

In search for a biochemical marker of overhydration in hemodialysis: the “magic bullet” yet to be found

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Hemodialysis (HD), a life-saving treatment for patients with end-stage renal disease (ESRD) who are not suitable for kidney transplantation or before they receive a transplant is characterized by several limitations that are not easy to overcome. The intermittent nature of the procedure (performed routinely every second or third day) exposes patients to “sinusoidal” fluctuations in solute concentrations and volume status. Patients that accumulate fluid over 48 to 72 hours must then become dehydrated within 4 hours on average to recover their “dry weight” (ie, optimal body weight without signs of overhydration). Thus fluid overload is experienced virtually by all patients prior to HD, but a large proportion of patients remain chronically overhydrated (ie, after dialysis and in the interdialytic period).

Overhydration in HD has been identified as one of the key risk factors leading to increased morbidity and mortality because it results, among others, in poor control of hypertension and left ventricular hypertrophy.¹⁻³ Therefore, defining “dry weight” and then identifying the degree of fluid overload before the procedure are important tasks in HD units. These crucial parameters are also quite challenging since simple clinical assessment of the hydration status does not adequately identify overhydration. Many indirect measures were developed for this purpose, including several bioimpedance-based techniques, assessment of an inferior vena cava diameter using an ultrasound, and more recently, the measurement and quantification of lung comets (using a chest ultrasound).^{4,5} It would be tempting to find a simple, reliable, and reproducible biochemical marker that would adequately reflect the degree of overhydration in HD subjects and to ask the laboratory how much extra fluid our patients carry.⁶

The paper of Schwermer et al.,⁷ published in the current issue of the *Polish Archives of Internal Medicine*, adds an important piece of knowledge

to the field. The authors measured several parameters of hydration using a bioimpedance analysis, anthropometric measures, and a broad spectrum of biomarkers (including biochemical indices of nutrition and inflammation, cardiac biomarkers, and lipids) with the main goal to estimate the usefulness of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the assessment of the hydration status in a large group of patients with ESRD on maintenance HD. In a substantial percentage of the patients, the authors were able to repeat the NT-proBNP measurement after a mean period of 35 weeks and to describe some trends in its concentrations. They divided the study group into quartiles according to baseline NT-proBNP concentrations and into 4 groups according to trends in NT-proBNP concentrations over time (“decrease”, “increase”, “stable high”, and “stable low”). Based on the obtained results, the authors concluded that NT-proBNP can serve as a valid marker of hypervolemia and may also be used as a predictor of outcome (with the highest NT-proBNP concentration at baseline and “increase” or “stable” category during follow-up linked to the poorest prognosis).

The study is important because it employs a very careful methodology in a large group of patients. Nevertheless, the results should be interpreted with caution. We are not fully convinced that NT-pro-BNP should really be adopted as a marker of the hydration status, based on the study by Schwermer et al.⁷ They acknowledged potential limitations of their study and listed the lack of echocardiographic assessment of cardiac structure and function as its main limitation. Indeed, in studies that employed the assessment of both cardiac function and hydration status, features of diastolic left ventricular dysfunction but no signs of fluid overload were found in HD patients with higher versus those with lower NT-proBNP values.⁸

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The “nonrenal” literature in the field emphasizes high sensitivity but low specificity of NT-proBNP in detecting heart failure (HF).⁹ Even in patients with apparently normal kidney function, this marker is influenced by several other factors than HF; it can be assumed that such a specificity is even lower for discrimination of any particular pathology (including HF or overhydration) in HD patients, who are characterized by much more confounding abnormalities (especially when the intermittent nature of HD treatment is taken into account). Factors listed as possible modifiers of NT-proBNP, except for systolic and diastolic HF, include valvular heart disease, left ventricular hypertrophy, coronary artery disease, toxic damage of the myocardium, pericardiac disease, but also anemia, hypertension, hyperaldosteronism, exposure to chemotherapy, chronic obstructive pulmonary disease, or hydrothorax. NT-proBNP levels are elevated in patients who suffer from micro- and macrovascular complications of diabetes, as compared to uncomplicated diabetes.^{10,11} As demonstrated by Bednarek-Skublewska et al.,¹² even the vitamin D status of HD patients may influence NT-proBNP levels (although with borderline statistical significance). A marathon run, which involves profound dehydration, is associated with a significant increase in NT-proBNP concentrations—this fact best illustrates uncoupling between hydration status and NT-proBNP concentrations in healthy individuals.¹³

The correlations between cardiac troponin T (cTnT), dialysis vintage, and NT-proBNP in the study by Schwermer et al.⁷ also suggest that factors other than the hydration status might affect NT-proBNP levels. cTnT was correlated with hydration status parameters in almost the same way as NT-proBNP; however, cTnT is not considered a hydration status parameter but an indicator of myocardial damage. Lower serum albumin levels in higher NT-proBNP quartiles might result from a dilution effect, but may also reflect a better nutritional and overall clinical status of study subjects (similarly to hemoglobin levels).

The authors cited several studies on the usefulness of NT-proBNP in assessing the hydration status. However, there are also contradictory data. For example, in a study by Onofriescu et al.,¹⁴ different patterns of ultrafiltration applied during dialysis did not result in any significant changes in body fluids but resulted in a significant decrease in NT-proBNP levels. In a study comparing different techniques of fluid overload identification and using bioimpedance spectroscopy as a reference method, Voroneanu et al.¹⁵ found that the measurement of NT-proBNP levels was associated with the lowest accuracy in identifying overhydration (and led to overestimation of fluid overload in the analyzed group). Of note, in the study by Schwermer et al.,⁷ several correlations between NT-proBNP and parameters of the hydration status were reported but with no conclusions as to the prevalence and degree of overhydration in this patient group (how much

“extra” liters or percentage of body weight above dry weight left after HD, ie, after completion of ultrafiltration). As mentioned before, most if not all of HD patients have fluid overload before dialysis; therefore, the identification of hypervolemia should rather be performed after HD.

In summary, we agree with Schwermer et al.⁷ that NT-proBNP is an important marker that should be measured in HD patients. However, we believe that its increasing concentrations should be considered as an indicator of a poor general status (due to multiple cardiac and noncardiac reasons, probably including chronic fluid overload) but not as a specific and reliable measure of the fluid status itself. We believe that based on the results of Schwermer et al.⁷ and those obtained by other investigators, the data are insufficient to consider NT-proBNP as superior to any other method of assessing the hydration (overhydration) status. This was admitted by authors who discussed several confounders other than the hydration status that might modify the relationship between baseline NT-proBNP levels, and even more so between trends in NT-proBNP over time, and survival. We agree with the words of caution provided by Schwermer et al.⁷ in their paper.

REFERENCES

- 1 Fischbach M, Zaloszczyk A, Shroff R. The interdialytic weight gain: a simple marker of left ventricular hypertrophy in children on chronic haemodialysis. *Pediatr Nephrol*. 2015; 30: 859-863.
- 2 de Araujo Antunes A, Vannini FD, de Arruda Silveira LV, et al. Associations between bioelectrical impedance parameters and cardiovascular events in chronic dialysis patients. *Int Urol Nephrol*. 2013; 45: 1397-1403.
- 3 Raimann J, Liu L, Ullao D, et al. Consequences of overhydration and the need for dry weight assessment. *Contrib Nephrol*. 2008; 161: 99-107.
- 4 Basso F, Milan Manani S, Cruz DN, et al. Comparison and reproducibility of techniques for fluid status assessment in chronic hemodialysis patients. *Cardiorenal Med*. 2013; 3: 104-112.
- 5 Siritopol D, Hogas S, Voroneanu L, et al. Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters. *Nephrol Dial Transplant*. 2013; 28: 2851-2859.
- 6 Stompór TP. Can we ask the lab how much extra fluid patients carry? *Nephron Clin Pract*. 2004; 97: 123-124.
- 7 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.
- 8 Kamano C, Osawa H, Hashimoto K, et al. N-Terminal pro-brain natriuretic peptide as a predictor of heart failure with preserved ejection fraction in hemodialysis patients without fluid overload. *Blood Purif*. 2012; 33: 37-43.
- 9 Don-Wauchope AC, McKelvie RS. Evidence based application of BNP/NT-proBNP testing in heart failure. *Clin Biochem*. 2015; 48: 236-246.
- 10 Hamano K, Nakadaira I, Suzuki J, Gonai M. N-terminal fragment of pro-brain natriuretic peptide is associated with diabetes microvascular complications in type 2 diabetes. *Vasc Health Risk Manag*. 2014; 10: 585-589.
- 11 Christenson ES, James T, Agrawal V, Park BH. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. *Clin Biochem*. 2015; 48: 223-235.
- 12 Bednarek-Skublewska A, Smoleń A, Jaroszyński A, et al. Effects of vitamin D3 on selected biochemical parameters of nutritional status, inflammation, and cardiovascular disease in patients undergoing long-term hemodialysis. *Pol Arch Med Wewn*. 2010; 120: 167-174.
- 13 Hewing B, Schattke S, Spethmann S, et al. Cardiac and renal function in a large cohort of amateur marathon runners. *Cardiovasc Ultrasound*. 2015; 13: 13.
- 14 Onofriescu M, Mardare NG, Segall L, et al. Randomized trial of bioelectrical impedance analysis versus clinical criteria for guiding ultrafiltration in hemodialysis patients: effects on blood pressure, hydration status, and arterial stiffness. *Int Urol Nephrol*. 2012; 44: 583-591.
- 15 Voroneanu L, Cusai C, Hogas S, et al. The relationship between chronic volume overload and elevated blood pressure in hemodialysis patients: use of bioimpedance provides a different perspective from echocardiography and biomarker methodologies. *Int Urol Nephrol*. 2010; 42: 789-797.