Elevation of B-type natriuretic peptide levels in acute respiratory distress syndrome

A case report

Micha Maeder[a], Peter Ammann[b], Hans Rickli[b], Markus Diethelm[a]

[a] Department of Internal Medicine, Division of Intensive Care, Hospital of St. Gallen, Switzerland
[b] Department of Internal Medicine, Division of Cardiology, Hospital of St. Gallen, Switzerland

Summary

Background: B-type natriuretic peptide (BNP) has been proven to be a biochemical marker of severity of congestive heart failure. We are aware of only few papers reporting the association of BNP elevation and pulmonary hypertension (primary, thromboembolic, or as a consequence of chronic obstructive pulmonary disease). Less is known about BNP in patients with acute respiratory distress syndrome (ARDS).

Case description and results: We present the case of a previously healthy 27-year-old man with parapneumonic ARDS and an extraordinarily increased BNP level. The ventricular systolic ejection fraction assessed echocardiographically was normal with no evidence of left ventricular diastolic dysfunction. However, a peak BNP level of >1300 pg/mL (normal <100 pg/mL) was recorded. Repeated BNP values were obtained on nine separate days over a period of 3 weeks of mechanical ventilation. With the respiratory improvement following the inhalation of nitric oxide BNP levels decreased to 113 pg/mL. The possible pathophysiological mechanisms of BNP release are discussed.

Conclusion: There is evidence for BNP elevation in the absence left ventricular dysfunction. This case is an example of impressively high BNP levels associated with ARDS, probably attributable to right ventricular overload due to increased pulmonary vascular resistance.

Key words: B-type natriuretic peptide; acute respiratory distress syndrome; inhaled nitric oxide; right ventricle

Introduction

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by the cardiac ventricles in response to volume and pressure overload. BNP exhibits vasodilatory and natriuretic effects and counterbalances the deleterious effects of the renin-angiotensin-system in heart failure [1]. BNP as marker of left ventricular (LV) wall stretch and consecutive neurohumoral activation has emerged as a widely used tool in the diagnosis and exclusion of congestive heart failure (CHF) [1, 2]. Less is known about natriuretic peptides in sepsis and acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Elevated A-type natriuretic peptide (formerly atrial natriuretic peptide, ANP) levels have been found in patients with sepsis [3] and ALI/ARDS [4, 5] and have been associated with sepsis-induced myocardial depression [3] and severity of ARDS [4], whereas only one study demonstrated elevated BNP levels in patients with ARDS [5]. These BNP values were moderately high and have been shown to correlate with pulmonary and systemic vascular resistance, but not with the partial pressure of arterial oxygen (paO_2) or the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (paO_2/FiO_2) [5]. We report very high BNP levels in a young patient with ARDS.

Case report

A 27-year-old previously healthy man without cardiovascular risk factors was admitted to our intensive care unit because of acute respiratory decompensation. Chest x-ray showed bilateral pulmonary infiltrates and left-sided pleural effusion. Intravenous antibiotic treatment with clarithromycin 500 mg q12h, amoxicillin-clavulanate

2.2 g q8h and doxycycline 100 mg q12h was instituted. A bronchial secretion specimen revealed β-haemolytic group B streptococci, susceptible to all the currently used antibiotics. Pleurocentesis was consistent with parapneumonic effusion. Within hours the chest x-ray showed extensive bilateral alveolar opacities, and the patient had to be intubated and mechanically ventilated (figure 1). After 48 hours of intubation (in the subsequent text "day" refers to the "day of intubation") the maximal fraction of inspired oxygen (FiO_2 1.0) was necessary and respiratory acidosis occurred. The antibiotic regimen was replaced by clarithromycin 500 mg q12h and piperacillin-tazobactam 4.5 g q8h. Transthoracic echocardiography revealed a normal sized, non-hypertrophic left ventricle (left ventricular muscle mass index 64 g/m²) the ejection fraction being 70%. The transmitral inflow pattern was normal (ratio of early peak flow velocity to atrial peak flow velocity (E/A ratio) 1.5, deceleration time 200 ms). The right ventricle was not dilated, and right ventricular (RV) ejection frac-

tion was normal. No tricuspid regurgitation could be detected. There was a small pericardial effusion (day 2). The following criteria for ARDS were fulfilled: 1) acute onset, 2) bilateral infiltrates on chest radiography, 3) absence of clinical or echocardiographic evidence of left atrial hypertension, and 4) paO_2/FiO_2 of 200 or less [6]. Laboratory analyses showed normal cardiac troponin I levels, but a markedly elevated BNP level (1110 pg/mL, Biosite Diagnostics, San Diego, California), which was even higher (>1300 pg/mL) the following day.

On the fifth day treatment with inhaled nitric oxide (iNO) was instituted (5 to 25 ppm). From the 4th to the 19th day respiratory tidal volumes were between 4.8 and 6.4 mL/kg body weight with a respiratory rate between 28 to 31 cycles/min, and PEEP was between 5 and 12 cm H_2O. Methylprednisolone in a dosage of 125 mg (2 mg/kg body weight) q24h was given from day 8 to day 16 and was then reduced to 80 mg q 24h. Minimal paO_2/FiO_2 was 57 mm Hg (day 7), maximal pCO_2 was 88 mm Hg (day 8), minimal pH was 7.21 (day 8), and maximal lactate was 1.7 mmol/L.

Table 1 demonstrates BNP levels during mechanical ventilation. Figure 2 summarises important clinical and laboratory variables (values assessed and blood samples taken between 6 and 8 a.m. of each day). Pulmonary recovery went parallel with a massive reduction of BNP levels from >1300 pg/mL to 113 pg/mL (days 3 to 14). Apart from norepinephrine up to a maximal dosage of 20 mcg/min from day 1 to 4 for sustained hypotension despite adequate administration of fluids, no additional therapy with inotropic agents, systemic vasodilators or diuretics was required to stabilise haemodynamics and to maintain diuresis. Mean arterial pressure was not higher than 70 mm Hg during the first week. Creatinine did not exceed a level of 100 mcmol/L during hospitalisation. After 21 days of mechanical ventilation our patient could be extubated. Five days later BNP was 23 pg/mL.

Figure 1

Chest radiograph showing extensive bilateral alveolar opacities.

Figure 2

Time course of BNP, oxygenation, and haemodynamics. Note that the left-sided scale (until 1500) concerns BNP levels, whereas the right-sided scale (until 400) concerns the other three variables. Treatment with iNO and methylprednisolone are indicated.
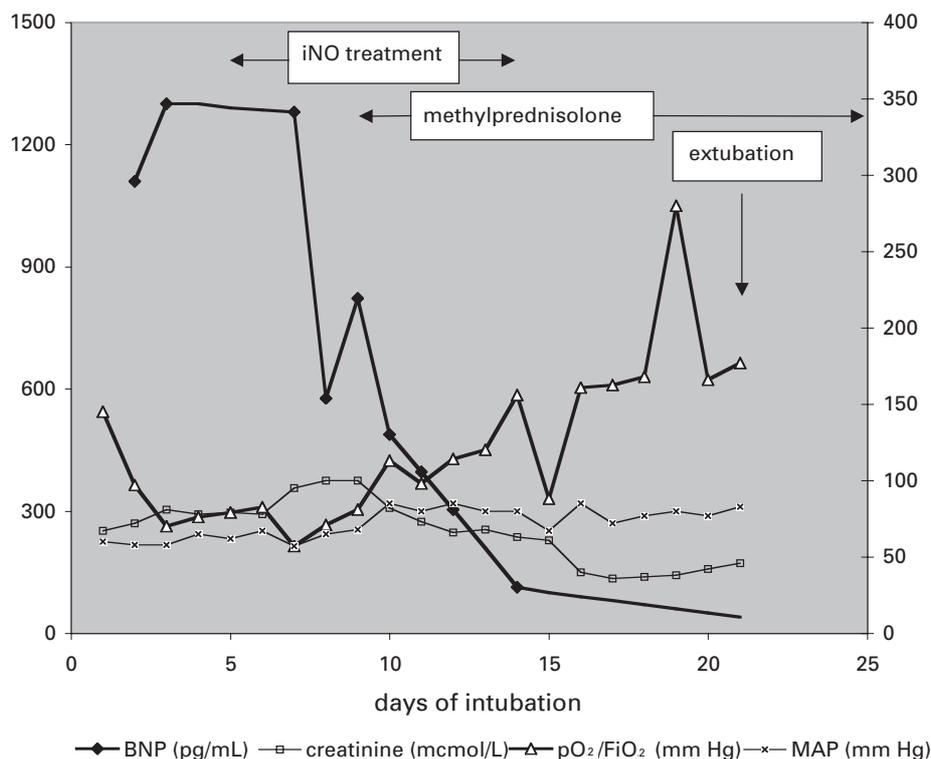
Table 1

B-type natriuretic peptide (BNP) levels on nine different days while the patient was intubated and corresponding clinical and laboratory variables.
PO$_2$ = partial pressure of arterial oxygen; FiO$_2$ = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; CVP = central venous pressure; MAP = mean arterial pressure; HR = heart rate; CRP = C-reactive protein.

Intubation day	BNP (pg/mL)	pO$_2$/FiO$_2$ (mm Hg)	PEEP (cm H$_2$O)	CVP (cm H$_2$O)	MAP (mm Hg)	HR (bpm)	CRP (mg/L)	Creatinine (mcmol/L)	Troponin I (mcg/L)
2	1110	97	6	10	58	110	216	72	<0.3
3	>1300	70	10	15	58	95	299	81	<0.3
7	1280	57	10	11	57	90	219	95	
8	577	71	12	8	65	95	213	100	
9	822	81	12	11	68	85	189	100	
10	488	113	12	21	98	80	80	82	<0.3
11	396	98	12	20	90	75	36	73	
12	304	114	10	17	98	85	21	66	
14	113	156	8	12	93	80	26	63	

Discussion

Pressure or volume overload of both ventricles due to different underlying conditions induces BNP release. Left ventricular systolic dysfunction [1, 2] as well as LV diastolic dysfunction [7] are well known conditions associated with BNP secretion. Patients with LV systolic dysfunction have higher BNP levels than those with isolated LV diastolic dysfunction in most cases. However, there is a considerable overlap between the two groups [8]. Levels higher than 1000 pg/ml usually are observed in patients with systolic left ventricular pump failure [1, 2]. Beyond LV dysfunction, there are reports of volume and pressure overload of the right ventricle leading to slightly to moderately elevated BNP levels [9]. BNP levels secreted by the right ventricular (RV) myocardium are said not to exceed 300–600 pg/mL [2] and not to be as high as in cases of elevated LV end-diastolic pressure [1, 2]. Acute cor pulmonale as a consequence of increased pulmonary vascular resistance (PVR) is known to occur in 60% of patients with ARDS submitted to conventional mechanical ventilation without airway pressure limitation [10] and still in 25% of patients with ARDS submitted to protective ventilatory support [10], which might cause BNP elevation as it does chronic RV pressure overload [9].

In patients with sepsis, biventricular dilatation and depression of ventricular ejection fraction as a consequence of not precisely known mediators can occur [11]. Decreased peripheral resistance results in reduced LV afterload and therefore sometimes allows maintaining or even elevating cardiac output despite the presence of depressed LV contractility. In contrast, PVR in sepsis and ARDS increases and may lead to RV overload and decreased RV output in the presence of impaired RV contractility [11]. This reversible phenomenon of sepsis-induced cardiac depression usually lasts for about 7 to 10 days and is detectable by echocardiography [11]. Despite the absence of common risk factors for the development of LV diastolic dysfunction including hypertension, older age and female gender [12] isolated diastolic dysfunction

may occur even in young patients with septic shock [13]. However, regarding the high normal LV ejection fraction and the normal mitral inflow pattern neither systolic nor diastolic left ventricular dysfunction may have caused the massive BNP release in the case presented here. Recently, elevated BNP levels in patients with septic shock were shown to be inversely correlated with the cardiac index [14]. Preserved diuresis and haemodynamic stability without positive inotropic drugs or diuretics as well as the echocardiographic finding of a high normal LV ejection fraction let us assume that our patient was not suffering from low cardiac output. Additionally, our patient had repeatedly normal levels of cardiac troponin I, which is an argument against myocardial damage during hospitalisation even during the time of BNP elevation. Troponin I is known as a marker of depressed LV ejection fraction and a poor prognosis in critically ill patients without acute coronary syndromes [15]. Norepinephrine is a predominantly α-receptor agonist with systemic and pulmonary vasoconstrictor properties [16]. Its use during the first four days might have caused an increase in LV afterload causing BNP release. But the fact that mean arterial pressure did not exceed 70 mm Hg in response to norepinephrine administration with an absence of signs of impaired cardiac output, speaks against a massive increase in systemic vascular resistance leading to maximal BNP release. On the other hand, we suggest that acute cor pulmonale due to hypoxic vasoconstriction in ARDS [10, 16] and a further increase in PVR due to norepinephrine infusion [16] might have caused BNP elevation. Echocardiographic signs of RV overload, eg, RV dilatation, may be absent, particularly if PEEP is used and causes relative hypovolaemia by reducing of venous return [17]. Treatment with iNO can improve oxygenation and reduce PVR in a subgroup of patient with ARDS (responders) by its local vasodilatatory effects on preconstricted vessels in ventilated regions of the lung thereby reducing intrapulmonary shunting [16]. We assume that the

very high BNP levels and their rapid decline mainly reflect RV overload and relief from overload respectively. The transient worsening of oxygenation on day 15 might correspond to a rebound effect after iNO therapy had been stopped. Since echocardiographic signs of RV overload were not present and pulmonary hypertension could not be assessed while tricuspid regurgitation was absent, we can not absolutely exclude BNP release due to other mechanisms than myocardial overload. There is evidence that BNP elevation in critically ill patients occurs at least in part independently of RV or LV overload, especially in patients with acute pathologies of the central nervous system, eg, subarachnoid haemorrhage [18, own observations]. BNP is cleared from plasma by two distinct mechanisms: natriuretic peptide receptor C-mediated endocytosis and degradation by membrane-bound neutral endopeptidase 24.11. The normal half life is 18–22 minutes [1]. Increased BNP release due to neurohumoral activation other than myocyte stretch or impaired BNP clearance may occur in patients with septic shock and may explain the plasma levels presented here. Data on the influence of glucocorticoids on plasma levels of natriuretic peptides are based on experimental studies with controversial findings. Dexamethasone

seems to up-regulate ANP genes in rat ventricular myocytes [19], but also enhances concentrations of neutral endopeptidase 24.11 in human vascular smooth muscle cells [20], which in turn favours degradation of natriuretic peptides. The effect of methylprednisolone administration on BNP levels in our patient therefore remains speculative.

In conclusion, even very high BNP levels in critically ill patients do not exclusively implicate left-sided heart failure in all cases, but might reflect RV overload due to increased PVR in severe pulmonary disease or changes in BNP release and clearance not directly related to myocardial stretch. The widespread use of BNP testing and prospective clinical studies with the use of pulmonary artery catheters probably will further clarify the impact of BNP testing in critically ill patients.

Correspondence:
Micha Maeder, MD
Department of Internal Medicine
Division of Intensive Care
Hospital of St. Gallen
Rorschacherstrasse
CH-9007 St. Gallen
E-Mail: micha.maeder@kssg.ch

References

1 Tabbibizar R, Maisel A. The impact of B-type natriuretic peptide levels on the diagnosis and management of congestive heart failure. Curr Opin Cardiol 2002;17:340–5.

2 Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnoea. J Am Coll Cardiol 2002;39:202–9.

3 Hartemink KJ, Groeneveld ABJ, De Groot MCM, Strack van Schijndel RJM, Van Kamp G, Thijs LG. α-atrial natriuretic peptide, cyclic guanosine monophosphate, and endothelin in plasma as markers of myocardial depression in human septic shock. Crit Care Med 2001;29:80–7.

4 Tanabe M, Ueda M, Endo M, Kitajima M. Effects of acute lung injury and coexisting disorders on plasma concentrations of atrial natriuretic peptide. Crit Care Med 1994;22:1762–8.

5 Mitaka C, Hirata Y, Nagura T, Tsunoda Y, Itoh M, Amaha K. Increased plasma concentrations of brain natriuretic peptide in patients with acute lung injury. J Crit Care 1997;12:66–71.

6 Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334–49.

7 Cabanes L, Richaud-Thiriez B, Fulla Y, Heloire F, Vuillemard C, Weber S, et al. Brain natriuretic peptide blood levels in the differential diagnosis of dyspnea. Chest 2001;120:2047–50.

8 Maisel A, McCord J, Nowak RM, Hollander JE, Wu AHB, Duc P, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. J Am Coll Cardiol 2003;41:2010–7.

9 Nagaya N, Nishikimi T, Okanao Y, Uematsu M, Satoh T, Kyotani S, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202–8.

10 Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 2001;29:1551–5.

11 Krishnagopalan S, Kumar A, Parillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. Curr Opin Crit Care 2002;8:376–88.

12 Angeja BG, Grossmann W. Evaluation and management of diastolic heart failure. Circulation 2003;107:659–63.

13 Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997;23:553–60.

14 Witthaut R, Busch C, Fraunberger P, Walli A, Seidel D, Pilz G, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. Intensive Care Med 2003;29:1696–702.

15 Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol 2003;41:2004–9.

16 Papazian L, Roch A, Bregon F, Thirion X, Gaillat F, Saux P, et al. Inhaled nitric oxide and vasoconstrictors in acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:473–9.

17 Jardin F, Dubourg O, Bourdarias JP. Echocardiographic pattern of acute cor pulmonale. Chest 1997;111:209–17.

18 Berendes E, Van Aken H, Raufhake C, Schmidt C, Assmann G, Walter M. Differential secretions of atrial and brain natriuretic peptide in critically ill patients. Anaesth Analg 2001;93:676–82.

19 Nishimori T, Tsujino M, Sato K, Imai T, Marumo F, Hirata Y. Dexamethason-induced up-regulation of adrenomedullin and atrial natriuretic peptide genes in cultured rat ventricular myocytes. J Mol Cell Cardiol 1997;29:2125–30.

20 Graf K, Schaper C, Grafe M, Fleck E, Kunkel G. Glucocorticoids and protein kinase C regulate neutral endopeptidase 24.11 in human vascular smooth muscle cells. Basic Res Cardiol 1998;93:11–7.

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

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

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

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly