Clinical Criteria and Biochemical Markers for the Detection of Systolic Dysfunction

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ABSTRACT

Background: This study was designed to assess the use of clinical criteria and biochemical testing to detect systolic dysfunction. Our goal is to develop strategies that may enhance the detection and treatment of patients with early ventricular dysfunction while reducing the use of echocardiography.

Methods and Results: We compared the predictive characteristics of the plasma brain natriuretic peptide (BNP) concentration with that of a 5-point clinical score derived from elements of the history, electrocardiogram, and chest radiograph in outpatients (n = 466) referred for echocardiography because of symptoms of heart failure or risk factors for systolic dysfunction. Systolic dysfunction was defined as an ejection fraction (EF) less than 45% and was present in 10.9% of patients. By receiver operating characteristic analysis, BNP was sensitive and specific for the detection of systolic dysfunction, with an area under the receiver operating characteristic curve for the detection of EF less than 45% of 0.79. The BNP assay was abnormal in 41% of patients and identified a group with a high prevalence of systolic dysfunction (21% with an EF less than 45%), whereas a normal BNP value identified a group with a low prevalence of systolic dysfunction (4% with an EF less than 45%). The clinical score was positive in 43% of the population and identified a group with a high prevalence of systolic dysfunction (24% with an EF less than 45%). A normal score identified a group with a low prevalence of systolic dysfunction (1% with an EF less than 45%).

Conclusion: This study supports previous studies, which showed that BNP assay predicts systolic dysfunction with acceptable sensitivity and specificity, and it underscores the effectiveness of additional readily available clinical criteria. Both of these strategies should be considered in screening for left ventricular dysfunction in populations at risk while limiting expensive cardiac imaging modalities.

Key words: diagnosis, heart, natriuretic peptide, ventricular function.

Heart failure afflicts 4.8 million people in the United States, with up to 700,000 new cases diagnosed per year (1). Consensus guidelines recommend that echocardiography be performed in patients with symptoms of heart failure (1). This report also acknowledges that up to 20 million people in the United States may have asymptomatic systolic dysfunction and recommends that these patients be treated with angiotensin-converting enzyme inhibitors. However, no guidelines for screening for asymptomatic systolic dysfunction were offered.

Despite the absence of guidelines, screening for systolic dysfunction is ongoing in clinical practice because evaluation of systolic function is one of the most common primary indications for transthoracic echocardiography (2). The number of transthoracic 2-dimensional echocardiograms performed by cardiologists on Medi...
care beneficiaries increased from 212,000 in 1986 to 2.2 million in 1992 and to 2.6 million in 1994. In 1994, the total Medicare reimbursement to cardiologists for echocardiographic procedures was more than $600 million, representing 20% of the total spent on cardiovascular services and the number 1 service provided by cardiologists, ranked by dollars spent.

Concern over cost and global access to echocardiography has led to interest in more cost effective and easily accessible strategies to detect systolic dysfunction, which could help optimize use of health care resources. The most cost effective would incorporate commonly obtained clinical criteria while another would be the use of the emerging availability of plasma brain natriuretic peptide (BNP) as a marker of left ventricular dysfunction. Studies have suggested that BNP is sensitive and specific for the detection of reduced ejection fraction (EF) (3–7). Indeed, the use of BNP to triage patients to echocardiography has been advocated (8).

In the current study, we assessed the ability of clinical and biochemical (BNP assay) criteria to stratify by risk patients referred to echocardiography specifically for assessment of systolic function. Our objective was to determine if either criterion could accurately identify low-risk populations in whom echocardiography could be safely omitted.

### Methods

#### Study Population

The study population comprised 466 consecutive outpatients referred to the Mayo Clinic Echocardiography Laboratory for assessment of systolic function. The reason for referral was identified, and only patients with a primary indication to assess ventricular function were included. The reason for referral was further classified as 1) symptoms of heart failure that included 1 or more of the following: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, edema, or fatigue; or 2) risk factors for systolic dysfunction that included 1 or more of the following: diabetes, coronary artery disease, clinical history of myocardial infarction, hypertension, heavy alcohol use, family history of cardiomyopathy, previous clinical diagnosis of heart failure (without current symptoms), history of chemotherapy with anthracyclines, frequent palpitations, abnormal electrocardiogram, or abnormal chest radiograph. Patients with previously documented left ventricular systolic dysfunction, those known to have a valve prosthesis, native valve disease, congenital heart disease, cardiomyopathy, or renal failure (plasma creatinine concentration more than 2.5 mg/dL), and those referred for evaluation of a cardiac murmur in whom primary valvular disease was suspected or in whom cardiac symptoms were absent, or for evaluation of systemic or extracardiac disease (eg, amyloidosis) were excluded. Just before or after routine echocardiographic study, phlebotomy was performed in the seated position at the echocardiography laboratory. No other postural restrictions were imposed before phlebotomy. Medications were not withheld before the study. This protocol was approved by the Institutional Review Board of the Mayo Foundation, and all patients provided written informed consent.

#### Echocardiography

Transthoracic echocardiographic examinations were conducted in the Mayo Clinic Echocardiography Laboratory as a routine examination by Mayo Clinic Echocardiography Laboratory staff unaware of this study. EF was determined according to previously validated and published techniques that are used routinely in the Mayo Clinic Echocardiography Laboratory and incorporate M-mode and 2-dimensional image analysis (5,9–11). Briefly, in the absence of regional wall motion abnormalities, the midcavity left ventricular dimensions measured from M-mode echocardiograms are used to calculate the EF. If extensive regional wall motion abnormalities are present, endocardial tracing is used in 2 orthogonal axes and the EF is calculated from the modified Simpson formula. In the small proportion of patients in whom orientation of the heart precludes accurate M-mode measurements or endocardial tracing, the EF is estimated by the echocardiologist interpreting the echocardiogram. The presence or absence of other potentially significant echocardiographic findings that may be associated with elevated plasma BNP levels was assessed. Specifically assessed were the presence of an increased left ventricular mass index; regional wall motion abnormality (but normal global systolic function); more than trivial mitral or aortic stenosis; more than moderate mitral, tricuspid, or aortic regurgitation; a TR velocity greater than 2.5 m/s indicating elevation of pulmonary artery systolic pressures; the presence of right ventricular dysfunction; or the presence of a shortened mitral early filling velocity deceleration time (less than 150 ms) suggesting increased left atrial pressures.

#### BNP Assay

Blood for humoral analysis was placed in ethylenediaminetetraacetic acid–treated tubes and immediately placed on ice. After centrifugation at 2,500 rpm and 3°C, the plasma was decanted and stored at −80°C until analysis. Plasma concentration of BNP was determined by immunoradiometric assay (nonextracted) using antibody to human BNP (Shionogi Co Ltd, Tokyo, Japan), as previously described (5). A BNP level greater than 37 pg/mL was defined prospectively as abnormal because
this is the mean $+2 \text{ SD}$ in normal subjects, as previously reported from our laboratory (5).

**Clinical Assessment**

The patients’ clinical records were reviewed by an observer blinded to the results of the natriuretic peptide levels or echocardiography to determine the clinical characteristics as recorded by the clinicians referring the patients for echocardiography.

We prospectively specified clinical criteria that we believed would be predictive of high or low risk for systolic dysfunction. Data readily available in most settings and not requiring advanced examination skills were chosen to enhance the use of clinical criteria for noncardiologists. Patients were considered to be at high risk if they had 1 or more of the following: 1) history of myocardial infarction, 2) previous diagnosis of congestive heart failure, 3) current orthopnea or paroxysmal nocturnal dyspnea, 4) presence of pathologic Q waves or an intraventricular conduction defect on electrocardiogram, or 5) cardiomegaly, pulmonary venous hypertension, or interstitial edema on chest radiograph. Patients were considered at low risk for systolic dysfunction if they had none of the above. The predictive characteristics of this scoring system for the prediction of systolic dysfunction were then determined.

The electrocardiogram was assessed according to the usual routine at our institution by using a computer algorithm, with abnormal studies interpreted by a physician (12,13). Pathologic Q waves were considered to be present if they were $\geq 20 \text{ ms}$ in duration. Bundle or fascicular block was diagnosed by standard criteria.

The chest radiograph was reviewed by a radiologist according to the usual routine at our institution, and the presence or absence of cardiomegaly, pulmonary venous hypertension, or pulmonary edema was noted.

**Statistical Analysis**

Values are expressed as mean $\pm \text{ SD}$. The relative ability of natriuretic peptide assays to identify an EF less than 45% was assessed by receiver operating characteristic (ROC) analysis. To assess whether natriuretic peptide assays have any information content, the areas under the ROC curves were compared with 0.5 (area under line of no information) using Wilcoxon rank sum statistics (14), as previously described (5). Next, the areas under the ROC curves for detecting an EF less than 45% were compared between peptides with DeLong’s method (15) as previously described (5). Statistical significance was judged at the .05 level of significance.

**Results**

**Patient Characteristics**

Table 1 reports the clinical characteristics of the patients. Overall, 33% of patients had symptoms thought to be suggestive of congestive heart failure. The others were referred for echocardiography to assess EF because of the presence of risk factors for left ventricular systolic dysfunction.

**BNP for Detecting Reduced Systolic Function**

The ability of BNP to detect a decreased EF was assessed with ROC analysis (Fig. 1). The area under the ROC curve for BNP to detect an EF less than 45% was significantly greater than .5. The area under the ROC curve for BNP to detect an EF less than 45% was similar in patients with (.83) and those without (.78) symptoms of congestive heart failure. The area under the ROC curve for BNP to detect only severe systolic dysfunction (an EF less than 35%) was .90.

An abnormal BNP value (greater than 37 pg/mL) was present in 189 (41%) patients and absent in 277 patients. In the group with an abnormal BNP, 40 of 189 had an EF less than 45%, for a prevalence of 21%. In the group with a normal BNP (59% of the study population), 11 of 277 had an EF less than 45%, for a prevalence of 4%. Only 2 patients with a normal BNP and an EF less than 45% had severe systolic dysfunction (EF less than 35%). The sensitivity, specificity, and negative and positive predictive values for the prespecified partition value of BNP to detect EF less than 45% are reported in Table 2.

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of the Patient Population</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Median age (yr)</td>
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<tr>
<td>Male, % of patients</td>
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<tr>
<td>Reason for echocardiographic referral, % of patients</td>
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<tr>
<td>Symptoms of CHF</td>
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<tr>
<td>Risk factors for LV dysfunction</td>
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<tr>
<td>Past history, % of patients</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>EF &lt;45%, no. of patients (%)</td>
</tr>
<tr>
<td>Medications, % of patients</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>$\beta$-Blockers</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Nitrates</td>
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<td>Calcium channel blockers</td>
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<td>Digoxin</td>
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ACE, angiotensin-converting enzyme; CHF, congestive heart failure; LV, left ventricular.
Clinical Score for the Identification of High- and Low-Risk Groups

The predictive characteristics of the clinical score for the prediction of an EF less than 45% are reported in Table 2. An abnormal clinical score (1 or more of the prospectively identified variables) was present in 201 (43%) patients and absent in 265 patients. In the group with a positive score, 48 of 201 had an EF less than 45%, for a prevalence of 24%. In the group with a negative score (57% of the study population), 3 of 265 had an EF less than 45%, for a prevalence of 1%. Only 1 patient with a negative score and an EF less than 45% had severe systolic dysfunction (EF less than 35%).

The possibility that BNP may provide incremental value to the clinical score was assessed. Of the 265 patients with a negative clinical score, BNP was abnormal in 72 and normal in 193. Of the 193 patients with a negative clinical score and a negative BNP, only 1 had an EF less than 45%, for a prevalence of .5%. Of the 72 subjects with a negative clinical score and a positive BNP, 2 of the 72 (2.8%) had an EF less than 45%. Given the high sensitivity of the clinical score, performing BNP in this group was not of great incremental value. Of the 201 subjects with a positive clinical score, BNP was also positive in 117, of which 38 (32%) had an EF less than 45%. Eighty-four subjects had a positive clinical score and a negative BNP, of which 10 (12%) had an EF less than 45%.

Table 2. Predictive Characteristics of Clinical Score and BNP Assay for the Identification of an EF Less Than 45% or Less Than 35%

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>Clinical score*</td>
<td>EF &lt;45%</td>
<td>94</td>
<td>63</td>
<td>24</td>
</tr>
<tr>
<td>BNP assay†</td>
<td></td>
<td>79</td>
<td>64</td>
<td>21</td>
</tr>
<tr>
<td>Clinical score*</td>
<td>EF &lt;35%</td>
<td>95</td>
<td>59</td>
<td>99</td>
</tr>
<tr>
<td>BNP assay†</td>
<td></td>
<td>90</td>
<td>61</td>
<td>9.8</td>
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PPV, positive predictive value; NPV, negative predictive value; BNP, brain natriuretic peptide; EF, ejection fraction.

* One or more of the 5 factors ranked positive is a positive score; none of 5 factors is a negative score.
† A BNP assay value of >37 pg/mL is positive, and a value of <37 pg/mL is negative.

Presence of Other Significant Cardiac Abnormalities

The patient selection criteria were designed to select patients in whom the sole indication was for assessment of systolic function. Patients suspected of having significant primary valvular disease were specifically excluded from the study. We examined the frequency of factors other than an EF less than 45% that may cause symptoms of heart failure in patients referred with symptoms of heart failure. None of these patients had significant stenosis of the mitral or aortic valve and no patients had significant aortic regurgitation. Five patients had grade III or IV mitral regurgitation, but all of these patients also had reduced EF. Ten patients had Doppler evidence of elevated left atrial pressure, as indicated by a reduced deceleration time, but all of these patients also had reduced systolic function. Nine patients had right ventricular dysfunction, 5 of whom had reduced EF.

We also examined the prevalence of any potential
cardiac abnormality that might be associated with an increase in plasma BNP in subjects with an abnormal or normal BNP level. An ejection fraction of less than 45% or 1 of these additional factors was present in 74% of those with an abnormal BNP and 36% of those with a normal BNP.

Discussion

We investigated the ability of clinical data and plasma BNP concentration to detect systolic dysfunction in patients being referred to echocardiography to assess systolic function because of symptoms of congestive heart failure or risk factors for systolic dysfunction at a large outpatient echocardiographic laboratory. In this population, the prevalence of a reduced EF (less than 45%) was 10.9%. Patients could be divided into high- and low-risk groups based on either a simple clinical score incorporating the history, chest radiograph, and electrocardiogram or based on the plasma level of BNP. The predictive characteristics of the clinical score were actually better than that of the BNP level. As the clinical score was negative and BNP was normal in approximately 60% of the population, using either the clinical score or BNP to triage patients to echocardiography would allow nearly 60% fewer echocardiograms to be performed, with negative predictive values of 99% and 96%, respectively, in this population with a moderate prevalence (10.9%) of systolic dysfunction.

Use of a Clinical Score to Stratify Patients at Risk for Systolic Dysfunction

Unlike stress testing to detect coronary artery disease, no accepted guidelines are available to define pretest probability of systolic dysfunction in populations at risk. Although an American College of Cardiology/American Heart Association task force recently published guidelines for the clinical application of echocardiography (16), the recommendations are relatively broad in regard to which patients should undergo echocardiography for the detection of systolic dysfunction. Specifically, assessment of global ventricular function at rest is a class I indication for echocardiography in patients with chronic ischemic heart disease. However, no specifics are given as to which patients should undergo such assessment. Given the large numbers of patients with coronary artery disease, more specific guidelines would be helpful. Echocardiography is clearly recommended for patients with a clinical diagnosis of heart failure. However, symptoms of mild heart failure can be non-specific. Thus, echocardiography is also recommended for patients with symptoms of dyspnea or edema if there is known or suspected cardiac disease, evidence of elevated central venous pressure, or an inability to assess central venous pressure. Again, what constitutes known or suspected cardiac disease is subject to broad interpretation, and noncardiologists often have difficulty confidently assessing central venous pressure. Thus, a clearly defined and simple set of guidelines that assess probability of systolic dysfunction would provide more guidance to the clinician as to when systolic dysfunction is likely enough to be present to warrant cardiac imaging and could reduce the use of health care resources for imaging procedures.

In the current study, the presence of 1 or more of 5 simple clinical factors readily available from the history, electrocardiogram, and chest radiograph provided excellent separation of high- and low-risk groups. This score does not require advance cardiac examination skills and is available on most patients undergoing an evaluation. Several previous studies have investigated the use of clinical scoring systems for prediction of systolic dysfunction and these were reviewed recently (17). The majority of these studies have reported excellent predictive values for different clinical scores, which usually incorporate history, physical examination, the electrocardiogram, and the chest radiograph. Despite these findings, our study and that of others (2) suggest that the prevalence of systolic dysfunction is not high in outpatients specifically referred for evaluation of systolic function, suggesting that patients may not be appropriately selected for echocardiography (18) and that simple criteria to better guide its use in the detection of systolic dysfunction are needed.

BNP Assay as a Blood Test for Systolic Dysfunction

Several blood tests have been developed to detect life-threatening medical conditions. A blood test to detect systolic dysfunction would be useful in screening patients who are at risk for systolic dysfunction because asymptomatic systolic dysfunction may be quite common (6) and because treatment of asymptomatic patients is recommended to reduce or delay onset of heart failure and mortality (1). Although all patients with a strong probability of heart failure should undergo echocardiography (1,19), symptoms of mild heart failure are non-specific and a blood test to exclude systolic dysfunction during the initial approach to these patients would be useful and allow more expeditious pursuit of potential noncardiac causes of dyspnea, edema, or fatigue. Widespread interest in this concept led to the development of rapid assay systems for BNP. As currently developed, some kits would provide costs and turnaround times comparable with those of prostate-specific antigen testing. Other ultrarapid point-of-care assay systems are being developed. In the current study, the predictive value of BNP for the detection of systolic dysfunction
was similar to that previously reported in different patient populations. The value obtained for the area under the ROC curve (auc) for BNP in the detection of an EF less than 45% in this study (auc = .79) was similar to that previously reported by our laboratory for detection of EF less than 45% in a smaller population of patients referred to coronary angiography (auc = .85) (5). Furthermore, when using a prospectively defined partition value for BNP based on the mean +2 SD in a reference normal population, the predictive characteristics of BNP assay were similar in our previous and current studies. The auc for detection of an EF less than 35% (auc = .90) was similar to that reported by McDonagh et al. (6) for detection of an EF less than 30% in the general population with a similar age (age greater than 55 years, auc = .85).

The predictive characteristics of BNP assay are similar to those of tests used to screen for other life-threatening diseases. The area under the ROC curves reported for BNP for the detection of systolic dysfunction (.83 to .90) (5–7) is similar to or better than that reported for prostate-specific antigen for detection of prostate cancer (.81 to .94) (20,21), mammography for detection of breast cancer (.85) (22), urinary amylase for detection of acute pancreatitis (.845) (23), and Papanicolaou smears for detection of cervical cancer (.70) (24). Furthermore, the sensitivity and specificity of the BNP assay for the detection of systolic dysfunction exceed those of stress imaging for the detection of coronary artery disease (13).

Thus, the current study supports previous studies (Table 3) indicating that BNP assay may be useful in the detection or exclusion of systolic dysfunction in patients at risk, enabling more widespread screening for systolic dysfunction while reducing the use of echocardiography or other cardiac imaging modalities in the clinical population (8).

A limitation of the BNP assay in this study was its lack of specificity, with a relatively modest positive predictive value for left ventricular systolic dysfunction. There was a higher prevalence of other cardiac structural and functional abnormalities in subjects with an abnormal BNP level than in those with a normal BNP level. A limitation of the current study was the lack of a comprehensive assessment of diastolic function, which precluded identification of individuals with diastolic dysfunction and increased left atrial pressures. Although we did identify subjects with a very restrictive mitral inflow pattern (deceleration time less than 150 ms), this criterion identifies only the subjects with advanced diastolic dysfunction and marked elevation of filling pressures (25). We have recently reported that subjects with moderate elevation of filling pressures caused by isolated diastolic dysfunction (as assessed by comprehensive Doppler techniques) have increased BNP levels (26,27).

### Importance of Screening for Systolic Dysfunction in Patients at Risk

The importance of screening and treatment of systolic dysfunction to “prevent” heart failure has been emphasized (1,28,29). If we are to meaningfully implement recommendations concerning treatment of patients with asymptomatic or minimally symptomatic systolic dysfunction, an appropriate strategy to identify such patients must be developed. The findings of the current study are pertinent to this issue. By finding a widely available and less expensive method to identify high-risk patients, we provide an approach whereby patients at highest risk can be distinguished and referred to cardiac imaging, thus improving detection while limiting use of echocardiography.

### Acknowledgment

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### References

1. Packer M, Cohn JN, on behalf of the Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure: Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83:2A–77A
2. Krumholz HM, Douglas PS, Goldman L, Waksmonski C: Clinical utility of transthoracic two-dimensional and


8. Struthers AD: Plasma concentrations of brain natriuretic peptide: will this new test reduce the need for cardiac investigations? (editorial) Br Heart J 1993;70:397–8


