Heart Failure and B-Type Natriuretic Protein

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Define heart failure and discuss its signs and symptoms.
2. Describe how heart failure is classified and explain NYHA functional criteria.
3. Explain the role biomarkers can play in heart failure.
4. Discuss the physiologic role of BNP and its origin in healthy individuals versus HF patients.
5. Describe the synthesis and release of BNP noting proteolytic cleavage products.
6. State the current recommendations for BNP use.
7. Interpret BNP values in the context of heart failure.

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Heart Failure: Pathology

Heart failure (HF) is a syndrome of varying but progressive severity in which the ability of the heart to pump blood is compromised. It has been said that, "…heart failure is a primary complication of virtually every form of heart disease"[1]. In general, prior to developing HF, a disease or condition exists that stresses the cardiovascular system. The body possesses several feedback mechanisms that adapt to stress and maintain acute cardiovascular function. However, many of these adaptations are themselves toxic and degrade cardiac function over the long term[2].

Several common chronic progressive conditions such as hypertension, acute coronary syndrome, a previous myocardial infarction or diabetes mellitus are precursors to HF[3]. At diagnosis, one-year mortality is nearly 10% and five-year mortality is about 50%[4].

The clinical presentation of HF is variable. Patients may present without symptoms but with evidence of left ventricular structural or functional changes. Classic signs and symptoms include breathing difficulty, fatigue after modest physical exertion and fluid retention resulting in peripheral edema and pulmonary congestion.

Heart Failure: Clinical Summary

In addition to the individual toll, heart failure (HF) is a public health problem whose morbidity and mortality are significant burdens on the health care system. According to the American Heart Association (AHA)[4], in 2006 the prevalence of HF in the US was 5.7 million people, or 2.5% of the population. In 2005, HF was the primary cause of 58,933 deaths and a contributing factor in an additional 233,281 deaths. That same year, the total direct cost of medical treatment for HF was $33.7 billion. Additionally, there were indirect costs of $3.5 billion resulting from HF mortality. While these expenses

represent a substantial burden on our health care system and our economy, it does not take into account costs derived from lost productivity due to HF morbidity. Thus, the combined direct and indirect costs reflect a fraction of the true societal cost of this disease[4]. Moreover, the incidence of HF increases in elderly populations, and for this reason, the public health burden of HF is predicted to rise proportionally as America ages.

Heart failure is classified into several forms based on dysfunction and clinical presentation. Acute HF may describe rapid de novo HF as might occur after an insult to the heart, for instance, a myocardial infarction (MI) or atrial fibrillation. Alternatively, acute HF may be a sudden change in the severity of the signs and symptoms of HF, signaling a need for immediate medical attention. Chronic HF is a condition with long term but relatively stable symptoms.

HF can also be designated as systolic or diastolic depending upon whether the dysfunction is primarily due to a defect in chamber contraction (systolic) or filling (diastolic). Cardiac remodeling is a frequent cause of systolic heart failure. As the left ventricle grows enlarged and fibrotic, the position of the valves may change causing regurgitation into the atria upon ventricular contraction. Thus, a systolic defect in contraction leads to a defect in filling or diastolic heart failure. This is an example of how compensatory adaptations lead to short term preservation of cardiac function but long term progression to the HF syndrome.

Finally, HF can be described as left HF or right HF. Left HF is associated with increased pulmonary pressure and the symptoms of congestive HF (i.e. fluid in the lungs), while right HF raises systemic pressure causing lower extremity edema. As seen with diastolic and systolic HF, left versus right categorizations are interrelated and a defect in one may lead to a defect in the other as HF progresses.

Heart Failure: Diagnosis

Historically, HF treatment has been based on a clinical classification of symptoms developed by the New York Heart Association (NYHA) known as the NYHA functional criteria (Table 1a)[5, 6]. These criteria group patients into a functional class based upon the level of activity required to elicit symptoms at the time of evaluation. However, a patient's symptoms vary considerably with time. Also, some patients who are asymptomatic may die suddenly from HF. For these reasons the American College of Cardiology and the American Heart Association (ACC/AHA) developed a staging system to complement the NYHA functional class system which reflects the progressive nature of HF and is used to direct therapy (bottom, Table 1b)[7]. Stages are based on the degree of cardiovascular disease and once a patient has been classified at a higher stage they can never return to a lower stage. This is in direct contrast to the NYHA functional classes, in which a patient's symptoms may improve. The ACC/AHA staging system reflects the current understanding that symptoms are not well correlated to the severity of HF and that treatment of more advanced HF should reflect the extent of disease rather than symptom severity. Importantly, the ACC/AHA staging system includes non-cardiac morbidities that predispose for HF and asymptomatic heart disease as the earliest stages (A and B respectively) in the development of HF. Stage C represents individuals with structural heart disease and symptomatic HF while Stage D represents refractory HF requiring specialized intervention.

Beta-natriuretic Peptide; Heart Failure Marker

The diagnosis of HF is a clinical one that is informed by laboratory, radiological and cardiac testing. A biomarker that assists in HF diagnosis or prognosis has high value to clinicians. However, there is no single diagnostic test. Chest X-rays can reveal lung congestion and sometimes cardiac hypertrophy, and help exclude pulmonary causes of dyspnea. ECG is useful in the exclusion of HF as this test is unlikely to be normal in a HF patient. MRI and echocardiography assess cardiac structure and function. Catheterization is an invasive procedure for

measurement of intracardiac pressures and estimation of left ventricle contraction efficiency (known as ejection fraction) and cardiac output[7, 8].

Since 1998, biochemical markers have become increasingly important in the evaluation of HF[9]. B-type (or brain) natriuretic peptide (BNP) is a member of a family of peptides, the natriuretic peptides that increase urinary excretion of sodium (natriuresis) and water (diuresis) and stimulate vasodilatation[10,11]. The first natriuretic peptide described, atrial natriuretic peptide (ANP), was characterized by experiments in which supernatants from rat atrial wall homogenates were injected into healthy rats, generating potent sodium, chloride, urine and potassium excretion[12, 13]. These experiments were performed because atrial, but not ventricular, myocytes have protein-containing secretory granules resembling granules in cells that produce polypeptide hormones[14,15]. Experimental conditions that affect sodium and water balance in animals lead to parallel changes in atrial myocyte granules[16]. These findings led to the hypothesis that atrial myocytes produce a peptide hormone capable of regulating water and sodium status. By preparing and injecting soluble myocyte homogenates from the atria and ventricles of rats into other rats and observing the effects on electrolyte and water excretion, de Bold *et al*. were able to establish the heart as an endocrine organ[12].

BNP was first identified in porcine (pig) brain[17]. Peptide sequencing established it as distinct from, but closely related to ANP[18]. The initial discovery of the peptide in brain resulted in the name *brain natriuretic peptide* and the acronym BNP. However, further research established the primary site of BNP expression and secretion as the atria[19]. This has led to BNP being renamed beta-type natriuretic peptide[20]. This designation maintains its association with ANP and maintains continuity of the acronym without the confusing and incorrect designation of brain as the tissue of origin.

Five years after the biochemical description of the effects of ANP on salt and water homeostasis, Burnett observed that ANP levels rise in HF patients[21]. In a healthy population, the levels of BNP are about 1/10th the level of ANP, but in patients with HF, BNP rises up to several hundred fold[22]. This increase is due to the abnormal secretion of a large amount of BNP from cardiac ventricles in HF and made BNP the preferred disease marker for this disease. Circulating levels of BNP and NT-proBNP (see below) rise with increased wall tension, secondary to excess fluid volume within the heart[23, 24]. Thus BNP is a direct marker of congestive cardiac pressure.

BNP is translated as a 134-amino acid pre-pro-hormone (preproBNP, figure 1) containing a 26 amino acid signal sequence necessary for secretion. This signal sequence is necessary for transport across the membrane of the sarcoplasmic reticulum (SR), an event that is required for eventual secretion into the circulation. The SR is the endoplasmic reticulum (ER) of contractile muscle cells. It is distinguished from the ER by its role in calcium storage and release during muscle contraction. The other functional roles of the SR, including post-translational modification are essentially identical to those of the ER. Within the SR, the 26-amino acid signal sequence of preproBNP is removed before the C-terminal end of the peptide has completed translation. Once the signal sequence is cleaved, preproBNP becomes proBNP, a peptide of 108 amino acids. ProBNP is then cleaved into a 32 amino acid BNP peptide and a biologically inactive N-terminal fragment, 76 amino acids in length (NT-proBNP, Figure 1).

Laboratory assays are available for both BNP and NT-proBNP (collectively, BNPs) and are useful in the evaluation of patients with HF[25, 26].

In 2005 the American College of Cardiology and the American Heart Association (ACC/AHA) released updated guidance for the Diagnosis and Management of Heart Failure in Adults[3]. The groups recommend BNPs to complement clinical judgment when differentiating HF dyspnea from dyspnea of other causes. The ACC/AHA guidelines substantially reflect

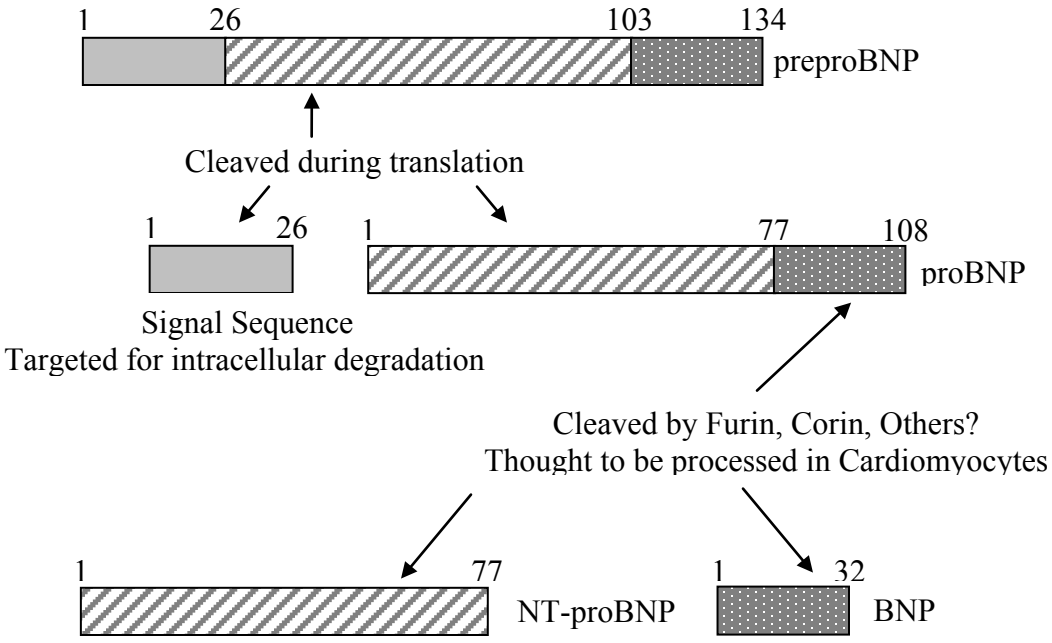

Figure 1: Processing of preproBNP to yield circulating NT-proBNP and BNP

the guidance of the National Academy of Clinical Biochemistry (NACB) in their recommendation to use BNP or NT-proBNP testing to rule out or confirm the diagnosis of HF among acute patients presenting with ambiguous signs and symptoms[9]. A BNP cutoff of 100 pg/mL or a NT-proBNP cut off of 900 pg/mL for patients ≥50 years were accepted to yield appropriate sensitivity and specificity for establishing acute HF (BNP 100 pg/mL, sensitivity = 90%, specificity = 76%; NT-proBNP 900 pg/mL, sensitivity = 90%, specificity = 85%).

Both groups warn that since BNP levels are higher in women and people over 60, clinicians should evaluate BNP levels in relation to patient demographics. Additionally, they recommended investigating the possibility of HF in patients with elevated BNP and suitable symptoms.

BNP levels correlate with the staging of HF. As Table 1 demonstrates, BNP levels increase as patients' progress in NYHA classification level. Although reference intervals differ across institutions, values of 200–400 pg/mL generally correspond to moderate HF while values > 400 pg/mL indicate severe HF. However, there is wide variation of BNP levels for patients within a NYHA functional class and overlap between them. Specific reference intervals are recommended and are available which consider both gender and age.

Beta-natriuretic Peptide; Current Research

Studies in 2008–2009 have investigated the utility of BNP or NT-proBNP for HF prognosis[27-29], to screen elderly populations for early signs of HF[30], to guide HF therapy[31] or to evaluate conditions other than HF[32, 33]. Both the ACC/AHA and NACB guidance committees published guidance in 2009 on the proper role of BNP and NT-proBNP in these situations[3,34]. While both committees endorse continued research and note some promising studies, they recommend that BNPs not be used for assessment of cardiovascular disease or HF risk. Although BNPs have a role in HF assessment, they have not yet been validated as cardiovascular risk markers in the same sense as hsCRP.

Since 1998, BNP and NT-proBNP have become more important in the assessment of potential HF pa-

Table 1. Classification and staging systems

A. NYHA HF Classification by Functional Capacity	**Median BNP Concentration[40]**
Class I: Patients with cardiac disease but without l imitation of physical activity.	83.1 pg/mL
Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Symptomatic with ordinary physical activity.	235 pg/mL
Class III: Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes symptoms.	459 pg/mL
Class IV: Patients with cardiac disease resulting in symptoms even at rest.	1119 pg/mL
B. ACC/AHA staging system *Objective assessment based on evidence of cardiovascular disease*	
A: No evidence of CV disease **B:** Evidence of minimal CV disease **C:** Evidence of moderate CV disease **D:** Evidence of severe CV disease	

tients. It has also become increasingly apparent that our methods for quantifying these peptides need to be more fully characterized. The biochemistry of BNP translation, secretion and proteolytic processing was reviewed in 2008[35]. The proteases corin and furin were shown to cleave proBNP into BNP and NT-proBNP. Furin is a membrane-bound protease. Corin is expressed in the Golgi and shuttles between the Golgi and the plasma membrane. Thus, NT-proBNP could be processed during maturation by the Golgi or during secretion into the circulation. Recent reports have shown that intact, unprocessed proBNP circulates[36], as do proteolytically clipped and glycol-sylated forms of NT-proBNP[37,38]. There are also reports of proteolytically clipped molecules derived from BNP circulating in blood[39].

Due to these post-translational modifications and proteolytic cleavage events, laboratory tests differ in their detection of the circulating forms of BNP and NT-proBNP. This difference introduces uncontrolled error between tests. Additionally, it leads to a decrease in the correlation between what we measure and what we'd like to measure. Finally, it raises the question of which species of BNP would be best to measure.

There is much work to be done to ascertain and define the complete role for BNPs in the evaluation and treatment of HF. Areas of research include identifying and characterizing the different species of BNPs and their interaction with various commercial tests that are in use in the laboratory. Additionally, research into the use of BNPs in evaluating other cardiac conditions as well as in the prognosis and potential to guide therapeutic decisions will continue.

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edited for length and clarity. We look forward to hearing from you.

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