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N-terminal-pro-brain natriuretic peptide elevations in the course of septic and non-septic shock reflect systolic left ventricular dysfunction assessed by transpulmonary thermodilution

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ABSTRACT

Background: The cardiac correlates, if any, of N-terminal probrain natriuretic peptide (NT-proBNP) levels in septic and non-septic shock patients remain controversial.
Methods: In the 38 septic and 22 non-septic shock patients in the transpulmonary thermodilution arm of a previous 2-center randomized controlled trial comparing pulmonary artery catheterization with transpulmonary thermodilution, serial (daily for 3 days) and paired measurements (n = 145) were obtained of NT-proBNP and transpulmonary dilution variables as global ejection fraction (GEF), left ventricular preload-recruitable stroke work (PRSW) and diastolic compliance.
Results: Elevated NT-proBNP inversely related to low GEF and PRSW in pooled data ($r = -0.45$, $P < 0.001$). The 72 h course of NT-proBNP was inversely associated with PRSW, independent of age, gender, creatinine, norepinephrine treatment and diastolic compliance, without differences between septic and non-septic shock. Over the 72 h study period, NT-proBNP levels were higher in 28 day non-survivors than survivors, independent of type of shock and disease severity.
Conclusions: In septic and non-septic shock, NT-proBNP elevations reflect systolic left ventricular dysfunction and are associated with a poor outcome. They may help recognition of cardiac dysfunction in shock and its management when invasive hemodynamic monitoring is not yet instituted.

1. Introduction

The causes and consequences of plasma elevations of the cardiac N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the critically ill remain highly controversial, partly because many factors may be involved [1–3]. Elevated levels have been used, with varying success, to help diagnosing the cause of respiratory insufficiency [3–10] and to prognosticate outcome of critical illness after surgery or sepsis [9,11–28], among others. In contrast, shock and hypovolemia are expected not to increase the hormone levels, because of decreased cardiac wall stress (increased stiffness may be pivotal in releasing natriuretic peptides [29]), unless associated with cardiac disease or involvement [6,13,30–32]. In sepsis-like conditions, a key issue is whether BNP or its prohormone is a marker of the inflammatory response [2,12,18,31,33,34], or of diastolic or systolic cardiac dysfunction [11,14,23,24,35] or both [32,36]. Indeed, endotoxin injection or sepsis may elevate NT-proBNP even without hemodynamic changes or cardiac dysfunction [33,37].

Methods to evaluate cardiac function in the critically ill to elucidate the mechanisms of (NT-pro)BNP release included echocardiography [1,4,6,8,10,11,14,15,20,24,32,33,36] and pulmonary artery catheterization [3–5,7,10,13,16,34,38] but many studies did not look at both diastolic and systolic function indices nor compared septic and non-septic patients with different etiology and severity of cardiac disease [1,4,8,11,13,15,20,21,24,26,32,33,35,38]. In any case, the relation between filling pressures of the heart and NT-proBNP levels was poor at best [3–5,7,9,10,11,25,33]. Many studies used single admission values rather than courses over time [1,4,5,15,19,23,32], while confounding by age, gender, obesity, renal disease, and treatment [1] has not always been taken into account [2,3,7,15,20,26,33]. Serial measurements have been obtained in only few studies and some addressed the changes in cardiac filling and function in time and their relation to BNP levels, which was sometimes poor [3,24,33,38].

In contrast, we evaluated cardiac function by transpulmonary thermodilution (TPTD) and suggested that NT-proBNP elevations inversely related to, primarily, systolic rather than diastolic function parameters, both in sepsis and non-sepsis [39]. The latter study included

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systolic function indices as the global ejection fraction (GEF), ie stroke volume divided by global end-diastolic volume, and preload-recruitable stroke work index (PRSW), represented by the ratio of left ventricular stroke work to end-diastolic volume, which may be less dependent on (after)loading than the GEF [39–41]. As a diastolic function index the end-diastolic volume to pressure ratio (compliance) can be used [39]. The study [39], however, was relatively small (18 sepsis patients not in shock) and lacked longitudinal measurements to answer the question whether NT-pro BP levels in the course of time indeed reflect changes in left ventricular function.

Because of the continuing controversies, we set out to serially evaluate NT-proBNP levels in TPTD-monitored shock patients of septic and non-septic origin. The hypothesis was that the hormone levels better reflect systolic than diastolic indices of cardiac dysfunction both in septic and non-septic shock.

2. Patients and methods

This is a randomized, non-blinded, 2-centre clinical trial conducted in intensive care units (ICUs) in The Netherlands from February 2007 to July 2009 (trial registration number: NL14119.029.06, CCMO, The Netherlands) reported previously [42]. Patients meeting inclusion criteria were randomly assigned to receive either a TPTD or pulmonary artery catheter when inclusion criteria for advanced hemodynamic monitoring were met. For the current research we only included the TPTD arm of the study and therefore only describe the protocol followed in this arm of the study. The medical ethics committee at each study center had approved of the protocol.

2.1. In- and exclusion criteria

In brief, patients were eligible when they were on mechanical ventilation with an expected stay in the ICU >48 h in the presence of shock, indicating a clinical reason for invasive hemodynamic monitoring. We consecutively included patients in septic and non-septic shock. Shock was defined by acute circulatory failure characterized by persistent arterial hypotension defined as a mean arterial pressure <65 mm Hg (or <80 mm Hg with previous hypertension) despite assumingly adequate volume resuscitation and/or the need for vasopressors to maintain a mean arterial pressure ≥65 mm Hg (or ≥80 mm Hg in case of known hypertension). Septic shock was defined by shock plus two or more of the following for systemic inflammatory response syndrome criteria: abnormal body temperature (>38 °C, <36 °C), tachycardia (>90 beats/min), mechanical ventilation, and abnormal white blood cell counts (≤4 or ≥12 × 10^9 /L or >10% immature bands) plus a clinically evident and/or microbiologically proven focus on infection. Non-septic shock was shock after 1) (surgery for) major trauma (Injury Severity Score >25, without documented traumatic brain injury); 2) elective and emergency major abdominal surgery (including esophageal or gastric resection, liver surgery, pancreatic surgery, colorectal surgery); 3) cardiac surgery (coronary bypass surgery, aortic root and/or valvular surgery); 4) major vascular surgery (aorta and iliac/mesenteric reconstructions); and 5) cardiogenic shock or terminal congestive heart failure. There were no patients with obstructive shock caused by pulmonary embolism. Exclusion criteria were age <18 or >80 years, pregnancy, preterminal illness with life expectancy <24 h, therapeutic hypothermia after cardiac arrest, traumatic brain injury, known (unrepaired) cardiac or vascular aneurysms, bifemoral vascular surgery or known pulmonary hypertension.

2.2. Study protocol

In brief, the TPTD catheter (PiCCO; Pulsion Medical Systems AG, Munich, Germany) was inserted in the femoral artery. Fluid resuscitation and hemodynamic management was guided by TPTD-derived parameters according to a predefined algorithm [42], up to 72 h after enrollment. Fluid challenges were performed by synthetic colloids at a dose of 250–500 mL per 30 min when indicated clinically and according to the TPTD parameters defining upper limits of safe infusion. Fluid challenges were withheld when the safety limits by TPTD monitoring had been reached and when there was ≥10% rise in cardiac output. Norepinephrine was the vasopressor drug of first choice in our ICU's, which was continuously infused and dosed on the basis of hemodynamic responses. End points of resuscitation, reflecting adequacy of hemodynamic management, were mean arterial pressure ≥65 mm Hg (or ≥80 mm Hg in case of known hypertension), $S_{cv}O_2$ ≥70%, lactate clearance, diuresis ≥0.5 mL/kg/h (unless development of intrinsic renal failure), and restoration of peripheral perfusion deficits.

2.3. Therapeutic protocol

All patients were pressure-controlled ventilated (Servo-*i*, Maquette, Sweden or Evita 4, Dräger, Lübeck, Germany), aiming at tidal volumes <8 mL/kg predicted body weight and positive end-expiratory pressure was dosed (≤20 cm H_2O) to maintain arterial PO_2 ≥65 mm Hg at an inspiratory O_2 fraction of about 40%. Pressure-controlled ventilation was changed into pressure-support ventilation when clinically justified. Weaning was attempted through clinical protocols. After 72 h, vasopressors and inotropic drugs were administered and dosed on clinical grounds. Sedatives, analgesics, and antibiotics were also prescribed by attending physicians according to clinical guidelines. Systemic corticosteroids were initialized in case of persistent vasopressor-dependent septic shock, defined as a norepinephrine dose >1 mg/h.

2.4. Data collection, measurements and assays

Hemodynamic measurements were done at the mid chest level with patients in supine position, after calibration and zeroing to atmospheric pressure, at least every 24 h (0, 24, 48 and 72 h after enrolment). These included measurements of mean arterial pressure (MAP, mm Hg) via routine radial artery catheter, central venous pressure (CVP, mm Hg) and TPTD parameters. The latter were performed through an injection of a 20-mL ice-cold (4 °C) saline bolus through a central venous catheter. Measurements were obtained in triplicate and averaged, including cardiac output and global end-diastolic volume, indexed to body surface yielding cardiac index (CI) and global end-diastolic volume index (GEDVI, n 680–800 mL/m^2), respectively. Global ejection fraction (GEF, n 25–35%) was calculated from stroke volume (CI/heart rate)/GEDVI/4, a measure of left ventricular ejection fraction in the absence of severe right heart dysfunction [43,44]. Left ventricular stroke work (LVSWI, n 45–60 cJ/m^2) was calculated from mean arterial pressure times stroke volume index (×0.0136). PRSW was derived from LVSWI/GEDVI/4 (or MAP × GEF, n 20–30 mm Hg), a relatively load-independent measure of left ventricular function in the absence of severe right heart dysfunction [40,41], and diastolic compliance from GEDVI/CVP, mL/mm Hg/m^2. Arterial blood samples were taken at least every 24 h, at baseline, and up to 72 h after enrollment. Lactate (n < 2 mmol/L) and creatinine levels (n < 130 μmol/L) were measured (i-STAT 1, Abbott, Abbott Park, IL, USA and Boehringer-Mannheim Hitachi analyzers 911 and 747, Almere, The Netherlands). For measurement of NT-proBNP plasma levels blood was collected in tubes containing EDTA. Within 2 h, blood samples were centrifuged for 10 min at 3000 rpm at ambient temperature. Plasma was stored at −80 °C until analyzed. An electrochemiluminescence immunoassay for NT-proBNP was performed with the Modular analytics E170 system (Roche, Mannheim, Germany). The upper limits of normal for healthy volunteers (95th percentile) according to the manufacturer's recommendations for age were 97.3 pg/mL (18–44 years), 121 pg/mL (45–54 years), 198 pg/mL (55–64 years), 285 pg/mL (65–74 years), and 526 pg/mL (≥75 years). The lower detection limit was 5 pg/mL. The upper detection limit of the assay for diluted samples was 70,000 pg/mL. Doses and types of inotropic/vasopressor drugs were registered. Daily

measured clinical and laboratory variables allowed calculation of Sequential Organ Failure Assessment (SOFA score). Patients were followed until death or hospital discharge.

2.5. Statistical analysis

The main study parameters were non-normally distributed (Kolmogorov–Smirnov test $P < 0.05$) and logarithmically converted before analysis. Baseline variables were compared with Student-t, Mann–Whitney U or Fisher exact test, where appropriate. We used generalized estimating equations (GEE) to study relations of NT-proBNP plasma levels with variables in time, taking repeated observations in the same patients into account. Standardized regression coefficients were calculated. Receiver operating characteristic curves (ROC) were constructed to evaluate the predictive values of NT-proBNP levels and optimal cutoff values (Youden index) with associated sensitivity, specificity and positive and negative predictive values were calculated. All tests were two-sided and a $P < 0.05$ was considered statistically significant. Exact P values > 0.001 are reported. Data are summarized as mean ± standard deviation (SD).

3. Results

3.1. Patient characteristics

Table 1 summarizes patient data. Disease severity and in hospital mortality was higher in septic than in non-septic shock. Non-septic shock patients had more cardiac premorbidity. Within the 72 h observation period 9 septic patients had died and 2 had been discharged, so that, together with technical failures, 65 TPTD measurements and 68 NT-proBNP measurements at the 240 observation points were missing and 145 paired observations over time were available for analysis.

Table 1
Patient characteristics.

	Septic shock N = 38	Non-septic shock n = 22	P
Age, years	67 ± 19	69 ± 13	0.82
Male/female sex, no. (%)	20 (53)/18 (47)	15 (68)/7 (32)	0.29
Body mass index, kg/m^2	25 ± 4	27 ± 4	0.17
APACHE II	27 ± 13	24 ± 11	0.019
SOFA	10 ± 6	10 ± 4	0.77
Comorbidity			
Cardiovascular	11 (29)	16 (73)	0.001
Respiratory	3 (8)	0	0.29
Renal	4 (11)	2 (9)	1.0
Neurologic	3 (8)	1 (1)	1.0
Diagnostic group			
Sepsis, respiratory	13 (34)	-	
Abdominal	17 (45)	-	
Other	8 (21)		
Non-sepsis, nonsurgical	–	7 (32)	
Cardiac surgery	–	6 (27)	
Vascular surgery	–	4 (18)	
Trauma	–	1 (1)	
Other surgery	–	4 (18)	
Associated micro-organisms in sepsis			
Gram-positive	6 (16)	–	
Gram-negative	14 (37)	–	
Other	5 (13)	–	
Bacteremia	12 (31)	–	
Length of stay ICU, day	17 ± 18	30 ± 24	0.003
Mortality day 28	17 (45)	5 (28)	0.10
Mortality ICU	16 (42)	5 (28)	0.17
In-hospital mortality	20 (53)	5 (28)	0.031

Means ± SD or number (percentage), where appropriate. Abbreviations: APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure.

Table 2
Hemodynamic and biochemical values at baseline and 72 h.

		Septic shock N = 38	Non-septic shock n = 22	P
HR, /min	t = 0	107 ± 22	89 ± 19	0.002
	t = 72	91 ± 22	90 ± 14	0.75
CVP, mm Hg	t = 0	12 ± 6	12 ± 5	0.92
	t = 72	9 ± 4	11 ± 5	0.11
MAP, mm Hg	t = 0	78 ± 14	83 ± 18	0.30
	t = 72	87 ± 12	90 ± 16	0.42
GEDVI, mL/m^2	t = 0	779 ± 174	831 ± 217	0.31
	t = 72	759 ± 170	901 ± 232	0.041
Compliance, mL/mm Hg/m^2	t = 0	76 ± 40	79 ± 33	0.82
	t = 72	150 ± 158	106 ± 87	1.0
CI, L/min/m^2	t = 0	3.5 ± 1.3	2.9 ± 0.9	0.054
	t = 72	3.9 ± 1.1	3.4 ± 0.8	0.11
LVSWI, cJ/m^2	t = 0	34 ± 12	37 ± 12	0.47
	t = 72	53 ± 16	48 ± 16	0.36
GEF, %	t = 0	18 ± 7	17 ± 8	0.86
	t = 72	25 ± 8	19 ± 6	0.01
PRSW, mm Hg	t = 0	14 ± 5	14 ± 6	0.87
	t = 72	18 ± 7	15 ± 6	0.054
Norepinephrine, μg/kg/min	t = 0	0.53 ± 0.39	0.28 ± 0.28	0.027
	t = 72	.22 ± 0.33	0.11 ± 0.18	0.29
Lactate, mmol/L	t = 0	4.1 ± 3.0	3.4 ± 2.4	0.3
	t = 72	2.0 ± 1.2	1.4 ± 0.8	0.06
Creatinine, μmol/L	t = 0	174 ± 140	174 ± 99	0.99
	t = 72	138 ± 100	170 ± 101	0.27
Leukocytes, ×10^9/L	t = 0	13.1 ± 10.5	11.7 ± 10.7	0.54
	t = 72	17.5 ± 8.0	17.5 ± 22.0	0.99
NT-proBNP, pg/mL	t = 0	9028 ± 16,627	3986 ± 5450	0.48
	t = 72	3249 ± 5776	4691 ± 5192	0.89

Mean ± SD. Abbreviations: HR, heart rate; CVP, central venous pressure; MAP, mean arterial pressure; GEDVI, global end-diastolic volume index; CI, cardiac index; LVSWI, left ventricular stroke work index; GEF, global ejection fraction; PRSW, preload-recruitable stroke work.

3.2. NT-proBNP and cardiac function

In Table 2 the courses of hemodynamic and biochemical variables in the shock groups are summarized and compared. Septic shock patients had a more increased heart rate, higher CI, lower GEDVI and reversible depression of GEF and PRSW as compared to non-septic shock patients and yet their NT-proBNP levels did not differ. They also received higher norepinephrine doses. In Table 3, the standardized regression coefficients are reported for NT-proBNP levels versus general and cardiac variables. It shows that NT-proBNP levels are affected by age and PRSW in both septic and non-septic shock, and that creatinine levels

Table 3
Standardized regression coefficient for NT-proBNP versus general and cardiac variables over 72 h.

	Septic shock	P	Non-septic shock	P
General				
Age, years	0.41	0.004	0.38	0.028
Gender	–	0.99	–	<0.001
BMI, kg/m^2	0.08	0.48	−0.37	0.019
SOFA	0.17	<0.001	0.07	0.68
Creatinine, μmol/L	0.38	0.001	0.00	0.49
Norepinephrine, μg/kg/min	0.40	<0.001	0.13	0.16
Cardiac				
CVP, mm Hg	0.10	0.086	−0.03	0.38
GEDVI, mL/m^2	0.25	0.23	0.00	0.17
Compliance, mm Hg/mL/m^2	−0.09	0.016	0.16	0.28
LVSWI, cJ/m^2	−0.26	0.001	−0.16	0.085
GEF	−0.37	<0.001	−0.14	0.38
PRSW, mm Hg	−0.43	<0.001	−0.21	0.007

Abbreviations: BMI, body mass index; SOFA, sequential organ failure assessment; CVP, central venous pressure; GEDVI, global end-diastolic volume index; LVSWI, left ventricular stroke work index; GEF, global ejection fraction; PRSW, preload-recruitable stroke work.

Table 4
Multivariate generalized estimating equations to predict NT-proBNP over 72 h.

	Standardized regression coefficient	P
Age, year	0.17	0.07
Gender, m/f	–	0.08
BMI, kg/m^2	−0.10	0.23
Creatinine, μmol/L	0.19	0.006
Septic/non-septic shock	–	0.62
Norepinephrine, μg/kg/min	0.11	0.16
Compliance, mL/mm Hg/m^2	0.03	0.52
Preload-recruitable stroke work, mm Hg	−0.27	0.002

Abbreviations: BMI, body mass index.

and norepinephrine doses and thus SOFA scores were associated with the prohormone levels particularly in septic shock. In multivariate GEE (Table 4), NT-proBNP levels in the 72 h course of the study primarily related to PRSW, irrespective of shock origin and independently of other variables that could affect the prohormone level (Table 3). Fig. 1 shows the inverse linear correlation between the variables for pooled data, which were log-transformed for the sake of clarity. LVSWI ($r = -0.37$, $P < 0.001$) and GEF also inversely correlated to NT-proBNP ($r = -0.38$, $P < 0.001$). GEF and PRSW correlated at $r = 0.90$, $P < 0.001$ ($n = 175$).

3.3. Prediction

We took a GEF < 20% and a corresponding (from linear regression) PRSW <15 mm Hg as evidence for systolic cardiac dysfunction. The AUROC of NT-proBNP for GEF < 20% was 0.69 ($P < 0.001$), with 94% specificity, 36% sensitivity, 85% positive predictive value and 53% negative predictive value at a cutoff of 6248 pg/mL. The AUROC of NT-proBNP for PRSW <15 mm Hg was 0.72 ($P < 0.001$) with specificity of 55%, sensitivity of 82%, positive predictive value of 68% of and negative predictive value of 72% at a cutoff of 1480 pg/mL.

3.4. Mortality

Baseline NT-proBNP levels were higher in non-survivors than in survivors at day 28 ($P = 0.032$). Over the 72 h study period, NT-proBNP levels were higher in 28 day non-survivors than survivors ($P = 0.038$), independent of septic/non-septic shock ($P = 0.65$) and APACHE II score ($P = 0.29$). ICU and hospital non-survivors also had higher baseline NT-proBNP levels than survivors ($P = 0.06$).

4. Discussion

The current study suggests that NT-proBNP levels are elevated in septic and non-septic shock and associated, in time, with systolic rather than diastolic left ventricular dysfunction, assessed by TPTD. Elevations prognosticate a poor outcome.

We used the GEDVI as a parameter to normalize stroke volume and work, to yield a measure of GEF and PRSW, respectively, as done before [39]. Indeed, TPTD-derived function indices correlate with left ventricular function indices at echocardiography, in the absence of severe right heart dysfunction [43,44]. An argument in favor of the latter is the absence of a relation between CVP and NT-proBNP, since right ventricular overloading would increase both, even though NT-proBNP may be more sensitive to left than right ventricular dysfunction [6]. Moreover, the myocardial depression of sepsis affects right and left ventricles similarly [45], so that left ventricular dilatation is expected to contribute to GEDVI. Conversely, our results obtained longitudinally and in a relatively large cohort of septic patients, confirm the earlier finding of a relation between hormone levels and (TPTD-derived) indices of systolic rather than diastolic left ventricular dysfunction, irrespective of underlying condition (39). This is in line with some literature [4,5,11,15,20,23,24,32,35,36], but not with others suggesting a primarily inflammatory origin of increased plasma NT-proBNP levels in sepsis [2,12,31,33,34]. The inverse relation with LVSWI agrees with the literature [5]. Our data also agree with studies suggesting an inverse relationship between NT-proBNP elevations and fractional area contraction or ejection fraction

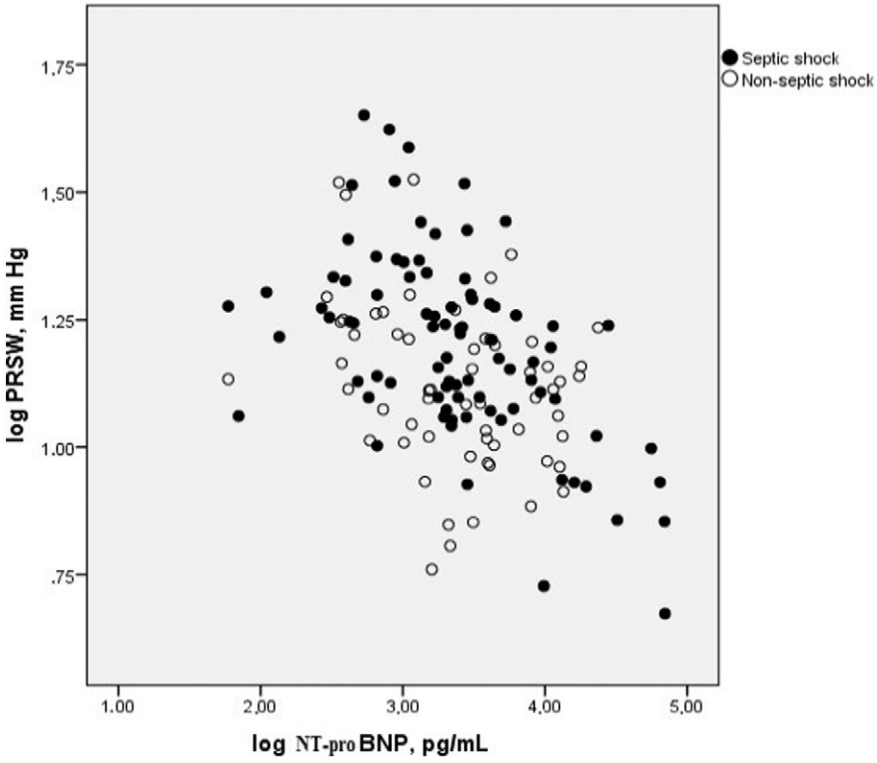

Fig. 1. Relation between (logarithmically converted) NT-proBNP levels and preload-recruitable stroke work (PRSW, mm Hg), for pooled data ($n = 145$) in the 72 h period: $r = -0.45$, $P < 0.001$.

(by echocardiography) in sepsis [4,11,14,24,36]. In our study, the inverse relation between NT-proBNP with PRSW was even somewhat stronger than that with GEF, suggesting that NT-proBNP is sensitive to changes in systolic cardiac function in sepsis, irrespective of loading conditions (40,41).

The current study, in contrast with our previous one [39], suggests no difference in left ventricular function between septic and non-septic shock patients. However, the myocardial depression of sepsis may have somewhat been obscured in this comparison because of more cardiac premorbidity and probably more frequent preexistent left ventricular dysfunction in the non-septic shock group. In any case, the higher NT-proBNP levels associated with septic shock than non-septic shock reported in the literature are not confirmed in the current study [31]. Postoperative elevations of NT-proBNP have been documented after cardiac, vascular and other types of surgery and to prognosticate postoperative (cardiac) complications, even though causes of the postoperative increases often remained obscure [9,12,16,17,25,26,28]. Our study suggests left ventricular dysfunction as a contributing factor when these postoperative patients manifest shock and need for postoperative resuscitation. This agrees with some studies [17], whereas others stressed the relationship with postoperative inflammatory changes and prognosis, at least after cardiac surgery [12]. Finally, in our cohort, NT-proBNP levels were of independent prognostic significance, regardless of underlying disease and its severity, as reported before [13–15,20,22–24,27,32,36].

Limitations of the study include the imperfect predictive values of increased NT-proBNP levels for low GEF and PRSW, possibly because of concomitant confounders or measurement errors (including that of TPTD). This should be weighted, in clinical practice, against the relative ease of the measurements and help in clinical decision making when, for instance, invasive hemodynamic monitoring is not yet applied. We did not evaluate cardiac function in the other arm of the randomized study, monitored with help of a pulmonary artery catheter, since this does not allow calculation of GEF and PRSW.

In conclusion, our current, serial data suggest that NT-proBNP elevations in critically patients with circulatory shock point to systolic left ventricular dysfunction, irrespective of the type of shock, and to a poor outcome thereof. They may help to recognize and follow cardiac dysfunction in shock and help its management, when invasive hemodynamic monitoring is not yet instituted.

Conflicts of interest

None.

Acknowledgments

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