

B-Type Natriuretic Peptide: A Novel Clinical Tool for Diagnosis and Management of Heart Failure

Gil Segev, MD

Jannet F. Lewis, MD

According to statistics reported by the American Heart Association, an estimated 4.9 million Americans had congestive heart failure (CHF) and another 550,000 were diagnosed with the disease in 2000.¹ Often the final stage of cardiovascular disease, CHF is the most frequent reason that Americans 65 years of age or older are brought to the emergency department (ED) and the most common cause of hospitalization in this age group, with 900,000 admissions each year.² Patients admitted with decompensated heart failure have significant hospital mortality and early readmission rates.³

Morbidity and mortality of heart failure can potentially be lowered with accurate diagnosis and appropriate treatment of the disease in early stages.⁴ Unfortunately, early clinical diagnosis of CHF is challenging in the ED or urgent care setting. The signs and symptoms often are nonspecific,^{5,6} making it difficult to pinpoint CHF as the cause of dyspnea, particularly in a patient who has concurrent pulmonary disease. In addition, tests often used to diagnose CHF are not highly reliable. Physical examination, including jugular venous distention, pulmonary rales, abdominal jugular reflux, and peripheral edema suggest fluid overload but are not sensitive or specific signs.⁷⁻⁹ The best clinical predictors of heart failure are increased heart size on chest radiograph (81% accuracy), history of CHF (75% accuracy), pulmonary rales on physical examination (69% accuracy), and a history of paroxysmal nocturnal dyspnea (60% accuracy).¹⁰ Although echocardiography is considered the gold standard for the detection of left ventricular dysfunction, it cannot consistently differentiate between acute and chronic conditions.¹¹ Furthermore, echocardiography is expensive and may not be readily available in the emergent care environment. Thus, a blood test that could rapidly and accurately confirm or exclude the diagnosis of CHF in the urgent care setting would be a valuable clinical tool.

In recent decades, a family of cardiac neurohor-

mones called *natriuretic peptides* has been identified and found to have diagnostic, prognostic, and therapeutic potential in cardiovascular disease. Levels of one of these neurohormones—B-type natriuretic peptide (BNP)—have been found to be elevated in patients with left ventricular dysfunction, suggesting that measurement of BNP can aid in the diagnosis of CHF. This article summarizes emerging evidence of the clinical uses of BNP in the diagnosis and management of heart failure.

THE NATRIURETIC PEPTIDES

Biologic Action

Left ventricular dysfunction leads to the activation of several neuronal and hormonal pathways, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the endothelin pathway. These responses initially are beneficial in maintaining tissue perfusion but eventually are detrimental, causing cardiac toxicity and hypertension.¹² Natriuretic peptides are cardiac neurohormones produced by the heart and vasculature to counteract the harmful effects of fluid and sodium retention. Three natriuretic peptides have been identified:

- A-type natriuretic peptide is secreted mainly by the atria in response to chamber dilation.
- B-type natriuretic peptide (formerly named *brain natriuretic peptide* because of its discovery in pig brain) is released by the ventricles in response to increased end-diastolic pressure and volume expansion.^{13,14} BNP helps to regulate blood pressure and fluid balance by counterbalancing the renin-angiotensin system. The major effects of BNP are to increase excretion of sodium and water, decrease secretion of aldosterone and renin, and thereby serve as a vasodilator.¹⁵

Dr. Segev is a Hospitalist at Sibley Hospital in Washington, DC. Dr. Lewis is a Professor of Medicine, Division of Cardiology, George Washington University School of Medicine and Health Sciences, and Director, Noninvasive Cardiology, George Washington University Hospital, Washington, DC.

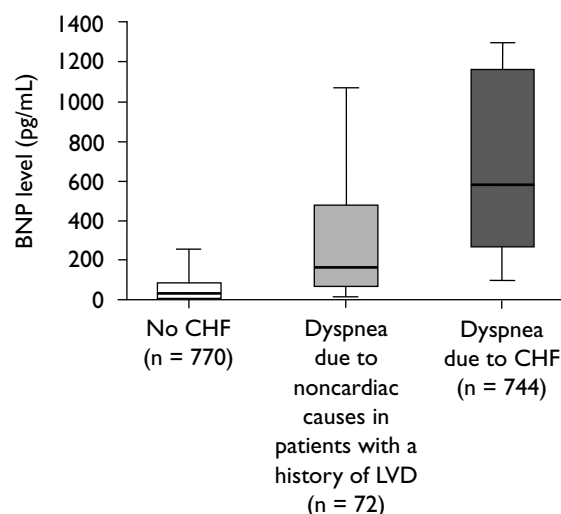


Figure 1. Box plots showing median levels of B-type natriuretic peptide (BNP) measured in 1586 patients presenting to the emergency department with acute dyspnea. Boxes show interquartile ranges, and I bars represent highest and lowest values. CHF = congestive heart failure; LVD = left ventricular dysfunction. (Adapted with permission from Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:163. Copyright © 2002, Massachusetts Medical Society. All rights reserved.)

- C-type natriuretic peptide is produced and released by the endothelial cells in response to shear stress.¹²

Factors Affecting BNP Levels

Several factors affect baseline average BNP levels. Women have slightly higher levels than men, and older people have higher levels than younger people.^{9,16,17} BNP levels are elevated in endocrine disease (ie, primary hyperaldosteronism, Cushing syndrome), renal failure, cirrhosis, cardiac inflammation (ie, myocarditis), and primary pulmonary hypertension.¹⁶ BNP levels correlate directly with left ventricular mass.¹⁷ Any condition that increases the volume or activates the stretch receptors of the ventricles can elevate BNP levels. BNP levels do not appear to have important circadian rhythm fluctuations.¹⁶

BNP MEASUREMENT AS A DIAGNOSTIC TOOL

The first BNP assay to be approved by the US Food and Drug Administration (FDA) is a fluorescent immunoassay that quantitatively measures BNP levels in blood or plasma. Once placed in the testing kit, the

sample moves into a chamber that contains murine fluorescent antibodies. A reaction occurs, and the device is placed in an immunofluorescent reader to measure the BNP concentration. The assay detects levels as low as 5 pg/mL and as high as 5000 pg/mL. The test can be performed at the bedside in 15 minutes. More recently approved by the FDA is an assay that measures the N-terminal fragment of the BNP prohormone (ie, N-terminal BNP). This terminal peptide is produced with the release of BNP, has a longer half-life, and is not affected by exogenous BNP.

Diagnosis of Heart Failure

In a prospective study, Maisel et al¹⁰ evaluated the use of BNP levels for diagnosis of CHF in 1586 patients presenting to the ED with acute dyspnea. The clinical diagnosis of CHF or no CHF was made by 2 independent cardiologists who reviewed all available data for study participants with the exception of BNP measurements. The final diagnosis was decompensated CHF in 47% of patients, dyspnea due to noncardiac etiology in 5% of patients with a past history of left ventricular dysfunction, and no CHF in 49% of patients.¹⁰ **Figure 1** shows the BNP values for the 3 study groups. Plasma BNP concentrations were markedly higher in patients with clinically diagnosed heart failure compared to those without heart failure (675 ± 450 pg/mL versus 110 ± 225 pg/mL). Intermediate values were found in the patients with baseline left ventricular dysfunction but without an acute exacerbation (346 ± 390 pg/mL). A plasma BNP level greater than 100 pg/mL diagnosed decompensated heart failure with a sensitivity of 90% and a specificity of 76%. A BNP level less than 50 pg/mL had a negative predictive value of 96%.¹⁰ In this study, the authors found BNP level to be the single most accurate predictor of the presence or absence of CHF; a BNP cutoff value of 100 pg/mL was more accurate (83%) than either the National Health and Nutrition Examination Survey or Framingham criteria for the diagnosis of CHF (67% and 73%, respectively).¹⁰

In a study by Morrison et al,¹⁸ BNP levels accurately distinguished CHF from pulmonary disease. A BNP level of 94 pg/mL had a sensitivity of 86%, a specificity of 98%, and an accuracy of 91%. Moreover, in patients with coexistent chronic obstructive pulmonary disease (COPD) and CHF, a COPD exacerbation was associated with an average BNP value of 47 pg/mL, whereas patients with decompensated CHF had an average BNP value of 731 pg/mL (**Figure 2**).¹⁸ Certain clinical situations, however, may limit the ability of BNP to differentiate between pulmonary and cardiac disease. For example, pneumonia can trigger decompensated CHF,

and COPD exacerbations can result in worsening cor pulmonale with right ventricular volume overload. In these patients, BNP levels are likely to be elevated. Large pulmonary emboli also have been shown to be associated with elevated BNP levels (in the 200–300 pg/mL range), likely due to right ventricular pressure increases.¹⁸

Diagnosis of Diastolic Dysfunction

Several studies have demonstrated that one third or more of patients presenting with CHF have normal left ventricular systolic function.¹⁹⁻²¹ These patients, who most often have systemic hypertension, are believed to have heart failure due to diastolic dysfunction. Lubien et al¹⁹ showed that BNP levels were predictive of diastolic dysfunction. In patients with echocardiographic assessment of diastolic function, elevated BNP levels correlated with diastolic abnormalities seen on echocardiography. The correlations were observed whether or not a history of heart failure symptoms was present. Patients were classified by diastolic filling pattern as *normal*, *impaired relaxation*, *pseudonormal*, or *restrictive*. Patients with abnormal left ventricular diastolic function had a mean BNP level of 286 pg/mL, and those classified as normal had a mean BNP value of 33 pg/mL.¹⁹ Patients with restrictive filling patterns on echocardiography had the highest mean BNP level, 408 pg/ml. In addition, symptomatic patients had higher BNP levels in each diastolic filling pattern group. A BNP level of 62 pg/mL had a sensitivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction on echocardiography.

BNP levels alone cannot distinguish diastolic from systolic dysfunction. These data suggest, however, that a low BNP level in a patient with normal left ventricular systolic function by echocardiography may effectively exclude significant diastolic dysfunction. Conversely, an elevated BNP level in a patient with normal systolic function is consistent with diastolic dysfunction as assessed by Doppler echocardiography.¹⁹

BNP MEASUREMENT FOR PROGNOSIS AND MANAGEMENT Risk Stratification in CHF

The prognosis for patients with CHF varies considerably and is influenced by various clinical and hemodynamic factors. Several studies suggest prognostic value of BNP measurement.

Outcome after diagnosis. Measurement of BNP in the urgent care setting appears to be useful for risk stratification of patients after CHF diagnosis. Harrison et al²² measured BNP levels in 325 patients who present-

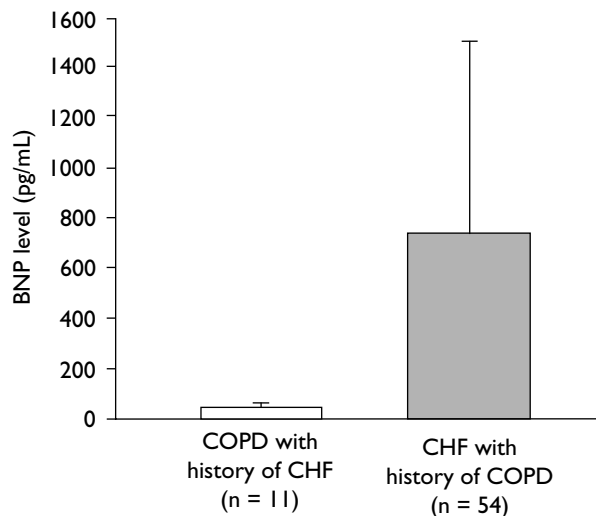


Figure 2. B-type natriuretic peptide (BNP) levels in patients with a past history of chronic obstructive pulmonary disease (COPD) but a final diagnosis of acute congestive heart failure (CHF) as well as patients with a past history of CHF but a final diagnosis of acute pulmonary disease. Data are expressed as mean \pm standard error for BNP values. (Adapted with permission from Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:207.)

ed to the ED with dyspnea and then followed the patients for 6 months. BNP levels at the time of the initial urgent care visit closely correlated with outcomes, including the endpoints of heart failure death, hospital admission (cardiac), or repeat ED visit for CHF.²² The 6-month cumulative probability of a CHF event was 51% in patients with initial BNP levels greater than 480 pg/mL but only 2.5% in patients with initial BNP values less than 230 pg/mL (**Figure 3**).

Risk for sudden cardiac death. Mortality in CHF is attributable to sudden death in as many as 50% of patients.²³ There is growing evidence that implantable cardiac defibrillators potentially reduce overall mortality in CHF by preventing sudden cardiac death.²⁴ The challenge is to identify the subset of patients who are most susceptible to sudden death and therefore most likely to benefit from defibrillator implantation.

BNP level may be helpful in identifying these high-risk patients. Increased ventricular stretch and pressure cause electrophysiologic abnormalities that predispose patients to arrhythmias. Cellular hypertrophy can prolong action potential duration,²⁵ and increased myocardial stretch slows conduction, triggering after-depolarizations

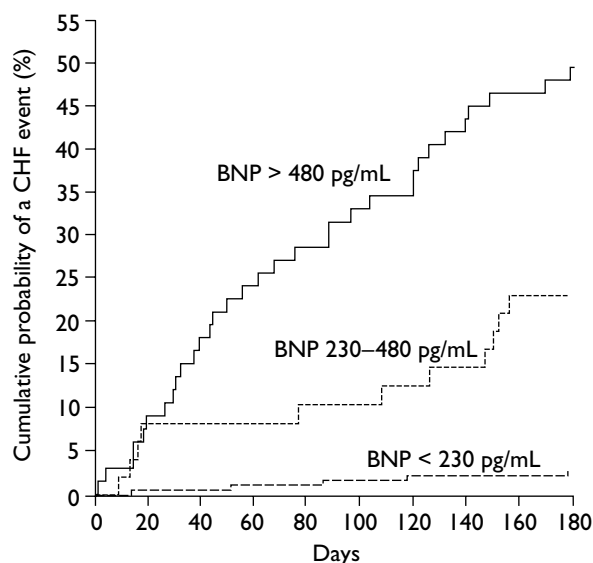


Figure 3. Reverse Kaplan-Meier plot showing cumulative risk for any congestive heart failure (CHF) event (emergency department visit or hospitalization for CHF or death from CHF) stratified by B-type natriuretic peptide (BNP) levels. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels greater than 480 pg/mL had a 6-month cumulative probability of a CHF event of 51%. Patients with BNP levels less than 230 pg/mL had only a 2.5% probability of a CHF event. (Adapted with permission from Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med* 2002;39:134.)

and ventricular ectopic beats.²⁶ These changes have arrhythmogenic consequences and also may be associated with increased BNP levels.²⁷ Berger et al²³ studied the relationship of BNP and sudden cardiac death in patients with left ventricular systolic dysfunction (ie, ejection fraction $\leq 35\%$); patients with BNP levels less than 130 pg/mL had a significantly higher sudden death-free survival rate (99%) than patients with BNP levels greater than 130 pg/mL (81%).²³ Further studies are needed to confirm these findings and to clarify the role of BNP levels in selecting patients for defibrillator implantation.

Survival after acute coronary syndromes. BNP level is elevated in patients with acute myocardial infarction and is a strong independent predictor of left ventricular function, heart failure, and long-term survival.^{28–31} de Lemos et al³² obtained a BNP level after the onset of ischemic symptoms in more than 2500 patients. BNP level showed direct correlation with the risk of death,

heart failure, and myocardial infarction. The unadjusted death rate increased in a stepwise fashion among patients in increasing quartiles of baseline BNP levels. The odds ratios for death at 10 months were 3.8, 4.0, and 5.8 in the second, third, and fourth quartiles of BNP levels, respectively.³² These findings demonstrate the utility of BNP level for risk stratification after presentation with acute coronary syndrome.

Use of BNP to Guide Care Decisions

BNP level may be useful to guide diuretic and vasodilator therapy in patients with CHF. Maisel et al¹⁰ demonstrated that plasma BNP levels directly correlated with functional CHF class and ranged from 244 ± 286 pg/mL in New York Heart Association class I to 817 ± 435 pg/mL in class IV. A study by Kazanegra et al³³ also showed a strong correlation between pulmonary wedge pressure reduction and decreasing BNP levels. Other studies suggest that BNP levels may be helpful for timing discharge after hospitalization for decompensated CHF³⁴ as well as for guiding outpatient management after discharge.³⁵ Use of BNP-guided drug management in the outpatient setting has been associated with reduced incidence of cardiovascular death, readmission, and new episodes of decompensated CHF.³⁵

BNP FOR TREATMENT OF HEART FAILURE

BNP has been predominantly studied for its diagnostic and prognostic role in patients with CHF. However, the natriuretic peptide also is available in a recombinant form—nesiritide—an intravenous medication that has been shown to be effective for treatment of decompensated CHF.³⁶ Nesiritide has been associated with symptomatic improvement (reduction of dyspnea) as well as favorable hemodynamic changes. It causes preload and afterload reduction, natriuresis, diuresis, suppression of the renin-angiotensin-aldosterone axis, and lowering of norepinephrine.³⁷ In a trial of 432 patients with decompensated CHF, nesiritide reduced dyspnea by 57% and improved global clinical status by 67%.³⁶ The agent also produced significant reductions in pulmonary capillary wedge pressure and systemic vascular resistance and increases in cardiac index. Clinical and hemodynamic improvements in patients receiving nesiritide appear comparable to standard intravenous therapy.³⁶

Asymptomatic hypotension is the most common adverse effect of nesiritide therapy and is dose-related.³⁸ Ventricular arrhythmias are less commonly observed in patients treated with intravenous nesiritide compared with dobutamine infusion.³⁹

CONCLUSION

CHF is a very common clinical entity, particularly among the elderly, but is often misdiagnosed in urgent care settings because of nonspecific symptoms and physical findings. BNP is a new assay that offers high sensitivity and specificity for detecting patients with CHF. The test appears particularly useful in patients presenting with dyspnea not clearly of cardiac etiology. Because of its high negative predictive value, BNP testing is a good screening tool and reliably excludes the diagnosis of heart failure.

BNP levels correlate with left ventricular end-diastolic pressure, pulmonary artery wedge pressure and atrial pressure, ventricular systolic and diastolic dysfunction, and left ventricular hypertrophy. BNP testing may offer a less invasive approach to monitoring cardiac and pulmonary pressures than the use of Swan-Ganz catheterization. BNP testing also may be useful in guiding inpatient and outpatient therapy. BNP levels correlate with prognosis in patients with CHF and following myocardial infarction. Higher levels are associated with greater morbidity and mortality, including sudden death. These findings suggest that patients with higher BNP levels should be more closely monitored and considered for defibrillator implantation.²³

BNP is an exciting new diagnostic and prognostic biomarker in CHF patients. Ongoing research promises to clarify the role of BNP testing by researchers and clinicians concerned with diagnosis and management of patients with heart failure.

HP

REFERENCES

- American Heart Association. Heart disease and stroke statistics—2003 update. Dallas (TX): The Association; 2002. Available at www.americanheart.org. Accessed 24 Jul 2003.
- Krumholz HM, Chen YT, Wan Y, et al. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J* 2000;139(1 Pt 1):72-7.
- Rich MW, Freedland KE. Effect of DRGs on three-month readmission rate of geriatric patients with heart failure. *Am J Public Health* 1988;78:680-2.
- Studies of left ventricular dysfunction (SOLVD)—rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction [published erratum appears in *Am J Cardiol* 1990;66:1026]. *Am J Cardiol* 1990;66:315-22.
- Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;261:884-8.
- Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
- Butman SM, Ewy GA, Standen JR, et al. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distention. *J Am Coll Cardiol* 1993;22:968-74.
- Marantz PR, Kaplan MC, Alderman MH. Clinical diagnosis of congestive heart failure in patients with acute dyspnea. *Chest* 1990;97:776-81.
- Peacock WF 4th. The B-type natriuretic peptide assay: a rapid test for heart failure. *Cleve Clin J Med* 2002;69:243-51.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.
- Devereux RB, Liebson PR, Horan MJ. Recommendations concerning use of echocardiography in hypertension and general population research. *Hypertension* 1987;9(2 Pt 2):II97-104.
- Baughman KL. B-type natriuretic peptide—a window to the heart. *N Engl J Med* 2002;347:158-9.
- Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an “emergency” cardiac hormone against ventricular overload. *J Clin Invest* 1995;96:1280-7.
- Nakao K, Ogawa Y, Suga S, Imura H. Molecular biology and biochemistry of the natriuretic peptide system. I: Natriuretic peptides. *J Hypertens* 1992;10:907-12.
- Struthers AD. Ten years of natriuretic peptide research: a new dawn for their diagnostic and therapeutic use? *BMJ* 1994;308:1615-9.
- Jensen KT, Carstens J, Ivarsen P, Pedersen EB. A new, fast and reliable radioimmunoassay of brain natriuretic peptide in human plasma. Reference values in healthy subjects and in patients with different diseases. *Scand J Clin Lab Invest* 1997;57:529-40.
- Sayama H, Nakamura Y, Saito N, et al. Relationship between left ventricular geometry and brain natriuretic peptide levels in elderly subjects. *Gerontology* 2000;46:71-7.
- Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202-9.
- Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of a B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings [published erratum appears in *Circulation* 2002;106:387]. *Circulation* 2002;105:595-601.
- Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.
- Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med* 1992;117:502-10.
- Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med* 2002;39:131-8.

23. Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392-7.
24. Gold MR, Nisam S. Primary prevention of sudden cardiac death with implantable cardioverter defibrillators: lessons learned from MADIT and MUSTT. Multicenter Automatic Defibrillator Implantation Trial. Multicenter Unsustained Tachycardia Trial. *Pacing Clin Electrophysiol* 2000;23(11 Pt 2):1981-5.
25. Zhu WX, Johnson SB, Brandt R, et al. Impact of volume loading and load reduction on ventricular refractoriness and conduction properties in canine congestive heart failure. *J Am Coll Cardiol* 1997;30:825-33.
26. Cameron JS, Myerburg RJ, Wong SS, et al. Electrophysiologic consequences of chronic experimentally induced left ventricular pressure overload. *J Am Coll Cardiol* 1983; 2:481-7.
27. Tomaselli GF, Beuckelmann DJ, Calkins HG, et al. Sudden cardiac death in heart failure. The role of abnormal repolarization. *Circulation* 1994;90:2534-9.
28. Omland T, Aakvaag A, Bonarjee VV, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. *Circulation* 1996;93:1963-9.
29. Horio T, Shimada K, Kohno M, et al. Serial changes in atrial and brain natriuretic peptides in patients with acute myocardial infarction treated with early coronary angioplasty. *Am Heart J* 1993;126:293-9.
30. Arakawa N, Nakamura M, Aoki H, Hiramori K. Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction. *J Am Coll Cardiol* 1996; 27:1656-61.
31. Nagaya N, Nishikimi T, Goto Y, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. *Am Heart J* 1998;135:21-8.
32. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345: 1014-21.
33. Kazanegra R, Chen V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated with decompensated heart failure: a pilot study. *J Card Fail* 2001;7:21-9.
34. Cheng V, Kazanegra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001;37:386-91.
35. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126-30.
36. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group [published errata appear in *N Engl J Med* 2000; 343:896 and 2000;343:1504]. *N Engl J Med* 2000;343: 246-53.
37. Brunner-La Rocca HP, Kaye DM, Woods RL, et al. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. *J Am Coll Cardiol* 2001;37:1221-7.
38. Nesiritide for decompensated congestive heart failure [letter]. *Med Lett Drugs Ther* 2001;43:100-1.
39. Burger AJ, Elkayam U, Neibaur MT, et al. Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. *Am J Cardiol* 2001;88:35-9.

Copyright 2003 by Turner White Communications Inc., Wayne, PA. All rights reserved.