

# Serial Monitoring of B-Type Natriuretic Peptide in Heart Failure Patients

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## ABSTRACT

The measurements of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), when taken together with conventional clinical assessment, may assist in making the prognosis and also for making serial adjustment of such treatment. But although such commercial assays are currently approved for the diagnosis of heart failure, the role of the natriuretic peptides for monitoring the success of congestive heart failure (CHF) therapy has not as yet been submitted for regulatory approval. Moreover, because of the intra-individual biologic variation of the BNP or because of multiple factors that affect the BNP levels, the magnitude of the change of BNP levels must be large to confidently interpret BNP changes within an individual, and just how large has not been determined. Yet the levels of plasma BNP and NT-pro BNP are well correlated with the concurrent haemodynamic measurements and indicators of left ventricular systolic function. Also, BNP and NT-pro BNP serve as significant prognostic information and it is possible that adjustment of anti-heart failure therapy according to serial measurements of BNP (in addition to the standard clinical assessment) may offer improved outcomes. Better understanding of the test characteristics is needed before we can effectively use this valuable test to guide therapeutic strategies. (**Korean Circulation J 2007;37:393–398**)

**KEY WORDS :** Heart failure ; Natriuretic peptides ; B-type natriuretic peptide.

## Introduction

When a patient displays increasing cardiac dysfunction, the synthesis and release of cardiac natriuretic peptides rises incrementally in concert with other observed neurohormonal responses during heart failure.<sup>1)</sup> Therefore, increased B-type natriuretic peptide (BNP) and/or N-terminal proBNP (NT-proBNP) have been proposed as markers for symptomatic ventricular dysfunction, and they can help physicians make the diagnosis of cardiac dyspnea.<sup>2-7)</sup> Therefore, measurements of BNP or NT-proBNP, when taken together with conventional clinical assessment, may assist in the decision of whether or not to initiate anti-heart failure pharmacotherapy and also for the serial adjustment of such treatment (Fig. 1).<sup>8)</sup> A large body of published observational data attests to the power of plasma measurements of BNP or NT-proBNP to assist in the diagnosis of symptomatic heart failure and to provide independent prediction of death and later cardiovascular events during both acute and chronic heart failure.<sup>9)</sup> Serial BNP measurements have recently provided

incremental information that goes beyond the clinical presentation or they can be used as an end point to assess the efficacy of heart failure therapy and as a prognostic marker of heart failure.<sup>8-11)</sup> Although commercial assays are currently approved for the diagnosis of heart failure, the role of the natriuretic peptides for monitoring the success of congestive heart failure (CHF) therapy or as a therapeutic target for heart failure has not yet been submitted for regulatory approval.

The following brief review summarizes the available information concerning the reported relationship between changes in the plasma concentrations of BNP or NT-pro BNP and the clinical outcomes. We also summarize the clinical significance and some of the limitations of serial monitoring the BNP or NT-pro BNP.

## The BNP or NT-Pro BNP Levels as a Treatment Target for Heart Failure

In many conditions, the treatment can be titrated against a target. For example, for hypertension this is the blood pressure, for diabetes this is the blood sugar level and for hypercholesterolemia this is the cholesterol level. Patients with acute heart failure have high mortality and a very frequent readmission rate after discharge. Therefore, to identify the high risk patients and monitor the

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success of treatments are major issues. The method and factors to identify the patients who are at a high risk of death or readmission and to monitor treatment success are the clinical symptoms and signs, the New York Heart Association (NYHA) class, echocardiography and the BNP or NT-proBNP test.<sup>9)</sup> But in the real clinical world,

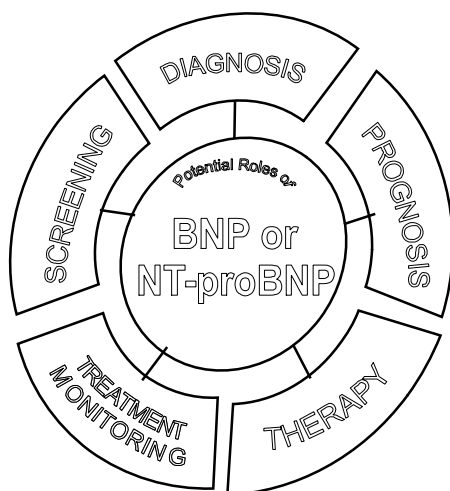


Fig. 1. Diagram of the potential roles of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP). Testing for either BNP or NT-proBNP has a number of possible uses for the treatment of heart failure: screening for asymptomatic left ventricular dysfunction, diagnosis, risk stratification, determining the prognosis and treatment monitoring.

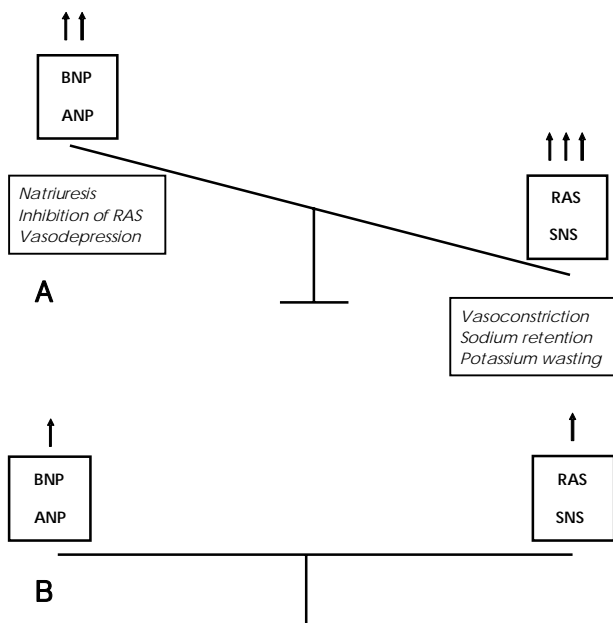


Fig. 2. Neuro-hormone imbalance in heart failure. For patients with heart failure, the rennin-angiotensin-aldosterone system, the sympathetic nerve system and the endothelin systems are activated over the counter-regulatory natriuretic peptide (BNP, ANP) systems or other systems (A). Therefore, neurohormonal imbalance is a significant patho-physiologic mechanism in heart failure. After treatment, recovery of the neurohormonal balance means stabilization of the heart failure status (B). BNP: B-type natriuretic peptide, ANP: A-type natriuretic peptide, RAS: renin-angiotensin-aldosterone system, SNS: sympathetic nervous system.

congestion suggesting an elevated pulmonary capillary wedge pressure (PCWP) often does not translate into signs or symptoms. Among the patients with severe heart failure and elevated PCWP, some patients revealed no congestion or rales. Also, haemodynamic congestion may not be recognized clinically or it doesn't translate into symptoms/signs until late.<sup>12/13)</sup> Even though several profiles have been shown to be effective, there is currently no target in the clinical profiles for the treatment of heart failure that is objective, reliable, practical and inexpensive. The BNP levels correlate positively with the cardiac filling pressures and volumes and they are inversely-related to the left ventricular ejection fraction. Also, neuro-hormonal imbalance between the rennin-angiotensin-aldosterone system and the natriuretic peptide system is a significant patho-physiologic mechanism of heart failure (Fig. 2A). After treatment, recovery of neuro-hormonal balance means stabilization of the heart failure status (Fig. 2B). The BNP level during follow-up of heart failure patients has been considered to be a sort of biochemical Swan-Ganz catheter, and this is analogous to the HbA1c level in patients with diabetes mellitus or the AFP level in patients with hepatocellular carcinoma. Because the BNP levels correlate with the atrial and ventricular filling pressures, it is reasonable to ask whether changes in the BNP can mirror the effectiveness of therapies designed to reduce filling pressures. According to the data by Dr. Maisel (Fig. 3), as the wedge pressure fell, so did the BNP level during 24 hours of treatment in patient with acute heart failure.<sup>14)</sup> It is interesting to note that even after the wedge pressures normalized in these patients, the BNP levels continued to decline. This reflects continual neuro-hormonal normalization and the BNP was a relatively good indicator for monitoring treatment. Therefore, it is possible to accept that BNP

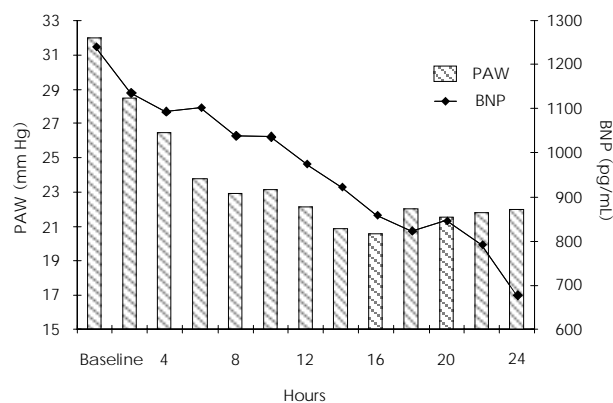


Fig. 3. Relationship of the B-type natriuretic peptide (BNP) levels and the pulmonary wedge pressure (PAW) in patients with heart failure.<sup>14)</sup> During 24 hours of treatment for patient with decompensated congestive heart failure, the wedge pressure decreased below 20 mm Hg within 16 hours and then remained there. As the wedge pressure fell, so did the BNP level. It is interesting to note that even after the wedge pressures normalized in these patients, the BNP levels continued to decline. This reflects continual neuro-hormonal normalization and the BNP was a relatively good indicator for treatment monitoring.

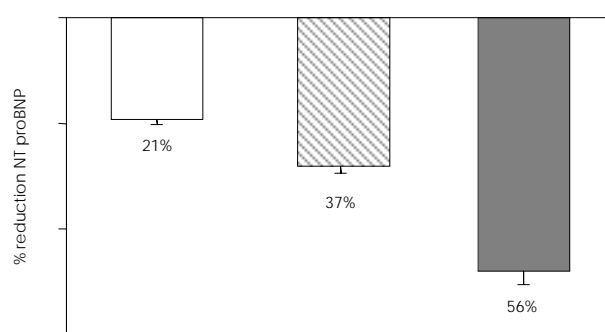
or NT-proBNP is currently a good target for the treatment of heart failure; it is objective, reliable, practical and inexpensive.

### Treatment Monitoring by B-Type Natriuretic Peptide Serial Measurements

As mentioned above, the BNP or NT proBNP may be a reliable target for the treatment of heart failure, yet important questions need to be addressed. First, how should the results of serial measurements of BNP or NT-proBNP be interpreted? Second, how many BNP levels should be determined in the hospital? Finally, is it possible to use the BNP or NT-proBNP measurements in out-patient clinics?

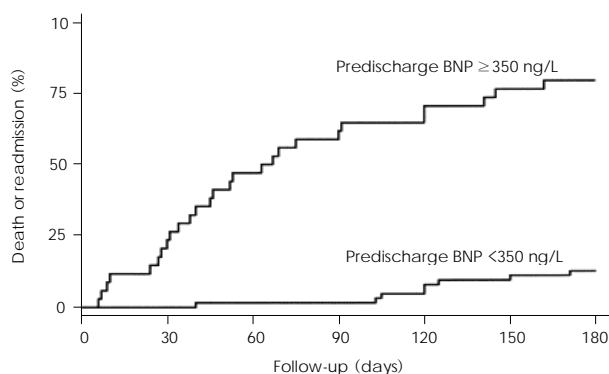
The first issue is interpretation of the BNP changes in heart failure. For patients with heart failure, their BNP levels decrease with adequate medical therapy when the disease is improved or stabilized. The decrease of BNP correlates with clinical benefit, improvement of the functional parameters like the ejection fraction (EF) and the surrogate parameters of therapy success like the renin levels and a decreased heart rate. Furthermore, patients who were most likely to have a cardiac event had higher BNP levels both at the times of admission and discharge.<sup>8)</sup> Also, elevated BNP levels may offer superior prognostic information to the critical care practitioner to help identify those patients who are at the highest risk for mortality. Changes in the BNP and NT-proBNP levels over time are associated with concurrent changes in the EF or ventricular volumes and the clinical symptoms, suggesting that these natriuretic peptides may potentially serve as useful surrogate markers for patients with progressive heart failure. Also, these observations of the serial measurements of the BNP and evaluating their changes served as significant clinical information for heart failure. The data from several studies demonstrated that changes in BNP correlated with changes in the NYHA status or prognosis. Lopez et al. demonstrated that this BNP level was decreased by 21% in the patients who maintained a state of decompensated heart failure, but the level was improved by 57% in the patients whose heart failure completely recovered to a chronically stable state (Fig. 4).<sup>8)</sup> For our data, the BNP level at the time of the initial visit was  $1400.5 \pm 1205.4$  pg/mL and this decreased by 67.2% to  $439.0 \pm 697.6$  pg/mL 1-3 months later in the patients with acute heart failure who showed a good clinical outcome, and the BNP levels were decreased significantly in patients with a poor prognosis (8.7%) compared to those with a good prognosis. Therefore, the results of serial measurements of BNP are interpreted as a reduction of the BNP level means clinical improvement and this causes good clinical results.<sup>11)</sup>

The second question is that how many BNP levels we



**Fig. 4.** Percent reduction in the N-terminal proBNP (NT-proBNP) levels according to the clinical course during hospitalization.<sup>8)</sup> The NT-proBNP levels were significantly lower in patients with complete resolution than those in the patients with an insufficient response to therapy ( $p < 0.05$ ). BNP: B-type natriuretic peptide.

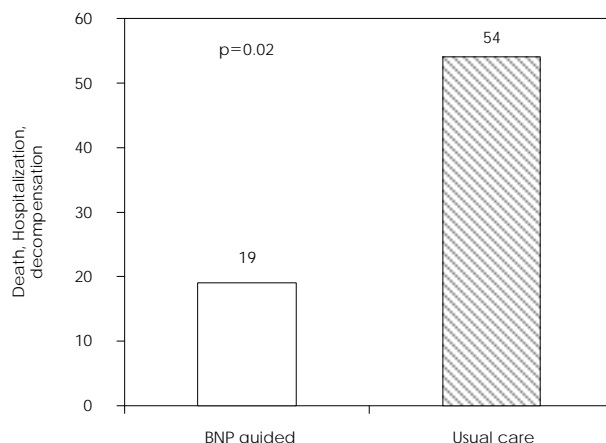
should obtain in the hospital. According to many articles, checking the BNP levels at admission or the first visit provides useful information for the diagnosis of HF or the assessment of the HF severity. Some reports have suggested that when the plasma BNP is measured shortly before discharge in the patients who have been recently admitted to the hospital for the treatment of decompensated heart failure, such levels assist in the prediction of the risk of death or readmission to the hospital at intervals of between 30 and 180 days after discharge. Cheng et al.<sup>15)</sup> reported on the results from a group of 72 patients who were admitted with decompensated heart failure over a 10-month period. The BNP levels were measured at admission and before discharge. In those patients who were destined to die or be readmitted to the hospital within 30 days, their plasma BNP levels were higher on average ( $1569 \pm 224$  pg/mL vs.  $906 \pm 96$  pg/mL) and they tended to rise rather than fall during their inpatient stay (to the predischage levels of  $1801 \pm 273$  pg/mL) compared with those patients who did not later incur death or readmission (in this group, the predischage levels were  $690 \pm 103$  pg/mL). The authors found that a BNP level of 950 pg/mL before discharge had a 90% negative predictive value for 30-day death and/or readmission. They suggested that a target BNP level might exist that would be associated with greater patient stability after discharge.<sup>15)</sup> In a report by Logeart et al., they demonstrated that between admission and before discharge, the BNP levels fell on average by 50%.<sup>9)</sup> These authors found that a BNP level of 350 pg/mL was optimal for the prediction of death and/or readmission to the hospital with heart failure over a 6-month follow-up period. When the derivation and validation groups were combined, a clear stepwise increase in risk of these 6-month end points was observed with increasing levels of plasma BNP. Before discharge, a BNP level of 350 pg/mL conferred a 16% risk; if the level was between 350 and 700 pg/mL, then the risk rose to 60% and if a BNP level before discharge was in excess of 700 pg/mL, then the risk was 93% (Fig. 5).<sup>9)</sup> Hence, there is a power-



**Fig. 5.** Kaplan-Meier curves according to the predefined B-type natriuretic peptide (BNP) cut off (350 ng/L).<sup>9)</sup> PredischARGE BNP levels >350 ng/L are strongly related to death or re-admission (HR=12.6 [5.7 to 28.1],  $p=0.0001$ ), and the rate of events reached 23.5% at one month and 79.4% at six months.

ful association between the plasma concentrations of BNP before discharge in patients who had been recently admitted and they had decompensated heart failure and a later risk in the short-to-intermediate term of either death or readmission to the hospital. So, how many BNP levels should we obtain in the hospital or during the early discharge period? Probably at least 2 times: the BNP should be checked during the hospital period (first at admission for the diagnosis of HF or the assessment of the HF severity, and second at the time of discharge or during the early discharge/follow-up period for identifying high-risk patients and to monitor treatment). However, no randomized controlled trial to date has tested the ability of such data to improve outcomes and evaluate the acceptable time for a BNP check-up.

The final issue is the usefulness of serially checking the BNP in the out-patient clinic. For ambulatory patients with established chronic symptomatic systolic heart failure, their BNP levels were revealed to be lower than that of acute heart failure patients and the plasma BNP levels in a subset of symptomatic patients were below what would be considered to be "diagnostic".<sup>16)</sup> In the Val-HeFT study, the BNP was measured at randomization and at the 4th month in patient with chronic heart failure.<sup>10)</sup> High baseline values of the BNP were related to high mortality and after 4 month, those patients with a highly reduced percentage of change of the BNP levels had a relatively lower risk than the other groups. In the outpatient setting, for patients with symptoms that suggest early decompensation, a rising BNP level should trigger either a clinic visit or diuretic adjustment. The measurement of BNP levels in out-patients clinic may be reliable monitoring markers with several advantages: the results are obtained quickly and they are not affected by eating or exercise, they help adjust the diuretic early after discharge and they reflect the exacerbation or success of treatment. But to date, no randomized controlled trial has tested the ability of BNP to predict



**Fig. 6.** Outcomes and treatment of heart failure as guided by N-terminal proBNP (NT-proBNP).<sup>19)</sup> This figure shows a significant reduction in events in that group whose treatment was adjusted according to serial measurements of plasma NT-proBNP. BNP: B-type natriuretic peptide.

the probability of outcomes or to evaluate the acceptable time for a BNP check-up in out-patients clinics.

### BNP or NT proBNP and the Prediction of a Response to Anti-Heart Failure Therapy

Because of the well reported correlations between plasma BNP/NT-proBNP and the concurrent haemodynamic measurements and the indicators of left ventricular systolic function,<sup>17)</sup> it is possible that adjusting antiheart failure therapy according to the serial measurements of BNP (in addition to standard clinical assessment) may offer improved outcomes. It has been well demonstrated that converting enzyme inhibitors and diuretics lower the BNP quite rapidly during the course of increased therapy for heart failure patients.<sup>18)</sup> Neurohormonal sub-studies from the landmark randomized controlled trials of the converting enzyme inhibitors for treating heart failure have suggested that the plasma neurohormonal status can predict the benefit from introducing such therapy. The sum of these findings were the rationale for the treatment of heart failure as guided by the plasma NT-proBNP levels (Fig. 6).<sup>19)</sup>

However, until the beta blocker therapy trials were launched, neither the BNP nor NT-proBNP levels have been measured in the neuro-hormonal sub-studies of randomized controlled trials concerned with therapy for heart failure. Yet there has been a recent French multicenter randomized study to evaluate the benefit of BNP-guided therapy on the outcome of CHF patients that were seen in clinical practice. For this study, a BNP-guided strategy for optimally treated CHF patients reduced the risk of CHF-related death or a hospital stay for CHF. The result was mainly obtained through an increased dosage of angiotensin converting enzyme inhibitor and beta-blocker.<sup>20)</sup> But because a cut off value for the

**Table 1.** Some clinical conditions for inappropriate BNP levels<sup>5)</sup>

Factors that can account for high BNP levels and no CHF
Age
Gender
Renal failure
Myocardial infarction
Lung disease with right-sided failure
Acute, large pulmonary embolism
Factors that can account for low BNP levels with CHF
Obese (BMI >30 kg/m <sup>2</sup> )
Flash pulmonary edema (<1-2 hrs)
CHF secondary to causes upstream from left ventricle
Acute mitral regurgitation
Mitral stenosis
Atrial myxoma
Stable NYHA class I patients with low ejection fractions

BNP: B-type natriuretic peptide, CHF: congestive heart failure, BMI: body mass index, NYHA: New York Heart Association

BNP or NT-pro BNP levels for adjusting anti-heart failure therapy has not been not determined, further studies are needed to determine the value.

### Limitations for Serial Monitoring of B-Type Natriuretic Peptide

As with everything, there are limitations to BNP testing, as it is not a stand-alone test. There are some factors that can account for high BNP levels and no heart failure, or there are factors that can account for low BNP levels with heart failure (Table 1).<sup>5)</sup> Especially in patients with renal failure, as the renal function deteriorates, the BNP level was noted to significantly increase. BNP levels of these patients were very high even though there was no evidence of systolic heart failure.<sup>21)22)</sup>

Despite that many publications have confirmed the relationship of the plasma BNP or NT-proBNP levels with cardiac function and the prognosis for heart failure, there is very little information available concerning the utility of single or serial measurements in therapeutic decision making. While the value of such measurements in other settings for heart failure and ventricular dysfunction has been determined, the value of the change in BNP levels, as an aid to the diagnosis of clinical deterioration in patients with established heart failure, has not been assessed. The limited data on the biological variation of BNP assays, which was obtained from normal subjects and a small number of patients with heart failure, underlines the potential difficulty in using the serial change of this parameter for determining patients' clinical deterioration. The intra-individual variation was as great as 60%, which is a far wider biological variation than that observed with other laboratory analyses.<sup>23)</sup> The explanation remains unclear, but it may reflect the multiple variables

involved in the homeostasis of natriuretic peptides, from transcription of the genetic message to the cellular secretion, metabolism and clearance, and the administered medical therapy, and all of these can affect the final value. The biological variations for BNP and NT-proBNP are sufficiently great that large differences in the results of serial testing are necessary before definitive conclusions regarding trends can be made. There are discordances in the result of BNP and NT-proBNP testing from day-to-day. Also, frequent testing (e.g. daily) for BNP and NT-proBNP to monitor therapy for patients with CHF is not indicated as the overall changes require several days to become evident.<sup>24)</sup>

### Conclusion

This review summarizes the clinical significance of BNP or NT-pro BNP assay for heart failure. The BNP or NT-pro BNP levels correlate with the atrial and ventricular filling pressures and the left ventricular systolic function, so it is a good target for treating heart failure. Serial changes of the BNP or NT-pro BNP over time can serve as surrogate markers in patients with progressive heart failure and these values give significant prognostic information and they can help track the therapeutic response of patients with heart failure. The reduction of the BNP level means clinical improvement and so heralds good clinical results. The adjustment of anti-heart failure therapy according to serial measurements of the BNP (in addition to the standard clinical assessment) may offer improved outcomes. Yet because of the intra-individual biologic variation of the BNP or the multiple factors affecting the BNP levels, to confidently interpret BNP changes within an individual, the magnitude of change must be large and just how large has not yet been determined. For serial measurements of the BNP to serve as a guideline for monitoring treatment or adjusting anti-heart failure treatment, further studies are needed to determine the best cut off or target level of serial BNP measurements in a variety of clinical settings.

### REFERENCES

- 1) 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.
- 2) Cowie MR, Struthers AD, Wood DA, et al. *Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care.* *Lancet* 1997;350:1349-53.
- 3) 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.
- 4) 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.
- 5) Maisel AS. *The diagnosis of acute congestive heart failure: role of*

- BNP measurements. *Heart Fail Rev* 2003;8:327-34.
- 6) Maisel AS, McCord J, Nowak RM, et al. *Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. J Am Coll Cardiol* 2003; 41:2010-7.
  - 7) Yoo BS, Kim WJ, Jung HS, et al. *The clinical experiences of B-type natriuretic peptide blood concentrations for diagnosis in congestive heart failure: the single hospital experience based on the large clinical database. Korean Circ J* 2004;34:684-92.
  - 8) Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, et al. *N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail* 2004;6:301-8.
  - 9) Logeart D, Thabut G, Jourdain P, et al. *Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol* 2004;43:635-41.
  - 10) Anand IS, Fisher LD, Chiang YT, et al. *Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation* 2003;107:1278-83.
  - 11) Chung IH, Yoo BS, Ryu HY, et al. *The relationship between the early follow-up BNP level and congestive status or prognosis in acute heart failure. Korean Circ J* 2006;36:200-7.
  - 12) Stevenson LW, Perloff JK. *The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA* 1989; 261:884-8.
  - 13) Mahdyoon H, Klein R, Eyler W, Lakier JB, Chakko SC, Gheorghiade M. *Radiographic pulmonary congestion in end-stage congestive heart failure. Am J Cardiol* 1989;63:625-7.
  - 14) Kazanegra R, Cheng V, 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.
  - 15) Cheng V, Kazanegra R, Garcia A, et al. *A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol* 2001;37:386-91.
  - 16) Tang WH, Girod JP, Lee MJ, et al. *Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. Circulation* 2003;108:2964-6.
  - 17) Richards AM, Crozier IG, Yandle TG, Espiner EA, Ikram H, Nicholls MG. *Brain natriuretic factor: regional plasma concentrations and correlations with haemodynamic state in cardiac disease. Br Heart J* 1993;69:414-7.
  - 18) Murdoch DR, McDonagh TA, Byrne J, et al. *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* 1999;138:1126-32.
  - 19) Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. *Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet* 2000;355:1126-30.
  - 20) Jourdain P, Jondeau G, Funck F, et al. *Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure. J Am Coll Cardiol* 2007;49:1733-9.
  - 21) Haug C, Metzele A, Steffgen J, Kochs M, Hombach V, Grunert A. *Increased brain natriuretic peptide and atrial natriuretic peptide plasma concentrations in dialysis-dependent chronic renal failure and in patients with elevated left ventricular filling pressure. Clin Invest* 1994;72:430-4.
  - 22) Wang HS, Yoo BS, Chung IH, et al. *Is B-type natriuretic peptide (BNP) measurement useful test for diagnosing systolic heart failure in patients with moderate to severe renal insufficiency? Korean Circ J* 2005;35:897-903.
  - 23) Wu AH, Smith A, Wiecek S, et al. *Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am J Cardiol* 2003;92:628-31.
  - 24) Wu AH, Smith A. *Biological variation of the natriuretic peptides and their role in monitoring patients with heart failure. Eur J Heart Fail* 2004;6:355-8.