Original article

Correlation between plasma B-type natriuretic peptide levels and left ventricular diastolic function using color kinetic imaging

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Summary

Background: B-type natriuretic peptide (BNP) has been used widely as an objective marker for severity and prognostic predictor of heart failure. Recently it has been reported that plasma BNP level is associated with left ventricular (LV) diastolic dysfunction. Color kinesis (CK), a technique based on acoustic quantification, has been developed to facilitate the evaluation of regional wall motion and LV function. The aim of this study is to investigate the relationship between plasma BNP levels and LV diastolic function using diastolic CK imaging.

Methods and results: The study included 65 subjects in sinus rhythm who were referred for echocardiography to evaluate cardiac function with simultaneous measurements of plasma BNP. Thirty-five patients were in New York Heart Association class I or II, and 15 were in class III or IV. We performed echocardiography with assessment of LV function, including LV ejection fraction (EF), transmitral flow (E/A), early diastolic mitral annular velocity (e'), and diastolic CK. Diastolic CK images, obtained from LV mid-papillary short-axis view, were analyzed using ICK software. The CK-diastolic index (CK-DI) was defined as the calculated LV segmental filling fraction during the first 30% of diastole, expressed as a percentage. The mean CK-DI was determined from the average CK-DI of six segments (anterior, anteroseptal, septal, inferior, posterior, lateral wall). Blood for BNP was collected on the same day as the echocardiographic study. We found significant correlations between mean CK-DI and log BNP ($r = -0.66, p < 0.0001$), whereas log BNP correlated weakly with EF ($r = -0.26$), $E/A$ ($r = 0.22$), $DT$ ($r = -0.15$) and $E/e'$ ($r = 0.41$).

Conclusion: Our results suggest that the plasma BNP level may be related to LV relaxation. The analysis of diastolic CK may be useful for quantitative assessment of LV diastolic function in patients with heart failure.

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Introduction

B-type natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload [1—3]. BNP has been used widely as an objective marker for severity and prognostic predictor of heart failure. Recently it has been reported that plasma BNP level is associated with not only left ventricular (LV) systolic dysfunction but also LV diastolic dysfunction [4—17].

Color kinesis (CK) is a real-time echocardiographic technique based on acoustic quantification that yields regional and global information on the magnitude and timing of LV wall motion by tracking and color-encoding endocardial motion throughout the cardiac cycle [18—21]. We previously reported that the analysis of diastolic CK is a useful method for quantitative evaluation of LV diastolic function and detecting delayed LV relaxation [22,23]. The aim of this study is to investigate the relationship between plasma BNP levels and LV diastolic function by using diastolic CK imaging.

Methods

Study population

The study included 65 subjects (33 males, 32 females, mean age 63 ± 15 years) in sinus rhythm who were referred for echocardiography to evaluate cardiac function with simultaneous measurements of the plasma BNP. Twenty-eight patients had idiopathic dilated cardiomyopathy; 17 had hypertensive heart disease; 5 had hypertension; 15 had normal echocardiographic examination, including LV dimension and systolic function. Thirty-five patients were in New York Heart Association (NYHA) class I or II, and 15 were in class III or IV. The exclusion criteria were (1) atrial fibrillation, (2) moderate to severe valvular disease assessed with color-flow Doppler, (3) coronary artery disease, (4) resting heart rate <55 or >90 beats/min, (5) renal dysfunction (defined as a creatinine value > 1.5 mg/dl), (6) pericardial effusion and previous pericardiotomy and (7) inadequate two-dimensional echocardiographic imaging.

In all study subjects, a transthoracic echocardiographic study including M-mode, two-dimensional imaging, pulsed Doppler, color-flow Doppler, tissue Doppler imaging (TDI), and CK images were performed with a commercially available ultrasound system (SONOS 7500, Philips Medical Systems, Andover, MA, USA). Using pulse Doppler echocardiography, peak velocities during rapid filling (E wave) and atrial contraction (A wave) were measured, and the E/A ratio and deceleration time of the E wave velocity (DT) were calculated. The early diastolic mitral annular velocity (e') was measured by TDI at septal side and LV ejection fraction (EF) was calculated by modified Simpson method.

CK study

Diastolic CK images were obtained in each subject from the LV mid-papillary short-axis view (Fig. 1). After image quality was optimized, the acoustic quantification system was activated. Gain controls, including total and lateral gain and time gain compensation, were adjusted to optimize tracking of the endocardial border. Color encoding of endocardial motion during diastole was triggered by the R wave of the ECG. The timing color encoding was set to start at end systole and terminate 19 frames (19 × 33 = 627 ms) later or at the ensuing R wave, whichever occurred first. Three non-consecutive CK images were stored in digital format on an optical disk for off-line analysis. The analysis of CK-diastolic image was performed by using commercially available ICK software (YD Co., Ltd., Nara, Japan). Using ICK software, the LV was automatically divided into six segments (anterior, anteroseptal, septal, inferior, posterior, lateral wall) based on segmentation recommended by the American Society of Echocardiography [24]. The CK-diastolic index (CK-DI) was defined as the calculated LV segmental filling fraction during the first 30% of diastole, expressed as a percentage. The mean CK-DI was determined from the average CK-DI of six segments (Fig. 2). For each subject, data obtained from three diastolic CK images were averaged. All of the participants provided informed consent for this study.

Plasma BNP measurements

Blood for BNP was collected on the same day as the echocardiographic studies in the fasting state. The plasma BNP level...
Correlation between BNP and LV diastolic function using CK imaging

Figure 2  Analysis of diastolic color kinesis by ICK software in a normal subject. Histograms show the percentage of each segmental left ventricle (LV) filling (left). Arrowheads represent the color kinesis-diastolic index (CK-DI) in each segments. Time-sequence curves reflect segmental filling in diastole (right). The mean CK-DI is calculated from the average CK-DI of six segments. Approximately 80% of maximum LV filling occurs during the first 30% of the diastolic filling time in normal subjects. sp, septal; asp, anteroseptal; ant, anterior; lat, lateral; pst, posterior; inf, inferior wall. (Reproduced from Harada et al. [22]).

Figure 3  Correlations between the log B-type natriuretic peptide (BNP) and diastolic parameters. Plasma BNP levels were better correlated with mean color kinesis-diastolic index (CK-DI) than the ratio of transmitral E wave velocity to e′ (E/e′).

was measured using a validated and commercially available immunoassay kits (Tosoh Ltd., Tokyo, Japan).

Statistical analysis

Data are expressed as mean value ± standard deviation. Correlations for plasma BNP levels and echocardiographic variables were examined using simple and multiple linear regression analysis. Natural log transformation was performed on BNP values before statistical analysis because of nonlinear distribution. Statistical significance was defined as p < 0.05.

Results

Clinical characteristics and echocardiographic variables of the 65 subjects are summarized in Table 1. Plasma BNP values ranged from 16.7 to 2087 pg/ml. All patients were able to be evaluated by CK-DI, including two examinations in two patients. A significant correlation was observed between plasma BNP and mean CK-DI \( r = -0.66, p < 0.0001 \) and E/e′ \( (r = 0.41, p < 0.01) \) (Fig. 3). However, plasma BNP levels correlated weakly with EF \( r = -0.26, p = 0.036 \) and other diastolic parameters, including E/A \( r = 0.22 \), DT \( r = -0.15 \) (Table 2). When multiple linear regression was performed, it was found that mean CK-DI \( p = 0.0019 \), e′ \( (p = 0.0329) \), and DT \( (p = 0.0473) \) were independent predictors of plasma BNP level (Table 2). Fig. 4 illustrates an example of a patient whose heart failure improved by medical treatment.

Discussion

The effects of BNP include natriuresis, diuresis, vasodilation, antifibrotic activity, and suppression of the renin–angiotensin–aldosterone system [2]. BNP levels are elevated in patients with symptomatic LV dysfunction and correlate with NYHA class as well as with prognosis [3,4]. Lubien et al. demonstrated that elevated BNP levels correlate with diastolic abnormalities on Doppler studies in patients with normal systolic function [8]. Furthermore, the heterogeneity of BNP levels in patients with systolic heart failure reflects the severity of diastolic abnormality, right ventricular function, and mitral regurgitation in addition to EF, age, and renal function [9]. Recently, Iwanaga et al. demonstrated that diastolic wall stress appears to be the most important stimulus of BNP secretion, not only in patients with systolic heart failure, but also in patients with diastolic heart failure [15]. Thus, these previous studies have suggested correlations between BNP levels and LV diastolic function.
LV diastolic function is generally composed of LV relaxation and stiffness. Myocardial relaxation, which occurs during isovolumic relaxation and early diastolic filling, is an active process involving the use of intracellular adenosine triphosphate and calcium by the myocardium. In disease states, relaxation abnormalities occur early and the inability of the LV to fill in early diastole significantly affects the rapid filling phase, resulting in a compensatory increase in filling with atrial contraction. The gold standards for diagnosing diastolic dysfunction are the time constant of relaxation (tau), which correlates with the rate of cardiac relaxation and pressure-volume curves obtained by direct invasive measurement to assess chamber compliance. However, these are not feasible for daily clinical practice, as they are tools for research investigation for the majority of patients. The longitudinal motion of the mitral annulus has been shown to reflect the rate of myocardial relaxation [25].

Preliminary studies suggest that the early diastolic mitral annulus velocity (e’) behaves as an index of LV relaxation with a significant inverse correlation between e’ and tau and with no change in e’ occurring with preload alterations [26–28]. Nagueh et al. reported that e’ had strong correlations with tau in canine experiments [25]. However, there was a weak correlation between e’ and tau in a clinical study with direct simultaneous measurement of LV pressure [29]. This result suggests that e’ is an index to be obtained from early diastole, but may be affected by not only myocardial relaxation but also stiffness. Nagueh et al. demonstrated that no significant difference in e’ was observed between impaired relaxation and pseudonormal pattern groups [30]. When e’ is reduced with progression of LV diastolic dysfunction, the measurement of e’ alone may not be satisfactory for accuracy to evaluate LV relaxation and the degree of diastolic dysfunction.

In the present study, analysis of diastolic CK was performed at the same time as BNP measurements because half-time of BNP is shortening. As a result, a good correlation to plasma BNP levels was demonstrated in mean CK-DI than E/e’, whereas plasma BNP levels correlated weakly with EF, E/A, and DT. This CK-DI, an index proposed by Ishii et al., is calculated LV segmental filling fraction during the first 30% of diastole with ICK software [31]. They reported that delayed early diastolic relaxation and dyssynchrony, which are considered to be caused by myocardial ischemic memory, can be detected using CK-DI [31–33]. We have previously reported that this CK-DI is superior in reproducibility, can be applied to quantitative evaluation of LV global diastolic function, and to differentiating between normal and pseudonormalized patterns of LV inflow [22,23]. Takeda et al. confirmed the significant correlation of tau with CK-DI of the whole heart, not with E/A, using an animal diastolic heart failure model [34]. However, the assessment for the relationship between mean CK-DI and LV relaxation will be necessary in a clinical study. Although E/e’ ratio is a useful index to estimate LV end-diastolic pulmonary capillary wedge or left atrial pressure, it is not a direct index of LV diastolic function. In contrast, CK-DI may be useful index to evaluate LV relaxation noninvasively. Our results suggest that plasma BNP levels may reflect LV relaxation, and it seems that their plasma levels were better correlated with mean CK-DI than E/e’ in the present study.

### Table 1 Clinical characteristics and echocardiographic variables of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>65</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>HT</td>
<td>5</td>
</tr>
<tr>
<td>DCM</td>
<td>28</td>
</tr>
<tr>
<td>HHD</td>
<td>17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 15</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>33/32</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>68 ± 13</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>513 ± 522</td>
</tr>
<tr>
<td>EF (%)</td>
<td>43 ± 16</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.9 ± 0.7</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>207 ± 87</td>
</tr>
<tr>
<td>e’ (cm/s)</td>
<td>3.6 ± 1.5</td>
</tr>
<tr>
<td>E/e’</td>
<td>17.4 ± 7.7</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number. BNP, B-type natriuretic peptide; DCM, dilated cardiomyopathy; DT, deceleration time of early transmitral velocities; e’, early diastolic mitral annular velocity; E/A, the ratio of early to late transmitral peak velocities; E/e’, the ratio of transmitral E wave velocity to e’; EF, ejection fraction; HHD, hypertensive heart disease; HR, heart rate; HT, hypertension; LVDD, left ventricular end-diastolic dimension.

### Table 2 Univariate and multivariate relationships of clinical and echocardiographic parameters to plasma log B-type natriuretic peptide.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate correlation coefficient</th>
<th>p-Value</th>
<th>Multivariate beta-coefficient</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.21</td>
<td>0.089</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>–0.26</td>
<td>0.036</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean CK-DI (%)</td>
<td>–0.66</td>
<td>&lt;0.0001</td>
<td>–0.49</td>
<td>0.002</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>–0.07</td>
<td>0.959</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.22</td>
<td>0.113</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>–0.15</td>
<td>0.373</td>
<td>–0.36</td>
<td>0.047</td>
</tr>
<tr>
<td>e’ (cm/s)</td>
<td>–0.10</td>
<td>0.479</td>
<td>–0.42</td>
<td>0.033</td>
</tr>
<tr>
<td>E/e’</td>
<td>0.41</td>
<td>0.004</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

CK-DI, color kinesis-diastolic index; DT, deceleration time of early transmitral velocities; e’, early diastolic mitral annular velocity; E/A, the ratio of early to late transmitral peak velocities; E/e’, the ratio of transmitral E wave velocity to e’; EF, ejection fraction; LVDD, left ventricular end-diastolic dimension; NS, not significant.
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Figure 4  Analysis of diastolic color kinesis using ICK software in a patient with hypertensive heart failure before (upper) and after medical treatment (lower). After treatment that included an angiotensin receptor antagonist, a significant improvement in mean color kinesis-diastolic index (CK-DI) was seen. BNP, B-type natriuretic peptide; EF, ejection fraction; E/e’, the ratio of transmitral E wave velocity to e’; sp, septal; asp, anteroseptal; ant, anterior; lat, lateral; pst, posterior; inf, inferior wall.

Study limitations

The present study has several limitations. First, since CK is based on acoustic quantification, it is important to obtain clear CK images and minimize noise. In the present study, we only analyzed the patients from whom adequate CK images could be obtained by tissue harmonic imaging. Second, the heart rate at the time of the examination is also important for CK analysis. A reduced diastolic time and fewer diastolic CK images lead to a reduction of temporal resolution in patients with tachycardia (heart rate > 90 beats/min). Because the current CK imaging method acquires up to 19 frames (19 × 33 = 627 ms), the number of frames is not enough to assess the total diastolic phase in patients with bradycardia (heart rate < 55 beats/min). The assessment of diastolic function by CK imaging is considered suitable for patients with a heart rate of 60—80 beats/min. Third, CK-DI is an index obtained from only a single section of the LV papillary short-axis view. It is necessary to observe several cross-sections for assessment of LV relaxation. Fourth, the relation between mean CK-DI and LV relaxation has not been demonstrated in the clinical setting. Finally, the mean CK-DI is determined from the average CK-DI of six LV segments in subjects without regional wall motion abnormality. Therefore, the assessment of LV diastolic function using CK-DI cannot be applied to patients with regional wall motion abnormalities.

Conclusions

We have introduced an analysis to evaluate LV diastolic function using diastolic CK imaging. A significant correlation between mean CK-DI and BNP suggests that plasma BNP levels may reflect LV relaxation. The analysis of diastolic CK may be useful for quantitative assessment of LV diastolic function in patients with heart failure.

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