Plasma Brain Natriuretic Peptide to Detect Preclinical Ventricular Systolic or Diastolic Dysfunction

A Community-Based Study

Margaret M. Redfield, MD; Richard J. Rodeheffer, MD; Steven J. Jacobsen, MD, PhD; Douglas W. Mahoney, MS; Kent R. Bailey, PhD; John C. Burnett, Jr, MD

Background—Preclinical systolic or diastolic dysfunction is associated with increased morbidity and mortality. We postulated that plasma brain natriuretic peptide (BNP) might serve as a biomarker for preclinical ventricular dysfunction (PCVD) but that the discriminatory values for BNP may vary with age and sex.

Methods and Results—We measured BNP, systolic and diastolic ventricular function, and clinical parameters in 2042 randomly selected residents of Olmsted County, Minn, aged 45 years or older. For preclinical systolic dysfunction, the areas under the receiver operating characteristics curve were higher for those with more severe (0.82 to 0.92) than any (0.51 to 0.74) systolic dysfunction and were similar in men and women and in younger and older persons. For preclinical diastolic dysfunction, the areas under the receiver operating characteristics curve were higher for those with moderate-to-severe (0.74 to 0.79) than any (0.52 to 0.68) diastolic dysfunction and were similar regardless of age or sex. Optimal discriminatory values of BNP varied with age and sex. Considering the prevalence of preclinical systolic or diastolic dysfunction and the predictive characteristics observed, using BNP to screen for PCVD would necessitate echo in 10% to 40% of those screened, with most confirmatory echocardiograms being negative, and would miss 10% to 60% of those affected.

Conclusions—BNP is a suboptimal screening test for PCVD in the population. (Circulation. 2004;109:3176-3181.)

Key Words: natriuretic peptides ▶ ventricular dysfunction ▶ diastole ▶ systole ▶ diagnosis

Preclinical systolic dysfunction is common in the population and is associated with progression to heart failure (HF) and increased mortality. Half of patients with HF have normal ejection fraction (EF), with diastolic dysfunction as the presumed cause of HF symptoms in these patients. In the community, diastolic dysfunction is common and is predictive of HF and death. Although more data are needed before screening for and treatment of preclinical ventricular dysfunction (PCVD) can be recommended in the community, an adequate screening test is needed before efficacy of screening strategies can be evaluated.

As recently summarized, several studies have evaluated the predictive characteristics of BNP for detecting preclinical systolic dysfunction in different settings and with different conclusions. Although a study in a clinical population suggested that BNP may have value for detection of diastolic dysfunction, no study has evaluated BNP for the detection of preclinical diastolic dysfunction in the general population.

In the present study, we assessed the ability of BNP to detect preclinical systolic or diastolic dysfunction in the population and in a high-risk subset (age ≥65 years and with known cardiovascular disease). Because BNP is higher in female subjects and increases with age among subjects without cardiovascular disease, we also sought to determine if age and sex influence the predictive characteristics or discriminatory value of BNP. Finally, the implications of the predictive characteristics of BNP for screening were explored, accounting for the prevalence of PCVD in the population.

Methods

The Mayo Foundation Institutional Review Board approved this study.

Study Setting

Using the resources of the Rochester Epidemiology Project, a random sample of Olmsted County, Minn, residents age ≥45 years was identified. The characteristics of the Olmsted County, Minn, population, the unique aspects of epidemiological research in this population, and the methodologies used in identifying this cohort have been described previously.

Medical Record Review

Community medical records were reviewed by trained nurse abstractors to determine if participants had a history of hypertension,
myocardial infarction, coronary artery disease, diabetes mellitus, or HF (Framingham criteria), as previously described. Subjects without a validated HF diagnosis but with ventricular dysfunction were considered to have PCVD, as previously described. A high-risk subset of the population was defined as subjects age ≥65 years who had a recognized diagnosis of cardiovascular disease (hypertension or coronary artery disease).

Doppler Echocardiography
The echocardiographic methods used in this study have been previously described in detail. EF was measured by M-mode, quantitative 2D, and semiquantitative 2D (visual estimate) methods in each subject. Correlation among methods was excellent. The baseline characteristics of the study sample and the high-risk subgroup are shown in Table 1. Subjects with HF or with ventricular dysfunction were excluded from the remainder of the analysis. Multivariable associations of log BNP with age, sex, and EF as well as age, sex, and diastolic dysfunction were assessed using least-squares regression. Potential interactions of age and sex with EF and diastolic dysfunction were also evaluated when considering the association of these variables with BNP. Receiver operating characteristics (ROC) analyses were used to assess the predictive accuracy of BNP for detecting EF ≥50%, EF ≤40%, any diastolic dysfunction, and moderate-to-severe diastolic dysfunction and were compared using the method of DeLong et al. The optimal cutoff for each end point was the corresponding BNP that resulted in a sensitivity and specificity closest in distance to the point of a perfect marker (ie, sensitivity of 100% and specificity of 100%).

Results
The baseline characteristics of the study sample and the high-risk subgroup are shown in Table 1. Subjects with HF were excluded from the remainder of the analysis.

Impact of Age and Sex on the Relationship Between BNP and PCVD
The distribution of BNP according to the level of EF and age or sex is shown in Figure 1. The distribution of BNP was shifted upward as EF decreased in older (≥65 years of age) persons (r = −0.144, P < 0.0001) and in men (r = −0.202, P < 0.0001), but this relationship was not observed in younger persons (r = 0.058, P = 0.052) or in women (r = 0.004, 0.202).
of EF

confidence intervals for the estimated AUC for the detection
area under the ROC curves (AUC) and the upper and lower
according to age and sex in the population are shown. The
systolic (Figure 3) and diastolic (Figure 4) dysfunction

The results of ROC analysis for the detection of preclinical

Receiver Operating Characteristics Analysis

The results of ROC analysis for the detection of preclinical systolic (Figure 3) and diastolic (Figure 4) dysfunction according to age and sex in the population are shown. The area under the ROC curves (AUC) and the upper and lower confidence intervals for the estimated AUC for the detection of EF ≤50% and EF ≤40% are displayed. Among all subgroups, the AUC was higher for the detection of EF ≤40% than for detection of EF ≤50%. The AUC for detection of EF <50% was similar in older and younger persons (P=0.99) and in men and women (P=0.475). The AUC for detection of EF <40% was again similar regardless of age group (P=0.428) and sex (P=0.334). Among all subgroups, the AUC was higher for the detection of moderate or severe diastolic dysfunction than for detection of any diastolic dysfunction. The AUC for detection of any diastolic dysfunction was similar between older and younger persons (P=0.922) and between men and women (P=0.774). The AUC for detection of moderate or severe diastolic dysfunction was similar regardless of age group (P=0.550) and sex (P=0.560).

Figure 1. Distribution of log BNP according to systolic function and sex or age. Top, Plots of the 5th and 95th (vertical lines), 25th and 75th (boxes), and 50th (horizontal line) percentile values for log BNP in female (left) and male (right) subjects with EF >50%, ≤50%, or ≤40%. Bottom, Similar plots in persons ≥65 years (left) or <65 years of age. Values of BNP <1.0 have been rounded to 1.0.

Figure 2. Distribution of log BNP according to diastolic function and sex or age. Top, Plots of the 5th and 95th (vertical lines), 25th and 75th (boxes), and 50th (horizontal line) percentile values for log BNP in female (left) and male (right) subjects with normal diastolic function (Normal), any diastolic dysfunction (Any DD), or moderate or severe diastolic dysfunction (Mod-Severe DD). Bottom, Similar plots in persons ≥65 years (left) or <65 years of age. Values of BNP <1.0 have been rounded to 1.0.

Figure 3. AUC for detection of variable degrees of systolic dysfunction according to age and sex. AUC (solid line) and 95th percentile confidence intervals (boxes) are shown for the detection of EF ≤50% (top) or EF ≤40% (bottom) according to age and sex. Light gray line indicates the line of no information (AUC=0.50). yrs indicates years of age.
In the total population without HF, 7.5% had "any" significant ventricular dysfunction, defined as EF ≤40% or moderate-to-severe diastolic dysfunction. The AUC for detection of any significant preclinical dysfunction was 0.79 (0.75 to 0.84), with an optimal BNP partition value of 25.9 pg/mL, having a sensitivity of 62% and a specificity of 63%. Using the age- and sex-adjusted normal BNP values for the partition values yielded a sensitivity of 44% and a specificity of 91%. The AUC was similar in men (0.82) and women (0.79) and in the high-risk group (0.74).

In the high-risk subgroup (n=396), the AUC for the detection of EF ≤40% was 0.82 (confidence interval, 0.71 to 0.93) in men and 0.74 (no confidence interval available) in women. Because of low prevalence of EF ≤40% in women, the AUC for the detection of moderate or severe diastolic dysfunction was 0.74 (0.62 to 0.86) in men and 0.73 (0.61 to 0.84) in women.

**Implications for Screening**

The AUCs for detection of EF <50% or mild diastolic dysfunction were consistently <0.70 and likely insufficient to allow their use as a screening test. Thus, we confined our further analysis to use of BNP to detect EF ≤40% or moderate or severe diastolic dysfunction.

The optimal BNP (from ROC analysis) for the detection of EF ≤40% or moderate or severe diastolic dysfunction according to age and sex in the population and in the high-risk group are shown in Tables 2 and 3. The optimal discriminatory BNP was higher in subjects older than age 65 years than in the total population and higher in women than in men both in the total population and in the high-risk group.

The sensitivity and specificity of BNP using the optimal discriminatory BNP or using a discriminatory value based on age- and sex-specific upper normal ranges are shown in Table 2 (for detection of EF ≤40%) and Table 3 (for detection of moderate or severe diastolic dysfunction). The prevalence of PCVD, the positive and negative likelihood ratios, the percentage of subjects screened who would need echocardiography (because of an abnormal BNP), the percent of echocardiograms that would be negative (false-positives), and the percent of those with the abnormality who would be missed (false-negatives) are displayed. The low prevalence of preclinical systolic dysfunction and the observed specificity mean that a large segment of the population screened would need an echocardiogram and that nearly all of these would be negative. Using a more specific discriminatory value based on upper normal value results in the need for fewer confirmatory echo studies but fails to detect at least 30% of those with preclinical systolic dysfunction.

**Table 2. BNP for Detection of Preclinical Systolic Dysfunction: Implications for Screening**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>BNP Partition Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>+LR</th>
<th>−LR</th>
<th>% Screened Needing Echo</th>
<th>% Echos That Are Negative</th>
<th>% With Disease Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical EF ≤40%, partition value based on optimal point on ROC curve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>1.1</td>
<td>54.5</td>
<td>90</td>
<td>76</td>
<td>3.8</td>
<td>0.1</td>
<td>24.2</td>
<td>96.0</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>2.0</td>
<td>75.3</td>
<td>80</td>
<td>72</td>
<td>2.9</td>
<td>0.3</td>
<td>29.3</td>
<td>94.4</td>
</tr>
<tr>
<td>Men</td>
<td>1.9</td>
<td>54.5</td>
<td>88</td>
<td>83</td>
<td>5.2</td>
<td>0.1</td>
<td>18.2</td>
<td>90.9</td>
</tr>
<tr>
<td>Women</td>
<td>0.3</td>
<td>98.5</td>
<td>67</td>
<td>87</td>
<td>5.2</td>
<td>0.4</td>
<td>12.9</td>
<td>98.4</td>
</tr>
<tr>
<td>High-risk men</td>
<td>5.3</td>
<td>66.3</td>
<td>85</td>
<td>73</td>
<td>3.1</td>
<td>0.2</td>
<td>29.1</td>
<td>88.8</td>
</tr>
<tr>
<td>High-risk women</td>
<td>0.6</td>
<td>128.8</td>
<td>50</td>
<td>82</td>
<td>2.8</td>
<td>0.6</td>
<td>17.9</td>
<td>98.6</td>
</tr>
<tr>
<td>Preclinical EF &lt;40%, partition value based on age- and sex-specific upper normal values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>1.1</td>
<td>*</td>
<td>65</td>
<td>87</td>
<td>5.0</td>
<td>0.4</td>
<td>13.2</td>
<td>94.8</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>2.0</td>
<td>*</td>
<td>67</td>
<td>80</td>
<td>3.4</td>
<td>0.4</td>
<td>21.3</td>
<td>93.6</td>
</tr>
<tr>
<td>Men</td>
<td>1.9</td>
<td>*</td>
<td>71</td>
<td>85</td>
<td>4.7</td>
<td>0.3</td>
<td>16.1</td>
<td>91.7</td>
</tr>
<tr>
<td>Women</td>
<td>0.3</td>
<td>*</td>
<td>33</td>
<td>89</td>
<td>3.0</td>
<td>0.8</td>
<td>10.6</td>
<td>99.1</td>
</tr>
<tr>
<td>High-risk men</td>
<td>5.3</td>
<td>*</td>
<td>80</td>
<td>65</td>
<td>2.3</td>
<td>0.3</td>
<td>37.6</td>
<td>88.7</td>
</tr>
<tr>
<td>High-risk women</td>
<td>0.6</td>
<td>*</td>
<td>0</td>
<td>77</td>
<td>0</td>
<td>1.3</td>
<td>23.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

+LR indicates positive likelihood ratio; −LR, negative likelihood ratio.

*Age- and sex-adjusted reference ranges, as previously described.8
For detection of moderate or severe diastolic dysfunction, sensitivity, specificity, and the likelihood ratios are less robust. Using the optimal discriminatory value again results in a large percentage of the screened population requiring an echo, with most being negative and 20% to 40% of those with diastolic dysfunction being missed. Using the more specific upper normal value reduces the number of echocardiograms needed but misses more (40% to 60%) of those with diastolic dysfunction.

### Discussion

Early detection and treatment of PCVD is suggested as an effective strategy to prevent or delay the onset of HF. Such a strategy would mandate screening for PCVD in the general population or high-risk subgroups. The United States Preventive Services Task Force and similar scientific groups advocate the following 3 minimum criteria for assessing screening:

1. Demonstration of the burden of suffering, ie, the prevalence and morbidity/mortality of the disease screened for; (2) an accurate screening test; and (3) evidence that early detection is effective, ie, screening (and subsequent intervention) reduces morbidity and mortality. Although the burden of suffering associated with PCVD has been established, the efficacy and cost of therapy, particularly in the context of a community screening and intervention strategy, remain poorly quantified, and to date, no ideal screening test exists. A few studies have evaluated the performance of BNP for detection of preclinical systolic dysfunction in population-based studies but with different approaches and different conclusions. Our findings on the use of BNP to screen for preclinical systolic dysfunction are similar to those previously reported by Vasan et al in the Framingham Heart Study (FHS) cohort. In that study, the AUCs for BNP to detect moderate-to-severe preclinical systolic dysfunction were 0.79 and 0.85, compared with 0.89 and 0.92 in the present study and women, respectively. These values are also similar to those observed in a small general practice-based study in the United Kingdom and in a smaller population-based study in Germany. In the FHS study and here, the prevalence of moderate-to-severe systolic dysfunction is relatively low (although substantial from a public health standpoint) and raises concerns about the ultimate cost-effectiveness of the test, because relatively large numbers of screened subjects would require echocardiograms. Nielsen et al reported that BNP with follow-up echocardiography was more cost-effective than echocardiography for ruling out systolic dysfunction in a cohort of subjects from the MONICA study. However, many would argue that a “rule-in” strategy is more appropriate when screening for abnormalities in populations with low prevalence. A preliminary analysis of the cost-effectiveness of screening suggested that screening for preclinical systolic dysfunction could be cost-effective in elderly men. However, this analysis did not factor in the impact of repeated screening and relied on clinical trials to estimate benefit of treatment, assumptions that may not be valid in community-based populations. Both the FHS study and the present study suggest that BNP is considerably less accurate for detection of milder degrees of systolic dysfunction, which is more common and also associated with increased risk. A screening tool that does not reliably detect milder levels of systolic dysfunction would limit ability to impact events. Lastly, high

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### Table 3. BNP for Detection of Preclinical Diastolic Dysfunction: Implications for Screening

<table>
<thead>
<tr>
<th>BNP Partition</th>
<th>Prevalence</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>+LR</th>
<th>−LR</th>
<th>% Screened Needing Echo</th>
<th>% Echos That Are Negative</th>
<th>% With Disease Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical moderate-to-severe diastolic dysfunction, partition value based on optimal point on ROC curve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>6.9</td>
<td>36.4</td>
<td>75</td>
<td>69</td>
<td>2.4</td>
<td>0.4</td>
<td>33.6</td>
<td>84.7</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>12.3</td>
<td>58.0</td>
<td>67</td>
<td>69</td>
<td>2.2</td>
<td>0.5</td>
<td>35.0</td>
<td>76.6</td>
</tr>
<tr>
<td>Men</td>
<td>6.7</td>
<td>20.6</td>
<td>81</td>
<td>64</td>
<td>2.2</td>
<td>0.3</td>
<td>38.8</td>
<td>86.0</td>
</tr>
<tr>
<td>Women</td>
<td>7.1</td>
<td>53.1</td>
<td>71</td>
<td>74</td>
<td>2.7</td>
<td>0.4</td>
<td>29.0</td>
<td>82.6</td>
</tr>
<tr>
<td>High-risk men</td>
<td>15.9</td>
<td>113.6</td>
<td>52</td>
<td>93</td>
<td>7.4</td>
<td>0.5</td>
<td>12.3</td>
<td>51.5</td>
</tr>
<tr>
<td>High-risk women</td>
<td>17.5</td>
<td>124.3</td>
<td>41</td>
<td>87</td>
<td>3.2</td>
<td>0.7</td>
<td>16.6</td>
<td>68.4</td>
</tr>
</tbody>
</table>

Preclinical moderate-to-severe diastolic dysfunction, partition value equals age- and sex-specific upper normal value

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>+LR</th>
<th>−LR</th>
<th>% Screened Needing Echo</th>
<th>% Echos That Are Negative</th>
<th>% With Disease Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>6.9</td>
<td>*</td>
<td>41</td>
<td>91</td>
<td>4.6</td>
<td>0.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>12.3</td>
<td>*</td>
<td>47</td>
<td>85</td>
<td>3.1</td>
<td>0.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Men</td>
<td>6.7</td>
<td>*</td>
<td>44</td>
<td>89</td>
<td>4.0</td>
<td>0.6</td>
<td>13.5</td>
</tr>
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<td>Women</td>
<td>7.1</td>
<td>*</td>
<td>39</td>
<td>92</td>
<td>4.9</td>
<td>0.7</td>
<td>10.0</td>
</tr>
<tr>
<td>High-risk men</td>
<td>15.9</td>
<td>*</td>
<td>58</td>
<td>70</td>
<td>1.9</td>
<td>0.6</td>
<td>34.4</td>
</tr>
<tr>
<td>High-risk women</td>
<td>17.5</td>
<td>*</td>
<td>56</td>
<td>84</td>
<td>3.5</td>
<td>0.5</td>
<td>22.7</td>
</tr>
</tbody>
</table>

+LR indicates positive likelihood ratio; −LR, negative likelihood ratio.

*Age- and sex-adjusted reference ranges, as previously described. A preliminary analysis of the cost-effectiveness of screening suggested that screening for preclinical systolic dysfunction could be cost-effective in elderly men. However, this analysis did not factor in the impact of repeated screening and relied on clinical trials to estimate benefit of treatment, assumptions that may not be valid in community-based populations. Both the FHS study and the present study suggest that BNP is considerably less accurate for detection of milder degrees of systolic dysfunction, which is more common and also associated with increased risk. A screening tool that does not reliably detect milder levels of systolic dysfunction would limit ability to impact events. Lastly, high
false-positive rates may lead to poor physician acceptance, which would limit use of screening.

No study has assessed the value of BNP for detection of rigorously defined preclinical diastolic dysfunction in a population-based setting. Doppler assessment of diastolic dysfunction is complex and not routinely performed. A screening test for diastolic dysfunction would aid in identification of such patients, but BNP performed relatively poorly for detection of diastolic dysfunction as well as for the detection of any moderate-to-severe ventricular dysfunction (EF <40% or moderate-to-severe diastolic dysfunction). It should be noted that although the comprehensive Doppler analysis used in the present study has many strengths, it is not an ideal “gold standard” but represents the best available noninvasive assessment of diastolic function and filling pressures.

In the present study, restricting use of BNP testing to a high-risk subgroup of the population would dramatically reduce the number of echocardiograms needed, but at least 90% of follow-up echocardiograms would still be negative when screening for systolic dysfunction, and many (40%) affected subjects would be undetected when screening for diastolic dysfunction.

Importantly, these analyses confirm that the impact of age and sex on BNP observed in subjects without cardiovascular disease is also apparent when the test is applied to subjects with cardiovascular disease. Optimal discriminatory values of BNP for detection of systolic and diastolic ventricular dysfunction vary according to age and sex. Thus, were BNP to be used to screen for PCSD, use of age- and sex-adjusted discriminatory values would be appropriate.

As efforts to decrease the incidence of HF by targeting PCVD proceed, 2 possibilities emerge. Limitations in sensitivity and specificity of BNP could be addressed by targeting only high-risk populations or searching for less-expensive confirmatory tests. Alternatively, new technologies could be used to develop a highly sensitive and specific screening test that is suitable for use in populations with low prevalence of disease. Protein profiling or biomarker panels may provide the high specificity and sensitivity needed for community screening.

In conclusion, although the performance of BNP for detection of moderate-to-severe preclinical systolic dysfunction is comparable with many screening tests, its limited utility for detection of milder systolic dysfunction and for diastolic dysfunction, the high rate of confirmatory testing needed, and the need for age- and sex-specific discriminatory values suggest that the search for a better screening tool should continue.

Acknowledgments

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References

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