THE NATRIURETIC PEPTIDES: AN EXPANDING ROLE IN CLINICAL MEDICINE

The importance of the various natriuretic peptides has become more apparent over the years.

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In 1981 it was observed that the infusion of atrial tissue extract into rats caused natriuresis.[1] This led to the discovery of atrial natriuretic peptide. Subsequent research has established that the various natriuretic peptides have a role in the body's defence against hypertension and plasma volume expansion.[2] The natriuretic peptide family consists of three types: atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type), secreted by the ventricle, and C-type peptide, originating in the endothelium.[2]

In left ventricular dysfunction, regardless of the cause, the neurohormonal system is activated, consisting of the:
- sympathetic nervous system
- renin-angiotensin-aldosterone pathway
- endothelin pathway.

These three systems, once activated, may initially compensate for the haemodynamic derangements that follow from left ventricular dysfunction, but eventually they become toxic to the heart and contribute to the clinical syndrome of heart failure.

Natriuretic peptides, on the other hand, are also stimulated in left ventricular dysfunction, but they represent the favourable side of neurohormonal activation for they actually endeavour to oppose the actions of the renin-angiotensin-aldosterone system, in addition to causing vasodilatation and natriuresis.[3] These changes are represented in Fig. 1.

PATHOPHYSIOLOGY

The release of natriuretic peptides into the circulation is stimulated by myocyte stretching of the failing myocardium.[2] The concentration in the plasma of natriuretic peptide is correlated with the extent of ventricular dysfunction, rising by as much as a factor of 30 in patients with advanced heart failure (New York Heart Association grade IV).[4]

Increasing plasma natriuretic peptide concentrations in patients with heart failure are also correlated with the development of cardiac arrhythmias and the degree of haemodynamic compromise in heart failure and furthermore predict long-term survival.[5] In clinical medicine, the natriuretic peptide that has found its way into clinical practice is the B-type (BNP). BNP is specifically secreted by the ventricles under pathological conditions.

B-type natriuretic peptide
The major site of origin of BNP under pathological conditions (ventricular stretch or increased wall tension) are the ventricles.[6] In Fig. 2 it is demonstrated that

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pro-BNP is split into BNP and an amino-terminal BNP (NT-pro-BNP). Currently NT-proBNP can be measured quite readily and the test is available in South Africa.

BNP: clinical utility

BNP is an effective way to 'rule out' heart failure or left ventricular dysfunction in patients with symptoms suggestive of heart failure, especially dyspnoea.[7]

Patients presenting in the emergency room with acute dyspnoea had a BNP level of 100 pg/ml with a sensitivity of 90% and a specificity of 73% in the diagnosis of heart failure. Two other studies confirmed this use of BNP in acute dyspnoea to rule out heart failure.[8,9]

The rapid BNP measurement in the emergency unit to diagnose heart failure, has demonstrated a diagnostic accuracy of BNP at a level of 100 pg/ml of 83.4%, with a negative predictive value at a level < 50 pg/ml of 96% and a receiver operating characteristic (ROC) curve of 0.91 (95% CI: 0.90 - 0.93).

Statistical figures like these confirm the usefulness of BNP measurements to rule out heart failure in patients presenting with dyspnoea but no other overt clinical signs of heart failure.

Comparative accuracy of BNP

In a study various methods to diagnose heart failure were compared. When the Framingham criteria for heart failure were used, the diagnostic accuracy was 75%. In comparison, the diagnostic accuracy of raised BNP levels was 83%.[10]

In a general community population

NT-proBNP performance in diagnosing heart failure in the community was tested in a study which demonstrated that a NT-proBNP level of > 36 pmol/l had a sensitivity of 100%, and a specificity of 70%, with a positive predictive value of 7% and a negative predictive value of 100%. The ROC-curve was 0.92 (95% CI: 0.82 - 1.0). The low positive predictive value may pose a problem in using BNP as a screening test in the general population because of a large number of 'false' positives. BNP may therefore not be useful in screening asymptomatic populations to diagnose heart failure.

In summary, it can be stated that the main value of NT-proBNP (or BNP) is to rule out heart failure in symptomatic patients where a diagnosis of heart failure is suspected.[11]

BNP levels in systolic and diastolic LV dysfunction

In a study comparing diastolic LV dysfunction and systolic dysfunction, both diagnosed on echocardiography, BNP levels were measured in both conditions and in healthy controls as a comparison:[12]

- in diastolic dysfunction BNP levels were 445 ± 150 pg/ml
- in systolic dysfunction BNP levels were 1 660 ± 404 pg/ml
- in healthy age-matched controls BNP levels were 24 ± 4 pg/ml.

This study shows that BNP levels are raised in all types of heart failure, more so in systolic dysfunction.
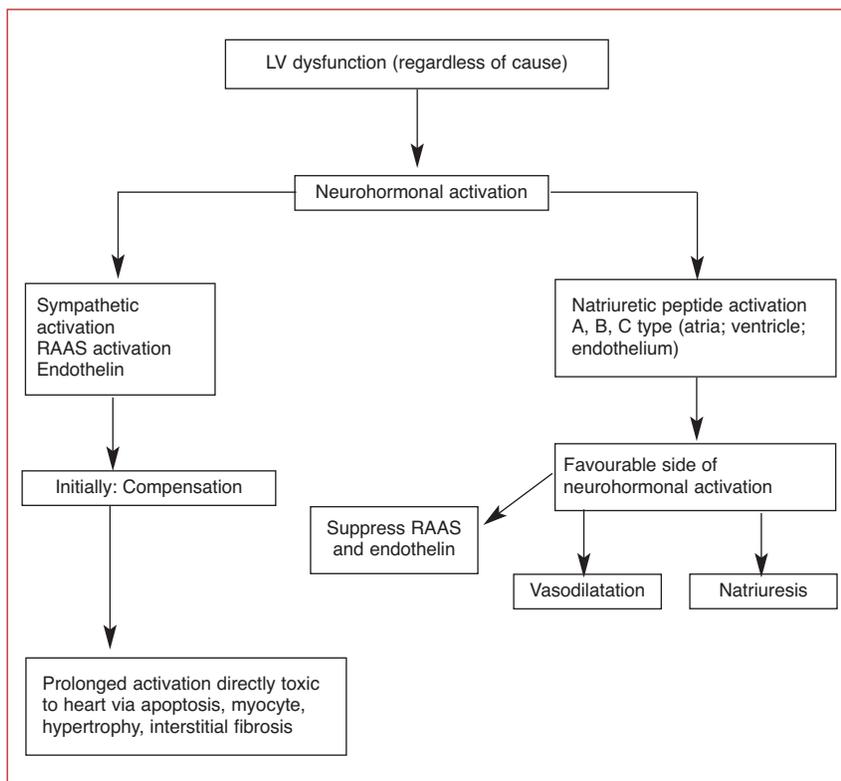

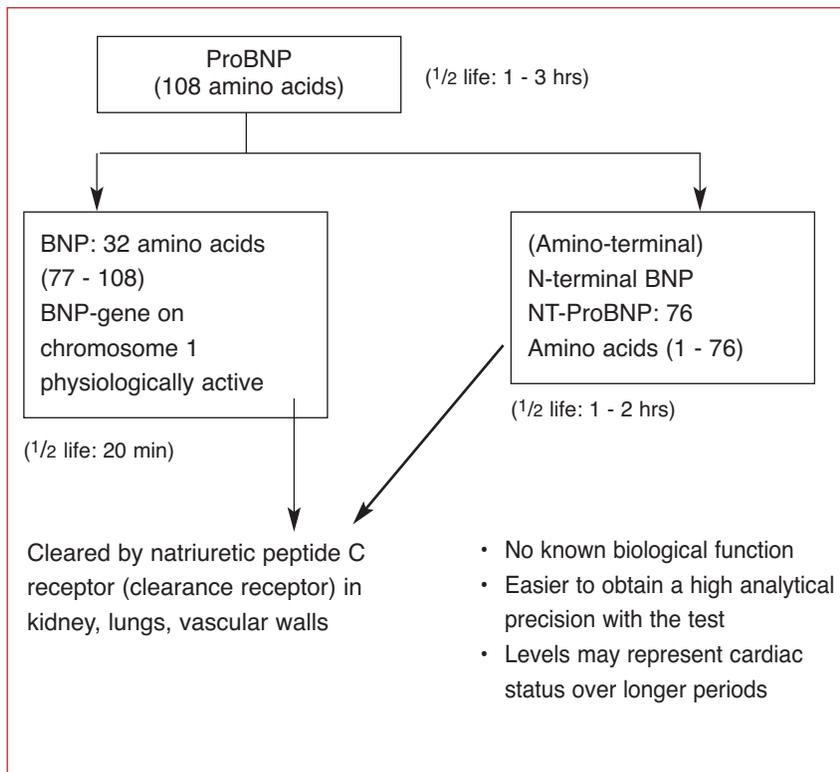*Fig. 1. Neurohormonal activation in heart failure.*

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ProBNP                    (1/2 life: 1 - 3 hrs)
(108 amino acids)

BNP: 32 amino acids              (Amino-terminal)
(77 - 108)                       N-terminal BNP
BNP-gene on                      NT-ProBNP: 76
chromosome 1                     Amino acids (1 - 76)
physiologically active
                                 (1/2 life: 1 - 2 hrs)
(1/2 life: 20 min)

Cleared by natriuretic peptide C   • No known biological function
receptor (clearance receptor) in   • Easier to obtain a high analytical
kidney, lungs, vascular walls        precision with the test
                                   • Levels may represent cardiac
                                     status over longer periods
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Fig. 2. BNP: Natural history.

Prognosis in heart failure

BNP can also be used to determine the prognosis of patients with heart failure. BNP has been used as a risk stratification in patients with heart failure when the BNP level is more than 440 pg/ml on admission. The sensitivity is 74% and specificity is 59% to predict future events in heart failure patients.[13]

In the Val-HeFT-trial, BNP values over 36 months were used to determine the prognosis of patients with heart failure. If the BNP (pg/ml) level was < 41; 41 – < 97; 97 – < 238 or ≥ 238, the corresponding mortality was 9.7%, 14.3%, 20.7% and 32.4%.

In summary, it can be stated that in heart failure, the higher the BNP level (including NT-proBNP), the worse the prognosis.

BNP levels in heart failure patients may also have other uses. Patients with heart failure whose BNP levels fell below 1 220 pg/ml at discharge were less likely to be readmitted with worsening heart failure.[14]

In heart failure patients with BNP levels of more than 480 pg/ml, the 6-month probability of admission or death was 42%. If, however, the BNP level was < 230 pg/ml, there was only a 2% probability of such an event.[15]

BNP level may serve as a prognostic marker for sudden death in heart failure, presumably due to a dysrhythmia. The BNP level was the only predictor for sudden death in heart failure patients with LVEF < 35% followed for 3 years.[16] The BNP had a cut-off level of 130 pg/ml in predicting sudden death. Could this be used in future as an indicator for the insertion of an intracardiac defibrillator (ICD) in heart failure patients? Practical applications like these need to be explored further.

Assessment of treatment efficacy in heart failure

BNP levels fall after treatment with a loop diuretic and ACE inhibitors.[17] In NT-proBNP guided treatment, 69 patients with a LVEF of < 40%, treatment was assigned according to clinical criteria or according to NT-proBNP level. At 6 months, 27% of patients in

the BNP group and 53% in the clinically guided group had a first cardiovascular (CV) event.[18] BNP levels can also be used as a marker of the effects of ACE inhibition.[19]

Prognosis in acute coronary syndrome (ACS)

The BNP level can be used to determine prognosis after an acute myocardial infarction (AMI). If BNP or NT-proBNP levels were combined with LVEF measurements, there was an improved prognostic risk prediction in patients with ACS.[20]

In another study to predict prognosis using BNP, 204 patients with an ST-segment-elevated myocardial infarction (STEMI), 220 with non-ST-segment elevated MI (non-STEMI) and 185 with unstable angina were investigated. Follow-up was 51 months. The NT-proBNP was lower (442 pmol/l) in survivors than in patients who died (1 306 pmol/l). The NT-proBNP level added prognostic information above and beyond Kilip class, age, and LVEF in patients with an ACS. Even peak troponin T levels did not alter the relationship.[21]

In summary, elevated NT-BNP levels are highly predictive of a worse outcome in the ACS.

Risk stratification in acute pulmonary embolism (PE)

The risk of death due to PE if the BNP level is > 21.7 pmol/l, is 17% (95% CI: 6 - 33%). The negative predictive value for an uneventful outcome of a BNP value < 21.7 pmol/l is 99% (95% CI: 93 - 100%).[22]

The optimal BNP cut-off level determined by ROC curve is < 50 pg/ml. A cut-off level of < 80 pg/ml identifies 95% of patients with a benign course after a PE.

An NT-proBNP level of < 500 pg/ml had a negative predictive value for adverse outcome of 97% (95% CI: 84 - 99%) in patients with PE.[23]

In summary, NT-proBNP levels can be used in patients with a pulmonary embolism to predict a poor outcome. This is probably because in a massive pulmonary embolism, the sudden stretching of the right ventricle causes the release of NT-proBNP.

Role of BNP in myocardial ischaemia

It has been demonstrated that BNP is elevated in unstable angina, and also elevates after balloon inflations during coronary angioplasty.[24,25] In experimental ischaemia in the rat myocardium of as little as 2 minutes, there is an immediate increase in BNP.[26] There is a suggestion that BNP modifies acute ischaemic myocardial injury and that BNP may influence post-infarction remodelling.[27] It may be that we will be using BNP in future as a general indicator of cardiac structural disease rather than a specific indicator of systolic dysfunction of the left ventricle only.[28]

References available on request.

IN A NUTSHELL

NT-proBNP can be readily measured and an elevated level can be used to diagnose, or at least select, those patients who need further investigation for heart failure.

A normal level of NT-proBNP will effectively 'rule out' heart failure, especially in those patients without overt clinical signs of heart failure.

The higher the levels of NT-proBNP in heart failure patients, patients with an acute coronary syndrome or patients with a pulmonary embolus, the worse the prognosis.

In this manner elevated levels of NT-proBNP can guide the practitioner to increase the intensity of therapy.

SINGLE SUTURE

FAST FOOD TRICKS

We all assume that people are getting fatter because they eat too much. But a recent item in *New Scientist* may suggest otherwise. According to researchers from the International Nutrition Group at the London School of Hygiene and Tropical Medicine, it may be that our food is too rich. What they are getting at is the energy density of the foods. Apparently, volunteers given low energy-density foods who ate as much as they liked lost weight, while their unfortunate counterparts given high energy-density foods gained. The problem seems to be fast foods. It seems that our bodies evolved to deal with an energy density of 450 kJ/100 g, while the average burger contains about 1 200 kJ/100 g. The typical British diet has an energy density of about 650 kJ/100 g. All you need to do is eat 200 g of fast food too many twice a week to gain a whopping 8 kg of body fat a year.

(Editor's note: Once again, more evidence for my conviction that all that matters in weight control is calories in versus calories out — on your bikes everyone!)

(Coghlan A. *New Scientist* 2003; 25 October, p.10.)