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EDITORIAL

Bedside Prognostication in Decompensated Heart Failure: No "Easy Button"

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Tailoring the management of heart failure to hemodynamics remains a perpetual challenge for the clinician. Although improved understanding of neurohormonal factors in hemodynamic regulation has led to the wider use of renin-angiotensin-aldosterone system blockers, β blockers, and vasodilators in acute decompensated heart failure (ADHF), diuretics remain the mainstay of treatment.[1] Diuresis and natriuresis counter fluid overload,[2] leading to decreased pulmonary capillary wedge pressure as well as central venous pressure; they relieve pulmonary congestion, and their effects on preload and afterload reduction result in improved hemodynamics. However these effects can also lower the cardiac output (by as much as 20%) and increase neurohormonal activation.[3] ADHF can be perceived as a state of prerenal azotemia signaling reduced perfusion to the kidney and other organs. Although the goal of diuretic therapy is effective decongestion, a delicate balance is needed to sustain renal (and other organ) perfusion in the face of declining intravascular volume. The process of managing ADHF with diuretics is a constant dance to find the sweet spot on the Frank-Starling curve where increased left ventricular end-diastolic pressure still leads to maintenance of, or a mild decrease in, cardiac output; normalization of stroke volume is not a realistic goal in the failing heart.[4,5]

See Article by Nogi et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Nogi and colleagues[6] propose a new classification that combines the assessment of renal perfusion and volume status to prognosticate ADHF outcomes.[6] They use the fractional excretion of urea nitrogen (FEUN) and estimated plasma volume status (ePVS) in combination to create 4 categories that can be intuitive for the clinician with regard to risk profiling. The FEUN has long been a clinical tool in the differential diagnosis of acute kidney injury, with a threshold of <35% being used to differentiate prerenal azotemia from intrinsic renal failure. It is believed to be more reliable than the fractional excretion of sodium in the setting of diuretic use.[7] It has found application in type 1 cardiorenal syndrome as a prognostic indicator of renal function recovery as well as overall survival.[8] Indeed, the present authors showed in a previous publication that low FEUN in this cohort of patients with ADHF was associated with a nearly 50% increase in postdischarge all-cause death, independently of other heart failure risk factors.[9] Compromised renal perfusion in the setting of ADHF can lead to poor outcomes, but clinicians are often faced with the conundrum that diuretics have either caused excessive intravascular volume depletion or failed to maintain the higher filling pressures required to preserve cardiac output as Frank-Starling reserve is lost.[10] Nogi et al apply this rationale to combine the FEUN, as an index of organ perfusion, with the ePVS as an index of circulating plasma volume, a threshold of >5.5 mL/g signifying congestion

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in patients with ADHF. Kobayashi et al found that the ePVS at discharge was independently associated with postdischarge clinical outcomes and improved the risk stratification of patients admitted for ADHF in 3 independent cohorts.[11] The ePVS is derived from hematocrit and hemoglobin values, a concept similar to intravascular volume monitoring in other familiar settings, such as ultrafiltration on hemodialysis.[12] The idea of combining 2 indexes that noninvasively assess hemodynamics and that have individually demonstrated prognostic significance in ADHF is a logical evolution and has merit.

Nogi et al[6] combine the FEUN and the ePVS and define 4 hemodynamic categories in their sizable cohort of 466 patients with ADHF. Predictably, class I with high FEUN and low ePVS has the best prognosis, and class IV with low FEUN and high ePVS has the worst prognosis. Interestingly, serum creatinine and cystatin C, tracked with ePVS, were higher in those having more circulatory congestion; other pertinent laboratory variables, such as hematocrit, hemoglobin, and serum albumin, tracked inversely with ePVS, and were lower in patients with higher ePVS; blood urea nitrogen and blood urea nitrogen/creatinine ratio, on the other hand, tracked inversely with and were higher in the patients with low FEUN who had low renal perfusion. Both renin-angiotensin-aldosterone system blocker and loop diuretic use was higher in the high ePVS category, which as a group also consisted of significantly older patients. Notably, class IV had nearly twice the proportion of patients with diabetes as class I. Stroke volume, cardiac output, and cardiac index, measured by echocardiography, were better preserved in the low ePVS categories. Over a median follow-up period of 28.1 months, there were 173 all-cause deaths (37.1%), 83 cardiovascular deaths (17.8%), and 121 heart failure readmissions (26.0%). Class IV demonstrated 4 times the mortality as class I, and the addition of ePVS to FEUN clearly improved risk stratification and discrimination compared with FEUN alone, shown in the authors' previous publication.[9] However, the separation of the categories for all the specified outcomes was driven by ePVS category. These outcome differences are in agreement with the patterns of the laboratory variables and echocardiographic data highlighted above.

How can we interpret the findings of this study in the context of clinical practice and care of the patient with heart failure? First, although the indexes proposed by the authors are rooted in physiology, ADHF is a complex disorder and reducing the hemodynamics to 2 derived indexes could place us in danger of oversimplification. Would these indexes affect therapeutic decision making, or are they just markers of disease severity? Although a low FEUN potentially reflects poor renal perfusion, it may not be synonymous with worsening renal function, raising the question of what may be the best way to evaluate kidney function through the heart failure trajectory.[13] Similarly, does a higher ePVS reflect more scope for diuresis or resistance to diuresis[14]? Second, which are the patients we could generalize these findings to? The authors gracefully acknowledge that there could be biases related to the study sample originating from a single center, with >50% of patients excluded for lack of urinary urea nitrogen measurements. However, we see that the findings were applicable across a range of cardiac hemodynamic profiles and ejection fractions at the time the index assessments were performed, after patients were stabilized from their immediate presentation. On the other hand, the classification provided better discrimination in patients with baseline chronic kidney disease with estimated glomerular filtration rate <60 mL/min, seen in three-quarters of the patients, than in those with normal kidney function. Urinary urea nitrogen is increased in the presence of intrinsic kidney disease[7] and, conceivably, renal hypoperfusion will have to be severe enough before FEUN declines. Moreover, the type of baseline cardiorenal physiology in this setting could incorporate features of type 1, 2, and 4 cardiorenal syndrome[15]; the level of renal dysfunction would independently contribute to salt and water retention, and the determining factor for survival could well be the adequacy of decongestion. It is unclear how robustly these findings would extend for patients with normal kidney function. Third, the study is framed as a prospective cohort study, showing a prognostic association between the combined index and mortality and other outcomes. Validating the classification with hemodynamic measurements from right-sided heart catheterization as a gold standard in a diagnostic test framework would be a valuable exercise.

These considerations and the results of the study tell us that decongestive therapy continues to have overriding importance[16,17]; they also imply that FEUN may be an imperfect marker of renal outcome. Despite a reduction in cardiac index and, therefore, renal perfusion from diuretic therapy, neurohormonal and autoregulatory adaptations can maintain the glomerular filtration rate by increasing the filtration fraction.[18] Observations from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, where pulmonary artery catheterization data were collected in 433 patients with ADHF, found no relationship between reduced cardiac index and renal dysfunction after discharge.[18] Another, perhaps underrecognized cause for reduction in glomerular filtration rate and sodium retention in patients with heart failure and elevated central venous pressures or tricuspid regurgitation is increased renal venous pressure and congestion.[19,20] Thus, small to moderate deteriorations in renal function, often encountered with aggressive diuresis, do not

signify tubular injury and should not direct dosing, as shown in the ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial.[21] These hemodynamic alterations also form the basis of diuretic resistance, which is common in heart failure,[14] and may be overcome by strategies such as additional nephron blockade with different diuretic classes[1] (thiazide or thiazide-like drugs or acetazolamide[22]).

Although invasive hemodynamics can yield gold standard information on filling pressures and cardiac output, bedside clinical examination for volume status and peripheral perfusion remains the daily bread and butter for the practicing clinician. The Nohria-Stevens clinical classification of ADHF is one such example, based on the adequacy of peripheral perfusion (warm versus cold) and the presence of congestion (dry versus wet); "warm and wet" is the most common profile encountered.[23] The current classification proposed by Nogi et al[6] uses simple indexes from routine laboratory testing to parallel this clinical classification and possibly improve on it. They suggest its use as appropriate for predischarge patients in whom we may want to establish a new baseline before ambulatory follow-up. Although we are constantly looking for better adjunctive tools to meaningfully improve noninvasive hemodynamic assessment in this challenging population, there is no "easy button" that will help us parse the conundrum of heart failure severity and volume status in patients with ADHF.

ARTICLE INFORMATION

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Disclosures

None.

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