Increases in serum levels of troponin I are associated with cardiac dysfunction and disease severity in pediatric patients with septic shock*

Kimberly E. Fenton, MD; Craig A. Sable, MD; Michael J. Bell, MD; Kantilal M. Patel, PhD; John T. Berger, MD

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Recall that serum biomarkers can be used to assess myocardial injury in pediatric patients with septic shock.

2. Identify the temporal sequence of alterations in serum levels of troponin I in pediatric patients with septic shock.

3. Recall that disturbances of systolic cardiac function are significantly associated with elevated serum levels of troponin I in septic shock.

The authors have disclosed that they have no financial relationship with commercial companies pertaining to this educational activity.

Visit the *Pediatric Critical Care Medicine* Online website (www.pccmjournal.com) for information on obtaining continuing medical education credit.

Objectives: Myocardial cell injury may contribute to cardiac dysfunction in septic shock. Troponin I is a biochemical marker of myocardial cell injury and death. We hypothesized that troponin I is increased in pediatric patients with septic shock and correlates with cardiac dysfunction and disease severity.

Design: Prospective, observational study.

Setting: Children's medical center.

Patients: Twenty-three patients with septic shock and cardiovascular failure were enrolled.

Measurements and Main Results: Serum troponin I was measured at admission and serially over 72 hrs. Within 24 hrs of study enrollment, echocardiograms were performed to determine left ventricular ejection fraction, systolic fractional shortening, heart rate corrected mean velocity of circumferential fiber shortening, and end-systolic wall stress. Requirement for inotropic support (stratified as low, moderate, or high), number of organ system failures, and other demographic data (including Pediatric Risk of Mortality III) were collected. Troponin I was increased on admission in 13 of 23 patients (57%) and at 12 hrs in ten of 22 patients (46%). In all cases, troponin I was maximal within 12 hrs of admission. Admission troponin I was inversely correlated to ejection fraction and fractional shortening and directly correlated to wall stress. Patients who had increased admission troponin I had lower heart rate corrected mean velocity of circumferential fiber shortening (preload and heart rate independent measure of left ventricular systolic function) and higher wall stress (measure of afterload) compared with patients with normal troponin I. Admission troponin I correlated with Pediatric Risk of Mortality III and organ system failure but did not correlate with requirement for inotropic support.

Conclusions: Troponin I was increased in >50% of septic children early in their illness. Increased admission troponin I was associated with decreased measures of systolic cardiac function, as measured by echocardiography, and correlated with severity of illness. Early myocardial cell injury may contribute to the development of subsequent organ failure in septic shock, and measuring troponin I on admission may be helpful in assessing severity of sepsis. (Pediatr Crit Care Med 2004; 5:533–538)

KEY WORDS: troponin I; septic shock; myocardial cell injury; pediatrics; cardiac dysfunction; disease severity

S epsis, along with its sequelae, is a common cause of morbidity and mortality in children. Septic shock is characterized by perturbations of cardiac function and/or peripheral vascular tone. Cardiac dysfunction in septic shock can be manifested by systolic and/or diastolic dysfunction (1–6). Some studies have found that younger children are more likely to have alterations primarily in cardiac function whereas older children are more likely to have alterations in peripheral vascular tone (7–9). These changes are reversible in the majority of patients,

---

with cardiac function returning to normal within 7–10 days in survivors and vasculopathy improving along a similar time period (3, 5, 8). Despite this recovery, secondary organ failure may still lead to significant morbidity and mortality (10).

Echocardiography can provide noninvasive measures of cardiac performance in children with septic shock. Wall stress analysis and ejection phase indexes allow for accurate assessments of ventricular systolic performance. Serial echocardiograms in pediatric patients with septic shock demonstrate intrinsic ventricular dysfunction in the majority of patients despite adequate volume resuscitation (8, 11). Echocardiography variables were found to normalize by 6 days in survivors, which is similar to the experience in adults with septic shock (8, 11, 12). Right heart catheterization can also reliably provide information about preload, afterload, and contractility. In children, however, catheterization requires skilled operators for effective use and is associated with some risk of morbidity (13).

The mechanisms underlying the myocardial dysfunction of sepsis are not fully understood. Coronary artery disease leading to occult myocardial ischemia may play a role in adults but is an unlikely mechanism in previously healthy children (4). Direct myocardial cytotoxicity of the products of septic shock or the actions of various mediators of sepsis, including cytokines, have been implicated as causative agents in adults and children (14–20). To investigate the role of myocardial cell injury in children with septic shock, we measured serum concentrations of troponin I (TnI). TnI is a protein released by cardiomyocytes after cellular injury, and we hypothesized that TnI would be increased in children with septic shock. We hypothesized that TnI would correlate with measures of cardiac dysfunction measured by echocardiography and clinical variables (including requirement for inotropic support and vasopressors, measures of disease severity, and the number of organ system failures).

MATERIALS AND METHODS

The Institutional Review Board of Children's National Medical Center approved this study. Patients admitted to the pediatric intensive care unit between January 2002 and February 2003 were eligible for this study. Informed consent from the parent or guardian and assent from the patient (if applicable) were obtained before study enrollment. Consecutive children ages 3 months to 18 yrs who met American College of Chest Physicians/Society of Critical Care Medicine consensus criteria for septic shock and cardiovascular failure were screened for enrollment (21). Using these consensus criteria, cardiovascular failure was defined as the requirement for inotropic support after adequate fluid resuscitation as determined by the clinical care team. A 12-lead electrocardiogram (EKG) was performed before study enrollment and was interpreted by an attending cardiologist. Since serum TnI would be increased during myocardial ischemia, patients with evidence of ischemia on EKG were excluded from the study. Infants <3 months of age can also have increased TnI without pathophysiologic abnormalities and were therefore excluded (22). Last, patients with primary conditions associated with myocardial ischemia or cell injury were also excluded (these included diagnoses of cardiomyopathy, myocarditis, pericarditis, endocarditis, cardiothoracic surgery or trauma within the past 14 days, Kawasaki's disease, congenital heart disease associated with an increased risk of myocardial infarction, and cardiopulmonary resuscitation (cardioversion and defibrillation within the previous 14 days). Because of these stringent enrollment criteria, five children who received cardiopulmonary resuscitation, two children who had EKG changes consistent with acute myocardial ischemia, and one child whose parents refused consent were screened but not enrolled. Additionally, two children died of cardiac arrest while the screening process was ongoing.

Blood for TnI determination was obtained after consent was obtained and entry criteria were met. In the vast majority of cases, entry criteria were met within the first several hours of pediatric intensive care unit admission. Serial samples were obtained from indwelling vascular catheters at admission into the study and then at 12, 24, 48, and 72 hrs after study admission as long as patients satisfied enrollment criteria. Serum TnI was determined using the Bayer I Immunoassay (Bayer Corporation, Tarrytown, NY). The Bayer I Immunoassay uses a sandwich immunoassay format whereby TnI antibody conjugates and monoclonal immunomagnetic antibodies are reacted with the patients' serum. This assay is substantially more sensitive in measuring TnI than previous assays, and therefore cutoff values ≥0.1 ng/mL were considered indicative of myocardial injury. Both our laboratory and the manufacturer consider levels <0.1 ng/mL to be "nondectectable." For the purpose of this article and for statistical analysis, we have arbitrarily assigned these nondetectable levels the value of 0.09 ng/mL. The reproducibility of these measurements as well as the pediatric reference range of TnI has been previously reported from our laboratory (22).

Echocardiograms (Sonos 5500, Philips Medical Systems, Andover, MA) were performed on all patients within 24 hrs of study entry by a sonographer without knowledge of TnI concentrations. Fluid resuscitation was completed, and the patients were maintained on vasoactive support at the time of the echocardiogram. Standard measures of left ventricular systolic function including ejection fraction (EF) and fractional shortening (FS) were calculated, in the case of EF by using a two-dimensional apical four-chamber view in accordance with Simpson's rule and in the case of FS by standard M mode (23). Preload and heart rate independent left ventricular systolic function was assessed using heart rate corrected mean velocity of circumferential fiber shortening (Vcf_c), and afterload was assessed by calculation of end-systolic wall stress (WS). Standard M mode calculations and blood pressure measurements were used for both Vcf_c (circ/sec) and WS (g/cm^2) (24, 25). To ensure reliable interpretation of echocardiographic data, a single cardiologist (CAS) performed all of the analysis of this data, while remaining blinded to TnI results.

Patient demographics were recorded from the medical record. Requirement for inotropic or vasoactive support was arbitrarily stratified as low (5–10 μg/kg/min of dopamine), moderate (11–15 μg/kg/min of dopamine), or high (>15 μg/kg/min or any dose of epinephrine or norepinephrine) for data analysis. During this study, no patients received phosphodiesterase inhibitors. Severity of illness was assessed by Pediatric Risk of Mortality (PRISM) III at 12 hrs after hospital admission (26). The total number of organ system failures (OSF) for the septic episode was calculated according to the criteria of Wilkinson et al. (10).

Nonparametric testing was performed using SAS software. TnI values ≥0.1 ng/mL were considered abnormally increased. and those <0.1 ng/mL were converted to 0.09 ng/mL for statistical analysis, based on the manufacturer's recommendations and published norms from noncritically ill children. Requirement for inotropic support was converted to ordinal data with low = 0, moderate = 1, and high = 2. Relationships between variables were analyzed using Pearson's correlation coefficient. After preliminary analysis, patients were then stratified into those with increased admission TnI (TnI positive) and patients with normal admission TnI (TnI negative). Differences between the two groups were analyzed using a Student's t-test.

RESULTS

A total of 23 patients were enrolled (14 females and nine males, median age 9 yrs,

range 6 months to 16 yrs), and patient demographics are summarized in Table 1. Median PRISM III score was 12.0 (range, 5–25). Ten of 23 patients required mechanical ventilation, whereas 12 of 23 patients required multiple inotropes/vasopressors. Fifteen of 23 patients had two or more organ failures, and the 28-day mortality rate was 4.3%. Eighty-seven TnI measurements were obtained from these children overall, and 37 (43%) were increased compared with published controls. TnI was increased on study admission in 13 of 23 patients (57%) and at 12 hrs in ten of 22 patients (46%). TnI was maximal within 12 hrs after study enrollment for most patients and was still increased above normal threshold values for three patients at 72 hrs (see Fig. 1).

Increased admission TnI was associated with decreased EF and FS ($r = -.66$, $p = .0022$ and $r = -.58$, $p = .0079$, respectively). Increased admission TnI was associated with increased WS ($r = .78$, $p = .0003$). Admission TnI and Vcf$_c$ were not significantly associated. Admission TnI was not significantly associated with an increased requirement for inotropes and vasoactive medications. Admission TnI correlated with increased disease severity as measured by PRISM III ($r = .50$, $p = .0150$) and with OSF ($r =$

$.61$, $p = .0018$). Increased TnI at time points after admission was not associated with changes in echocardiographic findings or requirements for inotropic or vasoactive support. However, TnI at 12 hrs and 24 hrs had a strong relationship with OSF ($r = .79$, $p = .0001$ and $r = .76$, $p = .0001$, respectively).

After patients were stratified into admission TnI groups, mean Vcf$_c$ was decreased and mean WS was increased in TnI-positive children compared with TnI-negative children (Vcf$_c$, 1.25 ± 0.16 vs. 1.32 ± 0.06, $p = .0196$; WS, 52 ± 3 vs. 33 ± 4, $p = .0052$). PRISM III score and requirement for inotropic support were not different after stratification, but mean EF and FS and the number of OSF approached significance (Table 2).

DISCUSSION

Clinical markers that are associated with organ failure and severity of illness during sepsis can be important tools for clinicians, researchers, and families. Knowing which patients would likely develop organ failure alerts clinicians to patients at risk. Researchers could effectively stratify patients earlier in the course of their disease to treatment groups for therapies with risks as well as

benefits. Patient families could be emotionally and psychologically prepared for the eventuality of the progression of the septic cascade. Our study is the first pediatric study to show that myocardial cell injury occurs in children with septic shock, other than previous reports regarding patients with meningococcemia. Although our study is small, it suggests that increased concentrations of a marker of cardiac myocyte injury compared with historical controls, TnI, is associated with the development of organ failure, increased severity of illness, and decreased measures of systolic function by echocardiogram. Confirmation of our findings and determinations of other serum markers in the future may complement established risk severity scores (i.e., PRISM and Acute Physiology and Chronic Health Evaluation [APACHE]) in determining morbidity and mortality from sepsis and septic shock.

TnI has several properties that make it an ideal candidate as a serum marker of injury. TnI is the inhibitory subunit of the troponin complex of the cardiomyocyte contractile apparatus and functions as an inhibitor of the calcium-regulated actin-myosin cross-bridge formation. Injury or death of cardiomyocytes disrupts the myocardial cellular membrane, and

Table 1. Patient demographics of children with septic shock included in study: Organisms were isolated from blood cultures unless otherwise specified

Age, Yrs	Diagnosis	PRISM III Score	TnI Increased	OSF, No.	Inotrope Requirement
14	Acute lymphoblastic leukemia, sepsis of unknown etiology	10	Yes	1	Moderate
0.5	*Streptococcus pneumoniae* meningitis and sepsis	5	No	2	Low
5	Sepsis of unknown etiology	13	No	2	High
8	Relapsed acute lymphoblastic leukemia, bone marrow transplant, sepsis of unknown etiology	5	No	1	High
13	Influenza B pneumonia and sepsis	19	Yes	3	High
9	Pulmonary hypertension, sepsis of unknown etiology	18	Yes	4	High
9	Systemic lupus erythematosis, *Staphylococcus aureus* sepsis	10	Yes	5	High
5	Menke's syndrome, *Pseudomonas aeriginosa* urosepsis	13	Yes	1	High
14	Acute myelocytic leukemia, bone marrow transplant, sepsis of unknown etiology	7	No	1	Low
12	Spina bifida, chronic renal failure, Gram-negative pneumonia	19	Yes	3	High
10	Acute myelocytic leukemia, polymicrobial sepsis (*Enterococcus faecium*, pediococcus, *Staphylococcus epidermidis*)	14	Yes	2	Moderate
13	*S. aureus* toxic shock	8	No	1	Low
7	Sepsis of unknown etiology	11	Yes	2	High
11	Sepsis of unknown etiology	5	No	1	Low
4	Acute myelocytic leukemia, bone marrow transplant, polymicrobial sepsis (*Escherichia coli* and *Candida krusei*)	9	No	2	Moderate
7	Encephalitis, sepsis of unknown etiology	25	Yes	4	High
12	Systemic lupus erythematosis, *S. pneumoniae* sepsis	11	Yes	1	High
16	Medulloblastoma, *Klebsiella pneumoniae* sepsis	12	No	1	Low
10	Acute lymphoblastic leukemia, *Bacillus* species sepsis	16	Yes	2	High
2	Acute myelogenous leukemia, *Streptococcus viridans* sepsis	9	Yes	2	High
1	*Streptococcus pyogenes* pneumonia and sepsis	17	Yes	2	Low
7	Juvenile pyelocytic astrocytoma, sepsis of unknown etiology	6	No	2	High
13	Nasopharyngeal carcinoma, sepsis of unknown etiology	12	Yes	2	High

PRISM, Pediatric Risk of Mortality; TnI, troponin I; OSF, organ system failure.
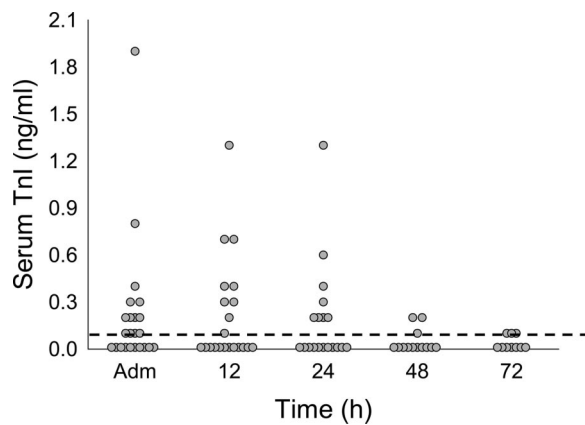
Figure 1. Serum troponin I (*TnI*) concentrations in children with septic shock over the first 72 hrs of critical illness. The *dashed line* demarcates the threshold of 0.1 ng/mL, determined to be abnormal using the Bayer I Immunoassay. Values <0.1 ng/mL are reported by our laboratory as "nondetectable levels" and are represented by the *circles* below the *threshold line*. *Adm*, at admission.

Table 2. Echocardiographic variables and outcome measures in children with sepsis who had increased troponin I (TnI) at study admission (TnI positive) compared with those with normal TnI on study admission (TnI negative)

Variable	TnI Positive	TnI Negative	Significance, p
Age, yrs	8.5 ± 1.2	8.9 ± 1.5	.81
PRISM III	13.9 ± 1.4	10.3 ± 1.7	.73
Inotrope requirement	1.54 ± 0.22	1.10 ± 0.31	.42
OSF, n	2.4 ± 0.4	1.6 ± 0.2	.08
EF, %	62 ± 4	68 ± 2	.05
FS, %	32 ± 3	39 ± 2	.09
Vcf$_c$, circ/sec	1.25 ± 0.16	1.33 ± 0.06	.02
WS, g/cm^2	52 ± 13	33 ± 4	.0052

Heart rate corrected mean velocity of circumferential fiber shortening (Vcf$_c$) was decreased and wall stress (WS) was increased in TnI-positive children compared with TnI-negative children (data represented as mean ± SEM, Student's *t*-test). Other variables were not different, but trends were observed in ejection fraction (EF), fractional shortening (FS), and the number of organ system failures (OSF).

TnI is released into the cardiac interstitium. Within minutes to hours, TnI can be detected in serum and lymphatics (27, 28). Since TnI is exclusively localized to the myocardium and its excretion is independent of renal and liver metabolism, it is an extremely sensitive and specific marker for cardiac myocyte injury and death (27–29). TnI can be measured using immunoassays with a high reliability (sensitivity and specificity >98%) in only a few hours (29, 30). Because of the rapidly available data from these assays and the high specificity of TnI to myocardial injury, TnI has become a commonly used marker for myocardial infarction and other forms of cardiac injury (31–33). Serum TnI increases within 3–9 hrs after onset of myocardial cell injury and remains increased for 5–7 days in cases of massive myocardial cell death (30, 32–34). The time course of TnI after more subtle forms of myocardial injury, such as during septic shock, is not well studied.

Our study is the first pediatric series to demonstrate increased TnI in children with generalized septic shock. Our data are in agreement with those from adults with sepsis and septic shock, where 50–80% of patients have increased TnI (17–20, 35). The only other available pediatric data regarding TnI during sepsis come from children with overwhelming meningococcal infection. Briassoulis and colleagues (36) showed that children with meningococcal septic shock had a significant increase in TnI. However, since a significant portion of the children in this study (23%) showed EKG findings consistent with myocardial ischemia and these children had much higher concentrations of serum TnI compared with those with a normal EKG, it is difficult to

conclude that sepsis alone was the cause of the observed increase in TnI. In another series of children with meningococcal sepsis, Thiru and colleagues (16) found that TnI was increased on admission to a similar degree as we have found in generalized septic shock (24% on admission, 62% within the first 2 days of illness) but ischemic heart disease was not excluded in these children. Since vascular thrombi are pathologic sequelae of meningococcal sepsis syndrome, it seems likely that occult thromboses of coronary arteries in meningococcal disease could be responsible for the TnI increases observed in these previous studies. Since none of our patients had either meningococcal sepsis or signs of purpura fulminans, our data demonstrate that all forms of sepsis can cause increased TnI, particularly early after sepsis begins. This suggests that myocardial cell injury could be an important factor in the pathogenesis of septic shock in children.

We found that increased admission TnI was associated with decreased admission EF and FS, suggesting that increased TnI is associated with decreased measures of systolic cardiac function. Echocardiography can measure or estimate important variables of cardiac systolic performance (heart rate, cardiac loading conditions [preload and afterload] and cardiac contractility) (23, 37, 38). Wall stress analysis and ejection phase indexes allow for hemodynamic calculations that account for physiologic conditions, which influence ventricular performance. These analyses can help to distinguish patients who have impaired contractility from patients who have altered loading conditions (8, 24, 39). In our study, increased TnI was associated with decreased EF and FS and increased WS. Despite this association, most of the patients had values of systolic function within the generally accepted normal range for children who are not critically ill. On average, EF was decreased by 10% and FS was decreased by 20% in the TnI-positive compared with the TnI-negative patients.

The preload and afterload on the heart can significantly affect EF and FS. We performed the load independent assessments of Vcf$_c$ and WS. Vcf$_c$ is a heart rate and preload independent calculation of systolic function and WS is a measure of afterload. These analyses have been validated in the pediatric septic shock population (8). Overall, we demonstrated a very close association between admission

> *By using the biochemical marker troponin I, our study suggests that myocardial cell injury may play a role in the myocardial dysfunction in pediatric patients with septic shock.*

TnI and WS but failed to demonstrate such a relationship with Vcf_c. However, when patients were stratified into groups, TnI-positive patients had a lower mean Vcf_c and a higher WS compared with the TnI-negative patients. This finding provides the best evidence that within a model that is not affected by loading conditions, patients with evidence of myocardial cell injury early in septic shock also have evidence of impaired ventricular contractility and increased cardiac afterload.

We found that increased admission TnI was associated with increased severity of illness measured by PRISM III and numbers of organ that fail during sepsis. This is the first study in either adults or children with sepsis to associate TnI with both of these longer term outcome variables. This finding is particularly intriguing because the TnI on admission was associated with of illness severity (PRISM III) and eventual organ dysfunction (OSF). This finding, if confirmed in larger series, suggests that screening children with sepsis for TnI can be of value in assessing the eventual outcome and suggests that early myocardial cell injury and death may contribute to the development of subsequent organ failure in pediatric patients with septic shock.

There are several limitations of our study. The mortality rate of the study patients was very low primarily because of our selection criteria. We used rigid entry criteria to avoid the bias of entering children with primary heart disease. Because of this, children with severe cardiac involvement from sepsis could not be definitively differentiated from patients with severe myocarditis or other primary heart diseases. As a result of these entry criteria, we have demonstrated that sepsis alone can cause an increase in this extremely sensitive marker of myocardial cell injury. A consequence of this process was to eliminate children with extreme perturbations in cardiac performance, and therefore the observed mortality rate was much lower than in previous studies. There are well-recognized limitations of echocardiography to quantitatively assess cardiac dysfunction that affect our results. We assessed left ventricular systolic performance only and could not account for the right ventricular or diastolic dysfunction that may occur in children with septic shock. Also, echocardiography uses geometric assumptions of the left ventricle that may vary between patients. Despite this, we were able to find important correlations between TnI and echocardiographic findings by using carefully chosen variables that were independent of loading conditions of the heart. It is possible that inadequate fluid resuscitation and excessive vasoconstrictive agents may contribute to the increased wall stress found in our patients. A more detailed study including patients with sepsis undergoing cardiac catheterization could aid in answering this question. Last, PRISM III and OSF are statistically linked measures of disease severity. By necessity, multiple laboratory values used in the PRISM III calculation are also used as definitions for OSF. So although our findings suggest that TnI is linked to both measures, a larger series of patients may be able to determine whether particular abnormalities are associated with admission TnI.

CONCLUSIONS

By using the biochemical marker TnI, our study suggests that myocardial cell injury may play a role in the myocardial dysfunction in pediatric patients with septic shock. TnI levels were frequently elevated in our pediatric population with septic shock. Increased admission TnI levels were associated with lower values of systolic cardiac function as measured by echocardiography and correlated with severity of illness. Early myocardial cell injury may contribute to the development of subsequent organ failure in septic shock, and measuring TnI on admission may help clinicians assess the degree of illness in children with sepsis.

REFERENCES

1. Ellrodt AG, Riedinger MS, Kimchi A, et al: Left ventricular performance in septic shock: Reversible segmental and global abnormalities. *Am Heart J* 1985; 110:402–409
2. Ognibene FP, Parker MM, Natanson C, et al: Depressed left ventricular performance: Response to volume infusion in patients with sepsis and septic shock. *Chest* 1988; 93:903–910
3. Parker MM, Shelhamer JH, Bacharach SL, et al: Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med* 1984; 100:483–490
4. Cunnion RE, Schaer GL, Parker MM, et al: The coronary circulation in human septic shock. *Circulation* 1986; 73:637–644
5. Kumar A, Haery C, Parillo JE: Myocardial dysfunction in septic shock. *Crit Care Clin* 2000; 16:251–287
6. Vincent JL, Gris P, Coffernils M, et al: Myocardial depression characterizes the fatal course of septic shock. *Surgery* 1992; 111:660–667
7. Pollack MM, Fields AI, Ruttiman UE: Distributions of cardiopulmonary variables in pediatric survivors and nonsurvivors of septic shock. *Crit Care Med* 1985; 13:454–459
8. Feltes TF, Pignatelli R, Kleinert S, et al: Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall stress analysis. *Crit Care Med* 1994; 22:1647–1658
9. Ceneviva G, Paschall JA, Maffei F, et al: Hemodynamic support in fluid refractory pediatric septic shock. *Pediatrics* 1998; 102:e19
10. Wilkinson JD, Pollack MM, Ruttiman UE, et al: Outcome of pediatric patients with multiple organ system failure. *Crit Care Med* 1986; 14:271–274
11. Courand JA, Marshall J, Chang Y, et al: Clinical applications of wall-stress analysis in the pediatric intensive care unit. *Crit Care Med* 2001; 29:526–533
12. Jardin F, Fourme T, Page B, et al: Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. *Chest* 1999; 116:1354–1359
13. Pulmonary Artery Consensus Conference: Consensus statement. *New Horiz* 1997; 5:175–194
14. Parillo JE, Burch C, Shelhamer J, et al: A circulating myocardial depressant substance in humans with septic shock. Patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. *J Clin Invest* 1985; 76:1539–1553
15. Kumar A, Thota V, Dee L, et al: Tumor necrosis factor-alpha and interleukin-1 beta are biological markers of left ventricular dysfunction in septic shock. *J Exp Med* 1996; 183:949–958
16. Thiru Y, Pathan N, Bignal S, et al: A myocardial cytotoxic process is involved in the cardiac dysfunction of meningococcal septic shock. *Crit Care Med* 2000; 28:872–877
17. Turner A, Tsamitros M, Bellamo R: Myocardial cell injury in septic shock. *Crit Care Med* 1999; 27:1775–1780

18. ver Elst KM, Spapen HD, Nguyen DN, et al: Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. *Clin Chem* 2000; 46:650–657

19. Fernandes CJ, Akamine N, Knobel E: Cardiac troponin: A new serum marker of myocardial injury in sepsis. *Intensive Care Med* 1999; 25:1165–1168

20. Ammann P, Fehr T, Minder EI, et al: Elevation of troponin I in sepsis and septic shock. *Intensive Care Med* 2001; 27:965–969

21. American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 101:1644–1655

22. Soldin SJ, Murthy JN, Agarwalla PK, et al: Pediatric reference ranges for creatine kinase, CKMB, troponin I, iron and cortisol. *Clin Biochem* 1999; 32:77–80

23. Schiller NB, Shah PM, Crawford M, et al: Recommendations for the quantification of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2:358–367

24. Colan SD, Borow KM, Neumann A: Left ventricular end-systolic wall stress-velocity of fiber shortening relation: A load-independent index of myocardial contractility. *JACC* 1984; 4:715–724

25. Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975; 56: 56–64

26. Pollack MM, Patel KM, Ruttiman UE: PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; 24:743–752

27. Katus HA, Scheffeld T, Remppis A, et al: Proteins of the troponin complex. *Lab Med* 1992; 23:311–317

28. Adams JE, Bodor GS, Davila-Roman VG, et al: Cardiac troponin I: A marker with a high specificity for cardiac injury. *Circulation* 1993; 1993:101–106

29. Mair J, Morandell D, Genser N, et al: Equivalent early sensitivities of myoglobin, creatine kinase, MB mass, creatine kinase isoform ratios and cardiac troponins I and T for acute myocardial infarction. *Clin Chem* 1995; 41: 1266–1272

30. Adams JE, Schectman KB, Landt Y, et al: Comparable detection of acute myocardial infarction by creatine kinase MB isoenzyme and troponin I. *Clin Chem* 1994; 40: 1291–1295

31. Falahati A, Sharkey S, Christensen D, et al: Implementation of serum cardiac troponin I as a marker for detection of acute myocardial infarction. *Am Heart J* 1999; 137:332–337

32. Myocardial Infarction Redefined—A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *JACC* 2000; 36: 959–969

33. Antman EM, Tanasijevic MJ, Thompson B, et al: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; 335:1342–1349

34. Zimmerman J, Fromm R, Meyer D, et al: Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999; 99:1671–1677

35. Arlati S, Brenna S, Prencipe L, et al: Myocardial necrosis in ICU patients with acute non-cardiac disease: A prospective study. *Intensive Care Med* 2000; 26:31–37

36. Briassoulis G, Narlioglou M, Zavras N, et al: Myocardial injury in meningococcus-induced purpura fulminans in children. *Intensive Care Med* 2001; 27:1073–1082

37. Schiller NB, Foster E: Analysis of left ventricular systolic function. *Heart* 1996; 75(Suppl 2):17–26

38. Snider AR, Serwer GA, Ritter S. Echocardiography in Pediatric Heart Disease. Second Edition. St. Louis, Mosby-Year Book, 1997

39. Colan SD, Facc IA, Parness MD, et al: Developmental modulation of myocardial mechanics: Age-and growth-related alterations in afterload and contractility. *JACC* 1992; 19: 619–629