B-Type Natriuretic Peptide and Cardiovascular Disease

Luís Beck da Silva, Carlos A. Ferreira, Celso Blacher, Paulo Leães, Haissam Haddad

Porto Alegre, RS / Ottawa, ON - Canadá

"Cardiologists and internists may now have a tool with which to determine whether a patient has congestive heart failure and to measure its severity, much as physicians routinely measure serum creatinine in patients with renal disease and perform liver-function tests in patients with hepatic disorders."

K. L. Baughman, Johns Hopkins

The discovery of an endocrine link between the heart and the kidneys has its basis in the electron microscopic finding that the striated muscle cells of the cardiac atria in mammals are differentiated both as contractile and as endocrine cells. Atrial natriuretic factor (ANF), a circulating peptide with natriuretic, diuretic, and vasorelaxant properties, was discovered in the early 1980s by A. J. de Bold, when it was considered the humoral link between the heart and kidney that had long been predicted [1]. Since then, a huge number of multidisciplinary investigations have been conducted to investigate the actual role of this peptide in the pathogenesis of cardiovascular and renal disease as well as in the regulation of salt and water excretion and blood pressure. These investigations have ended up being an example of "bench-to-bedside" research as B-type natriuretic peptide (BNP) now is reaching the clinical arena with increased expectations.

The aim of this review is to provide the clinician with an update on progress made and determining where we stand now in terms of incorporating BNP into daily clinical practice.

Natriuretic peptides

ANF, BNP (also called brain natriuretic peptide), and C-type natriuretic peptide (CNP) constitute the natriuretic-peptide family [2].

University of Ottawa Heart Institute, Canada and Hospital São Francisco, Santa Casa de Porto Alegre.
Mailing address: Haissam Haddad MD FRCPC - Heart Failure Program Director University of Ottawa Heart Institute - 40 Ruskin Street Suite H147, Ottawa - ON, K1Y 4W7 – Canada - E-mail: hhaddad@ottawaheart.ca

Their principal role is participation in cardiovascular homeostasis and modulation of cell growth. ANF mRNA has been found in many tissues but is most abundant in the atria of the heart. BNP was first isolated from brain homogenates but is also found in the circulation and the highest concentration is in myocardial tissue. Both ANF and BNP are normally produced by the cardiac muscle cells of the atria, from where they are released. However, under atypical conditions, such as in myocardial structural disease, BNP seems to be produced in larger amounts by the ventricles [3]. Collectively, the natriuretic peptides counterbalance the effects of the renin-angiotensin-aldosterone system. ANF and BNP plasma concentrations increase in response to atrial stretch, and they have been shown to be physiological antagonists of the effects of angiotensin II on vascular tone, aldosterone secretion, renal sodium reabsorption, and vascular-cell growth.

CNP is found predominantly in the brain and endothelial cells and plasma concentrations are very low [4]. For this reason, the most widely studied natriuretic peptides in cardiovascular disease are ANP and BNP (fig. 1).

BNP as a diagnostic tool

BNP has been studied as a reliable diagnostic tool to be used in the emergency room as a screening test in patients who complain of dyspnea.

Davis et al [5], after measuring ANF and BNP in 52 patients presenting to the emergency room with acute dyspnea, showed that plasma BNP concentrations on admission indicated the correct diagnosis more accurately than did ejection fraction or concentration of ANF. Dao et al [6] measured BNP in 250 patients presenting to emergency rooms with dyspnea as a primary symptom and were able to find significant discrepancies in BNP values between patients with and without congestive heart failure (CHF). In this study, BNP at a cutpoint of 80 pg/mL was highly sensitive and highly specific for the diagnosis of CHF. The negative predictive value of BNP values under 80 pg/mL was 98% for the diagnosis of CHF (fig. 2).

More recently, Harrison et al investigated whether BNP levels drawn in patients presenting with dyspnea to the emergency room were a predictor of future cardiac events. They reported that a BNP value of 480 pg/mL had a

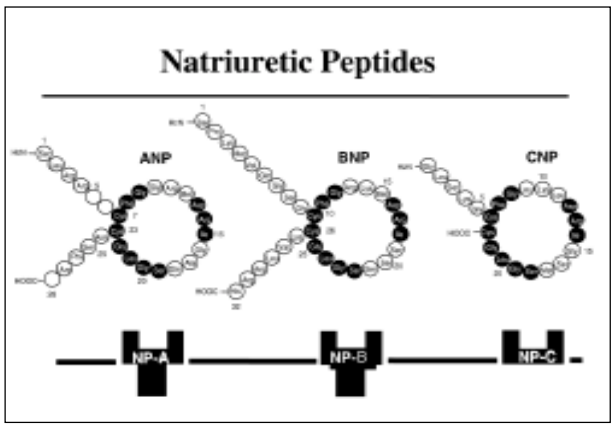

Fig. 1 - The Natriuretic Peptide Family.

sensitivity of 68%, specificity of 88%, and an accuracy of 85% for predicting a subsequent CHF endpoint in 6 months. Alternatively, patients with BNP levels less than 230 pg/mL had an excellent prognosis with only a 2.5% incidence of CHF endpoints. Finally, the authors concluded that in this study population, BNP levels measured in patients presenting with dyspnea to the emergency room are highly predictive of cardiac events over the next 6 months.

A large-scale, multicenter study has been recently completed in which 1586 patients with acute shortness of breath were examined with the aim of testing BNP in differentiating cardiac from noncardiac causes of dyspnea. Results show that BNP had good specificity and a high negative predictive value, with an area under the receiver-operating characteristic curve of 0.91. It also confirms the association between BNP plasma levels and the severity of CHF as indicated by New York Heart Association functional class (fig. 3). The same study demonstrated that a single BNP level was more accurate for diagnosis of CHF than both the Framingham criteria and the National Health and Nutrition Examination (NHANES) Score [7].

Receiver-operated characteristic (ROC) curves suggest that a BNP cutpoint of 100 pg/mL provides a reasonable means for discriminating between patients with and without CHF, with a sensitivity from 82.4% to detect CHF in general and up to 99% for NYHA class IV. The BNP test specificity exceeded 95% when comparing patients with and without CHF.

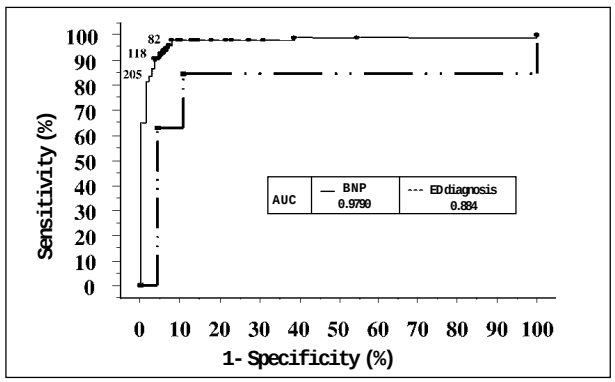

Fig. 2 - Receiver-operated curves for BNP and emergency department diagnosis of CHF, using all 250 patients. (Adapted from Dao et al [6]).

BNP and diagnosis of diastolic dysfunction

As many as 40% to 50% of patients with a diagnosis of CHF have normal systolic function, which implicates diastolic dysfunction as the most likely potential abnormality responsible for this disorder. The prevalence of diastolic heart failure increases with age, with an approximate incidence of 15% to 25% in patients <60 years of age, 35% to 40% in those between 60 and 70 years of age, and 50% in patients >70 years of age [8]. The diagnosis of diastolic heart failure cannot be distinguished from that of systolic heart failure based on history, physical examination, chest X-ray, and ECG alone [9]. Clinically, the diagnosis of abnormal diastolic performance is based on exclusion, ie, the absence of systolic dysfunction in patients with clinical CHF.

Krishnaswamy et al [10] reported the utility of BNP in distinguishing diastolic in addition to systolic dysfunction. Left ventricular (LV) function was assessed in 400 patients. In 147 patients, LV function was considered normal and BNP levels were low at 30±36 pg/mL, where those with systolic dysfunction had a mean level of 416±413 pg/mL. Patients with preserved systolic function but with diastolic dysfunction had values of 391±89 pg/mL (P<0.001 compared with normal). The area under the ROC curve for BNP levels to detect diastolic dysfunction by echocardiography in patients with CHF and normal systolic function was 0.958 [11]; and to detect any abnormal echocardiographic finding was 0.95 (91% confidence interval: 0.93 to 0.97) [10]. Other authors [12,13] have also reported increased levels of BNP in the presence of diastolic dysfunction.

More recently, Lubien et al [14] studied 294 patients referred for assessment of LV function by echocardiography. The goal was to differentiate the various LV filling patterns by Doppler velocity recordings in individuals with normal LV systolic function. Patients with systolic dysfunction were excluded. Patients diagnosed with any evidence of diastolic

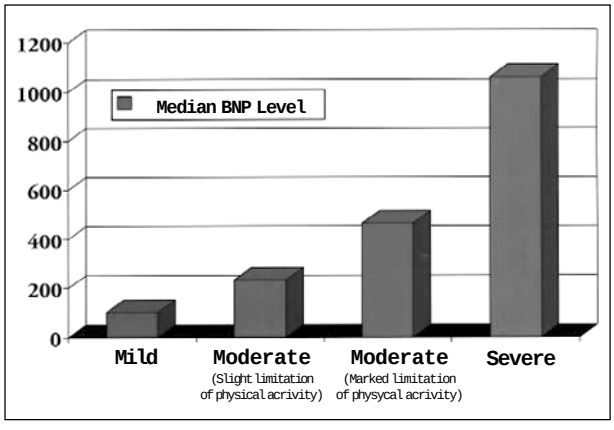

Fig. 3 - Relationship between BNP and congestive heart failure severity as measured by New York Heart Association Functional Class. (Copyright Biosite Diagnostics, 2001).

dysfunction had a mean BNP concentration of 286±31 pg/mL; those in the normal LV group had a mean BNP concentration of 33±3 pg/mL. Patients with restrictive-like filling patterns on echocardiography had the highest BNP levels (408±66 pg/ml), and patients with symptoms had higher BNP levels in all diastolic filling patterns (fig. 4). The area under the receiver-operating characteristic curve for BNP to detect any diastolic dysfunction in patients with normal systolic function was 0.92 (95% CI, 0.87 to 0.95; P<0.001). This is the first study of the different LV filling patterns visualized by Doppler velocity recordings and to finally conclude that a rapid assay for BNP can reliably detect the presence of diastolic abnormalities on echocardiography.

These studies concluded that BNP levels cannot alone differentiate between systolic and diastolic dysfunction and that a low BNP level in the setting of normal systolic function might likely rule out clinically significant diastolic dysfunction. In fact, for some patients, the finding of a normal BNP level may preclude the need for echocardiography. In patients with normal systolic function and clinical Congestive Heart Failure, an elevated BNP level appears to substantiate the diagnosis of diastolic dysfunction.

BNP and hemodynamic monitoring in heart failure

Clinical findings have demonstrated limited reliability for indicating the hemodynamic status of Congestive Heart Failure patients [15,16]. A number of reports [17,18] have suggested that "tailored vasodilatation," aimed at normalizing pulmonary artery wedge pressure and systemic vascular resistance in HF with ventricular dilation, results in a better clinical outcome than does empiric treatment. Stevenson et al [17] demonstrated a decade ago that patients with severe heart failure listed for transplant who were able to respond favorably to tailored therapy had a 1-year mortality of 38% while nonresponders had 83% 1-year mortality. The benefits of tailoring therapy with the help of a Swan-Ganz catheter resides on in the notion that reducing filling pressures to near normal levels leads to ideal cardiac output [17]. This could occur because of a reduction in mitral regurgitation, but also from decreases in myocardial oxygen consumption.

However, the tailored vasodilatation approach requires expensive inpatient care and an invasive procedure for insertion of a Swan-Ganz catheter. A simple and reliable blood test that correlates to changes in pulmonary wedge pressure during heart failure management would be of significant value.

Plasma concentrations of BNP not only reflect left ventricular filling pressure [19] but are also closely correlated to the changes in the pulmonary capillary wedge pressure during hospitalization (r=0.73, P<.05) [20]. Patients that failed to respond to tailored therapy could be identified by BNP levels, and these patients were also more likely to be re-admitted [20]. That being said, BNP may be an effective way to improve the in-hospital management of patients with severe heart failure as well as to allow the possibility of an outpatient tailored therapy, obviating the need for invasive hemodynamic monitoring.

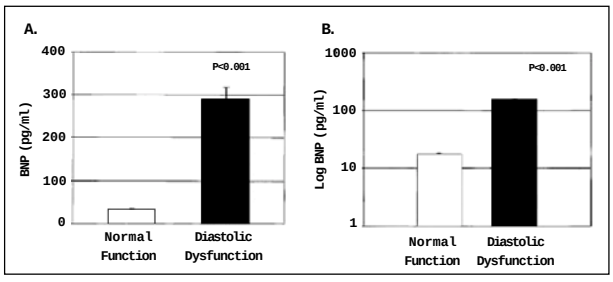

Fig. 4 - BNP levels in patients with normal function by echocardiography and with diastolic dysfunction. Data are expressed as both mean ± SEM (A) and geometric log mean (B). Both were significant at P<0.001. Adapted from Lubien et al. [14].

BNP and atrial fibrillation

Atrial fibrillation (A-Fib) is a frequent disease among the elderly, patients with Congestive Heart Failure, and elderly patients with Congestive Heart Failure. It is well known that BNP is a noninvasive tool that is reliably correlated with left ventricular end-diastolic pressure, and it is in fact a marker of the myocardial stretch [21]. A previous study[3] demonstrated that A-Fib is an independent determinant of higher plasma ANF levels. Although BNP and particularly ANF are expected to be elevated in patients with atrial fibrillation with or without LV dysfunction, it has been shown that both peptides tend to decrease after successful direct DC cardioversion [22]. Other authors [23] have shown that in patients with A-Fib, BNP is increased and the atrial myocardium itself has been reported as the source of increased BNP production. Another piece of evidence of correlation between arrhythmias that involve atrioventricular uncoupling and BNP levels comes from a study that showed increased plasma BNP levels in patients with a pacemaker in VVI mode when compared with a pacemaker in DDD or AAI mode [24]. After atrial cardioversion, BNP gradually drops [22].

BNP and ischemic heart disease

A significant number of studies have demonstrated that after a myocardial infarction, a higher level of BNP is associated with a larger infarct size [25], an increased likelihood of ventricular remodeling [26], a lower ejection fraction [27], and an increased risk of heart failure and death [28].

Most recently, BNP has been evaluated in the whole spectrum of acute coronary syndromes. A subgroup analysis from the OPUS TIMI 16 study revealed that higher levels of plasma BNP were associated with coronary stenoses greater than 50% and with positive exercise stress tests (P<0.001) [29].

De Lemos et al [30] reported that the baseline level of B-type natriuretic peptide was correlated with the risk of death, heart failure, or myocardial infarction at 30 days and 10 months. This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation (P=0.02), patients who had myocardial infarction

without ST-segment elevation (P<0.001), and patients who had unstable angina (P<0.001). Survivors had a mean BNP level of 80 pg/mL and patients who died within 30 days after the index MI had a mean BNP level of 153 pg/mL (P<0.001). These findings were independent of troponin levels, age, presence or absence of heart failure, renal failure, and ST segment deviation.

These authors concluded that a single measurement of BNP, obtained in the first few days after the onset of ischemic symptoms, provides predictive information for use in risk stratification across the spectrum of acute coronary syndromes. Cardiac neurohormonal activation may be key information among patients at high risk for death after acute coronary syndromes.

BNP in interventional procedures and acute coronary syndromes

BNP level has also been tested in the setting of percutaneous coronary interventions (PCI) and has been found to be elevated during and immediately after the balloon dilatation. Furthermore, plasma BNP levels returned to baseline shortly after the procedure [31]. The mechanism behind this finding is that BNP increases in response to acutely increased LV pressures secondary to transient myocardial ischemia induced by PCI. To confirm this tentative mechanism, Tateishi et al [32] studied a group of patients undergoing diagnostic coronary angiography and compared them to another group of patients undergoing coronary interventions. Although no hemodynamic changes were observed before and after the procedure, plasma BNP was increased only in the group of patients who underwent PCI. Considering this result, BNP would possibly account for minimal hemodynamic impact secondary to balloon-induced ischemia that is otherwise undetected by conventional hemodynamic measurements. The BNP variation during angioplasty may become a surrogate marker to indicate how much ischemic myocardium is under a particular coronary supply.

Finally, in agreement with the above-mentioned results, BNP level has been definitely associated with increased risk of cardiac events in 450 patients presenting with acute coronary syndromes. In a multi-marker approach for risk stratification in acute coronary syndromes, BNP has been shown to add independent prognostic information [33].

BNP and diabetes mellitus

It is well known that diabetic patients have an increased risk of ischemic heart disease and a higher incidence of Congestive Heart Failure. Diabetic patients also have a higher prevalence of both diastolic and systolic LV dysfunction [34]. These abnormalities are frequently asymptomatic particularly in diabetic patients, although they can be treated with well-established modalities with proven efficacy, such as ACE-inhibitors and beta-blockers [35].

Although echocardiography is the cornerstone for the diagnosis of LV dysfunction, in diabetic patients it has significant drawbacks: it is not readily available in diabetic clinics; it is usually reserved for symptomatic patients; and it is too expensive to be used as a screening tool, especially in asymptomatic patients. Yet, identification of diabetic patients with LV dysfunction is extremely important. To test the hypothesis of whether BNP levels would serve as a screening tool in diabetic patients to assess the presence or absence of cardiac dysfunction, Maisel et al [36] studied 111 diabetic patients referred for echocardiography to the San Diego Veterans Administration Healthcare System. In patients with normal LV function, BNP was 39±8 pg/mL. This was significantly less than that in patients with systolic dysfunction in which BNP was 379±138 pg/mL or in patients with diastolic dysfunction in which BNP was 474±106 pg/mL. Patients with systolic and diastolic dysfunction had BNP levels of 958±169 pg/mL. The area under the receiver-operating characteristic curve showing the sensitivity and specificity of BNP versus the echocardiographic diagnosis was 0.953. They concluded that a simple and rapid assay for BNP could be used to reliably screen diabetic patients for the presence or absence of LV dysfunction, especially for detecting early LV dysfunction in asymptomatic patients.

Conclusion

In summary, BNP is a neurohormone that is synthesized in the cardiac ventricles and is an indicator of raised intracardiac pressure. It may be increased due to a variety of structural cardiac diseases, such as Congestive Heart Failure, LV systolic or diastolic dysfunction, rapid atrial fibrillation, acute ischemia, or significant valve disease. Thus, the value of BNP resides in its high negative predictive value ($\geq$ 96%). Nevertheless, BNP is becoming a general screening test for echocardiogram requests, regardless of the reason for the echocardiogram, an extremely useful and reliable tool in the diagnosis and prediction of the severity of Congestive Heart Failure in the emergency room, a potential surrogate marker for hemodynamic monitoring in patients with severe heart failure, as well as a prognostic marker in patients who have had an acute myocardial infarction. Several other applications are under investigation, and some authors have dared to compare the usefulness of BNP in heart disease to the role that creatinine plays in patients with renal disease.

References

1. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981; 28:89-94.
2. Van D, Crijns HJ, Van V, Van G, De K, Lie KI. Atrial natriuretic peptide in patients with heart failure and chronic atrial fibrillation: role of duration of atrial fibrillation. Am Heart J 1998; 135:242-4.
3. Rossi A, Enriquez S, Burnett JC, Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. J Am Coll Cardiol 2000; 35:1256-62.
4. Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. Lancet 1997; 349:1307-10.
5. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994; 343:440-4.
6. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001; 37:379-85.
7. 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.
8. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure. N Engl J Med 2002; 347:161-7.
9. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-7.
10. Wong WF, Gold S, Fukuyama O, Blanchette PL. Diastolic dysfunction in elderly patients with congestive heart failure. Am J Cardiol 1989; 63:1526-8.
11. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. Ann Intern Med 1992; 117:502-10.
12. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med 2001; 111:274-9.
13. Lang CC, Prasad N, McAlpine HM, et al. Increased plasma levels of brain natriuretic peptide in patients with isolated diastolic dysfunction. Am Heart J 1994; 127:1635-6.
14. Yamamoto K, Burnett JC, Jougasaki M, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996; 28:988-94.
15. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002; 105:595-601.
16. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989; 261:884-8.
17. Rohde LE, Silva Neto LB, Lima MP, et al. Accuracy of clinical findings to determine hemodynamic status in outpatients with heart failure. J Card Fail 2001; 7:99
18. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. Am J Cardiol 1990; 66:1348-54.
19. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail 1999; 1:251-7.
20. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997; 96:509-16.
21. Kazanegra R, Van Cheng BS, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001; 7:21-9.
22. Maeda K, Takayoshi T, Wada A. 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.
23. Ohta Y, Shimada T, Yoshitomi H, et al. Drop in plasma brain natriuretic peptide levels after successful direct current cardioversion in chronic atrial fibrillation. Can J Cardiol 2001; 17:415-20.
24. Van D, Tjeerdsma G, Jan d, Boomsma F, Crijns HJ, Van V. Longstanding atrial fibrillation causes depletion of atrial natriuretic peptide in patients with advanced congestive heart failure. Eur J Heart Fail 2002; 4:255-62.
25. Inoue SI, Murakami Y, Sano K, Katoh H, Shimada T. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. J Card Fail 2000; 6:92-6.
26. Horie H, Tsutamoto T, Ishimoto N. Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. Pacing Clin Electrophysiol 1999; 22:282-90.
27. Arakawa N, Nakamura M, Aoki H, Hiramori K. Relationship between plasma level of brain natriuretic peptide and myocardial infarct size. Cardiology 1994; 85:334-40.
28. Nagaya N, Nishikimi T, Goto Y, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am Heart J 1998;135:21-8.
29. Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. Heart 1999; 81:114-20.
30. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998; 97:1921-9.
31. Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation 2000; 102:149-56.
32. De Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014-21.
33. Kyriakides ZS, Markianos M, Michalis L, Antoniadis A, Nikolaou NI, Kremastinos DT. Brain natriuretic peptide increases acutely and much more prominently than atrial natriuretic peptide during coronary angioplasty. Clin Cardiol 2000; 23:285-8.
34. Tateishi J, Masutani M, Ohyanagi M, Iwasaki T. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. Clin Cardiol 2000; 23:776-80.
35. Sabatine MS, Morrow DA, de L, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002; 105:1760-3.
36. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. J Am Soc Echocardiogr 2001; 14:885-91.
37. The SOLVD Investigattors. Effect of enalapril on mortality and the development. of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327:685-91.
38. Maisel AS, Morrison K, Demaria AN. The use of B-natriuretic peptide in assessing cardiac function in patients with diabetes mellitus. Circulation 2001; 104:2-3
39. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Med 2000; 343:246-53.