Research Article

B-Type Natriuretic Peptide and Intraventricular Conduction Delay in Idiopathic Nonischemic Dilated Cardiomyopathy

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Abstract

Background: Idiopathic nonischemic dilated cardiomyopathy (INIDCM) is associated with increased left ventricular diastolic volume and decreased left ventricular ejection fraction (LVEF). B-type natriuretic peptide (BNP) is secreted from the left ventricle in normal adults and patients who have left ventricular dysfunction and is useful in diagnosing acute heart failure from ischemic or nonischemic causes. Limited information is available about the association between intraventricular conduction delay (IVCD) and BNP levels in patients who have INIDCM.

Methods: In patients evaluated in urgent care for chest pain and acute shortness of breath, there were 33 patients who had INIDCM and 39 patients who had idiopathic dyspnea. Evaluation included determination of plasma BNP level, LVEF, and presence of IVCD.

Results: The mean BNP level was significantly greater in the INIDCM (947 ng/L) than idiopathic dyspnea group (43 ng/L; \( P \leq .001 \)). The mean LVEF was lower in the INIDCM (27%) than idiopathic dyspnea group (62%; \( P \leq .001 \)). There was high IVCD (QRS complex > 120 ms) in 10 patients (30%) who had INIDCM and none with idiopathic dyspnea. In the patients with INIDCM, patients who had high IVCD had greater mean BNP (initial and 3-mo follow-up) and lower LVEF than patients who had low IVCD (QRS duration \( \leq 120 \) ms).

Conclusions: Increased plasma BNP levels may facilitate the diagnosis of INIDCM and may be associated with high IVCD.

ABBREVIATIONS

BNP: B-type Natriuretic Peptide; INIDCM: Idiopathic Nonischemic Dilated Cardiomyopathy; IVCD: Intraventricular Conduction Delay; LVDV: Left Ventricular Diastolic Volume; LVEF: Left Ventricular Ejection Fraction

INTRODUCTION

Idiopathic nonischemic dilated cardiomyopathy (INIDCM) affects 2 million people in the United States and has an average life expectancy of < 5 years [1,2]. In INIDCM, patients have left ventricular dilation, increased left ventricular diastolic volume (LVDV), and decreased left ventricular ejection fraction (LVEF). However, the diagnosis of INIDCM may be delayed because early symptoms and signs may be vague and nonspecific. These patients do not have known causes of dilated cardiomyopathy such as coronary artery disease, valvular or congenital heart disease, myocarditis, drug toxicity, or alcohol abuse. There is a need for screening measures to facilitate the diagnosis of INIDCM.

Natriuretic peptides may be useful in the diagnosis of heart failure [2-4]. B-type natriuretic peptide (BNP) is secreted from the left ventricle in normal adults and patients who have left ventricular dysfunction and is useful in diagnosing acute heart failure from ischemic or nonischemic causes [5-7]. In patients with congestive heart failure, plasma BNP levels reflect the degree of ventricular overload; BNP levels are higher in patients who have dilated cardiomyopathy than mitral stenosis, and BNP levels are positively correlated with pulmonary capillary wedge pressure [8]. In patients with heart failure, plasma BNP level is higher in patients with decreased than normal LVEF, and plasma BNP may be a useful predictor of decreased LVEF and increased left ventricular end diastolic pressure [9-11]. Furthermore, increased plasma BNP levels may be a predictor of worsening heart failure and cardiac events in patients who have nonischemic dilated cardiomyopathy [12].
There is little information available about the relation between conduction disturbances and plasma BNP levels. Patients with high degree atrioventricular conduction block have elevated levels of plasma BNP [13]. At 6 months after acute myocardial infarction, plasma BNP levels are higher in patients with than without intraventricular conduction delay (IVCD), especially left and right bundle branch block [14,15]. Patients who have left bundle branch block after acute myocardial infarction have lower BNP levels when they are treated invasively than noninvasively [16]. During ventricular pacing, patients who have unimpaired heart function but who develop retrograde ventriculoatrial conduction also develop increased plasma BNP levels [17]. However, the effect of IVCD on BNP levels in patients who have INIDCM is unknown.

We hypothesized that elevated plasma BNP levels may be associated with IVCD in patients who have INIDCM. The purpose of the present study was to evaluate plasma BNP levels in patients who have INIDCM and to determine the relation between IVCD and plasma BNP levels in these patients.

METHODS

Subjects

From October 2003 to October 2004, there were 323 consecutive patients who presented to the urgent care department of a tertiary care university medical center because of chest pain and acute shortness of breath. Among these patients, there were 33 patients who had INIDCM and 39 patients who had idiopathic dyspnea, and these patients were included in the study. Patients were excluded for non-ST segment elevation acute coronary syndrome, ischemic cardiomyopathy, postpartum cardiomyopathy, and nonischemic cardiac disease caused by glycogen storage disease, lysosomal storage disease, sarcoidosis, Chagas disease, hemochromatosis, amyloidosis, or laminin deficiency. The study was approved by the Institutional Review Board of East Tennessee State University (IRB # 04-110sw), and all study subjects provided informed consent.

Evaluation

The medical records of patients were reviewed retrospectively for clinical symptoms and signs and results of laboratory studies, plasma BNP level at initial evaluation, 2-dimensional echocardiography, electrocardiogram, and coronary angiography. Electrocardiograms were evaluated for presence of high IVCD (defined as QRS complex duration > 120 ms) or low IVCD (QRS duration ≤ 120 ms) [18]. Plasma BNP levels were determined during evaluation in the urgent care department with a commercially available kit that used a fluorescence detection system with ethylenediaminetetraacetic acid as the anticoagulant (Triage B-Type Natriuretic Peptide Test, Biosite Diagnostics, Inc., San Diego, CA). Left ventricular dimensions, LVDV, and LVEF were determined from echocardiography as previously described [19].

Treatment

All patients in the idiopathic dyspnea group were treated symptomatically with bronchodilators and oxygen supplementation by nasal cannula. All patients in the INIDCM group had individualized treatment according to guideline-directed medical therapy for heart failure in the setting of left ventricular systolic dysfunction, including the combination of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker and β-blocker adjusted to target doses as tolerated, with diuretics adjusted as needed to control fluid retention. Aldosterone antagonists were added after optimization of therapy with angiotensin converting enzyme inhibitors and β-blockers. The guideline-directed medical therapy was provided for ≥ 3 months before reassessing left ventricular function to consider device implantation. If left ventricular function improved and primary prevention indications no longer applied, then device implantation was not indicated.

Statistical methods

The BNP levels and LVEF were compared between groups using analysis of variance, Mann-Whitney test, and analysis of covariance to account for possible effects of age, sex, hypertension, and Diabetes mellitus. The BNP data were markedly skewed, but no linear transformations reduced skew to below statistical significance. In addition, results were similar regardless of transformation. Therefore, all findings were presented as raw values. Relations were tested using correlation test, linear regression, and Spearman rank correlation. The χ² test (chi-square test) was used to compare the frequency of high IVCD between the patient groups. Statistical significance was defined by P ≤ .05.

RESULTS

Patients with INIDCM and idiopathic dyspnea had similar mean age, mean systolic blood pressure, and similar results of electrolyte and thyroid function tests (Table 1; thyroid function test data not shown). At initial evaluation, mean LVDV and plasma BNP levels were higher for patients with INIDCM than idiopathic dyspnea (Table 1). At 3-month follow-up, mean BNP level was significantly decreased in both groups but remained elevated (≥ 450 ng/L) in all patients who had INIDCM (Table 1). The initial mean LVEF was lower in patients with INIDCM than idiopathic dyspnea (Table 1), and this difference was independent of age, sex, hypertension, and diabetes. All 33 patients with INIDCM had LVEF < 45% and all 39 patients with idiopathic dyspnea had LVEF > 45% (Table 1). There was a significant negative correlation between BNP and LVEF in patients with INIDCM but not idiopathic dyspnea (Table 1 and Figure 1).

High IVCD (QRS complex > 120 ms) was significantly more frequent in patients with INIDCM than idiopathic dyspnea, and most patients with high IVCD had hypertension and diabetes mellitus (Tables 1 and 2). All patients who had high IVCD were aged > 55 years (Table 2). In the patients with INIDCM, patients who had high IVCD had greater mean BNP (initial and 3-mo follow-up) and lower LVEF than patients who had low IVCD (Table 2). The most common type of IVCD was left anterior hemiblock, and mean BNP level varied/did not vary with type of IVCD was greater in patients who had left bundle branch block than left anterior hemiblock (Table 3).

DISCUSSION

The present study confirmed the results of previous studies that showed increased plasma BNP levels in patients who have
heart failure. Patients who had INIDCM had higher mean LVDV, higher mean plasma BNP, lower mean LVEF, and higher frequency of IVCD than patients who had idiopathic dyspnea (Table 1). In addition, patients with INIDCM who had high IVCD had greater mean BNP levels than patients who had low IVCD (Table 2).

Although INIDCM typically presents with progressive congestive heart failure, initial laboratory analysis of INIDCM may be unremarkable except for elevated plasma BNP. The diagnosis of INIDCM may be delayed because of additional invasive and non-invasive procedures required for diagnosis, such as transthoracic echocardiogram and cardiac magnetic resonance imaging. However, elevated BNP levels may increase the index of suspicion for the diagnosis of INIDCM. In addition, the present findings that high IVCD is frequent in INIDCM also may be helpful diagnostically.

Although BNP may be isolated from brain tissue, the ventricular myocardium is the main source of BNP [20].

### Table 1: Demographic, Clinical, and Cardiac Parameters in Patients Who Had Idiopathic Nonischemic Dilated Cardiomyopathy and Idiopathic Dyspnea*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>INIDCM (QRS &gt; 120 ms)</th>
<th>Idiopathic dyspnea (QRS ≤ 120 ms)</th>
<th>P ≤ †</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>33</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>53 (35 to 71)</td>
<td>48 (22 to 70)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>19/14</td>
<td>20/19</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 (102 to 128)</td>
<td>113 (106 to 124)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 (62 to 78)</td>
<td>68 (60 to 74)</td>
<td>.001</td>
</tr>
<tr>
<td>Heart rate, resting (beats per min)</td>
<td>112 (110 to 130)</td>
<td>69 (62 to 79)</td>
<td>.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (46)</td>
<td>15 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (27)</td>
<td>10 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>New York Heart Association class (I/II/III/IV)</td>
<td>III</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Laboratory studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140 (136 to 144)</td>
<td>139 (137 to 141)</td>
<td>.02</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>1.0 (0.6 to 1.2)</td>
<td>0.7 (0.5 to 0.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42 (38 to 44)</td>
<td>44 (42 to 46)</td>
<td>.001</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/L)</td>
<td>0.8 (0.5 to 1.2)</td>
<td>1.2 (0.7 to 2.0)</td>
<td>.001</td>
</tr>
<tr>
<td>LVDV (mL)</td>
<td>151 (115 to 225)</td>
<td>70 (60 to 85)</td>
<td>.001</td>
</tr>
<tr>
<td>BNP (ng/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>947 (750 to 1980)</td>
<td>43 (20 to 80)</td>
<td>.001</td>
</tr>
<tr>
<td>3-mo follow-up</td>
<td>505 (450 to 750)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>P ≤ (initial vs 3 mo)†</td>
<td>.001</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 (20 to 30)</td>
<td>62 (55 to 70)</td>
<td>.001</td>
</tr>
</tbody>
</table>

### Table 2: Relation Between High and Low Intraventricular Conduction Delay and Cardiac Functional Parameters in Patients Who Had Idiopathic Nonischemic Dilated Cardiomyopathy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High IVCD (QRS &gt; 120 ms)</th>
<th>Low IVCD (QRS ≤ 120 ms)</th>
<th>P ≤ †</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>10 (30)†‡</td>
<td>23 (70)</td>
<td>.001</td>
</tr>
<tr>
<td>Comorbidities (no. [%] patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (100)</td>
<td>5 (22)</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (90)</td>
<td>0 (0)</td>
<td>.001</td>
</tr>
<tr>
<td>Left ventricular volume (cm³)</td>
<td>163 (120 to 225)</td>
<td>146 (115 to 175)</td>
<td>NS</td>
</tr>
<tr>
<td>BNP (ng/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>1305 (980 to 1980)</td>
<td>793 (750 to 830)</td>
<td>.001</td>
</tr>
<tr>
<td>3-mo follow-up</td>
<td>592 (480 to 750)</td>
<td>467 (450 to 480)</td>
<td>.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24 (20 to 26)</td>
<td>28 (25 to 70)</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Data reported as number (%) or mean (range, minimum to maximum). Abbreviations: BNP, B-type natriuretic peptide; INIDCM, idiopathic nonischemic dilated cardiomyopathy; IVCD, intraventricular conduction delay; LVDV, left ventricular diastolic volume; LVEF, left ventricular ejection fraction † NS, not significant (P > .05) ‡ Patients with high IVCD: 5 men and 5 women; mean age, 64 y; age range, 56 to 71 y.

**Figure 1** Relation between left ventricular ejection fraction (LVEF) and B-type natriuretic peptide (BNP) level in patients who had idiopathic dyspnea (A) or idiopathic nonischemic dilated cardiomyopathy (B).
present patients had increased LVDV and decreased LVEF, consistent with previous findings that BNP is synthesized, stored, and secreted by ventricular myocytes in response to ventricular stretch and wall stress [21]. The directly proportional response of BNP level to ventricular stretch is evidence that BNP may be a potentially useful marker in facilitating the diagnosis of INIDCM.

The present findings of high plasma BNP in patients who have INIDCM extends previous observations that showed high BNP levels in ischemic cardiomyopathy. The BNP level may be associated with different degrees of severity of congestive heart failure [22]. Previous studies showed low mean BNP levels in patients without congestive heart failure (23 ng/L), and mean BNP level was increased with increased severity of heart failure (New York Heart Association class, mean BNP level: class I, 149 ng/L; class II, 385 ng/L; class III, 614 ng/L; and class IV, 858 ng/L) [22,23]. With a cutoff of 100 ng/L, the plasma BNP level is useful in the diagnosis of class IV heart failure (symptoms at rest), with high negative predictive value (> 98%) and sensitivity (96%) [8]. In the present patients, the mean plasma BNP level initially was > 9-fold higher than the diagnostic threshold of 100 ng/L and remained elevated at 3 months after initial evaluation (Table 1).

A previous study showed that plasma BNP level may be more accurate in diagnosing ischemic congestive heart failure than clinical history, symptoms, physical examination, chest radiography, and electrocardiography [24]. The availability of plasma BNP levels may potentially decrease the failure to make the diagnosis of ischemic congestive heart failure in an emergency department [24]. The present study demonstrates the utility of BNP levels in patients without cardiac ischemia.

Ischemic cardiomyopathy causes regional wall involvement and predictable necrosis and scarring that may progress from the subendocardium to epicardium in a specific coronary vascular region [23,25]. However, INIDCM has a predilection for scarring in the mid-myocardium and epicardium [26]. Histologic findings in INIDCM may include interstitial or replacement fibrosis, myocyte disarray, and membrane abnormalities [27-30]. Fractionated recorded electrical activity in patients with INIDCM may be caused by nonuniform anisotropic conduction through myocardium separated by fibrous tissue [31]. This may have been the cause of frequent high IVCD in the present patients who had INIDCM (Table 1).

The BNP level may be elevated in isolated diastolic dysfunction detected by echocardiography [32,33]. Some patients may have normal LVEF associated with increased ventricular pressures and BNP levels in heart failure caused by abnormal diastolic function. The mean plasma BNP level was higher in the present patients with INIDCM than previous reports in patients with acute myocardial infarction [34], possibly because myocardial infarction may be localized to a smaller myocardial region whereas INIDCM may affect most ventricular myocytes. In the present study, BNP levels in INIDCM were similar to those previously reported for class IV heart failure, consistent with the global character of INIDCM and the sensitivity of BNP to reflect ventricular dysfunction, either ischemic or non-ischemic.

The frequent finding of high IVCD in patients who had INIDCM (Table 1) may be useful diagnostically, especially because high IVCD was associated with higher BNP levels and lower LVEF than low IVCD (Table 2). The diffuse myocardial involvement in INIDCM may be associated with progressive concomitant disease of Purkinje fibers, causing left bundle branch block and IVCD. The present patients with high IVCD may have had more advanced INIDCM associated with hypertension, diabetes mellitus, and higher plasma BNP levels than patients with low IVCD (Table 2).

Limitations of the present study included the small sample size of patients from 1 institution, which may limit the potential to generalize the findings to other types of medical centers. Furthermore, clinical information was limited to cardiac history, but increased plasma BNP may occur in other conditions such as subarachnoid hemorrhage [35]; therefore, INIDCM is not the only cause of elevated BNP, and caution must be exercised in the interpretation of elevated plasma BNP levels. In addition, no data were provided about treatment and clinical follow-up, which may limit the interpretation of the follow-up BNP levels at 3 months. Future studies may determine whether BNP levels may be useful in monitoring the efficacy of treatment and predicting prognosis. A previous study showed that increased BNP levels may decrease before implantation of implantable cardioverter-defibrillators [36], but long-term follow-up studies are important to determine the relation between treatment and longitudinal BNP levels in patients who have INIDCM.

In summary, the present study showed that patients who had INIDCM had higher mean LVDV, higher mean plasma BNP levels, lower mean LVEF, and higher frequency of IVCD than patients who had idiopathic dyspnea (Table 1). Patients with INIDCM who had high IVCD had greater mean BNP levels than patients who had low IVCD (Table 2). Elevated initial plasma BNP levels may provide important information about heart failure and may be associated with IVCD in patients who have INIDCM. The absence of signs of ischemic heart disease, elevated BNP and the presence of IVCD may increase the diagnostic suspicion for the presence of INIDCM before confirmatory studies are available such as transhoracic echocardiogram, cardiac magnetic resonance imaging, or coronary angiography.

REFERENCES


19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18: 1440-1463.


34. Dorobantu M, Fruntelata AG, Scafa-Udriste A, Tautu OF. B-Type Natriuretic Peptide (BNP) and Left Ventricular (LV) Function in Patients with ST-Segment Elevation Myocardial Infarction (STEMI). Maedica (Buchar). 2010; 5: 243-249.
