EDITORIAL

Urinary pH assessment in patients with acute heart failure and resistance to diuretics: a step forward to a precision medicine approach in the treatment of acute heart failure

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If you know neither the enemy nor yourself, you will succumb in every battle.

Sun Tzu, *The Art of War*

In a 21st century haunted by global diseases, one of the biggest pandemics cardiologists are fighting against is represented by heart failure (HF).[1] Among the few treatments available for acute decompensation phases, diuretics are the mainstays for addressing congestion and improve symptoms.[2,3] Even if their use has not been shown to significantly impact outcomes, patients who show diuretic resistance (DR), in terms of reduced diuretic response, will experience poor prognosis.[4] Precociously identifying patients with DR to apply a more aggressive treatment may help to improve outcomes.[5] Several markers and predictors of DR have been proposed for that purpose: among all, early spot urinary sodium expresses the very effect of diuretics and predicts the subsequent urinary response, worsening HF, and mortality.[5-8]

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Imiela et al[9] focus on the role of urinary pH (UpH) in this puzzling context of acute HF. In a retrospective analysis of 373 admissions for congestive HF and EF of less than 50%, patients with UpH of less than 6 experienced higher rates of in-hospital mortality, although not significant at the multivariate analysis, and of the composite end point of death, acute myocardial infarction, stroke, revascularization, and use of catecholamines. The authors also built a ROC curve to identify a cutoff value for DR (defined as ml urine/40 mg furosemide) which best predicted in-hospital death in their population; hence, they show that low UpH was related to DR. They concluded that acidic urine might be a risk factor for poor in-hospital outcomes and DR in acute HF.

The process of urine acidification is complex and depends on active H^+ excretion, HCO_3^- reabsorption and production on proximal and distal convoluted tubules and collector ducts, in which a central role is played by carbonic anhydrase. Final UpH is also influenced by the phosphates and ammonia buffer systems.

The rationale of using UpH for determining prognosis in HF first relies on the observation that acidic urine is prevalent in patients with chronic kidney disease, in part as a consequence of metabolic acidosis, and increases with its progression.[10] The close interplay between heart, kidney and the acid-base system, expressed for example by the role of the renin-angiotensin-aldosterone system on increasing the H^+ excretion, the potential cytotoxic effect of acidosis on cardiac cells, and the consequences of a reduced cardiac performance on renal function, has then been the basis for a work by Otaki et al[11] in 2013. This group first described, in a population of patients with chronic HF, that a UpH of less than 5.5 correlated with the composite end point of cardiac death and progressive HF requiring hospitalization in a 556-day median follow-up.

Based on these results, Imiela et al[9] explored the potential role of UpH in the acute setting and extended its application on the prediction of DR, although the reason why low UpH should predict DR remains speculative. Urinary acidosis may reflect acidemia, which can depolarize the membrane potential of the proximal tubule, impairing diuretics secretion.[5] Conversely, another explanation may rely on the urinary acidifying effect of loop diuretics, and patients needing higher

doses at home (therefore predisposed to DR) may present with lower UpH. In the study, there was no difference in terms of home loop diuretic use among the subgroups, but posology was not reported. Interestingly, the authors suggest that acetazolamide may represent a potential therapeutic treatment in the low UpH subgroup, in the light of its chloride-sparing and urine alkalizing effects.[12] A randomized controlled trial is currently ongoing to confirm the important decongestive role of acetazolamide as an add-on therapy,[13] but we agree that a specific indication for low UpH needs to be confirmed by evidence-based data.

The study proposed a simple and rapid criterion to identify a high-risk subgroup of patients with acute HF. The advantages of UpH also reside in the worldwide availability and the low cost of this test. While congratulating the authors for their work, several limitations need to be acknowledged, as already partially reported in the paper. First of all, the values of UpH, especially with dipstick tests, are extremely variable, as they are influenced by diet, water intake, altitude, comorbidities such as cancer and diabetes, pharmacologic treatments and infections. In particular, the cutoff of 6 is still in the range of normality and it is not clear why it was chosen for this study. Although loop diuretic efficiency was confirmed as a robust prognostic predictor, the difference in mean UpH values among the DR group and the non-DR group was remarkably small (5.8 vs 6). Moreover, lower UpH may reflect the higher prevalence of pneumonia with higher C-reactive protein and white blood cell count, and likely respiratory acidosis, in the group with worse outcome. Surely, a complete acid-base profile would help in understanding the role of urinary acidosis in HF patients, and a blood-gas test needs to be performed in similar studies in the future.

However, the novel idea of applying UpH in acute HF should be applauded. Considering the paucity of effective treatments for acute HF and the difficulty in predicting in-hospital courses of apparently stable patients, each tool for a better prognostic stratification can be useful. In practice, to improve the chances of success against an enemy, especially if we hold few weapons, it is crucial to know him. HF specialists should actually obtain a thorough picture of the patient's condition to optimize its management and anticipate and identify all conditions that may complicate the in-hospital course. It is now time for a precision medicine approach even in acute HF. The pivotal role of an individualized treatment finds its maximal expression in the latest European Society of Cardiology HF guidelines[1] that, for the first time, recommend to evaluate spot urinary sodium to tailor the best diuretic therapy based on patients' response.

Although further studies are needed to investigate the role of UpH in acute HF, the reported data provide a new potential metric of DR that may help the clinician to balance the labile alchemy between the need for reducing congestion, ensuring perfusion, and preserving renal function.

ARTICLE INFORMATION

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REFERENCES

1 McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27. [Epub ahead of print].

2 Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017; 377: 1964-1975.

3 Frea S, Pidello S, Volpe A, et al. Diuretic treatment in high-risk acute decompensation of advanced chronic heart failure – bolus intermittent vs. continuous infusion of furosemide: a randomized controlled trial. Clin Res Cardiol. 2020; 109: 417-425.

4 Mullens W, Damman K, Harjola V-P, et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21: 137-155.

5 Gupta R, Testani J, Collins S. Diuretic resistance in heart failure. Curr Heart Fail Rep. 2019; 16: 57-66.

6 Galluzzo A, Frea S, Boretto P, et al. Spot urinary sodium in acute decompensation of advanced heart failure and dilutional hyponatremia: insights from DRAIN trial. Clin Res Cardiol. 2020; 109: 1251-1259.

7 Galluzzo A, Bertaina M, Frea S. Urinary sodium evaluation: the missing target for diuretic treatment optimization in acute heart failure patients? Letter regarding the article 'Clinical importance of urinary sodium excretion in acute heart failure.' Eur J Heart Fail. 2020; 22: 1933.

8 Biegus J, Zymliński R, Testani J, et al. Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients. Eur J Heart Fail. 2021; 23: 729-739.

9 Imiela T, Imiela AM, Karczmarewicz G, Budaj A. Acidic urine as a novel risk factor for diuretic resistance and worse in-hospital prognosis in patients with acute heart failure. Polish Arch Intern Med. 2021; 131: 16054.

10 Nakanishi N, Fukui M, Tanaka M, et al. Low urine pH Is a predictor of chronic kidney disease. Kidney Blood Press Res. 2012; 35: 77-81.

11 Otaki Y, Watanabe T, Takahashi H, et al. Acidic urine is associated with poor prognosis in patients with chronic heart failure. Heart Vessels. 2013; 28: 735-741.

12 Kassamali R, Sica DA. Acetazolamide: a forgotten diuretic agent. Cardiol Rev. 2011; 19: 276-278.

13 Mullens W, Verbrugge FH, Nijst P, et al. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. Eur J Heart Fail. 2018; 20: 1591-1600.