The Efficacy of Brain Natriuretic Peptide Levels in Differentiating Constrictive Pericarditis From Restrictive Cardiomyopathy

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OBJECTIVES
We sought to determine the usefulness of brain natriuretic peptide (BNP) measurements to differentiate constrictive pericarditis (CP) from restrictive cardiomyopathy (RCMP).

BACKGROUND
The differentiation of CP from RCMP may be clinically difficult and often requires hemodynamic assessment. No laboratory marker has been shown to differentiate the two conditions.

METHODS
We measured BNP levels in 11 patients suspected of having either CP or RCMP. All patients had hemodynamic assessment the day of BNP measurements.

RESULTS
Six patients had CP and five patients had RCMP based on established hemodynamic criteria. Both CP and RCMP patients had similar elevation in intracardiac pressures. Despite similar pressures, the mean plasma BNP levels were significantly higher in RCMP compared to CP (825.8 ± 172.2 pg/ml vs. 128.0 ± 52.7 pg/ml, p < 0.001, respectively).

CONCLUSIONS
The BNP levels are significantly elevated in RCMP compared to CP patients; BNP may prove to be a useful noninvasive marker for the differentiation of the two conditions. (J Am Coll Cardiol 2005;45:1900–2) © 2005 by the American College of Cardiology Foundation

Restrictive cardiomyopathies (RCMP) such as amyloidosis and diseases of the pericardium cause impairment of diastolic function of the heart (1). Although etiologies of these diseases and their prognosis differ, they result in common clinical presentation that often leads to difficulty in making a specific diagnosis. In addition to patient history, physical examination, and traditional hemodynamic assessment, clinicians have recently relied on noninvasive techniques such as Doppler echocardiography, computed tomography, and magnetic resonance imaging to differentiate between the two states (1–5). However, there are no readily available blood markers to diagnose these states with a high degree of sensitivity and specificity.

Brain natriuretic peptide (BNP) is a cardiac hormone, synthesized by ventricular myocytes in response to ventricular dysfunction and wall stretch. Plasma BNP levels are increased in congestive heart failure exacerbations, whether due to systolic or diastolic dysfunction (6,7). In constrictive pericarditis (CP) the myocardium is intrinsically normal, and myocardial stretch is prevented by the constraining pericardium. Given that myocardial stretch is the predominant mechanism of BNP release, we postulated that the plasma BNP levels in CP would be low, despite elevated intracardiac pressures (8–10). It has been known that atrial natriuretic peptide is only modestly elevated in cardiac tamponade where there is no myocardial stretch. Thus, it has been speculated that natriuretic peptides may only be modestly elevated in CP as well (11). However, to date there has been no data regarding BNP and CP. The aim of this study was to assess the efficacy and reliability of plasma BNP levels in the differentiation of CP and RCMP.

METHODS
We prospectively enrolled 11 consecutive patients undergoing invasive hemodynamic assessment for the evaluation of CP or RCMP at Loyola University Medical Center during June 2003 to December 2004. Patients being evaluated for CP or RCMP had BNP levels drawn before or immediately after invasive hemodynamic assessment; BNP assay samples were processed and analyzed using the ADVIA Centaur system (Bayer, Tarrytown, New York). All patients who had possible constriction or RCMP and who needed hemodynamic study were eligible for the study. All patients were in New York Heart Association functional class III or IV. Heart transplant recipients or patients suspected of having both CP and RCMP were excluded from the study. All patients underwent left and right heart catheterization as part of clinical workup. When optimal pulmonary capillary wedge pressures (PCWP) could not be obtained, patients underwent transseptal catheterization with measurement of left atrial pressures (LAP). A respirometer was used to monitor respiration during pressure recording. Rapid intravascular volume expansion using 1,000 cc of normal saline at 38°C given over 10 min was used to identify hidden diastolic
filling abnormalities. Fluid challenge expands blood volume, which would demonstrate equalization of diastolic pressure to diagnose occult constriction.

Left ventricular ejection fraction was estimated by either echocardiography or left ventriculography. No medications were held before hemodynamic measurements, and no medications were given during hemodynamic measurements.

The diagnosis of either CP or RCMP was based on the following hemodynamic criteria: elevation and near equalization of all diastolic pressures, absence of inspiratory variation of right atrial pressure (RAP), exaggerated Y descent, and the square root sign on ventricular pressure curves. For the diagnosis of CP, the following criteria were needed: the presence of intracardiac and intrathoracic discor- dance and the presence of ventricular discordance. In addition, when indicated, the CP diagnosis was confirmed at surgery. Hemodynamic data recorded RAP, LAP by transseptal catheterization, pulmonary artery pressure (PAP), PCWP, left ventricular end-diastolic pressure (LVEDP) at plateau, right ventricular end-diastolic pressure, left ventricular ejection fraction.

Continuous data are presented as mean ± SD. All p values were two-sided, with values <0.05 considered significant. Descriptive statistics, Student t tests, and Fisher exact tests were performed to assess the data between CP and RCMP patients. The Institution Research Board Review Committee approved the protocol.

** RESULTS**

Eleven patients had hemodynamic confirmation of either CP or RCMP. Six patients had CP and five had RCMP. Four of the six CP patients had surgical confirmation of the disease and underwent pericardial stripping. Two CP patients refused surgery. All 11 patients had evidence of elevated intracardiac pressures with near equalization of all diastolic pressures. The baseline characteristics and hemodynamic data of the patients are summarized in Tables 1 and 2. There were four men in the CP group and two men in the RCMP group. Five of six CP patients were on a diuretic, and four of five RCMP patients were on diuretic therapy. The majority of CP (four of six) and RCMP (three of five) patients were on angiotensin-converting enzyme inhibitors. The majority of CP patients were also on beta-blockers (four of six) and spironolactones (three of six) while only one patient each was on beta-blockers or spironolactone in the RCMP group. Duration of illness varied in the two groups from months to years.

There was no significant difference in the mean RAP, LAP, LVEDP, and PAP between the two groups (Tables 1 and 2). The mean plasma BNP levels were significantly higher in RCMP compared to CP (825.8 ± 172.2 pg/ml vs. 128.0 ± 52.7 pg/ml, p < 0.001, respectively) (Fig. 1). Median values of BNP were 143 pg/ml (50 to 186 pg/ml) in the CP group and 756 pg/ml (639 to 1,060 pg/ml) in the RCMP group (p < 0.001). The normal range of BNP is 0 to 100 pg/ml.

One patient was excluded in the CP group because he also had severe aortic insufficiency and moderate mitral regurgitation. His BNP was 303 pg/ml with impaired left ventricular ejection fraction of 30%.

** DISCUSSION**

The accurate differentiation of CP versus RCMP constitutes a diagnostic challenge even to experienced clinicians. The clinical signs of diastolic heart failure reflect the degree of systemic and central venous congestion with either subtle

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**Abbreviations and Acronyms**

- BNP = brain natriuretic peptide
- CP = constrictive pericarditis
- LAP = left atrial pressure
- LVEDP = left ventricular end-diastolic pressure
- PAP = pulmonary artery pressure
- PCWP = pulmonary capillary wedge pressure
- RAP = right atrial pressure
- RCMP = restrictive cardiomyopathy

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**Table 1. Patient Characteristics and Hemodynamic Measurements**

<table>
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<tr>
<th>Pt.</th>
<th>Disease</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>BNP (pg/ml)</th>
<th>LAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>RA (mm Hg)</th>
<th>LVEF (%)</th>
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<td>19</td>
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BNP = brain natriuretic peptide; CP = constrictive pericarditis; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NA = not able to measure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RCMP = restrictive cardiomyopathy.
or overt fluid retention. Venous congestion, ascites, pedal edema, dyspnea on exertion, easy fatigability, and occasional orthopnea, which are caused by low cardiac output and increased lung stiffness due to interstitial but not alveolar edema, are found in both disease states. The basic challenge facing clinicians is to reliably distinguish between constriction’s ventricular filling impairment from pericardial constraint versus restriction’s ventricular filling impairment from impaired relaxation and decreased compliance in the face of overlapping signs and symptoms of congestion, and frequently nondiscriminating test results.

Our study is the first to use a readily available blood marker to differentiate constriction versus restriction among patients presenting with diastolic heart failure. Our study provides a novel observation that the level of BNP is elevated in patients with restriction while it is nearly normal in those with constriction. While there has been a study to show that plasma levels of BNP and BNP receptors are elevated in patients with RCMP, there was no data demonstrating the usefulness of BNP measurement in differentiating constriction from restriction (10,12). Although atrial natriuretic peptide is known to be modestly increased in patients with CP compared to congestive heart failure from other etiology, there has not been direct comparison between CP versus RCMP (11). Our data demonstrates that plasma BNP are “nearly normal” in patients with constrictive physiology of heart failure, and are grossly elevated in patients with restrictive physiology of heart failure despite nearly identical clinical and hemodynamic presentation. Although our patients had similar degrees of congestion, and nearly the same intracardiac pressure overload, their BNP response was strikingly different, which means that their underlying pathophysiologic mechanism of BNP release or BNP kinetics are different in constriction as opposed to restriction. It has been postulated that despite identical intracardiac diastolic pressures, the transmural distending pressure and forces are distinctly different between the two. In constriction, the intracardiac distending pressure is effectively counterbalanced by a stress force of thickened and constricting pericardium. The absence of cardiac stretch causes a decrease in the transmural wall tension that may lead to lower BNP release. Based on our data, BNP may be useful as a point-of-care triage in patients in whom diagnosis of CP or RCMP is difficult. As seen in our study, four of six CP patients received angiotensin-converting enzyme inhibitors and beta-blockers, which may be harmful in patients with CP.

Our study is limited by small sample size. We have excluded from our study patients with combined constrictive/restrictive pathologies such as heart transplant patients and patients with history of radiation-induced cardiomyopathies. We also excluded patients with concomitant valvular disease. These patients must be studied separately to determine if BNP has any meaningful diagnostic role for them. In our study we only measured BNP. A larger multicenter registry is needed to determine sensitivity, specificity, predictive accuracy, and limitations of plasma BNP levels in differentiating constriction from restriction.

Table 2. Hemodynamic Measurements Between CP and RCMP

<table>
<thead>
<tr>
<th>Group</th>
<th>CP</th>
<th>RCMP</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>LAP (mm Hg)</td>
<td>28.6 ± 7.2</td>
<td>30.3 ± 3.2</td>
<td>0.69</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>24.5 ± 3.2</td>
<td>26.6 ± 7.6</td>
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<td>PAP (mm Hg)</td>
<td>33.0 ± 9.6</td>
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<td>RAP (mm Hg)</td>
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<td>21.2 ± 8.0</td>
<td>0.97</td>
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<td>PCWP (mm Hg)</td>
<td>31.0 ± 8.3</td>
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<td>0.70</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60.0 ± 0.0</td>
<td>49.0 ± 13.4</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data is presented as mean ± standard deviation with 95% confidence interval. Abbreviations as in Table 1.

Figure 1. Mean brain natriuretic peptide (BNP) levels (pg/ml) in constrictive pericarditis (CP) and restrictive cardiomyopathy (RCMP) patients (p < 0.001). Open bar = CP; solid bar = RCMP.

REFERENCES