

NT-proBNP: a biomarker with new potential application

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In many clinical situations, the measurement of biochemical markers can be potentially used for diagnosis, risk assessment, prognosis, or therapeutic monitoring of the patient. A biomarker is a parameter that is objectively measured and may be regarded as an indicator of normal or pathological biological processes. B-type natriuretic peptide (BNP, a biologically active form) and N-terminal pro-BNP (NT-proBNP, a biologically inert form) are synthesized and released from the ventricular myocardium in the setting of volume or pressure overload. BNP and NT-proBNP are secreted at a ratio of 1:1 but NT-proBNP has a longer half-life than BNP (90–120 minutes vs 20 minutes). In addition, it shows better analytical characteristics, lower in-vivo and in-vitro degradation, higher circulating concentrations, lower biological variability, and can be measured in EDTA or heparinized plasma and serum.

The cleavage of proBNP to form BNP and NT-proBNP is no longer considered a simple process. It is now known that multiple glycosylated and proteolytically cleaved forms of natriuretic peptides are present in the circulation of healthy and ill individuals. O-linked glycosylation at multiple amino acid residues within the N-terminal and central portions of proBNP gives different glycosylated forms of NT-proBNP. Commercially available NT-proBNP immunoassays show little cross-reactivity with glycosylated proBNP but notable cross-reactivity with deglycosylated proBNP. Thus, NT-proBNP assays measure only a small fraction of the circulating NT-proBNP in most patients.¹ The measurement of a single natriuretic peptide may not be sufficient to fully understand the diagnostic and prognostic value of these biomarkers in a broad array of patients with varying degrees of acute and chronic heart failure.

BNP has a cardioprotective effect, improving myocardial relaxation and counteracting vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin–aldosterone system.² Both BNP and NT-proBNP have

been identified as good markers of myocardial hemodynamic stress, and their clinical utility is well established. BNP and NT-proBNP are clinically validated and significantly improve diagnostic accuracy for heart failure and provide prognostic information for risk stratification. The greatest diagnostic utility provided by the measurement of BNP is high accuracy in excluding the diagnosis of heart failure in a patient presenting with dyspnea (clinical sensitivity and negative predictive value for BNP and NT-proBNP is higher than 90%, but correction for age, sex, and body mass index is necessary for cutoff). However, they are not useful for a differential diagnosis of heart failure due to their relatively low specificity. The use of either BNP or NT-proBNP to diagnose decompensated heart failure in dyspnea patients with concomitant moderate renal disease (estimated glomerular filtration rate, 30–59 mL/min/1.73 m²) is generally clinically accepted.

NT-proBNP is a biomarker that results in the most added prognostic value on top of traditional risk factors for cardiovascular and all-cause mortality in incident hemodialysis (HD) patients.³ Serum NT-proBNP concentrations are elevated in nearly all HD patients in comparison with the general population, and the concentration depends on the time of measurement (before and after an HD session). The extent of this increase is associated with cardiovascular morbidity and mortality. Plasma NT-proBNP levels are elevated in approximately 100% of asymptomatic patients on chronic HD. This increase is caused by a high prevalence of structural and functional abnormalities in the left ventricle in dialysis patients.^{4,5}

The measurement of NT-proBNP levels in patients with end-stage renal disease (ESRD) receiving HD or peritoneal dialysis is clinically important as this marker has a significant prognostic value. There have been numerous studies showing the role of NT-proBNP in predicting all-cause and cardiovascular death independent of

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left ventricular mass and ejection fraction in HD patients without a history of heart failure and in peritoneal dialysis patients.^{5,6} It was shown that patients with NT-proBNP in the highest quartile had the highest risk of mortality and sudden cardiac death.⁷ Increased NT-proBNP levels together with cardiac troponin T are strongly associated with an adverse outcome in ESRD patients undergoing HD, and are useful tools for risk stratification in patients on chronic HD.⁸

Although circulating NT-proBNP levels may decline after dialysis, both pre- and postdialysis NT-proBNP levels remain a significant predictor of mortality independent of left ventricular mass and ejection fraction.⁹ HD patients often have asymptomatic coronary artery disease and left ventricular or diastolic dysfunction.¹⁰ Cardiac tissue remodeling is induced not only by ischemia but also by hypervolemia.

Schwermer et al.¹¹ in the current issue of *Pol Arch Med Wewn* investigated the usefulness of NT-proBNP as a hydration marker in HD patients along with its relation to nutritional status and prognosis. The authors emphasized the high mortality rate in HD patients due to excessive cardiovascular disease burden from coronary artery disease, left ventricular hypertrophy, and heart failure. It is well known that cardiac biomarkers are significant predictors of cardiovascular and all-cause mortality in ESRD patients.

The assessment of overhydration status is very important in patients on HD because adequate body hydration reduces hypertension and the risk for cardiovascular complications and death.¹² The estimation of body fluids using bioimpedance measurements is based on an inverse relation between body resistance and the total amount of body water and is increasingly common in clinical practice. With respect to a detailed assessment of body composition and nutritional status, an improvement in bioimpedance technique is needed. Nowadays, NT-proBNP is more frequently measured in dialysis patients; therefore, the idea of using this marker as an independent marker of hydration is very tempting. It has been already suggested that NT-proBNP may reflect hydration status in dialysis patients⁸ as serum NT-proBNP levels depend on changes in fluid distribution.⁵ More precisely, the serum level of NT-proBNP represents a combination of left ventricular hypertrophy, systolic dysfunction, and volume overload.⁵ Nongnuch et al.¹³ found a significant correlation between NT-proBNP levels and biochemical and clinical overhydration-related parameters, but this was not confirmed by Paniagua et al.¹⁴ A detailed study by Schwermer et al.¹¹ showed that NT-proBNP seems to be a valid biomarker of hypervolemia. The authors suggested the measurement of this marker for the assessment of hydration in HD units without access to bioimpedance methods or other objective techniques of assessing hydration status.

Laboratory measurements in chronic kidney disease-related disorders are very difficult to

interpret because they are multifactorial, and the serum matrix is frequently unpredictable. The interpretation of NT-proBNP must take into account intra- and interindividual variations both in healthy subjects and in those with stable chronic heart failure, as well as age (increase with age), sex (higher levels in women than in men), and body mass index (increase with body mass).

NT-proBNP holds promise for future diagnostic procedures in the dialysis population not only because of the early identification of patients at risk for cardiovascular complications and mortality but also because of the assessment of their overhydration status. The lack of a single set of "normal values" due to different clinical conditions leads to confusion in clinical application. Natriuretic peptides should not be used on their own but in addition to a medical history, physical examination, and other laboratory tests. As always, apart from perfect technology and sophisticated laboratory measurements, a careful clinical examination is strongly recommended.

REFERENCES

- 1 Seferian KR, Tamm NN, Semenov AG, et al. Immunodetection of glycosylated NT-proBNP circulating in human blood. *Clin Chem*. 2008; 54: 866-873.
- 2 Braunwald E. Biomarkers in heart failure. *N Engl J Med*. 2008; 358: 2148-2159.
- 3 Oh HJ, Lee MJ, Lee HS, et al. NT-proBNP: is it a more significant risk factor for mortality than troponin T in incident hemodialysis patients? *Medicine (Baltimore)*. 2014; 93: e241.
- 4 Satyan S, Light RP, Agarwal R. Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. *Am J Kidney Dis*. 2007; 50: 1009-1019.
- 5 Wang AY, Lam CW, Yu CM, et al. N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. *J Am Soc Nephrol*. 2007; 18: 321-330.
- 6 Zoccali C, Mallamaci, Benedetto FA P, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol*. 2001; 12: 1508-1515.
- 7 Winkler K, Wanner C, Drechsler C, et al. Change in N-terminal-pro-B-type-natriuretic-peptide and the risk of sudden death, stroke, myocardial infarction, and all-cause mortality in diabetic dialysis patients. *Eur Heart J*. 2008; 29: 2092-2099.
- 8 Sommerer C, Beimler J, Schwenger V, et al. Cardiac biomarkers and survival in haemodialysis patients. *Eur J Clin Invest*. 2007; 37: 350-356.
- 9 Madsen LH, Ladefoged S, Corell P, et al. N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int*. 2007; 71: 548-554.
- 10 Sommerer C, Hecke S, Schwenger V, et al. M. Cardiac biomarkers are influenced by dialysis characteristics. *Clin Nephrol*. 2007; 68: 392-400.
- 11 Schwermer K, Hoppe K, Radziszewska D, et al. N-terminal pro-brain natriuretic peptide is a valid marker of hypervolemia and a predictor of increased mortality in patients undergoing hemodialysis. *Pol Arch Med Wewn*. 2015; 125: 560-569.
- 12 Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant*. 2009; 24: 1574-1579.
- 13 Nongnuch A, Panorchan K, Davenport A. Predialysis NTproBNP predicts magnitude of extracellular volume overload in haemodialysis patients. *Am J Nephrol*. 2014; 40: 251-257.
- 14 Paniagua R, Ventura MD, Avila-Diaz M, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant*. 2010; 25: 551-557.