New Diagnostic Modalities in the Diagnosis of Heart Failure

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Heart failure (HF) is the one cardiovascular disease that is increasing in prevalence in the United States. As the population continues to age, the incidence will certainly be amplified. However, some studies have shown that HF is correctly diagnosed initially in only 50% of affected patients. Despite the use of history, physical examination, echocardiogram, and chest x-ray, the percentage of correct initial diagnosis of HF is low. Recognizing the symptoms of HF decompensations is often problematic because other diagnoses can mimic them.

There are two new diagnostic modalities that offer promise in improving HF diagnostic accuracy and identifying early HF decompensations. These diagnostic modalities include tests utilizing impedance cardiography and the B-type natriuretic peptide assay. They have the potential of increasing the accuracy of HF diagnosis and guide pharmacological treatment in the inpatient and outpatient settings. They may also assist in the recognition (or prediction) of acute HF decompensations.

Key words: heart failure ■ diagnosis ■ B-type natriuretic peptide ■ impedance cardiography ■ BioZ

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Heart failure (HF) is one of the only cardiovascular diseases that is increasing in prevalence in the United States. It is present in 6–10% of the population over the age of 65 and in 10% of those over the age of 80.[1] Stated in another manner, if a person reaches the age of 40, he has a 20% chance of developing HF before death. Each month over one million people in the United States reach the age of 65 and for the first time in U.S. history, there are more people older than 65 years of age than younger than 65 years.[2] HF morbidity and mortality is on the rise. Congestive HF (CHF) is the most frequent cause of hospitalization in patients over the age of 65, with three million patients having a primary or secondary discharge diagnosis of CHF yearly. One-year mortality ranges from 10–50% depending on the stage of the disease. These statistics will continue to grow as our population ages. HF knows no racial boundary; however, African-American patients are disproportionately affected with 3% of all adult black Americans afflicted, and they suffer higher morbidity and mortality rates.[3] The magnitude of the problem now and, if not effectively addressed, in the future is apparent.

With the extent of the problem as outlined, it is especially alarming to concede that HF is correctly diagnosed initially in only 50% of affected patients.[4,5] For example, patients who are elderly and/or obese may be treated for extended periods for a primary pulmonary disorder, when the accurate diagnosis is HF. The reasons for this are numerous, including the fact that some of the cardinal symptoms and signs of HF, such as dyspnea, edema, and exercise intolerance, have a broad differential diagnosis. Nevertheless, the need for an early and correct diagnosis is crucial. Studies have confirmed that an early diagnosis of HF leads to timely and appropriate treatment, resulting in a decrease in morbidity and mortality. In the survival and ventricular enlargement trial (SAVE)[6] and the preventive arm of the study of left ventricular systolic dysfunction (SOLVD) trials,[7] the use of angiotensin converting

enzyme inhibitor (ACEI) delayed or prevented the onset of overt symptomatic HF in patients with asymptomatic left ventricular dysfunction (ALVD). The American Cardiology of College/American Heart Association (ACC/AHA) HF guidelines developed a classification system (Figure 1)[8] to direct the focus not only on those with HF but importantly for those *at risk* of developing HF. The emphasis is on treating or preventing the risk factors that can lead to HF. The ACC/AHA HF guidelines do not recommend routine echocardiograms for people *without* symptoms or structural heart disease. This reluctance to endorse echocardiograms as a broad screening device for HF may principally be based on cost. A high number in the population would need to be screened resulting in a high cost to identify a few asymptomatic HF patients. The question has been asked how can asymptomatic HF patients be identified. A partial answer may be to screen those at high-risk *with a cost-effective test, allowing for early and accurate diagnosis, early treatment, and preventing/decreasing morbidities*. HF mortality rate is increasing despite medical advances and newer pharmacological agents. There is a need to prevent HF morbidities and reduce mortalities, which suggests there is a need to make an earlier and accurate HF diagnosis.[9] The ACC/AHA HF classification scheme with "prevention of HF" to the "treatment of end-stage HF" is meant to complement rather than replace the old New York Heart Association (NYHA) functional classification.

The history and physical examination are important steps in the assessment of HF and highly recommended in the ACC/AHA HF guidelines.[10] The Heart Failure Society of America (HFSA) devised a screening tool to help clinicians make an accurate clinical diagnosis. The tool is based on the acronym FACES.[11] Questions are asked about Fatigue, altered Activity or exercise pattern, Chest congestion, Edema of extremities and Shortness of breath. Patient assessment includes the history, a review of symptoms incorporating the concept of FACES, the physical examination, and the single most useful diagnostic test in the evaluation of patients with HF—the 2D echocardiogram coupled with Doppler flow studies.

Valuable cardiac information can be obtained from the echocardiogram. The size, shape, and function of the ventricles along with regional wall motion can be attained. The presence of thrombus can often be identified depending on its size and location in these patients who have a high risk for the development of thrombotic events. Identification of valvular abnormality, especially mitral regurgitation (MR), aortic stenosis (AS), and aortic regurgitation (AR) is important and can impact treatment options, preventing HF for those at high risk. Mitral valvuloplasty in severe MR and aortic replacement in significant AS or AR may improve left ventricular function and HF symptoms if correct timing of surgery is achieved. Other information that can be obtained from a routine echocardiogram include estimate of pulmonary pressures, presence and severity of diastolic dysfunction, and left ventricular hypertrophy. Presence of significant pericardial effusion can also be assessed.

However, obtaining an echocardiogram and having it interpreted in a timely manner is not always feasible. Echocardiography may have limited availability, depending on the time of day the study is needed. In addition, patients with comorbid conditions, such as chronic obstructive pulmonary disease and obesity, usually have poor acoustic windows rendering the test technically difficult if not impossible to perform. Tests like an electrocardiogram (ECG) are important but have no specific diagnostic features. A chest x-ray is frequently employed to evaluate the presence of congestion and cardiomeagly. However, it has many limitations, including low sensitivity and delayed correlation with clinical status changes.

Despite a good patient history, physical examination, and available diagnostic tests, with known limitations, the percentage of initial correct diagnosis of HF remains low. There is a search for additional tests to assist with initial HF diagnostic accuracy. Once the correct diagnosis is made, the question of early identification of acute symptoms indicative of decompensation needs to be addressed. Recognizing acute decompensations is often problematic because there are other diseases, such as depression and sepsis, that can mimic the symptoms. The capability of *predicting* decompensations enhances the diagnostic and therapeutic possibilities in this population. Healthcare professionals can predict the increased hospitalizations characteristically observed in HF patients after major holidays, such as Thanksgiving, July 4th, and Christmas. This is typically secondary to dietary indiscretions, the basis for a significant percentage of acute HF decompensations leading to hospitalizations.

There are two new diagnostic modalities that offer promise in improving HF diagnostic accuracy and possibly predicting or identifying early acute HF decompensations. These are impedance cardiography (ICG) (BioZ®, ICG Monitor, CardioDynamics International Corporation, San Diego, CA) and the B-type natriuretic peptide assay (BNP).

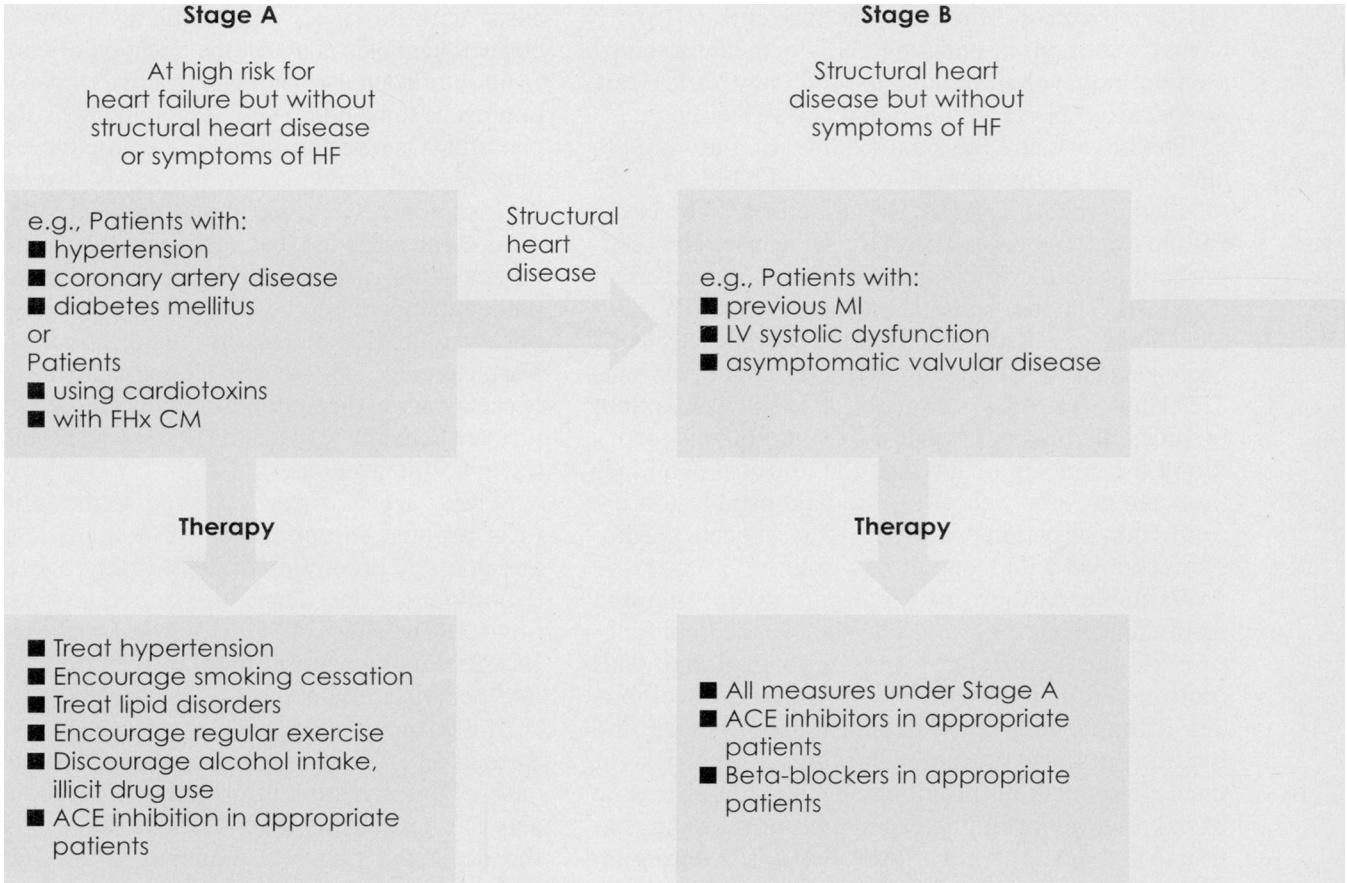
Impedance cardiography is a test as simple to perform as an ECG that provides clinically useful, noninvasive hemodynamic information. ICG requires four sets of dual sensors, two sets attached at the base of the neck and two sets attached at the side of the patient's chest at the level of the xiphoid process in the mid-axillary line (Figure 2). The skin is prepared

similar to the pre-ECG skin preparation. The inner sensors measure the baseline impedance to a low amplitude alternating current transmitted via the outer sensors. With each heartbeat, ICG measures the corresponding change in impedance. The baseline and the subsequent changes in impedance are used to calculate hemodynamic parameters. These parameters include cardiac output/cardiac index; stroke volume/stroke index; systemic vascular resistance/systemic vascular resistance index; measures of contractility, such as systolic time ratio, velocity index, and accelerated cardiac index; and thoracic fluid content (TFC). The TFC represents the total fluid content of the thorax (intravascular, intra-alveolar and interstitial). Therefore, a high TFC value indicates an excess of total thoracic fluids.[12] ICG is a validated, noninvasive method of determining hemodynamic parameters. Studies have documented its accuracy in comparison with Fick and thermodilution methods in critically ill patient populations.[13-16]

The pulmonary artery catheter (PAC), in use for over 30 years and placed in about one million patients yearly, is still the gold standard for obtaining similar hemodynamic values. But there is little information from large, multicenter randomized trials showing value and improved patient outcome. The potential complications are well documented. They include pulmonary artery (PA) rupture, PA thrombus, infection, and right atrial/ventricular perforation, catheter entrapment that may lead to rupture of the chordae, and tricuspid valve. A large multicenter trial is underway to evaluate effectiveness of PAC's in CHF—the Escape Trial.[17] When comparing the PAC to the BioZ, some advantages of the BioZ are obvious. It is noninvasive, requires minimal skill to perform, can be conducted in the critical care units, stepdown units, perioperative areas, emergency departments, or the outpatient clinics for a one-time measurement or continuous monitoring.

The cost of utilizing ICG versus PAC to provide hemodynamics is a difference of approximately $1,246–$3,461 per case depending on the hospital's cost for the procedure.[18] Silver et al. reported on the projected annualized cost savings by percent PAC volume reduction per month. As an example, a facility that performs five PAC procedures per month

Figure 1. Stages in the Evolution of Heart Failure/



and decreases the number by one per month can realize a cost savings of $25,572 per year.[19]

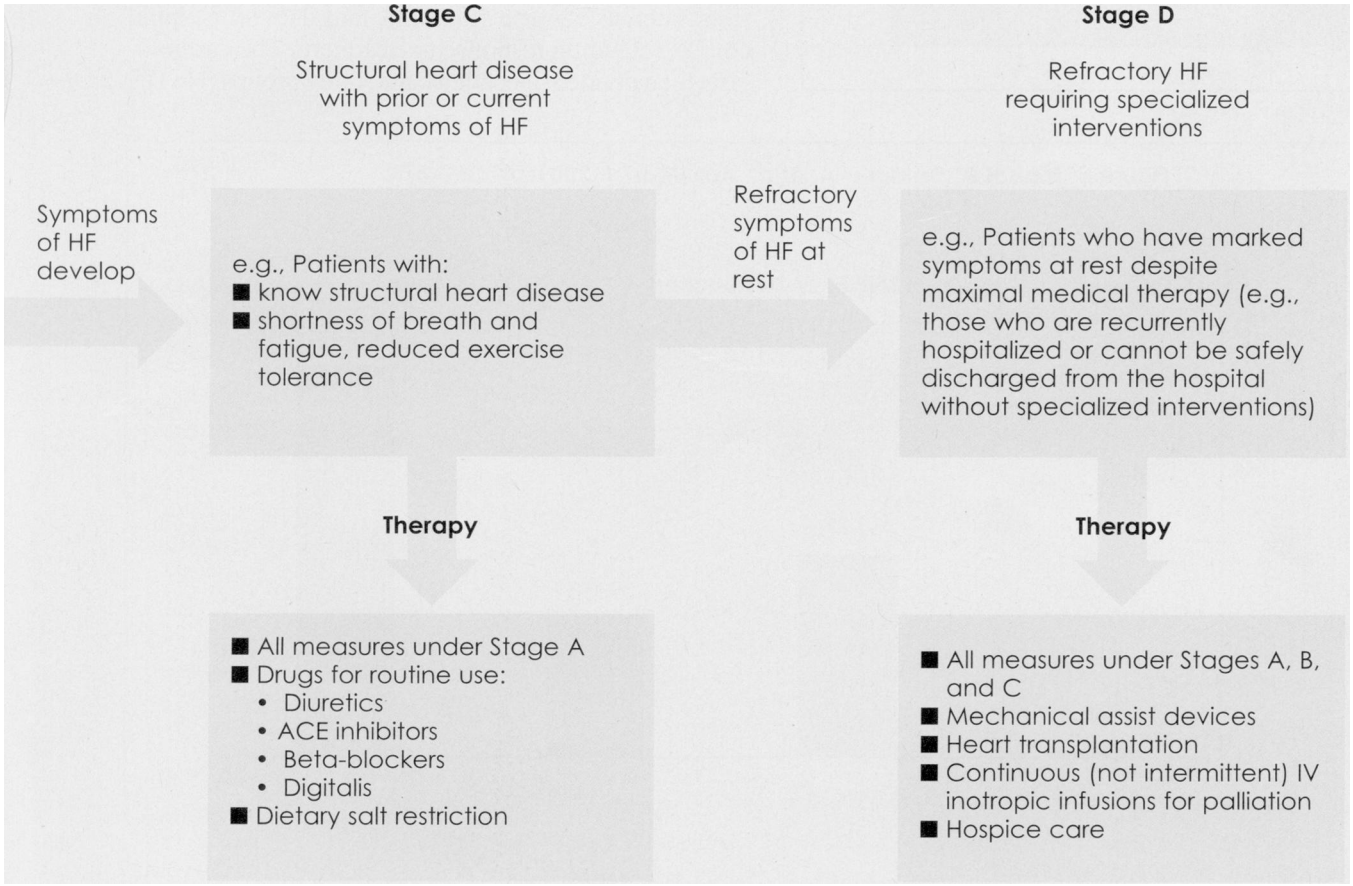
A summary of ICG clinical applications for the assessment of HF includes the ability to gauge whether symptoms are due to decompensation and objectively trend the changes of hemodynamic decompensation. ICG assists in the treatment of HF to determine the need for pharmacologic agents, guide in the selection of drug agents and dosing, and measure responses to therapy adjustments.[20]

A study in progress with the BioZ, the PRospective Evaluation and identification of cardiac Decompensation In patients with HF by impedance Cardiography Test (PREDICT trial) proposes to address if the hemodynamic parameters can accurately predict the occurrence of clinically important circulatory deterioration in patients with HF.[21]

The second new diagnostic modality, BNP, may rival the echocardiogram for providing the most useful diagnostic test although, as will be later shown, the role of the echocardiogram is still preserved. BNP is a 32-amino-acid peptide that is released from the cardiac myocytes in response to ventricular pressure or volume overload. Its chief physiologic effects include vasodilatation, increasing sodium and water excretion, and inhibition of the renin angiotensin aldosterone and sympathetic nervous activities.[22] The BNP test is a point-of-care fluorescence immunoassay blood test requiring approximately 5 cc of whole blood or plasma. Quantitative results are generated in about 15 minutes.[23] The utility of BNP in the diagnosis of HF, especially CHF, has been shown in a range of clinical trials. First, the evidence for its role in asymptomatic left ventricular dysfunction (ALVD) will be reviewed.

As the ACC/AHA HF classification supports HF prevention as the goal, but when this is not achieved, *early* identification is the next objective. The problem of asymptomatic HF is not benign. ALVD is at least as prevalent as CHF.[24] In the United States, an estimated 20 million people have asymptomatic left ventricular systolic dysfunction (ALVSD).[25] As mentioned previously, studies have shown that treating asymptomatic HF is beneficial. Treatment slows and may reverse the progression of the disease. Maisel et al.[26] studied subjects referred for echocardiography to evaluate the

Recommended Therapy by Stage



presence or absence of left ventricular dysfunction and illustrates that BNP, when applied to the right population, may be a reasonable screening test for this entity. BNP was able to differentiate between normal and abnormal left ventricular function. There was a significant increase in BNP seen in patients with echocardiographic evidence of systolic *or* diastolic dysfunction. The subset of systolic dysfunction with evidence of diastolic-restrictive dysfunction had a significantly higher BNP level, 1,077 ± 272 pg/ml, compared with systolic or diastolic only dysfunction which had BNP levels of 567 ± 113 pg/ml and 391 ± 89 pg/ml, respectively. Patients with no HF had an average level of 37 ± 6 pg/ml (Figure 3). The values of the systolic and diastolic function in this study illustrate that further testing to measure the ejection fraction would be required to differentiate the two disorders. In conjunction with an echocardiogram, BNP may become the gold standard for diagnosing diastolic dysfunction. As a screening test, BNP for HF may be more diagnostically helpful than the far-more-utilized prostate-specific antigen (PSA), Papanicolaou smears, or mammography used to screen for the corresponding prostate, cervical, and breast cancers. It has a high negative predictive value, meaning if the BNP value is low, this essentially rules out the presence of significant LVD. Therefore, it may preclude the need for an echocardiogram in patients with a very low value unless the test is necessary for other reasons.[27,28] The potential diagnostic importance of the BNP in symptomatic patients presenting to the ED was recently published.[29] This has significance because 80% of CHF emergency room visits yearly result in hospitalization.[30] A test that assists with correct triaging of HF patients would be beneficial. In Maisal's study,[31] 1,586 patients presenting to the emergency department with dyspnea were evaluated in the usual manner. In addition, a BNP level was drawn with the ED doctors blinded to the results. Later, two cardiologists reassessed the patients' records. They had access to all information: the ED records, results of diagnostic tests, such as echocardiograms, and data on hospital course, including response to treatment. The cardiologists then divided the patients into three groups: No HF,

Figure 2.

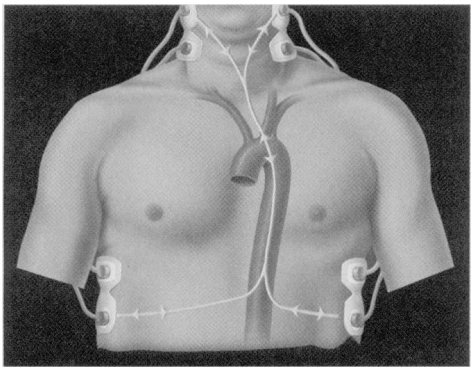
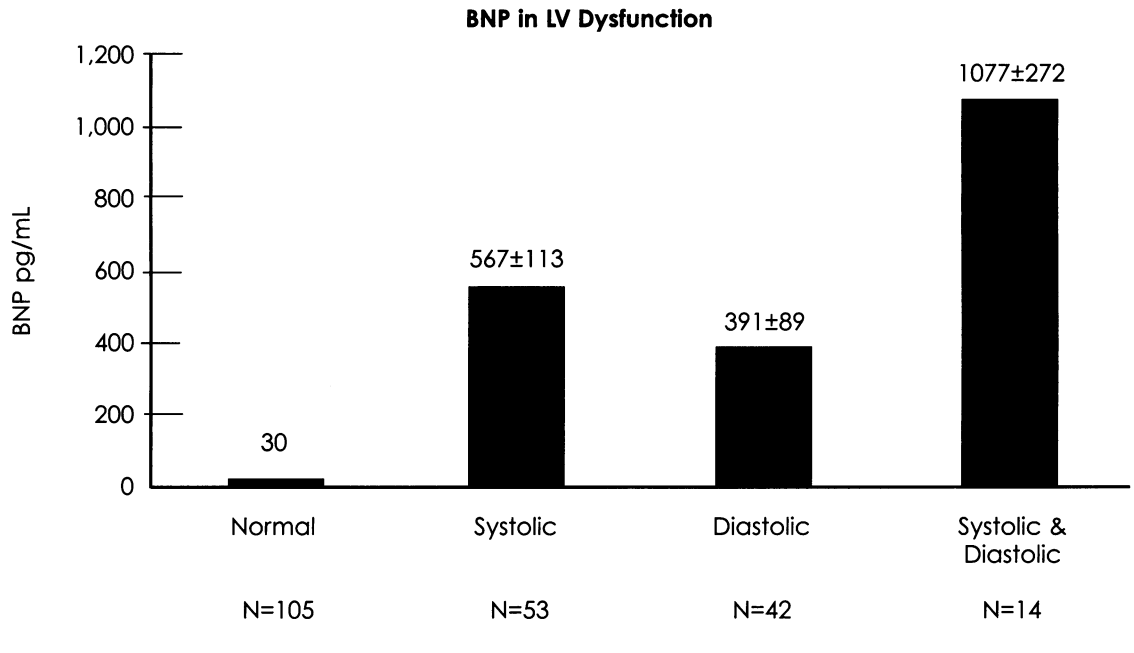


Figure 3. Maisel A, DeMaria A, et al. *Am Heart J.* 2001;141:367-374.



LVD without congestion, and LVD with congestion (CHF). The BNP levels were then unblinded. The results in Figure 4 demonstrate that BNP was able to significantly differentiate the patients in the three groups. Therefore, the ED physicians' diagnostic accuracy can be enhanced by the availability of BNP measurements.[32] In other studies, BNP is able to distinguish between those patients with dyspnea secondary to chronic obstructive pulmonary disease versus HF.[33-35] And in the patients presenting with edema, a cardinal symptom of HF, BNP could make a distinction between those with and without CHF.[36]

The BNP concentration increases as the pulmonary capillary wedge increases and, with treatment, the levels decrease temporally with the wedge pressure.[37] The more severe the congestion, the higher the BNP level, and it strongly correlates with the NYHA functional classification.[38] Tsutamoto et al.[39] showed that BNP values provide prognostic information independent of other variables previously associated with a poor prognosis. When patients were stratified into two groups on the basis of median plasma concentration of BNP (73 pg/ml), the survival rates were significantly ($p<0.0001$) lower in patients with plasma BNP concentration of >73 pg/ml. Plasma BNP concentration was approximately five-fold higher in nonsurvivors than in survivors.

As with several other diagnostic tests, the BNP is most useful when the pretest probability of the diagnosis is intermediate. For example, if the pretest probability is in the 50% range and the BNP level is 1,000 pg/ml, the post-test probability is increased to >90% range. Conversely, if in the same situation the BNP level is measured at 50 pg/ml, the post-test probability is reduced to approximately the 30% range. HF diagnosis nomograms[40] have been developed based on this type of Bayesian analysis. The promising role of the BNP assay ranges from its potential as a screening tool for ALVD in high-risk patients, accurately diagnosing HF when patients present with nonspecific symptoms, such as dyspnea or edema, help with recognizing decompensations in known HF patients, to its possible use in predicting survival. Studies are currently underway to define its role in tailoring or guiding therapy.[41]

Over 80% of patients presenting to the emergency room with symptoms suggestive of HF are admitted. Combine this information with the following HF readmission statistics: 2% of HF patients are readmitted within two days of discharge, 20% within one month, and 50% within six months. Innovative strategies are necessary in the approach to this disease. Attention to history and physical; prudent use of diagnostic tests; and an echocardiogram when indicated, including the two newer modalities—ICG and BNP—should positively affect the care of patients with HF starting with an improvement in the percentage of correct HF diagnosis.

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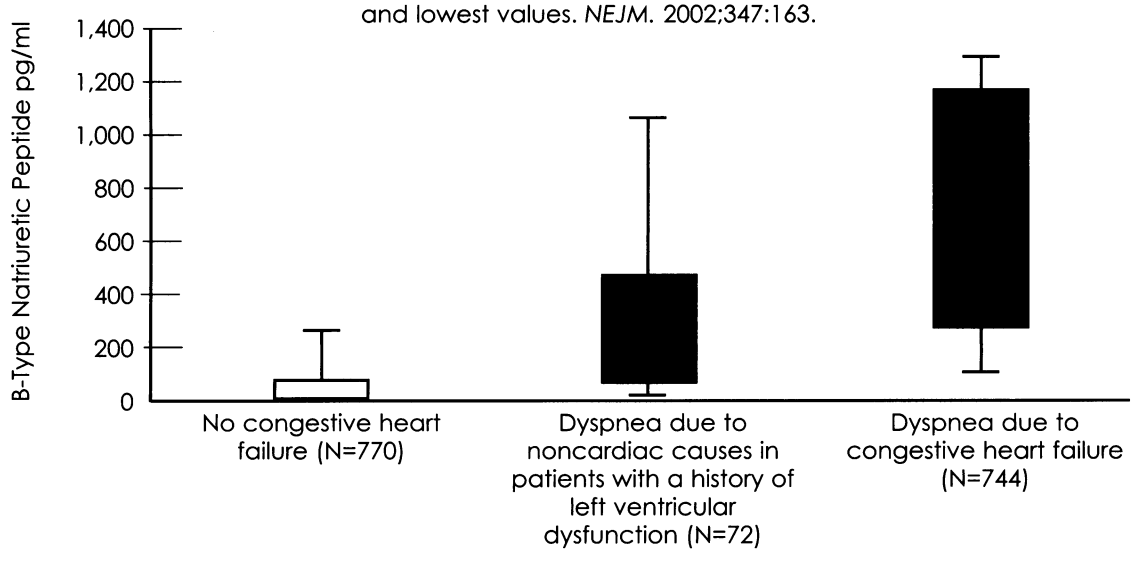
Figure 4. Box Plots Showing Median Levels of B-Type Natriuretic Peptide Measured in the Emergency Department in Three Groups of Patients. Boxes show Interquartile ranges, and I bars represent highest and lowest values. *NEJM.* 2002;347:163.



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