Changes in B-type Natriuretic Peptide and Related Hemodynamic Parameters Following a Fluid Challenge in Critically Ill Patients with Severe Sepsis or Septic Shock

Shahed Omar, Ahmad Ali, Yahya Atiya, Rudo Lufuno Mathivha, Joel M. Dulhunty[1]

Division of Critical care, Intensive Care Unit, Chris Hani Baragwanath Academic Hospital, University of Witwatersrand, Johannesburg, South Africa, [1]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, The Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia

Abstract

Context: Severe sepsis or septic shock. **Aims:** The aim of this study is to examine the effect of a fluid challenge on the B-type natriuretic peptide (BNP) and the hemodynamic state. **Settings and Design:** This observational study was conducted in an intensivist-led academic, mixed medical-surgical Intensive Care Unit. **Subjects and Methods:** Focused transthoracic echocardiogram, plasma BNP, and hemodynamic measurements were recorded at baseline and following a 500 ml fluid challenge in thirty patients. Independent predictors of the percentage (%) change in stroke volume (SV) were sought. Next, these independent predictors were assessed for a relationship with the percentage change in BNP. **Statistical Analysis Used:** Multiple linear regressions, Wilcoxon rank-sum test, *t*-test, and Pearson's correlation were used. Data analysis was carried out using SAS. The 5% significance level was used. **Results:** Using a multiple regression models, the percentage increase in SV was independently predicted by the percentage increase in mean arterial pressure, left ventricular end-diastolic volume/dimension (LVEDV/LVEDd), ejection fraction, and a decrease in Acute Physiology and Chronic Health Evaluation II score ($P < 0.0001$). Preload, measured using LVEDV1 (before the fluid challenge) was significantly larger in the fluid nonresponders (%SV increase <15%) vs. the responders (%SV increase ≥15%). Finally, the percentage change in BNP was positively correlated with left ventricular size at end diastole LVEDd, $r = 0.4$, $P < 0.035$). **Conclusions:** An increase in BNP soon after a fluid challenge may have some predictive utility of a large LVEDd, which in turn can be used to independently predict the SV response to a fluid challenge.

Keywords: B-type natriuretic peptide, critically ill, fluid challenge, hemodynamic, intensive care, sepsis, severe sepsis, shock

Introduction

Sepsis is among the top ten causes of death.[1-3] It is defined as a systemic inflammatory response syndrome of infectious origin. Progression results in severe sepsis, with the failure of one or more organ systems. Further progression leads to septic shock.[4] Death in septic patients has been suggested to be due to multiple organ failures (MOF).[5,6] The mortality of septic shock may be as high as 50%.[7] While treating the underlying cause of sepsis is important, symptomatic organ support is vital. This includes fluid resuscitation and vasoactive drugs to prevent MOF.[8] The decision to give more fluid or to initiate vasoactive agents remains challenging, with inadequate or excessive treatment associated with suboptimal outcomes. For example, a greater positive fluid balance has been associated with increased mortality, while the sequelae of hypovolemia are well known.[9,10] Added to these treatment challenges,

the markers of fluid resuscitation, such as central venous pressure and pulmonary artery occlusion pressure, are less reliable than previously thought.[11] Other dynamic markers may require special monitors or echocardiography skills.[12] A simple objective tool to guide the direction of fluid therapy is much needed.

The concept of a fluid challenge is used to determine if a single bolus of fluid administered will increase cardiac preload and cardiac output significantly.[13] Recent data suggest that only half of patients given a fluid challenge increase their oxygen

Address for correspondence: Dr. Shahed Omar,
32, Road Number 3, Victory Park, Johannesburg 2195, South Africa.
E-mail: shahedicu@gmail.com

How to cite this article: Omar S, Ali A, Atiya Y, Mathivha RL, Dulhunty JM. Changes in B-type natriuretic peptide and related hemodynamic parameters following a fluid challenge in critically ill patients with severe sepsis or septic shock. Indian J Crit Care Med 2017;21:117-21.

delivery and only about half of these, increase their oxygen consumption thereby benefiting from fluid.[14] Observational data show that even the use of the fluid challenge may not always have an impact on the prescription of further fluid when indicated by the presence of hypotension, oliguria, poor peripheral perfusion, elevated lactate, or even markers such as stroke volume (SV) variation and cardiac output.[15]

Recently, one of the natriuretic peptides, B-type natriuretic peptide (BNP), was found to be elevated in septic shock.[16] High levels of BNP and measures of left ventricular end-diastolic volume (LVEDV) and pressure were predictors of mortality.[17,18] BNP increases within an hour of physiological stimulation, such as caused by volume expansion and pressure overload of the cardiac ventricles. It is synthesized as a preprohormone and is ultimately processed to yield biologically active BNP and a fragment called NT-proBNP.[19]

The aim of this pilot study was to examine the effect of a fluid challenge on BNP and the hemodynamic state focusing on the basic left ventricular (LV) characteristics. We hypothesized that a significant increase in BNP from any baseline value, soon after the fluid challenge, would indicate that the left ventricle was overstretched thereby providing additional data that may inform further fluid therapy.

SUBJECTS AND METHODS

The study was approved by the local Human Research Ethics Committee. This observational study was conducted in an intensivist-led university-affiliated mixed medical-surgical Intensive Care Unit (ICU).

Patient population
Patients admitted to the ICU over a 6-month period were considered for enrolment. Eligible patients were those admitted to the adult ICU and were diagnosed as being in septic shock or with severe sepsis within 48 h of admission to the ICU. Patients were enrolled in the first 12 h of meeting eligibility criteria. The patients had to have had a fluid challenge requested by the treating physician who deemed the hemodynamic parameters abnormal, with signs of hypoperfusion, as described by the International Guidelines for the Management of Severe Sepsis and Septic Shock.[20] Patients with known cardiac disease or active hemorrhage were excluded from the study. The diagnosis of severe sepsis and septic shock was made using the consensus definitions of the American College of Chest Physicians/Society of Critical Care Medicine.[4]

Baseline data collection
Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated and recorded for the first 24 h following admission to the ICU.[21] Demographic data, including age, weight, height and gender, were also collected.

Procedure at initiation of fluid challenge
The mean arterial pressure (MAP) (MAP1) and heart rate (HR) (HR1) were recorded at the initiation of the fluid challenge. Blood was collected into an ethylenediaminetetraacetic acid (EDTA)

tube for the measurement of BNP at baseline (BNP1). A short focused transthoracic echocardiogram (TTE) was performed. A 500 ml fluid challenge was administered within 30 min.

Procedure at the end of fluid challenge
The MAP2 and HR2 were recorded at the end of the fluid challenge. A short focused TTE was repeated at the end of the fluid challenge. One hour after the completion of the fluid challenge, blood was collected into an EDTA tube for a second measurement of BNP (BNP2).

Focused transthoracic echocardiogram
Echocardiograms were performed by two intensive care echocardiographers who routinely perform TTEs in the ICU. The same operator performed both echocardiograms on each patient. The left parasternal long axis and short axis views were used for speed and consistency. The left ventricular end-diastolic dimension (LVEDd) was measured before (LVEDd1) and after (LVEDd2) the fluid challenge. Teichholz's m-mode formula was used to calculate the LVEDV (LVEDV1 and LVEDV2), SV (SV1 and SV2), and ejection fraction (EF) (EF1 and EF2) as above.[22] Impaired LV systolic function was defined as an EF measured at baseline (EF1) below 50%.[22-25]

B-type natriuretic peptide measurement
BNP was measured using the point of care Triage® instrument (Alere, San Diego, California, USA) utilizing a double-labeled fluorescent immunoassay.

Statistical analysis
Sample size
Calculation of sample size requirements was based on the modeling of the percentage change in SV as a function of selected study variables. In regression analysis, at least five cases (preferably 15–20) per estimated parameter are required; thus with thirty cases, the estimation of at most six parameters is possible, and we must be aware of the possibility of overfitting the data (i.e., the results may not be generalizable).

The relationship between the change in SV and the selected study variables was assessed by multiple linear regressions. Continuous variables were summarized by the mean, standard deviation, median, and interquartile range. Wilcoxon rank-sum test and the *t*-test were used for comparison of nonparametric and normally distributed continuous variables, respectively. Correlations were determined using Pearson's correlation. Data analysis was carried out using SAS. The 5% significance level was used.

RESULTS
Patient characteristics
Thirty patients with severe sepsis or septic shock were included in the study. At the time of enrolment, patients had two or more organ systems with dysfunction, requiring positive pressure ventilation and cardiovascular support in the form of either fluid support alone or fluid and vasopressor/inotrope support. Patients were admitted from several disciplines: trauma (9), surgery (6), obstetrics and gynecology (5), medicine (4),

vascular surgery (1), and other (5). There were 16 females and 14 males. Baseline demographics are shown in Table 1.

Hemodynamic characteristics

Table 2 shows hemodynamic parameters, echocardiographic measurements, and laboratory markers recorded at baseline and subsequent to a fluid challenge. The physiological parameters representing preload, afterload, and contractility in Table 2 are studied further in a multiple regression models. Thirteen (13) of the thirty (30) patients had impaired systolic function with an EF of <50% at baseline before a fluid challenge.

Fluid responders

Using multiple linear regressions, we explored the relationship between the percentage change (%) in SV and the following selected independent study variables to confirm and identify a group of fluid responders: percentage change in MAP, percentage change in LVEDV/LVEDd, percentage change in EF, percentage change in HR, and APACHE II score. There were no strong correlations ($r > 0.75$) between the independent variables used. The overall model was significant and explained 98% of the variation ($P < 0.0001$). Given all other variables in the model, a 1% increase in SV was associated with a 0.12% increase in MAP, a 1.1% increase in LVEDV, a 1.2% increase in EF, and a 0.6 point decrease in APACHE II score. Note that LVEDd was the only independent variable used to calculate LVEDV, and therefore these two variables were not considered separately.

Preload characteristics

Table 3 describes the relationship between the left ventricle and SV increase. LVEDV1 (before the fluid challenge) was significantly larger in the fluid nonresponders (%SV increase <15%) vs. the responders (%SV increase ≥15%). The percentage increase in LVEDV postfluid challenge was significantly higher in the fluid responders. Since LVEDV was calculated from LVEDd, these two variables were highly correlated (Pearson's $r = 0.93$, $P < 0.0001$ for LVEDd1 and LVEDV1).

Left ventricular size and B-type natriuretic peptide

We then looked at the relationship between change in BNP and the directly measured dimension of the left ventricular at end diastole (LVEDd). We found a significant but moderate correlation (Pearson's $r = 0.4$, $P < 0.035$) between percentage change in BNP and LVEDd before the fluid challenge (LVEDd1).

DISCUSSION

The aim of the study was to examine changes in the hemodynamic state and BNP after the implementation of a fluid challenge among critically ill patients with severe sepsis. Recent evidence suggests that a fluid restrictive strategy and active diuresis during the shock-free period may aid in the management of acute lung injury.[26,27] We selected a group of patients in whom a hemodynamic strategy might be useful. They were critically ill patients requiring pulmonary and cardiovascular support.

Table 1: Baseline demographics of study participants

Characteristic	Mean (SD)	Range
Age (years)	42 (16)	16 – 73
Weight (kg)	78 (21)	50 – 130
Height (cm)	168 (9.8)	150 – 190
Body surface area (BSA)	1.8 (0.2)	1.5 – 2.3
APACHE II	19.6 (5.8)	6 – 34

Table 2: Baseline and post fluid challenge data for physiological variables Means and medians are provided with standard deviations and interquartile ranges in parenthesis

Parameter	Baseline	Post fluid challenge
MAP (mmHg)	67 (12.2)	80.1 (14.1)
HR (beats/min)	124.1 (22.9)	118 (21.2)
LVEDd (cm)	4.9 (0.8)	5.5 (1.1)
LVEDV (ml/m²)	57.6 (46.4–69.8)	72.4 (55–87.5)
SV	29.1 (26–42.3)	41.1 (33.5–51.7)
EF (%)	0.57 (0.14)	0.57 (0.12)
FS	32.1 (11.9)	30.8 (10.2)
BNP (pg/ml)	223 (30–426)	251 (49–425)

Table 3: Preload characterictics in fluid responders and non responders defined by a threshold value of 15%. Means and medians are provided with standard deviations and interquartile ranges in parenthesis

Characteristic	SV increase ≥15%	SV increase <15%	P	Test
LVEDV1	53.7 (14.9)	66.6 (19.1)	0.048	T test
% change LVEDV	38 (22 to 60.3)	5.7 (-9 to 14.8)	0.0007	Wilcoxon
% change LVEDd	17.2 (10.4 to 25.6)	2.7 (-4.5 to 7.0)	0.0007	Wilcoxon

Sepsis induces reversible myocardial dysfunction that may manifest clinically with a reduced EF.[28,29] Septic cardiomyopathy occurs commonly and is often underappreciated as hemodynamic parameters may be within reference limits or elevated in the presence of a lowered systemic vascular resistance secondary to vasodilatation.[30,31] This is evident in our study as 43% of the group had impaired LV systolic function at baseline. In keeping with this, we also found that severity of illness (a higher APACHE II score) was an independent predictor of a smaller SV response to the fluid challenge.

Overall, we found significant changes in the hemodynamic state following the fluid challenge. The SV can be defined by cardiac function and venous return curves.[32] According to our multivariate model, the increase in SV was independently predicted by the increase in LVEDV/LVEDd (preload), MAP (afterload), and contractility (EF). The LVEDV1 (before fluid challenge) was greater and the percentage increase in LVEDV was smaller for smaller SV increments (nonresponder). These patients had a larger LV volume with likely overstretching of the muscle fibers beyond optimal

length, and hence a possible reduction in isometric tension and contraction. The question we hoped to answer was whether this state may be predicted by an increase in BNP.

The BNP gene contains a "TATTAT" sequence indicating a high turnover rate at an mRNA level and a high synthesis rate. Once a physiological stimulus occurs, expression occurs within an hour.[33] The BNP measurement was repeated after an hour of completion of the fluid challenge to detect an increase in volume or pressure, while keeping the period as short as possible to exclude other factors that may cause BNP to change. The goal was to select a time at which the BNP change was most likely due to the fluid challenge. The test is point of care with results available within 15 min at the bedside making it practical in the ICU. BNP levels have been found to be elevated in patients with symptomatic heart failure and also in critically ill patients.[18,34]

In this pilot study of only thirty patients, we found that the percent increase in BNP 1 h after the fluid challenge was positively correlated with a larger baseline LV size at end diastole. The characteristic of a fluid nonresponder was a smaller percentage increase in preload, associated with a larger baseline value, and this was predicted to some extent by the increase in BNP. An increase in BNP would imply that there was an increase in LV end-diastolic volume and pressure.[34] Even though high levels of BNP might be related to an alteration in BNP clearance during sepsis, acute ventricular stretching has been shown to result in further BNP release during these conditions.[16] We repeated the BNP at 1 h postcompletion of the fluid challenge in an attempt to isolate this relationship between BNP and fluid challenge from any other prevailing conditions that may impact on the BNP concentration. Rather than using the absolute value of BNP at any point, as this may be influenced by numerous other factors, we used the change in BNP at 60 min after completing the fluid challenge.

Limitations

First, we used a point of care BNP assay. It is important to note that the average coefficient of variation (precision) of the BNP assay according to the manufacturer's package insert is 15.4% (Triage® instrument, Alere, San Diego, California, USA). This large imprecision may introduce significant error. Second, our measurements for LVEDV were based on Teichholz's calculation, while more accurate measures exist. Third, we did not have a control group who did not receive a fluid challenge and therefore cannot completely exclude confounders for the change in BNP. Finally, it is a very small study.

Conclusions

We have described the hemodynamic response to a fluid challenge in a group of critically ill patients with severe sepsis who are likely to benefit from a fluid strategy. We have found that the SV response is dependent on the responses of the LVEDV/LVEDd, the MAP, and EF. Of these, there exists a moderate but significant relationship between baseline LV

size and % change in BNP regardless of its baseline value. The potential for using the change in BNP with the fluid challenge concept needs more rigorous evaluation.

Conflicts of interest

Shahed Omar received ± Rs. 12,000 from Alere SA and Ilex SA and BD for lectures given on unrelated topics.

References

1. Melamed A, Sorvillo FJ. The burden of sepsis-associated mortality in the United States from 1999 to 2005: An analysis of multiple-cause-of-death data. Crit Care 2009;13:R28.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546-54.
3. Daniels R. Surviving the first hours in sepsis: Getting the basics right (an intensivist's perspective). J Antimicrob Chemother 2011;66 Suppl 2:ii11-23.
4. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
5. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138-50.
6. Cohen J. The immunopathogenesis of sepsis. Nature 2002;420:885-91.
7. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med 1998;26:2078-86.
8. Girbes AR, Beishuizen A, Strack van Schijndel RJ. Pharmacological treatment of sepsis. Fundam Clin Pharmacol 2008;22:355-61.
9. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259-65.
10. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, *et al.* An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. Crit Care Med 2012;40:1753-60.
11. Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, *et al.* Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med 2007;35:64-8.
12. Slagt C, Breukers RM, Groeneveld AB. Choosing patient-tailored hemodynamic monitoring. Crit Care 2010;14:208.
13. Monnet X, Teboul JL. Assessment of volume responsiveness during mechanical ventilation: Recent advances. Crit Care 2013;17:217.
14. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, *et al.* Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med 2013;41:1412-20.
15. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, *et al.* Fluid challenges in intensive care: The FENICE study: A global inception cohort study. Intensive Care Med 2015;41:1529-37.
16. Pirracchio R, Deye N, Lukaszewicz AC, Mebazaa A, Cholley B, Matéo J, *et al.* Impaired plasma B-type natriuretic peptide clearance in human septic shock. Crit Care Med 2008;36:2542-6.
17. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, *et al.* Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma

angiotensin II and endothelin-1. Eur Heart J 1999;20:1799-807.

18. Meyer B, Huelsmann M, Wexberg P, Delle Karth G, Berger R, Moertl D, *et al.* N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. Crit Care Med 2007;35:2268-73.

19. McLean AS, Huang SJ. B-type natriuretic peptide to assess cardiac function in the critically ill. In: Vincent JL, editor. Yearbook of Intensive Care and Emergency Medicine 2005. Berlin: Springer; 2005. p. 151-60.

20. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.

21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-29.

22. Kaddoura S. Ch. 4. In: Hunter L, editor. Echo Made Easy. 2nd ed. Edinburgh: Churchill Livingstone; 2009. p. 70-3.

23. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, *et al.* Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100:483-90.

24. Parrillo JE. Pathogenetic mechanisms of septic shock. N Engl J Med 1993;328:1471-7.

25. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008;36:1701-6.

26. Neamu RF, Martin GS. Fluid management in acute respiratory distress syndrome. Curr Opin Crit Care 2013;19:24-30.

27. Seeley EJ. Updates in the management of acute lung injury: A focus on the overlap between AKI and ARDS. Adv Chronic Kidney Dis 2013;20:14-20.

28. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses *in vitro* myocardial cell performance. J Clin Invest 1985;76:1539-53.

29. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med 2007;35:1599-608.

30. Muller-Werdan U, Buerke M, Ebelt H, Heinroth KM, Herklotz A, Loppnow H, *et al.* Septic cardiomyopathy – A not yet discovered cardiomyopathy? Exp Clin Cardiol 2006;11:226-36.

31. Ebelt H, Werdan K. Sepsis and heart. Internist (Berl) 2010;51:844-9.

32. Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Curr Opin Crit Care 2011;17:290-5.

33. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, *et al.* Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. J Clin Invest 1995;96:1280-7.

34. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825-32.