B-Type Natriuretic Peptide as a Biomarker Beyond Heart Failure: Speculations and Opportunities

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Cardiac secretion of B-type natriuretic peptide (BNP) increases with the progression of heart failure (HF), and plasma measurement of BNP has emerged recently as a useful, cost-effective biomarker for the diagnosis and prognosis of HF. The diagnostic utility of BNP is complemented by its therapeutic use in decompensated HF. Although clinical use of BNP as a biomarker in HF is increasing, the specificity of BNP for HF is not robust, suggesting that other mechanisms beyond simple ventricular stretch stimulate BNP release. Several studies have shown that BNP levels increase in other cardiovascular disease states including ischemia, arrhythmias, fibrosis, cardiac hypertrophy, and coronary endothelial dysfunction. Furthermore, 2 important studies revealed recently that moderate elevations in BNP level, well below the HF range, have prognostic value for future cardiovascular events. Specifically, BNP levels greater than 20 pg/mL were associated with significantly increased risk of HF and atrial fibrillation. These observations increase speculation that elevated BNP levels represent a final common pathway for many cardiovascular pathologic states and that BNP can be used as a biomarker for non-HF mechanisms, preclinical disease, and other pathologic states of myocardial disease.

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AF = atrial fibrillation; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; HF = heart failure; LA = left atrial; NT = N-terminal; proBNP = prohormone BNP

The first report of a natriuretic peptide produced in the heart appeared more than 20 years ago. de Bold[1] in Canada and Kangawa and Matsuo[2] in Japan reported almost simultaneously the gene for atrial natriuretic peptide (ANP), which led to intensive research into the heart as an endocrine organ. Since this seminal discovery, a second cardiac peptide, B-type natriuretic peptide (BNP), was discovered with rapid translation of its biology into diagnostic application within the clinical practice of heart failure (HF).[3-5] B-type natriuretic peptide is synthesized in the normal heart primarily by the atrial myocardium and is localized to atrial secretory granules in a manner similar to ANP[6] (Figure 1). B-type natriuretic peptide is produced as pre–prohormone BNP (proBNP), processed to proBNP, and then cleaved by corin to mature, biologically active 32–amino acid BNP and non–biologically active N-terminal (NT)-proBNP[7] (Figure 2). As the heart fails and fetal gene programs are activated in ventricular cardiomyocytes, the ventricle becomes the principal site for BNP production,[6,8] and cardiac secretion of BNP, as with secretion of ANP, increases in HF[6,9] (Figure 1). Indeed, both BNP and NT-proBNP have emerged as useful and cost-effective biomarkers in the diagnosis and prognosis of preclinical asymptomatic left ventricular dysfunction.[10-15] Furthermore, the diagnostic utility of BNP is complemented by its use as an intravenous agent in the treatment of human decompensated HF.[16] However, even though the use of BNP as a biomarker in HF is increasing, the specificity of BNP for HF is not robust, and its use as a screening marker for asymptomatic disease is the goal of intense investigation.[17-19]

The low specificity of BNP for HF may suggest that other biochemical and mechanical stimuli beyond simple ventricular stretch are associated with the synthesis, processing, or release of BNP from the heart. Indeed, recent reports show that BNP has important prognostic implications in the settings of sepsis,[20] pulmonary embolism,[21,22] pulmonary hypertension,[23,24] and stable coronary artery disease.[25] Interestingly, Goetze et al[26,27] have shown that myocardial hypoxia in a porcine model quickly stimulates cardiac BNP expression and the rapid release of the newly synthesized proBNP. Humoral factors such as the local endothelial cell peptide endothelin[28] also have been shown to activate natriuretic peptide synthesis, as have cytokines such as tumor necrosis factor α[29] and transforming growth factor β.[30] Furthermore, chronic atrial fibrillation (AF) is associated with markedly elevated BNP levels, even in the absence of HF.[31] These observations increase speculation that BNP can serve as a biomarker for non-HF mechanisms, preclinical disease, and other pathologic states of myocardial disease including coronary endothelial dysfunction, myocardial ischemia, and arrhythmias. Relevant to this concept is the prognostic role of BNP in acute coronary syndrome; the magnitude of elevated BNP levels at the time patients entered a large multicenter trial for treatment of acute coronary syndrome was highly prognostic of death[32] (Figure 3).

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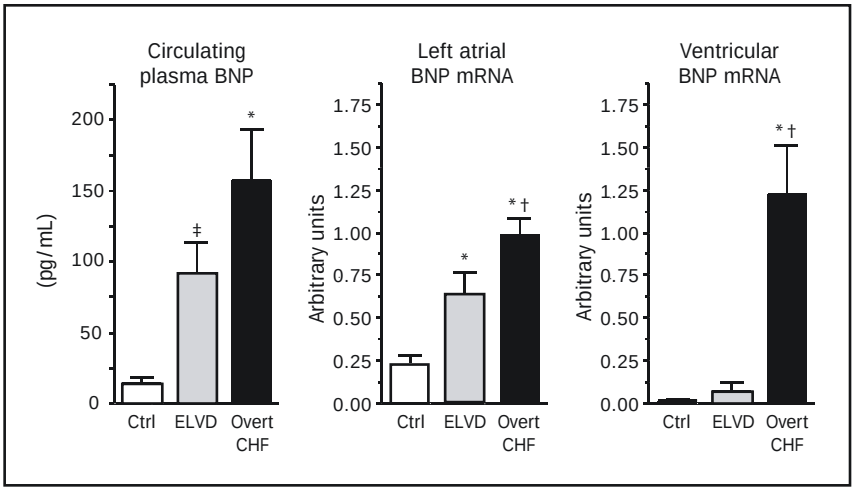

FIGURE 1. Circulating plasma B-type natriuretic peptide (BNP) (left) and BNP messenger RNA (mRNA) in left atrial (middle) and left ventricular (right) cardiac tissue from control (Crtl) dogs and from dogs with early left ventricular dysfunction (ELVD) and overt congestive heart failure (CHF). Middle and right, The amount of BNP mRNA is expressed in arbitrary units as a ratio of autoradiographic densities (BNP mRNA/glyseraldehyde-3-phosphate dehydrogenase [GAPDH] mRNA); n=5 dogs/group.
*P<.01 vs control.
†P<.02 vs ELVD.
‡P=.05 vs control.

BNP IN THE GENERAL POPULATION

To better understand the diagnostic potential of BNP beyond HF, a thorough understanding of its regulation in the general population is required. In the healthy adult population, BNP levels vary on the basis of many factors and have a wide range of values. Redfield et al[33] studied individuals with no cardiovascular disease risk factors and with normal

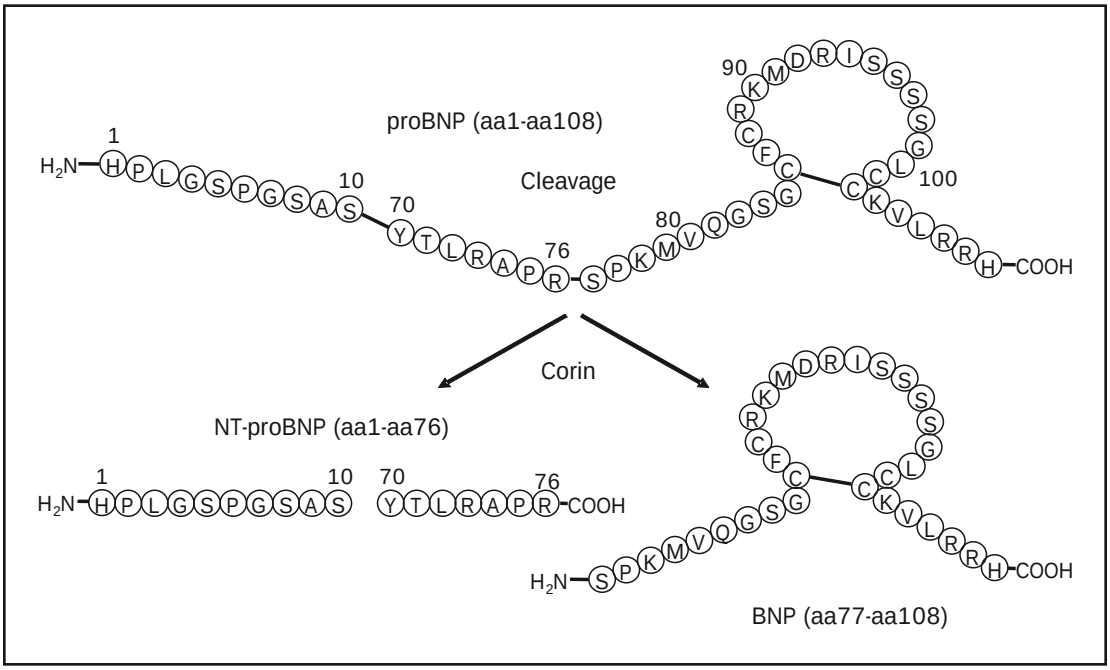

FIGURE 2. B-type natriuretic peptide (BNP) is produced as pre–prohormone BNP (proBNP), processed to proBNP, and then cleaved by corin to mature, biologically active 32–amino acid (aa) BNP and non–biologically active N-terminal (NT)-proBNP.

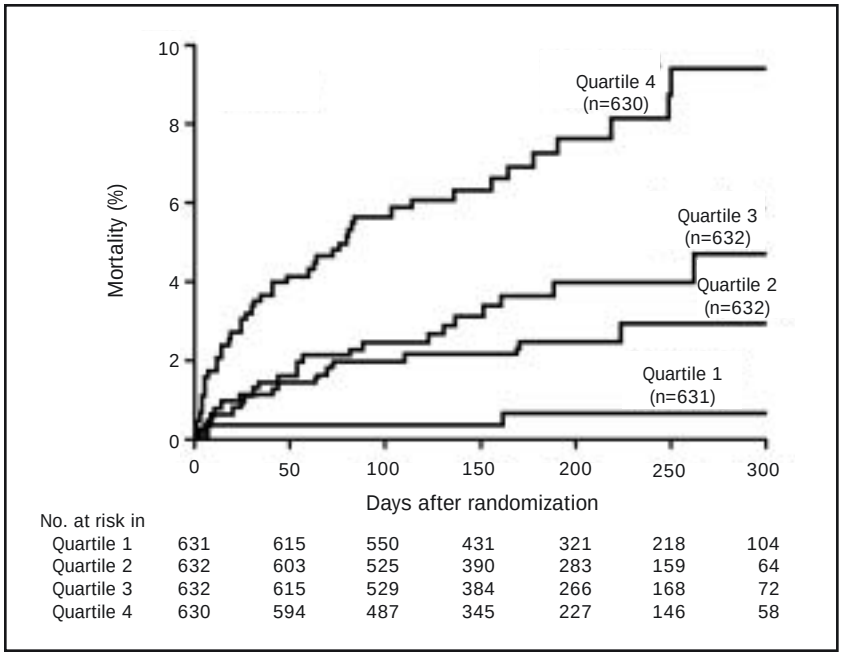

FIGURE 3. Kaplan-Meier curves show the cumulative incidence of death at 10 months, according to the quartile of B-type natriuretic peptide level at enrollment. The range of B-type natriuretic peptide levels was as follows: 5.0 to 43.6 pg/mL (quartile 1), 43.7 to 81.2 pg/mL (quartile 2), 81.3 to 137.8 pg/mL (quartile 3), and 137.9 to 1456.6 pg/mL (quartile 4). *P*<.001 for the trend among quartiles. From de Lemos et al,[32] with permission.

results on echocardiography in Olmsted County, Minnesota, and concluded that the normal range for BNP level should be interpreted by using age, sex, and assay (Figure 4). Obesity further affects BNP levels as seen in the reported inverse correlation between body mass index and plasma measurements.[34] The described age and sex differences are independent of renal function, blood pressure, and cardiac size and function. The reported sex variability is likely secondary to estrogen regulation of natriuretic peptide levels because hormone replacement therapy significantly increases BNP levels.[33]

The effect of age is more complicated. Although data are limited, there is evidence that alteration in the degradation, clearance, or production of BNP occurs with aging.[35,36] In humans, BNP is metabolized by a specific neutral endopeptidase in the renal proximal tubular brush border membranes after glomerular filtration.[37] In elderly persons, both the glomerular filtration rate and the renal tubular function decline,[38,39] and reduced metabolic capacity may help explain the increased circulating BNP concentrations. Although it has been suggested that age-related increases in BNP level are secondary to latent renal dysfunction,[40] Cataliotti et al[41] reported that in individuals with end-stage renal disease, BNP levels were independent of renal function. Clark et al[42] showed that with increasing age and in the absence of any renal dysfunction, there is a decrease in the renal clearance of the natriuretic peptides and an increase in plasma BNP levels. The controversy regarding renal dysfunction and BNP elevations in elderly persons remains, but clearly, decreased renal degradation partially accounts for the increased circulating BNP values seen with aging. Another key finding is that with aging, there is a decrease in the ratio of cyclic guanosine monophosphate to BNP, which indicates a decreased response to BNP and therefore dictates increased endogenous BNP production.[40] Also, a recent report showed that platelet-associated clearance receptors decrease as individuals age.[43] Other yet unidentified metabolic enzymes also account for BNP degradation.[44] Since angiotensin-converting enzyme increases with an individual's age, the activity and concentration of BNP-associated enzymes also may change with age.

Atrial volume is another correlate of BNP in the general population. Redfield et al[33] reported a positive correlation between plasma BNP concentrations and left atrial (LA) volume index. These and other results show that increases in the size of the atria, which is the primary source of BNP in the non-HF setting, result in increased plasma levels.

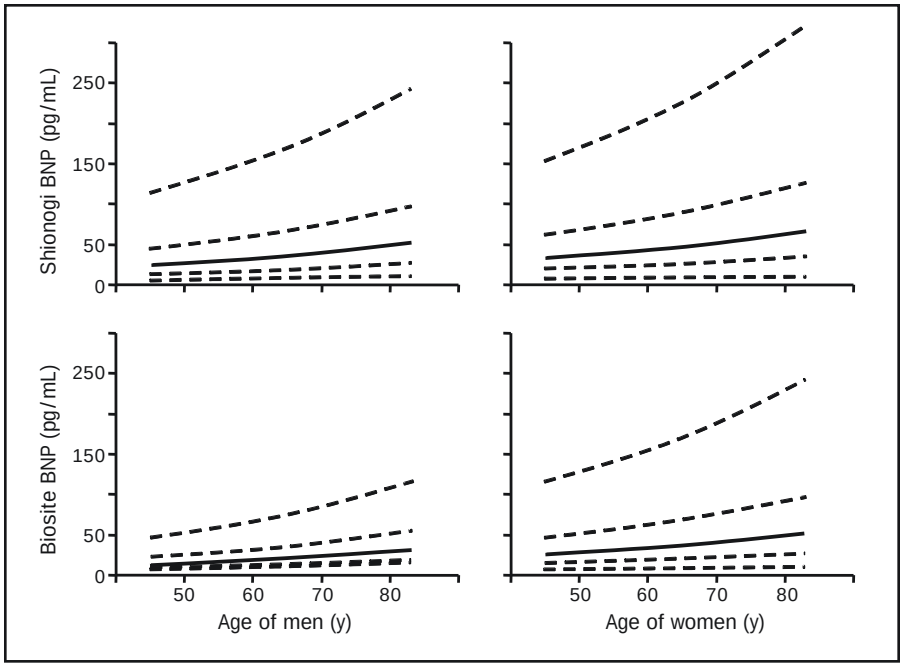

FIGURE 4. Plasma B-type natriuretic peptide (BNP) concentration as a function of age for each sex and assay system. The 5th, 25th, 50th, 75th, and 95th percentiles for BNP are shown, respectively, bottom to top in each nomogram according to age. From Redfield et al,[33] with permission from the American College of Cardiology Foundation.

Interestingly, the association between atrial volume and BNP is independent of age. Furthermore, although several studies reported that atrial volume increases with age in the general population,[45,46] Thomas et al[47] stated that atrial volume does not increase with healthy aging but is related to left ventricular systolic and diastolic dysfunction. It is now clear that age and atrial volume are independent predictors of BNP values. As BNP increases with age, could it serve as a marker for an accelerating aging process in the heart? The mechanisms of age- and sex-associated increases in BNP level are unfolding and are worthy of additional study.

IMPORTANCE OF MODERATELY ELEVATED LEVELS OF BNP WITHOUT HF

In general, measurement of circulating BNP is used to diagnose HF. However, recent studies support the concept that elevations in plasma BNP level in the absence of HF have prognostic importance.[48-50] Specifically, Wang et al[48] from the Framingham Heart Study reported in a prospective investigation in the general population without HF that with each SD increase in log BNP levels, there were significant increases in the risk of death, HF, AF, stroke or transient ischemic attack, and first cardiovascular event during 5.2 mean years of follow-up (Table 1). These increased risks were associated with only moderate elevation in BNP levels, as low as 20 pg/mL, which were well below the HF diagnosis threshold.[48] Echocardiographic measurements explained some associations between BNP and risk of cardiac events but did not attenuate the increased risk of HF and AF. Even when all other variables, including known cardiovascular risk factors, were controlled in this study, there was still increased risk associated with moderately elevated BNP levels. The reasons for this risk are unclear, but there is much speculation. Because undiagnosed diastolic dysfunction is common in the community,[51] the increased risk reported by Wang et al may be secondary to this parameter since it was not evaluated. As previously discussed, whether renal failure independently increases plasma BNP levels is controversial. Individuals with overt renal failure were excluded from the study. However, it is possible that individuals, especially elderly persons, with moderate elevations in BNP level had latent renal dysfunction, which predisposed them to heart disease independent of BNP levels.[52,53] Although the Framingham group adjusted for confounding variables, they had no subgroup with no cardiovascular disease risk factors; therefore, potentially confounding phenotypes exist that may account for their findings.

TABLE 1. **Multivariate Analysis of the Association of Plasma BNP Levels and Outcomes***

Outcome	Adjusted hazard ratio per 1 SD increment in log BNP values (95% CI)	*P* value	Adjusted hazard ratio for BNP values above 80th percentile (95% CI)	*P* value
Death†	1.27 (1.06-1.52)	.009	1.62 (1.08-2.42)	.02
First major cardiovascular event‡	1.28 (1.03-1.59)	.03	1.76 (1.06-2.92)	.03
Heart failure‡§	1.77 (1.31-2.41)	<.001	3.07 (1.51-6.26)	.002
Atrial fibrillation§	1.66 (1.30-2.11)	<.001	1.91 (1.13-3.25)	.02
Stroke or transient ischemic attack†‡	1.53 (1.16-2.02)	.002	1.99 (1.09-3.62)	.02
Coronary heart disease events	1.10 (0.89-1.37)	.37	1.30 (0.79-2.15)	.30

*For all outcomes, hazard ratios were adjusted for age, sex, presence or absence of hypertension, ratio of total cholesterol to high-density lipoprotein cholesterol, smoking status, presence or absence of diabetes mellitus, body mass index, and serum creatinine level. BNP = B-type natriuretic peptide; CI = confidence interval.
†Also adjusted for the presence or absence of prevalent cardiovascular disease.
‡Also adjusted for the presence or absence of prevalent atrial fibrillation.
§Also adjusted for the presence or absence of valvular disease and prevalent myocardial infarction.
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PHENOTYPE OF INDIVIDUALS WITH MODERATELY ELEVATED BNP LEVELS

Wang et al[48] reported that individuals with moderately elevated BNP levels have greater risks of HF and AF. This study excluded individuals with HF and a creatinine level greater than 2.0 mg/dL and adjusted for other diseases and risk factors. However, the phenotypical characteristics of individuals with moderately elevated BNP levels have not been described, and the cardiovascular risk factors, if any, that accompany moderately elevated BNP levels are unknown. Are moderately elevated BNP levels associated with increased risk of cardiovascular events in the absence of traditional risk factors? This is a pertinent question. Furthermore, is an elevated BNP level associated with abnormal echocardiographic parameters that independently predispose an individual to cardiovascular events? Understanding the phenotype will help determine whether BNP is unmasking preclinical disease or if well-documented cardiovascular risk factors are associated with moderately elevated BNP levels. Both conclusions are important and will affect the value of BNP as a screening tool for heart disease.

POTENTIAL MECHANISMS OF ELEVATED BNP LEVELS IN INDIVIDUALS WITHOUT HF

As previously discussed, it is increasingly recognized that myocardial processes beyond HF may increase circulating BNP levels, and recent research has begun to identify non-HF stimuli for elevated BNP levels. It is likely that diseases such as coronary artery disease, which involve myocardial ischemia, inflammation, and endothelial damage, lead to meaningful alterations in plasma BNP levels in individuals without HF. Indeed, in the setting of cerebrovascular disease, a synergy has been reported involving C-reactive protein, a marker for inflammation, and NT-proBNP to predict future HF.[54] Thus, these findings render BNP as more of a global marker for myocardial injury and suggest that BNP production is the final common pathway for a host of cardiovascular diseases. Furthermore, it is likely that preclinical cardiovascular disease, including but not limited to HF, leads to increases, although moderate, in BNP concentrations.

One potential cause for elevated BNP levels in the absence of HF is asymptomatic, preclinical coronary heart disease not seen on echocardiography. Goetze et al[26,27] showed that acute myocardial hypoxia results in an increase in cardiac BNP gene transcription, a release of proBNP from ventricular myocytes, and an increase in plasma proBNP. Although BNP levels were elevated in these studies, cardiac filling pressures were not measured. The authors stated that hypoxia increases both ANP and BNP gene transcription and peptide release in vitro. Furthermore, the release of BNP in response to hypoxia is extremely rapid, within 2 hours. Also, elevated levels of plasma BNP have been shown to be independently associated with induced ischemia in patients with stable coronary artery disease.[55] Ischemia-induced increases in BNP level likely reflect a teleological action in which BNP, a potent vasodilator, acts in a paracrine regulatory fashion to increase blood flow to the myocardium in the setting of hypoxia. To this point, Chong et al[56] report an inverse correlation between flow-mediated dilatation and BNP levels, suggesting that BNP levels increase with endothelial dysfunction, a risk factor for cardiovascular disease. Also, preliminary studies by Martin et al[57] support the concept that BNP may help identify underlying myocardial disease independent of HF compared with ANP or an altered molecular form of ANP.

We have reported that cardiac fibroblasts produce BNP and that BNP seems to retard collagen synthesis.[58] Also, ANP and BNP expression is intense in areas of cardiac fibrosis in a mouse model of deletion of the natriuretic peptide receptor-A to which ANP and BNP bind.[59] It is proposed that natriuretic peptide synthesis in fibroblasts is depressed in the normal state, but transcription is activated with activation of the angiotensin system and other neurohormonal pathways. Therefore, BNP activation seems to be a compensatory response to regulate collagen synthesis. Furthermore, it is proposed that natriuretic peptide synthesis increases by the same mechanisms that transform the cardiac fibroblast into a collagen-secreting cell. It is likely that cardiac fibrosis, which we know is associated with HF in the setting of preserved systolic function, is associated with enhanced secretion of BNP. This represents another opportunity to use elevated BNP levels to look beyond conventional clinical HF, and further studies are required to confirm the links between fibrosis and BNP.

Certain arrhythmias, specifically AF, also result in markedly elevated BNP levels.[31] In individuals with AF and with normal ventricular function, BNP and ANP are increased compared with controls.[60] Although there is some controversy about whether BNP is associated independently with AF,[61] Wozakowska-Kaplon[62] reported recently that in outpatients with AF, BNP levels decreased significantly 24 hours after sinus rhythm returned to normal. The specific molecular pathways that increase plasma BNP levels in AF have not been elucidated completely. Redfield et al[33] showed that plasma BNP levels were associated independently with LA volume and that LA volume is correlated with AF. Increased atrial stretch is likely responsible for elevated levels of plasma BNP associated with increasing LA volume because BNP is released primarily from the atria in the non-HF setting. Furthermore, atrial stretch has been implicated in atrial fibrosis and AF.[63,64] As previously noted, fibroblasts have been shown to produce BNP. The relationships among atrial volume, atrial stretch, and fibrosis may help explain the association between moderately elevated levels of BNP and increased risks of AF and HF. Also, increases in wall stress and the associated myocardial structural changes with cardiac overload and hypertension are likely to occur earlier and to a greater extent in the thin-walled atria. These atria are likely to be more sensitive to the BNP-secreting stimuli in disease states; thus, the resultant moderate increases in plasma BNP level may serve as a sensitive marker for early cardiovascular disease.

Levels of BNP may be influenced by changes in cardiomyocytes and cardiac fibroblasts, which are undetectable with current imaging techniques. These changes are likely secondary to subtle but functionally important myocardial injury. Indeed, Raizada et al[65] speculated that preclinical HF activates cellular responses in myocardial cells leading to moderate elevations in BNP level and that these elevations are due to increased wall stress that is sensed more in the thin-walled BNP-secreting atrium. Sayama et al[66] reported that the stimuli for cardiac hypertrophy, including hypertension and activation of neurohormonal pathways in cardiovascular disease, further stimulate the BNP gene with increased synthesis and release of this cardiac peptide. Therefore, it is plausible that increased BNP production serves as a protective reserve by the heart, which may have diagnostic implications. These results, along with the observations by Wang et al,[48] suggest that moderately elevated BNP levels unmask preclinical heart disease before diagnosis is possible with current technology.

It is likely that elevated BNP levels represent a final common pathway for many cardiovascular pathologic states. However, there is much to be learned regarding which specific biologic or mechanical processes lead to elevated BNP levels in individuals without HF. Furthermore, we must elucidate the links between these mechanisms that increase plasma BNP levels and the increased risk of cardiovascular events. Finally, we must determine whether moderately elevated BNP levels truly unmask asymptomatic, preclinical disease states that predispose patients to higher cardiovascular disease risk.

CALL TO ACTION

Screening for preclinical, asymptomatic heart disease by using moderately elevated BNP levels is an exciting possibility. Specifically, will it be possible to use moderately elevated BNP levels to accurately and cost-effectively predict preclinical, asymptomatic coronary artery disease, cardiac fibrosis, or future cardiovascular events? If so, then BNP level alone or combined with other biomarkers or clinical parameters would be a powerful marker for asymptomatic cardiovascular disease. The need to address preclinical disease is paramount because late-stage treatment of heart disease is costly and only minimally effective. The importance of identifying individuals with asymptomatic disease is highlighted by National Institutes of Health Director Elias Zerhouni's recent comments about the need to study preclinical disease and to increase our knowledge of molecular events before the disease emerges.[67]

Further issues need to be addressed. First, we must establish the phenotype of individuals with moderately elevated BNP levels. Characterization of the phenotype will allow better study of the individual and provide direction for future research. Second, studies must be initiated to evaluate the mechanisms of non-HF BNP level elevations with more in-depth investigation of myocardial structure

and function. Possibilities include coronary angiography, other forms of myocardial imaging, and myocardial biopsy in individuals with moderately elevated BNP levels. Finally, studies are needed to determine whether an intervention based on BNP levels improves cardiovascular outcomes.

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