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Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study

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Abstract *Objective:* To ascertain if, after an episode of hypotension, unnoticed myocardial necrosis could occur in critical care patients with acute non-cardiac illness and to search for signs of cardiac necrosis.
Design: A prospective observational study.
Setting: General intensive care unit (ICU) at a tertiary level hospital.
Patients: Thirty-one patients in two groups. Group 1 included 19 patients with severe sepsis/septic shock (ACCP/SCCM Consensus Conference). Group 2 included 12 patients with hypovolemic shock.
Interventions: Biochemical markers of myocardial necrosis (cardiac troponin I (cTnI), creatine kinase (CK), creatine kinase MB mass (CKMB) and myoglobin) were measured at 12 h (T1), 24 h (T2) and 48 h (T3) after enrollment. A standard 12-lead ECG was recorded upon enrollment (T0) and at T2. Anomalous Q-waves or ST segment depression or elevation was considered diagnostic for acute myocardial infarction (AMI). A hypotensive episode (arterial systolic pressure < 90 mmHg at heart rate > 100 bpm) was considered moderate if it lasted 30–60 min or severe if longer than 60 min.
Measurements and results: At T0 none of the patients had AMI on ECG. At T2 a non-Q AMI developed in five patients. Increased levels of troponin I, myoglobin, CK and CKMB were found in 74.2 %, 96.8 %, 74.2 % and 67.7 % of the patients, respectively. Cardiac troponin I increased in 11 out of 19 septic patients and in all hypovolemic patients. There was a significant difference between the groups ($p < 0.05$). All biochemical markers increased in relationship to the degree of hypotension with cTnI again showing a significant difference. The longer the hypotensive episode was, the greater was the increase (moderate hypotension: median 1.16; quartiles 0.55–3.44 ng/ml, severe hypotension: median 8.53; quartiles 1.1–20.7 ng/ml; $p < 0.05$). Abnormal levels of cTnI were more frequent in non-survivors than in survivors ($p < 0.05$).
Conclusions: Hypotension may cause cardiac damage in critically ill patients with acute non-cardiac diseases as shown by abnormal levels of cTnI. It is likely that a high number of these myocardial necroses may go unnoticed on the ECG.

Key words Shock · Sepsis · Hypovolemia · Cardiac troponin I · Myocardial necrosis

Introduction

Critical care patients are exposed to a high degree of non-cardiac stress, which increases myocardial oxygen consumption [1]. At the same time, the myocardial oxygen supply may be reduced by hypotension, tachycardia, hypoxemia, anemia and, in some patients, intrinsic coronary artery disease [2]. An unexpectedly high incidence of clinically unrecognized myocardial injury, according to elevated levels of cardiac troponin I (cTnI), has been reported in the critically ills [3, 4, 5]. Troponin I is a myocardial regulatory protein that is present at increased levels in plasma following myocardial damage [6, 7, 8]. Abnormally high troponin I values are often associated with the occurrence of hypotensive episodes [5, 9] and higher morbidity and mortality rates [4, 5]. Hypovolemia may play a role in troponin release from the cardiomyocytes. Subendocardial hemorrhages and necrosis have been found in the myocardium of severely injured patients after fatal hypovolemic shock [10].

Abnormally high troponin T values have been found in sepsis [11]. Myocardial dysfunction is reported to be an important factor contributing to the high mortality in septic patients [12]. During septic shock the coronary circulation displays abnormalities similar to those of the systemic circulation. A maldistribution of nutritive blood flow and a disturbance in convective and diffusive oxygen delivery (DO_2), as reflected by abnormally high coronary sinus oxygen content and low oxygen extraction, have been reported in both human and animal studies [13, 14, 15]. The resulting imbalance of DO_2 and oxygen consumption (VO_2) can raise the possibility of myocardial ischemia [16, 17]. The results of human post-mortem studies showed the presence of large areas of myofibrillar necrosis in the septic myocardium [18].

The aim of this study is to determine whether critically ill patients with non-cardiac illness sustain "unnoticed" myocardial necrosis after a hypotensive episode of septic or hypovolemic origin.

Materials and methods

Patients

We conducted a prospective observational study in a general intensive care unit (ICU) from October 15,1997 to May 15,1998. Patients were enrolled in two groups according to the following inclusion criteria: group 1 (G1): patients with severe sepsis/septic shock, as defined by the ACCP/SCCM Consensus Conference [19]; group 2 (G2): patients with hypovolemic shock (arterial hypotension and central venous pressure (CVP) < 5 cmH_2O). Patients who had had external heart massage, defibrillation or electrical cardioversion in the previous 7 days [20], symptoms and/or ECG signs typical of acute myocardial infarction (AMI) at enrollment, complete left branch block on ECG or chest trauma in the previous 7 days [20] were excluded from the study.

Cardiac markers

We measured the plasma concentration of cardiac troponin I(cTnI), creatine kinase (CK), creatine kinase MB mass (CKMB) and myoglobin. Blood was taken at 12 h (T1), 24 h (T2) and 48 h (T3) after enrollment (T0); plasma was immediately separated and stored at –20 °C until analysis. Because the time between the onset of hypovolemia or sepsis and enrollment varied considerably among patients, the peak values of biochemical markers were considered for data analysis.

The cTnI assay was performed by immunoassay method (OPUS, Dade-Behring Diagnostics). The minimum detection limit of the assay was 0.5 ng/ml (according to the manufacturer information), thus abnormal values were defined as higher than 0.5 ng/ml [21]. The upper limit of the reference range was 2.5 ng/ml [22]. Any blood level above 2.5 ng/ml was considered indicative of acute myocardial injury, while levels below 2.5 ng/ml defined the presence of minor myocardial injury.

The recommended manufacturer lower limits for CK, CKMB (mass) and myoglobin assays were 200 UI/ml, 5 ng/ml and 80 ng/ml, respectively. These values were confirmed by local laboratory experience.

Hypotension grading

A hypotensive episode was assessed by arterial systolic pressure (Psyst) lower than 90 mmHg at a heart rate above 100 bpm. Hypotensive episodes were considered non-significant if they lasted less than 30 min, moderate if 30–60 min in duration, and a duration of more than 60 min was considered severe.

Severity score

We documented the number and severity of organ dysfunction at T0 according to the Multiple Organ Dysfunction Score (MODS) [23].

Electrocardiogram

A standard 12-lead ECG was recorded at T0 and T2. The ECG criteria of Q and non-Q AMI [24] were based on the presence of any new anomalous Q wave (≥ 30 ms and ≥ 0.2 mV), or ST segment elevation or depression (≥ 0.10 mV) in at least two of the following leads: a) D2, D3 or aVf; b) V1–V6; c) D1, aVl. Patients with nonspecific ST-T segment changes (e.g. left ventricular hypertrophy, drugs) were enrolled only if unmodified with respect to previous baseline traces.

Clinical diagnosis of acute myocardial infarction

Localized or radiating substernal or epigastric pain accompanied by weakness, sweating, nausea, vomiting, anxiety or any otherwise unexplained sudden-onset breathlessness or loss of consciousness with cardiovascular collapse was considered compatible with AMI [25].

Anemia

Severe anemia was defined as a hemoglobin level of less than 7 g/dl.

Table 1 Clinical features of the 31 patients divided in two groups: G1: severe sepsis/septic shock and G2: hypovolemic shock

	G1 Severe Sepsis Septic Shock (n = 19)	G2 Hypovolemic Shock (n = 12)
AGE	56.2 ± 4.14	70.8 ± 3.62 P = 0.02
Coronary artery disease (CAD)		
history of CAD	2	5
risk factors	9	2
smoke	4	–
obesity	1	–
diabetes	2	–
hypertension	3	2
Clinical diagnosis at ICU admission		
pneumonia	6	–
trauma	5	6
head	1	–
thorax	2	–
abdomen	2	2
pelvis	1	3
femur	–	3
humerus/tibia	1	–
major surgery	4	6
abdominal	4	4
vascular	–	1
orthopedic	–	1
miscellaneous	4	–
severe burns	1	–
disseminated leptospyrosis	1	–
infective endocarditis	1	–
sepsis after liver transpl.	1	–
Skeletal muscle injury	14	12
trauma/surgery	10	12
infectious	4	–
Rhabdomyolisys	3	–

Table 2 Characteristics of the patients at enrollment (T0); G1: severe sepsis/septic shock G2: hypovolemic shock

	G1 Severe sepsis Septic Shock (n = 19)	G2 Hypovolemic Shock (n = 12)
Psyst (mm Hg)	96.4 ± 6.2	80.4 ± 6.8
PaO2/FiO2 ratio	198 ± 21	270 ± 42
MODS Score (pts)	8.26 ± 0.89	7.36 ± 0.74
N. of Organs	4.00 ± 0.25	4.18 ± 0.40
Dopamine	n = 9	n = 9
(γ/kg × min)*	5.5 (5.0–8.3)	10.0 (8.1–11.0)
Norepinephrine	n = 13	n = 2
(γ/kg × min)*	0.52 (0.32–0.93)	0.29 (0.21–0.37)
Hypotension grading		
absent	6	0
mild to moderate	3	6
severe	10	6
Anemia	0	6

* values are reported as median and quartiles

Outcome

Clinical outcome evaluation was the in-hospital mortality.

Data analysis

Data are presented as means ± SDs. The plasma concentrations of cardiac markers are presented as median and quartiles, due to non-normal distribution. Continuous normally distributed variables were compared using one-way analysis of variance, and the Mann-Whitney U-test was utilized for non-normally distributed variables. cTnI values lower than 0.5 ng/ml were arbitrarily fixed at 0.5 ng/ml to allow statistical comparison. The χ^2 test was used to compare categorical variables. The Kendall tau (τ) coefficient was calculated to correlate both the duration of hypotension and patient outcome (non-survivors = 1; survivors = 0) with abnormal cTnI levels. A p value less than 0.05 was considered statistically significant.

Results

Thirty-one patients, 19 with severe sepsis/septic shock and 12 with hypovolemic shock, were enrolled in the study. The patients' main clinical features are summarized in Table 1. Overall, septic patients were younger than hypovolemic patients ($p = 0.02$) and had a lower incidence of pre-existing coronary artery disease (2 patients in G1 and 5 patients in G2). The main diagnostic categories were pneumonia (6 patients), multiple injuries (11 patients) and major surgery (10 patients). Two patients who were admitted with thoracic trauma developed sepsis after 14 and 11 days, respectively. Twenty-six patients suffered from acute skeletal muscle damage, ranging from a mild form to severe rhabdomyolysis (3 patients). In three patients the muscular injury followed as a consequence of a severe infection (2 *Legionella pneumophila* and 1 disseminated leptospirosis). The characteristics of the two groups at enrollment are shown in Table 2. Both groups had comparable MODS scores and number of affected organs. Septic patients had a higher, although not significantly so, Psyst (96.4 ± 5.9 mmHg) and a lower PaO_2/FIO_2 ratio (198 ± 21) than hypovolemic patients (Psyst: 80.4 ± 6.8 mmHg; PaO_2/FIO_2: 270 ± 42). Severe anemia due to acute hemorrhagic shock was present in six patients.

Table 3 Plasma concentrations of biochemical markers in the two groups of patients; plasma values of biochemical markers are reported as median and quartiles

	G1 Severe sepsis Septic Shock (n = 19)	G2 Hypovolemic Shock (n = 12)
cTnI	0.84 ng/ml (0.5–26.3 ng/ml)	4.20 ng/ml (1.1–11.2 ng/ml)
Myoglobin	2320 ng/ml (324–4840 ng/ml)	2117 ng/ml (1095–6610 ng/ml)
CK-MB	6.91 ng/ml (4.0–29.7 ng/ml)	8.62 ng/ml (4.2–64.2 ng/ml)
CK	624 UI/ml (153–1430 UI/ml)	684 UI/ml (199–2331 UI/ml)

Electrocardiographic pattern

At T0 no signs of AMI on ECG were recognized in any of the patients. A normal ECG (16 in G1 and 7 in G2) was observed in 23 patients. Eight patients (3 patients in G1 and 5 patients in G2) had a precordial ST segment elevation of less than 1 mm related to the presence of left ventricular hypertrophy, as confirmed by previous baseline ECG recordings. Four anterior and one postero-basal non-Q AMI developed at T2 in four patients in G1 and one patient in G2 who had had normal ECGs previously. Two of the patients had a history of coronary artery disease. The postero-basal AMI was later confirmed post mortem.

Cardiac markers

Increased levels of myoglobin, CKMB and CK were observed, respectively, in 96.8 %, 67.7 % and 74.2 % of the patients. Their median concentration was higher in G2 than in G1 (Table 3). An abnormal cTnI level was found in 74.2 % of the patients (23 of 31), with a 58 % (11 of 19 patients) and 100 % incidence in septic and hypovolemic patients, respectively ($p < 0.05$). Median cTnI levels were higher, although not significantly so, in G2 than in G1 (Table 3). Values above 2.5 ng/ml were found in 14 patients (6 in G1 and 8 in G2). Patients with histories of coronary artery disease all had abnormal cTnI values (4.97 ng/ml; 0.76–13.0 ng/ml). Cardiac troponin I peaked at T1 in 11 out of 23 patients and at T2 in 8 patients.

Hypotension and cardiac markers

At T0 arterial hypotension, irrespective of the diagnostic group, was present in 25 out of 31 patients (80.6 %). Besides all hypovolemic patients, 13 of the septic patients were hypotensive due to septic shock. In the hypotensive patients the median concentration of the cardiac markers increased with the duration of hypotension (Table 4), and cTnI in particular was significantly higher in severe (8.53 ng/ml; 1.1–20.7 ng/ml), than in mild hypotension cases (1.16 ng/ml; 0.55–3.44 ng/ml; $p < 0.05$). Patients with severe hypotension also had higher cTnI levels than normotensive patients ($p < 0.05$). The duration of hypotension correlated with abnormal cTnI values (Kendall's $\tau = 0.48$; $p < 0.001$). Notably, a normal cTnI level was recorded in five of six patients when hypotension was absent.

In the six patients with hemorrhagic shock, cTnI levels were higher (7.57 ng/ml; 2.07–15.1 ng/ml) than in patients who were only hypotensive (1.26 ng/ml; 0.74–9.87 ng/ml).

All hypotensive patients needed catecholamines at enrollment: ten patients received dopamine (median 10.5; quartiles 8.1–12.0 γ/kg · min) and seven patients norepinephrine only (0.56; 0.37–1.76 γ/kg · min) while the last eight needed both (dopamine 5.5; 5.1–7.8 γ/kg · min, and norepinephrine 0.34; 0.24–0.66 γ/kg · min). At T3 twelve patients still received catecholamines.

Table 4 Plasma concentrations of biochemical markers with respect to duration of hypotension. Values are reported as median and quartiles

	No Hypotension (n = 6)	Mild Hypotension (n = 9)	Severe Hypotension (n = 16)
cTnI	0.5 ng/ml (0.5–0.5 ng/ml)	1.16 ng/ml (0.55–3.44 ng/ml)	8.50 ng/ml (§) (*) (1.1–20.7 ng/ml)
Myoglobin	372 ng/ml (177–388 ng/ml)	2240 ng/ml (1240–3170 ng/ml)	3002 ng/ml (§) (773–9485 ng/ml)
CK-MB	5 ng/ml (2.9–16.2 ng/ml)	8.3 ng/ml (5.2–14.1 ng/ml)	16.5 ng/ml (3.7–50.1 ng/ml)
CK	249 UI/ml (77–1586 UI/ml)	388 UI/ml (178–894 UI/ml)	705 UI/ml (358–1466 UI/ml)

(§) P < 0.05 with respect to "No Hypotension"
(*) P < 0.05 with respect to "Mild Hypotension"

Electrocardiogram and cardiac troponin I

The ECG failed to identify 18 of 23 patients with elevated levels of cTnI. It was diagnostic in 3 of 14 patients with acute myocardial injury and in only 2 of 9 patients with minor myocardial injury. Patients with non-Q AMI on ECG were more severely ill at enrollment (MODS score: 12.0 ± 1.7 vs 6.4 ± 0.5; $p < 0.0005$), and had higher, although not significantly so, cTnI levels (26.3 ng/ml; 1.47–27.2 ng/ml) than patients with unnoticed myocardial injury (4.97 ng/ml; 1.16–13.0 ng/ml).

Outcome

Sixteen patients died while in hospital (10 patients from G1 and 5 from G2). The deceased patients had higher serum cTnI levels (4.2 ng/ml; 1.0–23.4 ng/ml) than survivors (0.78 ng/ml; 0.5–11.4 ng/ml), although these differences were not statistically significant. An unfavorable outcome correlated slightly with abnormal cTnI values (Kendall's $\tau = 0.28$; $p < 0.05$).

Discussion

A low sensitivity of ECG in diagnosing the occurrence of acute myocardial injury has been reported in the critically ills [26, 27]. Both ST segment and T wave abnormalities may occur as a consequence of drug treatment, acid-base disturbance and electrolyte imbalance. A high frequency of non-specific ECG abnormalities had previously been observed in an ICU population of injured patients [28]. Although our ECG criteria had been able to recognize up to 86% of AMI from a large database study [24], only a small percentage of patients with myocardial injury was diagnosed in the present study. This ECG insensitivity supports our hypothesis that unnoticed myocardial damage may occur in critically ill patients with acute non-cardiac illness after a hypotensive episode. Previous studies [3, 4, 5] showed an unexpectedly high incidence of clinically unrecognized myocardial injury in the critically ills. The incidence of abnormally high cTnI values in these studies varied from 15 to 70%, depending on the cut-off [3, 4, 5]. Patients with elevated cTnI levels were more frequently hypotensive and in need of mechanical ventilation and inotropic support [5, 9]. Finally, increased morbidity and mortality were noted [3, 4, 5]. Surely the extreme sensitivity of cTnI assessment [6, 7, 8], which can reveal even minor cardiac injuries, may have overemphasized the ECG insensitivity in our study. Moreover, we did not record the ECG at any time point other than T2 , thus further lowering its diagnostic accuracy. However it should be noted that the majority of myocardial necrosis occurred within 24 h from enrollment, as shown by cTnI peak levels.

The main finding in this study is the relationship between the duration of hypotension and cTnI levels: the longer the hypotensive episode was, the higher was the cTnI elevation ($p < 0.05$). Arterial pressure is one of the most important determinants of myocardial blood flow. When systolic pressure falls below 80 mmHg, loss of the coronary "self-regulation" ensues and the potential for myocardial ischemia and infarction exists [29].

A lower, although not significantly so, cTnI level was observed in septic, than in hypovolemic, patients. This was quite surprising, because a higher troponin I level was expected in the septic, than in the hypovolemic, group. We speculated that in septic shock the maldistribution of coronary blood flow might produce, for a given level of hypotension, higher amounts of myocardial damage and, consequently, higher levels of troponin I than in hypovolemic shock. However, in the present study the septic patients were significantly younger ($p < 0.05$) and with a lower incidence of pre-existing coronary artery disease than the hypovolemic patients, so that a higher coronary reserve could be expected in the septic group. Moreover their Psyst values at enrollment were higher, although not significantly so, than in hypovolemic patients. Therefore we argue that septic patients could have a smaller extent of myocardial injury and, in consequence, lower levels of cTnI. Unfortunately the small number of subjects studied did not allow us to stratify patients according to the level of hypotension in order to check this hypothesis.

Myocardial lesions, indistinguishable from acute ischemia, have been observed post-mortem in patients who had received catecholamines for a prolonged period [30]. Beta-agonists seem to be more often involved although lesions have also been reported with alpha-agonists [31]. Serious cardiac complications, such as ischemia and infarction, occurred after administration of both intravenous and nebulized beta-agonists [32, 33]. Furthermore, the abuse of inhaled beta-agonists has strongly been associated with an increased risk of death from asthma [34]. Finally, acute myocardial damage has been observed in patients after exposure to high doses of endogenous catecholamines as occurs in pheochromocytoma and severe head injury [35, 36]. Recently, an association of enhanced systemic DO_2 (achieved with the use of dobutamine) with increased mortality from cardiac events related to secondary myocardial injury in the critically ills has been suggested [17]. In the present study the majority of hypotensive patients received catecholamines, thus the concurrent role of the latter in producing myocardial injury cannot be excluded. However it should be noted that in most patients the administered dose of sympathomimetics was within the usual clinical range and that myocardial injury was present within 24 h from enrollment in 19 out of 23 patients.

Myoglobin, CK and CKMB rose in hypotensive, as well as in normotensive, patients. This result is explained by the high proportion of patients suffering from acute skeletal muscle injury (Table 1) and by the relative lack of specificity for myocardial injury of these biochemical markers with respect to cTnI [6, 7, 8]. As in previous studies [4, 5] we observed a higher proportion of abnormal values of cTnI in non-survivors ($p < 0.05$), but whether this is a cause or an effect of their acute conditions remains to be answered by further studies.

In conclusion, hypotension may cause cardiac damage in critically ill patients with acute non-cardiac diseases, as shown by abnormal levels of cTnI. It is likely that a high number of these myocardial necroses may go unnoticed on ECG.

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