WHEN THE HEART FAILS:
Identifying And Treating Heart Failure

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Objectives:

1. To explain the role of natriuretic peptides in the ED diagnosis of congestive heart failure.
2. To explain the results of the PROACTION trial and the role of nesiritide in the treatment of congestive heart failure.

Congestive heart failure (CHF) is a worldwide problem of epidemic proportions and represents a tremendous burden to overall healthcare costs.

- More than 4.5 million Americans have heart failure and about 550,000 new cases are diagnosed each year.1
- The incidence is expected to increase dramatically due to our aging population (9.8% prevalence of heart failure in individuals over age 74),1 improved survival from acute coronary syndromes, and management advances in cardiovascular diseases.2-4
- In 1999 there were 54,913 deaths attributed primarily to heart failure, a mortality rate of 20.1 per 100,000 people. However, this is significantly increased in the elderly- 35.8 to 138.1 to 821.9 for those ages 65-74, 75-84, and >85 years.5
- In 1997, there were nearly one million CHF hospital discharges, a 150% increase from 1979. Ten million people are expected to have the disease by the year 2007.6

This translates into staggering economic expenditures. Hospitalization for heart failure exacerbation accounts for the largest expenditure for care of these patients; it is estimated to be about $23 billion per year. The Centers for Medicare and Medicaid Services identified CHF as the disease most worthy of cost-effective management.7

Emergency physicians have become the gatekeepers for this epidemic. One-third of all heart failure patients receive inpatient care each year and nearly 80% of emergency department (ED) presentations for heart failure are admitted.1,8 Emergency department patients seen, admitted, and treated in an inpatient bed for new onset heart failure or acute decompensation of CHF account for the majority of inpatient expenditures.9 Emergency physicians have an opportunity to have a significant impact on this epidemic if they can be armed with the proper diagnostic, therapeutic and risk-stratification tools.

DIAGNOSTIC ADVANCEMENTS

Until recently, a definitive diagnosis of CHF was often obtained after the patient was admitted to the hospital and had undergone echocardiography, right heart catheterization, or both. Rarely are these tests readily available in the ED, forcing the emergency physician to rely on history and physical examination, along with a few ancillary tests such as chest radiography and electrocardiography. The poor diagnostic accuracy of history and physical examination are well documented.10 While an S3 heart sound has a specificity of 99%, its sensitivity of 24% makes it less than ideal as a screening tool in the
Similarly, chest radiography misses 20% of echo-proven cardiomegaly, and many patients with chronic CHF will have elevated pulmonary capillary wedge pressures despite a lack of congestion on chest x-ray. While the signs and symptoms of CHF should raise the suspicion of CHF, a more objective test is needed to confirm the diagnosis.

**NATRIURETIC PEPTIDES**

The natriuretic peptides are promising markers of myocardial dysfunction and heart failure. It has been known for almost 50 years that the heart is not only a cardiorespiratory organ but an endocrine organ as well. In 1956, electron microscopy was used to demonstrate granules present in the atria that were absent in the ventricle, eventually shown to represent vesicles containing atrial natriuretic peptide (ANP). Henry and Pearce observed an increase in urine flow when a balloon was inflated in the atrium of a dog. Influenced by these initial investigations, subsequent studies have identified three natriuretic peptides: ANP (predominantly secreted from atrial myocardium), brain or b-type natriuretic peptide (BNP, predominantly secreted from ventricular myocardium) and c-type natriuretic peptide (CNP, predominantly secreted from vascular endothelium) (Figure 1).

Of these three peptides, BNP has been found to be the most useful. BNP is released under conditions of increased myocardial stretch and possesses vasodilatory and natriuretic properties. It is released as a prohormone and upon secretion from the myocyte it is cleaved into the biologically active BNP (32 amino acids in length) and the biologically inactive NT-proBNP (76 amino acids). BNP is primarily removed by natriuretic peptide receptors with a small amount of renal clearance, while NT-BNP is primarily cleared by the kidney (Table 1.).

**BNP**

In July of 2002, the Breathing Not Properly Multinational study confirmed findings from pilot studies that BNP was useful as a diagnostic marker in patients presenting to the ED with undifferentiated dyspnea. A BNP value <100 pg/ml virtually excludes CHF as a cause of dyspnea (sensitivity -90%, negative predictive value -89%). A patient with a BNP value over 400 pg/ml is highly likely to have CHF. However, there were a small percentage of patients with a history of CHF but “no acute exacerbation” that did have BNP values over 1000 pg/ml. Intermediate BNP levels (100-400 pg/ml) need
to be interpreted in the context of the patient’s clinical evaluation (Figure 2).

There will be a subset of patients where another disease process causes a rise in BNP and is responsible for the current episode of dyspnea. For instance, a young female with pleuritic chest pain may have right ventricular strain from a pulmonary embolus causing a 300-400 pg/ml rise in BNP.\(^{18,19}\) Knowledge of a patient’s compensated “dry weight” BNP would be useful during an acute decompensation, similar to baseline peak flows in an asthmatic with an acute asthma exacerbation (Figure 3).

The BNP study also demonstrated that those patients with diastolic dysfunction had significant elevations in BNP compared with those patients without CHF - median BNP 413 pg/ml in diastolic dysfunction and 821 pg/ml in systolic dysfunction.\(^{20}\)

While BNP has been helpful at levels < 100 pg/ml and > 400 pg/ml, there are some confounders when using the test. The cutoff levels mentioned above for patients with normal creatinine clearance do not apply to patients with renal insufficiency. In a separate analysis of the BNP study it was found that as creatinine clearance worsened the cut point for maximum diagnostic accuracy increased as well (Figure 4).\(^{21}\) For example, patients with non-cardiac dyspnea and moderately reduced renal function (eGFR 30-59 ml/min/1.73 m²) had a mean BNP level over 200 pg/ml (Figure 5). However, nearly 90% of subjects with a BNP value of > 500 pg/ml had CHF regardless of the severity of renal insufficiency.

Age and gender also appear to have an influence on BNP levels. Redfield and colleagues evaluated 2042 randomly selected residents of Olmstead County, Minnesota and found that in the subgroup of normal patients (n=767) that BNP values were significantly higher in women compared with men (p<0.001) (Table 2), and that BNP values increased with age within each gender.\(^{22}\) Interestingly, BNP was 21% higher in women taking hormone replacement therapy (HRT) than in women not on HRT.

**BNP SUMMARY**

Brain natriuretic peptide is most useful in excluding CHF as a diagnosis. With a high sensitivity and NPV at 100 pg/ml, it is highly unlikely that subjects with BNP’s < 100 pg/ml have CHF. Above 400 pg/ml, it is highly likely the patient suffers from decompensated CHF. However, a minority of patients will have “baseline” BNP values well above this level. In the area of 100-400 pg/ml, BNP requires clinical correlation because of the effect of age, sex, and other disease processes.

**NT-BNP**

While it has not been validated to the extent of BNP, recent studies of NT-BNP have confirmed earlier findings that NT-BNP is an accurate marker of left ventricular dysfunction.\(^{23-25}\) BNP and NT-BNP correlated well with each other (r²=0.94) and were predictive of New York Heart

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### TABLE 1. Characteristics of the BNP and NT-proBNP.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
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<tbody>
<tr>
<td>Size</td>
<td>32 AA</td>
<td>76 AA</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>Stability</td>
<td>Up to 4 hours at room temp</td>
<td>Up to 6 hours at room temp</td>
</tr>
<tr>
<td>Clearance</td>
<td>NPR-C, endopeptidase, kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td>Use with Nesiritide</td>
<td>No</td>
<td>Yes</td>
</tr>
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Association (NYHA) classification (both markers p<0.0001) and ejection fraction in 92 ambulatory patients (BNP p=0.0003 and NT-BNP p < 0.0001). NT-BNP proved to be a strong marker of reduced systolic function (EF < 40%) in a cohort of 2193 patients admitted to a general hospital. Those patients with reduced systolic function were detected at a sensitivity of 78%, specificity of 76%, negative predictive value of 96% and positive predictive value of 30%. These findings were similar to earlier studies performed with the BNP assay. One would expect overall lower diagnostic test characteristics when an assay is compared solely to left ventricular ejection fraction (LVEF) because there is a large cohort of patients with diastolic dysfunction that would have elevated NT-BNP values but have “normal” LVEF. This study also found that both serum creatinine and age added significant information when predicting a reduced LVEF.

In 415 ambulatory patients with possible heart failure, NT-BNP increased as EF worsened (Table 3). It was less helpful in patients with diastolic dysfunction, especially those with only mild relaxation abnormalities. Interestingly, while NT-BNP was helpful in those subjects where the examining cardiologist felt there was a “strong” (NT-BNP =227 pmol/L) or “no” (NT-BNP=66 pmol/L) suspicion of CHF, it was not helpful in the group with “moderate” clinical suspicion of CHF (mean NT-BNP = 85 pmol/L vs 73 pmol/L in normal subjects). This clinical scenario may be similar to the “intermediate” level seen with the BNP assay (100-400 pg/ml) where clinical suspicion combined with BNP levels may be most helpful. While those with creatinine > 130 µmol/L had a significantly elevated NT-BNP compared to those with normal creatinine (NT-BNP = 173 pmol/L vs 81 pmol/L, p<0.0001), multiple logistic regression revealed no correlation between creatinine and NT-BNP. Similar to previous studies, after multiple logistic regression, age > 75 years predicted an increased NT-BNP. The age-dependence of the NT-BNP assay was also seen in a study of 243 consecutive healthy subjects with no history of cardiovascular illness or CHF risk factors. The authors suggested the normal NT-BNP cut-off for subjects < 50 years should be 100 pg/ml and the normal cut-off for subjects > 50 years should be 200 pg/ml.
NT-BNP AND BNP SUMMARY

Both BNP and NT-BNP have been validated against LVEF and have been found to have similar test characteristics. While, BNP increases with age and sex, NT-BNP seems to do so at a much greater degree. A number of studies have found age-appropriate cut-offs for NT-BNP, and one of the commercially available assays (Roche™) suggests 2 cutoffs based on age (age < 75 normal cutoff = 125 pg/ml, age > 75 normal cutoff = 450 pg/ml). Both BNP and NT-BNP are elevated in patients with renal insufficiency even though they may have no clinical or echocardiographic evidence of CHF. While BNP's relationship to creatinine clearance has been well defined (> 90% chance of CHF when BNP > 500 pg/ml), the relationship with NT-BNP is less well delineated. Because only the kidney clears NT-BNP it would be expected that renal disease would have a much greater impact on interpretation of NT-BNP results than BNP results. Finally, while BNP has been confirmed in an ambulatory ED population, using hospital discharge diagnosis of CHF as the gold standard, which captures both systolic and diastolic dysfunction, NT-BNP has not been validated in a similar fashion.

HEART SOUNDS AND THE DIAGNOSIS OF CHF

Significance of S3 and S4 heart sound detection in CHF

While detection of an S3 can be “normal” in adolescents and young adults, its detection after the age of 40 is considered abnormal.28-30 Traditionally not very sensitive for left ventricular dysfunction, when detected, an S3 can be very predic-
tive of elevated left ventricular pressure. In a study of outpatients referred for cardiac catheterization, the detection of an S3 was the most specific finding of left ventricular end diastolic pressure (LVEDP) (95%). A more recent study has also found that the detection of an S3 has a high specificity and positive predictive value in detection of patients with low ejection fractions. Unfortunately, while having a high specificity for elevated filling pressures, an S3 has been reported to have a sensitivity of only 25%. Even more importantly, it has been suggested that patients with a detectable S3 have an increased risk of hospitalization and death compared to those patients without a detectable S3.

Similarly, the presence of an audible S4 appears to be suggestive of cardiac disease, but there have been conflicting data in previous studies. Spodick and Quarry found the presence of an S4 to be no more common in patients with heart disease than those without. However, the temporal relationship of the S4 to the P wave may be more important than the mere presence of an S4. Those patients with increasing LVEDP have a decrease in the time interval between the onset of atrial contraction (P wave) and the development of an S4 [the P-S4 interval (PS4I)]. Unfortunately, identification of an S3 or S4 is difficult in the ED setting and other clinical environments. In the aforementioned studies, which suggest a low incidence of S3 detection in heart failure, perhaps abnormal heart sounds may have been present but physicians were unable to detect them. Recent studies indicate that physicians are becoming less proficient at performing the physical examination, and physicians in residency programs have been shown to have poor cardiac auscultatory skills. Furthermore, interobserver agreement of S3 detection is poor, with board-certified cardiologists having no better agreement than house staff. Compounding the difficulty of S3 or S4 detection is the loud ED environment, confounding illnesses such as COPD and obesity that make detection difficult, and the inability of the patient to tolerate being placed in the ideal examining position (recumbent) because of their dyspnea.

**PHONOCARDIOGRAPHY**

While detection of an S3 or S4 may be useful as a diagnostic and prognostic tool in ED patients with dyspnea, the traditional method of auscultation is less than ideal. However, technology has been developed to aid the clinician at bedside diagnosis of an S3/S4. The Audicor™ phonocardiogram (Inovise Medical, Inc) uses a dual sensor in conjunction with standard ECG electrodes. The dual sensor simultaneously acquires electrical and acoustical data from the V3 and V4 position on the standard 12-lead ECG. This allows simultaneous recording of both the 12-lead ECG and the acoustical information. The phonocardiogram attaches to the standard ECG machine. The sensors on

<table>
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<tr>
<th>Gender</th>
<th>BNP Age 45-54</th>
<th>BNP Age 55-64</th>
<th>BNP Age 65-74</th>
<th>BNP Age 75-83</th>
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<td>Women</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Biosite</td>
<td>8-73</td>
<td>10-93</td>
<td>13-120</td>
<td>16-155</td>
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<td>Shionogi</td>
<td>7-157</td>
<td>9-192</td>
<td>11-233</td>
<td>13-284</td>
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<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Biosite</td>
<td>4-40</td>
<td>5-52</td>
<td>7-67</td>
<td>9-86</td>
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<tr>
<td>Shionogi</td>
<td>6-120</td>
<td>7-146</td>
<td>8-177</td>
<td>10-216</td>
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**TABLE 2.** Age and Gender-Specific Ranges for Plasma BNP (pg/ml).
leads V3 and V4 are only slightly larger than standard ECG leads. Diagnostic algorithms then analyze both types of data and report on the presence of an S3, S4 and left ventricular hypertrophy (LVH). While limited, the initial data on the use of this technology appear promising. Using a gold standard of expert over-read of printed acoustical heart sounds, the Audicor™ had a sensitivity of 71% and a specificity of 94% for detection of an S3 in a study of 314 patients. This technology has not been validated in a cohort of dyspneic ED patients.

**THERAPEUTIC ADVANCEMENTS**

While there have been numerous large scale trials over the last decade demonstrating the efficacy of beta-blockers and ACE inhibitors for the outpatient treatment of CHF, therapeutic trials involving ED patients with decompensated CHF have been lacking. In 2001 the FDA approved nesiritide (recombinant b-type natriuretic peptide) for use in acute decompensated heart failure. Nesiritide is a sterile, purified preparation of human B-type natriuretic peptide, manufactured from E. coli using recombinant DNA technology. Nesiritide leads to vasodilatation by binding to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells. There have been 3 large inpatient trials establishing the efficacy and safety of nesiritide. The first study evaluated the effect of nesiritide on both pulmonary capillary wedge pressure (PCWP) and symptomatic improvement when compared with placebo and standard therapy in hospitalized patients with decompensated CHF. This study established nesiritide’s ability to improve hemodynamic parameters to a greater degree than placebo (efficacy trial). It also demonstrated the ability of nesiritide to improve most clinical parameters of decompensated heart failure (comparative trial) to the same degree as standard care agents. Nesiritide was then compared to nitroglycerin in hospitalized patients with

<table>
<thead>
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<th>Echocardiographic finding</th>
<th>N</th>
<th>Mean (SD) N-terminal proBNP, pmol/L</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td></td>
<td></td>
<td>9.8-39.8</td>
<td>39.8-100</td>
<td>100-251</td>
<td>251-1007</td>
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<tr>
<td>Normal SFN and DFN</td>
<td>214</td>
<td>73 (56)</td>
<td>26</td>
<td>56</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Systolic dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EF 40-49%</td>
<td>55</td>
<td>89 (75)</td>
<td>18</td>
<td>55</td>
<td>24</td>
<td>4</td>
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<tr>
<td>EF 30-39%</td>
<td>45</td>
<td>152 (110)</td>
<td>9</td>
<td>33</td>
<td>40</td>
<td>18</td>
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<tr>
<td>EF &lt;30%</td>
<td>9</td>
<td>428 (352)</td>
<td>0</td>
<td>11</td>
<td>44</td>
<td>44</td>
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<tr>
<td>Isolated diastolic dysfunction</td>
<td>92</td>
<td>58 (39)</td>
<td>42</td>
<td>45</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Relaxation abnormalities</td>
<td>79</td>
<td>51 (31)</td>
<td>47</td>
<td>44</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Psuedonormal pattern</td>
<td>13</td>
<td>95 (58)</td>
<td>15</td>
<td>47</td>
<td>39</td>
<td>0</td>
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**TABLE 3.** Plasma N-terminal proBNP concentration in relation to cardiac function by Doppler echocardiography, and fractions of patients with different echocardiographic findings in the different quartiles of N-terminal proBNP concentration.
decompensated CHF. It was shown that nesiritide and nitroglycerin had similar effects on hemodynamic and clinical variables in these subjects. This study was criticized for the relatively small doses of nitroglycerin used (27-56 mcg/min), though both groups had similar changes in blood pressure. PRECEDENT was an open-label study that compared ventricular arrhythmias as well as clinical signs and symptoms in 255 patients with decompensated CHF receiving low-dose dobutamine (> 5 mcg/kg/min) or one of two nesiritide doses (0.015 or 0.030 mcg/kg/min infusion with no preceding bolus). Dobutamine significantly increased all endpoints of ventricular ectopy when compared to baseline Holter monitoring, while nesiritide produced less ventricular ectopy and no reflex tachycardia. The clinical significance of these outcomes is not clear. The authors argue that all premature ventricular beats are important because they not only increase the likelihood of ventricular failure and sudden death but also reduce stroke volume and worsen CHF. Though not powered for mortality, there were no differences in mortality at 14 days among the 3 treatment groups.

The PROACTION trial evaluated the efficacy of nesiritide use in ED patients with decompensated CHF. The results of this study were presented in abstract form at the American College of Cardiology conference in 2003. PROACTION was a multicenter, randomized, double blinded, pilot study of 250 patients that were felt to need prolonged treatment of decompensated heart failure evidenced by dyspnea at rest or walking less than 20 feet. Patients received nesiritide or placebo and standard therapy that included diuretics, O₂, morphine and non-parenteral nitrates for at least 12 hours in an observation unit (OU). ACE inhibitors were withheld for 3 hours. Other vasodilators and inotropes were withheld for 3 hours and discouraged for the first 12 hours. Patients were either admitted or discharged after a maximum of 24 hours in the ED but could be continued on study drug. The overall admission rate was 55% for placebo and 49% for nesiritide, while the admission rate for CHF was 38% for placebo and 30% for nesiritide. In the patients admitted to the hospital, there was a 57% (23% placebo and 10% nesiritide) decrease in hospital readmissions in the nesiritide group, and those that were hospitalized spent 45% less time (8.3 vs 4.6 days) in the hospital when compared to placebo. Though there were more deaths in the nesiritide group compared with placebo (5 vs 1) the study was not powered to evaluate mortality. Of the 6 deaths, possibly 3 in the nesiritide (1 CHF, 1 unexplained, 1 apnea) and 1 in the placebo (sudden death) group may have been related to CHF. There was no comment made on the readmission rate in the patients discharged directly from the OU.

Results of PROACTION indicate that nesiritide is likely a safe alternative to nitroglycerin in decompensated CHF, may decrease admission rates from an OU as well as decrease overall hospital length of stay in a 30-day time period. Future clinical studies need to identify the subgroups of ED patients where nesiritide may be cost-effective as first-line therapy such as renal insufficiency, systolic dysfunction, etc. Until then, the expense of nesiritide at a cost of approximately $500 for a 24-hour infusion compared with about $30 for nitroglycerin prohibits it from being first-line therapy in the majority of ED patients with CHF.
SUMMARY

Heart failure is a disease of epidemic proportions whose prevalence will continue to increase over the next decade. As the majority of CHF admissions come from the ED, the emergency physician is ideally positioned to have an immediate impact on admission rates and healthcare expenditures. In the last couple of years we have seen the validation of natriuretic peptides as markers of CHF, as well as the development of a synthetic natriuretic peptide (nesiritide) that may prove to be a promising first-line treatment modality in certain subgroups of ED patients with decompensated CHF. With the continued development of new diagnostic and therapeutic strategies, not only will emergency physicians be able to improve their diagnostic certainty, they will also become better able to implement cost-effective therapy.

REFERENCES


44. Inovise Medical, I., Performance for Audicor 1.0. Data on file with Inovise Medical, Inc.


49. Natrecor package insert. Scios (Sunnyvale, CA).


