permanent device implantation. We believe this system can be readily implemented in such clinical scenarios.

*Paul C. Zei, MD, PhD
*Cardiac Arrhythmia Service
75 Francis Street
Brigham and Women's Hospital
Boston, Massachusetts 02115
E-mail: pzei@partners.org

Robert E. Eckart, DO
Laurence M. Epstein, MD

REFERENCES

Brain Natriuretic Peptide Levels in Constrictive Pericarditis and Restrictive Cardiomyopathy

To the Editor: Constrictive pericarditis (CP) often is a challenging diagnosis despite sophisticated modalities (1–4). If a simple test could alert physicians to the possibility of CP in patients with evidence of heart failure, it would be valuable.

Recent data (5) suggest that brain natriuretic peptide (BNP), released in response to cardiac stretch (6), is normal or only minimally elevated in patients with CP and more elevated in patients with restrictive cardiomyopathy (RCMP). However, there are a variety of etiologies for CP. Many patients at our institution present after either mantle chest radiation and/or open heart surgical procedures (7). These patients may have additional myocardial damage that could raise BNP even when concomitant CP is present. To determine whether BNP levels in all patients with CP are different from those with restriction, we studied patients with well-documented CP and RCMP. We separated patients with CP into those with idiopathic disease and with CP due to secondary causes.

We reviewed 22 patients with surgically confirmed CP where BNP was measured pre-operatively. Patients were divided into those with idiopathic CP or secondary CP if there had been previous cardiac surgery or chest radiation. We identified patients with RCMP who had appropriately timed BNP values as a comparison group. The diagnosis of RCMP was made according to criteria by Hurrell et al. (4). These patients also had characteristic echocardiographic findings. The diagnosis of CP was confirmed at surgery.

Two-dimensional echocardiographic examinations were performed as previously reported (8); BNP measurements were performed with the Biosite assay (La Jolla, California) close to the time of the echocardiographic examinations and before surgical pericardectomy. The interval between echocardiogram and BNP measurement was 1.3 ± 7.4 days, and in all patients except 6, the interval was 1 day.

Summary statistics are presented as frequencies (percentages) for categorical variables, as mean ± SD for the normal variables, and as median and first and third quartile (Q1, Q3) for skewed variables. The normal distribution of the variables was verified performing the Shapiro-Wilk W test. Only BNP was very right skewed. Log10-transformed values of BNP (Log10BNP) were used in the analysis to obtain a normal distribution of the values. Categorical variables were compared by Fisher exact test, continuous normal variables by analysis of variance (followed by Tukey's HDS post-test). All tests were two-sided, and for all analyses p < 0.05 was considered statistically significant. Data were analyzed with JMP Version 5 (SAS Institute Inc., Cary, North Carolina).

Twenty-two patients had surgically confirmed CP, 11 patients had idiopathic CP, and 11 secondary CP (8 with previous cardiac surgery and 3 with radiation therapy). They were compared to 11 patients with RCMP. Patient characteristics are reported in Table 1. There were no significant differences among groups. Median BNP was 80 (44 to 193) ng/l for idiopathic CP, 278 (118 to 526) ng/l for secondary CP, and 499 (361 to 606) ng/l for RCMP. The Log10-BNP was 1.9 ± 0.3 ng/l for idiopathic CP, 2.4 ± 0.3 ng/l for secondary CP, and 2.7 ± 0.2 ng/l for RCMP. There was a statistically significant difference between the BNP values with idiopathic CP and RCMP (p < 0.05) and between patients with idiopathic CP and those with secondary CP (p < 0.05). There were no significant differences in BNP between patients with secondary CP and RCMP (Fig. 1).

All patients with BNP <150 ng/l had CP. Higher BNPs were seen in patients with secondary CP and RCMP. The only differentiating finding with RCMP was a BNP >650 ng/l, which did not occur with CP.

Our data confirm and extend those recently published (5). Brain natriuretic peptide levels were significantly lower in patients with idiopathic CP than those with RCMP. However, BNP is not significantly different in patients with CP secondary to previous
cardiac surgery or radiation compared to those with RCMP. Thus, BNP is a useful non-invasive marker to distinguish CP from RCMP when CP is not due to a secondary cause. Relatively normal BNP values in the setting of increased jugular venous pressure should point to a diagnostic possibility of CP.

The findings of higher BNP values in secondary constriction are important given in the modern era, previous cardiac surgery and/or radiation and RCMP. Relatively normal BNP levels in cases of idiopathic CP, compared to those with CP after surgery and/or radiation and RCMP. Relatively normal BNP levels in patients with right-sided heart failure should raise the suspicion of CP. Higher levels cannot distinguish between CP and RCMP, especially in patients with secondary CP.

In conclusion, BNP levels are significantly lower in patients with idiopathic CP, compared to those with CP after surgery and/or radiation and RCMP. Relatively normal BNP levels in patients with right-sided heart failure should raise the suspicion of CP. Higher levels cannot distinguish between CP and RCMP, especially in patients with secondary CP.

The results of our study are important in clinical practice. The differentiation of CP from RCMP can be more readily made in cases of idiopathic CP versus pure RCMP. However, in those cases of mixed myocardial and pericardial disease, the differential diagnosis becomes more difficult.

Our study was a retrospective study with a modest-sized cohort of non-consecutive patients. Hemodynamic data taken proximate to the BNP values were not uniformly available.

In conclusion, BNP levels are significantly lower in patients with idiopathic CP, compared to those with CP after surgery and/or radiation and RCMP. Relatively normal BNP levels in patients with right-sided heart failure should raise the suspicion of CP. Higher levels cannot distinguish between CP and RCMP, especially in patients with secondary CP.

Luciano Babuin, MD
Jorge R. Alegria, MD
Jae K. Oh, MD
Rick A. Nishimura, MD
*Allan S. Jaffe, MD

*Cardiovascular Division
Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905
E-mail: Jaffe.Allan@Mayo.edu

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Please note: Dr. Jaffe consults for many companies that make BNP assays and has both research grants and consultanthips with them, including Roche, Duke, and Beckman. In addition, he is a consultant for Abbott, Ortho, DiaDexus, and Sensera, all of whom make BNP assays. Of note, the BNP assay used in this study was not made by any of those companies. Drs. Babuin and Alegria contributed equally to this report.

REFERENCES


Table 1. Baseline Characteristics in the Patients With CP Idiopathic, CP Secondary, and RCMP

<table>
<thead>
<tr>
<th></th>
<th>CP Idiopathic (n = 11)</th>
<th>CP Secondary (n = 11)</th>
<th>RCMP (n = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), mean ± SD</td>
<td>51.7 ± 11.1</td>
<td>62.0 ± 10.3</td>
<td>58.8 ± 10.2</td>
<td>0.080</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>3 (27.3)</td>
<td>2 (18.2)</td>
<td>5 (45.4)</td>
<td>0.515</td>
</tr>
<tr>
<td>Pericardiectomy, n (%)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>30.5 ± 5.3</td>
<td>27.6 ± 4.2</td>
<td>29.1 ± 6.0</td>
<td>0.451</td>
</tr>
<tr>
<td>HR (beats/min), mean ± SD</td>
<td>85.9 ± 13.2</td>
<td>76.3 ± 16.9</td>
<td>76.0 ± 15.7</td>
<td>0.242</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean ± SD</td>
<td>113.4 ± 21.0</td>
<td>112.1 ± 13.8</td>
<td>118.0 ± 17.7</td>
<td>0.676</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean ± SD</td>
<td>70.1 ± 9.9</td>
<td>67.4 ± 11.5</td>
<td>69.2 ± 7.2</td>
<td>0.810</td>
</tr>
<tr>
<td>Ejection fraction (%), mean ± SD</td>
<td>54.0 ± 8.8</td>
<td>52.4 ± 8.4</td>
<td>55.6 ± 11.4</td>
<td>0.730</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²), mean ± SD (n)</td>
<td>2.7 ± 0.9 (9)</td>
<td>2.6 ± 0.8 (11)</td>
<td>2.5 ± 0.7 (10)</td>
<td>0.819</td>
</tr>
<tr>
<td>BNP (ng/l), median (Q1–Q3)</td>
<td>80 (44–193)</td>
<td>278 (118–526)</td>
<td>499 (361–606)</td>
<td></td>
</tr>
<tr>
<td>Log10-BNP (ng/l), mean ± SD</td>
<td>1.9 ± 0.3</td>
<td>2.4 ± 0.3*</td>
<td>2.7 ± 0.2*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. CP idiopathic.

BMI = body mass index; BNP = brain natriuretic peptide; CP = constrictive pericarditis; HR = heart rate; RCMP = restrictive cardiomyopathy.
Persistence of Neointimal Growth 12 Months After Intervention and Occurrence of Delayed Restenosis in Patients With Left Main Coronary Artery Disease Treated With Drug-Eluting Stents

To the Editor: Although long-term follow-up after drug-eluting stent (DES) implantation shows a sustained clinical benefit in several registries and randomized trials (1), little is known about the mechanism of action of DES on neointimal proliferation which has supported the concern that late restenosis (i.e., occurring beyond six months) might occur in humans (2).

The mechanism of action of DES on neointimal proliferation seems to be partially explained by a delay in vascular response, which has supported the concern that late restenosis (i.e., occurring beyond six months) might occur in humans.

This would be of clinical relevance especially for patients receiving DES implantation for the treatment of left main coronary artery (LMCA) disease, in whom restenosis is considered a major, and potentially fatal, complication after percutaneous intervention.

Up to March 6, 2004, a total of 110 consecutive patients were treated exclusively with one or more DES in the LMCA as part of an elective or non-elective revascularization procedure at our institution. Seventy-three patients received 6-month angiographic follow-up, of whom 15 underwent paired angiographic measures at 12 months, which was not preceded by target vessel reintervention, and constitute the patient population of the present report.

Quantitative angiographic analyses were performed with the use of edge-detection techniques (CAAS II, Pie Medical, Maastricht, the Netherlands). Binary restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion. Late loss was defined as the minimal lumen diameter (MLD) immediately after the index procedure minus the MLD at angiographic follow-up.

Continuous variables are shown as median and interquartile range and were compared using Wilcoxon test or a general liner mixed model followed by post-hoc analysis after log transformation. Probability was significant at a level of <0.05.

The characteristics of the study population (Table 1) did not differ with respect to the patients receiving no or six-month angiographic follow-up only.

The reason for repeating a second coronary angiogram included risk-stratification before non-cardiac major surgery in three (Patients #1, #6, and #14), evidence of inducible ischemia at non-invasive stress test in two (Patients #4 and #15), a staged procedure for the treatment of the right coronary artery in one (Patient #13), and the willingness to repeat a second coronary angiogram in the remaining nine after counselling about the potential consequence of in-stent restenosis at the time of the index procedure. No major adverse cardiovascular event previously occurred in this cohort of patients, and all except one were asymptomatic at the time of repeated catheterization.

Quantitative coronary analysis on paired measurements in the main treated branch (i.e., LMCA or LMCA and the proximal tract of the left anterior descending artery) is shown in Table 1. When all intervened coronary segments were cumulatively considered (n = 20), including the stented proximal tract of the circumflex artery in five patients receiving bifurcation stenting, the MLD decreased from 2.78 (2.49 to 2.95) after the procedure to 2.44 mm (2.07 to 3.09) (p = 0.37) and 2.25 (1.85 to 2.70) (p = 0.005 vs. post-procedure and p = 0.054 vs. 6-month) at 6 and 12 months, respectively. The late loss (mm) increased from 0.29 (0.07 to 0.4) at 6 months to 0.63 (0.37 to 0.76) after 12 months (p < 0.001) (Fig. 1). Cumulatively, Patient #13, presenting with mild intimal hyperplasia at 6 months, received a target vessel revascularization at 12 months due to severe focal in-stent restenosis in the mid-shaft of the LMCA (Fig. 1C), while a focal restenosis in the ostium of the circumflex artery detected at 12-month follow-up in Patient #2 was left untreated due to normal coronary reserve at non-invasive nuclear stress imaging.

Previous serial angiographic analyses showed that intimal hyperplasia peaks after 12 to 16 weeks after intervention and that restenosis rarely occurs beyond 3 months after bare metal stent implantation (3). These observations justify current practice to perform angiographic follow-up six to eight months after percutaneous coronary revascularization, when the intimal growth has ceased and the net lumen gain is likely to be maintained over time. Indeed, a partial regression of the in-stent intimal hyperplasia at longer-term follow-up in patients receiving bare metal stents has been reported (3).

When exactly neointima growth after DES implantation begins to subside remains largely unknown, but based on experimental findings, a late catch up phenomenon has been hypothesized (2). Of some concern is the fact that similar argumentations have been previously raised after intravascular brachytherapy, based on findings on animals, which were subsequently confirmed in humans (4). In the longest available angiographic follow-up after DES implantation, neointimal growth has been shown to mildly non-significantly progress beyond one year (1). Whether this would result in delayed restenosis remained unclear.

In our small series of patients undergoing serial angiographic monitoring, a significant increase of late loss between 6 and 12 months was noted, and, more importantly, one patient developed late in-stent restenosis of the LMCA, which necessitated reintervention.

Our preliminary findings raise several unanswered questions. This study was not pre-specified, as it was urged by the one-year