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Cardiac Hormones as Diagnostic Tools in Heart Failure

HEIKKI RUSKOAHO

Department of Pharmacology and Toxicology, Biocenter Oulu, FIN-90014 University of Oulu, Finland

In patients with heart failure, plasma levels of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and the N-terminal fragments of their prohormones (N-ANP and N-BNP) are elevated, because the cardiac hormonal system is activated by increased wall stretch due to increased volume and pressure overload. Patients suspected of having heart failure can be selected for further investigations on the basis of having an elevated plasma concentration of N-ANP, BNP, and N-BNP. High levels of cardiac hormones identify those at greatest risk for future serious cardiovascular events. Moreover, adjusting heart failure treatment to reduce plasma levels of N-BNP may improve outcome. Cardiac hormones are most useful clinically as a rule-out test. In acutely symptomatic patients, a very high negative predictive value is coupled with a relatively high positive predictive value. Measurement of cardiac hormones in patients with heart failure may reduce the need for hospitalizations and for more expensive investigations such as echocardiography. However, there have also been conflicting reports on the diagnostic value of cardiac hormones, they are not specific for any disease, and the magnitude of the effects of age and gender on BNP in the normal subgroup suggests that these parameters need to be considered when interpreting cardiac hormone levels. (*Endocrine Reviews* 24: 341–356, 2003)

I. Introduction

CONGESTIVE HEART FAILURE is characterized by the progressive activation of several endocrine systems. Increased levels of norepinephrine and endothelin-1, as well as the activation of the renin-angiotensin-aldosterone system, have been described to play a pathophysiological role in the progression of left ventricular dysfunction and development of heart failure (1). Unlike these vasoconstrictor neurohormones, the cardiac hormones, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), have beneficial, compensatory actions including vasodilation, natriuresis, growth suppression, and inhibition of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis (2–9). The activation of the cardiac endocrine system in patients with cardiac dysfunction has been the subject of intense research, because elevated circulating levels of these hormones have important diagnostic and therapeutic implications (10–19). The application of plasma cardiac hormone measurements to screening, prognosis, and treatment monitoring in heart failure has received a major stimulus through the recent introduction of rapid and sensitive tests. A bedside (point-of-care) assay for BNP received Federal Drug Administration (FDA) approval in 2000 and a fully automated blood test for quantification of N-terminal fragment of proBNP (N-BNP) in 2002 to aid in the diagnosis of congestive heart failure. This review is concerned with the background and the recent developments on the diagnostic use of the cardiac hormones in congestive heart failure.

Abbreviations: ACE, Angiotensin-converting enzyme; ANP, atrial natriuretic peptide; AT_1, type 1 angiotensin receptor; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; ET, endothelin; N-ANP, N-terminal fragment of proANP; N-BNP, N-terminal fragment of proBNP; NYHA, New York Heart Association; SHR, spontaneously hypertensive rats.

II. The Natriuretic Peptide Family

The natriuretic peptides are a group of structurally similar but genetically distinct peptides (Fig. 1). ANP and BNP are of cardiac origin, and C-type natriuretic peptide (CNP) is of endothelial origin. ANP is a cyclic 28-amino-acid polypeptide synthesized and secreted mainly by the atria in the normal adult heart. It is stored in atrial granules as the C-terminal part of the 126-amino-acid prohormone (proANP) (Fig. 2A). On secretion, $proANP_{1–126}$ is split by the serine protease corin (20) into an N-terminal fragment of 98 amino acids ($N\text{-}ANP_{1–98}$) and the biologically active $ANP_{99–126}$ in equimolar amounts (21). Thus, the measurements of N-ANP can be used to estimate the release of ANP from the heart. N-ANP has a significantly longer half-life (~10 times) in plasma compared with ANP (half-life of 2–5 min) and thus has up to 10–50 times the plasma concentration of ANP. N-ANP is also more stable under laboratory conditions than ANP (22, 23). ANP is rapidly removed from the circulation mainly through binding to clearance receptors (24) and hydrolysis by neutral endopeptidase (25). The plasma levels of ANP are variable (26), and its reliable measurement requires a laborious extraction step. Because N-ANP is less variable and has a longer half-life within circulation, N-ANP appears

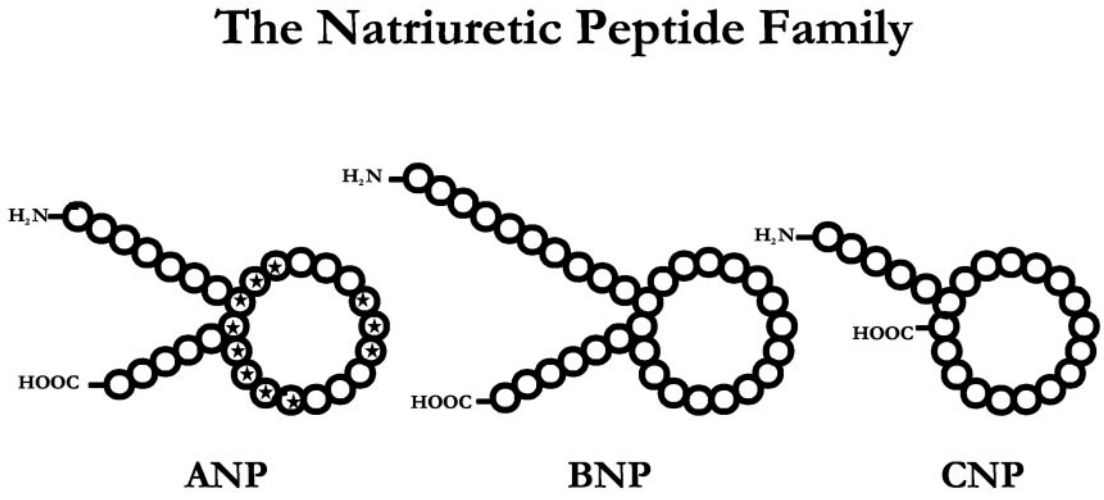

FIG. 1. The structures of natriuretic peptides. Identical amino acids for all natriuretic peptides are indicated by *stars*.

to be a more representative marker of prolonged cardiac overload than ANP.

BNP is a 32-amino-acid peptide that is structurally similar to ANP and contains a 17-amino-acid ring structure common to all natriuretic peptides (Fig. 1). BNP is produced as a prohormone, proBNP (108 amino acids), which is cleaved by furin (27) to form active $BNP_{77–108}$ and inactive $N\text{-}BNP_{1–76}$ molecules (Ref. 27; Fig. 2B). In addition to BNP and N-BNP, $proBNP_{1–108}$ may be present in human heart and plasma (28–32), suggesting that posttranslational processing of proBNP occurs within myocardium. BNP is more stable than ANP in plasma (23, 33–36) and has a longer half-life (22 min), which may be attributable to its lesser affinity for clearance receptors and neutral endopeptidases (21, 37, 38). There are very limited data available concerning the plasma half-life of N-BNP. Recently, Pemberton *et al.* (39) used deconvolution analysis of plasma immunoreactive N-BNP in an ovine experimental model of heart failure to compare the dynamic response of cardiac hormones during ventricular pacing. Deconvolution analysis showed that the half-life of approximately 70 min for N-BNP was 15-fold longer than that of BNP (39). Studies on the stability of N-BNP in stored plasma are similar to those reported for BNP (and better than ANP) and indicate that the laboratory handling, processing, and storage of N-BNP can be undertaken without special procedures (30, 31, 33, 40, 41). By analogy with the ANP hormonal system, N-BNP may be a more sensitive and specific marker of left ventricular dysfunction than BNP. Although BNP was originally discovered from the brain, the BNP peptide and mRNA levels are highest in the atria followed by the ventricles (5, 6, 16, 42–44).

CNP consists of 22 amino acids, is produced by the vascular endothelium, and has vasodilatory and antiproliferative effects on vascular smooth muscle (45). It has a local action in the blood vessels or within the organ where it is produced. CNP shares structural (Fig. 1) and physiological properties with the cardiac hormones ANP and BNP, but little is known about its pathophysiological role in chronic heart failure. Recently, Kalra *et al.* (46) assessed the hypothesis that CNP is produced by the heart in patients with heart failure. Myocardial CNP production was determined (difference in plasma levels between the aortic root and coronary sinus) in nine patients undergoing right and left heart catheterization. A step-up (29%) in plasma CNP concentration was found from the aorta to the coronary sinus (3.55 ± 1.53 *vs.* 4.59 ± 1.54 pg/ml). BNP levels increased by 57% from the aorta to the coronary sinus (86.0 ± 20.5 *vs.* 135.0 ± 42.2 pg/ml). Moreover, coronary sinus CNP levels correlated with mean pulmonary capillary wedge pressure (46). Thus, CNP may be also produced in the heart in patients with heart failure and may be an important new local mediator in the heart.

III. Mechanisms Regulating Cardiac ANP and BNP Synthesis and Release

In patients with heart failure, circulating plasma levels of ANP, BNP, and the N-terminal fragments of their prohormones (N-ANP and N-BNP) are elevated, because the cardiac hormonal system is activated by increased wall stretch (6). Lang and colleagues (47, 48) were the first to show conclusively that ANP is released from the atrium in response to wall stretch. The experiments were made in isolated perfused rat hearts by means of a modified Langendorff preparation, in which a change in intraatrial pressure was equal to transmural pressure gradient and thus atrial stretch. Increasing the perfusion rate produced a rise in right atrial pressure, which was accompanied by an increase in ANP released into the perfusate, indicating that atrial wall stretch alone is a major stimulus for cardiac hormone release (47, 48).

As in the atria, the principal stimulus controlling synthesis and release of ANP from the ventricles is wall stretch (49, 50). Furthermore, patients with heart failure have elevated circulating or tissue levels of norepinephrine, angiotensin II, endothelin (ET)-1, and cytokines, which can not only increase the hemodynamic stress on the ventricle but also directly stimulate ANP expression and release from cardiac myocytes (6, 7). The cardiac ventricles contribute significantly to the circulating ANP both in experimental animals and patients with heart failure and left ventricular hypertrophy (Ref. 6; Fig. 3). In spontaneously hypertensive rats (SHR), about 28%

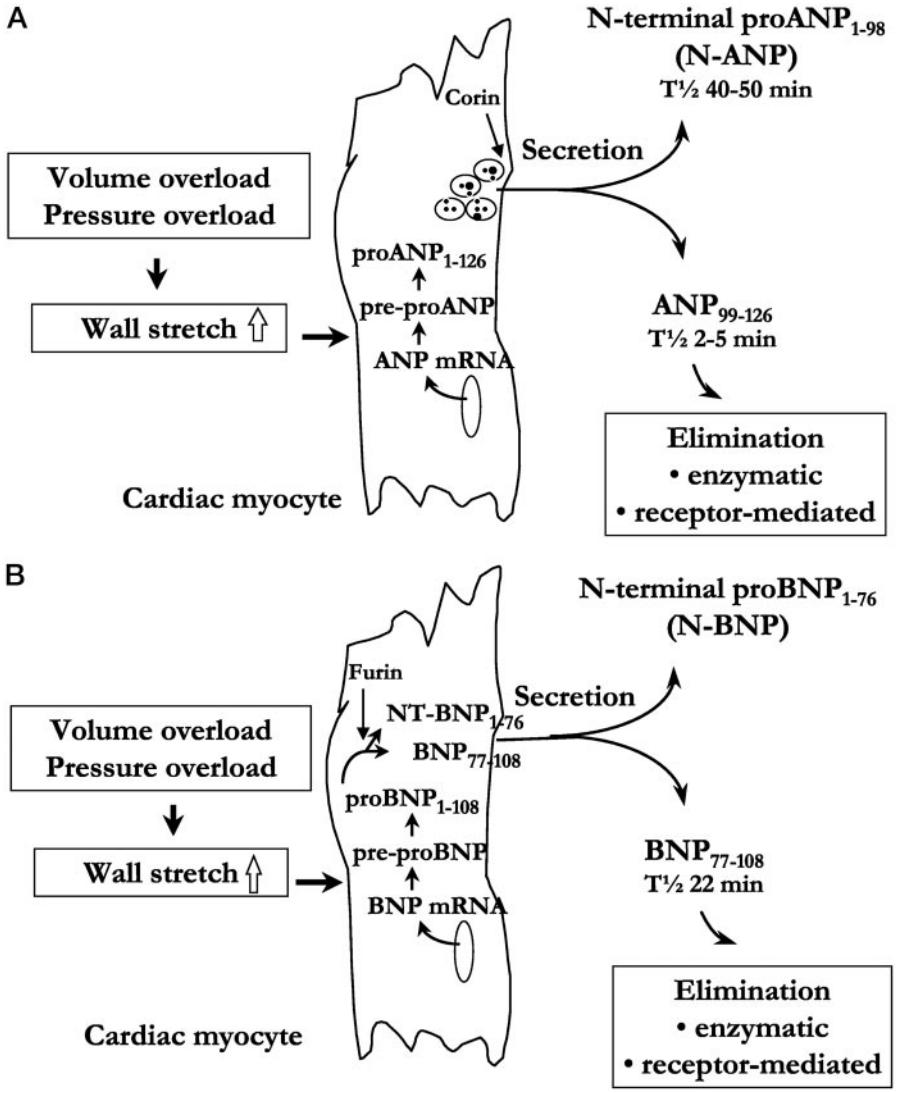

FIG. 2. Schematic representation of the synthesis and molecular forms of cardiac hormones in the heart and circulation. Half-life (T½) in the circulation is also indicated.

of the total amount of ANP released originates from ventricles (49). In severe congestive heart failure in the hamster, as much as 74% of ANP released into perfusion fluid is produced in the ventricles (51). In humans, increased ventricular ANP release from the ventricle has been seen in patients with dilated cardiomyopathy (52), and elevated plasma levels are associated with increased synthesis of ANP within both atrial and ventricular myocardium (6). Although the concentration is still higher in atria, given the larger left ventricular mass, the ventricular myocardium becomes a major source for circulating ANP and N-ANP in failing hearts. Thus, the increase in plasma ANP and N-ANP in patients with heart failure is due to enhanced atrial and ventricular synthesis and release, triggered by the increased cardiac volume and pressure overload.

Whereas ANP is secreted primarily by atrial myocytes, BNP is produced by both the atria and ventricles in the normal human heart (5–7, 16, 42, 44). In normal subjects, plasma concentrations of BNP are lower than those of ANP. However, compared with ANP and N-ANP, BNP and N-BNP exhibit a greater proportional rise in disease states (31, 53, 54) and thus have emerged as the preferred biomarkers for clinical development. Ventricular levels of BNP mRNA are substantially increased in response to chronic cardiac overload in the human heart (55) and in experimental models of cardiac overload including SHR (43, 56, 57) and rats with myocardial infarction (58). When tissue weight is taken into account, the total amount of BNP mRNA in the rat has been suggested to be three times greater in the ventricle than in the atrium in stroke-prone SHR (43). Moreover, in this experimental model approximately 60% of the secreted BNP was derived from the ventricle, although the BNP level in the ventricle is only 1% of that in the atrium (43). In another study, 38% of BNP and 16% of ANP originated from the ventricles of isolated perfused SHR hearts under identical experimental conditions (57). The predominant stimulus controlling the synthesis and release of BNP from the atria (59) and ventricles (57, 60) is wall stretch. An acute increase

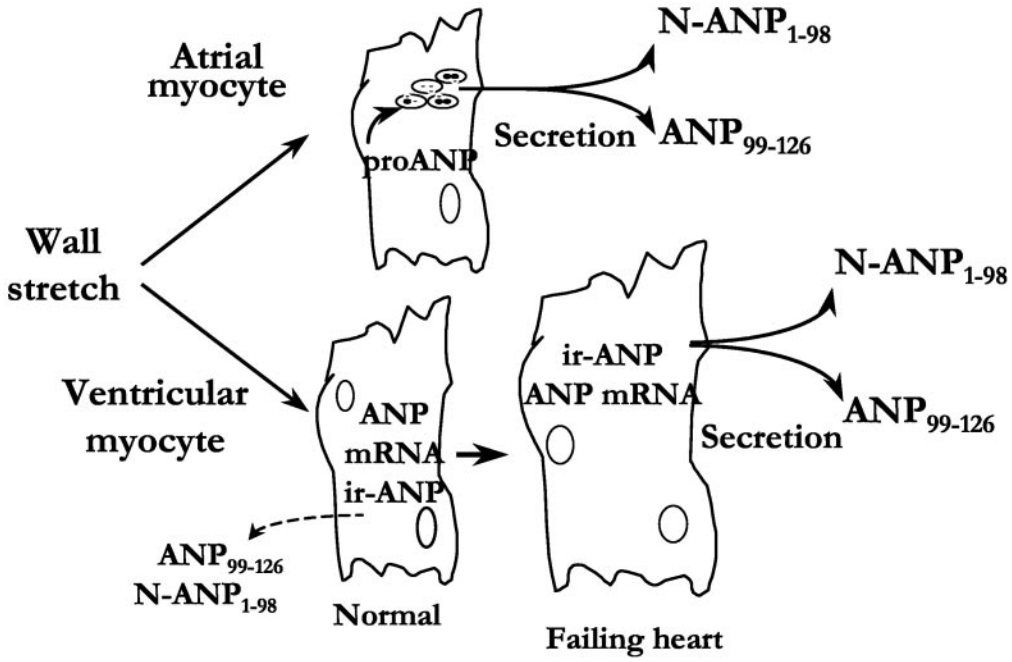

FIG. 3. Schematic representation of the synthesis and molecular forms of ANP in failing heart. Ventricular ANP gene expression and release are increased in patients with heart failure, reflecting the higher demand for cardiac hormone secretion due to increased cardiac pressure and volume overload. Thus, ANP is also a ventricular hormone.

in both atrial and ventricular BNP mRNA levels by pressure overload *in vivo* occurs within 1 h and mimics the rapid induction of protooncogenes in response to hemodynamic stress (60). Moreover, during acute pressure overload *in vivo* in rats, the increases in plasma BNP levels corresponded with changes in ventricular BNP mRNA levels (60). Experiments using cultured neonatal rat ventricular cells have also shown that cardiac myocytes are able to respond to mechanical stretch by increasing BNP secretion and gene expression without neurohumoral control (27, 61). In patients with heart failure, BNP release appears to be in direct proportion to ventricular volume expansion and pressure overload and ventricular wall stress (62, 63).

Although BNP appears to be synthesized and released mainly from the ventricle in response to wall stretch in failing hearts, significant amounts of BNP are also released from atria (5, 6, 7, 21). Indeed, in several experimental models of cardiac overload, the concentration of immunoreactive ANP in the ventricles is higher than that of BNP (6, 7). In deoxycorticosterone acetate-salt rats, BNP concentration and content, as well as BNP mRNA content, are higher in the atria than in ventricles, even taking into account the size of the ventricles compared with that of atria (64). In a rapid pacing-induced experimental model of congestive heart failure during developing left ventricular dysfunction, the atrial myocardium is the predominant site of BNP gene expression and production (65). Catheterization studies in patients with left ventricular hypertrophy have shown that the atrium-derived BNP significantly contributes to elevation of plasma BNP, reflecting atrial pressure and volume loading in these patients (66). It has also been shown that, in right atrial specimens from 21 patients who had undergone cardiac surgery, expression of BNP and BNP mRNA was augmented in the atria with increased pressure and distributed predominantly in the subendocardial side (67). Because the level of BNP mRNA correlated well with that of ANP mRNA (67), atrial pressure seems to regulate both ANP and BNP hormonal systems in these patients. More recently, it has been reported that plasma BNP is produced mainly by the atrium and not by the ventricle in patients with lone atrial fibrillation, with or without underlying heart disease (68). Taken together, BNP is produced both in the atrium and ventricles, and the predominant source of circulating BNP may be different depending on the severity and cause of cardiac disorder.

The storage of ANP in secretory granules provides a source for rapid release of the peptide (69). In contrast, cardiac BNP does not appear to be stored to the same extent as ANP (70), and, thus, increased release may require a longer stimulus to increase its rate of synthesis and subsequent secretion. Indeed, an increase in BNP secretion is preceded by an increase in mRNA in response to stretching of the right atrium, whereas stored ANP is immediately released (59). Similarly, in a canine model of early left ventricular dysfunction, BNP mRNA and tissue BNP remain low in the left ventricle, whereas, in severe congestive heart failure, BNP synthesis is markedly increased in the left ventricle and contributes significantly to the further increase in plasma BNP (65). In humans, acute iv saline loading (71) and changes in posture (72) that modify atrial pressure and acutely increase plasma ANP values (6) do not increase plasma BNP levels. However, several days of dietary salt loading results in an expected increase in plasma BNP (73, 74). The findings that ANP is an acutely responsive hormone and BNP levels better reflect sustained cardiac pressure and volume overload support the concept that BNP and N-BNP may be a more suitable marker of chronic ventricular dysfunction than ANP.

In addition to wall stretch, a variety of endocrine, paracrine, and autocrine factors that are activated in congestive heart failure (*e.g.*, norepinephrine, angiotensin II, ET-1, and cytokines) have been shown to affect ANP and BNP gene expression and release (75–82). Many studies have further indicated that angiotensin II, via the type 1 angiotensin receptor (AT_1), plays a critical role in the development of stretch-induced cardiac hypertrophy (83). ET-1 is also released rapidly when cultured endothelial cells are stretched (84). Recently, Liang and Gardner (85) showed that, in cultured neonatal ventricular cells, blockade of AT_1 receptors or ET-1 receptors suppressed stretch-induced BNP gene transcription by approximately 50%. The ET-1-dependent component of mechanical stretch-induced increase in BNP mRNA appeared to need the interaction of cardiac nonmyocytes and myocytes, because, in pure myocyte culture, stretch did not stimulate production of BNP (86). However, injection of the AT_1 receptor antagonist losartan or a mixed ET_A/ET_B-receptor antagonist, bosentan, had no effect on the acute pressure-overload-induced increase in ventricular BNP mRNA levels *in vivo* (87), suggesting that it is very likely that other paracrine and autocrine mechanism(s) are also involved in regulating cardiac BNP as well as ANP synthesis (6, 7). On the other hand, ET-1 has been reported to play a causal role in the activation of BNP gene expression by stretch in atrial tissue both *in vivo* and *in vitro* (79, 87). In contrast, in experimental animal models of chronic hypertension, atrial gene expression of natriuretic peptides may not be as sensitive to ET-1 and angiotensin II as is ventricular natriuretic peptide gene expression (75, 88, 89). These results suggest that endocrine, paracrine, and autocrine factors may differentially regulate atrial and ventricular cardiac hormone gene expression.

Although cardiac BNP gene expression increases rapidly in response to hemodynamic overload, some controversy persists regarding BNP gene expression in ventricular myocardium under normal conditions and in chronic cardiac overload. A number of studies both in the human and in animals describe either increased (42, 60, 65, 90, 91) or unchanged (56, 64, 92–95) left ventricular BNP mRNA levels in heart failure and hypertension. The reason for the normal BNP mRNA levels despite constant cardiac overload is not known but could result from transcriptional and/or translational mechanisms (96–99). BNP mRNA, like many other rapidly expressed genes, contains several AU-rich elements (sequences rich in A and U nucleotides) in the 3′ untranslated region (5) that may be involved in the translation-dependent mRNA degradation. To determine whether alterations in the rate of transcription of the BNP gene could account for the changes observed in BNP mRNA levels, Suo *et al*. (100) measured the activity of a −2.2-kbp BNP promoter fragment fused to the luciferase reporter gene by injecting it directly into beating left ventricle; they found that posttranscriptional control plays an important role in the regulation of left ventricular BNP gene expression *in vivo*. These results suggest that posttranscriptional mechanisms may contribute to blood BNP concentration used in the diagnosis of heart failure.

In view of the above (Table 1), the raised circulating levels of natriuretic peptides are associated with increased atrial wall stretch (due to volume expansion and pressure overload), ventricular wall stretch (due to reduced ventricular systolic and diastolic function) and synthesis (due to left ventricular hypertrophy), as well as with renal impairment and neurohumoral activation (*e.g.*, angiotensin II, ET-1, and norepinephrine). Therefore, raised plasma levels of natriuretic peptides, for example, in patients with renal insufficiency can be explained by 1) volume load and distension of the atria and ventricles and 2) reduced renal clearance of the peptides. Accordingly, the effects of renal dysfunction on plasma cardiac hormone levels may modify their diagnostic value as screening tools and markers of left ventricular dysfunction.

TABLE 1. Synthesis and release of cardiac hormones in chronic cardiac volume and pressure overload

ANP
• Permanent activation of the gene expression also in cardiac ventricles
• Production of ANP and N-ANP shifts proportionally from atria to ventricles
• Plasma levels are mostly regulated at the level of secretion
BNP
• Activation of the gene both in atria and ventricles
• Induction of synthesis is associated with the changes in release of BNP and N-BNP into circulation
• Plasma levels are regulated increasingly by synthesis in ventricles in failing hearts
Wall stretch
• Increases the synthesis and release of ANP, N-ANP, BNP, and N-BNP, and thus their plasma levels are increased in patients with ventricular dysfunction

IV. Measurement of Cardiac Hormones in Patients with Suspected Heart Failure

Heart failure is a major public health problem in the United States. It affects nearly 5 million Americans and is responsible for approximately 1 million hospitalizations and 50,000 deaths each year (101). The prevalence of symptomatic heart failure in Europe is estimated to be about 0.4–2% (102). The increasing mean life expectancy, together with improved survival rates in patients with other cardiovascular diseases and after myocardial infarction, is expected to result in a major increase in the prevalence of heart failure in the future. The asymptomatic form of left ventricular systolic dysfunction is estimated to be as common as symptomatic congestive heart failure (103).

The accuracy of diagnosis of heart failure by clinical means alone is often inadequate, especially in women, the elderly or the obese subjects, and when associated chronic pulmonary and cardiac diseases are present (104, 105). The diagnosis of congestive heart failure has been based on the severity of symptoms [the New York Heart Association (NYHA) functional classification], as well as on electrocardiogram and the chest x-ray. Echocardiography provides specific diagnostic and prognostic information, but it is not well suited for screening or rapid bedside diagnostics. Invasive measurements (coronary angiography, hemodynamic monitoring) do provide an objective indicator of the severity of heart failure, but none of them is indicated as a routine procedure (102). Thus, there is a need for biochemical diagnostic tests of cardiac impairment. Cardiac hormones have recently

emerged as potentially useful markers that may aid in the diagnosis of heart failure. The most recent guidelines for the diagnosis and treatment of chronic heart failure drawn by the European Society of Cardiology state that the circulating levels of natriuretic peptides may be most useful clinically as a rule-out test due to consistent and very high negative predictive values (102). According to the American College of Cardiology/American Heart Association practice guidelines for the evaluation and management of heart failure, the role of blood BNP in the identification of patients with congestive heart failure remains to be fully clarified (106).

Initial studies demonstrated that plasma ANP levels are elevated in patients with symptomatic congestive heart failure in proportion to the severity of the disease (44, 54, 107–111). Later, several studies have shown that plasma ANP and N-ANP are also significantly elevated in asymptomatic patients with left ventricular dysfunction, although less than in patients with obvious symptoms of heart failure (112, 113). More recently, BNP concentrations have been used to evaluate heart failure severity (114–118). BNP concentrations in patients with heart failure correlate with the NYHA functional class (119), hemodynamics (120), invasively measured left ventricular filling pressure (62, 121), left ventricular ejection fraction measured by radionuclide angiography (122) and echocardiography (123), and with other indices of heart failure such as the pulmonary artery wedge pressure (124). The BNP concentration can be used as an alternative to the 6-min walk test to assess the severity of heart failure (125) and predict functional capacity in patients with chronic heart failure (126). Hunt *et al*. (31) reported that BNP and N-BNP are significantly correlated with each other and with left ventricular ejection fraction. Moreover, the increase in N-BNP is much greater (4-fold) than that of BNP in subjects with moderate left ventricular dysfunction (31). Moreover, the plasma BNP values increase during right ventricle overload (127, 128).

Measurement of cardiac hormone level may be useful for identifying patients with suspected heart failure who need further diagnostic evaluation, especially when echocardiography is not readily available, or for supplementing echocardiography. Initially, Lerman *et al.* (112) demonstrated that N-ANP was raised consistently in NYHA class I patients with asymptomatic left ventricular dysfunction (documented with radionuclide angiography and clinical characterization) and was more sensitive and specific than ANP. Later, a number of studies (differing in design, methods, and the population studied) have examined the diagnostic value of different natriuretic peptides in relation to left ventricular systolic dysfunction in the general population (129, 130), in a population-based study (131), in health-screening programs (132), general practice (133–136), high-risk subjects (114, 137), subjects referred because of presumed heart failure (138, 139), subjects undergoing cardiac catheterization (140), in the urgent-care setting (117, 141), and in patients after myocardial infarction (142).

Cowie *et al.* (143) showed how BNP could rule out congestive heart failure in newly symptomatic subjects and identify patients who require further investigation in general practice. A BNP level of 22.2 pmol/liter (76.4 pg/ml) or higher (chosen for its negative predictive value of 98% for heart failure) had a sensitivity of 97%, a specificity of 84%, and positive predictive value of 70%. In the community-based study by McDonagh *et al.* (129), 1653 subjects between 25 and 74 yr old, randomly selected from patient lists of family physicians, underwent echocardiography and electrocardiography. A BNP level of 5.2 pmol/liter (17.9 pg/ml) or greater had a sensitivity of 76%, a specificity of 87%, and a negative predictive value of 97.5% for left ventricular dysfunction. In both studies, BNP was found to be more sensitive and specific compared with N-ANP in the detection of left ventricular systolic dysfunction, especially in the elderly. McDonagh *et al.* (129) also pointed out that measurement of natriuretic peptides, especially for high-risk patients, is at least as cost effective for the screening of heart failure as the use of prostate-specific antigen, mammography, or cervical smears for the screening of carcinoma. In the recent report Nielsen *et al.* (134) evaluated the diagnostic value of BNP in subjects without acute symptoms of heart failure in the general population. Their results suggest that low- and high-risk subjects can be identified by simple clinical parameters, and a subsequent sensitive BNP assay significantly rules out left ventricular systolic dysfunction in subjects less than 75 yr of age and at risk. Screening by BNP before echocardiogram was more cost effective than referring all subjects to echocardiography (134).

Clinical experience suggests that BNP may have utility in the urgent-care setting, where it has been used to accurately discriminate acute dyspnea due to congestive heart failure from other causes (117, 122, 141, 144). In a recent multinational sample of men and women seen in the emergency department with acute dyspnea (Breathing Not Properly Multinational Study, Ref. 141), BNP measurement would have added to clinical judgment in establishing final diagnosis of congestive heart failure. In those patients with an intermediate probability of congestive heart failure, BNP would have clarified the diagnosis in the majority of cases (74%; Ref. 141). In those in whom the plasma levels of BNP are normal, other causes of dyspnea should be considered. However, wider dispersion of BNP levels has been reported in patients with pulmonary diseases and severe dyspnea (145, 146).

Plasma cardiac hormones are also elevated in patients with left ventricular hypertrophy and left ventricular diastolic dysfunction (147–151). Plasma cardiac hormone levels have been reported to correlate with left ventricular mass in patients with hypertension (114, 147, 148, 150), although no correlation between left ventricular mass and N-BNP was found in a recent study (152). Plasma N-ANP level is also correlated with left ventricular mass in the general population (153, 154). Lang *et al.* (149) found substantially raised levels of plasma BNP and ANP in patients with isolated diastolic dysfunction in the absence of systolic failure or significant left ventricular hypertrophy. Yamamoto *et al.* (114) reported that BNP emerged as superior to either N-ANP or ANP as a marker of systolic or diastolic dysfunction and ventricular hypertrophy in patients with or at risk for cardiac disease. An increased BNP concentration (>15.7 pmol/liter or 54.0 pg/ml) was found to have a sensitivity of 81% and a specificity of 90% for the detection of echocardiographic left ventricular hypertrophy.

Recently, Maisel *et al.* (139) studied the utility of BNP in distinguishing diastolic in addition to systolic dysfunction. Two hundred patients were referred for the assessment of left ventricular function. In 105 patients, ventricular function was considered to be normal and BNP levels were low (37 ± 6 pg/ml), whereas those with systolic dysfunction had a mean level of 572 ± 115 pg/ml, and patients with diastolic dysfunction of 391 ± 89 pg/ml. This study supports other reports showing an increase in plasma BNP levels in the presence of diastolic dysfunction (114, 149, 151, 155). However, some studies show plasma natriuretic peptides to be normal unless systolic function develops (152). In general, it is difficult to be precise about the diagnosis of diastolic dysfunction. The diagnosis is in practice based on the finding of typical symptoms and signs of heart failure in patients who have preserved left ventricular systolic function (normal ejection fraction/normal left ventricular volumes) (102, 106). Moreover, most patients with heart failure and impairment of diastolic function also have impaired systolic function. Yet, a low BNP level in the setting of normal left ventricular systolic function by echocardiography may be able to rule out clinically significant diastolic abnormalities seen on echocardiography (156). Because BNP increases during exercise along with left ventricular filling pressure in heart failure patients, exercise measurement of BNP might even be a provocative test to identify chronic diastolic heart failure (157). These findings are of significant interest, because approximately 20–50% of patients with heart failure have preserved left ventricular systolic function (106, 158, 159), and randomized, controlled trials are ongoing for investigating the effect of the heart failure treatment in patients with preserved ejection fraction (160).

Although more clinical studies are needed to establish the optimal role of the cardiac hormones in the diagnosis of heart failure and in screening strategies, measurement of cardiac hormones can now be integrated into the care of patients with suspected heart failure. Although comparative data are limited, N-ANP, BNP, and N-BNP seem to provide qualitatively similar information. Incorporation of cardiac hormone measurement into the clinical evaluation aids the diagnosis of heart failure due to systolic and/or diastolic left ventricular dysfunction; a normal BNP level practically rules out the diagnosis of decompensated heart failure, whereas a markedly elevated BNP in patients with new-onset acute symptoms has a high positive predictive value for heart failure. The negative predictive value of cardiac hormones is especially high when individuals at high risk of left ventricular dysfunction are studied. It should be noted, however, that moderate elevations of plasma cardiac hormones lack specificity. In addition to congestive heart failure, myocardial infarction, ventricular hypertrophy, cardiomyopathy, valvular diseases, tachycardias, renal failure, and pulmonary diseases can all increase the levels of natriuretic peptides (13). Moreover, in very well-treated heart failure, even in the presence of sustained impairment of left ventricular ejection fraction, plasma natriuretic peptides may return to the normal range, and, therefore, as a screening test in patients with a provisional diagnosis of heart failure who are symptomatically well and have been well established on long-term therapy, BNP may be insufficient (161). Finally, recent data confirm that age-, gender-, and assay-specific values will be needed (131, 162). In a population-based cohort, Redfield *et al.* (131) found that BNP increases with age and is higher in women among subjects without cardiovascular disease or cardiac dysfunction. The optimal discriminatory value of BNP for the detection of systolic dysfunction in the population was higher in women and older persons (131). Interestingly, the association of female gender and BNP appears to be, in part, related to estrogen status, as BNP levels were higher in women using hormone replacement therapy (131).

V. Estimation of the Prognosis and Prediction of Future Cardiac Events

Despite the advances in the treatment of heart failure, prognosis in heart failure remains poor, with a 5-yr survival of less than 50% in severely symptomatic patients. Recent studies have confirmed the poor long-term prognosis even in patients with asymptomatic myocardial dysfunction (102). Because plasma ANP, N-ANP, BNP, and N-BNP levels are increased in proportion to the severity of left ventricular dysfunction and in parallel with the activation of other neurohormonal systems, the association of cardiac hormones with prognosis in patients with chronic heart failure is an expected finding. Initially, Gottlieb *et al.* (110) reported that ANP provides prognostic data on survival and hemodynamic abnormalities. Davis *et al.* (163) extended these findings and demonstrated ANP as a specific and sensitive test for predicting heart failure in elderly subjects. Moreover, the plasma ANP level was a predictor of cardiac mortality and heart failure in asymptomatic patients with left ventricular dysfunction after acute myocardial infarction (113). In the CONSENSUS II study (164), plasma ANP after acute myocardial infarction was strongly related to subsequent cardiovascular mortality. The prognostic implications of ANP in patients with heart failure and in asymptomatic patients with left ventricular dysfunction after myocardial infarction have been confirmed by others (165–168). Yet, N-ANP appears to be a much stronger predictor of death and other cardiac endpoints after myocardial infarction than ANP itself (169, 170). N-ANP was an independent predictor of outcome when considered in a multivariate model that included ejection fraction and other clinical variables, and was an even stronger predictor of cardiovascular death and heart failure than age, prior infarction, or ejection fraction (169).

A number of studies of chronic heart failure indicate that plasma BNP is also elevated in proportion to the degree of left ventricular dysfunction and continues to rise along with the progression of heart failure (14). BNP levels have prognostic significance in patients with chronic symptomatic left ventricular dysfunction (171, 172). In a prospective study of 85 patients with chronic heart failure, Tsutamoto *et al.* (171) showed that a single BNP plasma level independently predicted 2-yr mortality in patients with left ventricular ejection fraction of less than 45%. In a cohort of 541 85-yr-old subjects from a general population, BNP levels were significantly correlated with 5-yr all-cause mortality (172). Although BNP levels are correlated with age, sex, intracardiac filling pressures, left ventricular mass and ejection fraction, renal func-

tion, and symptoms, BNP provides prognostic information in patients with heart failure that is independent of these variables (173).

BNP levels are markedly increased in patients with acute myocardial infarction at the time of hospital admission (121, 174–176). Indeed, BNP levels are considerably higher than ANP levels during the first hours of infarction, increasing to levels 20 times those of ANP (121, 175). Patients with a large infarct may have a second BNP peak about 5 d later, possibly reflecting the remodeling process (121, 175). BNP is produced in increased amounts throughout the ventricular myocardium but principally from the infarct zone, most probably in response to increased regional wall stress (175). Also, in experimental acute myocardial infarction, BNP synthesis is augmented not only in infarcted tissue but also in noninfarcted tissue (58). The magnitude of the elevation of plasma BNP is related to the size of the infarction, the severity of global left ventricular dysfunction, or both (121, 175, 177). These findings suggest that transient ischemia might increase wall stress and induce BNP synthesis and release in proportion to the degree of ischemic insult. Consistent with this hypothesis, some studies of chronic heart failure indicate that circulating BNP levels are less closely related to the magnitude of depression in ejection fraction than are ANP levels (54).

Several studies have focused on the clinical implications of BNP activation after acute myocardial infarction. In one small study, N-BNP levels were higher in patients with unstable than in those with stable angina (178). When measured within 1 wk after myocardial infarction, BNP and N-BNP have been shown to provide prognostic information by identifying patients at risk for left ventricular dysfunction, heart failure, and death (142, 174, 179). Richards *et al.* (142) have shown sensitivity and specificity of 91% and 72% for N-BNP measured 2–4 d after myocardial infarction in predicting 2-yr survival. As in chronic heart failure, the prognostic value of BNP seems to be greater than that of left ventricular ejection fraction (142, 179). BNP may be useful in identifying postinfarct patients with left ventricular dysfunction likely to benefit from treatment (123, 177).

Recently, the prognostic application of BNP has been extended to include patients with unstable angina and non-ST-elevation myocardial infarction (180–184). In a 2525-patient substudy of the OPUS-TIMI 16 trial (180), BNP was measured approximately 40 h after the onset of symptoms. Rates of death and heart failure through 10 months increased with higher baseline levels of BNP. In multivariate analyses, the association between BNP and mortality was independent of age, renal function, ST deviation, troponin I, and C-reactive protein (180). In a small case-control study of patients with non-ST-elevation acute coronary syndrome, N-BNP levels were also higher among patients who died than those who survived (181). Jernberg *et al.* (182) observed in a consecutive series of patients with chest pain and no ST elevation that N-BNP levels measured at admission were strongly associated with long-term mortality. Finally, Omland *et al.* (183) measured N-BNP levels about 3 d after acute coronary syndrome in a heterogeneous, unselected patient population and correlated N-BNP with outcomes (an average follow-up period of more than 4 yr). After adjusting for age and left ventricular ejection fraction measured by echocardiography, an N-BNP level above the median remained associated with long-term mortality. The results seem to be similar in patients with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina (183).

These recent results confirm that plasma cardiac hormone elevation provides prognostic information that is independent of and additive to left ventricular ejection fraction and is associated with an adverse prognosis, regardless of the cause of hemodynamic impairment. BNP elevation in particular has been associated with adverse prognosis in cardiovascular conditions ranging from unstable angina to heart failure, and even in the general population (185). The relative importance of BNP, N-BNP, and N-ANP values in risk stratification in relation to predictive accuracy remains to be established in larger studies. The possibility that multiple samples could provide additional prognostic information should also be studied. Nevertheless, the current results show that individuals with a high plasma level of cardiac hormone should be carefully investigated for cardiovascular disease.

VI. Cardiac Hormone-Guided Treatment of Heart Failure

Cardiac hormone measurements may be used to optimize heart failure therapy, because ANP and BNP are increased according to the severity of cardiac impairment (107–109). In patients with heart failure, diuretics, angiotensin-converting enzyme (ACE) inhibitors, AT_1 receptor blockers, spironolactone, and organic nitrates have been shown to decrease plasma cardiac hormone levels in parallel with hemodynamic and clinical improvement (63, 118, 186–196). The effect of beta-blockers is less clear because variable effects on both plasma ANP and BNP have been described with acute and chronic beta-blocker treatment (197–202). It seems that, whereas acute beta blockade will result in an early rise in plasma cardiac hormone concentrations, prolonged treatment in association with improvement in cardiac function and reduction in filling pressure and cardiac volumes would be expected to result in a fall in plasma cardiac hormone levels. Indeed, both plasma ANP and BNP concentrations have been reported to decrease in response to carvedilol and metoprolol treatments (199, 202).

Recently, the clinical utility of drug-treatment dose titration to target BNP concentrations in patients with heart failure has been suggested as a useful option to improve outcomes. A preliminary report by Murdoch *et al.* (193), in which the authors compared the hemodynamic and neuroendocrine effects of tailored *vs.* empirical therapy, demonstrated that, with increased drug therapy, plasma BNP changed with parallel improvements in hemodynamic status. Motwani *et al.* (177) reported that BNP was superior to ANP in correlating with improvement in left ventricular ejection fraction with ACE inhibition after myocardial infarction. Moreover, baseline BNP concentrations appeared to predict the beneficial effect on survival associated with carvedilol, even though norepinephrine concentrations failed to demonstrate such a relationship (201, 202). Richards *et al.* (203) reported

a reduction in risk of death or heart failure in patients with high N-BNP levels treated with carvedilol. In 102 consecutive patients with severe congestive heart failure, persistently elevated BNP level was the most useful indicator of mortality after 3 months of drug therapy, including beta-blockers in almost one third of patients (173). In a study by Lee *et al.* (194), plasma BNP as compared with ANP and left ventricular ejection fraction was superior in assessing NYHA class during chronic treatment of heart failure.

More importantly, Troughton *et al.* (195) studied 69 patients with left ventricular dysfunction (left ventricular ejection fraction $< 40\%$ on echocardiography) and symptomatic heart failure (NYHA classes II–IV) receiving regular treatment with an ACE inhibitor and loop diuretic, with or without digoxin. Patients were randomized in a double-blind manner to receive drug treatment guided by plasma N-BNP or by standardized clinical assessment alone. When targets (N-BNP level < 200 pmol/liter) were not met, drug therapy (ACE inhibitor, loop diuretic, digoxin, additional diuretic and vasodilator) was increased in a stepwise fashion. The primary endpoint was total cardiovascular events, defined as hospital admission for any cardiovascular event plus any new outpatient episode of decompensated heart failure requiring increased medication, plus cardiac death (195). Plasma N-BNP concentrations decreased significantly below baseline in the hormone-guided group but not in the group treated according to clinical score (79 *vs.* 3 pmol/liter below baseline). The primary endpoint was reduced in the N-BNP group (19 *vs.* 54 clinical events, $P < 0.001$). Differences remained significant when considered as events per patient-year and also when hospitalization for decompensated heart failure was considered alone (195). This study suggests that drug treatment guided by plasma N-BNP concentrations results in fewer cardiovascular events than clinical care. Although the study requires confirmation from larger studies including the beta-blockers and in larger number of patients, treatments that unload the left ventricle and reduce left ventricular wall stress with simultaneous reduction in plasma cardiac hormone levels (particularly BNP and N-BNP) seem to result in an attenuation in the worsening of cardiac function as well as improvement in functional class and survival.

Cardiac hormone-guided treatment may also be useful as a convenient and safe alternative to invasive monitoring in evaluating hemodynamic status during therapeutic interventions. Recently, studies in patients with severe, decompensated heart failure demonstrate that ANP, N-ANP, and BNP levels can be rapidly reduced with vasodilator and diuretic therapy designed to lower ventricular filling pressures (124, 205). Interestingly, Cheng *et al.* (118) demonstrated that changes in BNP levels during treatment are strong predictors for outcome. Also, Stanek *et al.* (206) observed that repetitive measurement improves the predictive value of BNP plasma levels. Moreover, BNP plasma level is a promising method for determining which patients may benefit from implantable cardioverter-defibrillators (207). Overall, although much additional work remains to be done, these findings suggest that frequent natriuretic peptide, particularly N-BNP, measurement may be a useful blood test for detection of the progression of heart failure and a guide for optimizing treatment in heart failure.

VII. Recent Developments in Measurement of Cardiac Hormones

Before a biomarker is used routinely in clinical practice, rapid and inexpensive assays should be available. The test should augment the diagnostic or prognostic value of other indices and the results should help to guide specific patient management. In patients with suspected heart failure, N-ANP, BNP, and N-BNP seem to fulfill most of these criteria, although more work is needed to determine the optimal limits for clinical interpretation, as well as the specific therapeutic implications of sustained cardiac hormone elevation. The optimal timing of measurement is also unclear, although in studies performed to date the association between BNP and mortality appears to be relatively independent of the timing of measurement. Furthermore, for routine clinical use, it would be helpful to define specific cut-off value(s), although this may be complicated by the effects of age, sex, and assay characteristics on cardiac hormone levels. The cuf-off point chosen for the assay should be one that provides a very high negative predictive value with an adequate positive predictive value (*i.e.*, a test that reliably rules out heart failure).

Debate continues on which natriuretic peptide to actually measure, and, thus, direct comparisons of N-ANP, BNP, and N-BNP in screening, prognosis, and treatment monitoring are needed. In general, plasma levels of ANP and N-ANP correlate, as well as those of BNP and N-BNP (10–19). There are reports that BNP might be superior to ANP for risk assessment after myocardial infarction and that it may better reflect left ventricular structural and diastolic dysfunction. However, studies on the clinical usefulness of different assays in patients with heart failure have resulted in conflicting results, as discussed above. In some studies, the assay of N-ANP was shown to be as equally useful as other assays, whereas in many others BNP or N-BNP was found to be a better marker of cardiac function and structure (10–19). It should be noted that the sensitivity and specificity of each assay are influenced by the population studied (due to differences in the prevalence of disease). Furthermore, because cardiac function is a continuum, the application of categorical analytical methods with cut-offs that may vary between studies is challenging. Moreover, when comparing different diagnostic studies, problems arise from different definitions of a gold standard. The single most useful diagnostic test in the evaluation of patients with heart failure is the two-dimensional echocardiogram coupled with Doppler flow studies (102, 106). However, there is no diagnostic test for heart failure, because it is largely a clinical diagnosis that is based on specific symptoms (dyspnea and fatigue) and signs (fluid retention) and physical examination. Future studies will determine whether cardiac hormone levels can be part of a gold standard for the diagnosis of heart failure. Compatible with this, it has recently been suggested that the simplest definition for diastolic congestive heart failure might be an elevated BNP with normal left ventricular systolic function (156, 159).

It also remains to be established whether, in the diagnosis of heart failure, the simultaneous measurement of ANP and BNP (or N-ANP and N-BNP) can add value over that pro-

vided by ANP or BNP (N-ANP or N-BNP) alone. Because BNP is activated after more prolonged cardiac overload, ANP would be a good marker of acute volume load, hemodynamic changes, and heart failure due to rapid release of stored atrial ANP (13). There are also significant differences in the magnitude of the plasma levels of cardiac hormones in different chronic disease conditions (13, 208–210). In cardiac volume and pressure overload, ANP gene expression and the circulating levels of ANP and N-ANP are primarily induced by increased preload of the heart, whereas BNP is primarily sensitive to an increase of afterload (44, 208). Thus, raised plasma ANP or N-ANP levels would be associated with atrial overload (*e.g.*, tachycardia), whereas BNP and N-BNP would be better markers of ventricular overload (*e.g.*, myocardial infarction and aortic stenosis) (13). In agreement with this hypothesis, in 67 patients with aortic stenosis, BNP and N-BNP performed best in the detection of increased left ventricular mass, and N-ANP in the detection of increased left atrial pressure (211). N-BNP was significantly increased in mild left ventricular hypertrophy, whereas N-ANP was not (211). Markedly elevated circulating levels of both ANP and BNP suggest combined atrial and ventricular overload, as in dilated cardiomyopathy (13). A diagnostic test that combines the information obtainable from the activation of both the ANP and the BNP systems might therefore have the potential of higher clinical sensitivity.

Until recently, the routine use of plasma cardiac hormone levels as a diagnostic or prognostic help in heart failure had not been established. One reason is that the original competitive RIAs for ANP and BNP were time consuming, required extraction of the peptide from the plasma, and were difficult to perform (15). Two-site (sandwich) noncompetitive immunoassays using two different monoclonal antibodies for measurement of cardiac hormones have been developed to overcome the problems of competitive assays. Noncompetitive immunoluminometric assays for N-BNP are highly sensitive (212, 213). Recently, a fast, fully automated electrochemiluminescence immunoassay method (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland) compatible with routine workflow in the laboratory for quantification of N-BNP in plasma has been described (41). The application of plasma cardiac hormone measurements to diagnosis and prognosis in heart failure has received a major stimulus through the approval of both BNP and N-BNP assays by FDA. The Triage BNP assay from Biosite Diagnostics (San Diego, CA) provides a measurement of plasma BNP concentrations within 15 min from a few drops of whole blood. With the Elecsys proBNP assay, laboratories can have results ready to report to physicians in approximately 18 min using an automated platform. In comparison to BNP assay, the N-BNP test gives an accurate reading of activated BNP system due to congestive heart failure without interference from nesiritide, a recombinant BNP used for the treatment of acutely decompensated heart failure (214).

VIII. Conclusions

In patients with heart failure, circulating levels of ANP, BNP, and the N-terminal fragments of their prohormones (N-ANP and N-BNP) are elevated, because the cardiac hormonal system is activated by increased wall stretch due to increased volume and pressure overload. ANP and BNP are synthesized and released from atrial and ventricular myocardium in failing hearts. Patients suspected of having heart failure, especially in primary care, can be selected for further investigations by echocardiography or other tests of cardiac function on the basis of having an elevated plasma concentration of N-ANP, BNP, and N-BNP. High levels of cardiac hormones identify those at greatest risk for future serious cardiovascular events including death. Moreover, adjusting heart failure treatment to reduce plasma levels of N-BNP may improve outcome. Serial measurements of plasma cardiac hormone levels may be useful in noninvasively monitoring the progress of chronic heart failure and treatment effects. Cardiac hormones are most useful clinically as a rule-out test: a high level calls for further investigation, whereas a normal level has consistent and very high negative predictive value. In acutely symptomatic patients, a very high negative predictive value is coupled with a relatively high positive predictive value (in the order of 70%). Measurement of cardiac hormones in the diagnosis and management of patients with heart failure may reduce the need for hospitalizations and for more expensive cardiac investigations such as echocardiography. However, there have also been conflicting reports on the diagnostic value of cardiac hormones, they are not specific for any disease state, and the recent reports on the magnitude of the effects of age and gender on BNP in the normal subgroup suggests that these parameters need to be considered when interpreting cardiac hormone levels. With commercially available assays now in existence, it will be important to compare multiple cardiac hormone assays in the same cohorts of heart failure patients to increase the practicability of measurements of these peptides in routine clinical practice.

Acknowledgments

Address all correspondence and requests for reprints to: Heikki Ruskoaho, M.D., Ph.D., Department of Pharmacology and Toxicology, Faculty of Medicine, University of Oulu, P.O. Box 5000 (Aapistie 5), FIN-90014 University of Oulu, Finland. E-mail: heikki.ruskoaho@oulu.fi

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