The Emerging Roles of BNP and Accelerated Cardiac Protocols in Emergency Laboratory Medicine

CHARIS HAINAUT, WAYNE GADE

BACKGROUND: The role of the clinical laboratory in emergency cardiac medicine is rapidly evolving; with recent redefinitions of acute myocardial infarction (AMI) and unstable angina (UA) based on troponin levels, recommended acceleration of cardiac testing protocols, and increased clinical measurement of B-type natriuretic peptide (BNP). We briefly review the background pathophysiology of acute coronary syndromes (ACS) and congestive heart failure (CHF), along with an overview of the biochemistry and physiology of the natriuretic peptides.

METHODS: The assay principles and performance characteristics of the rapid BNP assays are discussed. The performance characteristics of troponin assays are at the center of controversy regarding the redefinition of AMI and UA, and will be discussed.

RESULTS: We review the rapidly expanding evidence regarding the clinical utility of BNP for CHF patients. While BNP has gained wide acceptance as a rapid diagnostic tool, considerable controversy remains concerning its potential for prognosis, screening, and therapeutic monitoring. Although a thorough discussion of the use of cardiac markers is well beyond the scope of this review, overviews of the redefinitions of AMI and UA, and the trend toward accelerated testing protocols to obtain a quicker diagnosis or ruling-out of AMI are included. In addition to accelerating the retesting of existing markers, a recent test for ischemia modified albumin (IMA) promises another quantum leap in cardiac diagnoses.

CONCLUSIONS: The positive impact of these developments on the healthcare costs and overall improvement in the quality of healthcare delivery will be discussed. A brief analysis of the downstream costs of BNP testing is also offered.

ABBREVIATIONS: ACS = acute coronary syndromes; AMI = acute myocardial infarction; BNP = B-type natriuretic peptide; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; ED = emergency department; hsCRP = high sensitivity C-reactive protein; IMA = ischemia modified albumin; LV = left ventricular; MI = myocardial infarction; NCAB = National Academy of Clinical Biochemists; NPV = negative predictive value; NYHA = New York Heart Association; PE = pulmonary embolism; RAAS = renin-angiotensin-aldosterone system; RV = right ventricular; UIA = unstable I angina.

INDEX TERMS: acute coronary syndromes; BNP; cardiac protocols; coronary testing; myocardial infarction.

Clin Lab Sci 2003;16(3):166

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LEARNING OBJECTIVES

After reading the following articles, the reader will demonstrate his/her understanding of the material by achieving the following:

1. Describe the biochemistry of the BNP and the other natriuretic peptides.
2. Describe the major physiologic responses to the elevation of BNP levels.
3. Discuss the mechanism by which the binding of BNP to the target cell results in alteration of Na^+ and water reabsorption.
4. Describe the formation of arterial plaque and the development of coronary artery disease and acute coronary syndromes (ACS).
5. Describe the physiological conditions that develop into CHF and cause the release of BNP.
6. Describe and interpret the diagnostic accuracy, sensitivity, specificity, and negative predictive values reported for rapid BNP assays.
7. Describe the trend toward "accelerated cardiac protocols," including which markers are suggested, and the suggested time-course of sequential testing.
8. Evaluate patient data and derive appropriate diagnostic conclusions.
9. Discuss the use of BNP for prognosis and screening of patients for LV dysfunction.
10. Discuss the interpretations of slightly elevated levels of troponin and C - reactive protein (CRP) as they relate to ACS and risk analysis.

CLINICAL LABORATORY'S ROLE IN CARDIAC MEDICINE

During the past few years, the clinical laboratory has assumed a much more active role in risk assessment and diagnosis of cardiac disease. While traditional lists of risk factors had focused primarily on family history, personal habits (smoking and sedentary life style), and related health characteristics (diabetes and obesity), most recent additions to the list of risk factors fall within the realm of clinical chemistry. These factors include high sensitivity C-reactive protein (hsCRP), measured LDL-cholesterol, homocysteine, and others.

As late as the mid 1990s, traditional cardiac markers were relatively non-specific and frequently took six to eight hours to elevate sufficiently for a physician to confirm the diagnosis of acute myocardial infarction (AMI). Prior to 2000, patients with dyspnea and chest pain presented an even more difficult differential diagnosis, because physicians had to distinguish between congestive heart failure (CHF), various chronic pulmonary disorders, pneumonia, other acute coronary syndromes (ACS), cardiomyopathies, and even such diverse possibilities as severe anemias and acute anxiety. As a result, the diagnosis of CHF frequently took hours or days and relied on expensive, often ambiguous, imaging evidence to exclude all other diagnoses and confirm CHF.

With the acceptance of new cardiac markers, and a recommended acceleration of testing protocols, many emergency cardiac units now expect to diagnose or rule out AMI within 90 minutes. Since 2000, diagnosing CHF has also become faster, easier, less expensive, and more reliable through the introduction of rapid laboratory testing for B-type natriuretic peptide (BNP).

This paper reviews the evidence supporting BNP as a rapid diagnostic test, capable of distinguishing CHF from other causes of ambiguous symptoms such as dyspnea and angina. The physiologic role of BNP in CHF and left ventricular disorders is also discussed, along with its use in prognosis, therapeutic monitoring, and staging of CHF patients. BNP's controversial role as a pre-screen for patients suspected of left ventricular (LV) dysfunction is also discussed. Finally, the emerging role of BNP is placed in the context of accelerated cardiac protocols with troponin, myoglobin, and ischemia-modified albumin to illustrate the active diagnostic role for the clinical laboratory in a wider range of cardiopulmonary conditions.

BACKGROUND OF CARDIAC DISEASES

Plaque formation and its relationship to inflammation

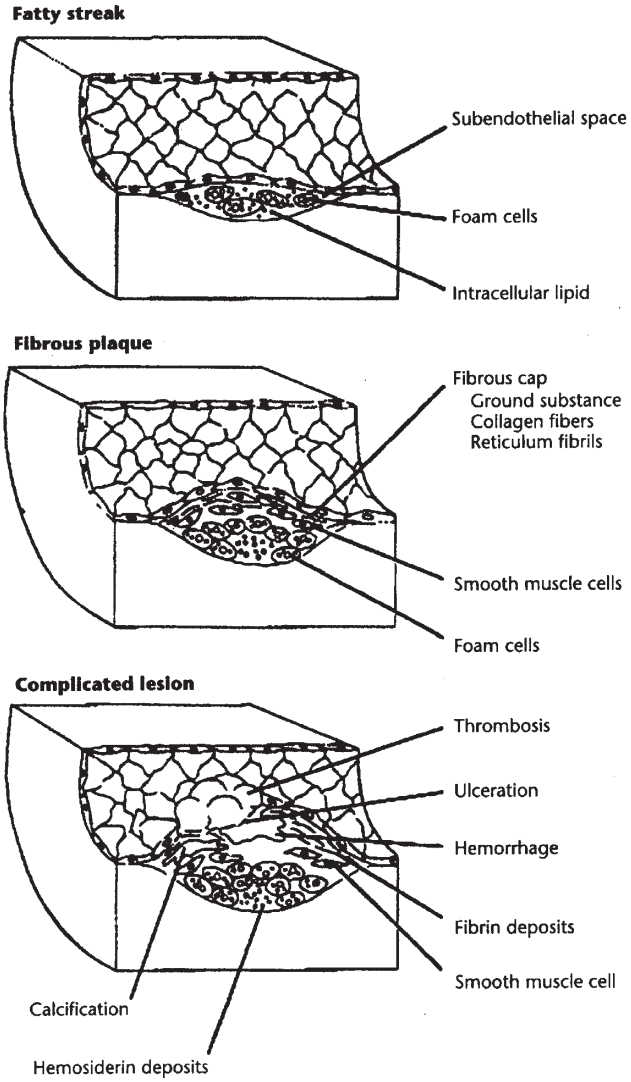
ACSs are described as a wide spectrum of conditions ranging from a thrombotic event causing complete occlusion of a coronary artery (an MI), to the partial occlusions associated with mild exertional angina.[1,2] Plaque development is the central process in ACS, and contributes directly to nearly 500,000 cardiac deaths, over three million hospital admissions, and estimates of between $10 billion and $56 billion in healthcare costs per year.[3,4]

Plaque formation is a complex, inflammatory process (illustrated by Figure 1) that is initiated by the oxidation of LDL lipoproteins, followed by their endocytosis by macrophages.[1,2] In patients at high risk for developing heart disease, large numbers of LDLs are engulfed and transform these macrophages into foam cells. Foam cells congregate in locations between the endothelial layer and underlying layers of extracellular matrix and smooth muscle in arterial walls. Foam cells also release chemotactic and growth-promoting substances reminiscent of a typical inflammatory response following an infec-

tion or allergic episode. The inflammatory aspect of the plaque development is further accentuated by reports that higher baseline levels of hsCRP are associated with an increased risk of heart disease.[5]

As plaques continue to enlarge, with increased fibrous material and calcification, they eventually bulge into the artery lumen and cause partial occlusion. Deposition of plaque material is a lifelong process that starts as fatty streaks in childhood and can continue until arteries become total occluded. Restricted blood flow (ischemia) leads to angina even in arteries that are only partially occluded. Plaque rupture can, of course lead to the thrombosis and total occlusion that define an AMI. Alternatively, near-total occlusion and/or microthrombosis is characteristic of unstable angina and often precedes an AMI as a pre-infarction, or mini-infarction.[6] Elevated levels of troponin below the myocardial infarction (MI) cutoff provide evidence of myocardial injury, and unify the concept that both MI and unstable angina (UA) belong on the same ACS continuum.[7] Note that even in the absence of plaque rupture or an acute event, partial occlusion causes increased vascular resistance, and thereby contributes significantly toward the development of most cases of CHF.

Figure 1. Steps in the development of arterial plaques



(Reprinted from Kaplan and others. Clinical chemistry, theory, analysis, correlation. 4th Ed., St Louis MO, Mosby, with permission.)

What is CHF and how common is it?
According to the 1996 Data Fact Sheet released by the National Heart, Lung, and Blood Institute, nearly five million Americans suffer from CHF, defined by an inability of the heart to provide sufficient circulation to the body (ischemia).[8] Dyspnea (shortness of breath) is generally the primary presenting symptom for CHF patients, with the accompanying hypoxia (inadequate oxygen delivery to tissues) frequently resulting in chest pain (angina).

CHF affects all age groups, with 400,000 new diagnoses, and more than 2.5 million hospitalizations each year. The incidence of CHF increases dramatically with age, affecting 2% of people ages 40 to 59 and 10% of those over 70. CHF is the leading cause of hospital admissions in the elderly, accounting for 20% of their total admissions. The five-year mortality rate for CHF patients approaches 50%. The incidence of CHF is expected to increase dramatically as the U.S. population ages, and as more patients survive an MI, but suffer myocardial damage resulting in CHF.[8]

Causes of congestive heart failure

Conditions that lead to CHF are listed in Table I, and can be divided into three categories. These categories include: 1) increased vascular resistance (atherosclerosis, pulmonary disease, and hypertension); 2) damaged cardiac tissue (previous ischemic heart disease or infection); or 3) malfunctions of heart valves, neuronal stimulation (arrhythmias), or cardiac muscle (cardiomyopathies).[2,4] Each of these conditions forces the heart to compensate until it fails to maintain adequate oxygenation and circulation.

The leading cause of CHF is coronary artery disease. The slow development of arterial plaques and partial occlusion of the arteries results in increased vascular resistance and increased cardiac workload.[9,10] Other conditions such as hypertension and edema can also increase vascular resistance.

Renal conditions, such as hyper-secretion of renin or aldosterone, or deficiencies in glomerular filtration can lead to hypertension. However, hypertension also results from normal compensation by kidneys and lungs in response to the decreased blood flow that is characteristic of CHF. This compensation includes activation of the Renin-Angiotensin-Aldosterone System (RAAS), which promotes retention of both sodium and water and leads to increased blood pressure. Regardless of the underlying cause, activation of RAAS forces the heart to increase the rate and strength of contractions to overcome the increased resistance. Thus, renal function can initiate and/or accelerate the multi-organ compensation spirals that can become uncontrolled, and lead to a worsening of CHF symptoms or decompensation (see Figure 2).[9]

Table 1. Conditions known to cause CHF

Coronary artery disease and atherosclerosis
Myocardial damage resulting from MIs or ischemic heart disease
Uncontrolled blood pressure (hypertension)
Pulmonary diseases such as COPD and pneumonia
Heart valve problems resulting from an infection or congenital defects
Cardiomyopathies (abnormalities of the heart muscles) and arrhythmias
Anemias or other hematological disorders that require coronary compensation

Edema can be caused by hypertension, renal protein losses (glomerular nephritis or nephrotic syndrome), increased vascular permeability, or decreased liver function. Whatever the origin, edema increases backpressure and continuance of a compensation spiral. Thus, it is often difficult to pinpoint the initiating factor among other factors that contribute to the spiral.

Plaque ruptures can lead to clot formation, total occlusion (an MI), and result in significant myocardial necrosis. The damaged tissue is replaced by fibrotic tissue, and the remaining muscle is forced to work harder. This sequence (illustrated in Figure 2) frequently leads to CHF in MI survivors.[9,10] Although Figure 2 describes the events initiated by an MI to cause myocardial damage, a similar chain of events could result from numerous other initiating events. For example, various forms of chronic obstructive pulmonary disease (COPD) can cause episodes of dyspnea, angina, and if hypoxia becomes too severe, they can damage myocardial tissue. Pulmonary disorders that impair gas diffusion (such as pulmonary fibrosis) can also cause hypoxic damage to cardiac or renal tissue, without the restricted blood flow that defines ischemia.[9] Heart valve dysfunction, arrhythmias, and cardiomyopathies cause inefficient contractions, decrease cardiac output, and lead to CHF. Again, compensation by other organs, including activation of RAAS, can initiate a compensation spiral and lead to further development of CHF.

Decompensation in CHF refers to a serious decrease in circulation that converts the chronic disease into an acute episode. Decreased circulation causes blood to pool in the veins (stenosis), and results in edema as fluids leak into extravascular spaces.[9-11] CHF can involve only one side of the heart or both sides; however, LV failure typically occurs first. LV failure causes inadequate circulation to peripheral tissues, and pulmonary edema develops as fluids build up in the lungs. Right ventricular (RV) failure causes peripheral edema because blood received from the body cannot be pumped toward the lungs for reoxygenation.[9,10] Pulmonary edema, resulting from LV failure, often leads to congestion and ischemic damage to the right side, or RV failure as shown in Figure 2.

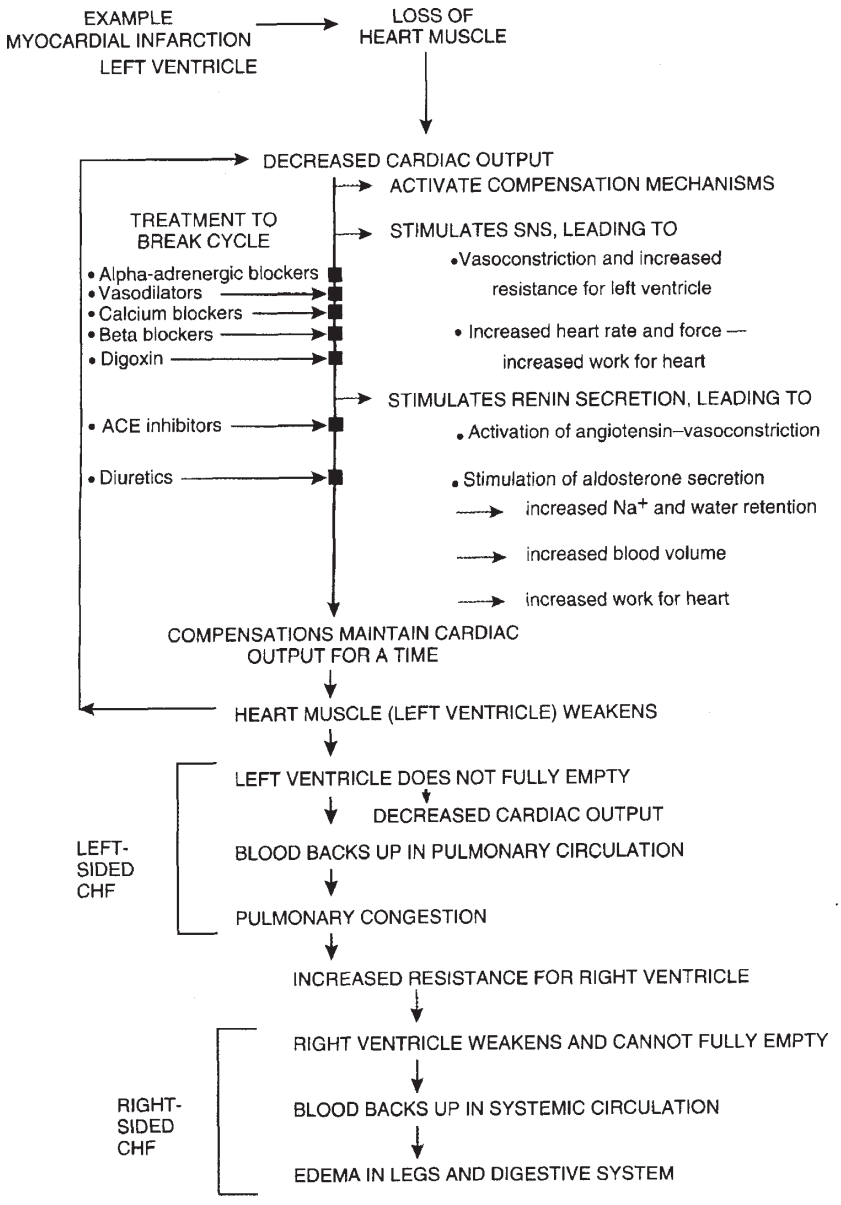
Symptoms and pathogenesis of CHF

Unless an acute event (such as an MI) causes immediate tissue damage, CHF frequently has an insidious onset.[9,10] Many patients are asymptomatic during early stages of heart fail-

ure because the body effectively compensates for the decreased circulation. Initially, the heart enlarges (hypertrophy) to compensate for inefficiency during the early stages of CHF. At some point, hypertrophy becomes limited, and inadequate cardiac output ultimately leads to a series of events similar to those described in Figure 2.

Once cardiac output has decreased substantially, blood will be diverted from other organs to maintain an adequate supply to the heart and brain. Decreases in renal circulation result in hypertension, decreased glomerular filtration, and azotemia (elevated BUN and creatinine). The first renal response is to activate RAAS. Another important renal response to ischemia is the release of erythropoietin, which stimulates the bone marrow to increase production of red blood cells. These two renal mechanisms normally help protect against dehydration, blood loss, hypoxia, and circulatory shock.[2,9] However, activation of RAAS and release of erythropoietin both cause increased blood pressure and volume. Therefore, each can be counterproductive to the CHF patient by increasing backpressure and workload for the failing heart.

Figure 2. The development of congestive heart failure following damage to heart muscle from an MI or other cause



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As overall circulation decreases in CHF, blood flow to organs such as the gastrointestinal tract decreases disproportionately as blood is diverted to more critical organs. This compensation works initially, but inevitably weakens the entire body. As the digestive tract loses blood flow, there is a loss of appetite with tendencies toward nausea and inadequate nutrition. Eventually, this further weakens the heart and body, and the patient becomes symptomatic. Early CHF symptoms include fatigue, dyspnea, persistent coughing or wheezing, edema, confusion, nausea, lack of appetite, and increased heart rate. Symptoms suggestive of LV failure are related primarily to pulmonary edema, and include a persistent cough and dyspnea. RV failure causes symptoms related to peripheral edema. Neurological symptoms such as confusion may result from fluctuations in electrolytes and critical metabolites such as glucose.

Once a diagnosis of CHF is made, the classification according to symptom

severity is done using the New York Heart Association (NYHA) System. Class I patients have asymptomatic CHF. Patients in Class II experience mild symptoms, such as exertional dyspnea, and minor limitations to normal physical activity. Class III is reserved for those limited to less-than-normal activity, and Class IV patients are severely limited, and usually bedridden. A summary of the activity levels for defining the NYHA categories of CHF patients is given in Table 2.

If the underlying condition is not corrected, the heart's capacity will continue to decrease, and physical activity will be severely restricted as seen in those in NYHA categories III and IV. Without intervention, the heart will ultimately decompensate, resulting in an acute episode.

Traditional diagnosis of CHF

The differential diagnosis of CHF must rule out all other causes of shortness of breath and chest pain. Until recently, the diagnosis of CHF depended on the medical history, symptoms, physical examination, and non-laboratory diagnostic tests. The medical history identifies contributing factors and symptoms, such as dyspnea, loss of appetite, swelling of the ankles and feet, or a persistent, non-productive cough.[9,10] Physical examination identifies hypertension, breath sounds, edema, abdominal fluid buildup, and swollen neck veins. If CHF is suggested, an electrocardiogram (ECG) and diagnostic imaging such as chest x-rays and echocardiography (cardiac ultrasound) are likely to be ordered to assess the heart's size, shape, and function. Exercise stress tests monitor the patient's physiological responses to treadmill exercise, and help assign patients to the appropriate NYHA category. Cardiac catheterization can confirm vascular occlusion and angioplasty is frequently used to treat a localized problem.

Acute pulmonary diseases, such as pneumonia, COPD, and pulmonary embolism (PE), also cause dyspnea and must also be ruled out in the acute care setting before CHF is diagnosed. One common consequence of acute pulmonary disorders is an increase in vascular permeability, which results in edema, congestion, and even a possibility of vascular shock (severe hypovolemia). Hypertension resulting from either renal or pulmonary conditions can also add stress to an overworked cardiovascular system. Thus, hypertension and dyspnea, the presenting symptoms in many CHF cases, can be similar in various renal and pulmonary diseases and can easily be misdiagnosed as CHF.[9,10] Furthermore, these conditions frequently contribute to myocardial damage and the congestion that help define CHF. Much of the clinical difficulty lies in identifying the initiating factor of the sequence of factors contributing to the downward compensation spiral.

Table 2. NYHA classification of CHF and correlation with BNP levels

NYHA class	Symptoms	BNP Levels*
I	Asymptomatic No limitation of normal activity	83.1 pg/mL (49.4-137 pg/mL)
II	Minimal limitation of normal activity, but activity limited during exercise	235 pg/mL (137-391 pg/mL)
III	Moderate limitation of even normal activity No significant exercise possible	459 pg/mL (200-871 pg/mL)
IV	Severe limitation of normal activity Frequently bedridden	1119 pg/mL (728- >1300 pg/mL)

*BNP levels from Wieczorek 2002. Am Heart J 2002;144(5):934-9.

Finally, a laboratory test for CHF

In the past, the diagnosis and staging of CHF patients was often difficult because symptoms were ambiguous, imaging tests were non-specific, and CHF frequently overlaps with other cardiopulmonary diseases. Since their discovery in 1988, the natriuretic peptides have been well documented as markers for CHF; however, the early RIA procedures were cumbersome and impractical for routine ED use.[11-25] In November 2000, the Food and Drug Administration approved a rapid assay for B-type natriuretic peptide (BNP), manufactured by BioSite. More recently, other manufacturers have added their versions of the rapid BNP assay. These breakthrough BNP assays are easy and require only 15 to 20 minutes, making them especially useful in the ED setting. Numerous studies, discussed below, have found the rapid BNP assays to be very useful in the diagnosis, staging, and prognosis of CHF.[11-22,27-32]

The biochemistry of BNP and ANP

All three members of the natriuretic peptide family (designated ANP, BNP, and CNP) possess a similar 17-amino acid looped structure. Each loop has 11

conserved residues and is held together by a disulfide bond between two cysteines.[23-25] Both A- and B-type natriuretic peptides reduce blood volume and pressure, and regulate electrolyte balance.[23-25] ANP is produced in the atrium of the heart, while BNP is made in the both the brain and ventricles of the heart. (CNP has less natriuretic effect, and does not appear to be clinically relevant.)

Both peptides are synthesized as preprohormones and processed to prohormones prior to release from the cell. Substantial amounts of ProANP are stored in secretory vesicles and can be released quickly as the active 28-amino acid peptide. In fact, ANP can be released by such minor stimuli as exercise.[11,23] By contrast, very little ProBNP is stored, so the increased release of BNP requires an upregulation of mRNA transcription prior to secretion from the left ventricle.[11,23-25] The active 32-amino acid BNP is normally found in lower plasma concentrations than the 76-residue precursor peptide (designated as NT-proBNP), which contains a long N-terminal sequence that is cleaved to form the active peptide.[23,25] This upregulation of transcription means the BNP response, triggered by ventricular overload, is slower and 'less volatile' than the ANP response.[23-25] For example, in cases where an MI causes cardiac damage, and results in the acute onset of CHF symptoms, the response of ANP is immediate, whereas the BNP levels can peak between 16 and 20 hours.[25] In addition, the primary clearance mechanisms, enzymatic degradation and receptor-mediated internalization, both favor the rapid turnover of ANP over BNP.[25] The reported half-life of ANP in humans is only two to four minutes, making ANP too variable, and less reliable for diagnostic purposes.[25]

Because CHF is typically a chronic disease, the stabile BNP response correlates well with cardiac overload, and LV failures.[11,23-25,30-33] Binding of either ANP or BNP to high-affinity target-cell receptors activates a signaling mechanism that causes elevated cGMP (cyclic-GMP) levels and results in their described effects.[23-25]

Natriuretic peptides counteract RAAS

Both ANP and BNP are released in response to volume expansion and pressure overload, and both counteract the RAAS cascade.[23-25] While the RAAS causes vasoconstriction, increased sodium reabsorption, and increased blood pressure, the natriuretic peptides inhibit sodium reabsorption and increase water excretion. An increase in glomerular filtration rate (GFR) results from BNP-induced dilation of the afferent arterioles and constriction of the efferent arterioles. The net effect of BNP is the increased excretion of both sodium and water, decreasing blood pressure and volume.[11,23-25] Because the same overload conditions that lead to CHF also cause BNP release, elevated BNP levels correlate well with the CHF diagnosis and prognosis. Hypertension, including pulmonary hypertension, is frequently seen in CHF patients; however, it is worth noting that hypertension alone does not directly cause release of BNP.[23,25]

Interesting studies with transgenic mice, which over-express the genes for natriuretic peptides, found ten-fold higher peptide levels and lower blood pressure. Furthermore, these mice avoided pulmonary hypertension when exposed to chronic hypoxia.[36] Another interesting role for BNP is implied by studies of mice that lacked the BNP gene. These mice produce no BNP and, under normal circumstances, did not develop hypertension or ventricular hypertrophy. Ventricular pressure overload would cause release of BNP in normal mice; however, these mice could not release BNP and developed focal fibrotic lesions.[37] This suggests that BNP has an antifibrotic effect, which counteracts the reported cardiac fibrosis promotion mediated by the RAAS system.

METHODS

Rapid BNP and NT-proBNP assays

Acceptance of the clinical utility of BNP has resulted in a new generation of immunoassays to fulfill the rapid turnaround times required for emergency medicine. In addition to different assay formats and methods of signal generation, researchers have chosen to detect different portions of the natriuretic peptides, such as NT-proBNP and mid-proBNP (detecting middle portion of pro-BNP), in addition to BNP itself.[25] A review of cardiac natriuretic peptide assays suggests that assays for NT-proBNP may be easier to develop than BNP due to the higher plasma concentrations of NT-proBNP.[25] Another important factor to be considered is the stability of various peptide fragments in plasma. Such assay differences would obviously necessitate different reference ranges and cutoff levels for results to be interpreted, and could result in confusion when results from different laboratories are compared.

Assay principle and performance characteristics of a rapid BNP assay

The most common rapid BNP assay (from BioSite, Inc., San Diego, CA) requires 250 mL of EDTA-anticoagulated blood or plasma, and uses membrane filtration and a sandwich immunoassay procedure to generate a fluorescent signal. If whole blood is used, the cells are removed by filtration and fluorescent-tagged antibodies are allowed to bind any BNP present.

In the reaction chamber, the sandwich is completed as the previously formed BNP-antibody complexes bind to capture antibodies attached to the solid phase. The measured intensity of fluorescence is related to the BNP level.

Assay performance characteristics of the BioSite BNP assay reported by Morrison included intraassay precision (coefficient of variation or CV) of 9.5%, 12.0%, and 13.9% for BNP levels of 28.8 ng/L, 584 ng/L, and 1180 ng/L, respectively.[14] Interassay values for the same specimens were 10%, 12.4%, and 14.8%, respectively. They reported an analytical range for the assay of 5.0 ng/L to 1,300 ng/L, and an excellent correlation coefficient of r = 0.9878, when plasma and whole blood were compared.[14] Although these authors stated that BNP concentrations compared from plasma and whole blood were "not significantly different", their reported equation (y = 0.925x + 13.439) suggests that there may be noticeable differences at both ends of the measurable range. However, at levels that represent therapeutic 'decision points', these sample variations would probably be insignificant and unlikely to alter treatment. A comparison of the rapid fluorescent BNP assay with the most common radiometric immunoassay resulted in a good correlation coefficient of r = 0.9236.[14]

As other assays, such as the newly approved NT-proBNP assay from Roche Diagnostics, and new generations of assays become commercially available, the performance expectations will be revised.

Performance characteristics of troponin assays

The Laboratory Practice Guidelines of the National Academy of Clinical Biochemists (NACB) in 1999 suggested that the high specificity of cardiac troponins, relative to previous markers, could lead to new interpretation of results.[6] The primary change was toward a two-decision limit system, which defined levels between the upper limit of the reference range and the AMI cutoff as indicative of "myocardial injury".[6] Given the clinical evidence that suggests important prognostic differences at low levels of troponin (<0.1ng/mL), assays must have rather extraordinary performance characteristics, at these low levels. For example, Morrow, reported an increased relative risk of 2.2 to 3.0 of death or MI within 43 days in patients whose troponin levels were >0.1 ng/mL.[38] However, at such low levels, very small variations due to slight inaccuracy or imprecision of the assay could impact treatment decisions. Although current troponin assays have excellent precision through most portions of the linear range (CV 2% to 4%), the requirement for 10% imprecision (CV) at levels as low as 0.01 ng/mL was not attained by any of the assays studied.[38]

Review of the clinical utility of BNP

BNP improves both speed of diagnosis and diagnostic accuracy in CHF

Dr Alan Maisel and his colleagues at the Veterans Administration Medical Center in San Diego, have investigated the use of the rapid BNP assay for the diagnosis CHF in ED patients presenting with dyspnea.[11-17] In one study, 250 patients who presented with dyspnea were diagnosed and treated by ED physicians without knowledge of BNP levels. Two cardiologists who were blinded to both the ED diagnosis and BNP results, retrospectively reviewed all traditional criteria of patient history, physical examination, imaging, or laboratory tests performed (including x-rays, systolic and diastolic function, and hemodynamic monitoring), and response to treatment.[12] Only after the cardiologists confirmed a diagnosis, were the ED diagnoses and BNP levels revealed. Confirmed CHF patients had much higher BNP levels, 1076 +/– 138 pg/mL, than COPD patients without CHF, 86 +/– 39 pg/mL.[12] Furthermore, the ED physicians (using traditional criteria) had incorrectly diagnosed 15 non-CHF patients as having CHF, and misdiagnosed another 15 true CHF patients with an inappropriate alternative diagnosis. Of these 30 misdiagnosed patients, 29 would have been correctly identified simply based on their BNP levels.[12]

In a similar study, 321 patients presenting with dyspnea were defined as CHF and/or non-CHF pulmonary diseases. The mean BNP levels of the CHF group were 758 pg/mL, compared to a mean level of 61 pg/mL for the COPD group.[14] Likewise, patients whose edema was caused by CHF had higher BNP levels (1038 +/– 116 pg/mL) than those with edema from other causes (63 +/– 16 pg/mL). This study demonstrated that mean BNP levels were less than 100 pg/mL in dyspneic patients with various pulmonary diagnoses of COPD, asthma, pneumonia, TB, acute bronchitis, and pulmonary fibrosis. However, BNP levels averaged 120 pg/mL in four lung cancer patients and 207 pg/mL in three patients with pulmonary embolism.[14] Interestingly, 11 patients were diagnosed with an acute COPD episode, even though they had a history of CHF. Successful therapy apparently had controlled their cardiac disorder, so their current diagnoses were COPD, and their mean BNP levels were only 47 pg/mL.[14]

Maisel and his colleagues have concluded that at BNP levels above 80 pg/mL, the sensitivity of the assay was 98% and specificity was 92%.[11,12] The negative predictive value (NPV) of BNP levels below the 80 pg/mL cutoff was 98%, giving physicians confidence that CHF was unlikely to be the cause

of dyspnea in patients with low BNP levels. In the multinational "Breathing Not Properly (BNP)" study, McCullough concluded that BNP levels alone had a higher diagnostic accuracy (82.1%) than clinical judgment of ED physicians blinded to BNP levels (74.0%). When clinical judgment was added to BNP levels, the diagnostic accuracy improved only slightly to 82.5%.[17]

BNP levels correlate with disease severity

Several studies have shown that BNP levels roughly correlate with disease severity.[11,12,22] Data presented in Table 2 show that even asymptomatic patients in NYHA category I had elevated BNP levels 83.1 pg/mL, while patients in category II had a mean level of 235 pg/mL.[22] Similar correlations between BNP levels and CHF severity have been made when patient symptoms were classified as mild, moderate, or severe.[12] Patients in stages I and II have few limitations in their normal activities, and may go undiagnosed until the disease progresses to later stages. Earlier diagnosis, based on elevated BNP levels might prevent further deterioration in some patients.[10,11]

BNP is also useful in prognosis

In 1997, Tsutamoto studied 85 patients with chronic CHF and reported that BNP, but not ANP, had independent prognostic value in a multivariate analysis of 14 hemodynamic and neurohormone variables.[21] Using a rapid assay, Berger found that BNP was the only independent predictor of sudden death in their study of 452 CHF patients with LV dysfunction. Patients with BNP values less than 130 pg/mL had a greater than 99% survival during the study, compared to only 81% survival for patients with BNP levels above the 130 pg/mL level.[27] The prognostic benefit indicated by these and other studies could help patients and hospitals avoid readmissions, and decrease morbidity and mortality rates in CHF patients.[26-32]

BNP levels predict outcomes for MI patients

Because a previous MI may cause tissue damage and lead to CHF, researchers wondered if BNP levels might help predict outcomes in patients with MI. Richards studied 121 MI patients and reported that early post-infarction decreases in BNP levels (within two to four days) were good predictors of future CHF episodes, nonfatal MIs, unstable angina episodes, and cardiac related deaths.[30] Richards also showed that higher BNP levels in 220 MI patients measured within four days of admission correlated well with LV dysfunction, and were a "powerful independent predictor" of increased risk of heart failure or death within 14 months.[31] Another study of 70 MI patients found that those with higher BNP levels had higher odds for cardiac death during an 18-month follow-up than patients with low BNP levels.[11,26] Harrison found that patients with high BNP levels (>450 pg/mL) had a greater than 51% chance of a further cardiac event (readmission or death) within six months, whereas CHF patients with lower BNP levels had only 2.5% reoccurrence.[29] Similarly, Omland also reported a strong correlation between elevated BNP levels in patients with acute coronary syndromes and early death.[32]

BNP used to pre-screen patients for LV failure

BNP levels may provide a valuable screen of patients normally referred for evaluation of LV function by echocardiography.[11,15,20-22] Echocardiograms identify CHF-related abnormalities such as thickening of heart walls and decreased or backward blood flow through the valves. One study followed 200 patients who were referred by a cardiologist for evaluation of LV function by echocardiography, without knowledge of BNP results.[15] Patients with LV dysfunction had much higher BNP levels (489 +/– 75 pg/mL) than those with normal LV function (29.5 +/– 62.4 pg/mL), suggesting that relatively inexpensive BNP assays could pre-screen patients for LV dysfunction prior to more expensive echocardiography.[11,15] Maisel asserted that low BNP levels (<80 pg/mL) had a negative predictive value of 98%, meaning that LV dysfunction is highly unlikely.[11] This confirms observations made previously that BNP levels can effectively pre-screen symptomatic patient populations.[20,21,33]

However, researchers of the Framingham Study recently cautioned that BNP-screening for the general community-based population, or even high-risk populations of asymptomatic patients, was not supported.[42] Ramachandran found that the low cutoffs required for adequate sensitivity in the asymptomatic populations, resulted in unacceptably poor specificity and, thus, the potential cost savings were negated. However, screening of the general population was accepted in Japan following large studies of asymptomatic patients.[43]

BNP levels used to monitor success of therapy

Monitoring of BNP levels to evaluate the success of therapies, such as ACE inhibitors, was supported by Murdoch.[33] Cheng reported that BNP levels correlate with success of treatment and outcome in 72 patients hospitalized with heart failure.[13] During this 30-day follow-up study, treatment was ineffective and BNP levels increased by 233 pg/mL during hospitalization for the 22 patients who died or were re-admitted. More successful treatment resulted in a mean decrease of 215 pg/mL BNP in 50 stabilized patients who were not re-admitted during the study.[13] Statistical analysis of

univariate predictors suggests that patients, who are discharged with low BNP levels below 450 pg/mL, or low NYHA classifications, have a better prognosis (less chance of re-admission within 30 days or death) than other patient groups. A decreased BNP or NYHA class during hospitalization was a good sign, but even this did not signify a good prognosis, unless their discharge levels of BNP or their NYHA classifications were low.[13]

The well-established benefits of ACE inhibitors in controlling CHF can be compromised by the risk of side effects, such as hypotension and kidney impairment.[34] Monitoring BNP levels, rather than treating empirically, might minimize these risks. Identifying patients with higher BNP levels following an acute episode might help physicians modify treatments and thereby decrease their risk for re-admission or death.

BNP used as a therapeutic

BNP infusions resulted in favorable decreases in blood pressure and increases in renal excretion.[23,39] However, the anticipation of therapeutic benefits for CHF patients is tempered by observations of decreased responsiveness to BNP in patients with severe CHF.[40] A possible mechanism for this deceased responsiveness may have been described by Tsutamoto, who showed that elevated BNP levels resulted in elevated cGMP levels in a group of chronic CHF patients who survived their two-year study.[21] However, in the nonsurvivors, elevated BNP levels did not cause the expected increases in cGMP.[21,23-25]

Note of caution: BNP is not totally specific for CHF. Although there is a good correlation with BNP elevations and CHF episodes, there are a number of other conditions that also cause BNP elevations.[23-25,41] Multiple traumas, abdominal or thoracic surgery, subarachnoid hemorrhage, and other brain disorders are all known to result in elevations of BNP. In addition, BNP was elevated in diabetic patients with renal complications, indicated by microalbuminuria.[41]

Accelerated protocols for testing BNP and other cardiac markers

A major diagnostic challenge for ED physicians treating patients presenting with chest pain and dyspnea is to quickly and accurately distinguish between MI patients in need of immediate thrombolytic intervention, and angina patients for whom thrombolytics themselves may be detrimental or even life threatening. Given the relatively short time span (20 to 30 minutes) between the thrombic event of an MI and the beginning of myocardial necrosis, it is essential that the distinction be made rapidly so that thrombolytic therapy can be initiated within its 'window' of maximum benefit. Thus, essential laboratory data must be rapidly available so that informed diagnostic decisions can be made.

Recently, researchers have focused on accelerated protocols for diagnosis of cardiac patients within the first few hours as another way to control healthcare costs.[4,44-46] For example, Ng proposed a 90-minute protocol in which cardiac markers are drawn on admission and again at 30-, 60-, and 90-minutes.[46] Similarly, McCord proposed a protocol for exclusion of AMIs within 90-minutes.[45] An accelerated protocol combining troponin, C-reactive protein, myoglobin, and BNP can assist with rapid diagnosis and risk stratification of ACS.[44] Much of the emphasis of early decision-making within emergency medicine is based on the benefits for patients who receive thrombolytics quickly, and the potential cost savings by avoiding unnecessary hospital admissions for observation of patients who can be quickly identified as non-critical.[4] In 1997, Roberts found that ED diagnosis based on acceleration of protocols saved an average of $567 compared with more conservative hospitalization.[4]

The Laboratory Practice Guidelines of the NACB recommended in 1999 that markers such as troponin should be tested at least every 2 to 4 hours until a diagnosis is confirmed.[6] In addition to troponin and CK-MB, most accelerated protocols use myoglobin, a rapidly appearing but less-specific marker to obtain a quicker diagnosis or exclusion of MI.[6,44-47] A sample accelerated algorithm for the combined use of BNP and cardiac markers (such as troponin and myoglobin) is shown in Figure 3.

C-reactive protein has been demonstrated to be an important, independent risk factor in long-term cardiac risk assessment in apparently healthy patients.[5,47-49] However, recent evidence shows that hsCRP values also add valuable information to standard cardiac markers for risk stratification in acute patients presenting with chest pains.[5,47-49] Other reports have demonstrated that soon after onset of pain, hsCRP elevations were an independent risk indicator.[48] These findings reaffirm an inflammatory aspect in ACS in addition the thrombolytic/necrotic aspect represented by markers such as troponin.[5,47-49]

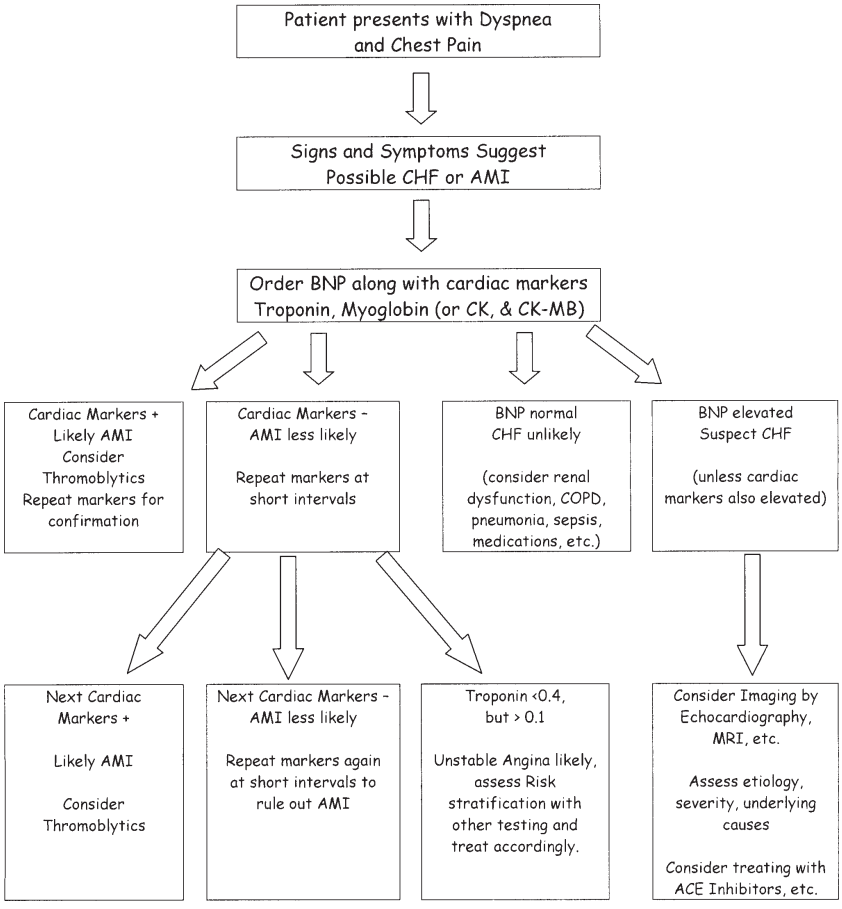
Detection of cardiac ischemia as well as AMIs

Several reviews have reported meta-analysis of published cardiac marker data for the diagnosis of AMI and also cardiac ischemia.[50-52] Not surprisingly, the common markers, which are released upon cell death, are substantially better at de-

tecting AMIs than ischemia, which may never result in necrosis. In general, these reviews confirm that a combination of cardiac markers is beneficial, as compared to any individual marker, and serial determinations of cardiac markers have much better sensitivity than single determination at presentation.[50,52]

Very recently, another exciting addition to cardiac testing appeared on the horizon for use in the diagnosis of MIs.[53-55] This assay, recently approved by the FDA, measures a reduction in the binding of exogenous cobalt to the amino terminus of albumin during ischemia. Because this assay detects a change due to ischemia rather than myocardial necrosis, these changes occur much earlier than even the elevation in myoglobin. Although this test is not intended for MI, the early confirmation of serious ischemia could potentially lead to much more rapid treatments of patients who are having an MI.[53-55]

Figure 3. Sample algorithm for use of BNP and cardiac markers (such as troponin, myoglobin, and possibly CK and CK-MB)



This figure is intended to provide a simplistic representation of a diagnostic algorithm using only clinical chemistry assays. Obviously, physician's algorithm would include EKG, history and examination results, etc. and could become much more complex.

Troponin and a redefinition of myocardial infarction and unstable angina

A further challenge to the emergency physician lies in accurately distinguishing between stable angina and unstable angina that is much more likely to proceed to a life threatening MI in the near future. Historically, there has been little hard evidence on which the ED physician could base a conclusion of stable versus unstable angina and physicians were forced to simply use their best clinical judgment. Evidence suggests that low troponin levels can be used as an objective measure of 'mini-infarcts' or 'pre-infarcts' that characterize UA and are associated with an increased likelihood of a heart attack within the next few weeks.[6,7]

In 1999, the NACB recommended a system of two cutoffs for troponin levels. The higher cutoff indicated an AMI, while a lower level (but still above the reference range) essentially redefined unstable angina.[6] Refinement of this concept has resulted in an intentional blurring of these distinctions to consider any elevated troponin as indicative of an ACS.[6,7] Simply put, an MI is further along the same ACS continuum than a UA, but the underlying processes are similar. This molecular level analysis may be valid, but it still leaves the clinician with therapeutic decisions to make. Several clinical evaluation schemes have sought to predict AMI and UA outcomes in order to assess the benefits of thrombolytics and other aggressive treatments for UA patients.[52] For example, Sabatine found significant benefit in treating UA patients with the glycoprotein llb/llla inhibitor, tirofiban.[52]

Cardiac risk stratification for non-acute patients

An understanding of plaque development helps explain several factors related to increased risk of heart disease (shown on Table 3). Historically, risk factor lists were dominated mostly by life-style and genetic predisposition factors such as family history, obesity, diabetes, smoking, sedentary life style, hypertension, stress, gender, age, and total cholesterol. Recently, molecular-level risk factors such as elevated baseline hsCRP, elevated homocysteine, lipoprotein a, and the LDL/HDL ratio, have been added to the lists. In general, these biochemical factors relate directly to the process of plaque development and inflammation. As our understanding of the process of plaque formation improves, risk assessment has also become more sophisticated and now focuses on factors that accelerate plaque deposition.

Conclusion and Summary of the Clinical Utility of BNP

Congestive heart failure is the leading cause of hospitalization of patients over 65 years of age, estimated at about 900,000 hospitalizations a year and costing roughly $30 billion. Almost 50% of discharged patients are re-admitted within six months, and their five-year mortality rate approaches 50%.[8] The use of the BNP assay when heart failure is suspected has the potential to reduce the diagnostic time, and identify those patients at high risk for experiencing recurrence. By identifying these high-risk patients, treatments might be modified to decrease risk of readmissions and reduce the length of stay and hospital costs. In addition, modified treatments might improve the quality of patients' lives, and prolong patient survival.

Table 3. Cardiac risk stratification factors

Clinical history factors	
Current smoking	Male gender
Diabetes mellitus	Obesity
Family history	Sedentary lifestyle
Hypertension	Stress
Increasing age	
Elevated clinical chemistries	
Homocysteine	Lipoprotein (a)
hsCRP	Total cholesterol
LDL/HDL Ratio	Triglycerides
LDL-cholesterol	

In addition to the benefits of prompt identification of CHF patients through their high BNP levels, the implications of low BNP levels are also important. Studies have reported NPVs of greater than 98%, indicating that physicians can essentially eliminate CHF from the differential diagnosis when a patient's BNP level is below 50 pg/mL.[11,12] Recent studies also found misdiagnosis of patients presenting with dyspnea to be a significant and costly problem when BNP is not available (initial diagnosis was made solely on history and clinical judgment).[12,17,18] The multinational BNP trials reported by McCullough showed that BNP levels alone had higher diagnostic accuracy than traditional clinical judgment by ED physicians.[17]

Cost analysis of testing vs downstream savings

In 1994, O'Connell estimated that approximately $38 billion in healthcare costs were associated with CHF (5.4% of total healthcare costs), with hospitalization accounting for approximately 60% of these costs.[56] Many of these healthcare dollars are spent on patients who have been admitted for further observation, awaiting a definitive diagnosis and initiation of treatment.[8,56] According to the National Healthcare Cost and Utilization Project (see website listings), the mean cost of a hospital admission for CHF was $15,024 in 2000 and the mean length of stay (LOS) was 5.6 days. The mean costs and LOS for AMIs and COPD diagnoses were $28,227 and 5.5 days, and $12,351 and 5.3 days, respectively. This is compared with 'non-specific chest pain' statistics of $7,488 and 1.8 days. Obviously, if even a small fraction of these costs can be avoided with a more rapid diagnosis and treatment for the more than one million CHF admissions, the total healthcare savings would be enormous.

With a 15-minute assay time for BNP, and an NPV of 98%, a BNP value below the cutoff level might avoid hospital admissions-for-observation of tens of thousands of non-CHF patients. At a cost to the laboratory of approximately $30, depending on volume, etc., and an approved reimbursement cost of $47, this assay would appear to be an extremely cost effective addition to the cardiac workup.

Savings will also be realized if BNP levels can provide an objective method to monitor or 'tailor' treatments such as ACE-inhibitors, rather than the current empirical approach.[34] Healthcare costs, morbidity, and mortality would be reduced if patient prognosis can be determined using BNP levels, and patients who should receive more aggressive treatments are identified.

Finally, the increased diagnostic accuracy described earlier needs to be considered.[12,17,18] These studies reported misdiagnosis of 10% to 20% by emergency staff that could have been largely avoided by consideration of BNP results alone. These results are confirmed in another study where nearly 18% of dyspnea patients were misdiagnosed, and in 90% of those, BNP would have helped correct the diagnosis.[18] Inclusion of BNP testing would obviously save unnecessary suffering, morbidity, and even mortality of the misdiagnosed patients, as well as saving the substantial financial burden of misdiagnosis.

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