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Biomarker for Cardiomyopathy-B-Type Natriuretic Peptide

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1. Introduction

Cardiomyopathy is cardiac condition in which the normal muscular function of the myocardium has been altered by a variety of etiologies. Atherosclerotic coronary artery disease is the most common cause of cardiomyopathy in North America and Europe. Idiopathic cardiomyopathy is the second most common cause, although this may partially include undiagnosed etiologies such as viral infection, drug toxicity, and genetic factors. Other causes include endocrine diseases, collagen vascular diseases, metabolic disorders (hemochromatosis, amyloidosis, glycogen storage disease), neuromuscular disorders, and granulomatous diseases (sarcoidosis).

The cardiac malfunctions are variable, namely left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, or both in accordance with etiologies and morphological findings (cardiac hypertrophy or dilatation). For example, hypertrophic cardiomyopathy initially has LV diastolic dysfunction, while amyloidosis that shows similar morphological change has LV systolic dysfunction. Ischemic or idiopathic cardiomyopathy with ventricular dilatation is represented by systolic dysfunction. Cardiac malfunctions are also altered on disease course. Initially, patients with cardiomyopathy may have asymptomatic LV systolic or diastolic dysfunction alone. However, adverse disease processes finally lead to both dysfunctions.

Imbalance between cardiac malfunctions and compensatory mechanisms worsens an outcome of cardiomyopathy. When abnormal LV filling pressure and volume is unable to be compensated by hemodynamic alterations such as the increases in heart rate and peripheral vascular tone by the accelerated vasoconstrictors including norepinephrine (NE), endothelin-1 (ET-1), and the renin-angiotensin-aldosterone (RAA), this imbalance precipitates decompensated heart failure (HF).

Early and simply identifying the decompensatory process is important therapeutic strategy in cardiomyopathy. Clinical utility of B-type natriuretic peptide (BNP) sensitively produced and secreted from heart in response to LV overload has been extended rapidly in patients with HF. At first, BNP emerged as a diagnostic marker for decompensated HF. Furthermore, BNP has been proved to predict a subsequent outcome in patients with HF. Recently, the efficiency of BNP-guided therapy in patients with HF has been demonstrated. In this chapter, we discuss about clinical utility of BNP assessments in patients with cardiomyopathy.

2. B-type natriuretic peptide (BNP)

BNP is predominantly secreted from the overloaded LV as a 76 aminoacid N-terminal fragment and a 32 aminoacid active hormone, and synthesis and release of BNP are adversely and rapidly accelerated in conjunction with the degree of LV wall stretch (1-2). In addition to this primary regulation, BNP synthesis can be also upregulated by tachycardia, glucocorticoids, thyroid hormones, vasoactive peptides such as ET-1, angiotensin II, and NE, and inflammatory cytokines. On the other hand, BNP is clearance via the binding to a natriuretic peptide receptor (NPR)-C of three NPRs (NPR-A, -B, -C). BNP is also inactivated by neutral endopeptidase, a zinc metallopeptidase which is expressed on the surface of endothelial cells, smooth-muscle cells, cardiac myocytes, renal epithelium, and fibroblasts.

BNP is included into compensatory mechanisms against HF. BNP promotes glomerular filtration and inhibits sodium reabsorption, resulting in natriuresis and diuresis. It reduces blood pressure through the relaxation of vascular smooth muscle and inhibits activations of not only central and peripheral sympathetic nerve systems but also cardiac sympathetic nervous system (3). Furthermore, it also inhibits the RAA system (4).

2.1 BNP as a diagnostic marker
2.1.1 BNP in heart failure

Plasma BNP levels have proven utility in the diagnostic evaluation of decompensated HF in patients with acute dyspnea (5-6). Particularly, BNP at a cutoff of 100 pg/ml could diagnose HF better than not only all other clinical parameters but also the clinical judgement by the emergency room physicians. However, BNP also has the diagostic limitation for HF. BNP is less accurate in detection of asymptomatic LV dysfunction than clinical parameters, because BNP has a close correlation with New York Heart Association (NYHA) functional class and patients with mild LV dysfunction often show normal range of BNP levels.

2.1.2 BNP in cardiomyopathy

BNP levels are raised in dilated, hypertrophic, and restrictive cardiomyopathies. Its increases seem to be different in accordance with cardiac malfunctions. BNP levels are generally higher in patients with systolic dysfunction than in those with isolated diastolic dysfunction, and highest in those with both dysfunctions (7). Furthermore, among patients with preserved LV systolic function, BNP correlates with the severity of diastolic dysfunction. BNP levels are raised in patients with impaired relaxation and especially highest in those with a restrictive filling pattern (8). BNP measurements may facilitate understanding the type and severity of cardiac malfunction on cardiomyopathy.

On the other hand, BNP measurement may be unavailable for distinguishing cardiomyopathies. Hypertrophic cardiomyopathy often shows extremely high levels of BNP, similarly to dilated cardiomyopathy (9). In addition, restrictive cardiomyopathy with systolic dysfunction also shows higher levels of BNP than that with diastolic dysfunction alone (8). However, several reports have demonstrated that BNP is able to distinguish constrictive pericarditis and restrictive cardiomyopathy, although these diseases overlap signs and symptoms of congestion (10). The level of BNP is elevated in patients with restriction, while level is nearly normal in those with constriction. The absence of cardiac stretch by constricting pericardium is thought to lead to lower BNP release.

2.2 BNP as a prognostic marker

Prognostic values of BNP have been identified in various heart diseases such as HF, cardiovascular diseases, and cardiomyopathy.

2.2.1 Heart failure

In patients with HF, higher levels of BNP have been implicated in increased risk of cardiovascular or all-cause mortality and readmission for decompensated HF. Furthermore, the cutoff points on the risk assessment curve are altered on time course after decompensated HF. In admitted patients for decompensated HF, the cutoff point of 800 pg/ml was associated with the increased risk of in-hospital mortality as shown by the ADHERE (Acute Decompensated Heart Failure National Registry) data (11). After the treatment, the predischarge cutoff point for the risk of readmission and mortality falls to about 500 pg/ml (12). The cutoff point further declined to abut 200 pg/ml in clinically stable outpatients after decompensated HF (13). These obsevations suggested that the therapeutic strategies for HF including a safe hospital discharge and the prevention of readmission or cardiac event may be guided by BNP measurement.

2.2.2 Cardiovascular diseases

In disorders other than HF, BNP also has prognostic value. BNP level is able to identify patients at the high risk group of adverse cardiac remodelling from patients with post-myocardial infarction, independent of age, history of HF, and LV ejection fraction (LVEF) (14). Even in patients with unstable angina alone, increased levels of BNP were associated with an increased risk of death (15). In right ventricular dysfunction resulting from pulmonary hypertension, BNP also provides similar prognostic information. These observations have extended the potential role of BNP measurement to risk stratification of cardiovascular events in patients with and without HF.

2.2.3 Cardiac inflammatory diseases; acute myocarditis

Acute myocarditis is able to be mainly divided into two disease conditions on a basis of clinicopathologic profiles, namely fulminant and non-fulminant myocarditis (16-17). Briefly, fulminant myocarditis is represented by the distinct onset of cardiac symptoms within 2 weeks following flu-like symptoms accompanied by histologically proven active myocarditis according to Dallas criteria and severe circulatory failure requiring high-dose intravenous catecholamines use (>5.0 γ) or mechanical circulatory assist devise, while non-fulminant myocarditis is by the indistinct onset of cardiac symptoms without those. Furthermore, these outcomes are distinguished by each unique clinical course (17). Non-fulminant myocarditis has been implicated in poorer long-term outcome than fulminant cases. A few patients with fulminant myocarditis lapsed into mortality from severely deteriorated circulatory collapse refractory to mechanical circulatory assist use or mechanical complications from its long-term use, including bleeding, infections, sepsis, and multiple organ failure. However, more than 80% of fulminant cases recover completely to an uncomplicated status, with cessation of myocardial inflammation and a generally favorable outcome, provided they are able to overcome poor cardiac condition successfully during acute phase (18). On the other hand, non-fulminant myocarditis without severe circulatory failure is likely to develop to chronic HF derived from dilated cardiomyopathy at chronic phase (16-17). Therefore, simple biomarkers to predict a requirement of mechanical assist devise use, outcome following its use, or the development to cardiomyopathy in patients with acute myocarditis have been sought.

Previously, we related various variables to short-term outcome in patients with fulminant myocarditis (19). In-hospital mortality was extremely higher in patients with fulminant myocarditis than in non-fulminant cases. Especially, extremely increased levels of interleukin-10, a major anti-inflammatory cytokine in serum on admission were associated with short-term outcome including mechanical assist use and in-hospital mortality in patients with acute myocarditis (Figure 1), which might be explained by its inhibitory effect on viral elimination from host. A major pathogenic factor of acute myocarditis and subsequent cardiomyopathy is viral infection, especially coxsackievirus B3 (Table 1).

| Virus | Type | Patient positive (%) | |
		Myocarditis	Dilated cardiomyopathy
Picornavirus	*Coxackie A, B*	*5-50%*	*5-15%*
	Echovirus	?	?
	Hepatitis A	?	?
	Hepatitis C	*0-15%*	*0-10%*
Orthomyxovirus	Influenza A, B	?	?
Paramyxovirus	RSV, Mumpus	?	<1%
Rubivirus/Toga virus	Rubella virus	?	<1%
Rhabdo virus	Rabies virus	?	?
Arbovirus/Tahyna	Dengue, yellow fever virus	?	?
Retrovirus/Lenti	HIV	Variable	?
Herpes virus	*Varicella-zoster*	*1-2%*	*1-2%*
	Cytomegalovirus	*1-15%*	*1-10%*
	Epstein-Barr virus	*1-3%*	*1-3%*
	Human herpes virus 6	*0-5%*	*0-5%*
	herpes simplex virus	0-3%	?
Mastadenovirus	*Adenovirus*	*5-20%*	*10-12%*
Parvovirus	*Parvo B 19 virus*	*10-30%*	*10-25%*

Table 1. Virus-induced myocarditis or cardiomyopathy

Hoffmann et al also reported that IL-10 expression in human peripheral monocytes was strongly and persistently induced by coxsackievirus B3 infection in spite of only slight production of other pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 (20). It has been reported that the inhibition of natural killer (NK) cells results in increased virus titers in the heart through delayed virus clearance (21). IL-10 inhibits the production of IFN-γ in NK cells, which has been demonstrated in association with susceptibility to Trypanosoma cruzi-induced myocarditis (22-23). In addition, it has been shown that IL-10 is transcribed in the myocardium parallel with viral replication in the acute and chronic stages of experimental Coxsackievirus B3 viral myocarditis (24-25). These findings imply that an extreme elevation of serum levels of IL-10, rather than TNF-α, on admission may reflect subsequent myocardial inflammation, which leads to the future deterioration of the disease, through delayed clearance of the virus.
On the other hand, high levels of IL-10 may reflect a favorable long-term outcome in patients with acute myocarditis. Studies using experimental models have demonstrated a protective role of IL-10 in the development of acute myocarditis (26-27). This mechanism was explained

by its suppressive effect against excessive and persistent immune response to viral infection or a subsequent autoimmune response leading to chronic myocardial injury. Cases with high level of IL-10 during acute phase may be not likely to develop to chronic myocarditis or cardiomyopathy. So far, almost studies with human myocarditis have been limited to a small number of patients. Further large number prospective studies are required to prove our idea.

In our previous study, the association of BNP with outcome was examined, also. Its levels in plasma were significantly increased in fulminant cases than in non-fulminant cases. However, we could not confirm its prognostic utility. In such cases, BNP may simply reflect the existence of circulatory failure alone.
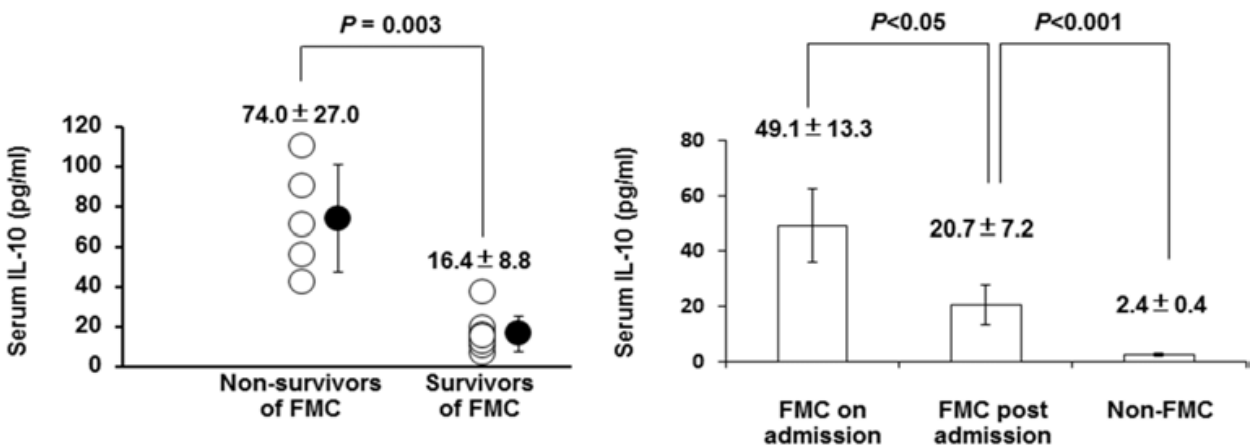
Serum levels of IL-10 were significantly increased in non-survivors than in survivors with fulminant myocarditis. IL-10 levels were significantly increased in not only patients with mechanical circulatory assist device on admission but also in those with it post admission, a few days after admission than in those without it throughout clinical course. IL: interleukin; FMC: fulminant myocarditis. (Nishii M, et al. J Am Coll Cardiol. 2004;44:1292-1297)

Fig. 1. Serum level of interleukin-10 in patients with acute myocarditis.

2.2.4 Cardiomyopathies

The HF is a major complication in cardiomyopathies such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathy (RCM). BNP must be a useful prognostic predictor for cardiomyopathies.

2.2.4.1 Dilated cardiomyopathy

Recently, we reported prognostic utility of BNP in clinically stable 83 outpatients with nonischemic DCM after decompensated HF (13). They were in a clinically stable status during at least 6 months after hospital discharge at relatively low BNP level, namely mean BNP level of about 200 pg/ml. This implied that pre-discharge BNP level may predict a post-discharge outcome in nonischemic DCM, as reported in general decompensated HF patients (12). Additionally, in this observation, the prognostic value of post-discharge BNP level was identified. Especially, among various predictors, levels at 6 months after hospital discharge showed the closest relation to the high risk of readmission for decompensated HF and mortality (Table 2). This association was explained by adverse cardiac remodeling. Persistently high levels of BNP during 6 months were related to poor improvement on cardiac remodeling (Figure 2).

Variable	Below vs. above median values			
	median level	HR	95% CI	P value
Univariate analysis				
Age	56	1.1895	0.7431-1.9246	0.47
Sex (Female)		1.0347	0.5886-2.0433	0.89
Hypertension		1.4902	0.8912-2.2819	0.18
Atrial fibrillation		1.2965	0.8885-2.0973	0.301
Ventricular tachycardia		1.2026	0.6132-2.1693	0.57
Beta-blocker use		1.6691	0.9056-2.5641	0.06
Diuretic use		1.3551	0.8086-2.1936	0.24
Echocardiographic parameters				
Left ventricular end-diastolic dimension at discharge	6.4 cm	0.8356	0.5189-1.3516	0.48
Left ventricular ejection fraction at discharge	30%	1.1629	0.7189-1.8729	0.54
Left atrial diastolic dimension at discharge	4.5 cm	1.3054	0.8106-2.1164	0.28
Left ventricular end-diastolic dimension at 6 months	6.0 cm	1.3866	0.8383-2.3598	0.22
Left ventricular ejection fraction at 6 months	36%	1.5019	0.9209-2.4641	0.11
Left atrial diastolic dimension at 6 months	4.25 cm	2.0003	1.2436-3.2233	0.0046
BNP measurements				
Plasma BNP level at discharge	180 pg/ml	1.2642	0.8051-1.9888	0.31
Plasma BNP level at 3 months	134 pg/ml	1.5097	0.9413-2.4212	0.09
Plasma BNP level at 6 months	174 pg/ml	2.2679	1.4336-3.5863	0.0005
Percentage change in BNP level between discharge and 3 months	-20.5%	1.4204	0.8863-2.2765	0.14
Percentage change in BNP level between discharge and 6 months	-11.5%	2.0127	1.2729-3.1757	0.0026
Multivariate analysis				
Plasma BNP level at 6 months	174 pg/ml	1.8427	1.1127-3.0426	0.0181
Percentage change in BNP level between discharge and 6 months	-11.5%	1.6538	0.9991-2.7214	0.051
Left atrial diastolic dimension at 6 months	4.25 cm	1.5678	0.9486-2.5904	0.0792

NYHA: New York Heart Association functional class; HR: hazard ratio; CI: confidence interval; BNP: B-type natriuretic peptide (Nishii M, et al. J Am Coll Cardiol. 2008;51:2329-2335)

Table 2. Univariate and multivariate Cox analyses of the incidence of death or readmission for heart failure.

2.2.4.2 Hypertrophic cardiomyopathy

Several reports have demonstrated that BNP levels reflect the severity of symptoms and HF in HCM (28-29). Additionally, high level of BNP has been related to cardiac events including silent myocardial ischemia (30), admission for HF, and mortality (31). On the other hand, our previous observation was unable to confirm these values, because even patients with high levels of BNP were in a clinically stable status. In HCM, BNP expression, however, is thought to occur as a response to not only hemodynamic changes resulting from diastolic dysfunction and obstruction but also histological changes such as myocardial fiber disarray, hypertrophy of myocytes, and fibrosis (32). Thus, even in clinically stable patients with HCM, extremely high levels may indicate a poor long-term outcome. Further studies are required to elucidate its prognostic value in HCM.

2.2.4.3 Restrictive cardiomyopathy

There is no report regarding prognostic value of BNP in RCM. However, when RCM had a further increase of LV end-diastolic pressure (LVEDP) or systolic dysfunction, BNP level would be more increased (7). BNP measurement may predict the occurrence of decompensated HF, although its value remains uncertain in RCM.

2.3 BNP-guided therapy

Efficiency of BNP-guided therapy on cardiomyopathies is not yet elucidated. However, BNP levels reflect therapeutic effect in patients with HF. Aggressive treatment with diuretics and vasodilators such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor antagonists reduce BNP level rapidly in conjunction with reduced intra-ventricular filling pressures. On the other hand, the effects of beta blockers on BNP concentrations are complex. Because adrenergic stimulation inhibits release of natriuretic peptides, beta blocking may initially increase BNP concentrations. By contrast, long-term use of beta blocker reduces BNP concentrations with the improvement in cardiac dysfunction. Thus, BNP measurement would help physicians to make clinical decisions to titrate pharmacological treatments.

BNP-guided therapy improves a treatment outcome in patients with HF. Two provocative pilot studies have prospectively assessed the utility of BNP to guide selection and intensity of pharmacotherapy. In one study, 69 symptomatic patients (NYHA class II to IV) with impaired systolic function defined as LVEF of <40% were randomly allocated to receive either standardised clinical assessment consist of symptoms and physical findings-guided therapy or N-terminal BNP-guided therapy (< 200 pmol/L) (33). During the follow up of at least 6 months, fewer patients had combined cardiovascular events (death, hospital admission, or heart failure decompensation) in the N-terminal BNP group than in the clinical group, which was associated with higher doses of ACEIs and diuretics. In a second multicenter randomised trial: The STARS-BNP Multicenter Study, 220 patients with symptomatic (NYHA class II to III) systolic HF defined as LVEF of <45% were randomized to medical treatments on either the basis of clinical findings from the physical examination and usual paraclinical and biological parameters or the basis of a decreasing BNP plasma levels of <100 pg/ml (34). After a mean follow-up of 15 months, significantly fewer patients had HF-related death in the BNP group than in the clinical group, which was in part associated with an increase in ACEIs and beta-blocker dosages.
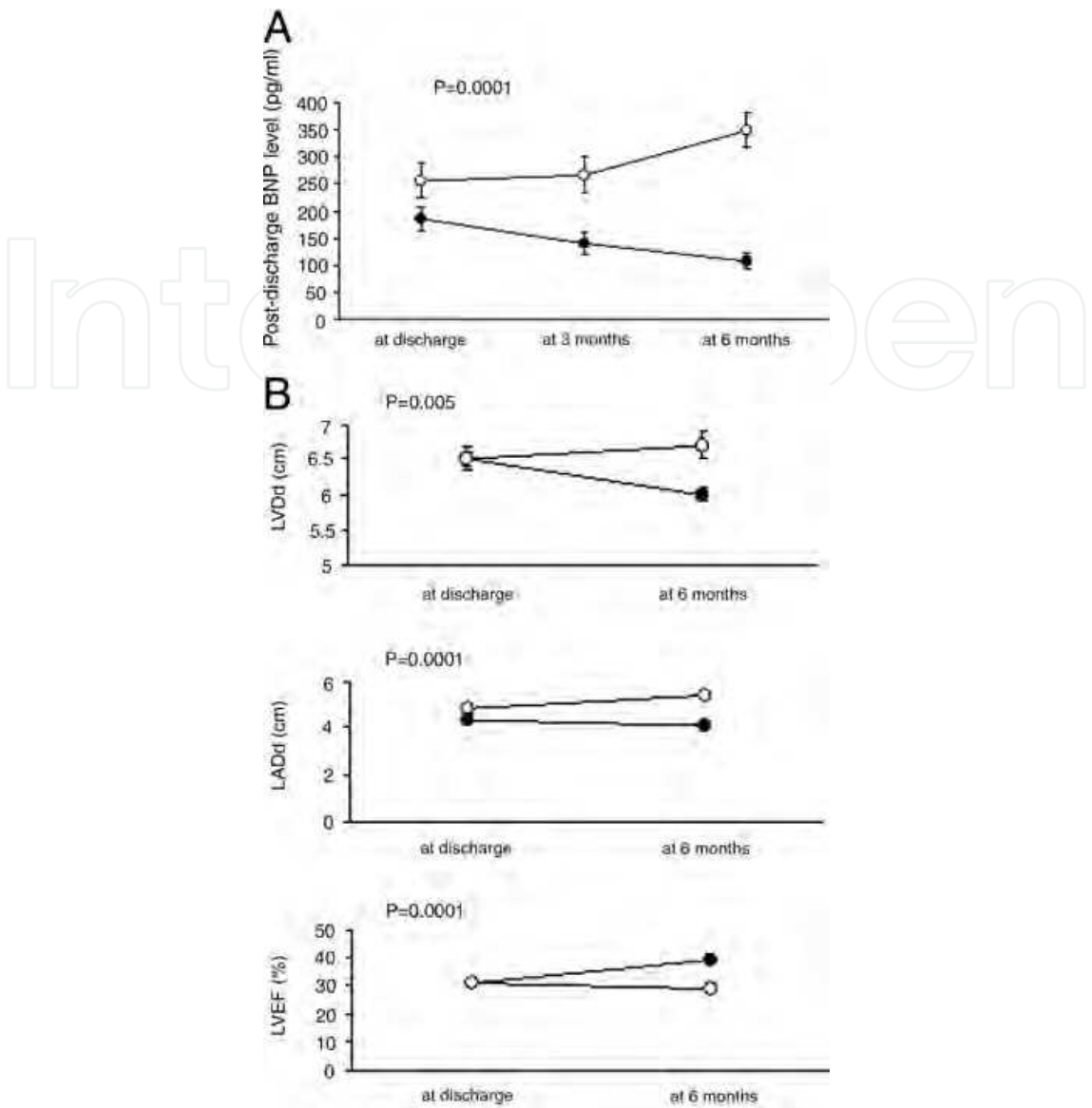
Fig. 2. Changes in B-type natriuretic peptide (BNP) levels and echocardiographic findings during a clinically compensated status in patients with dilated cardiomyopathy (Nishii M, et al. J Am Coll Cardiol. 2008;51:2329-2335)

Changes in BNP level at 3-month intervals after hospital discharge for decompensated heart failure (A) and in echocardiographic variables between discharge and 6 months (B). BNP levels were decreased during 6 months in event-free patients but not in readmitted patients, which was accompanied by the reduction of cardiac dimensions. Solid or open circles indicate BNP levels, echocardiographic dimensions (left ventricular end-diastolic dimension [LVDd]; left atrial diastolic dimension [LADd]), and left ventricular ejection fraction (LVEF) in event-free patients or patients readmitted for decompensated heart failure, respectively. Values are mean ± standard error of the mean. p values comparing changes in BNP and echocardiographic variables between readmitted patients and event-free patients are for repeated measures multivariate analysis of variance over 6 months.

On the other hand, it remained uncertain whether BNP guide is available for asymptomatic patients or not. We reported that in 83 outpatients with asymptomatic (NYHA class I to II)

systolic HF defined as LVEF of <40%, BNP cutoff point of about 200 pg/ml at 6 months after the discharge for decompensated HF can identify patients at the high risk of readmission and sudden death (13) (Figure 3). Interestingly, Beta blocker use and its dosage were significantly lower in high risk patients [>200 vs. <200 pg/ml: 60 vs. 100%, P=0.001; 8 ± 5 vs. 16 ± 5 mg/day (carvedilol), P=0.0003; 64 ± 22 vs. 107 ± 40 mg/day (metoprolol), P=0.036; respectively]. The cutoff point might determine the requirement of initiation or titration of beta blockers. Even in asymptomatic HF setting, BNP-guided therapy may be also helpful.

2.4 The limitations on BNP-guided therapy

We have to consider the limitations on BNP-guided therapy, also. Recent multicenter trial (the randomized Trial of Intensified vs. Standard Medical Therapy in Elderly Patients with Congestive Heart Failure: TIME-CHF) could not identify the advantage of BNP-guided therapy over symptom-guided therapy in 499 elderly patients aged more than 60 years with symptomatic (NYHA class II or greater) systolic HF (LVEF of <45%) and prior hospitalization for decompensated HF (35). They were randomized to N-terminal BNP-guided HF therapy (levels of less than two times the upper limit of normal) and symptom-guided HF therapy (NYHA class of less than II). However, the improvements of outcomes including mortality, hospitalization, and quality of life were similar in both groups. Especially in patients aged more than 75 years, BNP-guided HF therapy did not improve outcome. In general, dosages of drugs such as ACEIs and beta-blockers are increased more in patients receiving BNP–guided therapy. Although persistence in intensifying medical therapy seems to be indispensable for better outcome in young and middle aged patients, it may be harmful to push dosages to the limits in elderly patients aged more than 75 years. Additionally, BNP-guided therapy may be disadvantageous in patients with low output syndrome resulting from severe systolic and diastolic dysfunctions. Because such cases require more ventricular load as a compensatory mechanism for congestive HF, rapid titration of ACEIs, beta blockers, and diuretics on the basis of BNP-guided HF therapy may lead to further deterioration of HF. Furthermore, edtablished cardiomyopathy with irreversible LV dilatation often shows persistently high level of BNP despite aggressive treatment for HF. A unified level of BNP-guided therapy would be unavailable for such cases. These emphasize the need of setting up individual BNP target level in accordance with cardiac conditions.

2.5 Individual target threshold of BNP

To set up individual target threshold of BNP for the risk reduction that were associated with cardiac dilatation and identify its prognostic utility, clinically stable 113 patients with systolic HF after decompensated HF represented by non-ischemic dilated cardiomyopathy were examined. Among these patients, 32 patients reached end-point composed of readmission for decompensated HF or death. Various variables were related to its combined event, including atrial fibrillation, low LVEF below the best cutoff value of 34%, cardiac dilatation (CD) indicated by left ventricular end-diastolic dimension×LAD/wall thickness/body surface area above the best cutoff value of 115 /m², high levels of BNP above the best cutoff value of 195 pg/ml. Furthermore, we found a significant positive correlation between BNP level and CD specific for event-free patients. The rage between 95% confidence interval on this specific linear regression line were closely associated with an incidence rate of readmission or death, also (Figure 4A, B). Thus, we defined this rage as individual target threshold of BNP.
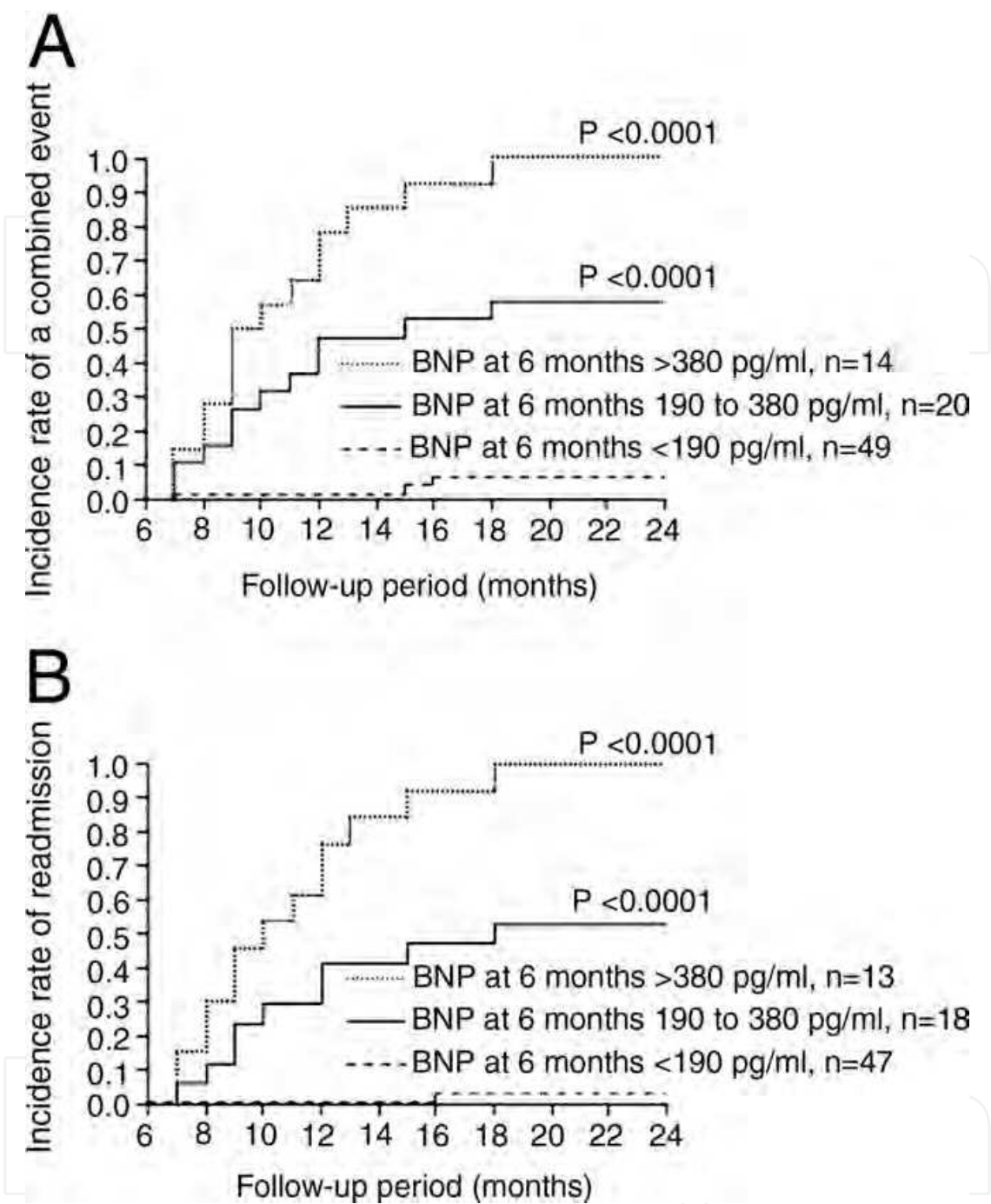
Fig. 3. Kaplan-Meier Analyses   (Nishii M, et al. J Am Coll Cardiol. 2008;51:2329-2335) Kaplan-Meier curves showing the incidence rate of readmission for decompensated heart failure or sudden death (A) or of readmission alone (B) according to 6-month post-discharge B-type natriuretic peptide (BNP) ranges in outpatients with dilated cardiomyopathy. The risk of a combined event increased in a stepwise fashion across increasing ranges of 6-month post-discharge BNP, namely at <190 pg/ml, 190 to 380 pg/ml, and >380 pg/ml (Fig. 2A). Further, Kaplan-Meier curves for incidence of readmission alone (Fig. 2B) showed the same pattern. B-type natriuretic peptide ranges were <190 (the best cutoff level for predicting readmission or sudden death), 190 to 380, and >380 (its 2-fold level) pg/ml. p < 0.0001 (the log-rank test) versus a BNP range of <190 pg/ml.

Next, we examined its prognostic advantage over other variables. When adjusted to high-risk patients with advanced dilated cardiomyopathy, namely symptomatic non-ischemic systolic HF (LVEF below 34%) complicated by severe cardiac dilatation (CD above 115 /m²), this individual target threshold alone was associated with the incidence rate (Figure 5). Based on Laplace Law (pressure x radius/2 wall thickness), this threshold may reflect individual optimal wall stretch for clinical stabilization. The left atrium (LA) acts as a reservoir during LV overload (36), and elevated LV filling pressure results in LA overload as well as LV diastolic dysfunction (37). Thus, LA dimension reflects intra-ventricular pressure, in part.

A combined assessment of BNP level and echocardiographic dimensions may facilitate individual disease management. Among overall patients, those with BNP levels over or under its target threshold required titration or withdrawal, respectively of pharmocological therapy including diuretics or vosadilators to keep a balance between ventricular load and cardiac function. Additionally, cases refractory to such pharmacological optimization may be considered application of mechanical circulatory assist device implantation or subsequent surgical intervention including heart transplantation.
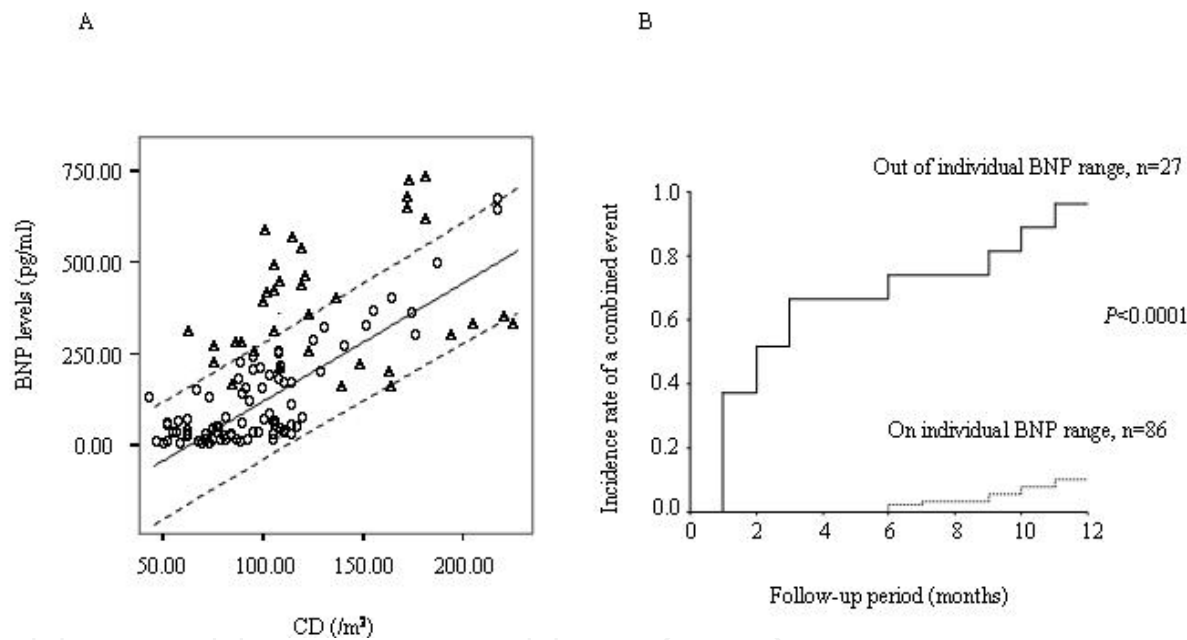

Fig. 4. Prognostic utility of individual target threshold of B-type natriuretic peptide (BNP) on readmission for decompensated heart failure or sudden death in patients with non-ischemic dilated cardiomyopathy

A: Individual target threshold of BNP. Event-free patients had a significantly positive correlation between BNP level and cardiac dilatation (CD) (r=0.88; P<0.0001), but event patients did not (r=0.26; P=0.421). BNP levels in event patients tended to be out of the range between dotted lines: 95% confidence interval (CI) on solid line: the linear regression line specific for event-free patients (BNP= -144.64 + 3.16×CD), namely individual target threshold of BNP. B: Kaplan-Meier curves showing the incidence rate of event according to individual target threshold of BNP. Out of this threshold was closely associated with an increase in event risk (the log-rank test: P<0.0001).

Open circles or triangles indicate even-free or event patients, respectively. CD was defined as left ventricular end-diastolic dimension×left atrial diastolic dimension/wall thickness/body surface area.
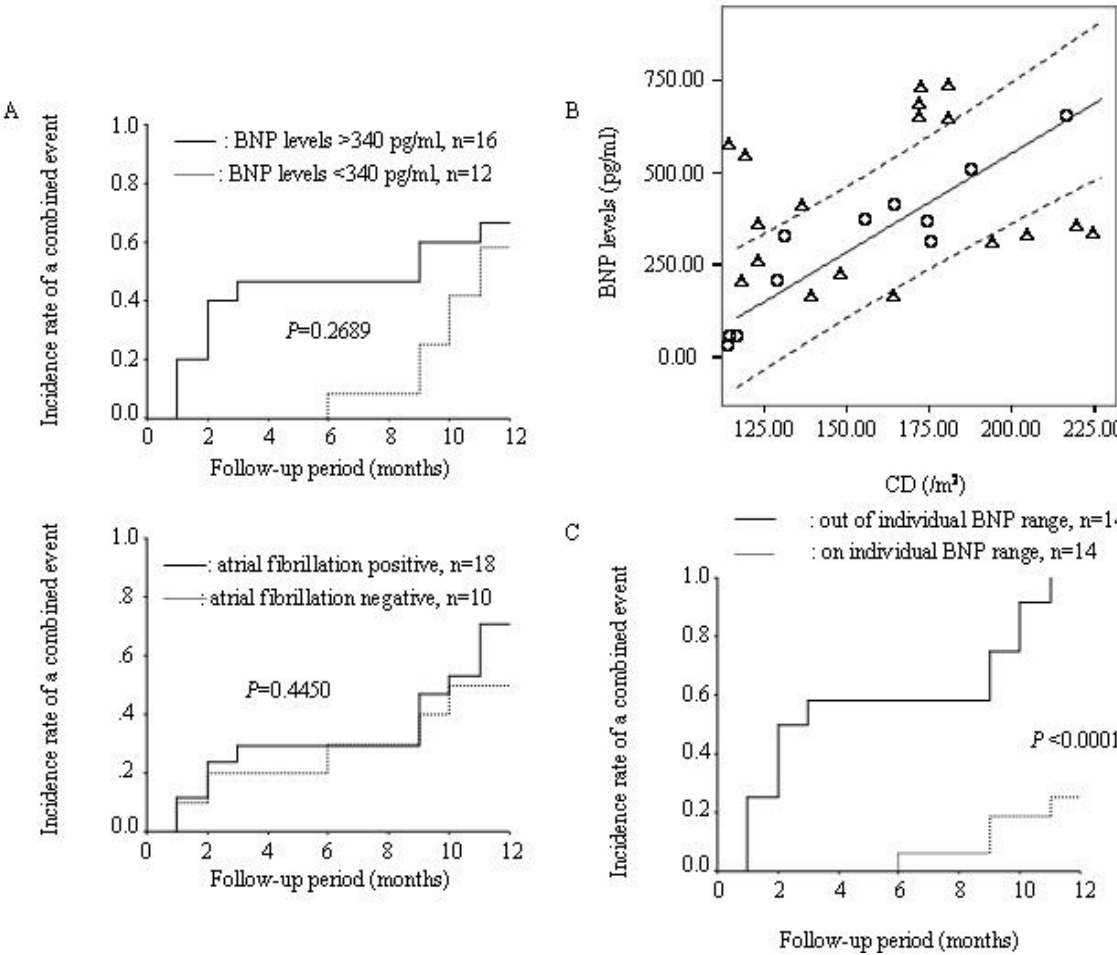
Fig. 5. Prognostic predictors on readmission for decompensated heart failure or death in patients with advanced dilated cardiomyopathy, namely symptomatic systolic heart failure (left ventricular ejection fraction below the best cutoff value of 34%) complicated by severe cardiac dilatation (CD) above the best cutoff value of 115 /m².
A: Kaplan-Meier curves showing the incidence rate of event according to levels of BNP above or below the best cutoff value of 340 pg/ml or atrial fibrillation. These variables had no significant association with an increase in event risk (the log-rank test; BNP levels: P=0.2689; atrial fibrillation: P=0.4450). B: Individual target threshold of BNP. Event-free patients had a significantly positive correlation between BNP level and CD (r=0.91; P<0.0001), independently of event patients (r=0.10; P=0.71). BNP levels in event patients tended to be out of individual target threshold of BNP between dotted lines: 95% confidence interval (CI) on solid line: the linear regression line specific for event-free patients C: Kaplan-Meier curves showing the incidence rate of event according to individual target threshold of BNP. Out of individual target threshold of BNP was significantly associated with an increase in event incidence (the log-rank test: P<0.0001).
Open circles or triangles indicate even-free or event patients. CD was defined as left ventricular end-diastolic dimension×left atrial diastolic dimension/wall thickness/body surface area.

The number of patients in our study is, however, relatively small, and our population was limited to only patients with non-ischemic dilated cardiomyopathy. Additional prospective multi-center studies including cases with ischemic heart disease would confirm our observation and extend it to various settings of systolic HF.

3. Conclusion

BNP measurement has facilitated the diagnosis of HF and decision of pharmacotherapy and improved outcome during the hospitalization and after the discharge for decompensated HF in cardiomyopathies, although BNP cutoff points for risk assessment are different on time course after decompensated HF and cardiac dysfunctions. On the other hand, availability of this BNP measurement was less especially in patients with advanced dilated cardiomyopathy as well as in elderly patients. However, individual target threshold of BNP for risk reduction related to cardiac dilatation exerted a strong prognostic power even in such advanced cases. This target threshold-guided therapy would facilitate individual disease management and thus contribute to further improvement of treatment outcome.

4. Acknowledgment

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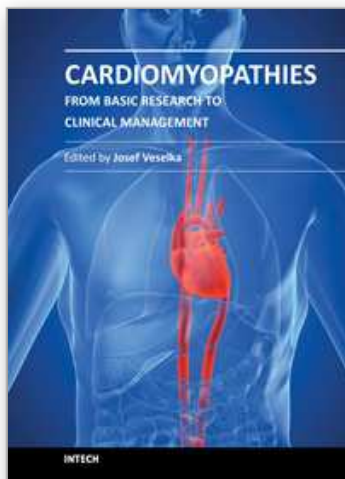
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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