

## Editorial

## Urinary Measurement of N-Terminal B Type Natriuretic Peptide in Patients With Cardiac Failure - Highway or Byway?

## Determinación de péptido natriurético tipo B aminoterminal urinario en pacientes con insuficiencia cardiaca: ¿autopista o carretera secundaria?

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Urine testing has the advantage of being convenient, familiar to a range of healthcare professionals, and non-invasive. Urine testing for albumin has a well-established role in the management of the diabetic patient and the assessment of renal disease. Urinary measurement of N-terminal B type natriuretic peptide (NTproBNP) has been proposed as a potential tool for detection of cardiac failure. Such an approach would be ideally suited for community-based diagnosis and potentially useful for the emergency department. Point of care testing (POCT) is already available for measurement of both B type natriuretic peptide (BNP) and NTproBNP in whole blood. If a POCT method for NTproBNP measurement in urine could be developed it could provide a convenient, simple test for heart failure. The clinical diagnosis of heart failure is notoriously difficult. In a systematic review comparing clinical symptoms and signs, the electrocardiogram, and chest radiography, the poor diagnostic efficiency of clinical symptoms and signs was demonstrated and the diagnostic superiority of natriuretic peptide measurements confirmed.<sup>1</sup> It has been estimated that 30%-60% of referrals from primary to secondary care for investigation of suspected heart failure are subsequently found to be inappropriate. A strategy to reduce inappropriate referrals with suspected heart failure would therefore be invaluable, especially in the prevailing climate of scarce healthcare resources. If inappropriate referrals could be reduced by urine POCT for NTproBNP there would be a strong argument on the basis of cost economics to utilize such a test. The cost efficiency of ruling out heart failure using serum B type natriuretic peptide measurement has already been demonstrated.<sup>2</sup>

In order to be routinely used, diagnostic tests must be evidence-based. In assessing the value of urinary measurement it is necessary to consider if the test meets the criteria of being APT: analytically (A) suitable; plausible (P) biologically and clinically; and having a treatment (T) impact.

There are a number of analytical factors to be taken into consideration if NTproBNP is to be measured in urine. Current commercial assays for NTproBNP are optimized for use in serum or

plasma. They are not currently licensed for measurement of urine. To date there has only been one analytical evaluation of the suitability of urine for measurement.<sup>3</sup> The study found that NTproBNP was stable in urine for up to 48 h at room temperature. However, when urine samples had a known amount of NTproBNP spiked in, the recovery of the added NTproBNP was low and varied from 16%-55%. This questions the analytical validity of urinary measurements. Recovery of the spiked NTproBNP should have been close to 100% and should have been consistent. A range of factors influences the collection of urine samples, and the composition of urine varies markedly from individual to individual. Variation in urine concentration can be compensated for by additional measurement of urine creatinine. The need for an additional measurement adds further complexity to the relative simplicity of urine testing.

The biological plausibility of NTproBNP measurement in urine requires knowledge of how NTproBNP is handled by the kidney. There has been a degree of controversy on the mechanism of clearance and degradation of NTproBNP and the impact of renal function on the validity of NTproBNP measurements in patients with renal dysfunction. This controversy has predominantly concerned itself with a claimed advantage of BNP measurement over NTproBNP measurement in patients with renal dysfunction. A side effect has been some clarification of understanding of the mechanisms of clearance. A series of catheterization studies examined the renal extraction of both BNP and NTproBNP. Comparing renal extraction of BNP and NTproBNP in healthy volunteers undergoing exercise, it was demonstrated that although there was an arteriovenous difference for both, the values were comparable. Renal extraction of BNP and NTproBNP accounted for only 15% to 20% of the total removed.<sup>4</sup> Previous studies of patients referred for cardiac catheterisation have demonstrated comparable values. In a selective catheterization study of patients with hypertension or cirrhosis, extraction of BNP and NTproBNP was compared across the renal vascular bed and the lower body peripheral vascular bed. This study showed that there was comparable extraction of BNP (16%) and NTproBNP (16%) across the renal vascular bed, but significant extraction of BNP (12.5%) in the lower body peripheral vascular bed with no extraction of NTproBNP.<sup>5</sup> A study of 165 hypertensive patients undergoing catheterization for suspected renal artery stenosis examined renal clearance of BNP and NTproBNP and also assessed

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estimated glomerular filtration rate (eGFR). The authors were able to demonstrate that clearance of both peptides was similar, was equally affected by eGFR, and behaved as would be expected for small peptides.<sup>6</sup> When urinary NTproBNP measurements are compared with serum values there appears to be a threshold effect at an NTproBNP value of approximately 846 ng/L (100 pmol/L). However, the relationship between urinary NTproBNP and renal function appears to be complicated.<sup>3</sup> Impairment of renal function may reduce clearance but may also result in reduced intra-renal catabolism or resorption. The implication from the current evidence is that urinary NTproBNP will be affected by renal function but not in a predictable fashion. In contrast, the evidence is that NTproBNP remains diagnostically useful in patients with chronic kidney disease.<sup>7</sup> When patients with end-stage renal disease are examined by cardiac imaging, it is the evidence of diffuse myocardial injury that predicts elevation of NTproBNP and an adverse prognosis.<sup>8</sup>

The clinical plausibility of urinary NTproBNP measurement will depend on the diagnostic efficiency for confirmation and exclusion of heart failure. There are two clinical scenarios to be considered: exclusion of heart failure in ambulant patients and the confirmation or exclusion of acute heart failure in patients presenting to the emergency department with dyspnea.

The only clinical study that has examined urinary NTproBNP measurement for the diagnosis of chronic heart failure in the community did not use the current commercially available assay.<sup>9</sup> The study examined diagnostic performance by receiver operating characteristic (ROC) curve analysis and compared the area under the curve (AUC). The AUCs for urinary and plasma N-BNP were reported as 0.831 and 0.840, respectively. In this study, the disease prevalence was low although the total sample size was reasonable (28 cases, n = 1308).

There have been four studies that examined the non-community population. One used a non-commercial assay and compared 34 acute hospitalized heart failure patients with 82 controls for a final diagnosis of acute heart failure.<sup>10</sup> The AUC was 0.93 for urinary NTproBNP measurement and 0.96 for plasma NTproBNP. The three that utilized the current commercially available assay have examined slightly different populations. Two have assessed diagnostic performance. Both used a final diagnosis of heart failure incorporating echocardiography for the assessment of cardiac function, but neither study separated systolic from diastolic dysfunction. One study showed diagnostic equivalence, with AUCs of 0.96 for urinary NTproBNP and 0.98 for plasma NTproBNP measurement, but had a high disease prevalence (96 cases, n = 116).<sup>11</sup> An elevated urinary NTproBNP was associated with an adverse prognosis, although serum NTproBNP measurements performed slightly better than urinary measurements (0.80 vs 0.75, serum vs urine). The population is reported as consecutive patients with heart failure but it is not stated if these were ambulant outpatients or hospital admissions. The second study reported a significantly worse AUC for urinary NTproBNP measurement of 0.72, compared to 0.94 for serum measurement (47 cases, n = 123).<sup>3</sup> The population studied is reported as patients hospitalized for heart failure. There are several differences between the two studies. First, the populations do not appear to be similar in terms of the severity of heart failure. The study showing diagnostic equivalence<sup>11</sup> had the majority of patients in New York Heart Association (NYHA) heart failure class I or II (which suggests they may have been ambulant clinic patients); the second study<sup>3</sup> examined patients with NYHA heart failure class III and IV. Second, one study used frozen samples, which were subsequently thawed then spun prior to analysis, whereas the study reporting lower accuracy used fresh samples. The frozen, thawed, and spun samples may have had less analytical interference.

The third study utilizing the commercially available assay examined 138 patients admitted with acute decompensated heart failure. The article, published in *Revista Española de Cardiología*, compared the ability of plasma and urinary NTproBNP measurement to predict an adverse prognosis instead of comparing diagnostic accuracy.<sup>12</sup> The authors found that plasma but not urinary NTproBNP predicted an adverse prognosis (death or heart failure re-admission) even when patients were subdivided according to eGFR (above or below 60) or left ventricular ejection fraction (above or below 45%). This was in contrast to their previous findings in a less severely ill population.<sup>11</sup>

Treatment of patients with heart failure is well defined, with a range of therapies which produced both symptomatic and prognostic improvement. The measurement of serum or plasma NTproBNP for diagnosis is well established<sup>13,14</sup> and there is evidence that these measurements may be valuable in guiding therapy.<sup>15</sup> The value of urinary measurements appears to be more limited. From the evidence to date, they may have diagnostic value in community screening but appear to be much less efficient in patients with increasing severity of heart failure and in acute heart failure. Unfortunately, patients in the community may have severe but unrecognized heart failure. In addition, urine measurements appear to be more prone to interference from renal dysfunction. They also suffer from the problem of the variability of urine concentration. Such variation can be allowed for by simultaneous creatinine measurement. Correction of urinary NTproBNP for creatinine improved diagnostic efficiency, but not enough to make urinary NTproBNP of equivalent diagnostic performance to serum measurement.<sup>3</sup> Correction for urine creatinine did not improve prognostic efficiency of urinary NTproBNP measurement.<sup>12</sup>

Finally, in the patient presenting with suspected heart failure to either the primary care physician or hospital practitioner, assessment includes more than NTproBNP measurement alone. There is usually a need to assess renal function as well as other organ systems. Urinary measurement is insufficient for this.

In conclusion, urinary NTproBNP measurement would appear to be suitable for community screening rather than as a mainstream diagnostic test. Urinary NTproBNP measurement will therefore have diagnostic application if community screening of patients for heart failure is shown to be valuable, if there is a validated urinary NTproBNP measurement method, and if large-scale prospective studies confirm the diagnostic accuracy of urinary NTproBNP measurement for this purpose. That is a lot of ifs.

## CONFLICTS OF INTEREST

None declared.

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