Journal of Zhejiang University SCIENCE
ISSN 1009-3095
http://www.zju.edu.cn/jzus
E-mail: jzus@zju.edu.cn

Brain natriuretic peptide and optimal management of heart failure

LI Nan (李 楠), WANG Jian-an (王建安)‡

(*Division of Clinical Pharmacology and Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China*)

E-mail: nli_zum@yahoo.com.cn; wang_jian_an@tom.com

Received Dec. 17, 2004; revision accepted Apr. 3, 2005

Abstract: Aside from the important role of brain natriuretic peptide (BNP) in diagnosis, and differential diagnosis of heart failure, this biological peptide has proved to be an independent surrogate marker of rehospitalization and death of the fatal disease. Several randomized clinical trials demonstrated that drugs such as beta blocker, angiotensin converting enzyme inhibitor, spironolactone and amiodarone have beneficial effects in decreasing circulating BNP level during the management of chronic heart failure. The optimization of clinical decision-making appeals for a representative surrogate marker for heart failure prognosis. The serial point-of-care assessments of BNP concentration provide a therapeutic goal of clinical multi-therapy and an objective guidance for optimal treatment of heart failure. Nevertheless new questions and problems in this area remain to be clarified. On the basis of current research advances, this article gives an overview of BNP peptide and its property and role in the management of heart failure.

Key words: Brain natriuretic peptide (BNP), Heart failure, Drug therapy
doi:10.1631/jzus.2005.B0877 **Document code:** A **CLC number:** R54

BRAIN NATRIURETIC PEPTIDE

Several studies demonstrated that the heart is an endocrine organ (Henry and Pearce, 1956; Kisch, 1956; de Bold, 1985; de Bold *et al*., 1981; 1996; 2001). Atrial natriuretic peptide (ANP) was the first cardiac hormone identified in 1984 (Kangawa *et al*., 1984; de Bold *et al*., 1981). Later on, a new compound from pig brain was found, which had similar natriuretic and diuretic effects as ANP (Sudoh *et al*., 1988). This peptide was named brain (B-type) natriuretic peptide (BNP) whose actual site of synthesis is the ventricular myocardium (Mukoyama *et al*., 1991). After discovery of BNP in 1988, a third compound called C-type natriuretic peptide (CNP) was identified from pig brain in 1990 (Sudoh *et al*., 1990). Among the natriuretic peptide family, CNP is different from ANP and BNP in structure and is in higher level in the central nervous system and vascular tissues than in heart (Minamino *et al*., 1991).

BNP is constitutively released from ventricular myocyte as a preprohormone of 134 amino acids, which are cleaved into a proBNP hormone. Upon being stimulated into secretion, it is further cleaved to a 76 amino acid N-terminal fragment (N-terminal BNP) and a 32 amino acid active hormone and released into the blood (Hama *et al*., 1995; Fig.1). The N-terminal portion is a biologically inactive protein. BNP is synthesized in bursts as the promoter region of BNP gene contains the rapid-turnover nucleic acid sequence TATTTAT (Sudoh *et al*., 1989). BNP gene expression may increase very rapidly in response to myocyte stretch (Hama *et al*., 1995). The level of BNP in circulation is closely related to left ventricular pressure (Yoshimura *et al*., 1993).

BIOLOGICAL ACTIVITY OF BNP

Numerous studies found that the biological actions of BNP cover kidney, vascular vessels, endocrine and heart. The earliest finding of BNP biological

‡ Corresponding author

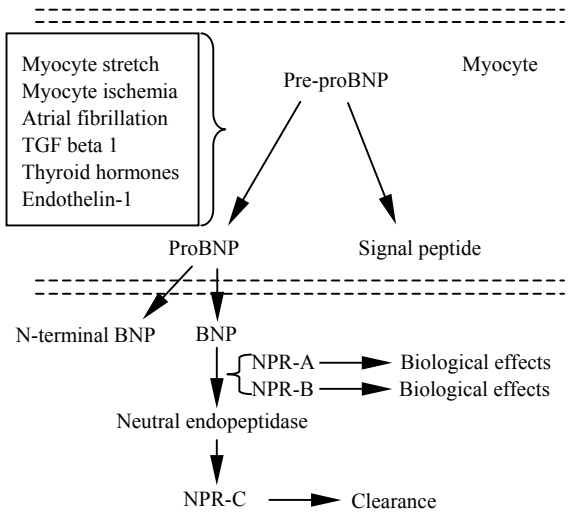

Fig.1 Illustration of secretion, binding and clearance of BNP. BNP's biological effects are due to its binding to both NPR-A and NPR-B. TGF-beta 1: Transforming growth factor-beta 1; NPR: Natriuretic peptide receptor

action was the increase of glomerular filtration rate, renal plasma flow, urine flow rate and inhibiting distal sodium reabsorption, causing natriuresis and diuresis (Richards *et al*., 1993; Jensen *et al*., 1998). BNP can inhibit cardiac sympathetic nervous system activity by reducing norepinephrine spillover at low dose, suppressing renin activity and the renin-angiotensin-aldosterone system by suppressing plasma aldosterone (Brunner-La Rocca *et al*., 2001; Clarkson *et al*., 1996). BNP has antiproliferative and antifibrotic actions in the heart and vascular tissues (Cao and Gardner, 1995; Fujisaki *et al*., 1995). BNP may relax myocardium and vascular smooth muscle, causing arterial and venous dilation (Clarkson *et al*., 1995; van der Zander *et al*., 1999; 2002). This action leads to blood pressure reduction and ventricular preload release. The recombinant human BNP may attenuate both pulmonary capillary wedge pressure and mean pulmonary artery pressure during exercise (Maisel, 2003). BNP can increase ANP and adrenomedullin level indicating a hormonal interaction (Hunt *et al*., 1995; Lainchbury *et al*., 1999). In general, the actions of BNP are similar to ANP, while CNP acts in the local vasculature in central nervous system as a vasodilator and inhibitor of vascular cell proliferation (Charles *et al*., 1996).

Among three natriuretic peptide receptors (NPR): NPR-A, NPR-B and NPR-C, NPR-A is a binding receptor, while NPR-C is a clearance receptor of BNP (Suga *et al*., 1992). BNP's biological effect is due to its binding to both NPR-A and NPR-B (Koller and Goeddel, 1992). The affinity of NPR-C for BNP may influence the plasma half-life of BNP. BNP is inactivated by neutral endopeptidase (Rademaker *et al*., 1997). ANP is similar to BNP, but CNP is binding to NPR-B.

ROLE OF BNP IN HEART FAILURE

BNP is not only taken as a cardiac biomarker but also a surrogate marker of heart failure, acute coronary syndrome, and myocardial infarction, because BNP is associated with all cause mortality independent of age, NYHA (New York Heart Association) class, previous myocardial infarction, and left ventricular ejection fraction. More and more studies revealed that BNP plays an important role in stratifying the severity of heart failure, the differential diagnosis of cardiac or pulmonary dyspnea. However, with regard to management of heart failure, there are still some questions lefts to answer. For example, when ACE (angiotensin converting enzyme) inhibitor or β blocker has been titrated to maximal dose in a patient, how long should be the duration of maintaining maximal dose? What is the reasonable combination of multi-drug therapy? Has BNP similar value in ethnically different patients? Two randomized trials showed that maximal suppression of BNP concentration should be a reasonable goal of therapeutic strategy. In this review, we will focus on the role of BNP in the management of heart failure.

BNP AND NEW CLASSIFICATION OF HEART FAILURE

It is known that BNP is significantly correlated with NYHA classification class (Maisel *et al*., 2002). The American Heart Association developed a heart failure classification and defined heart failure into four stages (Hunt *et al*., 2001). At stage A, patients are at high risk for development of heart failure but have no apparent structural abnormality of the heart. At stage B, patients have a structural abnormality of the heart but have never had symptoms of heart failure. At stage C, patients have a structural abnormality of the

heart and have current or previous symptoms of heart failure. At stage D, patients have end-stage symptoms of heart failure not responsive to standard treatment. In contrast to the traditional NYHA classification used to describe functional limitations and therefore is a subjective parameter, the new classification is an objective one that emphasizes the evolution and progression of heart failure.

Unlike the traditional view of heart failure that focuses on the hemodynamic involved in the syndrome, the structural, functional, and biologic alterations of heart failure can account for the clinical outcomes of the disease's management. There are several models established to illustrate the cascade of heart failure mechanisms. The conventional hemodynamic model of heart failure emphasized the effect of an altered load on the failing ventricle and introduced vasodilators and inotropic agents. The neurohumoral model emphasized the importance of activation of the rennin-angiotensin-aldosterone axis and the sympathetic nervous system in the progression of cardiac dysfunction. The most important advance is the recognition that cardiac hormones synthesized within the myocardium and excreted in an autocrine and paracrine manner. Representatively, BNP is produced by the ventricular myocardium in response to myocyte stretch and ischemia. The vasodilatory and natriuretic effects of BNP counteract the opposing actions of angiotensin II and aldosterone.

Left ventricular remodeling of heart failure is the process of mechanical, neurohormonal, or genetic alteration in ventricular size, shape, and function. The characteristics of left ventricular remodeling include hypertrophy, loss of myocytes, and gain of interstitial fibrosis. It is a common progressive process that occurs in myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease. BNP has a putative role in the counteractive response to ischemia. In patients with chronic stable angina, the alteration level of BNP was correlated with the size of the ischemic area (Tateishi *et al*., 2000; Kyriakides *et al*., 2000). BNP level in patients with unstable angina is higher than that in patients with stable angina or in healthy patients (Kikuta *et al*., 1996). Reversible ischemia may increase left ventricular wall stress to cause an elevation of BNP level in circulation. BNP level is closely correlated to the severity of diastolic dysfunction provided the systolic function is preserved (Lubien *et al*., 2002). Our clinical data showed that in patients with or without ischemic and non-ischemic heart failure, BNP level was inversely related to the left ventricular ejection fraction and end diastolic dimension (Fig.2 and Fig.3).

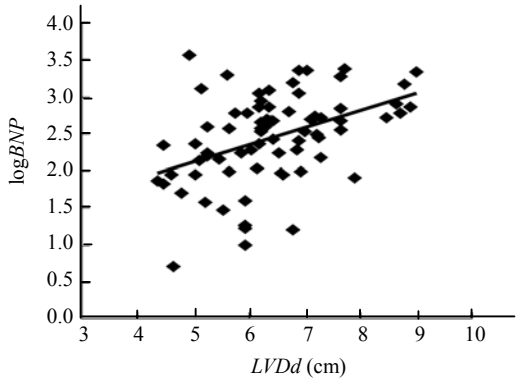

Fig.2 Correlation between left ventricular end diastolic dimension (LVDd) and log*BNP* in 78 Chinese patients with or without heart failure

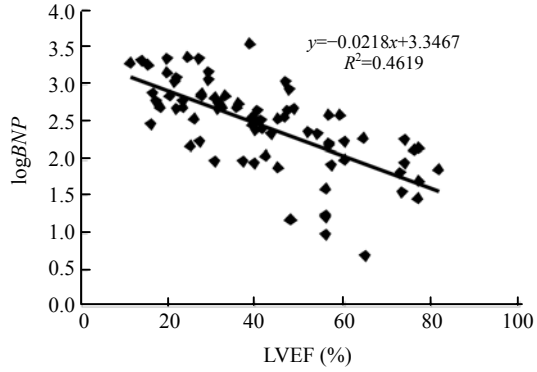

Fig.3 Correlation between left ventricular ejection fraction (LVEF) and log*BNP* in 78 Chinese patients with or without heart failure

On the other hand, the reverse remodeling process is a mechanism through which a variety of treatments control the heart failure syndromes. The reverse remodeling is associated with the pharmacological effects of ACE inhibitors, beta-adrenergic antagonists and aldosterone antagonists, or non-pharmacological effects of cardiac resynchronization and cardiac transplantation. All these therapeutic interventions promote a return to a more normal ventricular size and shape.

The correlation between BNP and the new heart failure classification remains to be clarified. BNP might not be a superior screening test to diagnose heart failure patient at stage B, who is asymptomatic

but has structure disorder. But BNP can sensitively and accurately reflect the progression or reverse remodeling process of heart failure. In patients with chronic heart failure, BNP was more closely associated with mortality than was NYHA class or ejection fraction or peak oxygen uptake during exercise testing. In patients with decompensated heart failure, BNP was associated with readmission for heart failure and outcomes after presentation to the emergency department for heart failure. Moreover, log*BNP* was the independent predictor superior to 16 other indices for sudden death in patients with chronic heart failure (Berger *et al*., 2002).

MANAGEMENT OF HEART FAILURE

Life style modification

Basic habits of moderate sodium restriction, weight monitoring, and adherence to medication schedules may aid in avoiding fluid retention or alerting the patient to its presence. A regularly scheduled exercise program such as walk is recommended as it may have beneficial effects on symptoms. Smoking cessation is advised and moderation of wine intake is encouraged.

Multi-drug therapy

New guidelines for the evaluation and management of chronic heart failure were published by the American College of Cardiology. ACE inhibitors and angiotensin-receptor blockers (ARB) decrease afterload by interfering with the rennin-angiotensin-aldosterone system, resulting in peripheral vasodilatation. Drugs of the both class can affect left ventricular hypertrophy, remodeling, and renal blood flow. ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, thereby minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium and causes natriuresis in the kidney. ACE inhibitors in heart failure management and after a myocardial infarction improve symptoms, cardiac performance, survival rate, and decrease rehospitalization rate. Beta-blockers inhibit the sympathetic nervous system and adrenergic receptors. They slow the heart rate, decrease blood pressure, and have a direct beneficial effect on the myocardium, enhancing reverse remodeling. Non-beta 1 selective beta-blockers can also block the alpha-adrenergic receptors and induce vasodilatation. Aldosterone stimulates renal sodium retention, potassium excretion and promotes ventricular and vascular hypertrophy. Selective or non-selective aldosterone antagonists counteract the effects of aldosterone. Diuretics decrease preload by stimulating natriuresis in the kidneys. Digoxin affects the Na^+/K^+-ATPase pump in the myocardial cell to increase contractility. Inotropics such as dobutamine and milrinone increase myocardial contractility. The combination of hydralazine and isosorbide dinitrate counteracts peripheral vasoconstriction and cause vasodilatation. The new drug Nesiritide (recombinant human brain natriuretic peptide) decreases pulmonary capillary wedge pressure and improves cardiac index and urinary flow rate in a dose-dependent manner (Fonarow, 2003; Zineh *et al*., 2003). It decreases preload by improving urinary flow and stimulates diuresis. In addition, it decreases norepinephrine and aldosterone concentrations and decreases afterload by vasodilatation.

Nonpharmacological therapy

Cardiac resynchronization therapy with biventricular pacing improves left ventricular function and favors reverse remodeling. Cardiac resynchronization therapy, stem cell transplantation and cardiac transplantation are promising nonpharmacological therapies when heart failure responds poorly to poly-pharmacological therapy.

BNP IN MANAGEMENT OF CHRONIC HEART FAILURE

BNP concentration can fall quickly in patients with decompensated heart failure after aggressive treatment with diuretics, vasodilators, ACE inhibitor, ARB, beta-blockers and aldosterone antagonist (Table 1). The BNP concentration when euvolumia is achieved is closely related to the prognosis of heart failure. The further reduction of BNP concentration after comprehensive treatment including titration of ACE inhibitor or β blocker may reflect the real reverse remodeling process. It should be stressed that serial monitoring of BNP concentration is superior to

assessment of BNP on admission for once, as the alteration of BNP concentration is a result of a dynamic process. Clinically, reverse remodeling may be judged by a reduction in left ventricular end-systolic volume by >15%. With this criterion, patients can be divided into responders and non-responders. However, among the non-responders some patients may have reduced BNP concentrations while others have sustained BNP concentration. The reduction of BNP may precede the alteration of ventricular sizes and therefore sensitively indicate an effective therapeutic strategy. The concept of BNP guided therapy is based on the two randomized trials. Whether titration of vasodilator according to blood BNP concentration is of value in individual optimization of vasodilator therapy in heart failure was investigated (Murdoch *et al*., 1999). Twenty patients with mild to moderate heart failure were randomly assigned to titration of ACE inhibitor dose according to serial measurement of blood BNP concentration or empirical ACE inhibitor therapy for 8 weeks. The results showed that the BNP guided therapy group was associated with significant reduction of BNP concentration that was significantly greater than the empirical therapy group (−42% vs −12%, P=0.03). Another study sought to determine whether BNP guided therapy would produce outcome superior to empirical therapy (Troughton *et al*., 2000). Study of sixty-nine heart failure patients who received either symptom-guided therapy or N-terminal BNP-guided therapy showed that the group assigned to N-terminal BNP-guided treatment received higher doses of ACE inhibitors, diuretics and spironolactone. Heart failure events in the N-terminal BNP-guided group were fewer than those in the symptom-guided group after 10 months of follow-up. More randomized trials to select BNP-guided non-pharmacological therapy (such as biventricular pacemaker and stem cell transplantation) are recommended.

BNP ALGORITHM IN HEART FAILURE MANAGEMENT

A BNP algorithm can be established to aid the clinical decision-making including selection of drug, titration of drug dose or nonpharmacological therapy (Fig.4). The euvolumia can be set as the primary goal of treatment for decompensated heart failure with BNP concentration as an evidence of discharge other than improvement of symptoms, because high level of BNP not only predicts the rehospitalization within 30 d but also indicates a high incidence of death. The further goal of treatment is reverse remodeling. BNP concentration assessment is adjunct to echocardiogram indices and might be much more sensitively and accurately judging response and non-response to reverse remodeling. Serial assessment of BNP concentration and clinical decision-making shall be

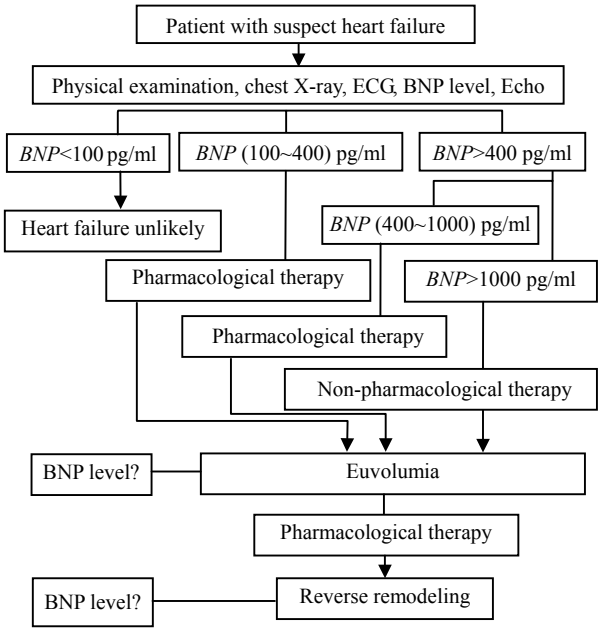

Fig.4 Algorithm for routine BNP assessment in the treatment of heart failure

Table 1 Impact of drug interventions on blood BNP level in heart failure studies

Authors	Drugs	BNP	Heart failure type
Sanderson *et al*., 1995	Beta blocker	↓	Heart failure
van Veldhuisen *et al*., 1998	ACE inhibitor	↓	Chronic heart failure
Murdoch *et al*., 1999	Vasodilator	↓	Chronic heart failure
Tsutamoto *et al*., 2001	Spironolactone	↓	Congestive heart failure
Latini *et al*., 2002	Valsartan	↓	Heart failure
Shiga *et al*., 2003	Amiodarone	↓	Heart failure
Tsutamoto *et al*., 1997	Digitalis	↑	Congestive heart failure

routinely recorded in a computed feedback system to reflect more precisely the dynamic procedure of heart failure management. As a surrogate marker of heart failure endpoints, the lowest or normal BNP concentration achieved after intervention indicates a promising prognosis while sustained BNP concentration alerts a poor prognosis. For the purpose of better efficacy and lower adverse reaction in the management of chronic heart failure, establishing a computed feedback system is suggested to manage all personnel, diagnostic and therapeutic information of each patient including dynamic change of BNP.

References

Berger, R., Huelsman, M., Strecker, K., Bojic, A., Moser, P., Stanek, B., Pacher, R., 2002. Brain natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*, **105**(20):2392-2397.

Brunner-La Rocca, H.P., Kaye, D.M., Woods, R.L., Hastings, J., Esler, M.D., 2001. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. *J. Am. Coll. Cardiol.*, **37**(5):1221-1227.

Cao, L., Gardner, D.G., 1995. Natriuretic peptides inhibit DNA synthesis in cardiac fibroblasts. *Hypertension*, **25**(2):227-234.

Charles, C.J., Espiner, E.A., Richards, A.M., Nicholls, M.G., Yandle, T.G., 1996. Comparative bioactivity of atrial, brain, and C-type natriuretic peptides in conscious sheep. *Am. J. Physiol.*, **270**(6 Pt 2):R1324-1331.

Clarkson, P.B., Wheeldon, N.M., Macleod, C., Coutie, W., MacDonald, T.M., 1995. Brain natriuretic peptide: Effect on left ventricular filling patterns in healthy subjects. *Clin. Sci. (Lond)*, **88**(2):159-164.

Clarkson, P.B., Wheeldon, N.M., MacFadyen, R.J., Pringle, S.D., MacDonald, T.M., 1996. Effects of brain natriuretic peptide on exercise hemodynamics and neurohormones in isolated diastolic heart failure. *Circulation*, **93**(11): 2037-2042.

de Bold, A.J., 1985. Atrial natriuretic factor: A hormone produced by the heart. *Science*, **230**(4727):767-770.

de Bold, A.J., Borenstein, H.B., Veress, A.T., Sonnenberg, H., 1981. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci.*, **28**(1):89-94.

de Bold, A.J., Bruneau, B.G., Kuroski de Bold, M.L., 1996. Mechanical and neuroendocrine regulation of the endocrine heart. *Cardiovasc. Res.*, **31**(1):7-18.

de Bold, A.J., Ma, K.K., Zhang, Y., de Bold, M.L., Bensimon, M., Khoshbaten, A., 2001. The physiological and pathophysiological modulation of the endocrine function of the heart. *Can. J. Physiol. Pharmacol.*, **79**(8):705-714.

Fonarow, G.C., 2003. Brain natriuretic peptide: Spectrum of application. Nesiritide (recombinant BNP) for heart failure. *Heart Fail Rev.*, **8**(4):321-325.

Fujisaki, H., Ito, H., Hirata, Y., Tanaka, M., Hata, M., Lin, M., Adachi, S., Akimoto, H., Marumo, F., Hiroe, M., 1995. Natriuretic peptides inhibit angiotensin II-induced proliferation of rat cardiac fibroblasts by blocking endothelin-1 gene expression. *J. Clin. Invest.*, **96**(2): 1059-1065.

Hama, N., Itoh, H., Shirakami, G., Nakagawa, O., Suga, S., Ogawa, Y., Masuda, I., Nakanishi, K., Yoshimasa, T., Hashimoto, Y., 1995. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. *Circulation*, **92**(6):1558-1564.

Henry, J.P., Pearce, J.W., 1956. The possible role of cardiac atrial stretch receptors in the induction of changes in urine flow. *J. Physiol.*, **131**(3):572-585.

Hunt, P.J., Espiner, E.A., Richards, A.M., Yandle, T.G., Frampton, C., Nicholls, M.G., 1995. Interactions of atrial and brain natriuretic peptides at pathophysiological levels in normal men. *Am. J. Physiol.*, **269**(6 Pt 2):R1397-1403.

Hunt, S.A., Baker, D.W., Chin, M.H., Cinquegrani, M.P., Feldman, A.M., Francis, G.S., Ganiats, T.G., Goldstein, S., Gregoratos, G., Jessup, M.L., *et al*., 2001. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines (committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J. Am. Coll. Cardiol.*, **38**:2101-2113.

Jensen, K.T., Carstens, J., Pedersen, E.B., 1998. Effect of BNP on renal hemodynamics tubular function and vasoactive hormones in humans. *Am. J. Physiol.*, **274**(1 Pt 2): F63-F72.

Kangawa, K., Fukuda, A., Kubota, I., Hayashi, Y., Minamitake, Y., Matsuo, H., 1984. Human atrial natriuretic polypeptides (hANP): Purification, structure synthesis and biological activity. *J. Hypertens. Suppl.*, **2**(3):S321-S323.

Kikuta, K., Yasue, H., Yoshimura, M., Morita, E., Sumida, H., Kato, H., Kugiyama, K., Ogawa, H., Okumura, K., Ogawa, Y., *et al*., 1996. Increased plasma levels of B-type natriuretic peptide in patients with unstable angina. *Am. Heart J.*, **132**(1 Pt 1):101-107.

Kisch, B., 1956. Electron microscopy of the atrium of the heart. I. Guinea pig. *Exp. Med. Surg.*, **14**(2-3):99-112.

Koller, K.J., Goeddel, D.V., 1992. Molecular biology of the natriuretic peptides and their receptors. *Circulation*, **86**(4):1081-1088.

Kyriakides, Z.S., Markianos, M., Michalis, L., Antoniadis, A., Nikolaou, N.I., Kremastinos, D.T., 2000. Brain natriuretic peptide increases acutely and much more prominently than atrial natriuretic peptide during coronary angioplasty. *Clin. Cardiol.*, **23**(4):285-288.

Lainchbury, J.G., Nicholls, M.G., Espiner, E.A., Yandle, T.G., Lewis, L.K., Richards, A.M., 1999. Bioactivity and interactions of adrenomedullin and brain natriuretic peptide in patients with heart failure. *Hypertension*, **34**(1):70-75.

Latini, R., Masson, S., Anand, I., Judd, D., Maggioni, A.P., Chiang, Y.T., Bevilacqua, M., Salio, M., Cardano, P., Dunselman, P.H., *et al*., 2002. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: The Valsartan Heart Failure Trial (Val-HeFT). *Circulation*, **106**(19): 2454-2458.

Lubien, E., DeMaria, A., Krishnaswamy, P., Clopton, P., Koon, J., Kazanegra, R., Gardetto, N., Wanner, E., Maisel, A.S., 2002. Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. *Circulation*, **105**(5):595-601.

Maisel, A.S., 2003. Nesiritide: A new therapy for the treatment of heart failure. *Cardiovasc. Toxicol.*, **3**(1):37-42.

Maisel, A.S., Krishnaswamy, P., Nowak, R.M., McCord, J., Hollander, J.E., Duc, P., Omland, T., Storrow, A.B., Abraham, W.T., Wu, A.H., *et al*., 2002. Breathing not properly multinational study investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N. Engl. J. Med.*, **347**(3): 161-167.

Minamino, N., Makino, Y., Tateyama, H., Kangawa, K., Matsuo, H., 1991. Characterization of immunoreactive human C-type natriuretic peptide in brain and heart. *Biochem. Biophys. Res. Commun.*, **179**(1):535-542.

Mukoyama, M., Nakao, K., Hosoda, K., Suga, S., Saito, Y., Ogawa, Y., Shirakami, G., Jougasaki, M., Obata, K., Yasue, H., 1991. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J. Clin. Invest.*, **87**(4): 1402-1412.

Murdoch, D.R., McDonagh, T.A., Byrne, J., Blue, L., Farmer, R., Morton, J.J., Dargie, H.J., 1999. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: Randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. *Am. Heart J.*, **138**(6 Pt 1):1126-1132.

Rademaker, M.T., Charles, C.J., Kosoglou, T., Protter, A.A., Espiner, E.A., Nicholls, M.G., Richards, A.M., 1997. Clearance receptors and endopeptidase: Equal role in natriuretic peptide metabolism in heart failure. *Am. J. Physiol.*, **273**(5 Pt 2):H2372-2379.

Richards, A.M., Crozier, I.G., Holmes, S.J., Espiner, E.A., Yandle, T.G., Frampton, C., 1993. Brain natriuretic peptide: Natriuretic and endocrine effects in essential hypertension. *J. Hypertens.*, **11**(2):163-170.

Sanderson, J.E., Chan, W.W., Hung, Y.T., Chan, S.K., Shum, I.O., Raymond, K., Woo, K.S., 1995. Effect of low dose beta blockers on atrial and ventricular (B type) natriuretic factor in heart failure: A double blind, randomised comparison of metoprolol and a third generation vasodilating beta blocker. *Br. Heart J.*, **74**(5):502-507.

Shiga, T., Hosaka, F., Wakaumi, M., Matsuda, N., Tanizaki, K., Kajimoto, K., Shoda, M., Hagiwara, N., Kasanuki, H., 2003. Amiodarone decreases plasma brain natriuretic peptide level in patients with heart failure and ventricular tachyarrhythmia. *Cardiovasc. Drugs Ther.*, **17**(4): 325-333.

Sudoh, T., Kangawa, K., Minamino, N., Matsuo, H., 1988. A new natriuretic peptide in porcine brain. *Nature*, **332**(6159):78-81.

Sudoh, T., Maekawa, K., Kojima, M., Minamino, N., Kangawa, K., Matsuo, H., 1989. Cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide. *Biochem. Biophys. Res. Commun.*, **159**(3): 1427-1434.

Sudoh, T., Minamino, N., Kangawa, K., Matsuo, H., 1990. C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain. *Biochem. Biophys. Res. Commun.*, **168**(2):863-870.

Suga, S., Nakao, K., Hosoda, K., Mukoyama, M., Ogawa, Y., Shirakami, G., Arai, H., Saito, Y., Kambayashi, Y., Inouye, K., 1992. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. *Endocrinology*, **130**(1):229-239.

Tateishi, J., Masutani, M., Ohyanagi, M., Iwasaki, T., 2000. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin. Cardiol.*, **23**(10):776-780.

Troughton, R.W., Frampton, C.M., Yandle, T.G., Espiner, E.A., Nicholls, M.G., Richards, A.M., 2000. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet.*, **355**(9210):1126-1130.

Tsutamoto, T., Wada, A., Maeda, K., Hisanaga, T., Fukai, D., Maeda, Y., Ohnishi, M., Mabuchi, N., Kinoshita, M., 1997. Digitalis increases brain natriuretic peptide in patients with severe congestive heart failure. *Am. Heart J.*, **134**(5 Pt 1):910-916.

Tsutamoto, T., Wada, A., Maeda, K., Mabuchi, N., Hayashi, M., Tsutsui, T., Ohnishi, M., Sawaki, M., Fujii, M., Matsumoto, T., *et al*., 2001. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J. Am. Coll. Cardiol.*, **37**(5):1228-1233.

van der Zander, K., Houben, A.J., Kroon, A.A., de Leeuw, P.W., 1999. Effects of brain natriuretic peptide on forearm vasculature: Comparison with atrial natriuretic peptide. *Cardiovasc. Res.*, **44**(3):595-600.

van der Zander, K., Houben, A.J., Kroon, A.A., De Mey, J.G., Smits, P.A., de Leeuw, P.W., 2002. Nitric oxide and po-

tassium channels are involved in brain natriuretic peptide induced vasodilatation in man. *J. Hypertens.*, **20**(3):493-499.

van Veldhuisen, D.J., Genth-Zotz, S., Brouwer, J., Boomsma, F., Netzer, T., Man In'T Veld, A.J., Pinto, Y.M., Lie, K.I., Crijns, H.J., 1998. High- versus low-dose ACE inhibition in chronic heart failure: A double-blind, placebo-controlled study of imidapril. *J. Am. Coll. Cardiol.*, **32**(7):1811-1818.

Yoshimura, M., Yasue, H., Okumura, K., Ogawa, H., Jougasaki, M., Mukoyama, M., Nakao, K., Imura, H., 1993. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation*, **87**(2):464-469.

Zineh, I., Schofield, R.S., Johnson, J.A., 2003. The evolving role of nesiritide in advanced or decompensated heart failure. *Pharmacotherapy*, **23**(10):1266-1280.