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BNP and NT-proBNP levels in patients with sepsis

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1. ABSTRACT

Sepsis is a severe complication of critically ill patients that is characterized by the systemic inflammatory response syndrome (SIRS). The increased levels of B-type natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are related with dysfunction of the cardiovascular system and systemic inflammation. In recent years, BNP and NT-proBNP have been the focus of studies evaluating the severity and prognosis of sepsis. In this study, we will review the role of BNP and NT-proBNP in sepsis.

2. INTRODUCTION

Sepsis is a severe complication of critically ill patients with severe trauma, extensive burns, shock, or severe infections. Sepsis is characterized by the systemic inflammatory response syndrome (SIRS), which develops into the multiple organ dysfunction syndrome (MODS) when complicated by infection. The occurrence and development of sepsis depends on risk factors, including infection, inflammation, and abnormal immune and coagulation function, reflecting a series of pathophysiologic changes. Sepsis develops rapidly and leads to a high mortality rate (1,2). In the United States, approximately 750,000 patients develop sepsis each year, among which 225,000 die, resulting in high treatment costs (3,4).

It is crucial to evaluate the severity of sepsis and provide early intervention to patients to reduce sepsis mortality. There have been many studies involving the indicators by which the severity and prognosis of sepsis can be evaluated. Procalcitonin (PCT) (5-8), C-reactive protein (CRP) (9,10), and protein C (PC) /activated protein C (APC) (11-13) have been widely identified as predictors of sepsis. In recent years, brain natriuretic peptide (BNP), now known as B-type natriuretic peptide (also BNP), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) have become better known, and studies involving BNP or NT-proBNP in the evaluation of the severity and prognosis of sepsis have been on the rise (14).

3. BIOLOGIC CHARACTERISTICS OF BNP AND NT-PROBNP

3.1. Introduction

The natriuretic peptide (NP) system includes A-, B- (BNP), C-, and D-type natriuretic peptide (15,16). BNP was originally identified in extracts of porcine brain by Sudoh in 1988 (17), and shown to be similar to atrial natriuretic peptide (ANP). ANP causes diuresis, natriuresis, an expansion of blood vessels, and a reduction of blood pressure (17).

3.2. Gene structure and expression of BNP and NT-proBNP

The BNP gene is located on human chromosome 1, and is in series with the ANP gene, which is in the 8,000 bases upstream of the BNP gene. In 1989, the complete nucleotide sequence of BNP was described, and the 5'untranslated region sequence was described by a molecular analysis and tissue-specific gene expression study in 1996. The BNP gene is 1922 bp with 3 exons and 2 introns, including a highly-conserved sequence (TATTAT). In the human BNP gene, both enhancer elements exist in the vicinity of the promoter and have a positive effect, such as GATA binding and SP1 elements, which can up-regulate gene transcription, and sub-elements with a negative effect, which can down-regulate transcription (18-20).

The BNP gene reverse transcribes into cDNA, which is composed of 1900 nucleotides, and then synthesizes mRNA encoding the precursor protein of BNP (pre-proBNP) with 134 amino acids. In the pre-proBNP protein, a 26-amino acid signal peptide is immediately removed, resulting in the formation of a 108-amino acid peptide (proBNP). Then, proBNP is decomposed into two parts by the proteolytic enzymes, protease furin and corin. One part is the N-terminal fragment, NT-proBNP, including 76 amino acids without biologic activity; the other part is BNP, which is composed of 32 amino acids with biological activity. BNP is characterized by a 17-amino acid ring, which is connected with cysteine disulfide and is significant for its biological activity (21,22).

3.3. Synthesis and secretion of BNP and NT-proBNP

In humans, BNP and NT-proBNP are mainly synthesized and secreted from ventricles by the coronary sinus. In ventricles, the reserve of BNP and NT-proBNP are as low as 7% of ANP. In addition, BNP can also be synthesized and secreted from the adrenal medulla. In patients with primary aldosteronism, the level of BNP mRNA in the adrenal gland is increased, as well as the synthesis and secretion of BNP (23). An *in vitro* study demonstrated that the expression of the BNP gene can be stimulated by many factors, such as stress, ischemia, mechanical tension, and cytokines (including tumor necrosis factor, interleukin, and endothelin). Furthermore, the synthesis and secretion of BNP and NT-proBNP also increased in patients with heart failure, pulmonary embolism, acute or chronic cor pulmonale, renal failure, anemia, hyperthyroidism, or sepsis (24-31).

3.4. Mechanism of BNP in humans

BNP is activated through binding to receptors at the cell surface. Three types of BNP receptors (A-type natriuretic factor receptor [NPRA], B-type natriuretic factor receptor [NPRB], and C-type natriuretic factor receptor [NPRC]) have been identified. NPRA and NPRB are transmembrane receptors with guanylate cyclase (GC) activity and can synthesize cyclic guanosine monophosphate (cGMP), which can mediate most biological effects of BNP, such as diuresis, natriuresis, dilation of blood vessels, reduction of blood pressure, regulation of body fluid volume, and maintaining electrolyte balance. NPRC is a removal receptor with a short cytoplasmic domain of 37 amino acid residues, which participates in the clearance of BNP in the circulation. NPRA, NPRB, and NPRC are distributed within target organs, including the kidneys, heart, vessels, adrenal glands, and central nervous system. Phosphorylation and dephosphorylation regulate the activity of NPR. When NPR is phosphorylated, NPR becomes sensitive to its ligand. When NPR dephosphorylates, sensitivity to the ligand is decreased (32-34).

3.5. Degradation and inactivation of BNP and NT-proBNP

The half-life of BNP is 22 min in humans. The majority of BNP is degraded in the lungs and kidneys. The mechanisms underlying BNP degradation are as follows: BNP is degraded by breaking the Cys7-Phe8 bond in its ring structure by neutral metal endopeptidase with zinc; and BNP binds with NPRC and is degraded by NPRC-mediated intracellular chemotaxis (18,35). Of note, it has not been confirmed which mechanism of BNP degradation is dominant, or whether the mechanisms are equivalent (Figure 1).

The half-life of NT-proBNP is 120 min in blood, but NT-proBNP remains in the circulation for 12 h. Because NT-proBNP is metabolized in the kidneys, the level of NT-proBNP can be increased in patients with diseases that damage renal function. Thus, the level of NT-proBNP is usually higher than BNP in humans. Because NT-proBNP cannot be degraded by endopeptidase, the level of NT-proBNP is more accurate than BNP in assessing cardiovascular function and state, especially for patients taking medications which inhibit neutral endopeptidase activity (21).

4. ASSAY OF BNP

In the United States and Europe, two assay methods for BNP are widely accepted, which actually test BNP or NT-proBNP (36). One method is the rapid immunofluorescence detection of BNP (Biosite Diagnostics, San Diego, CA, USA), which can be used for point-of-care testing and provide results within 15 min. This method is more adaptable in the clinic than traditional immunoassay methods and can be used in patients with various conditions in different departments when rapid results are needed emergently. The other method is the electrochemiluminescence detection method (Roche Diagnostics GmbH, Gasel, Germany), which can provide results of NT-proBNP testing within 18 min. The normal range of BNP is 0.5-30 pg/ml (0.15-8.7 pmol/L). When the BNP level is > 100 pg/ml, chronic heart failure (CHF) can be diagnosed in patients > 55 years of age. The normal range of NT-proBNP is 68-112 pg/ml (8.2-13.3 pmol /L). In Europe, the standard for diagnosing CHF is 100 pg/ml for males and 150 pg/ml for females, while in the United States the standard is 125 pg/ml (37-39).

In addition, the Bayer Corporation developed an assay for BNP; the standard for CHF is 100 pg/ml (39) using this method.

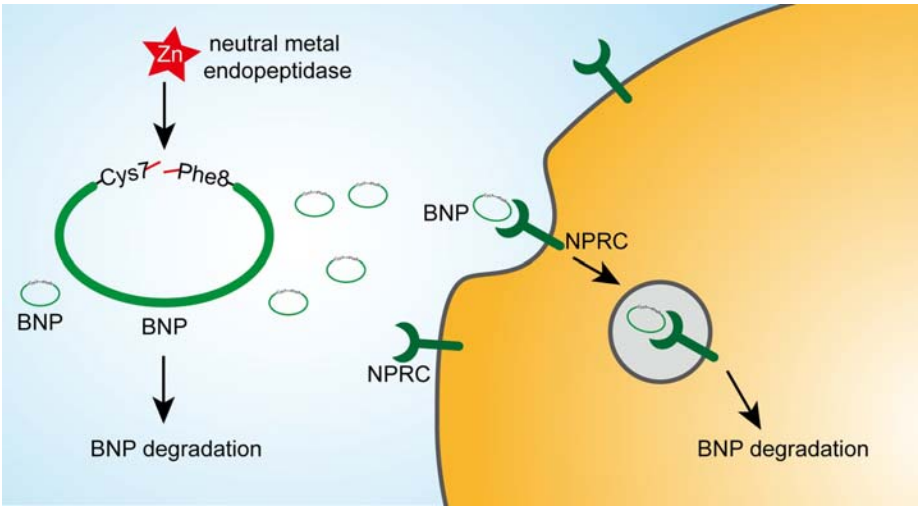

Figure 1. Degradation inactivation of BNP. The BNP degradations include two pathways. On one pathway, BNP is degraded by breaking the Cys7-Phe8 bond in its ring structure by neutral metal endopeptidase with zinc. On the other pathway, BNP binds with NPRC and is degraded by NPRC-mediated intracellular chemotaxis.

5. PHYSIOLOGIC FUNCTION

In humans the physiologic functions of BNP are as follows: BNP relaxes vessels, reduces the cardiac preload and sympathetic activity, and relaxes arteries and veins, resulting in fluid transfer from the blood vessels to the extravascular tissues; BNP reduces sympathetic activity by inhibiting the secretion of catecholamines and the spread of sympathetic impulses, and also reduces the activated threshold of passing impulses in the vagus nerve, resulting in inhibition of vasoconstriction and a bradycardic reflex to cardiac preload reduction; BNP resists mitotic activity leading to inhibition of vascular smooth muscle and endothelial cell proliferation; the role of BNP in sodium and water metabolism is similar to ANP; In the kidneys, BNP increases renal blood flow by diuresis and natriuresis, and inhibits the renin-angiotensin-aldosterone (RAA) system and direct tubular action; BNP relaxes afferent arterioles and constricts efferent arterioles to increase the glomerular filtration rate, resulting in an inhibition of reabsorption of sodium and water in the proximal convoluted tubule mediated by angiotensin II; in the renal collecting duct, BNP antagonizes vasopressin to retain water and sodium; BNP directly inhibits the secretion of renin and aldosterone; and in the central nervous system, BNP reduces the sympathetic activity of brainstem, directly inhibits the secretion of vasopressin, and inhibits salt appetite and thirst of central nervous system centers. All of these effects result in a sustained natriuretic effect; however, a further study on the relationship between BNP in the central nervous system and in the renal and cardiovascular systems is needed (42).

6. BNP AND NT-PROBNP IN SEPSIS

Studies which have focused on BNP and NT-proBNP in cardiovascular diseases have shown that BNP and NT-proBNP indicate the prognosis of acute myocardial infarction and heart failure, while BNP and NT-proBNP in the prognosis of sepsis has not been confirmed. Sepsis is a serious complication of acute critical illnesses, such as severe trauma, large-area burns, shock, and severe infections. Sepsis is characterized by SIRS, usually complicated by infections, which can develop into MODS and result in a high mortality rate and a poor prognosis (43). In assessing sepsis, PCT and CRP have been used traditionally, while BNP and NT-proBNP have received more attention in recent years (14).

6.1. The level of BNP and NT-proBNP in sepsis

The incidence of sepsis and septic shock has increased in recent years. Patients with sepsis and septic shock are usually complicated by cardiac insufficiency. In SIRS, an abundance of inflammatory media with cardiac toxicity is produced in patients with sepsis. Homeostasis of the cardiovascular system is disturbed when inflammation is strong, resulting in septic shock. Cardiac insufficiency is one of the most significant clinical manifestations of septic shock (44). Myocardial injury is considered as one of the early characteristics of septic shock, leading to hypoxia in peripheral tissues and patient death. It has been demonstrated that ventricular systolic dysfunction occurs in the early stage of patients with septic shock.

Several studies have shown increased levels of BNP and NT-proBNP in the plasma of patients with septic shock, especially patients with ventricular contractile insufficiency (45). The BNP level is negatively correlated with left ventricular ejection fraction (LVEF). Post and colleagues (46) conducted a prospective study with 93 septic shock patients, who were divided into one group with normal ventricular function (LEVF >50%) and another group of patients with impaired left ventricular function (LEVF <50%), and found that the BNP concentration in plasma represented a reliable marker for identification of patients developing sepsis-induced myocardial depression. The BNP concentration on day 5 may be used as a prognostic marker to identify patients

with an elevated risk for an adverse outcome. Charpentier and colleagues (47) reported similar findings. Dong and colleagues (48) have studied the levels of BNP and NT-proBNP in 96 newborns with neonatal septicemia The 96 patients were divided into a myocardial injury group and a non-myocardial injury group, and were tested for the levels of BNP and NT-proBNP in the plasma on the 2nd, 5th, and 10th days of septicemia and in infants of different gestational ages. The results were compared to creatine kinase isoenzyme and troponin I. Dong and colleagues (48) found that the levels of BNP and NT-proBNP in plasma increased in neonates with myocardial injury and sepsis, especially in premature infants. Rudiger and colleagues (49) found an increased level of BNP in 24 patients with sepsis, septic shock, or congestive heart failure. These findings raise the issue of whether or not the increased BNP level is related to inflammation or cardiac insufficiency secondary to sepsis. This issue is in need of further study.

6.2. The possible mechanism underlying increased BNP and NT-proBNP in sepsis

Multiple factors lead to increased levels of BNP and NT-proBNP in patients with sepsis. Indeed, primary cardiac insufficiency or systemic inflammation is a possible cause of the increased levels of BNP and NT-proBNP in patients with sepsis. In recent years, it has been accepted that the increased levels of BNP and NT-proBNP in the plasma of septic shock patients is due to cardiac insufficiency secondary to sepsis (50). Parker and colleagues (51) reported that the left and right ventricles are acutely dilated in patients with sepsis. In *in vivo* and *in vitro* experiments, Parker and colleagues (51) found that 60%-80% of BNP in plasma was from ventricular myocytes, and the overload ventricular pressure, overload volume, or ventricular dilatation is an important cause of BNP release.

In addition to cardiovascular function, systemic inflammation is related to increased BNP in the peripheral circulation. Meader and colleagues reported that BNP levels were > 500 pg /ml in 8 sepsis patients with normal left ventricular function, and confirmed by Renana and colleagues (52). These findings suggest that the increased BNP level can be explained by another mechanism. Another possible cause of the increased BNP level in patients with sepsis may be the release of large amounts of inflammatory cytokines (interleukins and tumor necrosis factor) and endotoxin. The inflammatory cytokines not only play a direct role in cardiac toxicity, but also participate in the expression of the BNP gene. An *in vitro* study showed that expression of the BNP gene was increased 1 h after lipopolysaccharide stimulation (53). In sepsis patients, the BNP level in blood was increased without cardiac insufficiency, while the level of BNP was positively correlated with the CRP level, suggesting the role of inflammation in the increase of BNP (54). In addition, pro-inflammatory cytokines can promote the heart to secrete BNP. It has been reported that pro-inflammatory cytokines (interleukin (IL)-1) can promote the increase of BNP in sepsis, and the expression of BNP in myocardial cells is increased after stimulation of IL-1beta *in vitro*. In sepsis, the level of IL-6 increased 100 times greater than heart failure, suggesting an important role of IL-6 in regulating BNP secretion in sepsis. Because inflammation can induce increased secretion and decreased degradation of BNP, the BNP level is increased in severe sepsis and septic shock.

6.3. The clinical application of BNP and NT- proBNP in sepsis

Sepsis is common in clinics with a high mortality and poor prognosis. In recent years, BNP and NT-proBNP have been applied in predicting the prognosis of patients with severe sepsis or septic shock. Rivers and colleagues (55) measured BNP levels 0, 3, 6, 12, 24, 36, 48, 60, and 72 h after admission in 252 patients with severe sepsis and septic shock, and found that elevated BNP levels (>100 pg/mL) occurred in 42% and 69% of patients at the time of presentation and at 24 h. They also found that a BNP > 210 pg/mL at 24 h was the most significant independent indicator of increased mortality (sensitivity, 79% and specificity, 59%), and the mortality was increased as the level of BNP increased. Thus, serial BNP levels may be a useful adjunct in the early detection, stratification, treatment, and prognostication of high-risk patients. Brueckmann and colleagues (56) tested NT-proBNP in 57 patients with severe sepsis using an enzyme-linked immunosorbent assay (ELISA), and found an increased plasma level of NT-proBNP. Brueckmann and colleagues (56) also found that the mortality increased 3.9-fold when the level of NT-proBNP was > 1400 pmol/L. Thus, NT-proBNP can be used as an index to judge the severity of sepsis. Kandil and colleagues (57) examined the relationship between BNP levels and the severity of sepsis independent of congestive heart failure. Kandil and colleagues (57) divided 49 subjects into the following 3 groups: 13 patients with septic shock; 18 patients with early sepsis; and 18 age-matched healthy controls. None of the subjects had co-morbid conditions (congestive heart failure or renal failure) and were followed for 21 days. The serum BNP levels were determined at the time of diagnosis of sepsis and at the time of patient improvement or deterioration. The results showed that patients with septic shock had significantly higher BNP levels on admission compared with the other 2 groups ($P<0.05$), and plasma BNP levels for patients with septic shock were positively correlated with Sequential Organ Failure Assessment scores ($r(2)=0.74$, $P<0.05$) and prognosticated survival. Ueda and colleagues (58) determined the BNP levels in 22 patients with septic shock, 11 patients with severe sepsis, and 20 healthy controls on the 1st, 2nd, and 4th days after admission, and found that the BNP level in patients was 987pg/ mL on day 2 and 7pg/ mL in healthy controls (sensitivity, 92%; specificity, 80%). Kotanidou and colleagues (59,60) reported that plasma NT-proBNP levels were elevated as sepsis increased in severity in 233 critical patients without cardiac disease, which was positively correlated with other inflammatory cytokines. The NT-proBNP level in patients who died was higher than in patients who survived, and has become the standard for diagnosing heart failure. Thus, the plasma NT-proBNP level can independently predict the prognosis of critically ill patients. Varpula and colleagues (61) found that NT-proBNP levels are frequently elevated in patients with severe sepsis and septic shock, which is related to

inhibitory factors in myocardial cells. Elevated NT-proBNP levels can be due to a synergistic effect with TNF-α, IL-1β, and other inflammatory mediators. Thus, the plasma NT-proBNP level may be a predictor of mortality in patients with sepsis.

7. CONCLUSIONS

In conclusion, increased BNP and NT-proBNP levels are related to dysfunction of the cardiovascular system and systemic inflammation. BNP and NT-proBNP can be used as a predictor of cardiac insufficiency secondary to sepsis, as well as a poor prognostic indicator of sepsis. However, additional clinical studies with large samples are needed to investigate the role of BNP and NT-proBNP in the early diagnosis and prognosis of sepsis patients.

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9. REFERENCES

1. AngusDC, Linde-Zwirble WT, Lidicker J. Epidemiology of severe sepsis in the United States: analysis of incidence, out-come, and associated costs of care. *Crit Care Med* 29 (7), 1303 – 1310. (2001)

2. Watson RS, Carcillo JA, Linde-Zwirble WT. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 167(5), 695-701. (2003)

3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348(16), 1546-54. (2003)

4. Burchardi H, Schneider H. Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. *Pharmacoeconomics* 22(12), 793-813. (2004)

5. Balci C, Sivaci R, Akbulut G, Karabekir HS. Procalcitonin levels as an early marker in patients with multiple trauma under intensive care. *J Int Med Res* 37(6), 1709-17. (2009)

6. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med* 34(7), 1996-2003. (2006)

7. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 7(3), 210-7. (2007)

8. Andrejaitiene J. The diagnostic value of procalcitonin in severe sepsis. *Medicina (Kaunas)* 42(1), 69-78. (2006)

9. Simon L, Saint-Louis P, Amre DK, Lacroix J, Gauvin F. Procalcitonin and C-reactive protein as markers of bacterial infection in critically ill children at onset of systemic inflammatory response syndrome. *Pediatr Crit Care Med* 9(4), 407-13. (2008)

10. Rey C, Los Arcos M, Concha A, Medina A, Prieto S, Martinez P, Prieto B. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. *Intensive Care Med* 33(3), 477-84. (2007)

11.de Pont AC, Schultz MJ. Anticoagulant properties of drotrecogin alfa (activated) during hemofiltration in patients with severe sepsis. *Crit Care*13(1), 113. (2009)

12. Waerhaug K, Kirov MY, Kuzkov VV. Recombinant human activated protein C ameliorates oleic acid-induced lung injury in awake sheep. *Crit Care* 12(6), R146. (2008)

13. Liu KD, Matthay MA. Protein C as a surrogate end-point for clinical trials of sepsis. *Crit Care* 12(2), 139. (2008)

14. Woodard GE, Rosado JA. Recent advances in natriuretic peptide research. *J Cell Mol Med* 11(6), 1263-71. (2007)

15. Cauliez B, Berthe MC, Lavoinne A. Brain natriuretic peptide: physiological, biological and clinical aspects. *Ann Biol Clin (Paris)* 63(1), 15-25. (2005)

16. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail* 6(3), 261-8. (2004)

17. Sudoh T, Kangawa K, Minamino N. A natriuretic peptide in porcine brain. *Nature* 322, 78. (1988)

18. Mair J. Biochemistry of B-type natriuretic peptide--where are we now? *Clin Chem Lab Med* 46(11), 1507-14. (2008)

19. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 6(3), 257-60. (2004)

20. Yandle T G. Biochemistry of natriuretic peptides . *J Intern Med* 235 (6) , 5612576. (1994)

21. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 6(3), 257-60. (2004)

22. Yamamot o K, Burnett JC Jr, JougasakiM. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 28, 9882-94. (1996)

23. Lee Y J, Lin S R, Shin S J. Brain natriuretic peptide is synthesized in the human adrenal medulla and it s messenger ribonucleic acid expression along with that of atrial nat riuretic peptide are enhanced in patients with

primary aldosteronism. *J Clin Endocrinol Metab* 79 (5), 147621482. (1994)

24. Martinez-Rumayor A, Richards AM. Biology of the natriuretic peptides. *Am J Cardiol* 101(3A), 3-8. (2008)

25. Omland T. Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. *Crit Care Med 36(1 Suppl)*, S17-27. (2008)

26. Bal L, Thierry S, Brocas E.B-type natriuretic peptide (BNP) and N-terminal-proBNP for heart failure diagnosis in shock or acute respiratory distress. *Acta Anaesthesiol Scand* 50(3), 340-7. (2006)

27. Dhar S, Pressman GS, Subramanian S. Natriuretic peptides and heart failure in the patient with chronic kidney disease: a review of current evidence. *Postgrad Med J* 85(1004), 299-302. (2009)

28. Mohammed AA, Januzzi JL Jr. Natriuretic peptide guided heart failure management. *Curr Clin Pharmacol* 4(2), 87-94. (2009)

29. Bertinchant JP. Brain natriuretic peptide (BNP) and N-terminal-pro BNP in chronic haemodialysed renal failure. *Arch Mal Coeur Vaiss* 97(9), 881-8. (2004)

30. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 49(2), 171-80. (2007)

31. Pakuła D, Marek B, Kajdaniuk D. Natriuretic peptides: their role in diagnosis and therapy. *Endokrynol Pol* 58(4), 364-74. (2007)

32. Potter L R , Abbey, Hosch S , Dickey D M. Natriuretic peptides, their receptors , and cyclic guanosine monophosphate-dependent signaling functions . *Endocr Rev* 27 (1), 47-72. (2006)

33. Jerczyńska H, Pawłowska Z. Natriuretic peptides--their receptors and role in cardiovascular system. *Postepy Biochem* 54(1), 35-42. (2008)

34. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handb Exp Pharmacol* (191), 341-66. (2009)

35. Goetze J P. Biochemistry of pro-B-type natriuretic peptide-derived peptides : the endocrine heart revisited. *Clin Chem* 50 (9), 1503-10. (2004)

36. MillerWL, Hart man K A, BurrittMF. Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. *Circulation* 116 (3), 249-57. (2007)

37. Shuping L. Clinical Application of Detecting B Type Natriuretic Peptide. *Modern Med* 5 (20), 42243. (2005)

38. Urek R, Cubrilo-Turek M. Natriuretic peptides in clinical practice. *Acta Med Croatica* 62(1), 53-6. (2008)

39. Lin MC, Nawarak J, Chen TY. Rapid detection of natriuretic peptides by a microfluidic LabChip analyzer with DNA aptamers: Application of natriuretic peptide detection. *Biomicrofluidics* 3(3), 34101. (2009)

40. McCullough PA, Omland T, Maisel AS. B-type natriuretic peptides: A diagnostic breakthrough for clinicians. *Rev Cardiovasc Med* 4, 72-80. (2003)

41. Nobata S, Ventura A, Kaiya H, Takei Y. Diversified cardiovascular actions of six homologous natriuretic peptides (ANP, BNP, VNP, CNP1, CNP3 and CNP4) in conscious eels. *Am J Physiol Regul Integr Comp Physiol (Epub ahead of print)*, (2010)

42. Sait o Y,Nakao K, It oh H. Brain natriuretic peptide is a novel cardiac hormone. *Biochem Biophys Res Comm* 158, 360-368. (1989)

43. Zhang Z, Chen X, Lin P, Jiang H, Xiong X, Zhang G. Retrospective analysis of clinical characteristics of septic cases in general intensive care unit. *Chin J Cfit Care Med* 28 (3), 212-214. (2008)

44. Court O, Kumar A, Parrillo J. Clinical review: Myocardial depression in sepsis and septic shock. *Crit Care* 6, 500 - 508. (2000)

45. Witthaut R, Busch C, Fraunberger P. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: Impact of interleukin-6 and sepsis as sociated left ventricular dysfunction. *Intensive Care Med* 29, 1696 - 1702. (2003)

46. Post F, Weilemann LS, Messow CM. B type natriuretic peptide as a marker for sepsis induced myocardial depression in intensive care patients . *Crit Care Med* 36(11), 3030-3037. (2008)

47. Charpentier J, Luyt CE, Fulla Y. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 32, 660 – 665. (2004)

48. Dong XY, Hui YC, Shen Y. Diagnostic value of plasma brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide in myocardial injury of neonatal septicemia. *Zhonghua Er Ke Za Zhi* 47(6), 462-5. (2009)

49. Rudiger A, Gasser S, Fischler M. Comparable increase of B -type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. *Crit Care Med* 34, 2140 – 2144. (2006)

50. McLean AS, Tang B, Nalos M. Increased B - type natriuretic peptide (BNP) level is a strong predictor for

cardiac dysfunction inintensive care unit patients . *Anaesth Intensive Care* 31, 21-27. (2003)

51. Parker MM, McCarthy KE, Ognibene F P. Right ventricular dys2function and dilatation, similar to left ventricular changes, charac2terize the cardiac depression of septic shock in humans. *Chest* 97, 126 - 131. (1990)

52. Renana Shor, Yoseph Rozenman B, Aharon Bolshinsky. BNP in septic patients without systoli c myocardial dysfunction. *European Journal of Internal Medicine* 17, 536 -540. (2006)

53. Tomaru KI, Arai M, Yokoyama T. Transcriptional activation of the BNP gene by lipopolysaccharide is mediated through GATA elements in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 34, 649-659. (2002)

54. Shor R, Rozenman Y, Bolhinsky A. BNP in septic patients without systolic myocardial dysfunction. *Eur J Intern Med* 17, 536-540. (2006)

55.Rivers E P , McCord J , Otero R. Clinical utility of B-type natriuretic peptide in early severe sepsis and septic shock. *J Intensive Care Med* 22 (6), 3632373. (2007)

56. Hoffmann U, Brueckmann M. A new language of natriuretic peptides in sepsis? *Crit Care Med* 36(9), 2686-7. (2008)

57. Emad Kandil, Joshua Burack. A Biomarker for the Diagnosis and Risk Stratification of Patients With Septic Shock. *Arch Surg* 143(3), 242-246. (2008)

58. Ueda S , Nishio K, Akai Y. Prognostic value of increased plasma levels of brain nat riuretic peptide in patient s with septic shock. *Shock* 26 (2), 134-139. (2006)

59. Wieczorek SJ, Wu AH, Christenson R. A rap id B - type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. *Am Heart J* 144 (5), 834 – 839. (2002)

60. Kotanidou A, Karsaliakos P. Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. *Shock* 31(4), 342-7. (2009)

61. Varpula M, Pulkki K, Karlsson S. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. *Crit Care Med* 35(5), 1277-83. (2007)

Abbreviations: SIRS: systemic inflammatory response syndrome; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; MODS: multiple organ dysfunction syndrome; PCT: Procalcitonin; CRP: C-reactive protein; PC: protein C; ANP: atrial natriuretic peptide; Cgmp: cyclic guanosine monophosphate; CHF: chronic heart failure; RAA: renin-angiotensin-aldosterone; LVEF: left ventricular ejection fraction; ELISA: enzyme-linked immunosorbent assay

Key Words: Systemic Inflammatory Response Syndrome, B-Type Natriuretic Peptide, Multiple Organ Dysfunction Syndrome, Atrial Natriuretic Peptide, Review

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