Measurement and significance of circulating natriuretic peptides in cardiovascular disease

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ABSTRACT

1. The major cardiovascular and renal actions of α-atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and the fact that the heart is strategically located to sense changes in intravascular volume indicate the importance of these peptides in the overall control of the extracellular fluid volume under normal and pathophysiological conditions.

2. This review examines the clinical and diagnostic significance of the measurement of plasma natriuretic peptides in diseases of the cardiovascular system with particular emphasis on the assessment of patients with heart failure.

3. Raised plasma levels of ANP and BNP have repeatedly been found in patients with heart disease originating from diverse causes including tachycardias, valvular stenosis or ventricular dysfunction. The raised circulating levels of natriuretic peptide (ANP, N-terminal proANP and BNP in particular) are associated with (i) raised atrial and pulmonary wedge pressures; (ii) reduced ventricular systolic and diastolic function; (iii) presence (and possibly geometric form) of left ventricular hypertrophy; and (iv) severe myocardial infarction. Although both plasma ANP and BNP are raised in the presence of left ventricular hypertrophy, BNP appears to be a better index of left ventricular hypertrophy.

4. Several situations where the measurement of natriuretic peptides may be of benefit in the overall assessment of heart disease are discussed. However, it is emphasized that the measurement of plasma natriuretic peptides alone appears to be of limited value as a specific diagnostic tool, given that raised levels are a consequence of haemodynamic and structural abnormalities arising from diverse pathological processes. Despite these limitations, the major value of plasma natriuretic peptides in the examination of patients with suspected heart disease rests on the premise that: (i) a normal value would not be consistent with cardiac disease; (ii) the presence of markedly raised levels may help to target those for subsequent detailed assessment of underlying cardiac dysfunction; and (iii) markedly raised levels of plasma natriuretic peptides after myocardial infarction can identify those at high risk of death.

INTRODUCTION

The functional significance of α-atrial natriuretic peptide (ANP) in the overall control of sodium balance is well documented and the high plasma levels found in conditions associated with raised central venous pressures suggest a significant pathophysiological role [1,2]. The importance of ANP in the control of sodium balance is

Key words: cardiovascular disease, heart failure, natriuretic peptides.
Abbreviations: ANP, α-atrial natriuretic peptide; BNP, brain natriuretic peptide; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure.
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reinforced by more recent experiments in transgenic mice in whom an ANP gene deletion or natriuretic peptide type A receptor knock-out led to substantial impairment in the renal response to volume overload [3,4].

Brain natriuretic peptide (BNP), originally isolated from porcine brain, and subsequently also isolated from the human heart, has a similar pattern of action to ANP [5]. Moreover, even though there are differences in prohormone processing, storage and release between ANP and BNP [6], circulating levels of BNP are also raised in patients with cardiovascular and/or renal disease. BNP may be even more important than ANP in heart failure as infusion studies in patients with heart failure demonstrated that BNP had more beneficial effects than ANP [7].

Considerable progress has now been made in two potentially important practical areas: the first is underlined by the development of endopeptidase inhibitors as therapeutic agents [8] and the second applies to the clinical significance of circulating natriuretic peptides. The present review examines the latter by focusing on the diagnostic and prognostic value of ANP and BNP in cardiovascular disease, with particular emphasis on heart failure. Heart failure is becoming an increasing public health problem [9] and there is a real need for relatively simple and inexpensive tests for the identification of patients with asymptomatic systolic dysfunction [10] and for prediction of outcome in those with severe heart failure [11].

MEASUREMENT OF CARDIAC AND CIRCULATING FORMS

The first radioimmunoassay procedures for the measurement of circulating ANP were reported not long after the structural identification of ANP and, at that time, it became evident that reliable measurement of plasma ANP would require extraction of the peptide from the plasma before radioimmunoassay [12,13]. Because of this, methods involving plasma extraction on a solid-phase resin (usually C-18) before radioimmunoassay or radioreceptor assay were routinely established. Plasma ANP concentrations reported in normal subjects have ranged from about 10 to 60 pg/ml [14]. To some extent, the source of this variation relates to methodological differences such as the exact extraction procedure, antibody specificity towards circulating ANP fragments, etc. Whether the plasma is acidified before extraction is also relevant as levels of plasma ANP were nearly 2-fold higher when the plasma was acidified before extraction through Sep-Pak cartridges [15].

Although within atrial tissue ANP is synthesized and stored as the high-molecular-mass precursor proANP (116); Figure 1), in normal human plasma, the low-molecular-mass ANP [17] and the N-terminal proANP appear to be the major circulating forms. The 126-amino-acid ANP precursor is absent (or is present at low concentration) in normal human plasma, but the levels are markedly raised in the plasma of patients with heart and/or kidney failure [18,19]. A dimeric form of human ANP (referred to as human β-ANP) was also identified in human atrial tissue and, despite the name, this peptide is distinct from BNP. Human β-ANP is also raised in the plasma of patients with heart failure [18], but its significance in diseases of the cardiovascular system is still unresolved.

Radioimmunoassay procedures for measuring the N-terminal segment of the ANP precursor have also been developed [20–22], and work on its molecular form suggests that the major circulating N-terminal form seems to be identical to proANP(1–98) (see Figure 1). In the plasma of normal subjects, the concentration of this peptide is considerably higher (more than 20-fold) than that of ANP, probably due to its slower clearance from the circulation; however, in general, plasma levels of these two forms are strongly correlated [21]. As ANP is stored within atrial granules mainly as the high-molecular-mass precursor [16], the presence of the N-terminal form in human plasma suggests that under normal circumstances the ANP precursor is processed to
the active ANP possibly during the secretion process, perhaps at the plasma membrane.

BNP was originally isolated from brain (hence its name), but immunoreactive BNP is found in plasma and in the heart as well as in brain tissue [23,24]. In fact, the concentration of BNP in pig brain is considerably less than that within the heart. In the normal human heart, BNP is synthesized both within atrial and ventricular tissue [23,24], suggesting that plasma BNP originates from the heart. More specifically, Yasue et al. [25] examined cardiac sources of BNP secretion compared with ANP. In normal subjects, they confirmed the step-up in plasma levels of ANP between the anterior ventricular vein and the coronary sinus and found no difference between the aortic root and the anterior ventricular vein. In contrast, there was a marked step-up of plasma BNP levels between the aortic root and the anterior ventricular vein but not between the latter and the coronary sinus, suggesting that, in the normal heart, BNP originates mainly from the left ventricle. Although ANP in the normal heart is secreted mainly from atrial tissue there are substantial differences in the amounts of ANP and/or BNP secreted by atrial and ventricular tissue. For instance, in normal subjects there are differences in the response of plasma ANP and BNP to volume expansion. In contrast to ANP, saline infusion or supine posture is not associated with significant increases in plasma BNP [26,27]. However, plasma levels of BNP are increased, although to a smaller extent than ANP (i.e. approximately 2-fold), after several days of a high sodium intake compared with a low sodium diet [28,29]. At the cellular level, ANP is stored predominantly in secretion granules thereby providing a source for rapid release. Cardiac BNP does not appear to be stored to the same extent as ANP and hence increased release may require a longer stimulus to increase its rate of synthesis and subsequent secretion.

Most radioimmunoassay methods for the measurement of plasma BNP [24–31] are also based on extraction on solid-phase resin (e.g. C-18). Plasma concentrations of immunoreactive BNP in normal subjects are much lower than those of ANP. A high-molecular-mass precursor [possibly proBNP(1–108)] and the low-molecular-mass BNP have been detected in human heart and plasma [27,30]. This contrasts with ANP, where the major form in human atrial tissue is the full proANP(1–126), and suggests that the post-translational processing of proBNP occurs within cardiomyocytes. The presence of both high-molecular-mass precursor and the low-molecular-mass BNP in human plasma raises the issue of specificity in that most current radioimmunoassays for BNP actually measure both forms rather than being a specific measure of BNP. In fact, in heart failure, as much as 75% of the total immunoreactive plasma BNP is of the high-molecular-mass form [27,31]. However, given the strong correlation between the levels of these two forms [27], it is evident that the total immunoreactive plasma level of BNP is still an index of augmented synthesis and secretion.

CIRCULATING NATRIURETIC PEPTIDES IN CARDIOVASCULAR DISEASE

The observation of increased circulating ANP in manoeuvres associated with an increase in central venous pressures (e.g. supine position, volume expansion, etc. [1,2]) clearly pointed to the importance of intra-atrial pressure/stretch as a major determinant of ANP secretion. Apart from secretion, peptide elimination is also important. ANP is rapidly removed from the circulation mainly through binding to clearance receptors and hydrolysis by neutral endopeptidase [32]. BNP also has a relatively short half-life within the circulation; the affinity of BNP for the clearance receptor is much less than that of ANP [33] and the relative importance of this elimination route for BNP remains unclear, but both peptides are inactivated by neutral endopeptidase [32].

In view of the above, it was not surprising to find markedly raised levels of ANP and BNP in conditions associated with (i) overt intravascular volume overload; (ii) increased central venous pressures; (iii) tachycardia; and (iv) reduced renal function. There are, however, significant differences in the magnitude of the plasma levels of ANP and BNP in different conditions (Table 1), and noticeable individual variation is also found within each disease. To some extent this variability is related to the severity of disease and to differences in the underlying pathophysiology (Figure 2). For example, raised levels of natriuretic peptides in renal failure [48,49] are probably due to (i) volume overload; (ii) intrinsic heart disease, and (iii) reduced renal clearance of the peptides; and, in those with tachycardia, the increased plasma ANP is more than likely a direct outcome of an increase in atrial pressure and distension.

Interestingly, raised levels of plasma natriuretic peptides have also been found in patients with essential hypertension [34,35], with average values in the hypertensive group about 2–3-fold higher than in normotensive controls. These observations are of interest as essential hypertension is not usually associated with overt volume expansion [50]. However, an increase in central venous pressure and pulmonary wedge pressure with normal cardiac pump function has been demonstrated in patients with essential hypertension [51]. This is not due to systemic volume retention but may arise from an increased central blood volume after systemic venous vasoconstriction. In patients with hypertension, the presence of left ventricular hypertrophy and of abnormal ventricular geometry also seems to contribute to plasma levels of ANP and of BNP in particular [35,36].
Table 1  Plasma ANP and BNP in some cardiovascular diseases
Symbols give approximate relative increases compared with controls (calculated from group averages): \( \_ \_ \_ \_ \), up to 3-fold; \( \_ \_ \_ \_ \), approx. 3–10-fold; \( \_ \_ \_ \_ \_ \), \( \sim \) 10-30-fold; \( \_ \_ \_ \_ \_ \_ \), \( \sim \) 30-fold. Table compiled from radioimmunoassay-based methods. Control values from one source [34] for plasma ANP and BNP: \( 2.8 \pm 0.2 \) pmol/l and \( 1.1 \pm 0.1 \) pmol/l respectively.

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<tr>
<th>Condition</th>
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\( ^a \) Higher values are found in those with LV hypertrophy (approx. 2–3-fold for ANP and up to approx. \( \sim \) 6.0-fold for BNP [35,36]). \( ^b \) Spontaneous atrial and ventricular tachycardias; ANP data from [37]. \( ^c \) Average group values of patients with congestive heart failure from various causes; individual values depend on severity and form of heart failure [39–42]. \( ^d \) Average group values in chronic renal failure from various causes; individual values depend on severity of renal failure, degree of volume expansion and presence of co-existing heart disease.

Markedly raised circulating levels of ANP have repeatedly been found in patients with heart disease originating from diverse causes including tachycardias [37,38], aortic or mitral stenosis [44,45,52] and dilated cardiomyopathy [44,52]. Plasma levels of ANP depend on the severity of disease (as assessed using NYHA criteria) and can reach extremely high values (more than 20-fold) in severe heart failure [39–42]. The increased plasma levels are associated with increased synthesis of ANP within atrial tissue [53,54], thereby accounting for the raised plasma proANP(1–126) and N-terminal proANP [18,22]. The association between circulating levels of ANP and the severity of heart failure reflects, to some extent, the higher atrial pressure associated with more severe heart failure. However, ventricular recruitment of ANP is also important given the augmented ANP expression in ventricular cardiocytes in humans with dilated cardiomyopathy [55]. In these conditions, while the concentration of ANP is still higher in atrial tissue, given the larger ventricular mass compared with the atrial mass, secretion from the ventricle may make a substantial contribution to plasma levels.

Plasma BNP originates mainly from the ventricles [25,56]. In normal subjects plasma concentrations of ANP are much higher than BNP, whereas in congestive heart failure plasma BNP – despite an atypical report of much higher values [57] – increases to levels of comparable magnitude or only slightly higher than ANP [42,58,59]. Moreover, plasma levels of the BNP precursor [27,30] and the N-terminal proBNP [60] are also increased, indicating increased synthesis and secretion of BNP. That raised plasma ANP is associated with atrial overload, whereas the presence of markedly elevated plasma ANP and BNP suggests both atrial and ventricular overload, can be seen from plasma peptide measurements in patients with mitral stenosis or dilated cardiomyopathy. In mitral stenosis, the plasma levels of ANP are higher than BNP; in contrast, in dilated cardiomyopathy, associated with both atrial and ventricular overload, there are marked increases in both ANP and BNP [44,45,52].

Given the distinct stimulation of the production of natriuretic peptides from both atrial and ventricular tissue, interest in the practical value of measurement of plasma ANP and BNP in heart disease has centred on the following questions:

1. Do plasma levels of natriuretic peptides provide any information about abnormal cardiac structure?
2. Is there an association between plasma levels of natriuretic peptides and systolic and diastolic dysfunction?
3. Can plasma natriuretic peptides be used to identify mild heart failure?
4. Do plasma levels of natriuretic peptides reflect the degree of ischaemic damage after myocardial infarction?
5. Does the measurement of plasma natriuretic peptides provide a useful aid in assessing prognosis in patients with heart disease?

**HISTOLOGICAL FEATURES AND LEFT VENTRICULAR HYPERTROPHY**

Work in animals with experimentally induced ventricular hypertrophy [61] has clearly demonstrated that expression of ANP is increased and that increased ventricular wall stress may be a major stimulus of this. In humans with dilated cardiomyopathy, the distinctly raised levels of plasma ANP and BNP are associated with substantial increases in ventricular ANP and BNP in both left and right-side ventricular tissue [62]. Immunohistological examination of ventricular tissue affected by dilated cardiomyopathy has demonstrated an identical distribution of ANP- and BNP-expressing myocytes located mainly within subendocardial layers, fibrous areas and perivascular regions [63]. These observations suggest that the increased expression of ventricular natriuretic peptides in dilated cardiomyopathy also depends on regional conditions apart from global haemodynamic stress. Raised levels of plasma ANP, and more specifically of BNP, have also been found in patients with hypertrophic cardiomyopathy in the presence of normal systolic function [46,64]. However, the higher values in those with obstructive cardiomyopathy were associated with a higher left ventricular end-diastolic pressure (LVEDP). Histological examination of endomyocardial biopsy showed that the ventricular sections from those with higher plasma BNP were also associated with greater myocardial fibre disarray, hypertrophy of myocytes and fibrosis.

Overexpression of BNP in hypertrophic cardiomyopathy appears to be a consequence of substantial ventricular wall stress arising from the high LVEDP and the presence of left ventricular hypertrophy, but in this condition, disease-specific structural factors (e.g. fibre disarray, fibrosis, etc.) existing well before the development of haemodynamic overload may also contribute to the increased expression of ventricular natriuretic peptides. This is consistent with the observation that in hypertrophic cardiomyopathy, where the right ventricle is not exposed to high pressures, ANP-containing myocytes were found in both right and left ventricular tissue. In contrast, in ventricular tissue affected by hypertensive heart disease, ANP-containing myocytes were found in left but not in right ventricular sections [65]. These observations, in conjunction with extensive work in animals, suggest that increased natriuretic peptide expression may not necessarily be associated with the growth-inducing processes underlying the development of cardiac hypertrophy, but that there may be different pools of intracellular natriuretic peptides that can respond separately to haemodynamic events (e.g. overload) and to structurally related factors (e.g. cardiac hypertrophy) (see [66]).

**SYSTOLIC AND DIASTOLIC DYSFUNCTION**

The association between pulmonary capillary wedge pressure and plasma ANP in patients with heart failure has been confirmed and extended in more recent work [67,68] that demonstrated positive associations between plasma ANP or BNP and LVEDP, pulmonary capillary wedge pressure and right atrial pressure, and negative associations between ANP or BNP and ejection fraction. Despite a positive relationship between both ANP and BNP and left ventricular (LV) systolic wall stress, plasma BNP appears to be a better index of ventricular overload. Recent studies [69,70] examined the diagnostic utility of raised plasma ANP, BNP and also N-terminal proANP to identify systolic dysfunction (ejection fraction less than 45%), and confirmed that BNP was a better index than ANP. Patients with heart failure frequently also have diastolic dysfunction; this can lead to elevated atrial pressures and symptoms of overt heart failure in the absence of systolic abnormalities. Lang et al. [43] found substantially raised levels of BNP and ANP (approximately 4-fold for both) in patients with isolated diastolic dysfunction in the absence of systolic failure or of significant LV hypertrophy. The presence of a larger left atrial size compared with controls suggested that the diastolic dysfunction was associated with raised atrial pressures thereby accounting, to some extent, for the raised ANP. Interestingly, BNP, but not ANP, was related to the degree of diastolic impairment, presumably due to raised ventricular wall stress as a consequence of the higher LVEDP. Because of the importance of diastolic dysfunction, other studies also examined plasma ANP and BNP (and N-terminal proANP) in relation to diastolic function in patients with heart failure. One study [71] in patients with known systolic dysfunction compared natriuretic peptide levels in those with restrictive or non-restrictive patterns as judged from Doppler-derived diastolic mitral blood flow. Patients with a restrictive pattern and more severe heart failure had much higher plasma levels of ANP and BNP. In another study, Yamamoto et al. [69] measured the time constant of LV relaxation from high-fidelity LV pressure recordings in a group of patients with a wide range of systolic and diastolic impairments and LV hypertrophy. Raised plasma BNP was also associated with the presence of impaired relaxation; in this case, BNP was a better measure than ANP or N-terminal proANP. Moreover,
the raised BNP was also associated with LV mass index. These results suggest that the higher ANP, and BNP in particular, may reflect LV structural and functional abnormalities, and that differences in diastolic dysfunction may provide a basis for differences in plasma ANP and/or BNP in patients with similar ejection fractions as those with diastolic dysfunction had higher levels for the same degree of systolic impairment.

**SCREENING FOR MILD HEART FAILURE**

A major reason for examining the possibility that moderately raised levels of natriuretic peptides may be indicative of the presence of systolic dysfunction in the absence of overt clinical signs is the difficulty in assessing the presence of mild LV systolic impairment. This is especially important in patients recovering from myocardial infarction; these patients would benefit from early treatment with angiotensin-converting enzyme inhibitors [10]. Earlier work [72] found significantly raised plasma ANP in patients with left ventricular dysfunction in the absence of overt heart failure, and Winters et al. [73] reported raised plasma N-terminal proANP in patients with mild heart failure (NYHA Class I). Subsequently, Lerman et al. [74] examined the predictive value of N-terminal proANP for mild heart failure in a prospective study and reported that raised levels of N-terminal proANP had a sensitivity of 90% and a specificity of 92% for the detection of patients with symptomless LV dysfunction. This high degree of prediction accuracy for plasma N-terminal proANP is rather surprising, although one explanation could be due to the singularly low levels of N-terminal proANP found in the control group. However, other studies indicate that BNP may be a better marker than ANP or N-terminal proANP in the identification of mild heart failure. Choy et al. [75] found that in patients with myocardial infarction without obvious signs of heart failure, plasma BNP could detect systolic dysfunction after acute myocardial infarction with greater sensitivity than conventional clinical examination. Omland et al. [76] confirmed the associations between plasma levels of natriuretic peptides and haemodynamic indices of systolic ventricular failure and that BNP seemed to be a better index of ventricular impairment. However, the diagnostic accuracy for symptomless heart failure was relatively modest. Three recent studies now provide more encouraging results. All three studies examined the diagnostic value of plasma natriuretic peptides to identify mild heart failure. The first [77], carried out in a select group of patients referred for coronary angiography, demonstrated that ANP, BNP and N-terminal proANP were strongly associated with indices of LV systolic dysfunction. Indeed, the relative risk of LV dysfunction was raised up to 10-fold in those with high levels of these peptides. The value of plasma natriuretic peptide was recognized by the significant increase in predictive accuracy when information on plasma natriuretic peptide was combined with clinical assessment. In fact, the predictive accuracy to identify heart failure was 59% from clinical information alone, and this increased to 81% when in conjunction with plasma N-terminal proANP, 74% with plasma ANP and 77% with plasma BNP. The other two recent investigations took a step further in that the authors examined the predictive value of natriuretic peptides in the primary diagnosis of heart failure and in screening for LV dysfunction in population-based studies. Cowie et al. [78] demonstrated that plasma BNP appeared to be better than ANP or N-terminal proANP in that it was associated with higher sensitivity and specificity for the identification of mild heart failure. Plasma BNP fared better than routine clinical examination in that a plasma BNP higher than the reference cut-off value positively identified 70% of those with heart failure.

Similar conclusions were reached by McDonagh et al. [79], who examined a large (1252 individuals) and unselected sample in a population-based survey. Importantly, this study confirmed that plasma natriuretic peptides (BNP and N-terminal proANP) are raised in people with LV dysfunction whether symptomatic or asymptomatic. As in the previous study, plasma BNP was better than N-terminal proANP; the sensitivity and specificity for BNP in the identification of LV dysfunction was 76% and 87% respectively. Although the positive predictive value was rather low, it should be noted that it was similar or even better than those reported for other screening tests such as the use of prostate specific antigen for the identification of prostate cancer and mammography for breast cancer [79].

**MYOCARDIAL INFARCTION AND ISCHAEMIC DAMAGE**

Several studies have reported raised plasma ANP and BNP after acute myocardial infarction even in the absence of overt ventricular failure and of raised atrial pressures; significant associations with markers of infarct size have also been reported [80,81]. Investigation of the time course of plasma ANP and BNP after acute myocardial infarction has demonstrated a biphasic response [47,82]. Both plasma levels of ANP and BNP were raised on the first day after infarction and, while ANP levels subsequently declined, BNP levels remained elevated during subsequent follow-up. Moreover, BNP levels were associated inversely with left ventricular ejection fraction (LVEF), positively with infarct size (assessed from myosin light chain I), and, more importantly, those with
a distinct biphasic response had more severe heart failure. The marked increase in plasma BNP immediately after infarction in those without previous heart failure suggests that the raised levels may be due to myocardial necrosis and/or increased mechanical stress on cardiac tissue. However, the increase in the second phase, mainly in plasma BNP, could not be explained entirely in terms of simple leakage from necrotic tissue but may be related to subsequent infarct expansion. Infarct expansion is frequently associated with an increase in ventricular wall stress [83], thereby providing the stimulus for increased synthesis and secretion of BNP. Although it remains to be seen whether natriuretic peptides will substitute for established biochemical markers of infarct size (e.g. creatine kinase and myosin light chain I), these observations suggest that measurement of natriuretic peptides after myocardial infarction may provide potentially important prognostic information.

**PROGNOSTIC SIGNIFICANCE**

Early studies on the prognostic significance of plasma ANP in patients with myocardial infarction or with chronic heart failure examined survival rates in relation to plasma ANP, and found that those with higher baseline levels of ANP had distinctively lower rates of survival than those with normal or only mildly increased plasma ANP [84]. Raised plasma levels of ANP, and of N-terminal proANP, have also been associated with increased mortality in elderly people [85]. Interestingly, this could not be explained entirely by overt heart disease at the time of sampling, suggesting increased peptide levels even in those with intrinsic asymptomatic cardiac disease.

In those with known heart disease, N-terminal proANP was of much greater prognostic value than ANP in identifying patients at a high risk of death after myocardial infarction. Moreover, in a multivariate analysis, N-terminal proANP was an independent predictor of cardiovascular mortality even when the multivariate model included age, other clinical indices of disease severity and LVEF [86,87]. N-Terminal proANP may be a more representative index of long-term ANP secretion in view of its longer half-life within the circulation. Further work, however, now suggests that BNP may be a better predictor of mortality after myocardial infarction. Darbar et al. [88] measured both ANP and BNP after acute myocardial infarction. Plasma peptides were measured 3 days after infarction with a median follow-up time of 19.7 months. The results demonstrated that whereas ANP was a good predictor of risk of developing symptomatic heart failure, plasma BNP was a significant independent predictor of cardiovascular mortality. In a separate study, Omland et al. [89] tested the value of ANP, N-terminal proANP and BNP as indicators of LV function and of long-term survival after acute myocardial infarction. The results from this study confirmed that all three peptides were powerful predictors of cardiovascular mortality but plasma BNP provided additional information independent of LVEF. The potential value of BNP is further underscored by another recent study [90] which demonstrated that, in patients with congestive heart failure, regardless of whether knowledge of LVEF was available, a high plasma BNP was a strong predictor of mortality.

**PERSPECTIVES**

The recognition of the associations between natriuretic peptides and cardiac haemodynamic and structural abnormalities has raised the real prospect that increased plasma levels of natriuretic peptides may be indicative of cardiac dysfunction. Although numerous studies suggest that ANP and BNP (or their precursor fragments) could be used to identify LV dysfunction, there has been considerable controversy about (i) which natriuretic peptide should actually be measured, and (ii) what is the practical value of plasma levels of these peptides in the assessment of heart disease. Regarding the first, one should keep in mind that raised plasma levels of ANP and BNP in patients with cardiovascular disease are usually also associated with higher levels of the corresponding precursors (and N-terminal segments), and thus peptide levels are strongly inter-correlated [21,22,27,34,48]. However, it is also apparent that differences in pathophysiology and/or differences in elimination rates may lead to subtle differences in the relative proportion of the plasma levels of these peptides. Therefore, to some extent, which peptide to measure depends on the specific disease under investigation; in view of this it is difficult to generalize, but current work suggests that, in the assessment of ventricular dysfunction and prediction of mortality outcome in those with severe heart failure, BNP appears to be better than N-terminal proANP and both in turn have advantages over ANP. The first two peptides also appear to be better than ANP in predicting mortality in elderly individuals.

Irrespective of which peptide is being measured, because the raised levels are a consequence of haemodynamic and structural abnormalities arising from diverse pathological processes (Figure 2), measurement of natriuretic peptides alone is of limited value as a specific diagnostic tool. The interpretation of plasma levels is clearly not straightforward and must be done within an appropriate clinical context. Indeed, knowledge of renal function (or plasma creatinine at least) is essential to eliminate renal failure as a possible cause of raised plasma levels. Moreover, the measurement of plasma BNP to discriminate whether in patients admitted with dyspnoea, the dyspnoea is due to acute lung disease or to heart
failure [91], should be used with caution as raised levels of BNP have also been found in patients with primary obstructive airway disease [92].

Despite these limitations, knowledge of plasma levels of natriuretic peptides may provide useful information about cardiac structure and function in several situations (Table 2). The possibility that the presence of high plasma levels of natriuretic peptides may be a better index of severity than the measurement of LVEF is of interest as severity of heart failure does not always correlate with reductions in EF [94]. While severe heart failure does not usually present with diagnostic difficulties, the same does not apply to mild heart failure, and in view of the several studies have examined the diagnostic utility of plasma natriuretic peptides for this condition. Despite earlier conflicting data, recent studies [77–79] have now confirmed that BNP is raised in both symptomatic and asymptomatic subjects with LV systolic dysfunction, pointing to the use of plasma BNP as a supplemental screening test for the identification of mild heart failure.

The value of plasma natriuretic peptides, and of BNP and N-terminal proANP in particular, in the assessment of patients with heart disease is also highlighted from studies on their prognostic significance in patients with myocardial infarction where the plasma levels of these peptides may identify those at high risk of cardiac mortality; this may be particularly relevant when measurements of LVEF are not available. Taken together, the results imply that the major value of plasma natriuretic peptides hinges on the premise that (i) a normal value would not be consistent with cardiac disease, and (ii) the presence of markedly raised levels may help to target those for subsequent detailed assessment of underlying cardiac dysfunction using more specialized procedures (e.g. echocardiography, radio-nuclide ventriculography, exercise testing, etc.).

A definitive assessment of the practical value of natriuretic peptide is bound to require (i) a more precise description of diagnostic and prognostic criteria in relation to the spectrum of disease being investigated – very relevant in patients with heart disease given the multiplicity of conditions likely to lead to heart failure; and (ii) validation of accuracy of prediction in groups of patients independent of those used in the derivation of the diagnostic criteria. This aside, the work reviewed clearly suggests that the measurement of plasma natriuretic peptides is likely to become a routine measure of substantial practical value as a supplementary tool in the assessment of heart disease. The recent development of monoclonal antibody-based radioimmunoassays for plasma BNP [95] provides a further step forward in the introduction of the measurement of plasma natriuretic peptides in clinical practice.

### Table 2 Conditions investigated for possible uses of plasma natriuretic peptides

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<th>Condition investigated</th>
<th>Refs.</th>
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<tr>
<td>Identification of LV hypertrophy in hypertension</td>
<td>[35,36]</td>
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<td>Recognition of obstructive hypertrophic cardiomyopathy</td>
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<tr>
<td>Prediction of mortality in the elderly</td>
<td>[84,85]</td>
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### References

36 Nishikimi, T., Yoshihara, F., Morimoto, A. et al. (1996) Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. Hypertension 28, 22–30
55 Saito, Y., Nakao, K., Ariai, H. et al. (1989) 
56 Hosoda, K., Nakao, K., Mukoyama, M. et al. (1991) 
Expression of brain natriuretic gene in human heart. Production in the ventricle. Hypertension 17, 1152–1155
57 Mukoyama, M., Nakao, K., Saito, Y. et al. (1990) 
Brain natriuretic and atrial natriuretic peptides in patients with ischemic heart disease with and without heart failure. Cardiology 87, 12–17
Natriuretic peptide system in heart failure. Circulation 88, 1004–1009
Developmental pattern of ventricular atrial natriuretic peptide (ANP) expression in chronically hypoxic rats as an indicator of the hypertrophic process. J. Mol. Cell Cardiol. 26, 753–767
Cellular localization and structural characterization of natriuretic peptide-expressing ventricular myocytes from patients with dilated cardiomyopathy. J. Histochem. Cytochem. 42, 1207–1214
64 Nishigaki, K., Tomita, M., Kagawa, K. et al. (1996) 
Marked expression of plasma brain natriuretic peptide is a special feature of hypertrophic obstructive cardiomyopathy. J. Am. Coll. Cardiol. 28, 1234–1242
Mechanical and neuroendocrine regulation of the endocardium. Circulation 134, 1–15
Brain natriuretic peptide is a sensitive indicator of impaired left-ventricular function in elderly patients with cardiovascular disease. Circulation 88, 451–457
69 Yamamoto, K., Burnet, Jr., J. C., Jougasaki, M. et al. (1996) 
Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 28, 988–994
70 Davidson, N. C., Naas, A. A., Hanson, J. K., Kennedy, N. S., Coutie, W. J. and Struthers, A. D. (1996) 
Comparison of atrial natriuretic peptide, B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am. J. Cardiol. 77, 828–831
71 Yu, C. M., Sanderson, J. E., Shum, I. O. L. et al. (1996) 
Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with restrictive filling pattern. Eur. Heart J. 17, 1694–1702
72 Francis, G. S., Benedict, C., Johnston, D. E. et al. (1990) 
Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 82, 1724–1729
The N-terminus and a 4000–MW peptide from the mid portion of the N-terminus of the atrial natriuretic factor prohormone each circulate in humans and increase in congestive heart failure. Circulation 80, 438–449
74 Lerman, A., Gibbons, R., Rodeheffer, R. J. et al. (1993) 
Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. Lancet 341, 1105–1109
75 Choy, A. M., Darbar, D., Lang, C. C. et al. (1994) 
Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. Heart 76, 232–237
77 Muders, F., Kromer, E. P., Griese, D. P. et al. (1997) 
Evaluation of plasma natriuretic peptides as markers for left ventricular dysfunction. Am. Heart J. 134, 442–449
Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 350, 1347–1351
79 McDonagh, T. A., Robb, S. D., Murdoch, D. R. et al. (1998) 
Biochemical detection of left-ventricular systolic dysfunction. Lancet 351, 9–13
Relationship between plasma level of brain natriuretic peptide and myocardial infarct size. Cardiology 85, 334–340
81 Naruse, M., Takeyama, Y., Tanabe, A. et al. (1994) 
Atrial and brain natriuretic peptides in cardiovascular diseases. Hypertension 23, 1231–1234
82 Horio, T., Shimada, K., Kohno, M. et al. (1993) 
85 Wallen, T., Landahal, S., Hedner, T. et al. (1997) 
86 Omland, T., Bonarjee, V. V., Nilsen, D. W. et al. (1993) 
87 Hall, C., Rouleau, J. L., Moye, L. et al. (1994) 
88 Darbar, D., Davidson, N. C., Gillespie, N. et al. (1996) 
Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction: comparison with plasma atrial natriuretic peptide (99–126) and clinical evaluation. Br. Heart J. 76, 284–287
89 Omland, T., Aakvaag, A., Bonarjee, V. V. et al. (1996) 
90 Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure. Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 96, 529–536
95 Murdoch, D. R., Byrne, J., Morton, J. J. et al. (1997) Brain natriuretic peptide is stable in whole blood and can be measured using a simple rapid assay: implications for clinical practice. Heart 78, 594–597