Characterization of Left Ventricular Filling Abnormalities and Its Relation to Elevated Plasma Brain Natriuretic Peptide Level in Acute to Chronic Diastolic Heart Failure

Shinji Nakao, MD; Akiko Goda, MD; Masao Yuba, MD; Misato Otsuka, MD; Mika Matsumoto, MD; Chikako Yoshida, MD; Mitsumasa Ohyanagi, MD*; Yoshiro Naito, MD; Masaaki Lee, MD; Takeshi Tsujino, MD; Tohru Masuyama, MD

Background Although Doppler left ventricular (LV) filling abnormalities have been extensively analyzed in patients with systolic heart failure (SHF), they have not yet been well characterized in patients with acute to chronic diastolic heart failure (DHF) in the light of plasma brain natriuretic peptide (BNP) levels.

Methods and Results In 25 patients presenting with acute DHF and 25 with acute SHF, echo Doppler parameters and plasma BNP levels were obtained on admission and in the chronic stage. The mitral E/A ratio was lower in DHF patients than in SHF patients in the acute stage (1.3±0.4 vs 1.8±0.9, p<0.05), and in the chronic stage of DHF the ratio decreased with plasma BNP level, but plasma BNP level was still greater than 100 pg/ml in 15 patients (60%). Among patients with DHF the plasma BNP level did not correlate with the mitral E/A ratio or deceleration time (r=0.25, p=NS; r=0.23, p=NS), but did with estimated pulmonary artery systolic pressure (r=0.64, p<0.01).

Conclusions A restrictive mitral flow velocity pattern is observed in only 25% of patients with DHF, so it is particularly important to recognize pseudonormalization in those with possible DHF. Persistently elevated plasma BNP level is not primarily caused by LV diastolic dysfunction, but by secondary alteration for hemodynamic adjustment (elevated LV end-diastolic pressure) in patients with DHF. (Circ J 2007; 71: 1412–1417)

Key Words: Brain natriuretic peptide; Diastole; Heart failure; Mitral flow

Heart failure (HF) with normal or minimally impaired systolic function is attributed to diastolic dysfunction and is termed “diastolic HF” (DHF). It frequently occurs in the elderly, females and those with hypertension, leading to a poor prognosis.1–7 Analysis of the pulsed Doppler transmitral flow velocity pattern is one of the most common ways of assessing left ventricular (LV) diastolic dysfunction. The transmitral flow velocity pattern has been well characterized in patients with HF caused by LV systolic dysfunction (systolic HF, SHF), and it shows a characteristic transition first from a normal to a relaxation abnormality pattern, and then to a pseudonormal pattern and finally a restrictive pattern8–11. The same or similar grading system has been applied to those with DHF with little clinical evidence. Gandhi et al reported that the mitral flow velocity pattern did not show a restrictive pattern in hypertensive patients with an LV ejection fraction (EF) of at least 0.50 associated with acute pulmonary edema12. In the follow-up of their patients, treatment was associated with an increase in the early diastolic mitral flow velocity that was in a direction opposite to that expected from the widely-used grading of LV diastolic dysfunction. More importantly, Yamamoto et al clearly showed a lack of correlation between LV end-diastolic pressure and mitral flow velocity indexes among patients with preserved LV systolic function in contrast to the close correlations of these among patients with LV systolic dysfunction.13 Thus, we may consider that DHF has not yet been well characterized from the viewpoint of the transition of the transmitral flow velocity pattern, which accounts for an absence of practical and definitive diagnostic criteria for DHF. Currently, the diagnosis of DHF is made primarily on the basis of symptoms and exclusion criteria;14 however, symptoms such as exertional dyspnea, paroxysmal nocturnal dyspnea, and pedal edema are not specific to HF. Some may well argue against the diagnostic criteria,15,16 and this doubt about the diagnosis has limited the recognition of the clinical and social importance of DHF.

Brain natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the ventricles.17 Elevation of the plasma BNP level is considered to reflect ventricular structural and functional alterations. Although its clinical utility as a biochemical marker of LV systolic dysfunction has been reported, its positive predictive value is only 10–20%.22 The plasma BNP concentration is also elevated in those with DHF, or even at a risk of DHF, among subjects with preserved LV systolic function; however, the
mechanism for the elevation of plasma BNP level in those patients has not been elucidated yet. Thus, in the present study we repeated echo Doppler studies of LV diastolic filling and measurements of plasma BNP level in the acute and chronic stages of DHF in order to (1) characterize the LV diastolic filling abnormalities in the acute stage and (2) determine the elevated plasma BNP level with a risk of DHF primarily because of LV diastolic dysfunction or because of secondary hemodynamic alteration.

**Methods**

**Selection of Patients**

To enroll patients with a history of definitive overt DHF (DHF group) from the institutional medical records, we identified patients who presented to the emergency department with definitive pulmonary edema with preserved systolic function between January 2004 and May 2005. During this period, 125 patients had an acute onset of dyspnea, respiratory distress, and pulmonary rales caused by pulmonary congestion, as confirmed by chest radiography, in the absence of an acute coronary syndrome. Of these patients, those who met the following entry criteria were identified: (1) echocardiographic confirmation of EF >55% on or just before admission; (2) relief of symptoms by treatment with diuretics and/or vasodilators after the emergency admission, and (3) data for echo Doppler studies and plasma BNP level. Patients with congenital heart disease, severe valve disease, or renal failure (serum creatinine concentration >2.0 mg/dl) or who were not followed up in the outpatient clinics were excluded. Among the patients who met these criteria, the DHF group comprised 25 patients who agreed to participate in this study. All of these patients were stable when they participated in this study (chronic stage). All of the patients were treated according to their physicians' principles. Angiotensin-converting enzyme inhibitors were used in 1 patient, angiotensin II receptor blockers in 16 patients, calcium-channel blockers in 9 patients, and ß-blockers in 11 patients.

As a control, 25 consecutive patients with HF because of LV systolic dysfunction who met all of the previous criteria for DHF except the value of LVEF were included. The LVEF was defined as <45% in this group. Angiotensin-converting enzyme inhibitors were used in 6 patients, angiotensin II receptor blockers in 17 patients, diuretics and/or vasodilators in 25 patients, calcium-channel blockers in 5 patients, and ß-blockers in 22 patients. The institutional ethics committee approved the study, and all participants gave informed consent.

**Transthoracic Echocardiographic Study**

In both groups, conventional transthoracic echocardiography and blood assay were conducted on admission before starting any medication. Transthoracic echocardiographic examinations were conducted to measure left atrial and LV cavity sizes and LV wall thickness, as previously described. EF was calculated by a modification of the method of Quinones et al and LV mass was estimated from the formula of Devereux et al. In patients with sinus rhythm, the pulsed Doppler transmitral flow velocity pattern was recorded to measure the ratio of peak mitral early diastolic flow wave (E-wave) velocity to peak mitral flow wave velocity at atrial contraction (A-wave velocity) (E/A ratio) and the deceleration time of the mitral E-wave velocity. EF was used to grade the LV diastolic dysfunction. EF ratio <0.75, mild; E/A ratio 0.75–1.5, moderate; E/A ratio >1.5, severe.

In addition, the presence of tricuspid regurgitation was carefully examined by color Doppler flow imaging, and if present, continuous wave Doppler echocardiography was used to measure the peak flow velocity. Right ventricular or pulmonary arterial systolic pressure (PASP) was determined from the velocity by applying the simplified Bernoulli equation on the assumption that right atrial pressure was 10 mmHg.

**BNP Study**

The plasma BNP level was measured using an immunoradiometric assay with commercially available kits (Shionogi Co Ltd, Osaka, Japan) to determine the correlation with the echo Doppler parameters. All of the measurements were repeated in the chronic stage when symptoms of HF had diminished. All of the measurements were repeated at an interval of 21–70 days (mean, 32). At the time, any symptoms of acute HF had been relieved.

**Statistical Analysis**

Values are expressed as mean ± SD. All statistical analyses were performed using commercially available statistical software (StatView version 5.0, SAS Institute Inc, Cary, NC, USA). Discrete variables were summarized by frequency percentages and analyzed with the chi-square test. Differences between 2 groups were assessed using Student's t-test. Results were considered statistically significant at p<0.05.
Results

Patient Characteristics

Characteristics of the DHF and SHF groups are summarized in Table 1. A history of hypertension was present in 22 (88%) patients of the DHF group and in 18 (72%) patients of the SHF group.

LV Diastolic Filling in the Acute Stage

The mitral E/A ratio was greater in the SHF group than in the DHF group in the acute stage (p<0.05). Similarly, the mitral deceleration time was shorter in the SHF group than in the DHF group in the acute stage (p<0.05). When the graded data for mitral flow velocity pattern were compared between the DHF and SHF groups, severe LV diastolic dysfunction was more frequently observed in the SHF group than in the DHF group (p<0.05; Fig 2), whereas moderate LV diastolic dysfunction (pseudonormal pattern) was more frequently observed in the DHF group than in the SHF group. Tricuspid regurgitation was detected in 21 (84%) patients in the DHF group and in 21 (84%) patients in the SHF group. Estimated PASP did not differ between the 2 groups. Estimated PASP was greater than 35 mmHg in 80% of the DHF and 78% of the SHF group.

LV Diastolic Filling in the Chronic Stage

The mitral E/A ratio and estimated PASP decreased and deceleration time increased in both the DHF and SHF
groups. The magnitude of the changes in these parameters did not differ between the groups (Table 2).

**Plasma BNP Level**

The plasma BNP level was elevated in both the DHF and SHF groups in the acute stage, and in the chronic stage it decreased in both groups, but was still above 100 pg/ml in 15 (60%) patients with DHF. When echo Doppler correlates of plasma BNP level were studied in patients with DHF, the plasma BNP level did not correlate with either the mitral E/A ratio or deceleration time (r=0.26, p=NS; r=0.23, p=NS). Estimated PASP correlated well with plasma BNP level (r=0.68, p<0.01; Fig 3A) and the plasma BNP level correlated with both mitral E/A ratio and estimated PASP in patients with SHF (r=0.36, p<0.05, and r=0.63, p<0.01, respectively, Fig 3B). The regression line for the relation between estimated PASP and plasma BNP level was similar in both groups.

**Discussion**

In the present study we clearly show that the restrictive pattern (severe LV diastolic dysfunction) is infrequent in patients with acute DHF, indicating that differentiation of a pseudonormal pattern from the truly normal pattern is most important in patients with acute DHF. Estimation of PASP using continuous-wave Doppler tricuspid regurgitant flow velocity may help in this differentiation because it is frequently elevated in patients with DHF. When the serial changes in the echo Doppler parameters were analyzed from the acute to chronic stages in the light of associated changes in the plasma BNP level, the plasma BNP level correlated better with PASP than with the mitral flow velocity parameters. These findings suggest that elevation of the plasma BNP level in patients with DHF is not primarily caused by an alteration of the LV factors affecting diastolic filling, such as prolonged LV relaxation and stiffened left ventricle, but rather by a secondary hemodynamic alteration. Persistent elevation of the plasma BNP level may be indicative of elevated left atrial pressure in patients with DHF.

**LV Diastolic Filling Abnormalities in the Acute Stage of HF**

Because LV systolic function is preserved, abnormal findings are observed only in the diastolic parameters in echo Doppler studies in patients with DHF. It is well documented that the mitral flow velocity pattern shows a restrictive pattern in patients with severe SHF, but the results of
the present study show that it rarely exhibits a restrictive pattern, even in patients with acute and severe DHF in whom the PASP is elevated to a level comparable with that in patients with acute and severe SHF. The A-wave velocity was slightly, although statistically significantly, greater in DHF patients than in SHF patients in the acute stage, and this may at least partially account for this finding. We postulate several possible reasons, such as the effects of left atrial size or compliance, and changes in the left atrial contractile force in DHF patients, to explain the relatively high A-wave velocity in DHF patients; however, the mechanism needs to be clarified in future studies by recording LV and left atrial pressures simultaneously with the mitral flow velocity pattern in patients with DHF. The E/A ratio in the acute phase was smaller in the DHF group than in the SHF group, although the BNP level or PASP was almost the same in the DHF and SHF groups. In the chronic phase, there was no difference in either the E/A ratio or deceleration time between the 2 groups, suggesting that the changes in E/A or deceleration time from the acute phase may be smaller in DHF.

From the clinical viewpoint, the high incidence of a pseudonormal mitral flow velocity pattern among DHF patients means clinicians frequently must differentiate the pseudonormal from a truly normal pattern. Considering that symptoms of HF are often atypical, the lack of any gold standard for HF may lead to misdiagnosis, but is less likely in those with SHF because the decreased EF warns of the possibility of HF; however, the examiner may not even consider HF in patients with preserved LVEF and an apparently normal mitral flow velocity pattern. Such oversight may be prevented if the estimation of PASP is attempted in every patient in the daily echo Doppler studies. In the present study, the estimated PASP was greater than 35 mmHg in 80% of patients with DHF. If only those with detectable tricuspid regurgitation are taken into account, DHF was recognizable in 90% of patients in this study. The data from the present study are obviously not enough to draw a conclusion regarding the value of tricuspid regurgitation method, because of the limitations of sample size and study design, but should be studied in the near future. Ommen et al reported that the combination of tissue Doppler imaging of the mitral annulus and mitral inflow velocity patterns provides a better estimate of LV filling pressures and the value of other methods, such as those based on tissue Doppler mitral annular velocity, pulmonary venous flow velocity pattern and the Valsalva maneuver, should be also studied in future.

Plasma BNP Level in Patients With DHF

It is well known that the plasma BNP level is elevated not only in patients with HF, regardless of the presence or absence of LV systolic dysfunction, but also in patients with asymptomatic LV systolic dysfunction. Most recently, the plasma BNP level was shown to be elevated in patients with DHF, even in those with preserved LV systolic function and only at a risk of DHF. The present findings support these previous findings. The plasma BNP level decreased following treatment; however, normalization was observed only in a small number of patients with DHF. Thus, we attempted to clarify whether prolonged elevation of the plasma BNP level is primarily caused by abnormal LV diastolic dysfunction or by persistent secondary hemodynamic alteration. There was only a weak correlation between the plasma BNP level and the parameters of LV diastolic filling. In contrast, the plasma BNP level correlated well with the estimated PASP in patients with DHF, suggesting that persistent elevation of plasma BNP level in the chronic stage of DHF is caused by a persistent secondary hemodynamic alteration. This is consistent with a recent study in which echo and LV pressure measurements were used to show that plasma BNP levels reflect LV end-diastolic wall stress in patients with chronic DHF. In other words, decreases in left atrial pressure may be incomplete in DHF patients with elevation of the plasma BNP level, even after relief or diminution of the symptoms of HF. It does not necessarily mean that additional diuretics or preload reduction are needed, because excessive preload reduction easily provokes hypotension or even shock in patients with DHF.

Study Limitations

First, LV pressure was not measured mainly because of ethical issues. Second, the EF was measured by Quinones method and accordingly, it might be required to convert a linear measurement to a 3-dimensional volume to more accurately calculate the EF. Third, aging certainly affects the mitral flow velocity pattern. It is possible that the difference in the E/A ratio between the DHF and SHF groups was related to the difference in age; however, the difference in the mean age was not large enough to explain the mitral E/A ratio findings. Fourth, medical treatment was not uniform among the patients, partly because guidelines for the management of DHF have not been established. Fifth, the number of study subjects was not large and the DHF group included only patients who had a definitive history of acute pulmonary edema under echocardiographic confirmation of EF ≥55% on admission and who were still followed up in the outpatient clinics. Such strict inclusion criteria are responsible for the small number of the subjects, but have minimized the effects of inaccurate diagnosis of DHF that have been frequently debated in discussion of the reliability of conclusions of DHF studies. Finally, Redfield et al recently demonstrated that combined analysis of pulsed Doppler transmitral and pulmonary venous flow velocity patterns and tissue Doppler imaging of mitral annular motion provided a grading of LV diastolic dysfunction. Pulmonary venous flow velocity patterns and mitral annular motion were not analyzed in this study, so we can not deny the value of the additional Doppler echocardiographic parameters in detecting or characterizing patients with DHF.

Conclusions

A restrictive mitral flow velocity pattern is infrequent in patients with DHF. Because the mitral flow velocity pattern is usually pseudonormal, even in patients with acute DHF to a severe degree, it is particularly important to recognize pseudonormalization in those with possible HF and preserved LV systolic function. The plasma BNP level correlated better with estimated PASP than with parameters of LV diastolic filling in patients with DHF, indicating that an elevated plasma BNP level with a risk of DHF is not primarily caused by LV diastolic dysfunction but is a secondary alteration for hemodynamic adjustment.

References

LV Filling and BNP in DHF


