



This Week in the Journal

July 18, 2002

“Rapid measurement of B-type natriuretic peptide is useful in establishing or excluding the diagnosis of congestive heart failure.”

B-Type Natriuretic Peptide in the Diagnosis of Heart Failure

B-type natriuretic peptide is released from the ventricles of the heart in response to hemodynamic stress, and blood levels of B-type natriuretic peptide may be useful in the diagnosis of heart failure. In this study, a rapid, bedside immunoassay for B-type natriuretic peptide was used to make or exclude the diagnosis of heart failure in patients with acute dyspnea from various causes. The assay was found to have good sensitivity and excellent specificity in the diagnosis of heart failure.

Measurement of B-type natriuretic peptide levels is not a stand-alone test for heart failure. It will be of most value when used in conjunction with clinical observations, especially when the cause of acute dyspnea is unclear. The finding of a low level of B-type natriuretic peptide (less than 50 pg per milliliter) is good evidence of the absence of heart failure.

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Hepatitis B e Antigen and Hepatocellular Carcinoma

This prospective cohort study of 11,893 men in Taiwan examined the relation between the base-line prevalence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) and the subsequent development of hepatocellular carcinoma. There were 39 cases of hepatocellular carcinoma per 100,000 person-years of follow-up among men who were negative for both antigens at enrollment, 324 cases per 100,000 person-years among men who were positive for HBsAg but negative for HBeAg, and 1169 cases per 100,000 person-years among those who were positive for both HBsAg and HBeAg.

Chronic hepatitis B virus infection is known to be associated with an increased risk of hepatocellular carcinoma. This study demonstrates a strong association between the presence of HBeAg and the subsequent development of hepatocellular carcinoma and suggests a potential role for HBeAg testing to identify high-risk patients who would be candidates for antiviral drug therapy and close monitoring for early detection of liver cancer.

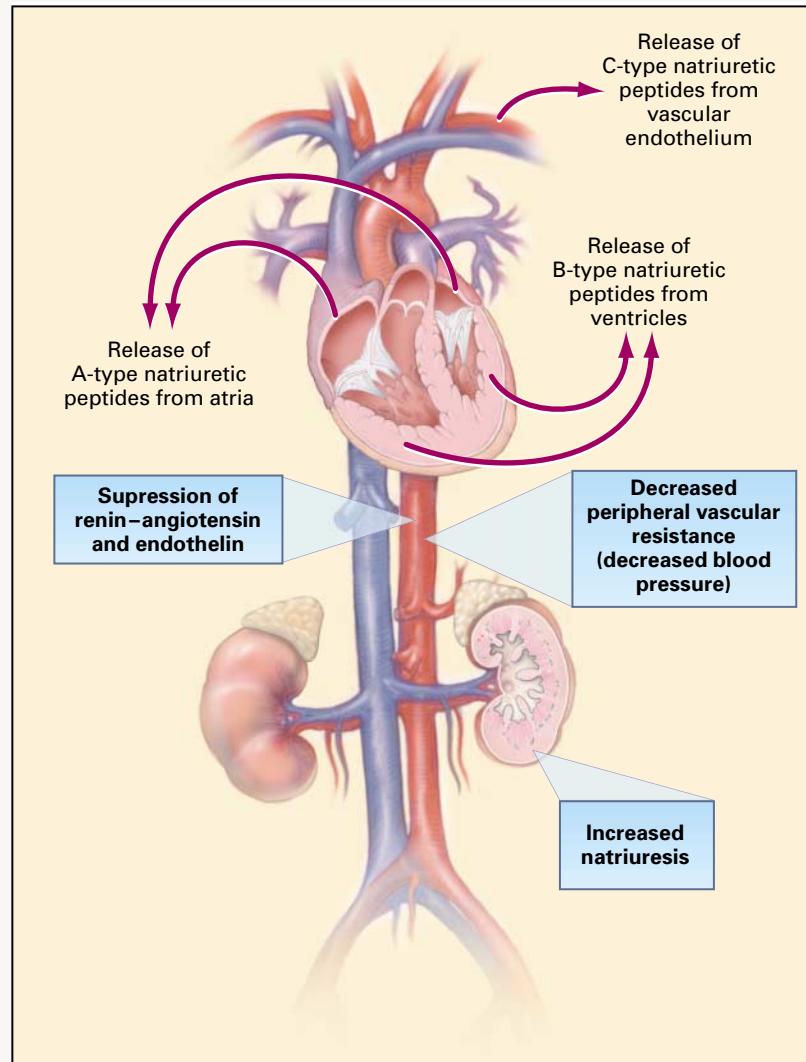
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PERSPECTIVE

B-Type Natriuretic Peptide — A Window to the Heart

Left ventricular dysfunction, regardless of its cause, results in characteristic hemodynamic derangements and a process of neurohormonal activation. Among the neuronal and hormonal pathways activated are the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the endothelin pathway. Each of these pathways has hemodynamic effects that maintain tissue perfusion and blood pressure, and the sympathetic nervous system also stimulates the heart rate and myocardial contractility. Although these responses initially compensate for hemodynamic derangements, prolonged elevation of norepinephrine, renin, angiotensin I and II, aldosterone, and endothelin becomes directly toxic to the heart, accelerating processes such as apoptosis, myocyte hypertrophy, and interstitial fibrosis.

Natriuretic peptides represent a favorable side of neurohormonal activation. The natriuretic peptides are produced by the heart and vasculature and, unlike the other neurohormonal pathways affected by left ventricular dysfunction, appear to improve the loading conditions of the failing heart through their diuretic, natriuretic, and vasodilator properties (see Figure). A-type (atrial) natriuretic peptide is secreted primarily by the atrial myocardium in response to dilatation. B-type natriuretic peptide (initially called brain natriuretic peptide) is manufactured and released almost exclusively by the ventricular myocardium in response to elevations of



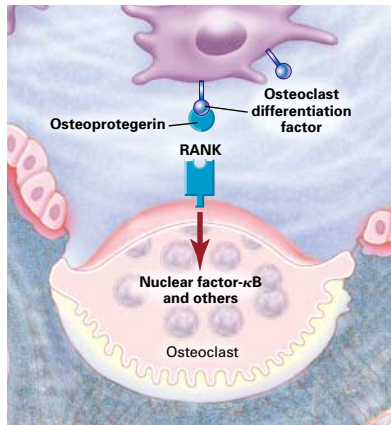
The ABCs of Natriuretic Peptides.

A-type natriuretic peptide is released by the atria, B-type natriuretic peptide primarily by the ventricles, and C-type natriuretic peptide by the vascular endothelium in response to increased filling pressure and volume of shear stress. The hormones have a short half-life and cause natriuresis and vasodilation, as well as suppression of renin-angiotensin and endothelin.

end-diastolic pressure and volume. C-type natriuretic peptide, which was discovered recently, is produced and released by endothelial cells in response to shear stress.

All three types of responsible cells (atrial, ventricular, and endothelial) respond to hemodynamic stress by activating transcription of the genes encoding the natriuretic peptides

in order to manufacture peptides that are not normally produced in these cells. In each of these anatomical areas, the higher the stress, the greater the level of natriuretic peptide produced and released into the bloodstream. There is some evidence that these peptides also inhibit the renin-angiotensin system and the endothelin pathway. Nesir-



Osteoprotegerin Deficiency and Juvenile Paget's Disease

Juvenile Paget's disease is an autosomal recessive osteopathy characterized by rapidly remodeling woven bone, osteopenia, fractures, and progressive skeletal deformity. Its molecular basis is not known. Since osteoprotegerin suppresses bone turnover, functioning as a decoy receptor for osteoclast differentiation factor, the authors sought to identify mutations in the gene for this protein (*TNFRSF11B*) in two unrelated Navajo patients. Studies that included polymerase-chain-reaction amplification followed by direct sequencing, as well as Southern blotting of genomic DNA, revealed a homozygous deletion of *TNFRSF11B* in both patients.

Juvenile Paget's disease results from osteoprotegerin deficiency induced by the homozygous deletion of TNFRSF11B. Consequently, circulating levels of soluble osteoclast differentiation factor are elevated.

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itide, a synthetic recombinant human B-type natriuretic peptide, was recently approved by the Food and Drug Administration for short-term infusion in patients with congestive heart failure to improve signs and symptoms of volume overload and cardiac decompensation. This therapy represents a novel approach to the "physiologic" management of heart failure, enhancing naturally occurring protective mechanisms.

The important study by Maisel et al. in this issue of the *Journal* (see pages 161–167) confirms the value of B-type natriuretic peptide in the diagnosis of congestive heart failure and demonstrates an association between the concentration of B-type natriuretic peptide in the circulation and the severity of congestive heart failure, as indicated by the New York Heart Association functional class. The level of B-type natriuretic peptide appears to correlate with other well-established markers of neurohormonal activation, including sympathetic stimulation, endothelin levels, and renin–angiotensin–aldosterone levels; however, B-type natriuretic pep-

tide has the advantage that it can be measured rapidly and accurately at the point of care.

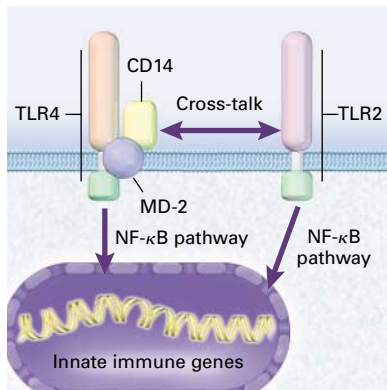
Studies by Maisel et al. and by others suggest that B-type natriuretic peptide levels can be used to confirm the diagnosis of congestive heart failure; to measure the severity of left ventricular compromise; to quantify the functional class; to estimate the prognosis and predict future cardiac events, including sudden death from cardiac causes in patients with cardiomyopathy; and to evaluate the efficacy of therapy for heart failure.

Cardiologists and internists may now have a tool with which to determine whether a patient has congestive heart failure and to measure its severity, much as physicians routinely measure serum creatinine in patients with renal disease and perform liver-function tests in patients with hepatic disorders. One can imagine that this study will spark the imagination of clinicians and investigators, who will then seek to extend the boundaries of usefulness of the measurement of B-type natriuretic peptide. Levels of this

peptide appear to be most helpful in confirming the diagnosis of congestive heart failure in patients in whom the diagnosis is uncertain, such as those with pulmonary or systemic diseases and symptoms similar to those of cardiac congestion and a low-output state or those with coexisting cardiac and pulmonary or systemic illnesses, in whom there is some ambiguity regarding the cause of the symptoms. Measurement of B-type natriuretic peptide appears to be more helpful than standard diagnostic studies, including electrocardiography and chest radiography, and it may be more cost effective than echocardiography. The availability of this laboratory test, however, should not deter physicians from obtaining an appropriate history and performing a careful physical examination to diagnose and treat congestive heart failure.

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Toll-like Receptor 4 Polymorphisms and Atherogenesis

Toll-like receptor 4 (TLR4) mediates the innate immune response to gram-negative bacteria and other pathogens. This study found that a common polymorphism of TLR4 (Asp299Gly), which attenuates receptor signaling, is associated with an increased risk of systemic infection, lower circulating levels of certain inflammatory markers, and a reduced risk of atherosclerosis.

The findings support the concept that inflammation is involved in the pathogenesis of atherosclerosis and that genetic factors that attenuate the inflammatory response may reduce the risk of atherosclerosis.

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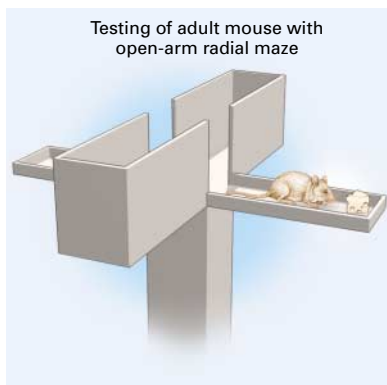
“One out of eight new mothers will have postpartum depression. In women with previous episodes, the risk of recurrence is one in four.”

Clinical Practice: Postpartum Depression

A woman visits the doctor for her six-week postpartum evaluation. She reports that she cannot sleep even if her baby sleeps. She cries daily and worries constantly. She does not feel hungry and is not eating regularly. Making decisions is overwhelming. How should she be evaluated and treated?

This article reviews ways of identifying and managing postpartum depression.

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Clinical Implications of Basic Research: Early Genetic Influences on Behavior

In a recently published study, investigators at Columbia University reported on a mouse model in which the forebrain serotonin-1A receptor was knocked out. The mice demonstrated inhibition of certain aspects of behavior. For example, when placed in an open area the affected mice were less likely to explore than normal mice. In this commentary, Dr. Freedman discusses the implications of this provocative research for the genetic control of human behavior.

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