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BRIEF REPORT

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Cardiac troponin: a new serum marker of myocardial injury in sepsis

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Abstract *Objective*: Echocardiogram-derived left ventricular ejection fraction (LVEF) is usually utilized to evaluate left ventricular function, including that of septic patients. However, LVEF is greatly influenced by afterload. The aim of this study was to test the hypothesis that troponin I, a serum marker of myocardial injury, may be able to detect left ventricular involvement by the septic process, being at least as sensitive an indicator of left ventricular dysfunction as LVEF in these patients.
Design: Comparison of echocardiogram-derived LVEF with serum levels of troponin I in ten critically ill septic patients.
Setting: General intensive care unit in a tertiary care private hospital.
Patients: Ten critically ill septic patients with no previous documented heart disease.
Measurements and results: Patients were simultaneously submitted to a two-dimensional echocardiogram and troponin I determinations. LVEFs and troponin I levels were analyzed in a two-by-two table in order to validate troponin I as a new biochemical marker of myocardial injury in sepsis. All the patients whose LVEF was < 0.5 had elevated troponin I levels (kappa = 0.61, $p = 0.035$).
Conclusions: Identification of myocardial dysfunction in septic patients has been a challenging task. Troponin I, a serum marker of myocardial injury, may be of great help in the recognition of myocardial involvement by sepsis in a noninvasive and readily available way.

Key words Troponin I · Myocardial dysfunction · Sepsis · Myocardial injury

Introduction

Myocardial dysfunction is a common feature of sepsis, although it may not be clinically apparent from echocardiogram-derived left ventricular ejection fraction (LVEF) due to the reduction in afterload [1]. Additionally, LVEF may be particularly misleading among nonsurviving patients since LVEF may remain normal or near normal despite a compromised stroke volume due to a failure of the LV to dilate and hence boost stroke volume via the Frank-Starling mechanism [2].

Our data from histopathological studies of cardiac tissue from septic patients revealed a classical acute inflammatory response characterized by a polymorphonuclear cell interstitial infiltration and varying amounts of cellular tissue necrosis [3]. On the other hand, some studies suggest that the reduction in myocardial contractility associated with sepsis may occur even in the absence of changes in myocardial structure [4]. Therefore, a method that could identify myocardial injury in sepsis in a simple, practical way would be of great interest. Nevertheless, to our knowledge, a very sensitive and specific marker of myocardial injury in sepsis is not available. In recent years, several studies have suggested that troponin I (TnI) serum levels seem to be the most sensitive and specific marker for the diagnosis of is-

Table 1 Patients' profiles

Patient	Sex	Age (years)	Apache II	Etiology	TnI (ng/ml)	LVEF	Outcome
VF	F	35	14	Abdominal sepsis	6.7	0.42	Survived
TM	F	30	26	Urinary sepsis	3.6	0.26	Survived
GM	M	34	25	Soft tissue sepsis	0	0.72	Survived
VF	F	35	22	Peritonitis	0	0.56	Survived
LC	M	24	43	Pneumonia immunocompromised host	1	0.67	Died
YP	M	20	15	Peritonitis	0.8	0.23	Survived
AL	M	28	9	Burn sepsis	0	0.72	Survived
MC	M	25	33	Abdominal sepsis	2	0.26	Died
SS	F	31	27	Necrotizing colitis	1.1	0.78	Died
AO	M	39	35	Soft tissue sepsis	0	0.70	Died

chemic myocardial injury [5]. We hypothesize that it may also identify myocardial involvement in sepsis even in patients with normal or near-normal LVEF. To test this hypothesis, ten critically ill septic patients with no evidence of prior cardiac disease were prospectively evaluated in a blind fashion, comparing echocardiogram-derived LVEF with serum levels of TnI.

Patients and methods

During a 6-month period, ten critically ill septic patients according to Bone × s criteria [6], who had been admitted to the intensive care unit (ICU) underwent invasive monitoring for optimal management. None had previous documented heart disease as defined by symptoms or signs of heart involvement, cardiac enlargement, electrocardiographic abnormalities, or initial wedge pressure above 20 mmHg. The patients' profiles are given in Table 1.

Every patient had a pulmonary artery catheter (Swan-Ganz, model 93A 131 7F Edwards-Baxter laboratories) inserted for optimal medical management. Pressures were obtained immediately after echocardiography and troponin measurements and were recorded by a monitor at the bedside (Siemens, Sirecust 1281, Boston Mass., USA). Dobutamine and norepinephrine were titrated as necessary by the ICU staff (Table 3). In all patients the radial artery was catheterized for continuous invasive blood pressure monitoring.

Within 12 h of admission they were submitted to a two-dimensional echocardiogram performed at the bedside (Toshiba SSH-140 Masu, Japan) and TnI measurements. The study was approved by the local ethical committee. Six of ten patients were on mechanical ventilation and four were not. The mode of mechanical ventilation was pressure controlled ventilation in all six patients. Those on mechanical ventilation were sedated with midazolam, whereas those breathing spontaneously were not sedated.

The investigators were not responsible or directly involved with the care of the patients. The echocardiograms were all done by one professional who was not involved with the clinical management of the patients nor participated in the study. Likewise, TnI levels were measured as part of the routine of the hospital laboratory and nobody in the laboratory was involved in the study.

Two-dimensional echocardiographic studies

Using the apical window, a long axis four-chamber view was selected and echocardiographic images were recorded for further quantitative analysis. Using a microcomputer, stop-motion frames were digitized and displayed on the screen to delineate the endocardial outlines of both ventricles. Left ventricular and right ventricular end-diastolic (LVED, RVED) and end-systolic (LVES, RVES) areas were automatically processed and the global LVEF was calculated from LVED and LVES volumes by the formula: LVEDV – LVESV/LVEDV. The cutoff point for detecting myocardial left ventricular dysfunction was estimated as 0.5.

TnI measurements

The assay (Stratus Cardiac Troponin-I Fluorometric Enzyme Immunoassay) is an automated two-site, immunoassay which utilizes two monoclonal antibodies that are specific for the cardiac isotype of TnI. The enzymatic rate generated by the bound antibody fraction, which is directly proportional to the concentration of troponin I in the sample, was measured by front surface fluorescence. The limit of detection of the assay was determined to be 0.60 ng/ml and was also considered the cutoff value. Assay calibration was performed with each new kit of Stratus Cardiac Troponin I reagents. During each 24-h period, at least two levels of control material were assayed in order to validate the calibration curve. The calculated assay values (as determined by the microprocessor within the instrument) were printed out based upon this stored curve.

Statistical analysis

In order to measure the strength of the agreement between these two methods (LVEF and TnI) we employed the kappa calculations:

$$\text{Kappa} = \frac{P(0)-P(E)}{1-P(E)}$$

where P(0) is the observed proportion of agreements and P(E) is the expected proportion of agreements.

By assuming moderate to high correlation rates, the statistical analysis utilized a kappa = 0.61, $p = 0.035$, and a sample size of ten patients was needed (Table 2).

Table 2 Validating troponin I against LVEF as assessed by echocardiogram: data analyzed in a 2 × 2 table

	LVEF < 0.5	LVEF > 0.5	Total
Troponin > 0.6 ng/ml	4 (40 %)	2 (20 %)	6 (60 %)
Troponin < 0.6 ng/ml	0 (0 %)	4 (40 %)	4 (40 %)
Total	4 (40 %)	6 (60 %)	10 (100 %)

Measurement of agreement	Kappa	Value	Asymp. std. error[a]	Approx. T[b]	Approx. sig.
		0.615	0.225	2.108	0.035
No. of valid cases		10			

[a] Not assuming the null hypothesis
[b] Using the asymptotic standard error assuming the null hypothesis

Table 3 Hemodynamic data from septic patients within 12 h of admission to the ICU (*D* dobutamine, *N* norepinephrine, *HR* heart rate, *CI* cardiac index, *LVSWI* left ventricular stroke work index, *PCWP* pulmonary capillary wedge pressure, *SVRI* systemic vascular resistance index, *MV* mechanical ventilation)

Patient	Drugs (μg/kg per min)	HR (beats/min)	MAP (mm Hg)	CI (l · min–1 · m–2)	LVSWI (g · m · m^{-2})	PCWP (mm Hg)	SVRI (dyne · s · cm–5 · m^{-2})	MV
VF	None	150	90	4.6	30	19	1419	No
TM	D 4.8 N 0.9	137	58	5.6	25	12	651	Yes
GM	None	110	67	4.8	27	21	708	Yes
VF	D 5.4	125	99	5.4	45	21	1241	No
LC	D 3.9 N 0.1	125	50	3.2	10	21	864	Yes
YP	D 12.5	117	84	4.4	32	20	1371	No
AL	None	92	103	6.6	71	30	1119	No
MC	D 18.8 N 0.47	117	59	4.4	19	22	796	Yes
SS	None	115	63	3.1	20	8	1445	Yes
AO	D 10.4	109	64	3.1	19	14	1380	Yes

Results

We observed a 40 % incidence of sepsis-induced cardiac dysfunction among our septic patients. TnI detected all patients with a low ejection fraction. In two patients with normal left ventricular function, TnI was also elevated, suggesting that they had minor myocardial damage that could not be detected by LVEF determinations. Table 2 shows the results of LVEF and serum levels of TnI in a 2 × 2 table. We had a 40 % mortality (four patients) and three of them had elevated TnI levels, whereas the remaining three patients with increased TnI levels survived and were discharged from the hospital.

Four patients did not receive inotropic support at the time of monitoring. The remaining six patients were receiving either dobutamine alone (three patients) or dobutamine in association with norerpinephrine due to hemodynamic instability. Pulmonary capillary wedge pressure was high (> 18 mmHg) in seven patients and was not related to myocardial dysfunction as assessed by echocardiography. The hemodynamic parameters of the patients are summarized in Table 3.

The cardiac index was in the normal range in three patients despite increased heart rate. The remaining seven patients had a high cardiac index which was not related to LVEF or TnI levels.

Discussion

Clinical studies have shown that myocardial contractility is reduced in sepsis and that this is associated with mortality [7]. However, detection of myocardial depression is difficult in septic patients. Echocardiogram-derived LVEF is widely used to assess LV function because it is noninvasive and commonly available [8, 9]. However, LVEF may not be ideal to identify myocardial dysfunction in these patients because of the well-known "unloading phenomenon" determined by cytokines, which tend to mask an eventual cardiac dysfunction due to reduced impedance to LV flow. Therefore, the

search for an ideal indicator for myocardial dysfunction in sepsis is still an ongoing and important issue.

The ability to detect myocardial injury in a noninvasive and readily available way might open a new avenue that would allow early identification of myocardial involvement by the septic process independent of indices that measure overall cardiovascular function and that reflect the net result of ventricle-vascular interaction such as LVEF or cardiac index. We hypothesized that TnI, a serum marker of myocardial injury utilized to detect myocardial ischemia [10], could identify myocardial injury in sepsis as well.

Cardiac function was assessed early in the course of the disease in ten septic patients by echocardiographic studies combined with simultaneous right-heart catheterization. Myocardial dysfunction, characterized by a low LVEF was observed in 40 % of the patients. These patients represented a spectrum from mild to severe illness, as their Acute Physiology and Chronic Health Evaluation II score ranged from 9 to 43. Myocardial dysfunction characterized by a low LVEF (< 50 %) was observed in 40 % (four patients).

TnI was elevated in 60 % of these patients. This included all four patients with low LVEF and an additional two patients with LVEF > 60 %. This suggests that besides identifying patients with evolving cardiac failure, TnI, by detecting minor myocardial damage in stages that could perhaps be incipient, may also identify patients with myocardial injury with "compensated" overall cardiac performance in stages with normal or near normal LVEF.

Among critically ill patients, recognized cardiac dysfunction is an independent predictor of hospital mortality. A recent report has correlated elevated levels of serum TnI with a higher mortality in early sepsis [11]. Although this study included a sample of ten patients and LVEF and TnI were determined only once in the course of the disease, the exciting results obtained make this biochemical marker a very promising tool for the easy and practical identification of myocardial injury in sepsis. Further studies are necessary to confirm these findings.

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