A feeling in the waters: diagnosis of heart failure using urinary natriuretic peptides

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ABSTRACT

Plasma levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP (N-BNP) are highly sensitive markers of ventricular dysfunction and/or hypertrophy and, in established disease, offer prognostic value and may be useful for guidance of therapy. Ng and co-workers report in this issue of Clinical Science that urinary levels of N-BNP may be as useful as plasma levels for the discrimination of patients with and without heart failure. This raises the potential for a relatively simple urine test that could be used for the diagnosis of heart failure. Roles in prognostication and the guidance of therapy may also be possible but, perhaps of most significance, measurement of urinary N-BNP may be applied to screening of patients at high risk of heart failure. The main limitations of the study were that the sample of heart failure patients comprised only 34 individuals with New York Heart Association functional Class IV and that the observed correlation between levels of urinary N-BNP and plasma creatinine seemed counter-intuitive. The latter issue needs clarification, as renal impairment is a frequent co-morbidity among patients with heart failure and will potentially confound any observed association between ventricular dysfunction and urinary N-BNP levels. Another caveat is that it is unclear if testing for urinary N-BNP can be cheaply and conveniently administered on a large scale. Nevertheless, this first demonstration of elevated N-BNP in the urine of patients with heart failure raises a number of exciting possibilities with regard to the management of patients with established or possible heart failure. Further investigation is required and eagerly awaited.

Among the complex neurohormonal alterations that occur in heart failure is activation of the natriuretic peptides, which exert counter-regulatory actions to the raft of co-activated vasoconstrictors and anti-natriuretic factors. The three known natriuretic peptides, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), induce natriuresis and diuresis, promote vascular relaxation, inhibit the synthesis and action of vasoconstrictor peptides and inhibit sympathetic nervous activity [1–4]. ANP and BNP are synthesized by cardiac myocytes and released primarily in response to atrial stretch. CNP seems to occur widely in the body, including in endothelial cells [5].

Somewhat paradoxically, because their actions are generally overwhelmed by those of vasoconstrictors and anti-natriuretic factors in established heart failure, levels of natriuretic peptides are reliable markers of ventricular dysfunction and correlate with disease severity. BNP has been the most widely studied, and consistent population-based data have now accumulated to show that plasma levels of BNP, and its precursor N-terminal pro-BNP (N-BNP), are highly sensitive to the presence of ventricular dysfunction and/or hypertrophy, even among asymptomatic individuals [6,7]. This high sensitivity makes the assays useful for discriminating between cardiac and non-cardiac causes of dyspnoea, particularly in the emergency setting [8]. Plasma BNP and N-BNP levels also offer prognostic value in existing heart failure [9,10] and predict for future heart failure following myocardial infarction [11]. In addition, plasma N-BNP has been shown to be useful for guidance of heart failure therapy [12].

Against this background, the report by Ng et al. [13] in this issue of Clinical Science is of particular interest

Key words: diagnosis, heart failure, urinary natriuretic peptide, validity.

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; N-BNP, N-terminal pro-BNP.

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and potential importance. The study compared urinary levels of N-ANP, N-BNP and CNP and plasma levels of N-BNP between patients hospitalized for heart failure and age- and sex-matched patients with echocardiographically determined normal systolic function. A significant elevation was observed in all four measurements of natriuretic peptides among heart failure patients and, in the case of the urinary parameters, this finding was noted even after adjustment for urinary creatinine. The receiver operated characteristic (ROC) for urinary N-BNP for the diagnosis of heart failure was very similar to that of plasma N-BNP.

These data raise the potential for a relatively simple urine test that could be used for the diagnosis of heart failure. Roles in prognostication and the guidance of heart failure therapy may also be possible (in line with the uses of plasma BNP and N-BNP) but, perhaps of most significance, measurement of urinary N-BNP may be applied to screening of patients at high risk of heart failure to select those for subsequent, more definitive tests. Indeed, a home N-BNP diagnostic kit, in a manner similar to that of testing for other biological substances in urine, may be a future reality, especially if designed to be fully or semi-quantitative.

However, a number of caveats need to be considered. First, the sample of heart failure patients comprised only 34 individuals and, although they were consecutively recruited, similar observations in a much larger cohort would be required before the findings can be considered sufficiently robust.

Secondly, the range of values observed for urinary N-BNP was much smaller than that for plasma N-BNP, suggesting that urinary N-BNP may be less sensitive a discriminator between less severe forms of heart failure and normal subjects. Indeed, the subjects of the study were all of New York Heart Association functional Class IV on admission to hospital. Clinically, it is not difficult to make a diagnosis in a patient with Class IV symptoms and there would be greater utility in urinary N-BNP being able to discriminate between less severe disease (where the diagnosis may be in doubt) and patients with symptoms for reasons other than cardiac disease. Even better would be a demonstration of a correlation between levels of urinary N-BNP and objective measurements of ventricular dysfunction across a wide range of both scales.

Thirdly, the association between levels of urinary N-BNP and renal impairment remains unclear. Ng et al. [13] found that urinary N-BNP correlated with plasma creatinine, which is counter-intuitive given that excretion of N-BNP is dependent on glomerular filtration [14]. This issue needs clarification as renal impairment is a frequent co-morbidity among patients with heart failure and will potentially confound any observed association between ventricular dysfunction and urinary N-BNP levels.

Finally, for any test to have clinical utility, it also needs to be reproducible and, importantly, relatively inexpensive and convenient to administer. Ng et al. [13] have developed assays for urinary natriuretic peptides that seem to have reasonable reproducibility, at least in the limited setting of their study, but there is no indication that these can be cheaply and widely applied.

Nevertheless, despite these caveats, this first demonstration of elevated N-BNP in the urine of patients with heart failure raises a number of exciting possibilities with regard to the management of this progressive, lethal condition. Further investigation is required and eagerly awaited.

REFERENCES