Nonheart failure-associated elevation of amino terminal pro-brain natriuretic peptide in the setting of sepsis

Simona L Bar MD, Elizabeth Swiggum MD FRCPC, Lynn Straatman MD FRCPC, Andrew Ignaszewski MD FRCPC

SL Bar, E Swiggum, L Straatman, A Ignaszewski. Nonheart failure-associated elevation of amino terminal pro-brain natriuretic peptide in the setting of sepsis. Can J Cardiol 2006;22(3):263-266.

In addition to its importance in clinical assessment, N-terminal pro-brain natriuretic peptide (NT pro-BNP) is a valuable marker for evaluation of treatment and prognosis of heart failure. However, there are situations where NT pro-BNP is not related to myocardial dysfunction. Two cases of sepsis with markedly elevated NT pro-BNP levels that are not indicative of depressed myocardial function are described.

Key Words: *Congestive heart failure; Natriuretic peptides; Shock*

L'élévation du pro-peptide natriurétique cérébral N-terminal non associé à une insuffisance cardiaque en présence d'une sepsie

Outre son importance dans l'évaluation clinique, le pro-peptide natriurétique cérébral N-terminal (NT pro-BNP) est un marqueur valable d'évaluation du traitement et un pronostic d'insuffisance cardiaque. Cependant, dans certaines situations, le NT pro-BNP n'est pas relié à une dysfonction myocardique. Deux cas de sepsie accompagnés de taux manifestement élevés de NT pro-BNP non indicatifs d'une fonction myocardique déprimée sont décrits.

One-half of a century has been spent debating the etiology of depressed myocardial function in septic shock (1). Brain natriuretic peptide (BNP) is a new biomarker for cardiac dysfunction, and most data in the literature associate its increased levels with depressed myocardial function (2-5). However, increased levels of BNP have also been found in critical illnesses associated with shock (eg, sepsis), apparently not related to myocardial dysfunction. In human myocardium, BNP is secreted in response to myocardial stretch. Its release promotes natriuresis and diuresis, and it has a vasodilatory effect on systemic circulation (6). As such, it reduces preload, venous return and filling pressures with a subsequent reduction in cardiac output (7). The measured BNP increases in response to increases in left ventricular (LV) end-diastolic pressure, pulmonary artery wedge pressure, atrial pressure and LV hypertrophy (8). BNP level is also associated with echocardiographic dysfunction and clinical outcomes (9). The degree of cardiac dysfunction determines the magnitude of increase in BNP level (10).

The BNP gene contains an encoded protein consisting of 108 peptides, called pro-BNP (11). The cleavage of pro-BNP within the heart results in two components produced in equal amounts: BNP 32 (the active hormone) and N-terminal (NT) pro-BNP (the inactive fragment) (12). The plasma half-life of NT pro-BNP is approximately 2 h in comparison with that of BNP 32 (20 min) (13), which explains the higher level of NT pro-BNP in myocardial dysfunction (14).

In addition to the documented relationship between BNP and myocardial dysfunction mentioned above, there are other conditions associated with increased BNP level that include primary pulmonary hypertension, myocarditis, cardiac allograft rejection, arrhythmogenic right ventricle with decreased LV ejection fraction (EF), renal failure, Kawasaki disease, ascitic cirrhosis and endocrine diseases (Cushing's syndrome, primary hyperaldosteronism) (8). Other patient characteristics that may influence the BNP level, independent of disease, are advancing age, probably reflecting LV subclinical abnormalities (15) and female sex, both of which result in increased BNP level (15,16). Two additional studies have confirmed the correlation of NT pro-BNP with age, but not with sex (17,18). In contrast, obesity is associated with decreased levels of BNP, probably as a result of increased clearance through a receptor contained in adipose tissue (19).

Parker et al (20) demonstrated that myocardial depression is also present in human septic shock and is associated with ventricular dilation and decreased LVEF (20). We present two cases of septic shock with markedly increased levels of NT pro-BNP with no evidence of myocardial dysfunction based on evaluation using echocardiography and catheterization. Also described are possible explanations of elevated NT pro-BNP in a setting not related to myocardial dysfunction. Thus, there are situations where the predictive value of BNP is not correlated with the magnitude of heart failure. Consequently, we emphasized the need for a comprehensive evaluation using clinical assessment in addition to measurement of NT pro-BNP.

CASE PRESENTATIONS

Patient 1

A 79-year-old man with documented hypertension and mitral regurgitation was admitted for mitral valve repair and pulmonary vein ablation therapy for chronic atrial fibrillation. Normal coronaries were documented angiographically. His LVEF before surgery was 65%. Mitral valve annuloplasty and pulmonary vein ablation were performed, and a dual-mode, dual-pacing, dual-sensing pacemaker was subsequently inserted

Healthy Heart Program, St Paul's Hospital, Vancouver, British Columbia
Correspondence and reprints: Dr Andrew Ignaszewski, Healthy Heart Program, St Paul's Hospital, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6. Telephone 604-806-3649, fax 604-806-8590, e-mail AIgnaszewski@providencehealth.bc.ca
Received for publication April 20, 2005. Accepted July 12, 2005

following a Mobitz II AV block. During the follow-up period, the patient developed progressive dyspnea with minimal exertion. NT pro-BNP concentration was 3431 pg/mL (laboratory normal less than 855 pg/mL). Echocardiography revealed severe mitral regurgitation caused by a dehiscent mitral valve ring. He returned to the operating room to have a redo tissue mitral valve replacement. On the third postoperative day, his temperature increased to 37.9°C, and he developed acute renal failure with a creatinine concentration of 371 µmol/L (normal range 40 µmol/L to 120 µmol/L). A second NT pro-BNP concentration was 17,470 pg/mL. The postoperative course was complicated by aspiration pneumonia with Gram-negative *Serratia* that were revealed in blood cultures together with coagulase-negative *Staphylococcus*. The patient was intubated and treated with broad-spectrum antibiotics (vancomycin and ceftazidime). A new echocardiographic study showed an LVEF of 60%, moderate tricuspid regurgitation and trivial mitral regurgitation. There was no echocardiographic evidence of endocarditis. Pulmonary artery (PA) systolic pressure was 62 mmHg. The patient developed markedly increased work of breathing. Pulmonary capillary wedge pressure (PCWP) was 14 mmHg, cardiac index (CI) was 4.8 L/min/m^2, and systemic vascular resistance (SVR) was 339 dynes/s × cm^{-5}.

Repeat NT pro-BNP was 9980 pg/mL. White blood cell count was 12.0 g/L (normal range 4 g/L to 11 g/L), and creatinine rose to 460 µmol/L (baseline 111 µmol/L). Chest x-ray showed extensive consolidation on the right lower lobe and left middle lung. The patient was diagnosed as having ventilator-associated pneumonia with *Staphylococcus aureus* (cultured in sputum) and, subsequently, septic shock. Therapy with antibiotics and inotropes were instituted. The patient was transferred to the intensive care unit with hypoxemic respiratory failure and hemodynamic compromise, and measures of ventilatory and inotropic support were reinstituted. Despite maximal therapy, progression of septic shock was irreversible, and multiple organ system failure followed.

Patient 2

An 83-year-old woman with a previous myocardial infarction and aortic stenosis was admitted for coronary artery bypass graft surgery and aortic valve replacement. A previous heart catheterization showed normal right heart pressures, with a PA systolic pressure of 31/12 mmHg, PCWP of 11 mmHg, and a CI of 2 L/min/m^2. Coronary angiography showed a right coronary artery stenosis of 90% and a proximal left anterior descending artery stenosis of 80%. She also had chronic renal impairment with a baseline creatinine concentration of 115 µmol/L and a glomerular filtration rate of 40 mL/min. Preoperative echocardiography documented an LVEF of 65%, mild mitral regurgitation, aortic valve area of 0.8 cm^2 with a mean gradient of 30 mmHg and LV hypertrophy. Coronary artery bypass graft surgery was performed together with a bovine pericardial bioprosthetic aortic valve replacement with no postoperative complications. An intraoperative transesophageal echocardiogram showed normal left and right ventricular function with an LVEF of 70% and moderate mitral regurgitation. During the following days, she experienced episodes of atrial fibrillation with rapid ventricular response and sinus pauses of up to 8 s with subsequent insertion of a ventricle-paced, ventricle-sensed, inhibited, rate-responsive pacemaker. *Escherichia coli* was found in the urine culture and treated. During the postoperative period, she became progressively dyspneic with no symptomatic improvement despite escalating doses of diuretics (furosemide up to 280 mg/day intravenously and metolazone). Laboratory investigations included NT pro-BNP, extremely elevated at 28,000 pg/mL, that suggested significant myocardial depression. Objective examination revealed cool skin, a temperature of 35°C and blood pressure of 75/30 mmHg on milrinone; the heart was paced at 60 beats/min and the respiratory rate was 30 breaths/min. PA catheter measurement revealed a CI of 8.3 L/min/m^2, PA systolic pressure of 40/18 mmHg, PCWP of 18 mmHg and an SVR of 105 dynes/s × cm^{-5}. The diagnosis of septic shock was apparent. An echocardiographic study showed a well seated aortic valve prosthesis, LVEF of 70%, aortic valve area of 1.2 cm^2, gradient of 17 mmHg, severe mitral regurgitation, moderate tricuspid regurgitation, PA systolic pressure of 50 mmHg and no evidence of endocarditis. Vasopressor therapy (noradrenaline) was initiated, and antibiotic therapy was started empirically (piperacillin-tazobactam/vancomycin) for treatment of presumed endocarditis. Despite maximal therapy with inotropes and antibiotics, the progression of septic shock was irreversible. A subsequent/postmortem blood culture revealed coagulase-negative *Staphylococcus* sensitive to vancomycin.

DISCUSSION

We described two patients with septic shock, markedly elevated levels of NT pro-BNP and normal myocardial function documented on complementary investigations (heart catheterization and echocardiography). We have also described possible explanations for elevated NT pro-BNP in this setting unrelated to myocardial dysfunction. Even though BNP has been considered an optimal marker for cardiac dysfunction, the lack of data to provide a rationale for its changes during sepsis suggests that the clinical assessment should be incorporated when evaluating patients with presumed myocardial depression.

An association of elevated BNP with sepsis in critically ill patients has been reported (21), but the cause of BNP increase is not well understood. Sepsis is a systemic response to a localized injury, and a very common cause of mortality in intensive care units (22). One of the most important consequences of septic shock is cardiac dysfunction. Both systolic (23) and diastolic impairment (24) are present during sepsis. Recent studies have demonstrated a correlation of the severity of cardiac dysfunction with mortality (9). In survivors of the septic shock, cardiac dysfunction is transient with EF and ventricular dilation returning to normal in seven to 10 days (23). BNP increase is also transient. In contrast, in patients who do not survive, the lack of ventricular dilation and preservation of EF indicates a poor compensatory mechanism (9). Our cases are unusual in that NT pro-BNP levels were markedly elevated, suggesting significant myocardial depression. Nevertheless, normal LV systolic function and filling pressures were identified. The recent ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) (15) study has reported three patients with elevated NT pro-BNP in the setting of septic shock. A level of NT pro-BNP greater than 10,000 pg/mL has confirmed the diagnosis of heart failure in more than 99% of newly diagnosed cases and in 94% of heart failure cases. Additionally, age-stratified cutoff points have been included to increase diagnostic accuracy of heart failure (Table 1) (15). The association of NT pro-BNP with New York Heart Association (15) symptom severity described in the PRIDE study is presented in Table 2. NT pro-BNP assessment seems to

surpass clinical evaluation by direct comparison; however, we submit that a higher diagnostic yield will be achieved by using both clinical and laboratory evaluation (15).

Both of our patients progressed to septic shock. An increased level of BNP and vasodilation in septic shock is a consequence of the cytokine production (9,25,26). Tumour necrosis factor-alpha and interleukin-1beta are important cytokines released during sepsis, which are associated with myocardial depression (25). It has been demonstrated that these proinflammatory cytokines upregulate the BNP gene expression and secretion (27). In addition, cardiotrophin-1, a member of the interleukin-6 family, increases the BNP messenger RNA expression in vivo (28). One of the mechanisms by which BNP exerts its vasodilatory effect is nitric oxide (NO) production (29). The basal NO production is correlated with the severity of cardiac dysfunction and is reflected in the levels of plasma BNP (30). An increased NO production in sepsis can have both beneficial and deleterious effects. Beneficial effects manifest by vasodilation in systemic and pulmonary territories and an increase in myocardial oxygen supply, as well as a preservation of the CI. The deleterious effects manifest as a decrease in blood pressure and SVR, concomitant with poorer tissue oxygenation (31). Additionally, BNP exerts a cardiac antihypertrophic action independent of the endothelial NO production in diabetic rats (32). In septic shock, Gram-negative organisms mediate myocardial depression by a mechanism that involves NO release (33). By a similar mechanism, *S aureus* alpha toxin produces coronary vasoconstriction and myocardial depression (34). An additional study (35) reveals that endotoxin, which also modulates BNP expression and secretion, synergizes with a component of pathogen and nonpathogen Gram-positive bacteria to cause the release of NO (36). NO has the ability to autoregulate its own production, and by negative feedback (37) may counteract myocardial depression (31) and vasoconstriction in sepsis (38). Therefore, small quantities of NO are necessary to maintain myocardial contractility in sepsis (31), and NO generation may represent a compensatory mechanism in sepsis-induced coronary vasoconstriction and myocardial dysfunction.

Our patients had Gram-positive and Gram-negative bacteria in cultures at different times during their illness and they did not survive, which is consistent with a prior report that demonstrated a lack of LV dilation in patients who did not survive (9). It has been suggested that critically ill patients who do not present LV dilation and reduction of EF in response to sepsis are more likely to die and less likely to have an elevated BNP. In contrast, patients with septic shock who survive have elevated BNP levels and reduced EF which normalize quickly once medically stable (9). Interestingly, in our two cases, NT pro-BNP was markedly elevated. However, no LV dilation or systolic dysfunction resulted. This may illustrate a potential mechanism for increased mortality in septic patients who do not exhibit expected compensatory hemodynamic changes.

There are limitations to our study in terms of the measurement of the NO and cytokine production. In addition, both of our patients developed renal failure during their sepsis, a condition known to modify the NT pro-BNP level through decreased clearance or associated subclinical structural heart disease (15).

Heart failure is a chronic medical condition with a very poor prognosis (39). Hence, there is an imperative need for a greater diagnostic accuracy. The literature is expanding suggesting that NT pro-BNP is not a stand-alone test for predicting heart failure and likely requires inclusion in a scoring system where clinical assessment remains important in the diagnosis and management of heart failure.

TABLE 1
Correlation of age with concentration of N-terminal pro-brain natriuretic peptide (NT pro-BNP)

	Younger than 50 years of age	Between 50 and 75 years of age	Older than 75 years of age
NT pro-BNP concentration (pg/mL)	<450	<900	<1800

Adapted from reference 15

TABLE 2
Correlation of New York Heart Association (NYHA) class with N-terminal pro-brain natriuretic peptide (NT pro-BNP) concentration

NYHA class	II	III	IV
NT pro-BNP concentration (pg/mL)	1591	3438	5564

Adapted from reference 15

REFERENCES

1. Waisbren BA. Bacteremia due to Gram-negative bacilli other than the Salmonella: A clinical and therapeutic study. AMA Arch Internal Med 1951;88:467-88.
2. Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004;32:660-5.
3. de Groote P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak exercise oxygen consumption provide independent information for risk stratification in patients with stable congestive heart failure. J Am Coll Cardiol 2004;43:1584-9.
4. Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002;39:131-8.
5. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, vonScheidt W. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. J Am Coll Cardiol 2001;38:1934-41.
6. Valli N, Gobinet A, Bordenave L. Review of 10 years of the clinical use of brain natriuretic peptide in cardiology. J Lab Clin Med 1999;134:437-44.
7. Woods RL. Cardioprotective functions of atrial natriuretic peptide and B-type natriuretic peptide: A brief review. Clin Exp Pharmacol Physiol 2004;31:791-4.
8. Peacock WF IV. The B-type natriuretic peptide assay: A rapid test for heart failure. Cleve Clin J Med 2002;69:243-51.
9. Castillo JR, Zagler A, Carillo-Jimenez R, Hennekens CH. Brain natriuretic peptide: A potential marker for mortality in septic shock. Int J Infect Dis 2004;8:271-4.
10. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: Effect of stretching. Endocrinology 1993;132:1961-70.
11. Sudoh T, Maekawa K, Kojima M, Minamino N, Kangawa K, Matsuo H. Cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide. Biochem Biophys Res Commun 1989;159:1427-34.
12. Hunt PJ, Espiner EA, Nicholls MG, Richards AM, Yandle TG. The role of the circulation in processing pro-brain natriuretic peptide (proBNP) to aminoterminal BNP and BNP-32. Peptides 1997;18:1475-81.
13. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. Rev Cardiovasc Med 2003;4(Suppl 4):S13-9.

14. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): A new marker of cardiac impairment. Clin Endocrinol (Oxf) 1997;47:287-96.
15. Baggish AL, Cameron R, Anwaruddin S, et al. A Clinical and Biochemical Critical Pathway for the Evaluation of Patients with Suspected Acute Congestive Heart Failure. The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Algorithm. Crit Pathways in Cardiol 2004;3:171-6.
16. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: Impact of age and gender. J Am Coll Cardiol 2002;40:976-82.
17. Maisel AS, Clopton P, Krishnaswamy P, et al. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: Results from the Breathing Not Properly (BNP) multinational study. Am Heart J 2004;147:1078-84.
18. Bay M, Kirk V, Parner J, et al. NT-proBNP: A new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. Heart 2003;89:150-4.
19. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590-5.
20. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. Chest 1990;97:126-31.
21. Chua G, Kang-Hoe L. Marked elevations in N-terminal brain natriuretic peptide levels in septic shock. Crit Care 2004;8:R248-50.
22. Fitch SJ, Gossage JR. Optimal management of septic shock: Rapid recognition and institution of therapy are crucial. Postgrad Med 2002;111:53-66.
23. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100:483-90.
24. Jafri SM, Lavine S, Field BE, Baharozian MT, Carlson RW. Left ventricular diastolic function in sepsis. Crit Care Med 1990;18:709-14.
25. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med 1996;183:949-58.
26. Witthaut R, Busch C, Fraunberger P, 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.
27. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004;36:505-13.
28. Hamanaka I, Saito Y, Nishikimi T, et al. Effects of cardiotrophin-1 on hemodynamics and endocrine function of the heart. Am J Physiol Heart Circ Physiol 2000;279:H388-96.
29. van der Zander K, Houben AJ, Kroon AA, De Mey JG, Smits PA, de Leeuw PW. Nitric oxide and potassium channels are involved in brain natriuretic peptide induced vasodilatation in man. J Hypertens 2002;20:493-9.
30. Ishibashi Y, Shimada T, Sakane T, et al. Contribution of endogenous nitric oxide to basal vasomotor tone of peripheral vessels and plasma B-type natriuretic peptide levels in patients with congestive heart. J Am Coll Cardiol 2000;36:1605-11.
31. Vincent JL, Zhang H, Szabo C, Preiser JC. Effects of nitric oxide in septic shock. Am J Respir Crit Care Med 2000;161:1781-5.
32. Rosenkranz AC, Hood SG, Woods RL, Dusting GJ, Ritchie RH. B-type natriuretic peptide prevents acute hypertrophic responses in the diabetic rat heart: Importance of cyclic GMP. Diabetes 2003;52:2389-95.
33. Panas D, Khadour FH, Szabo C, Schulz R. Proinflammatory cytokines depress cardiac efficiency by a nitric oxide-dependent mechanism. Am J Physiol 1998;275:H1016-23.
34. Sibelius U, Grandel U, Buerke M, et al. Staphylococcal alpha-toxin provokes coronary vasoconstriction and loss in myocardial contractility in perfused rat hearts: Role of thromboxane generation. Circulation 2000;101:78-85.
35. Witthaut R. Science review: Natriuretic peptides in critical illness. Crit Care 2004;8:342-9.
36. Wray GM, Foster SJ, Hinds CJ, Thiemermann C. A cell wall component from pathogenic and non-pathogenic Gram-positive bacteria (peptidoglycan) synergises with endotoxin to cause the release of tumour necrosis factor-alpha, nitric oxide production, shock, and multiple organ injury/dysfunction in the rat. Shock 2001;15:135-42.
37. Ravichandran LV, Johns RA, Rengasamy A. Direct and reversible inhibition of endothelial nitric oxide synthase by nitric oxide. Am J Physiol 1995;268:H2216-23.
38. Grandel U, Sibelius U, Schrickel J, et al. Biosynthesis of constitutive nitric oxide synthase-derived nitric oxide attenuates coronary vasoconstriction and myocardial depression in a model of septic heart failure induced by *Staphylococcus aureus* alpha-toxin. Crit Care Med 2001;29:1-7.
39. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.