death. Several pediatric studies have been published, each suggesting a different cTn value is predicative of postoperative complications (47, 48). Others suggest that there is no absolute troponin level that should be interpreted as "high risk" due to the multifactorial nature of postoperative troponin release (49).

Despite the exquisite sensitivity and specificity for detecting myocardial damage, a single troponin level may be difficult to interpret in the perioperative pediatric patient. The serum cTn concentration trend over time is important. A rising troponin value, particularly one still rising 24 hours after an adverse event, should prompt further investigation.

BNP

BNP is secreted predominantly by ventricular myocytes due to an increase in ventricular wall stress. It has emerged as an integral biomarker in the evaluation, management, and treatment for a variety of cardiac diseases (50). Synthesized as a larger precursor prohormone (pro-BNP), it is cleaved into the biologically active BNP and an inactive peptide (amino-terminal pro-BNP). Either peptide can be measured in the serum. Many disease processes can increase BNP levels including, acute coronary syndrome, congestive heart failure, myocarditis, CHD, septic shock, and renal failure (Table 2). Similar to troponin, normal NP values in healthy children vary based on age, with higher levels noted in the younger age groups (51, 52). Concentrations are variable and unreliable in normal newborns less than 4 days old due to the transition from fetal circulation (53). NP levels 100-fold higher than standard adult values have been demonstrated in healthy newborns, and then markedly decline to normal in early adolescence (52, 54, 55).

ACUTELY ILL AND PREVIOUSLY HEALTHY CHILD WITH ELEVATED BNP LEVELS

The ability of NPs to diagnose significant cardiac pathology has been demonstrated in prospective observational studies (56–58). Aside from undiagnosed CHD, the differential diagnosis for a critically ill child with elevated BNP levels includes myocarditis (59), dilated cardiomyopathy (60–62), arrhythmias (63), septic shock (64), pulmonary hypertension (65),

TABLE 2. Known Causes of Cardiac Troponin and Natriuretic Peptide Elevation

Cardiac	Noncardiac
Acute coronary syndrome	Sepsis/septic shock
Myocardial infarction	Acute kidney injury/renal failure
Congestive heart failure	Pulmonary hypertension
Post cardiopulmonary bypass	Pulmonary embolism
Myocarditis/pericarditis	Burn injury
Cardiomyopathy	Perinatal asphyxia (T)
Congenital heart disease	Hypovolemia (T)
Arrhythmias	Stroke/subarachnoid hemorrhage (T)
Heart transplant rejection	Acute respiratory distress syndrome (NP)
Cardiotoxic drugs	Sleep apnea (NP)
Myocardial contusion/trauma (T)	Hyperthyroidism (NP)
Diastolic dysfunction (NP)	Dexamethasone administration (NP)

NP = natriuretic peptide only, T = troponin only.

acute respiratory distress syndrome (66), and pulmonary embolus (67). Among the disease processes above, acute myocarditis/cardiomyopathy and septic shock can produce the most drastic increase in NP levels.

BNP LEVELS IN SEPTIC SHOCK

Children with septic shock generally receive large amounts of volume resuscitation on presentation, providing a stretch stimulus for BNP release. There may be a continued impetus for BNP production, as levels can remain elevated for several days (64). In fact, rising BNP concentrations during the first 3 days of septic shock is associated with increased mortality (68). NPs are increased in both systolic and diastolic sepsis-induced myocardial dysfunction and have been increasingly utilized as an independent prognostic marker of mortality (69–71). They may also serve as an "early warning" indicator of sepsis in patients with burn injury, even more so than stroke volume or systemic vascular resistance (72).

BNP LEVELS IN VARIOUS TYPES OF HEART DISEASE

BNP levels are generally elevated in children with heart disease when compared with healthy children. The degree of elevation is multifactorial, with alterations based on systolic versus diastolic dysfunction and pressure versus volume-loading conditions. Acute systolic dysfunction generates significantly higher BNP levels than diastolic dysfunction or anatomic cardiac defects (54, 56, 57, 73). Single ventricle patients increase NP production under duress (74); however, some have questioned the ability of the single ventricle to generate equal levels of NP based on reduced ventricular mass. A doubling of BNP in single ventricle patients was reported by Lowenthal et al (75) and associated with an odds ratio for heart failure of 2.2 (95% CI, 1.36–3.55; $p = 0.001$). Of note, the recommended cutoff point was more than 45 pg/ml for determining heart failure, which is less than half of the adult cutoff value for heart failure.

Acute hemodynamic changes in conjunction with a failing myocardium will increase NP expression. Children who died from fulminant myocarditis had significantly higher BNP concentrations (median, 7,843 pg/mL; range, 25–25,510 pg/mL) than those who survived (median, 2,061 pg/mL; range, 625–12,350 pg/mL) ($p = 0.03$) (59). Although the case numbers are small, the reported NP concentration in both nonsurvivors and survivors with myocarditis is remarkably high (59, 76).

NP IN THE PERIOPERATIVE CARDIAC SURGICAL PATIENT

There is strong evidence to support the use of pre- and postoperative NP levels as an independent predictor of mortality and morbidity following cardiac and noncardiac surgery in adults (77–79). The pediatric literature is less straightforward. Several studies indicate preoperative BNP levels correlate with a complicated postoperative course including low cardiac output syndrome, duration of mechanical ventilation, and mortality (80–84). However, nearly the same number of studies have reported no association between preoperative BNP levels and outcome in the systematic review by Afshani et al (85). The data for postoperative NP measurements are more convincing. A dozen studies compromising a total of 596 patients (85) demonstrated postoperative NP concentrations were predictive of duration of mechanical ventilation, length of ICU stay, inotrope use, low cardiac output syndrome, and mortality (80, 83, 84, 86–92). The biological activity of the natriuretic hormone system may be transiently decreased following cardiopulmonary bypass (93), with peak levels occurring between 6 and 24 hours postoperatively (80, 83, 86, 91). Age may also be a factor when interpreting perioperative BNP levels, as neonates have increased preoperative BNP levels that decrease following surgery (94). Amirnovin et al (89) smarty used each patient as their own control and discovered children with adverse outcomes had an elevated ratio of postoperative to preoperative values of greater than 45 (100% sensitivity and 82% specificity).

NPs can be used to detect cardiac stress and strain in a variety of clinical scenarios managed on a daily basis in the CICU. They may also aid in the prediction of extubation success and weaning from mechanical circulatory support (95–99). The heterogeneous nature of CHD and resultant hemodynamic perturbations can produce markedly varied BNP levels. If the child fails to improve as expected, checking a BNP might help guide therapeutic strategies and management by detecting alterations in volume or pressure load on the myocardium and prompt further investigation (such as an echocardiogram). More important than any single value is using each patient as their own unique control and monitoring serial concentrations over time.

CONCLUSION

Lactate, troponin, and BNP continue to be valuable biomarkers in the CICU. However, the use of these markers as a single measurement is handicapped by the wide variety of clinical scenarios in which they may be increased. The overall trend may be more useful than any single level with a persistent or rising value of more importance than an elevated initial value. Lactate, troponin, and BNP are one part of a cluster of markers in the CICU, but may provide value beyond that available from clinical data, thus facilitating the detection of subclinical phenomena or a new evolving process.

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