Usefulness of the brain natriuretic peptide to atrial natriuretic peptide ratio in determining the severity of mitral regurgitation

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BACKGROUND: Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels were characterized in subjects with mitral regurgitation (MR).

METHODS: Sixty-two cases of moderate or severe chronic MR were studied. The blood levels of neurohormonal factors were stratified by the known MR prognostic factors of New York Heart Association (NYHA) functional class, left ventricular end-diastolic diameters, left ventricular end-systolic diameter (LVDs), ejection fraction (EF), left atrial diameter and presence of atrial fibrillation (AF).

RESULTS: ANP levels were higher in NYHA class II and lower in classes I and III/IV ($P=0.0206$). BNP levels were higher in NYHA class II than class I ($P=0.0355$). The BNP/ANP ratio was significantly higher in NYHA classes II and III/IV than in class I ($P=0.0007$). To differentiate between NYHA classes I/II and III/IV, a cut-off BNP/ANP ratio of 2.97 produced a sensitivity of 78% and specificity of 87%. Compared with subjects in sinus rhythm, patients with AF had an enlarged left atrium and lower ANP levels. The BNP/ANP ratio correlated significantly with left atrial diameter, LVDs and EF ($r=0.429$, $P=0.0017$; $r=0.351$, $P=0.0117$; and $r=-0.349$, $P=0.0122$; respectively), and was significantly higher among all the known operative indications for MR tested (LVDs 45 mm or more, EF 60% or less, NYHA class II or greater and AF; $P=0.0073$, $P=0.003$, $P=0.0102$ and $P=0.0149$, respectively).

CONCLUSIONS: In chronic MR, levels of ANP and BNP, and the BNP/ANP ratio are potential indicators of disease severity.

Key Words: Atrial natriuretic peptide; Brain natriuretic peptide; Cardiac function; Heart failure; Mitral regurgitation

In chronic mitral regurgitation (MR), increased preload and reduced afterload due to unloading from the left ventricle (LV) into the left atrium (LA) leads to compensatory dilation of the LV and facilitates LV ejection. Although this response initially maintains cardiac output, myocardial decompensation eventually results in heart failure symptoms and an increased risk of sudden death. In addition, backflow into the LA results in enlargement of the LA, atrial fibrillation and elevated pulmonary pressures. In some patients, LV contractility is irreversibly impaired in the absence of symptoms (1-3). Thus, deferring surgical intervention often leads to irreversible post-operative LV dysfunction. Valve replacement or valvuloplasty is essential before the myocardial damage becomes irreversible.

L'utilité du ratio entre le peptide natriurétique cérébral et le peptide natriurétique auriculaire pour déterminer la gravité de la régurgitation mitrale

HISTORIQUE : Les taux de peptide natriurétique auriculaire (PNA) et de peptide natriurétique cérébral (PNC) étaient caractéristiques chez des sujets atteints de régurgitation mitrale (RM).

MÉTHODOLOGIE : On a étudié 62 cas de RG chronique modérée à grave. On a stratifié les taux sanguins de facteurs neuro-hormonaux selon les facteurs pronostiques connus de RM pour la classe fonctionnelle de la *New York Heart Association* (NYHA), les diamètres ventriculaires gauches en fin de diastole, le diamètre ventriculaire gauche en fin de systole (DVG), la fraction d'éjection (FE), le diamètre auriculaire gauche et la présence de fibrillation auriculaire (FA).

RÉSULTATS : Les taux de PNA étaient plus élevés dans la classe II de la NYHA et plus faibles dans les classes I et III/IV ($P=0,0206$). Les taux de PNC étaient plus élevés dans la classe II de la NYHA que dans la classe I ($p = 0,0355$). Le ratio PNA/PNC était considérablement plus élevé dans les classes II et III/IV de la NYHA que dans la classe I ($P=0,0007$). Pour distinguer la classe I/II de la NYHA de la classe III/IV, un ratio PNA/PNC seuil de 2,97 produisait une sensibilité de 78 % et une spécificité de 87 %. Par rapport aux sujets ayant un rythme sinusal, les patients atteints de FA présentaient une hypertrophie auriculaire gauche et des taux de PNA plus faibles. Le ratio PNA/PNC était corrélé de manière significative avec le diamètre auriculaire gauche, les DVG et la FE ($r = 0,429$, $p = 0,0017$; $r = 0,351$, $p = 0,0117$; et $r = -0,349$, $p = 0,0122$; respectivement) et était considérablement plus élevé dans toutes les indications connues de RM évaluées (DVG 45 mm ou plus, FE 60 % ou moins, classe II de la NYHA ou plus et FA; $p = 0,0073$, $p = 0,003$, $p = 0,0102$ et $p = 0,0149$, respectivement).

CONCLUSIONS : En cas de RM chronique, les taux de PNA et de PNC et le ratio PNA/PNC sont des indicateurs potentiels de la gravité de la maladie.

Early valvuloplasty conducted when heart failure is mild has been reported to improve prognosis (4). In clinical practice, however, it remains difficult to decide the timing of surgery defined by mild heart failure symptoms and preserved cardiac function.

Some reports have shown that preoperative LV function (LV end-diastolic diameter [LVDd], LV end-systolic diameter [LVDs] and ejection fraction [EF]), LV wall thickness, LA size, LA area, pulmonary hypertension, and atrial fibrillation are good predictors of survival and postoperative LV dysfunction. The American College of Cardiology/American Heart Association guidelines recommend considering symptoms and LV function, especially EF and LVDs, as useful parameters in

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TABLE 1
Baseline characteristics of patients grouped according to functional severity

Variable	Overall (n=62)	NYHA class I (n=8)	NYHA class II (n=35)	NYHA class III/IV (n=19)	P (by ANOVA or χ^2)
Age, years (mean $\pm$ SD)	63.6 $\pm$ 13.2	54.7 $\pm$ 16.4	64.6 $\pm$ 13.1	65.3 $\pm$ 11.4	0.1582
Male sex, %	76				
Prolapse/torn chordae tendineae, n	62/3				
Systolic BP, mmHg (mean $\pm$ SD)	123.6 $\pm$ 20.8	122.3 $\pm$ 14.6	124.6 $\pm$ 20.0	121.7 $\pm$ 22.8	0.9019
Diastolic BP, mmHg (mean $\pm$ SD)	69.9 $\pm$ 12.9	70.3 $\pm$ 7.3	69.1 $\pm$ 11.0	71.7 $\pm$ 19.0	0.8474
Heart rate, beats/min (mean $\pm$ SD)	71.9 $\pm$ 12.8	67.8 $\pm$ 11.7	70.9 $\pm$ 11.9	76.3 $\pm$ 15.1	0.3497
Serum creatinine, μ mol/L (mean $\pm$ SD)	97.2 $\pm$ 35.4	79.6 $\pm$ 26.5	88.4 $\pm$ 17.7	132.6 $\pm$ 44.2*†	0.0043
Serum sodium, mmol/L (mean $\pm$ SD)	140.2 $\pm$ 2.5	140.6 $\pm$ 2.2	140.2 $\pm$ 2.8	140.1 $\pm$ 2.2	0.0810
Serum potassium, mmol/L (mean $\pm$ SD)	4.0 $\pm$ 0.4	3.9 $\pm$ 0.3	4.1 $\pm$ 0.4	4.0 $\pm$ 0.5	0.8372
Atrial fibrillation, n	37	1	20	16	0.0022†
Concomitant drugs, n					
Digitalis		2	19	8	0.2889†
Furosemide		0	20	19	0.0068†
Spironolactone		0	13	6	0.1202†
Angiotensin-converting enzyme inhibitors		3	13	10	0.9126†
Angiotensin receptor blockers		0	2	3	0.2877†
Nitrates		0	13	9	0.0604†
Calcium antagonists		2	7	2	0.5802†

* $P < 0.05$ versus New York Heart Association (NYHA) class I, Tukey-Kramer's post hoc test; † $P < 0.05$ versus NYHA class II, Tukey-Kramer's post hoc test; ‡Goodness-of-fit test for χ^2 . BP Blood pressure

clinical decision making on the timing of an operation (2). However, little data are available on the association of neurohormonal factors with operative indication. With the above background, we evaluated whether atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels may indicate the severity of MR and timing of surgery by comparison with the known prognostic factors and operative indications.

METHODS

Sixty-two cases of chronic MR with at least moderate regurgitation on echocardiography or at least Sellar class 3 regurgitation on LV angiography diagnosed in the Department of Cardiology at the Aoyama Hospital (Tokyo, Japan) between 1996 and 2002 were studied. The cases included 47 men and 15 women with a mean ($\pm$ SD) age of 63.6 $\pm$ 13.2 years (range 31 to 85 years). Patients with acute heart failure and acute exacerbations of chronic heart failure were excluded. MR was caused by prolapse in all 62 cases and by torn chordae tendineae in three cases, as revealed by echocardiography. Seven patients had a history of hypertension, four patients had diabetes and one patient had cerebrovascular disease. The degree of heart failure according to the New York Heart Association (NYHA) functional classification was class I in eight cases, class II in 35 cases, class III in 14 cases and class IV in five cases. The medical therapy, clinical findings and biochemical profiles by NYHA class are shown in Table 1.

At the hospital, all patients were treated with maximal medical treatment using diuretics and vasodilators. After patients were stabilized, blood was collected in the early morning, with the patients at rest for radioimmunoassay measurements of the ANP, BNP and serum norepinephrine levels, plasma renin activity and plasma aldosterone concentration. Cardiac function was evaluated by echocardiography, and LA diameter (LAd), LVDd, LVDs, EF and right ventricular systolic pressure (RVSP) were measured. In five NYHA class I cases, tricuspid regurgitation was not detected, and RVSP could not be measured. Operative criteria for MR were

determined in accordance with the American College of Cardiology/American Heart Association guidelines (2).

Echocardiographic methods

All subjects underwent standard two-dimensional echocardiography with a commercially available system (Hewlett Packard Sonos 5500, Hewlett Packard, USA) using a multifrequency MHz transducer. LV and LA dimensions were obtained by M-mode echocardiography, guided by two-dimensional imaging. Mitral valve prolapse was defined as the superior displacement of the leaflets during systole in a two-dimensional echocardiographic long-axis view of the LV. The degree of MR was assessed by the size, penetration and flow velocity of the regurgitant jet (5).

Measurement of natriuretic peptide levels

Once patients had been in a supine position for at least 60 min after waking, a blood sample drawn from a peripheral vein was immediately placed on ice and transferred to the laboratory at the same hospital. After plasma extraction, the samples were stored in a deep freezer until they were used. BNP and ANP levels were measured by standard radioimmunoassay (Shionoria ANP kit and Shionoria BNP kit, Shionogi & Co, Japan) within 24 h. The normal values of ANP and BNP are less than 13.9 pmol/L (43 pg/mL), and less than 5.3 pmol/L (18.4 pg/mL), respectively.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD, unless otherwise stated. Differences between groups described by categorical variables were analyzed by the χ^2 test for goodness-of-fit. Simple linear regression analyses were performed to correlate neurohormonal levels with echocardiographic parameters and NYHA functional class. Clinical variables and NYHA class were assessed by ANOVA, followed by Tukey-Kramer's post hoc test, as appropriate. For the relationship between neurohormonal levels and operative criteria, a Mann-Whitney's U test was performed. All $P < 0.05$ were regarded

TABLE 2
Clinical results of patients grouped according to functional severity

Variable	NYHA class I (n=8)	NYHA class II (n=35)	NYHA class III/IV (n=19)	P (by ANOVA)
Echocardiography (mean $\pm$ SD)				
LVDd, mm	60.6 $\pm$ 6.8	59.7 $\pm$ 6.7	66.7 $\pm$ 11.2 [†]	0.0232
LVDs, mm	36.4 $\pm$ 5.7	37.6 $\pm$ 7.0	46.4 $\pm$ 8.8 ^{*†}	0.0004
EF, %	64.8 $\pm$ 7.0	61.0 $\pm$ 9.1	51.7 $\pm$ 9.5 ^{*†}	0.0007
LAd, mm	41.1 $\pm$ 1.6	49.5 $\pm$ 9.0	64.2 $\pm$ 12.3 ^{*†}	<0.0001
RVSP, mmHg	33.1 $\pm$ 3.6	51.8 $\pm$ 16.2	52.8 $\pm$ 14.1	0.1180
Neurohormones (mean $\pm$ SD)				
PRA, ng/L/s	1.2 $\pm$ 1.3	1.3 $\pm$ 1.3	1.5 $\pm$ 1.0	0.7318
PAC, nmol/L	0.24 $\pm$ 0.09	0.35 $\pm$ 0.32	0.28 $\pm$ 0.24	0.5996
sNA, pmol/L	1243.2 $\pm$ 355.2	2545.6 $\pm$ 1065.6	3078.4 $\pm$ 1953.6	0.0796
ANP, pmol/L	8.4 $\pm$ 10.7	35.9 $\pm$ 36.9	16.3 $\pm$ 15.4	0.0206
BNP, pmol/L	7.7 $\pm$ 11.6	62.1 $\pm$ 56.0 [*]	56.6 $\pm$ 43.9	0.0355

Clinical variables and New York Heart Association (NYHA) class were assessed by ANOVA, and then Tukey-Kramer's post hoc test, as appropriate. * $P < 0.05$ versus NYHA class I; [†] $P < 0.05$ versus NYHA class II. ANP Atrial natriuretic peptide; BNP Brain natriuretic peptide; EF Ejection fraction; LAd Left atrial diameter; LVDd Left ventricular end-diastolic diameter; LVDs Left ventricular end-systolic diameter; PRA Plasma renin activity; PAC Plasma aldosterone concentration; RVSP Right ventricular systolic pressure; sNA Serum norepinephrine

Figure 1 Relationship of the New York Heart Association (NYHA) functional class with atrial natriuretic peptide (ANP) level, brain natriuretic peptide (BNP) level and the BNP/ANP ratio. No significant increases in ANP or BNP levels were observed in NYHA class III/IV. The BNP/ANP ratio increases with increased severity according to NYHA class

as having statistical significance. To determine whether the BNP/ANP ratio predicts the severity of heart failure, the receiver-operating characteristic (ROC) curves for various cut-off BNP/ANP ratios were compared with NYHA class. Analyses were performed using StatView 5.0 software (SAS Institute, USA) and SPBS 9.37 software (ComWorks Co Ltd, Japan).

RESULTS

NYHA functional class and echocardiographic variables or neurohormonal plasma levels

As shown Table 2, the LVDd was significantly larger in class III/IV (ANOVA, $P = 0.0232$; Tukey-Kramer's post hoc test, class II versus class III/IV, $P < 0.05$) and LVDs was also significantly larger in class III/IV (ANOVA, $P = 0.0004$; Tukey-Kramer's post hoc test, class I versus class III/IV, $P < 0.05$; class II versus class III/IV, $P < 0.05$). EF was significantly lower in NYHA class III/IV (ANOVA, $P = 0.0007$; Tukey-Kramer's post hoc test, class I versus class III/IV, $P < 0.05$; class II versus class III/IV, $P < 0.05$). The LAd was significantly dilated in NYHA classes III/IV (ANOVA, $P < 0.0001$; Tukey-Kramer's

TABLE 3
Correlation coefficients of neurohormones with cardiac function

Parameter		γ	P
Neurohormones	Cardiac function		
PAC	Left atrial diameter	0.269	0.0742
	Left ventricular end-diastolic diameter	0.485	0.0008
	Left ventricular end-systolic diameter	0.361	0.0159
	Ejection fraction	-0.064	0.6801
PRA	Left atrial diameter	0.339	0.0227
	Left ventricular end-diastolic diameter	-0.056	0.7195
	Left ventricular end-systolic diameter	-0.054	0.7297
	Ejection fraction	0.023	0.8821
sNA	Left atrial diameter	0.475	0.0030
	Left ventricular end-diastolic diameter	0.461	0.0047
	Left ventricular end-systolic diameter	0.247	0.1465
	Ejection fraction	0.121	0.4812
ANP	Left atrial diameter	-0.179	0.1899
	Left ventricular end-diastolic diameter	-0.196	0.1546
	Left ventricular end-systolic diameter	-0.222	0.1063
	Ejection fraction	0.150	0.2802
BNP	Left atrial diameter	-0.038	0.7873
	Left ventricular end-diastolic diameter	-0.098	0.4838
	Left ventricular end-systolic diameter	-0.017	0.9038
	Ejection fraction	-0.095	0.4991
BNP/ANP ratio	Left atrial diameter	0.429	0.0017
	Left ventricular end-diastolic diameter	0.215	0.1300
	Left ventricular end-systolic diameter	0.351	0.0117
	Ejection fraction	-0.349	0.0122

ANP Atrial natriuretic peptide; BNP Brain natriuretic peptide; PAC Plasma aldosterone concentration; PRA Plasma renin activity; sNA Serum norepinephrine

post hoc test, class I versus class III/IV, $P < 0.05$; class II versus class III/IV, $P < 0.05$). RVSP was not significantly different among the NYHA functional classes (ANOVA, $P = 0.1180$).

There were no differences in plasma renin activity, plasma aldosterone concentrations or serum norepinephrine levels between patients in NYHA classes I, II and III/IV. The ANP level was significantly different among NYHA classes, showing a tendency to increase in class II and significantly decrease in classes III/IV (ANOVA, $P = 0.0206$). The corresponding BNP level was higher in NYHA class II (ANOVA, $P = 0.0355$; Tukey-Kramer's post hoc test, class I versus class II: $P < 0.05$) (Table 2 and Figure 1).

Echocardiographic variables and neurohormonal plasma levels

A weak correlation was observed between plasma aldosterone concentration and LVDd ($r = 0.485$, $P = 0.0008$) or LVDs ($r = 0.361$, $P = 0.0159$), between plasma renin activity and LAd ($r = 0.339$, $P = 0.0227$), and between norepinephrine and LAd ($r = 0.475$, $P = 0.003$) or LVDd ($r = 0.461$, $P = 0.0047$). ANP and BNP levels showed no correlation with LAd, LVDd, LVDs and EF (Table 3).

LA size, atrial fibrillation and natriuretic peptides

Overall analysis showed no correlation between ANP levels and LAd ($r = -0.073$). While ANP levels increased with a mild increase in LAd, they decreased when the LAd was markedly

Figure 2) Relationship of left atrial diameter (LAd) and brain natriuretic peptide (BNP) to atrial natriuretic peptide (ANP) ratio. The BNP/ANP ratio showed a positive correlation with LAd. Patients with atrial fibrillation (closed circles) had larger LAd than patients in sinus rhythm (open circles)

Figure 3) Comparison of brain natriuretic peptide (BNP) to atrial natriuretic peptide (ANP) ratio by operative indications according to the American College of Cardiology/American Heart Association guidelines. Mann-Whitney's U test was performed. Box plot shows median (centre line), first and third quartiles (top and bottom of box), and lowest and highest values (vertical lines) of ANP and BNP level, and BNP/ANP ratio. Significant differences in BNP/ANP ratio were observed for all the American College of Cardiology/American Heart Association indications, comprising New York Heart Association (NYHA) functional class, left ventricular end-systolic diameter (LVDs), ejection fraction (EF) and presence of atrial fibrillation

increased with increased atrial fibrillation. BNP levels showed the same tendency (Figure 2).

BNP/ANP ratio

The mean ($\pm$ SD) BNP/ANP ratio (1.1 ± 0.9 versus 2.4 ± 1.9 versus 4.6 ± 2.8 in NYHA classes I, II and III/IV, respectively) increased significantly in NYHA class III/IV (ANOVA, $P=0.0007$; Tukey-Kramer's post hoc test, class I versus classes III/IV, $P<0.05$; class II versus class III/IV, $P<0.05$) (Figure 1).

A weak correlation was detected between the BNP/ANP ratio and LVDs ($r=0.351$, $P=0.0117$) or EF ($r=-0.349$, $P=0.0122$) (Table 3). The BNP/ANP ratio increased with an increase in atrial diameter ($r=0.429$, $P=0.0017$) (Figure 2).

Operative indication and neurohormonal levels

The neurohormonal levels were compared between two groups divided by the known operative indications for MR, namely,

TABLE 4
Sensitivity and specificity of natriuretic peptide levels and echocardiographic parameters for symptoms

Variable	NYHA class I versus class II/III/IV			NYHA class I/II versus class III/IV		
	Sensitivity (%)	Specificity (%)	AUROC	Sensitivity (%)	Specificity (%)	AUROC
BNP	96	71	0.91	NA	NA	0.56
ANP	70	13	0.16	47	64	0.61
BNP/ANP	88	83	0.82	78	87	0.86
LAd	84	100	0.89	61	95	0.86
LVDs	38	100	0.66	39	100	0.79
EF	39	88	0.75	90	51	0.72

ANP Atrial natriuretic peptide; AUROC Area under the receiver-operating characteristic curve; BNP Brain natriuretic peptide; EF Ejection fraction; LAd Left atrial diameter; LVDs Left ventricular end-systolic diameter; NA Not available; NYHA New York Heart Association

NYHA class II or greater, EF 60% or less, LVDs 45 mm or larger and the presence of atrial fibrillation. No significant differences in plasma renin activity and plasma aldosterone concentration were observed for all the operative indications. The serum norepinephrine level was significantly higher in NYHA class II or greater ($P=0.0083$) and atrial fibrillation ($P=0.0288$). ANP level was significantly higher in NYHA class II or greater ($P=0.0055$), and BNP level was significantly higher in NYHA class II or greater ($P=0.0006$) and atrial fibrillation ($P=0.0019$). The BNP/ANP ratio was significantly higher in EF of 60% or less ($P=0.0030$), LVDs 45 mm or more ($P=0.0073$), NYHA class II or greater ($P=0.0102$) and the presence of atrial fibrillation ($P=0.0149$) (Figure 3).

ROC curves for NYHA classification

The clinical use of the BNP/ANP ratio as an indicator of disease severity was analyzed by ROC curves. The sensitivity, specificity and area under the ROC curve for symptoms by natriuretic peptide levels and echocardiographic measures are shown in Table 4. For NYHA classes II/III/IV, a cut-off BNP/ANP ratio of 1.20 produced a sensitivity of 88%, specificity of 83% and area under the ROC curve of 0.82. For NYHA class III/IV, a cut-off BNP/ANP ratio of 2.97 produced a sensitivity of 78%, specificity of 87% and area under the ROC curve of 0.86 (Figure 4). The area under the ROC curve was higher for each of the BNP/ANP ratios than for levels of ANP and BNP, as well as the echocardiographic measures of the LVDd, LVDs and EF.

DISCUSSION

In the present study, ANP and BNP levels increased among all moderate or severe chronic MR cases. However, while ANP and BNP levels increased with the progression of heart failure symptoms, no increases were observed in NYHA class III/IV; in fact, ANP levels showed a decrease in this class. On the other hand, ANP and BNP levels showed no primary correlation with LV function measurements such as LAd, LV diameters and LVEF. Although ANP levels increased initially with atrial enlargement, they decreased when the enlargement became marked. Similarly, BNP levels tended to decrease with marked enlargement of the atrium. However, the BNP/ANP ratio increased with the progression of heart failure symptoms, decreased LV function and larger LAd.

Activation of the neurohormonal system is a self-compensatory mechanism against heart failure. Neurohormonal factors, such as the vasoconstrictors norepinephrine, renin and endothelin-1, play important roles in the pathogenesis of heart failure and have been reported to be prognostic predictors of heart failure (6-8). ANP and BNP are secreted from cardiomyocytes secondary to increased atrial and ventricular wall stretch. After release from the heart, the circulating natriuretic peptides bind to peripheral receptors, resulting in natriuresis, vasodilation, inhibition of the renin-angiotensin-aldosterone system and cardioprotection.

Little data are available on neurohormonal factors in valvular disorders, especially the kinetics of natriuretic peptides. In valvular disorders, ANP and BNP levels are affected by the site of valve damage (mitral, aortic, etc), the form of damage (regurgitation, stenosis), the severity of valve dysfunction (regurgitant fraction, effective orifice area), as well as ventricular and atrial function (9-13). Chronic LV volume overload as a result of MR leads to compensatory dilation of the LV. In addition, backflow into the LA results in enlargement of the LA, atrial fibrillation and pulmonary hypertension. MR is characterized by chronic volume overload and atrial fibrillation causing extensive degenerative change in the atrium (14,15). In MR, ANP and BNP levels are expected to vary depending on the severity and duration of individual cardiac cavity overload (10,11).

ANP is mainly stored as secretion granules in atrial myocytes, and secretion is rapid (15). Overstretching of the atrial muscle and increased depolarization are proposed to be the stimuli for ANP secretion (16,17). Although ANP levels increase in atrial fibrillation, reports (18-21) have indicated that levels are lower among patients with atrial fibrillation of longer duration due to the degenerative change (atrophy and fibrosis) of atrial myocytes. In MR, chronic atrial overload and atrial fibrillation probably lower the ANP level.

BNP is a cardiac neurohormone specifically secreted from the ventricle in response to volume expansion and pressure overload (22-25). BNP is a truly ventricular hormone, and responds to changes in LV filling pressure. BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides (26,27). BNP level provides prognostic information independent of other variables previously associated with mortality and sudden death in patients with chronic heart failure, and is more useful than ANP or norepinephrine for predicting a poor prognosis (27,28).

BNP mRNA is expressed in atrial muscle, where BNP is also secreted; both have been reported to increase by atrial fibrillation and hypertrophy (24,29-32). Although the kinetics of atrial-derived BNP in heart failure are not fully known, some studies (23-25) propose that the atrium is the major source of secretion in the early stage of lowered cardiac function, and that BNP levels from the ventricle increase after the progression to heart failure. BNP and ANP are structurally similar, and BNP is probably also stored in secretion granules (16,33). Therefore, in chronic atrial fibrillation, it is likely that BNP secretion also decreases due to degeneration or atrophy and fibrosis of the atrial muscle, similar to ANP. In chronic MR, we speculate that despite an increase in levels of the mainly ventricle-derived BNP, the atrium-derived BNP levels may decrease when atrial damage becomes severe, and as a result, the net BNP level does not increase.

Figure 4) Receiver-operating characteristic curves for the brain natriuretic peptide (BNP) to atrial natriuretic peptide (ANP) ratio to determine the severity for heart failure. Areas under the curve are 0.82 (New York Heart Association [NYHA] class I versus class II/III/IV) and 0.86 (NYHA class I/II versus class III/IV)

Clinical implications

In practice, clinical decision on operative indication is most difficult for NYHA class II patients with mild symptoms. In the present study, ANP levels, BNP levels and the BNP/ANP ratios vary greatly in NYHA class II, probably reflecting a wide spectrum of disease conditions in this group. In clinical practice, assessment of symptoms may be difficult. It is likely that in some patients, the symptoms were not a consequence of MR, while others were classified as asymptomatic because they undertook little activity or neglected subtle symptoms. The results of the present study suggest that natriuretic peptide testing may add to the information obtained by echocardiography in the assessment of MR in clinical practice.

Limitations

BNP is mainly secreted in the ventricle, proportional to volume expansion and pressure overload (25). Cheung and Kumana (34) suggested that the BNP level reflects the long-term intravascular volume, rather than the momentary volume. On the other hand, Tsutamoto et al (27), Cheng et al (35) and Nakagawa et al (36) considered BNP to be an emergency hormone, responding instantaneously to ventricular volume overload. Unfortunately, we have little information on the stability or reproducibility of BNP levels measured over time in heart failure patients who have a stable course (37,38). In the present study, ANP and BNP levels were measured only once in the majority of patients. While changes in BNP level are supposed to reflect the pathology of heart failure, whether a single-baseline measurement determination during chronic heart failure accurately reflects the disease condition remains to be studied.

Much of the data in the present study highlight the ability of the BNP/ANP ratio to distinguish between NYHA class II to IV patients and class I patients. Unfortunately, we could only enrol eight class I patients in the study. Although the NYHA functional class was determined based on each patient's subjective symptoms, we could not obtain objective data, such as exercise oxygen uptake, to confirm patient functional status. Therefore, to elucidate the significance of the BNP/ANP ratio, future clinical studies that include more patients with mild MR and that collect exercise oxygen uptake data are needed.

CONCLUSION

The present study suggests that the BNP/ANP ratio is increased in chronic MR as a result of decreased ANP and BNP levels, which is due to atrial degeneration, as well as an increase in BNP levels, which is due to ventricular overload. In chronic MR, the levels of ANP and BNP, as well as the BNP/ANP ratio, are potential indicators of disease severity. A prospective study is needed to determine whether the BNP/ANP ratio can be used to predict mortality and morbidity in patients treated medically, and predict the postoperative course in those treated surgically.

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