



## Sepsis-Associated Myocardial Dysfunction\*

### Diagnostic and Prognostic Impact of Cardiac Troponins and Natriuretic Peptides

Micha Maeder, MD; Thomas Fehr, MD; Hans Rickli, MD; and Peter Ammann, MD

Myocardial dysfunction, which is characterized by transient biventricular impairment of intrinsic myocardial contractility, is a common complication in patients with sepsis. Left ventricular systolic dysfunction is reflected by a reduced left ventricular stroke work index or, less accurately, by an impaired left ventricular ejection fraction (LVEF). Early recognition of myocardial dysfunction is crucial for the administration of the most appropriate therapy. Cardiac troponins and natriuretic peptides are biomarkers that were previously introduced for diagnosis and risk stratification in patients with acute coronary syndrome and congestive heart failure, respectively. However, their prognostic and diagnostic impact in critically ill patients warrants definition. The elevation of cardiac troponin levels in patients with sepsis, severe sepsis, or septic shock has been shown to indicate left ventricular dysfunction and a poor prognosis. Troponin release in this population occurs in the absence of flow-limiting coronary artery disease, suggesting the presence of mechanisms other than thrombotic coronary artery occlusion, probably a transient loss in membrane integrity with subsequent troponin leakage or microvascular thrombotic injury. In contrast to the rather uniform results of studies dealing with cardiac troponins, the impact of raised B-type natriuretic peptide (BNP) levels in patients with sepsis is less clear. The relationship between BNP and both LVEF and left-sided filling pressures is weak, and data on the prognostic impact of high BNP levels in patients with sepsis are conflicting. Mechanisms other than left ventricular wall stress may contribute to BNP release, including right ventricular overload, catecholamine therapy, renal failure, diseases of the CNS, and cytokine up-regulation. Whereas cardiac troponins may be integrated into the monitoring of myocardial dysfunction in patients with severe sepsis or septic shock to identify those patients requiring early and aggressive supportive therapy, the routine use of BNP and other natriuretic peptides in this setting is discouraged at the moment. (CHEST 2006; 129:1349–1366)

**Key words:** cardiac troponins; myocardial dysfunction; natriuretic peptides; sepsis; septic shock

**Abbreviations:** ACS = acute coronary syndrome; ANP = A-type natriuretic peptide; APACHE = acute physiology and chronic health evaluation; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CHF = congestive heart failure; cTnI = cardiac troponin I; cTnT = cardiac troponin T; E/A = ratio of early peak flow velocity to atrial peak flow velocity; LVEF = left ventricular ejection fraction; LVFAC = left ventricular fractional area contraction; LVSWI = left ventricular stroke work index; NT-proANP = N-terminal-pro-A-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAC = pulmonary artery catheter; PCWP = pulmonary capillary wedge pressure; S/D = ratio of systolic to diastolic pulmonary vein flow velocity; SIRS = systemic inflammatory response syndrome

**Learning Objectives:** 1. Assess myocardial dysfunction in sepsis and early recognition for administration of optimal therapy. 2. Analyze the elevation of cardiac troponins in patients with sepsis, severe sepsis or septic shock. 3. Evaluate the relationship between BNP (B-type natriuretic peptide) and both left ventricular ejection fraction and left-sided filling pressures.

Despite advances in therapy, sepsis causes > 200,000 deaths per year in the United States, thus equaling the number of patients dying from

myocardial infarction.<sup>1</sup> Myocardial dysfunction is a common complication in patients with severe sepsis, and early recognition and aggressive supportive ther-

apy are mandatory as mortality in patients with septic shock is still high.<sup>2</sup> The value of the use of pulmonary artery catheters (PACs) has come under scrutiny after studies<sup>3</sup> have failed to prove a survival benefit for patients treated with PAC-guided therapy compared to those in whom PACs were not used. Nevertheless, information about cardiac performance is needed for the selection of the most appropriate catecholamine regimen after adequate fluid resuscitation.<sup>4</sup> In the past few years, the following two groups of biomarkers have emerged as potential candidates for the evaluation and quantification of cardiac dysfunction in patients with sepsis:

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cardiac troponins; and natriuretic peptides.<sup>5-15</sup> These biomarkers were initially introduced for use in diagnosis and risk stratification in patients with acute coronary syndrome (ACS)<sup>16</sup> and congestive heart failure (CHF) respectively,<sup>17,18</sup> but their spectrum of application is widening. The aim of the present review is to provide clinicians with a summary of the current evidence about the prognostic and diagnostic impact of cardiac troponins and natriuretic peptides in patients with sepsis-associated myocardial dysfunction. The available data on cardiac troponins and natriuretic peptides and the possible underlying pathophysiologic mechanisms are discussed in the light of studies on these biomarkers in patients without sepsis.

## DEFINITIONS

Sepsis has been defined as the presence of the systemic inflammatory response syndrome (SIRS) in response to a culture-proven infection.<sup>19</sup> However, SIRS can result not only from infection, but also from a variety of conditions such as autoimmune disorders, vasculitis, thromboembolism, and burns,

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\*From the Division of Cardiology (Drs. Maeder, Rickli, and Ammann), Department of Internal Medicine, Kantonsspital St. Gallen, Switzerland; and Transplantation Biology Research Center (Dr. Fehr), Massachusetts General Hospital/Harvard Medical School, Boston, MD.

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Correspondence to: Micha Maeder, MD, Division of Cardiology, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland; e-mail: [micha.maeder@bluewin.ch](mailto:micha.maeder@bluewin.ch)

or after surgery. The severity of sepsis is graded according to the associated organ dysfunction and hemodynamic compromise. The original definitions have been revisited by a group of experts,<sup>20</sup> but, apart from expanding the list of signs and symptoms of sepsis, no relevant changes have been made. In a recently published review, Annane and coworkers<sup>2</sup> propose a very practical modification of the definitions including exact hemodynamic definitions of septic shock. It is important to recognize that the original definitions relied only on the degree of vasodilatation, whereas in the modification by both the International Sepsis Definition Conference<sup>20</sup> and Annane et al<sup>2</sup> myocardial depression defined as low cardiac index or echocardiographic evidence of cardiac dysfunction has been included in the definition of severe sepsis (Table 1).<sup>2,20</sup>

## MYOCARDIAL DYSFUNCTION AND HEMODYNAMIC ASSESSMENT

### *Prevalence*

Abnormalities of cardiac function are quite common in patients with sepsis. The prevalence of this transient phenomenon critically depends on the population studied, the definition applied, and the time point during the course of the disease. Approximately 50% of patients with severe sepsis and septic shock seem to have any form of impairment of left ventricular systolic function.<sup>4,9</sup>

### *Pathomechanisms*

The phenomenon of myocardial depression is mediated by circulating depressant substances,<sup>21-24</sup> which until now have been incompletely characterized. Among those on a list of possible candidates, tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  play a central role.<sup>21,22</sup> In addition, interleukin-6 has been shown<sup>24</sup> to be a key mediator of myocardial dysfunction in children with meningococcal septic shock. A comprehensive discussion of the numerous pathways involved in the complex pathogenesis of sepsis is beyond the aim of the present clinically oriented review, but can be found elsewhere.<sup>23</sup>

### *Clinical Presentation and Hemodynamics*

The hemodynamic pattern in human septic shock is generally characterized by a hypercirculatory state including decreased systemic vascular resistance and a markedly increased cardiac index after adequate fluid resuscitation. Nevertheless, several studies have revealed clear evidence of intrinsic depressed left ventricular performance in patients with septic shock. The

**Table 1—Definitions of SIRS and Different Degrees of Severity of Sepsis<sup>2,19</sup>**

Condition	Description
SIRS	Two or more of the following conditions: temperature > 38.5°C or < 35.0°C; heart rate of > 90 beats/min; respiratory rate of > 20 breaths/min or PaCO <sub>2</sub> of < 32 mm Hg; and WBC count of > 12,000 cells/mL, < 4,000 cells/mL, or > 10% immature (band) forms
Sepsis	SIRS in response to documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection, <i>eg</i> , ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	Sepsis and at least one of the following signs of organ hypoperfusion or organ dysfunction: areas of mottled skin; capillary refilling of ≥ 3 s; urinary output of < 0.5 mL/kg for at least 1 h or renal replacement therapy; lactate > 2 mmol/L; abrupt change in mental status or abnormal EEG findings; platelet count of < 100,000 cells/mL or disseminated intravascular coagulation; acute lung injury/ARDS; and cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and one of the following conditions: systemic mean BP of < 60 mm Hg (< 80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline solution, or PCWP between 12 and 20 mm Hg; and need for dopamine of < 5 µg/kg/min, or norepinephrine or epinephrine of < 0.25 µg/kg/min to maintain mean BP at > 60 mm Hg (80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine at > 15 µg/kg/min, or norepinephrine or epinephrine at > 0.25 µg/kg/min to maintain mean BP at > 60 mm Hg (80 mm Hg if previous hypertension)

phenomenon of “myocardial depression” was first described by Parker and coworkers,<sup>25</sup> who performed serial radionuclide ventriculograms in 20 patients with septic shock, 7 of whom died during their stay in the ICU. Ten of 13 survivors had a reversibly depressed left ventricular ejection fraction (LVEF) of < 0.4, whereas none of the nonsurvivors had an LVEF of < 0.4. Survivors had substantially increased left ventricular end-diastolic and end-systolic volumes, and, thus, preserved stroke volumes despite impaired LVEF, whereas in nonsurvivors ventricular dimensions remained normal. Nonsurvivors had a lower mean systemic vascular resistance index than survivors. Mean stroke volume indexes did not differ between survivors and nonsurvivors.<sup>25</sup> These changes normalized within 10 days after the onset of septic shock. The authors postulated that all patients with septic shock may develop myocardial depression, but nonsurvivors would have a lower systemic vascular resistance index than survivors. They concluded that the lower afterload may result in normal LVEF in nonsurvivors despite a reduced myocardial contractility.<sup>25</sup> Another study<sup>26</sup> by the same group revealed that patients with septic shock, and even those with normotensive sepsis, have a markedly abnormal response in left ventricular stroke work index (LVSWI), which is a measure of external left ventricular work, to volume infusion, indicating that in patients with sepsis an impairment of intrinsic myocardial performance is present. In this study, however, no outcome data are presented; therefore, it remains unknown whether there were any differences in LVSWI between survivors and nonsurvivors, and also whether the previous findings on the prognostic impact of LVEF and systemic vascular resistance index could be confirmed.

Similar changes have been observed in the right ventricle (*ie*, dilatation and reduction of contractility,

which are expressed as right ventricular stroke work index). In contrast to the left ventricular pattern, changes in right ventricular performance occurred in both survivors and nonsurvivors, but normalization was seen only in survivors.<sup>27</sup>

In accordance with the results of the study by Parker et al,<sup>25</sup> some studies<sup>4,9</sup> evaluating cardiac performance in patients with sepsis by echocardiography found an LVEF (using transthoracic echocardiography) or a left ventricular fractional area contraction (LVFAC) [using transesophageal echocardiography] of < 50% in approximately 50% of patients with severe sepsis and septic shock. However, the typical pattern of left ventricular dilation in combination with an impaired LVEF was found in only one study,<sup>9</sup> whereas in another study<sup>4</sup> ventricular dimensions were normal despite low LVEF. Many other studies did not report left ventricular dimensions. Very interesting data came from a comprehensive study<sup>28</sup> employing both transesophageal echocardiography and invasive monitoring to assess systolic and diastolic left ventricular function in patients with septic shock. Based on an analysis of transmitral inflow and pulmonary vein flow patterns, patients were subdivided into the following three subsets: (1) ratio of early peak flow velocity to atrial peak flow velocity (E/A) of > 1 and a ratio of systolic to diastolic pulmonary vein flow velocity (S/D) of > 1; (2) E/A of > 1 and S/D of < 1; and (3) E/A of < 1 and S/D of < 1. By analysis of other hemodynamic variables derived from PAC and transesophageal echocardiography measurements, these three groups were characterized as follows: (1) normal LVFAC, normal transmitral and pulmonary flow (*ie*, E/A of > 1 and S/D > 1), corresponding to normal systolic and diastolic left ventricular function; (2) normal LVFAC, abnormal pulmonary vein flow (*ie*, E/A of > 1 and S/D of < 1 [called *pseudonormal transmitral inflow*]), which has

**Table 2—Prospective Studies on Cardiac Troponin Levels in Critically Ill Adults Mainly Including Patients With Sepsis\***

Study	Study Population (Age, † yr)	Severity of Disease	Assessment of LV Performance	Troponin Positivity	In-Hospital Mortality	Relationships Among Cardiac Troponin Level, LV Performance, and Outcome	Exclusion of Flow-Limiting CAD
Fernandes et al <sup>5</sup>	10 pts with sepsis (30 ± 6)	APACHE II score: 25 ± 11	PAC, TTE	cTnI (cutoff, 0.6 μg/L): 6/10 pts (60%)	4/10 pts (40%); cTnI+, 3 pts	All pts with LVEF < 0.5 were cTnI+; cardiac index and cTnI not related	Not done
Spies et al <sup>6</sup>	26 pts with sepsis (approximately 60)	APACHE II: approximately 48	PAC	cTnT (cutoff, 0.2 μg/L): 18/26 pts (69%)	cTnT+, 15/18 pts (83%); cTnT—, 3/8 pts (37%)	Higher mortality in cTnT+ pts (p = 0.02)	Not done
Turner et al <sup>7</sup>	G1: 15 pts with septic shock (70; age range, 24–77); G2: 6 pts without sepsis, but receiving mechanical ventilation (61; age range, 24–77)	APACHE II score: G1, 24 (range, 3–39); G2, 14.5 (range, 8–23)	PAC (except one pt)	cTnI (cutoff, 0.4 μg/L): G1, 12 of 15 pts (80%); G2, 1/6 pts (17%)	G1, 4/15 pts (27%); G2, 0/6 pts; cTnI+, 4/13 pts (31%); cTnI—, 0/8 pts	Correlation minimum LVSWI and maximum cTnI level (r = -0.72); correlation maximum vasopressor dose and maximum cTnI (r = 0.55)	Not done
Arlati et al <sup>8</sup>	G1: 19 pts with severe sepsis or septic shock (56 ± 4); G2: 12 pts with hypovolemic shock (71 ± 4)	PaO <sub>2</sub> /FIO <sub>2</sub> ratio: G1, 198 ± 21 mm Hg; G2, 270 ± 42 mm Hg	Not assessed; hypotension (MAP < 90 mm Hg) graded as moderate (30–60 min) or severe (> 60 min)	cTnI (cutoff, 0.5 μg/L): G1, 11/19 pts (58%); G2, 12/12 pts (100%)	G1, 10/19 pts (53%); G2, 5/12 pts (42%)	Correlation abnormal cTnI levels and duration of hypotension (Kendall τ, 0.48); weak correlation abnormal cTnI levels and outcome (r = 0.28)	Not done; 2 pts in G1 and 5 pts in G2 had a history of CAD, all of whom were cTnI+; 4 pts from G1 and 1 pt from G2 had ECG evidence of MI
Ver Elst et al <sup>9</sup>	46 pts with septic shock (66; IQR, 54–74)	APACHE II score: 24 (IQR, 20–30)	PAC; TEE: LV dysfunction defined as LVEDD > 60 mm, LVEDV > 120 mL, and LVFAC < 0.4	cTnI (cutoff, 0.4 μg/L): 23/46 pts (50%); cTnT (cutoff, 0.1 μg/L): 16/45 pts (36%)	21/46 pts (46%)	LV dysfunction in 78% of cTnI+ pts, but only in 9% of cTnI— pts (p < 0.0001); correlation ICU admission APACHE II score and peak cTnI (r value, NA) and cTnT (r value, NA); correlation cTnI and LV dysfunction (r value, NA)	Autopsy performed in 7 cTnI+ and 5 cTnI—pts; LV free wall rupture in 1 cTnI— pt, MI in 1 cTnI+ pt; no MI in 10 pts; contraction band necrosis in 3 cTnI+ pts and in 1 cTnI— pt
Ammann et al <sup>10</sup>	G1: 20 pts with SIRS (n = 3), sepsis (n = 9), or septic shock (n = 8) [66 ± 8]; G2: age and sex-matched control subjects	NA	Not systematically assessed	cTnI (cutoff, 0.1 μg/L): G1, 17/20 pts (85%); G2, 0	G1, 6/20 pts (30%); G2, 0 pts; cTnI+, 5/17 pts (29%); cTnI—, 1/9 pts (11%)	Not assessed	In 10/17 cTnI+ pts (59%) relevant CAD ruled out by autopsy, coronary angiography, or stress echocardiography

Table 2—Continued

Study	Study Population (Age, † y)	Severity of Disease	Assessment of LV Performance	Troponin Positivity	In-Hospital Mortality	Relationships Among Cardiac Troponin Level, LV Performance, and Outcome	Exclusion of Flow-Limiting CAD
Ammann et al <sup>11</sup>	58 critically ill pts, 27/58 (47%) with SIRS/sepsis, 24/58 (41%) with septic shock (55 ± 21)	SAPS II score: 42 ± 15	TTE	cTnI and cTnT (cutoff, 0.1 µg/L): 32/58 of all pts (55%); and 32/51 (63%) of the SIRS/sepsis/septic shock pts	16/58 (28%)	Lower LVEF in cTnI/T+ pts (48 ± 13%) vs cTnI/T— pts (60 ± 10%; p = 0.0006); correlation cTnI and LVEF (r = -0.44); higher mortality in cTnI/T+ pts (p = 0.018)	In 72% of cTnI/T+ pts, relevant CAD excluded by autopsy, coronary angiography, or stress echocardiography
Mehta et al <sup>12</sup>	37 pts with septic shock (approximately 68)	APACHE II score: approximately 24	TTE	cTnI (cutoff, 1.0 µg/L): 16/43 pts (43%)	cTnI+: 10/16 (63%) cTnI-: 5/21 (24%)	Correlation cTnI with LVEF (r = -0.7); higher APACHE II score and mortality in cTnI+ pts	Not performed

\*G = group; IQR = interquartile range; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; MI = myocardial infarction; NA = not available; FIO<sub>2</sub> = fraction of inspired oxygen; SAPS = simplified acute physiology score; TTE = transthoracic echocardiography; TEE = transesophageal echocardiography; MAP = mean arterial pressure; pt = patient.

†Values in parentheses are mean ± SD, unless otherwise indicated.

been interpreted as isolated diastolic dysfunction; and (3) decreased LVFAC, abnormal transmitral and pulmonary vein flow pattern (*ie*, E/A of < 1 and S/D of < 1), which might be explained by diastolic dysfunction as a consequence of systolic dysfunction. The patients in the latter group were significantly older and had a higher mortality rate than those patients in the other two groups. There was no significant difference in systemic vascular resistance or LVSWI between the groups. This study is limited by a small number of patients, but, interestingly, it revealed that patients with lower LVFAC have worse outcome,<sup>28</sup> which is contradictory to the results of the study by Parker et al,<sup>25</sup> and that patients with preserved LVFAC have better outcome regardless of the presence of diastolic dysfunction.

### Prognosis and Rationale for the Use of Biomarkers

In the landmark study by Parker et al,<sup>25</sup> patients were grouped according to their mortality, and patients showing left ventricular dilation and depression of LVEF had a good prognosis. Paradoxically, many studies using echocardiography, including the above-mentioned transesophageal investigation by Poelaert et al,<sup>28</sup> have shown that an impaired LVEF is associated with a poor prognosis.<sup>4,28</sup> This might be

explained by the fact that in patients with septic shock the measurement of LVEF alone does not sufficiently characterize the underlying hemodynamic pattern, and that outcome depends on parameters other than LVEF. An analysis using PAC data has revealed that a heart rate of < 106 beats/min at the initial evaluation, and a heart rate < 95 beats/min and a systemic vascular resistance index of > 1,529 dyne · s · cm<sup>-5</sup> per m<sup>2</sup> 24 h after the onset of shock predicted survival.<sup>29</sup> Regarding the fact that the insertion of a PAC is an invasive procedure without proven survival benefit, and a comprehensive echocardiographic study requires a high degree of training and sometimes is not available within 24 h, a biomarker accurately detecting myocardial dysfunction and providing prognostic information in patients with sepsis would be of paramount interest.

## CARDIAC TROPONINS

### Background

Cardiac troponins are regulatory proteins of the thin actin filaments of the cardiac muscle.<sup>30</sup> Myocardial cell injury results in the release of cardiac troponin I (cTnI) and cardiac troponin T (cTnT),

which differ from troponin isoforms of the skeletal muscle, and thus are highly sensitive and specific biomarkers of myocardial damage.<sup>30,31</sup> The measurement of cTnI and cTnT levels in blood is standard for diagnosis and risk stratification in patients with ACS.<sup>32</sup> The currently employed tests use monoclonal antibodies against several different epitopes of the cTnI and cTnT molecules. Cardiac troponin levels start to rise 3 to 4 h after the onset of myocardial infarction and also, presumably, other causes of myocardial damage, respectively, and remain elevated for 4 to 10 days.<sup>33</sup> Due to their widespread use, raised levels of cardiac troponins have been found in patients with many conditions other than myocardial ischemia due to flow-limiting coronary artery disease (CAD) including pulmonary embolism, renal failure, and sepsis.<sup>30,34</sup>

### *Studies in Unselected Critically Ill Patients*

Among unselected critically ill patients, 15.3% (32 of 209 patients; cTnI cutoff, > 3.6  $\mu\text{g/L}$ ),<sup>35</sup> 15.8% (41 of 260 patients; cTnI cutoff, > 1.5  $\mu\text{g/L}$ ),<sup>36</sup> and 25% (53 of 213 patients; cTnI cutoff, > 0.4  $\mu\text{g/L}$ )<sup>37</sup> had elevated cTnI levels. Patients with raised troponin levels included those with acute myocardial infarction and those with troponin level elevation due to conditions other than myocardial infarction. Mortality among troponin-positive patients was higher compared to that among troponin-negative patients, irrespective of the cause of troponin positivity.<sup>35,37</sup> Patients with elevated troponin levels were more likely to be hypotensive, needed more therapy with vasoactive agents, received mechanical ventilation more often, and had longer stays in the ICU.<sup>35</sup> A small study<sup>38</sup> including consecutive patients admitted to the ICU because of an indication for mechanical ventilation, or after thoracic or vascular surgery, found elevated cTnT levels (cutoff, 0.1  $\mu\text{g/L}$ ) in 11 of 34 patients (32%). However, in this study,<sup>38</sup> four cTnT-positive patients had acute myocardial infarction, and thus conclusions about the impact of cTnT in ICU patients are limited.

### *Studies in Patients With Sepsis*

Studies restricted to patients with sepsis or critically ill patients, of whom most had SIRS or sepsis, are summarized in Table 2. Several authors reported a relationship between elevated cTnI or cTnT levels and left ventricular dysfunction assessed either by echocardiography (LVEF)<sup>5,9,11,12</sup> or PAC (LVSWI).<sup>7</sup> In addition, the duration of hypotension<sup>8</sup> and the maximal number of vasopressor doses administered<sup>7</sup> were found to be correlated to cardiac troponin levels. Finally, elevated troponin levels have been shown to be related to the severity of the disease as

expressed by global scores such as the acute physiology and chronic health evaluation (APACHE) II score or simplified acute physiology score II<sup>9,12</sup> as well as short-term prognosis.<sup>6,8,11,12</sup> The studies differ with respect to the incidence of troponin positivity, which may be explained by the heterogeneity of study populations, the type of troponin studied (*ie*, cTnI, cTnT, or both), and the cutoff level of the troponin test applied. Nevertheless, the results of these studies were very similar in concluding that elevated troponin levels in patients with sepsis indicate a higher severity of disease, the presence of myocardial dysfunction, and a worse prognosis.

### *Mechanism of Troponin Release*

Whereas the diagnostic and prognostic impact of elevated cardiac troponin levels in patients with sepsis has been established, the underlying mechanisms still require clarification. Measurements by coronary sinus thermodilution catheters revealed that coronary blood flow did not differ between patients with septic shock and healthy subjects as long as the heart rate was < 100 beats/min, and that coronary blood flow was even higher in patients with septic shock compared to healthy subjects if the heart rate was > 100 beats/min. There was no difference in coronary blood flow between patients with septic shock who developed myocardial depression and those who did not, and in no patient was net myocardial lactate production demonstrated.<sup>39,40</sup> In addition, several animal models have shown that myocardial oxygen metabolism and high-energy phosphate levels are well-preserved during experimental septic shock.<sup>22,41</sup> Nevertheless, it is still a matter of debate whether troponin release in patients with sepsis reflects irreversible myocardial damage or reversible myocardial depression.<sup>42</sup> Whereas troponin levels are elevated for several days in patients with myocardial infarction, transient, short-lasting (*ie*, a few hours) increases in cardiac troponin levels in patients with unstable angina have been observed,<sup>16</sup> which suggests that troponin leakage due to ischemia or other stimuli is possible even if myocardial necrosis does not occur. Experimental evidence supporting this theory was provided by Piper and coworkers,<sup>43</sup> who demonstrated reversible membranous bleb formation in rat cardiomyocytes during limited periods of hypoxia and the consecutive release of myocardial enzymes in cell supernatant. In addition, in the study by Ver Elst et al<sup>9</sup> histopathologic examination revealed contraction band necrosis in only half of patients with a positive pre-mortem troponin level, but also in one troponin-

negative patient, suggesting that troponin release does not necessarily indicate myocardial cell necrosis.

However, in many ICU patients with sepsis troponin release can still be due to preexisting flow-limiting CAD, and myocardial necrosis precipitated by sepsis-associated tachycardia and anemia. These patients cannot be differentiated from those without CAD and real sepsis-induced troponin release at bedside. With regard to this limitation, most of the studies that have been cited were hampered by the fact that the presence of an underlying CAD was not systematically sought. In the largest prospective study<sup>11</sup> on the topic, we could exclude flow-limiting CAD in the majority of troponin-positive patients who had sepsis and septic shock by stress echocardiography, coronary angiography, or autopsy. Nevertheless, myocardial injury due to microvascular thrombosis could still play a role. There is a close relationship between the presence of inflammatory cytokines and a procoagulant state in patients with severe sepsis.<sup>44</sup> Diminished levels of activated protein C are associated with reduced inhibition of the procoagulant factors V and VIII, as well as impaired fibrinolysis,<sup>44</sup> and the infusion of recombinant human activated protein C (drotrecogin- $\alpha$ ) has been shown to reduce mortality in patients with severe sepsis and a high risk of death,<sup>44</sup> but not in those with a low risk of death based on the initial APACHE II score.<sup>45</sup> In this context, the possibility of small-vessel thrombosis with subsequent myocardial microinfarction and troponin release cannot be excluded. Interestingly, a recently published study<sup>46</sup> revealed lower cTnI levels in patients with severe sepsis who had been treated with drotrecogin- $\alpha$  ( $n = 23$ ) on day 2 of therapy compared to a similar group of patients not receiving the drug ( $n = 34$ ). There was a nonsignificant trend toward lower mortality in the drotrecogin- $\alpha$  group (22% vs 32%, respectively;  $p = 0.11$ ). However, it remains unclear whether the smaller troponin release in the drotrecogin- $\alpha$  group indicates less microvascular injury with subsequently lower mortality following the therapy applied, or whether the lower cTnI levels reflect the better prognosis of the drotrecogin- $\alpha$  group independent of the effect of the drug. In addition, regarding the above-mentioned correlation between troponin levels and the maximal vasopressor doses administered,<sup>7</sup> catecholamine toxicity has to be considered as another possible underlying mechanism.

### *Renal Dysfunction and Cardiac Troponins*

There is a large body of evidence that, in patients who have been treated with maintenance hemodialysis, cardiac troponin levels can be raised even in the

absence of ACS,<sup>47-49</sup> and especially that cTnT level elevation is predictive for cardiovascular events and mortality.<sup>47,48</sup> In addition, some investigators have found a relationship between cTnT and significant coronary atherosclerosis<sup>48</sup> and left ventricular hypertrophy,<sup>49</sup> respectively. However, the exact mechanism of troponin release in patients with renal failure is still unknown.

Several studies<sup>47-50</sup> in patients with end-stage renal failure have revealed a low specificity of cardiac troponins for the assessment of ACS, especially of cTnT, which is excreted mainly by the kidney.<sup>50</sup> Similarly, we must assume that in these patients sepsis-associated cardiac troponins do not have the same predictive value for impaired LVEF and worse outcome compared to those with normal or moderately impaired renal function. However, the degree above which renal dysfunction cardiac troponins can be raised in the absence of ACS, and whether the findings from studies in patients with chronic renal failure can also be applied to those with sepsis-associated acute renal failure requiring hemodialysis or hemofiltration is currently unknown. Therefore, the cautious interpretation of elevated troponin levels in patients with significant renal dysfunction is warranted in any clinical situation.

## NATRIURETIC PEPTIDES

### *B-Type Natriuretic Peptide*

*Background:* The 32-amino-acid B-type natriuretic peptide (BNP) and the 76-amino-acid N-terminal-pro-BNP (NT-proBNP) are the most extensively studied members of the family of natriuretic peptides. The prohormone pro-BNP is synthesized in bursts and cleaved into the active BNP and the biologically inactive NT-proBNP, which are constitutively released from ventricular myocytes. In contrast to A-type natriuretic peptide (ANP), BNP and NT-proBNP are not stored in granules, but BNP gene expression can increase very rapidly. The main stimulus for BNP synthesis and release is myocyte stretch.<sup>51</sup> BNP exhibits natriuretic and vasodilatory effects, and counteracts the effects of the renin-angiotensinogen-angiotensin system.<sup>51</sup> In the emergency department, BNP has been proven to be a helpful tool in distinguishing dyspnea caused by CHF from noncardiac dyspnea.<sup>17</sup> The measurement of a single BNP level significantly improves the management of patients presenting with acute dyspnea, and thus reduces hospital stay and medical costs.<sup>18</sup> In the setting of acute dyspnea, a BNP level of  $< 100$  pg/mL makes the diagnosis of CHF unlikely, whereas BNP levels of  $> 400$  pg/mL<sup>52</sup> or  $> 500$  pg/mL<sup>18</sup> are associated with a high probability

**Table 3—Studies on the Impact of BNP Measurement in Critically Ill Patients\***

Study	Study Population (Age,† y)	Severity of Disease	Serum Creatinine Level‡	Assessment of LV Performance	BNP Levels	Mortality	Relationships Among BNP, LV Performance, and Outcome
Witthaut et al <sup>13</sup>	G1, 17 pts with septic shock (61 ± 2.7 yr); G2, 19 subjects without sepsis or heart disease (61 ± 2.1 yr)	G1: APACHE II score, 28.4 ± 1.2; all mechanically ventilated	G1, 97 ± 27 μmol/L	PAC: G1: CI, 4.5 ± 0.2 L/min/m <sup>2</sup> ; G2: CI, 3.4 ± 0.5 L/min/m <sup>2</sup>	G1, 12.4 ± 3.6 pg/mL; G2, 5.5 ± 0.7 pg/mL	28 d: G1, 5/28 pts (29%)	BNP correlated with CI ( <i>r</i> = -0.56); APACHE II score not correlated with BNP
Charpentier et al <sup>4</sup>	9 pts with severe sepsis and 25 pts with septic shock (56 yr)	SAPS II score: 43 ± 2.5; 18/34 pts (53%) mechanically ventilated	NA	TTE or TEE: 15/34 of pts with LVFAC < 0.5 (44%)	Day 1: LVFAC < 0.5, 425 ± 184 pg/mL; LVFAC ≥ 0.5, 95.6 ± 30 pg/mL Days 3 and 4: nonsurvivors, 905 ± 246 pg/mL; Survivors, 181 ± 46 pg/mL	28 d: 10/34 pts (29%)	Higher BNP levels in pts with LVFAC < 0.5 than in those with LVFAC > 0.5; higher BNP levels in nonsurvivors
Cuthbertson et al <sup>14</sup>	G1, 35 pts with sepsis (age, 66 yr; range, 55–74 yr); G2, 43 pts without sepsis (age, 66 yr; range, 55–74 yr)	APACHE II score, 24 (range, 19–31); SAPS II score, 45 (range, 33–58)	137 μmol/L (range, 92–222 μmol/L)	Not assessed	At ICU admission: G1, 498 pg/mL (range, 242–884 pg/mL); G2, 213 pg/mL (range, 71–564 pg/mL) At 24 h: G1, 500 pg/mL (range, 239–1,017 pg/mL); G2, 319 pg/mL (range, 132–808 pg/mL)	30 d: 27/78 pts (35%)	Trend toward higher BNP levels in survivors ( <i>p</i> = 0.28); higher ICU admission BNP levels in pts with sepsis than in pts without sepsis ( <i>p</i> = 0.02); higher baseline BNP levels in pts with age ≥ 65 yr ( <i>p</i> = 0.04) and serum creatinine ≥ 110 μmol/L ( <i>p</i> = 0.02).
Cuthbertson et al <sup>14</sup>	Subgroup analysis: 35 pts with sepsis (age, 66 yr; range, 55–74 yr)	APACHE II score, 24 (range, 20–31); SAPS II score, 50 (range, 35–59)	Survivors, 169 μmol/L (range, 110–293 μmol/L); Nonsurvivor, 260 μmol/L (range, 142–298 μmol/L)	Not assessed	At ICU admission: survivors, 651 pg/mL (range, 242–1023 pg/mL); nonsurvivors, 377 pg/mL (range, 85–683 pg/mL) At 24 h: 500 pg/mL (range, 235–1,026 pg/mL); survivors, 662 pg/mL (range, 339–1,230 pg/mL); nonsurvivors, 377 pg/mL (range, 85–683 pg/mL)	30 d: 10/35 pts (29%)	Trend toward higher BNP levels on ICU admission ( <i>p</i> = 0.21) and at 24 h ( <i>p</i> = 0.11) in survivors

of CHF. The intermediate range (BNP, 100 to 400 or 500 pg/mL) is a gray zone, where several conditions including stable left ventricular dysfunction and noncardiac conditions have to be considered.<sup>18</sup>

*Studies in Critically Ill Patients:* Several studies have addressed the questions whether BNP could

accurately predict left-sided filling pressures and thus replace invasive monitoring for guidance of fluid resuscitation and vasopressor therapy, and whether BNP is of prognostic value in patients with sepsis.<sup>4,13–15,53,54</sup> However, in contrast to the rather uniform data on the impact of raised cardiac troponin levels in patients with sepsis, studies on the value

Table 3—Continued

Study	Study Population (Age, † yr)	Severity of Disease	Serum Creatinine Level‡	Assessment of LV Performance	BNP Levels	Mortality	Relationships Among BNP, LV Performance, and Outcome
Tung et al <sup>15</sup>	49 pts with shock; G1, 7 pts with cardiogenic shock (CI, < 2.2 L/min/m <sup>2</sup> ; PCWP, > 18 mm Hg); G2, 42 pts with noncardiogenic shock	APACHE II score, 21.8 ± 6.9; 36/49 pts (73%) mechanically ventilated	Survivors, 159 μmol/L (range, 88–194 μmol/L); Nonsurvivors, 177 μmol/L (range, 124–292 μmol/L)	PAC: G1: CI, 1.6 ± 0.3 L/min/m <sup>2</sup> ; PCWP, 24 ± 4 mm Hg; G2: CI, 3.4 ± 1.3 L/min/m <sup>2</sup> ; PCWP, 18 ± 7 mm Hg	1,133 ± 1,416 pg/mL (median, 482 pg/mL); G1, 739 ± 471 pg/mL (median, 768 pg/mL); G2, 1,199 ± 1,511 pg/mL (median, 432 pg/mL)	In ICU: 19/49 pts (38%)	No correlation between BNP and CI (p = 0.59) and PCWP (p = 0.56), higher BNP levels in nonsurvivors than in survivors (p = 0.002), correlation between log BNP quartiles and ICU mortality
Forfia et al <sup>55</sup>	40 pts with CHF (n = 12), sepsis/ARDS (n = 12), after abdominal/vascular surgery (n = 13)/trauma (n = 3) with PAC indication (age, 62 yr; range, 52–73 y)	Mechanical ventilation, 26/40 pts (65%)	NA; two thirds of pts with renal insufficiency (acute, 25%; chronic, 75%)	PAC: PCWP, 14 mm Hg (range, 10–22 mm Hg); CI, 3.1 L/min/m <sup>2</sup> (range, 2.1–4.2 L/min/m <sup>2</sup> ); TTE: LVEF, 50% (range, 20–60%)	420 pg/mL (range, 197–1,740 pg/mL)	In-hospital: 14/40 pts (35%)	Weak correlation between BNP and PCWP (r = 0.4); correlation between BNP and LVEF (r = -0.49) and estimated creatinine clearance (r = -0.35); estimated creatinine clearance independent predictor of BNP levels
Jefic et al <sup>56</sup>	41 pts with hypoxic respiratory failure (age, 66.5 ± 16 y); sepsis/septic shock in 20 pts	APACHE II score, 18.5 ± 1; 39/41 pts (95%) ventilated	NA; creatinine clearance 60.5 ± 7 mL/min	PAC: 34 pts with LVSWI of < 35 g/m/m <sup>2</sup> ; 18 pts with PCWP > 15 mm Hg	LVSWSI > 35 g/m/m <sup>2</sup> , 639 ± 286 pg/mL; LVSWSI < 35 g/m/m <sup>2</sup> , 916 ± 128 pg/mL	30 d: 17/40 pts (43%)§	Correlation BNP, and CI (r = -0.44), LVSWI (r = -0.62), creatinine clearance (r = -0.50), BNP not correlated with PCWP; BNP no different in survivors/nonsurvivors

\*CI = cardiac index. See Table 2 for abbreviations not used in the text.

†Values in parentheses are mean ± SD, unless otherwise noted.

‡To convert from mg/dL to μmol/L, multiply serum creatinine values by 88.4.

§Outcome not available for one patient.

of BNP testing in critically ill patients revealed conflicting results (Table 3).

The pilot study by Witthaut and coworkers<sup>13</sup> showed an inverse correlation between BNP and cardiac index ( $r = -0.56$ ), whereas BNP correlated neither with stroke volume nor LVSWI, nor pulmonary capillary wedge pressure (PCWP). Plasma BNP levels in patients with septic shock were higher than those in control subjects, but absolute values were

very low (Table 3), which might have been due to the uncommon type of assay employed or the fact that blood samples had been stored for several years before undergoing analysis. In contrast to the data obtained by Witthaut et al,<sup>13</sup> Tung et al<sup>15</sup> did not find a correlation between BNP level and cardiac index in 49 patients with different forms of shock who had a PAC in place.<sup>15</sup> Interestingly, BNP level was also not correlated with PCWP, but a BNP level of < 350

pg/mL had a very high negative predictive value for the presence of cardiogenic shock.<sup>15</sup> The two studies by McLean and associates<sup>53,54</sup> revealed that among unselected patients in a mixed ICU (surgical/internal) the BNP level measured at ICU admission could identify those patients who had any cardiac abnormality, as assessed by transthoracic echocardiography, within 2 h after ICU admission. In both studies, patients with cardiac abnormalities had higher BNP levels than those without. However, the vast majority of patients in these two studies did not have sepsis, and thus the conclusions on the topic under discussion are limited. In a study<sup>4</sup> that was restricted to patients with severe sepsis (n = 9) or septic shock (n = 25), BNP levels were markedly higher in patients with impaired systolic left ventricular function than in those with preserved systolic left ventricular function at days 1 to 4 during their ICU stay. In addition, at days 2 and 3 BNP levels were higher in nonsurvivors compared to survivors. A BNP cutoff value of > 190 pg/mL could differentiate survivors from nonsurvivors with a sensitivity of 70% and a specificity of 67%.<sup>4</sup> A prognostic impact of BNP with respect to mortality was also found by Tung et al<sup>15</sup> in evaluating BNP levels in 49 ICU patients with shock, mainly of noncardiac origin. In contrast, a very recent study<sup>14</sup> analyzing 78 patients who had been admitted consecutively to a general ICU (with sepsis, 35 patients; without sepsis, 43 patients) revealed a trend toward higher BNP levels in survivors compared to nonsurvivors. When the analysis was restricted to the patients with sepsis, who had higher BNP levels than those without sepsis, the same trend was observed.<sup>14</sup> Other studies<sup>55,56</sup> did not find any prognostic information of BNP levels in critically ill patients.

In the past few years, it has become obvious that previous studies<sup>57–59</sup> in patients with CHF demonstrating a close relationship between BNP levels and left-sided filling pressures cannot be confirmed in critically ill patients. In three studies, markedly elevated BNP levels, but very weak correlations ( $r = 0.4$ )<sup>55</sup> or even no significant correlations<sup>15,56</sup> between PCWP and BNP have been found in ICU patients requiring invasive monitoring, of whom a considerable percentage had sepsis (Table 3). Of particular interest are the findings by Jelic and coworkers,<sup>56</sup> who found that BNP level could not differentiate high vs low PCWP respiratory failure. Whereas BNP level was not related to PCWP, a weak inverse correlation between BNP and LVSWI ( $r = -0.48$ ) has been found. However, there was no significant difference in BNP levels between patients with an LVSWI of > 35 g/m/m<sup>2</sup> and those with an LVSWI of < 35 g/m/m<sup>2</sup>.<sup>56</sup> It is important to recog-

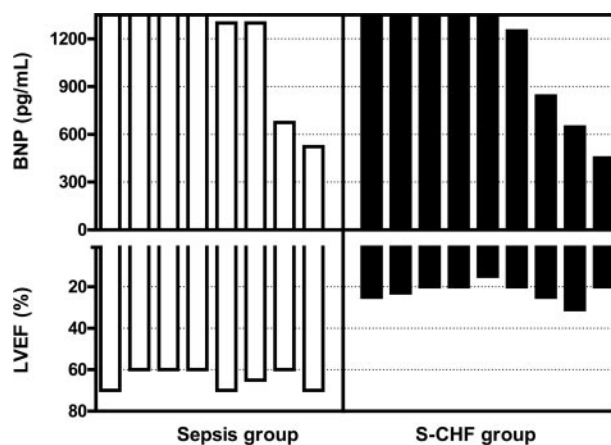


FIGURE 1. Comparison of BNP levels in eight patients with CHF due to severely impaired LVEF (systolic CHF [S-CHF]) and eight patients with sepsis, severe sepsis, or septic shock. S-CHF group: mean LVEF,  $23 \pm 3.9\%$ . Sepsis group: mean LVEF,  $64.4 \pm 4.9\%$ ;  $p < 0.0001$ . Note the very similar BNP levels in the two groups despite a highly significant difference in LVEF. The data are from Maeder et al.<sup>60</sup>

nize that the degree of BNP elevation in patients with sepsis can be considerably high, even though a cardiac disorder is not obvious. A small retrospective analysis revealed that BNP levels in patients with sepsis and preserved systolic left ventricular function can be as high as that in patients admitted to the hospital because of CHF due to severely impaired systolic left ventricular function (sepsis, six of eight patients with a BNP level of > 1,000 pg/mL; CHF, five of eight patients with BNP of > 1,000 pg/mL) [Fig 1].<sup>60</sup>

**Mechanism of BNP Release:** BNP is obviously not a reliable predictor of cardiac performance expressed as LVEF in patients with sepsis, which is not surprising, however. Data from the Breathing Not Properly Multinational study<sup>61</sup> suggest that BNP has only a modest discriminatory value in differentiating patients with preserved LVEF from those with impaired LVEF in the emergency department setting, and thus LVEF cannot be estimated relying on a patient's BNP level. In addition, as systemic vascular resistance can be markedly lowered in patients with sepsis leading to unloading of the left ventricle, intrinsic myocardial depression, as measured by LVSWI, can be present even if the echocardiographically assessed LVEF is preserved. In contrast to systolic left ventricular function, a clear correlation between the degree of left ventricular diastolic dysfunction (*ie*, impaired relaxation, pseudonormal pattern, and restrictive pattern) and BNP levels has been identified previously.<sup>62</sup> As left ventricular diastolic dysfunction has been found in patients with

sepsis,<sup>28</sup> it might contribute to the raised BNP levels in patients with sepsis and preserved LVEF. However, the relationship between parameters of left ventricular diastolic function and BNP has not been evaluated systematically in previous studies in this setting.

Although wall stress is thought to be the major stimulus for BNP release, data from the above-mentioned studies in critically ill patients<sup>15,55,56</sup> and also more recent data obtained from patients with CHF<sup>63,64</sup> refute the hypothesis that BNP level could serve as a reliable indicator for PCWP. Volume resuscitation could theoretically cause BNP release by the elevation of both left-sided and right-sided filling pressures. In fact, a recently published case report<sup>65</sup> demonstrated that acute fluid loading was followed by an increase in both right-ventricular end-diastolic diameter and BNP. But only few studies have addressed this issue, and only limited conclusions can be drawn at the moment. Charpentier and coworkers<sup>4</sup> reported that patients with an LVFAC of  $< 0.5$  had significantly higher BNP levels and also had received significantly more fluids during the first 24 h than those with an LVFAC of  $> 0.5$ . In contrast, Roch and coworkers<sup>66</sup> found that in a multivariate analysis fluid loading was not a significant predictor of a high NT-proBNP level. Whereas the correlation between BNP level and PCWP has been found to be weak or even absent, few data exist on the effect of fluid loading on BNP levels, and the relationships among right ventricular dimension, central venous pressure, and BNP level, and thus fluid loading could still have an effect on BNP levels.

It has been well-recognized that in a subgroup of CHF patients BNP levels remain high despite a significant fall in PCWP following therapy,<sup>56</sup> and that patients with high pre-hospital discharge BNP levels are at high risk of readmission after decompensated CHF.<sup>67</sup> This phenomenon, which is called *BNP memory* by some authors, along with the weak correlation between BNP and PCWP, suggests that beyond left ventricular filling pressures other stimuli might account for BNP release, including right ventricular strain, renal failure, catecholamine therapy, and cytokine up-regulation.

In patients with chronic right ventricular overload (*ie*, volume overload due to atrial septal defect or pressure overload due to primary or thromboembolic pulmonary hypertension), BNP level has been shown to increase depending on the extent of right ventricular dysfunction.<sup>68</sup> Acute right ventricular overload following pulmonary embolism can also lead to BNP release,<sup>69</sup> and the degree of BNP elevation is predictive of the occurrence of right ventricular failure in this setting.<sup>70</sup> In patients with sepsis, pulmonary

vascular resistance can increase markedly due to associated acute lung injury or ARDS, and even if submitted to protective ventilatory support, acute cor pulmonale develops in 25% of patients with ARDS,<sup>71</sup> which is probably associated with BNP release. There has been one study<sup>72</sup> that has reported moderately elevated BNP levels in patients with ARDS. BNP levels were correlated with pulmonary and systemic vascular resistance but not with PaO<sub>2</sub> or the PaO<sub>2</sub>/fraction of inspired oxygen ratio.<sup>72</sup> Another report<sup>73</sup> has documented the normalization of very high BNP levels in a patient with severe ARDS following successful therapy.

In addition, the influence of catecholamine therapy has to be taken into account. The preferred vasopressor used to treat patients with septic shock is norepinephrine,<sup>74</sup> which is a predominantly  $\alpha$ -receptor agonist with systemic and pulmonary vasoconstrictor properties.<sup>75</sup> However, in patients with septic shock norepinephrine has been shown even to enhance cardiac index due to its  $\beta$ -adrenergic properties<sup>75</sup> and thus might influence the echocardiographically assessed LVEF in sepsis patients, leading to an overestimation of the true left ventricular systolic function. In contrast, elevated pulmonary vascular resistance due to hypoxic vasoconstriction in patients with severe pulmonary disease might further increase due to norepinephrine infusion, thereby increasing right ventricular afterload.<sup>76</sup>

*Renal Failure and BNP:* Beyond heart failure, elevated BNP levels have been found in patients with end-stage renal failure,<sup>77</sup> and thus patients with advanced renal failure have been excluded from most BNP studies. An analysis of the Breathing Not Properly Multinational Study<sup>78</sup> found a weak inverse correlation between BNP level and the estimated creatinine clearance in patients presenting with acute dyspnea. In addition, a substudy of the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation trial<sup>79</sup> revealed that patients with kidney disease (estimated creatinine clearance,  $< 60$  mL/min/1.73 m<sup>2</sup>; patients with a serum creatinine level of  $> 250$   $\mu$ mol/L were excluded) had higher BNP levels than patients without, and that in patients with kidney disease BNP testing did not improve their management. This is a very important issue, since changes in renal function can occur very rapidly in patients with sepsis. However, data on the relationship between BNP level and renal function in ICU patients are sparse. McLean et al<sup>54</sup> identified a weak correlation between BNP and serum creatinine levels. Unfortunately, the estimated levels for creatinine clearance have not been calculated, and thus this finding has only limited value. A much higher impact of renal function on BNP levels was found by Forfia

and associates,<sup>55</sup> who reported fourfold greater BNP levels in patients with impaired renal function (estimated creatinine clearance, < 60 mL/min) compared to patients with normal renal function despite similar PCWP values, cardiac index, and LVEF. Interestingly, BNP was better correlated with PCWP in patients with preserved renal function compared to those with impaired renal function.<sup>55</sup> An effect of renal function on BNP levels was also reported by Cuthbertson et al,<sup>14</sup> who found that patients with a serum creatinine level of > 110  $\mu\text{mol/L}$  had higher BNP levels ( $p = 0.02$ ) than those with a serum creatinine level of < 110  $\mu\text{mol/L}$ . The very recent study by Jelic et al<sup>56</sup> revealed an inverse correlation between BNP level and estimated creatinine clearance. Obviously, even moderate renal failure has a significant impact on BNP levels, a fact that must be taken into account when interpreting BNP levels in ICU patients.

*Diseases of the CNS and BNP:* The level of BNP, initially called “brain natriuretic peptide” after its detection in the porcine brain,<sup>80</sup> has been reported to be elevated in patients with subarachnoid hemorrhage,<sup>81</sup> but also in patients with other diseases of the CNS such as epilepsy<sup>82</sup> and stroke.<sup>83</sup> However, in the study by McLean et al,<sup>54</sup> BNP levels did not differ between 10 patients with neurologic problems, including subarachnoid hemorrhage and cerebral tumors, and those without.<sup>54</sup> In contrast, a recent study revealed that two thirds of 174 patients with ischemic stroke had NT-proBNP values clearly above the normal ranges, whereas elevated cTnI or cTnT levels have been detected in < 10% of patients.<sup>83</sup> However, a significant relation for any of these biomarkers to morbidity and mortality after stroke has not been found.<sup>83</sup> Elevated BNP levels in patients with subarachnoid hemorrhage have been shown to be associated with the severity of associated vasospasms,<sup>84</sup> but also with measures of myocardial performance including regional wall motion abnormalities, impaired LVEF, diastolic dysfunction, cTnI elevation, and pulmonary edema.<sup>85</sup> The elevation of BNP and NT-BNP levels in patients with pathologies of the CNS have been attributed to high sympathetic outflow or the damage of certain regions of the brain with consecutively impaired regulation of BNP release.<sup>83</sup> The absolute mean BNP values in patients with subarachnoid hemorrhage<sup>83,84</sup> are low compared to those in patients with decompensated CHF and many patients with severe sepsis or septic shock, whereas the median NT-proBNP values in stroke patients range between 1,618 and 4,589 pg/mL,<sup>83</sup> which is higher than the recently proposed<sup>86</sup> cutoff of 1,500 pg/mL as a discriminating marker for an adverse short-term outcome in patients with CHF

and fits the range of levels found in patients with severe sepsis or septic shock. Therefore, in patients with sepsis who have pathologies of the CNS (*eg*, meningitis, brain abscess, or previous head trauma) elevated BNP or NT-proBNP levels are difficult to interpret.

### *Other Natriuretic Peptides*

Several other members of the family of natriuretic peptides have been evaluated as markers of disease severity in critically ill patients. In 14 patients with septic shock, the mean plasma ANP level was fivefold higher than that in healthy subjects.<sup>87</sup> In another study<sup>88</sup> including 14 patients with septic shock, inverse correlations between ANP and LVSWI ( $r = -0.86$ ) and right ventricular stroke work index ( $r = -0.65$ ), and a positive relationship between ANP and dopamine dose on day 1 of the ICU stay have been reported. In the study by Witthaut et al,<sup>13</sup> the mean ( $\pm$  SD) values for ANP were found to be several fold higher than those in control subjects (septic shock patients,  $82.7 \pm 9.9$ ; control subjects,  $14.9 \pm 1.2$  pg/mL;  $p < 0.01$ ). There was a good correlation between ANP and interleukin-6 ( $r = 0.73$ ), whereas ANP was not significantly correlated with any hemodynamic parameter.

By analyzing the levels of the prohormone pro-ANP (using the measurement of mid-regional pro-ANP levels by a newly developed assay) in 101 consecutive critically ill patients (in 53 patients with sepsis, severe sepsis, or septic shock), Morgenthaler and associates<sup>89</sup> found significantly lower median levels in survivors (194 pg/mL; range, 20 to 2,000 pg/mL) than in nonsurvivors (853 pg/mL; range, 100 to 2,000 pg/mL;  $p < 0.001$ ). They calculated a pro-ANP threshold level of 530 pg/mL to predict death in the ICU. The area under the curve of the receiver operating characteristic curve with respect to outcome prediction was slightly higher for pro-ANP (0.88) than for the established APACHE II score (0.86).<sup>89</sup> In contrast, in an analysis of 57 patients with severe sepsis, the N-terminal part of the prohormone, N-terminal-pro-ANP (NT-proANP), was not predictive of survival.<sup>46</sup> However, it has been proposed that NT-proANP undergoes further fragmentation, and that immunoassays for NT-proANP might underestimate the true levels of NT-proANP secreted into the circulation.<sup>89</sup>

Recent data have suggested that NT-proBNP might be a better, but by no means perfect marker of myocardial dysfunction and prognosis in patients with severe sepsis and septic shock compared to BNP (Table 4). After a pilot study<sup>90</sup> had reported markedly elevated NT-proBNP levels in six patients with septic shock, the study by Roch et al<sup>66</sup> evaluated

**Table 4—Studies on the Impact of NT-proBNP Measurement in Critically Ill Patients\***

Study	Study Population (Age, † y)	Severity of Disease	Serum Creatinine Level‡	Assessment of LV Performance	NT-pro-BNP Levels	Mortality	Relationships Among BNP, LV Performance, and Outcome
Roch et al <sup>66</sup>	39 pts with septic shock and mechanical ventilation (63 ± 12 y)	SAPS II score on ICU admission, 52 ± 21	Nonsurvivors, 225 ± 77 μmol/L; survivors, 161 ± 81 μmol/L	PAC: LVSWI at 12 h: Nonsurvivors, 28 ± 11 g/m/m <sup>2</sup> ; Survivors, 42 ± 18 g/m/m <sup>2</sup> LVSWI at 24 h: Nonsurvivors, 30 ± 12 g/m/m <sup>2</sup> ; survivors, 43 ± 23 g/m/m <sup>2</sup>	Highest level in the first 24-h period: nonsurvivors, 34,028 pg/mL (range, 11,735–49,320 pg/mL) survivors, 7,856 pg/mL (range, 1,291–12,972 pg/mL; Pts with lowest LVSWI < 35g g/m/m <sup>2</sup> , 16,122 pg/mL (range, 8,414–48,839 pg/mL); Pts with lowest LVSWI > 35 g/m/m <sup>2</sup> , 4,799 pg/mL (range, 2,090–9,966 pg/mL)	In hospital, 24/39 pts (56%)	Correlation between NT-pro-BNP, and LVSWI ( $r = -0.34$ ); the highest NT-proBNP level in the 24-h period after study inclusion was an independent predictor of ICU mortality; NT-proBNP > 13,600 pg/mL predicted ICU mortality with an accuracy of 77%
Jelic et al <sup>66</sup>	41 pts with respiratory failure defined as hypoxemia‡ and infiltrates on chest x-ray (66.5 ± 16 y); sepsis/septic shock in 20 pts	APACHE II score, 18.5 ± 1; 39/41 pts (95%) mechanically ventilated	NA; creatinine clearance, 60.5 ± 7 mL/min	PAC: 34 pts with LVSWI < 35 g/m/m <sup>2</sup> , 18 pts with PCWP > 15 mm Hg	LVSWI < 35 g/m/m <sup>2</sup> , 13,528 ± 2,399 pg/mL; LVSWI > 35 g/m/m <sup>2</sup> , 1,236 ± 83 pg/mL; nonsurvivors, 11,777 ± 2,990 pg/mL; survivors, 11,630 ± 3,182 pg/mL	30 d, 17/40 pts (43%)	NT-proBNP correlated with LVSWI ( $r = -0.62$ ) and CI ( $r = -0.44$ ), no correlation with PCWP; NT-proBNP cannot differentiate low vs high PCWP respiratory failure; NT-proBNP correlated with creatinine clearance ( $r = -0.6$ ); NT-proBNP without prognostic value
Brueckmann et al <sup>46</sup>	57 pts with severe sepsis (55 ± 16.3 y)	APACHE II score, 26 (range, 19–30); 45/57 pts (79%) needed vasopressors	97 μmol/L (range, 81–163 μmol/L)	PAC: LVSWI, 36.6 ± 11.1 g/m/m <sup>2</sup> ; CI, 4.5 L/min/m <sup>2</sup> ; TTE (n = 29): 6 pts with LVEF 35–50%, 4 pts with LVEF < 35%	Nonsurvivors, 1,431 pg/mL (range, 712–1,920 pg/mL); survivors, 493 pg/mL (range, 314–1,126 pg/mL)	28 d, 16/57 pts (28%)	NT-proBNP correlated with creatinine ( $r = 0.58$ ), cTnI levels ( $r = 0.68$ ), APACHE II score ( $r = 0.42$ ); higher NT-proBNP levels in nonsurvivors than in survivors; NT-proBNP level significant predictor for mortality

\*See Tables 2 and 3 for abbreviations not used in the text.

†Values in parentheses are mean ± SD, unless otherwise noted.

‡To convert from mg/dL to μmol/L, multiply serum creatinine values by 88.4.

§Oxygen saturation, < 90%; or arterial oxygen pressure, < 60 mm Hg. ||Outcome not available for one patient.

NT-proBNP levels in 39 patients with septic shock who received mechanical ventilation and found higher median maximal NT-proBNP levels in nonsurvivors (34,028 pg/mL; interquartile range, 11,735 to 49,320 pg/mL) compared to survivors (7,856 pg/mL; interquartile range, 1,291 to 12,972 pg/mL;  $p = 0.002$ ). An NT-proBNP level of  $> 13,600$  pg/mL during the 24-h period after study inclusion has been shown to predict ICU mortality with a sensitivity of 73% and a specificity of 83% (area under the curve, 0.8). The NT-proBNP level was higher in nonsurvivors than in survivors at each time between study inclusion and day 7. In addition, a weak inverse correlation between NT-proBNP level and LVSWI ( $r = -0.34$ ) was found. The lowest LVSWI value during the first 24 h after study inclusion was the only independent predictor of an NT-proBNP level of  $> 13,600$  pg/mL.<sup>66</sup> These results are supported by those of a recent study<sup>56</sup> indicating that NT-proBNP level was better correlated with LVSWI than BNP level in patients with respiratory failure of septic and nonseptic origin, and that in contrast to BNP levels, NT-proBNP levels were significantly higher in patients with an LVSWI of  $< 35$  g/m/m<sup>2</sup> than in those with an LVSWI of  $> 35$  g/m/m<sup>2</sup>. However, NT-proBNP level could neither differentiate between high-PCWP vs low-PCWP respiratory failure nor predict the prognosis in this study setting, which was not restricted to patients with sepsis.<sup>56</sup> An advantage of NT-proBNP over BNP might be its longer half-life (NT-proBNP half-life, 2 h; BNP half-life, 20 min).<sup>66</sup> NT-proBNP may reflect hemodynamics and inflammatory stimuli over a longer period and thus might be more representative of the presence or absence of myocardial dysfunction and prognosis.

#### RELATIONSHIP BETWEEN CARDIAC TROPONINS AND NATRIURETIC PEPTIDES

Cardiac troponins and natriuretic peptides provide different information about myocardial dysfunction. Troponin release indicates minimal myocyte damage or loss of cell membrane integrity, and thus gives structural information, whereas BNP reflects wall stress, and thus provides functional information. Raised levels of both cardiac troponins and natriuretic peptides have been found in patients with a variety of conditions associated with overload or the damage of either or both cardiac ventricles other than ACS and CHF, including pulmonary embolism,<sup>68,91</sup> pulmonary hypertension,<sup>69,92</sup> sepsis,<sup>4-13</sup> and drug toxicity.<sup>93,94</sup> However, there have been only a few studies<sup>2,4,14</sup> available that have assessed cardiac troponins and natriuretic peptides simultaneously in

patients with sepsis. In the study by Charpentier et al,<sup>4</sup> plasma levels of cTnI increased at days 2 and 3 in patients with myocardial dysfunction and returned to normal after day 3, which was very similar to the pattern seen for BNP. Whereas BNP levels were significantly higher in nonsurvivors compared to survivors at days 2 and 3, this was not the case for cTnI levels.<sup>4</sup> In the study by Cuthbertson et al,<sup>14</sup> BNP and cTnI levels on ICU admission were higher in patients with sepsis than in other ICU patients. However, neither BNP nor cTnI levels on ICU admission or at 24 h after ICU admission were predictive for outcome in the whole study group or in the sepsis subgroup.<sup>14</sup> In the analysis by Roch and coworkers,<sup>66</sup> both NT-pro-BNP and cTnI levels were higher in nonsurvivors compared to survivors. However, only NT-pro-BNP level was a significant predictor of ICU death.<sup>66</sup> A recent study<sup>46</sup> in 57 patients with severe sepsis found a fairly good correlation between NT-proBNP and cTnI levels ( $r = 0.68$ ), which might indicate a relationship between the degree of structural myocyte damage and functional myocardial impairment.

Interestingly, one study<sup>95</sup> revealed that in about 50% of patients with advanced CHF cTnI levels were detectable in the absence of ACS, and that patients with elevated cTnI levels had higher PCWP, cardiac index, and BNP levels, and higher mortality than cTnI-negative patients. It has been hypothesized that, in response to wall stress, intracellular signaling cascades are activated, resulting in myocyte apoptosis and thus troponin release.<sup>95</sup> However, regarding the elevation of interleukin-6 both in patients with sepsis and CHF (to a lesser degree in CHF patients, however),<sup>13,96,97</sup> troponin leakage following the up-regulation of inflammatory cytokines has to be considered as an alternative explanation. The fact that even in healthy people raised levels of cTnT<sup>98,99</sup> and cTnI,<sup>98</sup> as well as BNP<sup>98</sup> are found after prolonged strenuous exercise, and that after a triathlon LVEF, fractional shortening, and stroke volume have been shown to be significantly different from prerace values despite unchanged preload and even decreased afterload, and to recover to baseline levels within 48 h,<sup>100</sup> strengthens the assumption that transient myocardial depression with short-lasting troponin leakage in the absence of myocyte necrosis and BNP release following an inflammatory process (eg, sepsis and extreme endurance exercise) does really exist. Interestingly, experimental evidence for a direct up-regulation of the BNP gene by lipopolysaccharides has come from a study in rats.<sup>101</sup> Regarding the weak correlation between BNP level and hemodynamic parameters, a similar up-regulation of proBNP synthesis and the release of BNP and NT-pro-BNP mediated by cytokines must be



therapies in patients with severe sepsis and septic shock. The high prognostic impact of an early aggressive therapy including fluid resuscitation, transfusion of packed RBCs, and dobutamine in an attempt to achieve a central venous saturation of  $\geq 70\%$  has been proven,<sup>105</sup> whereas many other interventions have failed to improve prognosis in patients with sepsis. It remains to be shown whether either cardiac troponins or natriuretic peptides will be able to identify patients who derive the highest benefit from aggressive therapy, and whether an approach combining the information coming from both of these biomarkers might be useful. Until now, the routine use of natriuretic peptides in patients with sepsis should be discouraged. However, we recommend the use of cardiac troponins as a part of the monitoring of patients with severe sepsis and septic shock with respect to predicting prognosis and impaired systolic left ventricular function.

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