EDITORIAL

Variability of NT-proBNP levels in heart failure: implications for clinical application

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The international guidelines to aid diagnosis of new-onset heart failure endorse B-type cardiac natriuretic peptides (BNP and NT-proBNP).[1] Changes in BNP or NT-proBNP, or both, over weeks or months are associated with parallel changes in morbidity and mortality in both acute and chronic heart failure over follow-up of between 30 days and 2 years.[2–4] Serial measurements of B-type peptides are of potential value in titrating therapy and in monitoring heart failure and may improve clinical outcomes.

Troughton *et al* studied 69 patients with systolic heart failure randomised to receive treatment guided by plasma NT-proBNP concentrations or clinical assessment.[5] Over follow-up (median 9.5 months) there were fewer cardiovascular events (death, hospital admission or heart failure decompensation) within the hormone-guided group (19 vs 54, $p = 0.02$).

Jourdain *et al* studied 220 patients (NYHA II–IV and ejection fraction <45%) from 21 centres in France.[6] Treatment directed to suppress BNP below 100 pg/ml resulted in fewer deaths or admissions for heart failure than standard care (25 vs 57 over 15 months follow-up, $p<0.001$).

''STARBRITE'' investigators reported results from 130 patients from three sites (left ventricular ejection fraction <35%) assigned to treatment guided by BNP or by clinical assessment.[7] Over 90 days the BNP group exhibited a trend towards more days alive and out of hospital, lower BNP values ($p = 0.02$) with no significant difference in creatinine or systolic blood pressure, and significantly greater doses of converting enzyme inhibitors and β blockers in association with fewer increases in diuretic drugs. Hence, treatment guided by BNP was associated with greater use of evidence-based drugs.

To aid monitoring and titration of treatment, the variability of plasma B-type peptides within patients with stable heart failure needs to be sufficiently low so that clinically commonplace variations represent genuine alterations in cardiac status. Excessive random or ''unexplained'' biological variation will confound attempts to employ serial peptide measurements to adjust treatment. In this issue of *Heart*, Cortés *et al* have assessed variability of both plasma and urine NT-proBNP immunoreactivity at 12-month intervals over 2 years in 74 patients with stable heart failure (***see article on page 957***).[8] Plasma and urine results were stable, with coefficients of reproducibility (CR = 1.96 × SD of the interval percentage change in plasma peptide level) between 20% and 25% for change over 12- and 24-month intervals. Concurrent coefficients of reproducibility for urinary NT-proBNP were 7–10%. They suggest that variations in peptide exceeding 22% in plasma and 7% in urine within a 12-month interval may indicate ''pathophysiological changes''.

Variation in peptide immunoassay results reflects measurement precision (analytical variability (CVa)) in addition to changes in secretion and clearance (biological variability (CVi)). Analytical variability depends upon the assay employed, whereas biological variability reflects the complex interplay of haemodynamic and neurohormonal stimuli that control peptide secretion and clearance. Wu *et al* measured plasma NT-proBNP levels in eight normal subjects from four plasma samples taken at 2-week intervals,[9] yielding significant percentage serial change values ($SCV = 2.77\ (CVa^2+CVi^2)^{1/2}$) of 92% for NT-proBNP and 129–168% for BNP. Subsequently, the authors applied these SCVs to patients with recently decompensated heart failure.[10] This can be challenged in that levels of peptide within normal subjects are low (often bordering on the detection limits of the immunoassays), and small absolute changes in peptide concentrations, of little biological significance, can result in an apparently high percentage variation.

The appropriate reference group in which to establish variability is within patients with stable heart failure. Bruins *et al* studied 43 patients with stable heart failure with serial sampling within 1 day, on consecutive days and at weekly intervals over 6 weeks.[11] Baseline levels of BNP were 134 pg/ml (interquartile range 0–1640 pg/ml) and 570 pg/ml (17–5408 pg/ml) for NT-proBNP. Coefficients of variation (CVs) within day, day to day and week to week were 12%, 27% and 41%, respectively, for BNP, and 9%, 20% and 35% for NT-proBNP; yielding SCVs for within day, day to day and week to week of 32%, 74% and 113% for BNP and 25%, 55% and 98%, respectively, for NT-proBNP.

SCVs are influenced by the degree of care taken to establish that the patients assessed are truly stable. Schou *et al* selected 20 patients fulfilling 22 inclusion and exclusion criteria of clinical stability.[12] The intraindividual CV over a 1-week interval of plasma BNP was 15% and of NT-proBNP 8%.

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Abbreviations: BNP, B-type natriuretic peptide; CV, coefficient of variation; NT-proBNP, N-terminal pro-brain natriuretic peptide; SCV, serial change value

Given CVa of 3% for BNP and 1% for NT-proBNP, these measurements yielded SCVs of 43% for BNP and 23% for NT-proBNP. This latter SCV corresponds well with the values suggested in the current report from Cortés *et al*.[8] The findings are also corroborated by reports from the author's laboratory.[13] In eight patients with rigorously defined stable heart failure studied under standardised experimental conditions, including regulated diet and posture, intraindividual CVs for samples taken 6 weeks apart averaged 10% for NT-proBNP with an SCV of 30% (a mean change of 160 pg/ml against a background mean level of 550 pg/ml). However, in a ''real life'' sample of 10 ambulant subjects with heart failure participating in a clinical trial of treatment guided by NT-proBNP levels,[14] somewhat greater variability was found, with a CVi of 38% and an SCV of 105%.

The cause of this degree of biological variability and the impact it has upon the clinical value of serial measurements is the crucial point under consideration. If serial BNP and NT-proBNP are perceived as existing within a framework of random variation around a homoeostatic set point, the degree of variation described could make serial measurements meaningless, as implied by some previous investigators.[9 10] However, in view of the encouraging epidemiological data and the pilot studies of hormone-guided treatment,[2–7] this view and mode of analysis are clearly overly simplistic. The variation seen is likely to reflect alterations in peptide secretion due to active physiological processes, just as for variations in blood pressure or heart rate. Secretion of B-type peptides is under complex control modulated by multiple haemodynamic, neurohormonal and immunological factors, which are dynamic and in toto contribute to cardiac remodelling and risk of frank clinical decompensation. Clerico and colleagues suggest that variations in BNP or NT-proBNP greater than three times the standard deviation of the assay variability should be regarded as clinically significant.[15]

In due course the question will be resolved by the accumulation of empirical data from prospective randomised controlled trials of the management of heart failure guided by serial measurements of B-type peptides. There are at least five such trials under way within New Zealand, Europe and the United States.[14]

URINE IMMUNOASSAYS OF B-TYPE PEPTIDES

Despite some promising initial reports, questions remain about urinary NT-proBNP assay results. Protagonists of this approach used immunoassays developed for plasma NT-proBNP applied to urine.[16 17]

Ng *et al* conducted a community screening study of 1360 subjects.[18] They found that areas under receiver operating curves were similar for both plasma and urine NT-proBNP for the diagnosis of significant ventricular dysfunction. They calculated that the number of patients requiring pre-screening by urinary NT-proBNP to lead to detection of one case of significant left ventricular systolic dysfunction (confirmed by echocardiography) was 17 compared with 29 using plasma NT-proBNP. The product of plasma and urinary results improved the area under the curve of the receiver operating curve to 0.92, with a negative predictive value of 99.9%, and further reduced the number of cases proceeding to echocardiography to detect one case of left ventricular systolic dysfunction to 11.

In a previous report, Cortés *et al*[17] using the Roche Elecsys NT-proBNP assay on urine samples, found that the area under the curve for urinary NT-proBNP in the diagnosis of heart failure was 0.96. Cortés found average NT-proBNP levels of 166 pmol/l in 96 patients with heart failure, whereas Ng found that mean plasma NT-proBNP levels in 28 patients with left ventricular systolic dysfunction was 360 pmol/l. Urine concentrations were 11 pmol/l from the group previously reported by Cortés *et al* in comparison with levels of 69 pmol/l from Ng *et al*. It is not clear whether these two immunoassays are detecting the same entity within urine. Urine NT-proBNP immunoassays have had no published biochemical validation. The same criteria for validation and clinical uptake should be applied to urine assays as to any plasma assay. This requires high performance liquid chromatography, with or without additional mass spectroscopy studies, to confirm that the immunoreactive substance in urine is genuine NT-proBNP. Until then, clinical application of urine measurements of NT-proBNP remains experimental.

CONCLUSION

In conclusion, serial measurements of plasma NT-proBNP or BNP, or both, offer the tantalising possibility of added objectivity in the titration of anti-heart failure treatment and continuing monitoring of chronic heart failure. Several reports suggest that this strategy improves clinical outcomes. Within 2 years, several clinical trials testing this strategy will report their results. The question as to whether biological variability in plasma peptide levels confounds this application will then be answered by a substantive body of empirical evidence. If positive, these results will confirm serial measurements of NT-proBNP or BNP, or both, as a routine tool and part of the ''standard of care'' for management of chronic heart failure.

Conflict of interest: None declared

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