

Cardiac troponin-I as a marker of myocardial dysfunction in children with septic shock

Fuat Gurkan^a, Asuman Alkaya^a, Aydin Ece^a, Kenan Haspolat^a, Mehmet Bosnak^a, Meki Bilici^a, Mehmet Kervancioglu^a, Zubal Aritürk^b

^a Department of Paediatrics in Dicle University Medical Faculty, Diyarbakir, Turkey

^b Department of Cardiology in Dicle University Medical Faculty, Diyarbakir, Turkey

Summary

Objectives: Cardiac depression is well known in severe sepsis and septic shock. Our aim was to investigate the incidence of myocardial ischaemia as shown by cardiac troponin I (cTnI) levels in patients with septic shock and to evaluate the correlation with myocardial dysfunction measured by echocardiography.

Methods: The study was performed in the paediatric intensive care unit in Dicle University Hospital, Turkey, between January 2001 and December 2002. Patients in septic shock, with a mean age of 6.4 ± 2.8 months, were simultaneously submitted to a two-dimensional echocardiogram and biochemical investigation on admission.

Results: The mean serum cTnI level of the patients was 3.1 ± 2.6 ng/ml (0.01–9.80 ng/ml) and the mean LVEF value was calculated as $48\% \pm 11\%$. 21 patients (75%) had a cTnI level ≥ 0.6 ng/ml, and 15 patients (54%) had a LVEF < 0.5 . For cTnI levels ≥ 0.6 ng/ml, sensitivity and specificity

were 93.3% and 46.2%, and positive and negative predictive values were 66.7% and 85.7% respectively. For cTnI values ≥ 2.0 ng/ml, sensitivity and specificity were 86.7% and 76.9%, and positive and negative predictive values were 81.3% and 83.3%, respectively. There was a statistically significant relationship between LV dysfunction and cTnI positivity ($r^2 = 0.316$, $p = 0.002$). No significant difference was found for the cTnI levels ≥ 0.6 ng/ml between non-survivors and survivors ($p > 0.05$).

Conclusion: Myocardial ischaemia and cell injury seem to be common in patients with septic shock and correlate with left ventricular dysfunction. Measurement of cTnI may be an easy and practical tool for monitoring cardiac damage in critically ill septic patients.

Key words: sepsis; child; cardiac troponin I; myocardial dysfunction; LVEF

Introduction

Myocardial dysfunction in the setting of acute organ dysfunction in severe sepsis and septic shock has been known for many years. This cardiac depression, mainly characterized by left ventricular failure, is estimated by echocardiogram-derived left ventricular ejection fraction (LVEF). In addition to the cardiac effects of the inflammatory responses in septic patients, cardiac tissue histopathology studies have also revealed cellular tissue necrosis, as a consequence of hypotension, the action of circulating myocardial depressant substances or the use of catecholamines [1]. Myocardial cell injury accompanies, causes or results from the decreased cardiac performance in sepsis.

Cardiac troponin I (cTnI) is a marker that is highly specific for ischaemic cardiac injury and may also be a very specific and sensitive marker of myocardial injury in septic children. High levels of cardiac troponins have been reported in many critically ill adult patients, including sepsis, without acute coronary syndromes [2–9], but there are no adequate reports of the investigation of cTnI in paediatric cases. Therefore, our aim in this study was to investigate the incidence of myocardial ischaemia as shown by cTnI levels in children with septic shock and to evaluate the correlation with myocardial dysfunction measured by echocardiography.

Materials and methods

This prospective study was performed in the paediatric intensive care unit of Dicle University Hospital, Turkey, between January 2001 and December 2002. Twenty-eight children with septic shock were enrolled into the study. We used the consensus guidelines known as Bone's criteria [10], which define septic shock as persistent hypotension despite fluid resuscitation with evidence of organ hypoperfusion (long capillary refill time) in cases of systemic inflammatory response syndrome (SIRS) in conjunction with infection. SIRS includes the following criteria: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >140 beats/min, respiratory rate >50 /min, white blood cell count $>12\,000/\text{mm}^3$, $<4000/\text{mm}^3$ or $>10\%$ immature cells.

Patients with any documented cardiothoracic event (congenital heart disease, cardiothoracic trauma, cardiopulmonary resuscitation, pericarditis, etc) were not included. Other exclusion criteria were the presence of an immunosuppressed state, haematological malignancy or any medical condition considered to be irreversible or lethal within 24 h of admission.

All patients were admitted to the intensive care unit directly. All were started on intravenous fluid, antibiotic

therapy and inotropic support, either with dopamine alone or in association with dobutamine, due to haemodynamic instability. At the same time patients were simultaneously submitted to a two dimensional echocardiogram (Hewlett Packard Somos 1000) and biochemical investigations. A colleague not otherwise involved in the management of the patient performed the echocardiogram.

All blood samples were stored at -70°C and serum levels of cTnI were detected by an enzyme linked one-step sandwich immunoassay (TOSOH A1A21 Fluoresans Chemistry). No haemolysed or EDTA-treated samples were included. The normal upper limit for the detection of cTnI was considered to be 0.60 ng/ml, this being the cut-off value [3]. A single technician unaware of the patient's diagnosis, treatment or outcome measured cTnI in all samples.

For statistical analysis we used the SPSS computer package (SPSS Inc., Chicago). Associations between the parameters were analyzed using Linear Regression Analyses. Fishers exact test was used for statistical analysis of contingency tables. A p value of less than 0.05 was considered as significant.

Results

Table 1
Troponin I against LVEF values in children with septic shock.

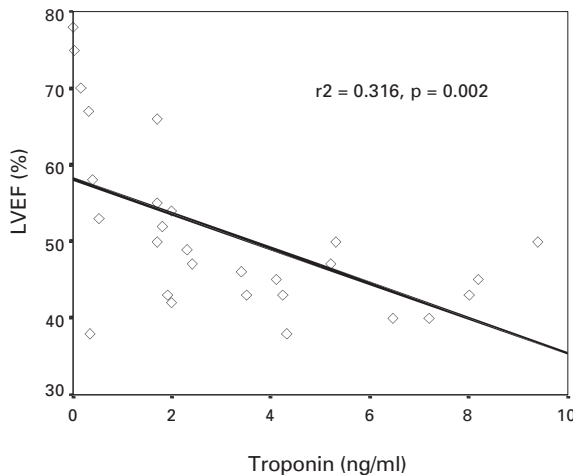
	LVEF <0.5	LVEF ≥ 0.5	Total	*P
Troponin ≥ 0.6 ng/ml	14	7	21	
Troponin < 0.6 ng/ml	1	6	7	0.025
Total	15	13	28	
Troponin ≥ 2.0 ng/ml	13	3	16	
Troponin < 2.0 ng/ml	2	10	12	0.002

* Fisher's exact test; LVEF: Left ventricular ejection fraction

Table 2
Sensitivity, specificity and predictive values of two different troponin I cut off points for low left ventricular ejection fraction.

	Cut off value	
	≥ 0.6 ng/ml	≥ 2.0 ng/ml
Sensitivity (%)	93.0	86.7
Specificity (%)	46.2	76.9
Positive predictive value (%)	66.7	81.3
Negative predictive value (%)	85.7	83.3

Figure 1
The relationship between serum troponin I levels and LVEF (Left ventricular ejection fraction).



28 cases, 16 males (57%) and 12 females (43%), with ages ranging from 45 days to 24 months with a mean of 6.4 ± 2.8 months were admitted to the study group. Pneumonia was the most frequent underlying cause (50%), followed by gastroenteritis (22%) and urosepsis (20%). Most cases had a history of antibiotic usage (78%) prior to admission. Bacteria were grown in blood culture in 6 (21%) patients: *Staphylococcus aureus* in three, *Enterobacter cloaca* in two and *Pseudomonas aeruginosa* in one. In other patients, the infectious focus was confirmed both clinically and by further laboratory investigations. Twenty patients (71%) survived and were discharged from hospital, while the remaining eight (29%) died.

Mean serum cTnI levels were 3.1 ± 2.6 ng/ml. Mean LVEF value was calculated as $48\% \pm 11\%$. There were 21 patients (75%) with cTnI levels ≥ 0.6 ng/ml and LVEF was below 50% in 15 (54%) patients. LVEFs and cTnI levels were analyzed in a two-by-two table (table 1). When 0.6 ng/ml was taken as the cut off value for cTnI, sensitivity and negative predictive values were higher, but specificity and positive predictive values were lower than those when cTnI ≥ 2.0 ng/ml was taken as the cut off value (table 2).

There was a statistically significant relationship between LV dysfunction and cTnI positivity ($r^2 = 0.316$, $p = 0.002$) (Figure). No significant difference was found for cTnI levels ≥ 0.6 ng/ml, between non-survivors and survivors, 7/8 vs. 14/20, respectively ($p > 0.05$).

Discussion

Cardiac troponin I is an isoform of a thin-filament contractile protein present in high concentrations in the myocardium but usually not expressed in regenerating skeletal muscle or in other tissues. It is the only known molecular marker of myocardial injury and is detectable within 6 hours of the damage [11]. A highly significant association between elevated serum troponin levels and clinical situations with acute coronary syndrome has been reported. In recent years, a number of studies have suggested a possible association between cTnI and myocardial injury in patients with non cardiac diseases [4-7, 12, 13]. Myocardial dysfunction is a characteristic component of septic shock contributing to the high mortality. It has been suggested that a possible relationship between cTnI measurements and decreased left ventricular function may aid the recognition of myocardial involvement in adult patients with sepsis [2-7]. Arlati et al. have reported elevated cTnI levels in 11 of 19 adult septic patients [6]. Fernandez et al. compared LVEF and troponin I values in ten critically ill septic patients. In their study all patients with a LVEF lower than 50% had elevated troponin I levels [3]. VerElst et al. have shown a strong association between left ventricular dysfunction and cTnI positivity in 48 patients with septic shock [4]. Guest et al. [9] reported increased cTnI in 5 of 16 septic cases (31%) and Turner et al. [5] in 12/15 (80%).

In paediatric series, a similar link between cardiac impairment and cTnI levels in sepsis has been reported in two different studies on meningococcal disease in children [14]. The incidence of myocardial ischaemia as shown by cTnI levels was found to be increased in both studies and correlated with myocardial dysfunction (EF) measured by echocardiography [11, 14]. In our study of children with septic shock, cTnI levels were also higher than the upper reference limits and cTnI elevations correlated with a decrease in LVEF, compatible with the previous reports on troponin and meningococcaemia in children. In our series, cTnI appeared to be at least as sensitive as LVEF and acts as a serum marker for myocardial injury and as an indicator of left ventricular dysfunction. There was a greater positive predictive value for troponin levels higher than 2.0 ng/ml.

Based on this relationship between LV dysfunction and cTnI positivity, we suggest that cell

death may play a role in the pathogenesis of myocardial dysfunction in children with septic shock. Inadequate myocardial performance, including left ventricular systolic depression and diastolic dilatation, is a common and early complication of septic shock, but studies of coronary blood flow and myocardial metabolism show neither a global myocardial ischaemia nor necrosis [1]. Elevated cTnI levels may be caused by ischaemic damage due to increased oxygen consumption as well as bacterial myocarditis, decreased perfusion and reduced oxygen delivery to the cardiac muscle. Additional factors such as hypotension, shock or the use of inotropic agents may also contribute to the cTnI elevation [6]. Our patients were all in a shock state requiring inotropic agents, however, in previous studies, elevated cTnI levels have also been reported in haemodynamically stable sepsis patients not receiving inotropic agents [7]. Further studies are needed to determine to what extent the myocardial damage is a cause or a result of LV dysfunction and in what way sepsis causes cTnI elevations.

Among critically ill patients, recognized cardiac dysfunction is an independent predictor of disease severity. Therefore, in clinical practice, serum cTnI measurements may provide an easier and more practical assessment of ongoing cardiac damage in critically ill patients than evaluation with echocardiography, which is often not available at the bedside of critically ill patients.

In conclusion, the relationship between cTnI as a marker of cell death and myocardial function suggests that "cell death" may have a role in the pathogenesis of myocardial dysfunction in septicaemia. cTnI may be a useful marker of cardiac damage in critical patients. The pathogenesis of cell death and its influence on cardiac dysfunction in patients with septic shock, the prognostic value of cTnI in these patients and whether it is a useful clinical tool remain to be determined in large scale studies.

Correspondence:

Assoc. Prof. Dr. Fuat Gurkan
Dicle University, Medical Faculty
Dept. of Paediatrics
Diyarbakir, Turkey
E-Mail: fuatgurkan@hotmail.com

References

- 1 Parker MM. Myocardial dysfunction in sepsis: Injury or depression? *Crit Care Med* 1999; 27:2035-6.
- 2 Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol* 2003; 41:2004-9.
- 3 Fernandes CJ, Akamine N, Knobel E. Cardiac troponin: a new serum marker of myocardial injury in sepsis. *Intensive Care Med* 1999;25:1165-8.
- 4 VerElst 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; 46:650-7.

- 5 Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. *Crit Care Med* 1999; 27:1775–80.
- 6 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; 26:31–7.
- 7 Ammann P, Fehr T, Minder EI, et al. Elevation of troponin I in sepsis and septic shock. *Intensive Care Med* 2001; 27:965–9.
- 8 Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation* 2002; 106:2871–2.
- 9 Guest TM, Ramanathan AV, Tuteur PG, et al. Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA* 1995; 273:1945–9.
- 10 Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–55.
- 11 Thiru Y, Pathan N, Bignall S, et al. A myocardial cytotoxic process is involved in the cardiac dysfunction of meningococcal septic shock. *Crit Care Med* 2000; 28:2979–83.
- 12 Checchia PA, Appel HJ, Kahn S, et al. Myocardial injury in children with respiratory syncytial virus infection. *Pediatr Crit Care Med* 2000; 1:146–50.
- 13 Khan IA, Tun A, Wattanasauwan N, et al. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. *Am J Emerg Med* 1999; 17:225–9.
- 14 Briassoulis G, Narlioglou M, Zavras N, Hatzis T. Myocardial injury in meningococcus-induced purpura fulminans in children. *Intensive Care Med* 2001; 27:1073–82.

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website <http://www.smw.ch> (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

Editorial Board

Prof. Jean-Michel Dayer, Geneva
 Prof. Peter Gehr, Berne
 Prof. André P. Perruchoud, Basel
 Prof. Andreas Schaffner, Zurich
 (Editor in chief)
 Prof. Werner Straub, Berne
 Prof. Ludwig von Segesser, Lausanne

International Advisory Committee

Prof. K. E. Juhani Airaksinen, Turku, Finland
 Prof. Anthony Bayes de Luna, Barcelona, Spain
 Prof. Hubert E. Blum, Freiburg, Germany
 Prof. Walter E. Haefeli, Heidelberg, Germany
 Prof. Nino Kuenzli, Los Angeles, USA
 Prof. René Lutter, Amsterdam, The Netherlands
 Prof. Claude Martin, Marseille, France
 Prof. Josef Patsch, Innsbruck, Austria
 Prof. Luigi Tavazzi, Pavia, Italy

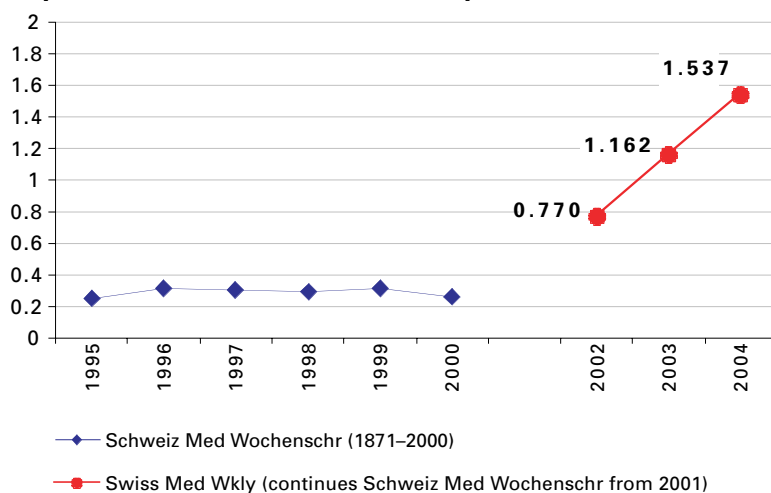
We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:

http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
 SMW Editorial Secretariat
 Farnsburgerstrasse 8
 CH-4132 Muttenz

Manuscripts: submission@smw.ch
 Letters to the editor: letters@smw.ch
 Editorial Board: red@smw.ch
 Internet: <http://www.smw.ch>