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Review

Clinical applications of B-type natriuretic peptide (BNP) testing

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Many claims have been made in recent years regarding the utility of plasma B-type natriuretic peptide (BNP) concentration measurements in the diagnosis, risk stratification and monitoring of patients with heart failure. This paper summarizes the current evidence and provides guidance for practising clinicians. Overall, plasma BNP testing appears to be of most value in the diagnostic arena, where it is likely to improve the performance of non-specialist physicians in diagnosing heart failure. In clinical practice, BNP testing is best used as a 'rule out' test for suspected cases of new heart failure in breathless patients presenting to either the outpatient or emergency care settings; it is not a replacement for echocardiography and full cardiological assessment, which will be required for patients with an elevated BNP concentration. Although work is ongoing in establishing the 'normal' values of BNP, heart failure appears to be highly unlikely below a plasma concentration of 100 pg/ml. However, as BNP levels rise with age and are affected by gender, comorbidity and drug therapy, the plasma BNP measurement should not be used in isolation from the clinical context.

Introduction

A growing body of evidence suggests that measurement of plasma B-type natriuretic peptide (BNP) concentrations represents a useful addition to the chest x-ray, electrocardiogram, and Doppler echocardiography in the clinical assessment of patients suspected to have heart failure, both in the outpatient and in the emergency care settings. In particular, BNP appears to have clinical utility in excluding a diagnosis of heart failure in patients with symptoms of breathlessness or fluid retention, and may provide prognostic information in those with heart failure

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or other cardiac disease. There is also some evidence that it may prove useful in monitoring therapy for heart failure.

This paper summarizes the current evidence for the use of BNP measurement in the diagnosis, risk stratification and monitoring of patients with heart failure, and provides guidance for practising clinicians.

Background

B-type natriuretic peptide (BNP) is one of a family of structurally similar peptide hormones that also includes atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. Both ANP and BNP are secreted by atrial and ventricular myocytes, although the major site of production of BNP is the left ventricle.[1–5] BNP, which is produced by cleavage of a precursor protein (proBNP) into BNP and the biologically inactive peptide NT-proBNP, causes natriuresis, diuresis, vasodilatation and smooth muscle relaxation.[6–12] ANP has similar properties to BNP, but is chiefly produced by the atria.[1,6–8] Plasma concentrations of both BNP and ANP rise in various pathological states, particularly where there is increased cardiac chamber wall stretch,[2] an expanded fluid volume (e.g. in heart failure, renal failure, primary hyperaldosteronism) or reduced clearance of peptides (renal failure). ANP secretion is by immediate release from atrial storage granules in response to atrial stretch, while BNP secretion is controlled at the transcriptional level, usually requiring a longer-term stimulus.

Plasma BNP concentrations are raised in patients with heart failure, rising in line with NYHA class.[13] Furthermore, studies have shown that the greater the cardiac damage the higher the plasma BNP concentration.[14]

'Normal' values of BNP have yet to be fully established, although plasma BNP concentrations are known to be affected by age, gender, renal failure and drug use, particularly drugs such as diuretics and beta-blockers.

Practical considerations regarding natriuretic peptide assays

At present, there are two natriuretic peptide assays commercially available in both the USA and Europe that can be used in routine clinical and laboratory practice. The first is a rapid fluorescence immunoassay for BNP, which provides results within 15 min on a point-of-care patient testing device (Biosite Diagnostics, San Diego).[15] Results on this device generally correlate well with results from radioimmunoassay.[16] This method may be particularly attractive in clinical situations where access to a laboratory is difficult or when a rapid result is required.

The second is an electrochemiluminescent assay available for measuring NT-proBNP with a processing time of only 18 min (Roche Diagnostics GmbH, Basel).[17]

The reference ranges for BNP and NT-proBNP vary depending on the assay method employed and the nature of the control population.[18] In general, the plasma BNP concentration rises with age and may be slightly higher in women than in men.[19,20] A suggested 'normal' range for BNP is 0.5–30 pg/ml (0.15–8.7 pmol/l).[21] For NT-proBNP a suggested reference range is 68–112 pg/ml (8.2–13.3 pmol/l).[22]

The suggested decision cut-point for the detection of heart failure for the BNP point-of-care assay is 100 pg/ml in those aged more than 55 years. For NT-proBNP the recommended decision cut points are 100 pg/ml for men and 150 pg/ml for women in Europe, but 125 pg/ml for both genders in the USA.

A further laboratory-based assay for BNP is available currently in Europe only and is manufactured by Bayer. The decision cut-point for the diagnosis of heart failure is identical to that of the Biosite assay—100 pg/ml.

Laboratory vs point of care testing

Whether the assay is performed in a central laboratory (the NT-proBNP assay) or by point-of-care testing (the BNP assay) will depend on the level of organization within the hospital; there are few head-to-head comparisons of the two assays, and the results of ongoing studies are awaited.

Measurement in a central laboratory offers the comfort of tight quality control and may be preferred since, at present, acute treatment decisions rarely depend on the BNP test result. However, for emergency care patients, the test result should be available within 1 h of blood collection. Point-of-care testing is justifiable where the central laboratory cannot provide a test result within 1 h from blood collection on a 24-h basis, or where the transportation time of the sample to the lab is more than one day (in whole blood stored at room temperature, BNP is stable for up to one day). It is vital to ensure appropriate training of the individuals who will carry out the testing, and regular quality control assessment.

Point-of-care testing is increasingly used in cardiovascular medicine as it offers the ability to provide rapid results and consequently rapid adjustment in therapy. It is also consistent with the modern approach to organizing care for patients with stable heart failure, whereby all investigations are performed and management decisions are made at a single visit, which is clearly more convenient for patients as it potentially reduces the number of follow-up visits required.

In addition to its demonstrated utility in the emergency care setting, point-of-care testing is likely to be of particular value for diagnostic purposes in primary care, where it may find a role in rationalizing demand for echocardiography services. However, the feasibility of its use will depend on local cost and reimbursement considerations.

BNP and NT-proBNP testing in clinical practice

Testing for either BNP or NT-proBNP has a number of possible uses in heart failure practice:

- Diagnosis
- Screening for asymptomatic left ventricular dysfunction
- Risk stratification and prognostication
- Treatment monitoring.

Diagnosis

Evidence for the role of BNP in the diagnosis of heart failure has been obtained in both the outpatient and emergency care settings. The two populations are quite different: patients admitted acutely are usually more functionally impaired with shorter duration of symptoms and the aetiology is more often acute coronary disease. Among outpatients the symptoms may be milder and of more insidious onset, making diagnosis more difficult; only half of patients with a suspected diagnosis of heart failure have the diagnosis confirmed on fuller assessment by a cardiologist.[23,24] The situation is further compounded by variable primary care access to cardiac investigations such as echocardiography and to specialists, both across Europe and within certain countries such as the UK.

Outpatient/clinic setting

In the population-based Hillingdon Heart Failure Study, one-third of patients referred to a rapid access clinic by a primary care physician with a new diagnosis of heart failure had the diagnosis confirmed on further assessment.[25] The diagnostic value of the plasma BNP concentration compared with the clinical opinion of an expert panel was very high. The area under the receiver-operating characteristic (ROC) curve for plasma BNP was 0.96, compared with 0.79 for cardiothoracic ratio on chest X-ray.

Taking a cut-off value of 22 pmol/l (76.4 pg/ml) combined a very high negative predictive value (98%) with an acceptable positive predictive value of 70%—with a sensitivity of 97% and specificity of 84%. Therefore, this study suggests there is a potential for the BNP test to improve the efficiency of referring patients for further assessment. The findings of this study are currently being validated in the multicenter UK Natriuretic Peptide Diagnosis Study, which will report in 2003.

Recently, the Natriuretic Peptides in the Community study of 304 patients presenting to a GP with shortness of breath or oedema found that only 25% of cases met the ESC definition of heart failure.[26] When the GP was given clinical information (ECG, chest X-ray, echocardiography) the accuracy of the GP diagnosis improved by 7%, but giving clinical information together with the NTproBNP test result improved the accuracy of the diagnosis by 21% (P=0.002). The area under the ROC curve for plasma NTproBNP was 0.82. The diagnostic threshold for NTproBNP that combined optimal sensitivity and specificity for diagnosing heart failure was 125 pmol/l. For clinical use in the community, therefore, a recommended diagnostic threshold of between 100 and 150 pmol/l was thought to be appropriate.

NTpro-BNP levels may also have some utility when revisiting a historical diagnosis of heart failure in the community setting. This was demonstrated in a sample of 103 patients labeled as having heart failure,[27] among whom only 35 were found to have heart failure according to ESC criteria. NT-proBNP assay gave an AUC of 0.80. Using an NT-proBNP cut-point of >36 pmol/l gave 100% sensitivity, 18% specificity, 100% negative predictive value and 39% positive predictive value in this primary care setting among patients on treatment for 'heart failure'.

Emergency care setting

The accuracy of diagnosis of heart failure by clinical means and standard testing is often inadequate in the emergency care setting. In the Breathing Not Properly (BNP) study, which was conducted in academic centres in North America and Europe, more than 40% of emergency room doctors showed significant indecision regarding the diagnosis when blinded to the BNP values. The plasma BNP concentration was identified a major independent predictor of heart failure.[28]

In this study, using a plasma BNP cutpoint of 100 pg/ml gave a sensitivity of 90% (95% Confidence interval 88–92%) and a specificity of 76% (73–79%). BNP was significantly more accurate than clinical judgment and traditional diagnostic methods in identifying patients with heart failure (81% vs 74%, P=0.0001).[29] The proportion of patients in whom the clinician was uncertain of the diagnosis would have been reduced from 43% to 11% had the BNP concentration been made available to the clinician (P=0.0001).

In the United States, the Food and Drug Administration-approved level of BNP used to separate heart failure from other causes of dyspnoea is 100 pg/ml using the point of care testing system from Biosite Diagnostics. This value was chosen for its 95% sensitivity in separating NYHA classes I to IV of heart failure from patients who do not have heart failure. Pending further work on cut-points, it should remain the cut-off of choice in patients who present with breathlessness; it has a high negative predictive value for heart failure (whether systolic or diastolic) and therefore will minimize the risk of a patient with heart failure being 'missed'.

Large centres experienced in the diagnostic use of point of care BNP testing may use a more complex algorithm to guide management based on the BNP values,[30] recognizing that the probability of heart failure being present increases steeply as the BNP concentration rises.

However, it is important to remember that BNP is not a stand-alone diagnostic test; it must be used and interpreted in a wider clinical context, particularly regarding age and gender. In particular, clinicians must be aware that several clinical circumstances can alter the clinical interpretation of BNP concentrations. These include ischaemia, infarction and renal insufficiency, which lead to elevation of circulating BNP concentrations. In addition, beta-blockade may have a variable effect on circulating BNP concentrations, and ACE inhibitors and diuretics will reduce BNP concentrations.[31,32]

Practical application

Patients presenting in primary care/outpatient setting

- In new patients presenting with suspected heart failure in the outpatient setting, BNP testing is most useful as a 'rule-out' test for heart failure.[33]
- A clinical history should be taken and physical examination performed. If the BNP is below the decision cut-point ('normal') then heart failure is very unlikely and the patient should be investigated for other problems. If the BNP concentration is raised then there is a strong possibility that the patient has heart failure for which they should be fully investigated. This approach is included in the guidelines of the European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic Heart Failure.[33]
- For practical clinical purposes a 'decision cut point' of 100 pg/ml appears to provide optimum diagnostic accuracy. If the BNP is <100 pg/ml in untreated patients, then heart failure is highly unlikely. The decision cut-points recommended in Europe for NT-proBNP are 100 pg/ml for males and 150 pg/ml for women, and in the USA 125 pg/ml for both genders.

Patients presenting in the emergency care setting

- In new patients presenting to emergency services with dyspnoea, a history, physical examination and a chest X-ray and ECG should be undertaken together with laboratory measurements that include BNP testing.[30]
- If the BNP is <100 pg/ml, then heart failure is highly unlikely.

For patients with an existing diagnosis of heart failure and who are taking many pharmacological agents BNP testing may offer some help (particularly if a baseline measurement is available) but such patients are most likely to need a full cardiological assessment in any case.

Screening for left ventricular systolic dysfunction

After an acute myocardial infarction, plasma BNP concentration rises in proportion to the size of the infarct.[34] It has been suggested that BNP measurement may have a role in screening for left ventricular systolic dysfunction in patients after myocardial infarction, and also in the general population.

Among post-MI patients, plasma BNP concentrations are inversely associated with ejection fraction.[35,36] One study compared plasma BNP concentrations with quantitative and qualitative echocardiography, clinical evaluation and a clinical scoring system in 75 patients who had survived the first two days after an acute myocardial infarction.[37] A cut-off value of 15 pmol/l (52 pg/ml) gave a sensitivity of 84% and a specificity of 62% for detecting a left ventricular ejection fraction <40% on echocardiography. However, other studies have been less convincing.[38,39]

Similarly, there are inconclusive data for the role of screening for asymptomatic left ventricular systolic dysfunction in the general population.

In a community-based study of randomly selected primary care subjects aged 25–74 years in Glasgow, a plasma BNP concentration of 5.2 pmol/l (17.9 pg/ml) was found to have a sensitivity of 76% and a specificity of 87% for left ventricular systolic dysfunction as defined by an EF ≤30% on echocardiography.[40] In this population, in which there was a relatively low prevalence of left ventricular dysfunction, the positive predictive value was only 16%, although at the chosen cut-point the negative predictive value was 97.5%. Confining analysis to those over 55 years of age increased the positive predictive value to 32%.

Another primary care based study of subjects aged 70–84 years showed that those with echocardiographic left ventricular systolic dysfunction had a higher plasma BNP concentration than those with no evidence of systolic dysfunction (39.3 pmol/l vs 15.8 pmol/l); the area under the ROC curve was high at 0.85.[41] A cut-off point of 18.7 pmol/l (64 pg/ml) gave 92% sensitivity and 65% specificity for the diagnosis of left ventricular systolic dysfunction with a negative predictive value of 99% but with a positive predictive value of only 18%. The authors concluded that a BNP measurement of less than 18.7 pmol/l (64 pg/ml) would rule out significant left ventricular systolic dysfunction.

However, other studies have suggested BNP has a limited diagnostic utility in identifying left ventricular systolic dysfunction in the community.[42,43] In part this may be because plasma BNP concentrations are not specific for left ventricular systolic dysfunction and the degree of elevation of plasma concentration may be much less marked in those who are asymptomatic.

Practical application

- BNP testing is not appropriate for screening large asymptomatic populations for left ventricular systolic dysfunction
- There may be some value in using plasma BNP to screen high risk subgroups of the population such as patients after MI, patients with diabetes or those with chronic history of poorly controlled hypertension,

although echocardiography is likely to remain the main method of assessing left ventricular function in this setting.

More work is needed with regard to screening before a recommendation to change current practice can be made.

BNP and NT-proBNP as prognostic indicators in heart failure

BNP has been suggested as a means of identifying those heart failure patients at high risk of death or hospitalization, in order to target therapy and enable selection for tertiary or quaternary services.

Plasma BNP concentrations are higher in patients with more severe symptoms and in those with more severe cardiac damage.[44] A raised BNP is able to differentiate between moderate and severe impairment of left ventricular function.[45] In addition, BNP also correlates well with cardiopulmonary exercise capacity and with composite measures of heart failure severity, such as the Heart Failure Survival Score.[46]

BNP is an independent predictor of death in patients with chronic heart failure, and is superior to atrial natriuretic peptide (ANP) for predicting mortality.[47] In this study, each 10 pg/ml increase in plasma BNP was associated with a 3% increase in the risk of cardiac death over the follow-up period. BNP is also an independent predictor of all-cause mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction, being superior to norepinephrine and left ventricular volumes.[48]

In patients with acute heart failure, BNP has been shown to be an independent predictor of cardiovascular mortality,[49] and is also predictive of outcome in patients hospitalized with decompensated heart failure.[50] Importantly, this last study suggested that measuring plasma BNP concentrations before discharge may help to identify patients with heart failure who are at a low risk of re-admission within the next month (area under the ROC curve 0.73).

Recent data in a small outpatient cohort with congestive heart failure suggested that both BNP and NT-ANP had predictive value for event-free survival to one year.[51]

BNP may have a role in selecting patients with advanced heart failure for transplantation. One recent study looked at patients with severe left ventricular function and heart failure. BNP concentrations were the strongest predictor of mortality at four years of follow-up.[52] In an ambulant heart failure clinic population, plasma BNP was at least equivalent to the Heart Failure Survival Score (which is commonly used for assessing patients for transplantation) in risk stratification.[46]

It has been suggested that the more traditional measures used to select patients for transplantation may not be appropriate in the present beta-blocker era. For instance, peak VO_2 does not appear to have the same prognostic value in patients on beta-blockers; this also appears to be true for NT-proBNP, ejection fraction and noradrenaline.[53] However, recent data from Glasgow on 128 consecutive patients who were taking beta-blockers and were awaiting transplantation show that the only independent predictor of all cause mortality was an NT-proBNP value above the median of 1498 pg/ml (RR=4.6, P=0.01).[54]

A recent study looking at 452 ambulatory patients with left ventricular dysfunction in whom there was a high rate of sudden death found that the BNP concentration was the only independent predictor of sudden death.[55]

Practical application

In specialist centres, measurement of plasma BNP concentrations may prove a useful addition to clinical assessment in situations where risk stratification is required, for instance in selecting patients with advanced heart failure for transplantation or for guiding referral for device selection (implantable cardioverter-defibrillators, resynchronization therapy and so on).

Further studies are needed to determine whether measuring plasma BNP should be used as a stand-alone test or in conjunction with scoring systems such as the Heart Failure Survival Score. Similarly, further work is needed to determine whether a single measurement is sufficient to predict the patient's prognosis or whether the change in concentration over time and with treatment provides more information.

BNP and NTproBNP in monitoring of patients with heart failure

Plasma BNP concentrations are known to fall rapidly on treatment of patients with heart failure.[56,57] In the clinic setting, patients whose functional status improved between visits showed a statistically significant reduction in plasma BNP concentration of about 50%; other variables such as NT-proANP and ANP or ejection fraction showed no statistically significant change.[58] Pilot data have suggested that vasodilator treatment can be titrated to reduce BNP concentrations towards the normal range in patients with mild to moderate heart failure.[59]

However, the monitoring of therapy by measuring plasma BNP concentration is complicated by the wide variation of plasma BNP levels reported in patients with symptomatic heart failure, which may make titration to a 'target' dose of BNP difficult. Furthermore, recent data show a progressive rise in a variety of natriuretic peptides as patients' renal function deteriorates.[60] As yet it is unclear what reduction in creatinine clearance is necessary for this effect appear; it may be relatively modest but nevertheless has implications for targeting of therapy. Reducing the plasma BNP concentration in the clinical setting by stepping up the diuretic dose may result in the patient developing worsening renal function, which may offset the expected reduction in BNP. Therefore, to titrate drugs

against BNP is therefore not as simple an idea as it first appears.

Nevertheless, there is some evidence of the possible benefit of a BNP-guided approach to therapy (with diuretics and ACE inhibitors) from a randomized trial conducted in 69 patients with symptomatic heart failure due to left ventricular systolic dysfunction.[61] Half the patients received therapy guided by plasma NT-proBNP measurement; therapy in the remaining patients was guided by clinical monitoring at the same frequency, but with the physician blinded to the NT-proBNP result. Clinical monitoring was based on scores assigned to 10 symptoms or signs of heart failure used in the Framingham criteria for heart failure.

The study found significantly fewer total cardiovascular events (deaths, hospital admissions or episodes of decompensation of heart failure) in the group randomized to NT-proBNP-guided therapy (target NT-proBNP concentration 200 pmol/l [1680 pg/ml]) compared to a similar group of patients in whom therapy was guided by commonly used clinical variables (P=0.02). Both time to first cardiovascular event and time to first heart failure event or death were significantly delayed (P=0.034 and P=0.049 respectively).

A larger study with a lower target NT-proBNP concentration (100 pmol/l [840 pg/ml]) is now underway in patients taking beta-blockers and spironolactone as well as diuretics and ACE-inhibitors. This study (BATTLE-SCARRED) may provide firmer evidence as to whether or not NT-proBNP can be used as a biochemical surrogate end-point in the monitoring of the treatment of patients with heart failure due to left ventricular systolic dysfunction. In addition, the multicentre Rapid Assessment of Bedside BNP in Treatment of Heart Failure (RABBIT) study or the French multicentre study Suivi du Traitement dans l'insuffisAnce caRdiaque Systolique (STARS) may provide answers regarding the appropriate 'target' plasma BNP concentration.

BNP may also find a role in guiding introduction of therapy for patients with heart failure. One study conducted in patients with chronic stable heart failure due to left ventricular systolic dysfunction suggested that the beta-blocker carvedilol was most efficacious in patients with higher pre-treatment BNP concentrations (above 24 pmol/l [82.5 pg/ml]).[62] This hypothesis has not been examined in a prospective randomized trial. However, a similar finding for NT-proBNP has also been reported.[63] Further work is required before BNP measurement can have a role in guiding the introduction of beta-blockade (and other therapies) in heart failure.

Practical application

At present, there are too few data available to make a firm recommendation regarding target BNP levels and levels at which treatment should be altered. However, rising BNP concentrations should alert the clinician to decompensation. Regular monitoring of BNP may also help to stratify the follow-up interval for more rational planning of discharge and clinical review.

Panel—Ongoing studies of natriuretic peptides in patients with heart failure

Study	Title	Aim	Reporting
UKNPS	United Kingdom Natriuretic Peptide Study	To determine the clinical utility of plasma BNP and NT-proBNP in ruling out heart failure (a multi-centre study)	2003
BATTLE-SCARRED	BNP-Assisted Treatment To Lessen Serial Cardiovascular Readmissions and Death	To compare heart failure management guided by NT-proBNP measurements with treatment guided by rigorous clinical evaluation	2004
RABBIT	Rapid Assessment of Bedside BNP in Treatment of Heart Failure	To determine whether utilization of BNP at the bedside provides better guidance of management than standard means	2004
STARS	Suivi du Traitement dans l'insuffisAnce caRdiaque Systolique. Treatment monitoring of systolic cardiac insufficiency (dysfunction)	To compare heart failure management guided by BNP measurements with treatment guided by clinical and echocardiographic evaluation	2004

Potential future uses of BNP and NTproBNP testing

It is likely that the future will see a shift from the use of BNP only in patients with heart failure to use also in other cardiac disorders. Recent data suggest that BNP is the best predictor of 30-day mortality in patients with acute coronary syndromes[64] while other workers have shown that an NTproBNP level above the median value predicts four-year mortality in acute coronary syndromes.[65] Further work is required.

There may also be a potential for utilizing plasma BNP concentrations in screening for left ventricular diastolic dysfunction.

Some 20–50% of patients with the diagnosis of heart failure have preserved systolic function on echocardiography, with diastolic dysfunction as the most likely potential cardiac abnormality.[66,67] The proportion of

patients with heart failure due to isolated diastolic abnormalities rises with age. In most cases, 'diastolic' heart failure cannot be distinguished from 'systolic' heart failure on the basis of history, physical examination, chest X-ray and ECG alone. Rather, the diagnosis of abnormal diastolic performance is most often based on exclusion of significant systolic dysfunction or valve disease in patients with heart failure.

Lubien and colleagues measured plasma BNP levels in 294 patients referred for echocardiography other than for assessment of abnormal systolic function, valve disease, possible endocarditis, or possible intracardiac thrombus.[68] Those patients with abnormal LV diastolic function (n=119) had a mean plasma BNP concentration of 286±31 pg/ml while the normal LV group (n=175) had a mean BNP concentration of 33±3 pg/ml. Plasma concentrations were particularly elevated in patients with restrictive filling patterns and in those with symptoms. The area under the ROC curve for the detection of any diastolic dysfunction was 0.92 (95% CI 0.87–.95, P<0.001). A BNP value of 62 pg/ml (18 pmol/l) gave a sensitivity of 85%, specificity of 83% and an accuracy of 84% for detecting isolated diastolic dysfunction.

Therefore, in patients with normal systolic left ventricular function and no valve disease, an elevated plasma BNP concentration is highly suggestive of clinically significant diastolic dysfunction. This suspicion should be even stronger if the Doppler examination is also abnormal.

Conclusion

On the basis of current evidence, plasma BNP testing is of most value in the diagnostic arena where it is likely to improve the performance of non-specialist physicians in diagnosing heart failure.

In clinical practice, BNP testing is best used as a 'rule out' test for suspected cases of new heart failure in breathless patients presenting to either the outpatient and emergency care settings; it is not a replacement for echocardiography and full cardiological assessment, which will be required for patients with an elevated BNP concentration. Although further work is ongoing in establishing the 'normal' values of BNP heart failure appears to be highly unlikely below a plasma concentration of 100 pg/ml.

However, it should be remembered that BNP levels rise with age and are affected by gender, comorbidity and drug therapy. Therefore, the plasma BNP measurement should not be used in isolation from the clinical context.

For cardiologists, measurement of plasma BNP levels may be helpful in guiding therapy and monitoring the course of heart failure, particularly in alerting clinicians to decompensation.

Measurement of BNP concentrations may also prove a useful addition to clinical assessment in situations where risk stratification is required, for instance in selecting patients with advanced heart failure for transplantation or for guiding referral for device selection in patients at risk of sudden death. Further research will inform this area.

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