EDITORIAL

Natriuretic peptides as a prognostic marker and therapeutic target in heart failure

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Natriuretic peptides may have an increasing role in assisting clinicians to target treatment in patients with chronic heart failure

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NATRIURETIC PEPTIDES AND OUTCOME PREDICTION

It is not surprising that a peptide which correlates with intracardiac pressure reflects prognosis. Natriuretic peptides and chiefly BNP have been shown to predict both short and long term outcome in heart failure. Treatments for this condition are becoming even more complex and costly. We now not only have drug treatment but more expensive entities such as implantable cardioverter-defibrillators (ICDs) and transplantation. The current ways of assessing patients for these complex interventions are expensive, sometimes invasive, and time consuming. There would be obvious merit if we could target expensive treatments by way of one simple blood test like BNP.

DECOMPENSATED HEART FAILURE, READMISSION, AND DEATH

Hospital readmission of patients for heart failure is common, distressing for the patient, and expensive for the health service. It would be preferable to identify patients at high risk of readmission before discharge so that they could be treated more aggressively. It is known that BNP concentrations fall during acute treatment of heart failure.⁷ It therefore seems sensible to speculate that BNP could predict the response to treatment. Indeed, in a recent study of 50 consecutive patients admitted with decompensated heart failure, BNP concentrations were indeed related to hospital readmission and death within six months. Not only was the pre-discharge value related to short term outcome, but relative changes in BNP concentration also predicted prognosis. There was a larger decrease in BNP in patients who were event-free during follow up. Those with an increase of BNP following treatment almost all had further events. These results indicate that both changes in BNP concentrations and the pre-discharge value predict short term outcome. This study is in agreement with others suggesting that changes in BNP value during acute treatment is a very strong predictor of short term death and readmission.⁸

Despite advances in treatment, patients with chronic heart failure (CHF) still have high rates of mortality and hospital readmission. There is a real need for a relatively simple prognostic indicator in heart failure patients so that treatments can be better targeted. Natriuretic peptides have been shown to be powerful prognostic markers not only in the setting of heart failure but in those with cardiovascular disease and in the general population as a whole.^{1,2} Not only do natriuretic peptides predict prognosis but they may help us treat our heart failure patients more appropriately by using them as a target for therapy. Here we evaluate how measuring these peptides might fit into everyday clinical practice.

Both atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are synthesised as high molecular weight precursors and then cleaved within their C-terminal regions to give the biologically active peptides, ANP and BNP. The remaining N-terminal fragments as well as the active forms are both released into the circulation. Plasma ANP and BNP and the corresponding N-terminal proANP (N-terminal ANP) and N-terminal proBNP (N-terminal BNP) are increased in conditions which increase ventricular volume expansion and pressure overload.

BRAIN NATRIURETIC PEPTIDES

The principal source of plasma BNP is the cardiac ventricles, which therefore suggests that it may be a more sensitive and specific marker of ventricular disorders and prognosis than other natriuretic peptides. Indeed plasma BNP is a more important predictor of morbidity (including hospital readmission) and mortality in patients with chronic symptomatic heart failure than plasma ANP.³ This prognostic information is independent of other variables previously associated with a poor prognosis. Intriguingly, BNP also predicts all cause mortality in the general population and in those with no evidence of left ventricular systolic dysfunction.⁴ BNP has also been shown to be a more sensitive biomarker than ANP for left ventricular dysfunction and prognosis in patients with acute coronary syndrome and in patients with advanced congestive heart failure.^{2,5,6}

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Abbreviations: ACE, angiotensin converting enzyme; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CHF, chronic heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, multicenter automatic defibrillator implantation trial; NYHA, New York Heart Association; Val-HeFT, valsartan heart failure trial

NATRIURETIC PEPTIDES AND MILD HEART FAILURE

Not only can natriuretic peptides predict outcome in patients with severe and symptomatic heart failure, they can also predict prognosis in those with mild, asymptomatic, and minimally symptomatic left ventricular (LV) impairment. This suggests the importance of early detection and treatment of this group of patients to improve prognosis. In a prospective study of 290 consecutive patients with asymptomatic or minimally symptomatic and newly symptomatic LV dysfunction, BNP was a more important predictor of future cardiovascular events (worsening heart failure, myocardial infarction, cardiac death) than ANP.⁵ In a stepwise multivariate analysis of 21 variables such as clinical characteristics, treatment, haemodynamics, and neurohumoral factors, only a high value of BNP was an independent predictor of mortality in these patients. This leads us to speculate that reducing plasma BNP concentrations with aggressive treatment early may reduce mortality in heart failure patients regardless of New York Heart Association (NYHA) class.

NATRIURETIC PEPTIDES AND PROGNOSIS IN THE GENERAL POPULATION

Natriuretic peptides are known to be raised and predict outcome in both symptomatic and asymptomatic left ventricular impairment. They also predict mortality in the population as a whole regardless of left ventricular systolic function or evidence of cardiovascular disease. In a population based study of 1640 people aged between 25 and 74 years in Glasgow, BNP independently predicted the four year all cause mortality in this group.⁴ An exceedingly interesting finding was that even patients with preserved left ventricular systolic function who had a high BNP concentration also had a worse prognosis. Other causes of a high BNP such as left ventricular hypertrophy, which is a treatable independent predictor of future cardiovascular events and renal impairment, should be considered. BNP has also been shown to be the strongest independent predictor of five year all cause mortality in an elderly population with and without evidence of cardiovascular disease.⁹ There is impaired left ventricular diastolic filling with ageing and BNP has been shown to be an independent prognostic marker of mortality in isolated diastolic heart failure.

PROGNOSTIC VALUE OF GUIDING TREATMENT ACCORDING TO SERIAL MEASUREMENTS OF NATRIURETIC PEPTIDES

Preliminary data suggest that titration of drugs and doses to decrease BNP concentrations in patients with CHF may be beneficial in terms of reducing readmission, episodes of decompensated heart failure, and cardiovascular death.⁷⁻¹⁰ Intensive treatment with diuretics and vasodilators lead to a rapid fall in BNP concentrations along with intracardiac filling pressures. Chronic use of angiotensin converting enzyme (ACE) inhibitors, angiotensin 2 receptor antagonists, and spironolactone lead to reductions in natriuretic peptide values.¹⁻⁷ After introduction of a β blocker, natriuretic peptide concentrations initially rise, then fall due to improved LV function and haemodynamic variables. A substudy of Val-HeFT (valsartan heart failure trial) is the largest study so far to confirm the prognostic importance of neurohormones in patients with moderate to severe heart failure.¹ The investigators measured BNP and noradrenaline (norepinephrine) before randomisation and during follow up in 4300 patients. The incidence of all cause mortality and first morbid event was significantly higher in patients with baseline BNP above the median value of 181 pg/ml. This was the first study to supply evidence that changes in BNP over time are associated with corresponding changes in mortality and morbidity. Indeed, patients with the greatest percentage decrease in

BNP at four months had the lowest mortality and morbidity. Conversely, patients with the highest percentage increase in BNP had the highest subsequent increase in events.

Cheng *et al* recently reported the importance of changes in BNP concentrations during hospitalisation and treatment for heart failure.¹¹ Patients who died or were readmitted within 30 days had an increase in their BNP concentration whereas a decrease in this value conferred a better prognosis.

Hospital readmission rates for CHF are extremely high and a simple, quick method for allowing clinicians to make a decision regarding further titration of treatment and discharge would be invaluable. The current strategy for titrating ACE inhibitors and β blockers is crude and uses a "one dose fits all" regimen corresponding to the doses used in the large clinical trials. The problem with a "one dose fits all" model is that it may lead to a subtherapeutic pharmacological dose for individual patients, inadequate suppression of neurohormonal activation, and therefore an increase in mortality and morbidity. Conversely, these doses may be over treating other patients and leading to the unnecessary risk of side effects from the medication. Moreover, pharmacological treatment of heart failure is becoming progressively more complex and practical guidelines for management of individual patients are lacking. A better approach may be to tailor treatment towards reducing natriuretic peptide concentrations and therefore mortality and morbidity. Troughton and colleagues showed for the first time in a pilot study of 69 patients with symptomatic heart failure that titrating management according to the N-terminal BNP value reduced cardiovascular events compared to standard clinical assessment and symptom guided treatment.¹² This was an important, albeit small, study conducted before β blocker treatment was routine and clearly confirmation is required from larger clinical studies using β blockers.

In a recently presented study of 220 patients (NYHA II–IV and ejection fraction < 45%), BNP guided treatment to a concentration < 100 pg/ml reduced cardiovascular events and hospitalisation by 54% compared to usual clinical titration of treatment.¹³ Clearly, BNP testing may prove to be useful for choosing the appropriate medications and doses not only to improve symptoms but also prognosis. Moreover, patients with high BNP values who do not respond to pharmacological treatment should be considered for more invasive and intensive treatments such as ICD implantation and cardiac transplantation. N-terminal BNP is a more powerful predictor of mortality than traditional criteria such as Vo_2max and heart failure survival score.¹⁴ BNP and N-terminal BNP therefore fill the criteria for an excellent surrogate marker in heart failure and should be used in future clinical trials evaluating new therapeutic agents.

NATRIURETIC PEPTIDES AND TARGETING TREATMENTS

ICD implantation

The recent MADIT II (multicenter automatic defibrillator implantation trial) study showed that treating post-myocardial infarction patients with an LV ejection fraction (LVEF) of < 30% prophylactically with an ICD significantly reduced the risk of death by 30%.¹⁵ This study begs the question of whether ICDs could be targeted more precisely so that not all post-myocardial infarction patients with an LVEF < 30% need to receive an ICD. As much as 50% of mortality in patients with CHF is attributable to sudden death, with at least one study showing that log BNP is an independent predictor of sudden death in this group of patients.¹⁶ In a recent retrospective trial involving 51 heart failure patients (NYHA I–III) with an LVEF < 40%, a multivariate analysis identified N-terminal BNP as an independent predictor of ventricular tachyarrhythmias.¹⁷ There is the exciting prospect

of BNP measurement being used to help identify patients who are at high risk of sudden death and who could benefit from implantation of these expensive devices. Clearly, additional appropriately powered prospective studies using BNP to identify patients at high risk of sudden death and who would benefit from an ICD need to be performed.

Cardiac transplantation targeting

In a prospective study of 128 consecutive CHF patients referred for cardiac transplantation, plasma N-terminal BNP was the only independent predictor of all cause mortality at a concentration above 1498 pg/ml.¹⁸ Selection of patients for cardiac transplantation is complex and relies upon time consuming, cumbersome, and expensive parameters to measure. N-terminal BNP is an excellent independent predictor of death and a better prognostic marker than LVEF, VO_2max , and heart failure survival score. There is also significant correlation between plasma BNP and risk stratification criteria for cardiac transplantation. BNP and N-terminal BNP should prove helpful in the clinical work up of patients for whether they should be placed on a heart transplant waiting list or not.

CONCLUSION

Although natriuretic peptides began as aids to diagnosis, they appear to perform even better as prognostic markers and even therapeutic targets. BNP and N-terminal BNP are better prognostic markers than either N-terminal ANP or ANP to evaluate outcome in heart failure patients. Elevated plasma concentrations of BNP have been shown to be excellent independent predictors of mortality and readmission in this group of patients. Serial testing of BNP further enhances its prognostic value—that is, if BNP does not fall after aggressive treatment then this is indicative of a very poor prognosis. It appears that this simple and quick test may outperform other ways of risk stratifying heart failure patients. Perhaps patients with a persistently high BNP despite pharmacological treatment should be considered for other treatments to improve survival, such as an ICD or cardiac transplantation. Moreover, the prognostic ability of BNP seems to occur in patients without heart failure—for example, in patients sustaining an acute coronary syndrome, whether it be ST or non-ST segment elevation myocardial infarction or unstable angina.

Developments within BNP assay methodology should assist its introduction into routine clinical care. These developments are the recent introduction of rapid immuno-radiometric assay systems and the development of near patient tests which can produce a result within 15 minutes at the bedside. The problem at the moment with BNP as a diagnostic marker is that we do not yet know the normal range and therefore the ideal cut-off value for different populations as it changes with sex and age of the patients. An exciting future role for BNP would be for it to be used in the same way HbA1c is used in diabetics—as a beacon by which to individualise each patient's treatment to improve their individual prognosis. This may be a better use of BNP than as

a diagnostic marker, as it does not rely upon a cut-off but rather a relative change in concentration.

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Both authors declare that we have no competing interests.

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