Editorial

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More Efficient Sodium Removal by Ultrafiltration Compared to Diuretics in Acute Heart Failure; Underexplored and Overstated

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Abstract
Enhanced removal of sodium has often been cited as an advantage of ultrafiltration (UF) therapy over diuretic-based medical treatment in the management of acute decompensated heart failure. However, so far clinical studies have rarely evaluated the precise magnitude of sodium removal, and this assumption is largely based on the physiologic mechanisms and anecdotal observations that predate the contemporary management of heart failure. Recent data suggest that patients treated with UF experience substantial reduction in urinary sodium excretion possibly due to prolonged intravascular volume contraction. Consequently, the efficient sodium extraction through production of isotonic ultrafiltrate can be offset by urine hypotonicity. Based on the limited currently available data, it seems unlikely that the persistent benefits of UF could be solely explained by its greater efficiency in sodium removal. The design of the future studies should include frequent measurements of urine sodium to precisely compare the impact of UF and diuretics on sodium balance.

There has been a renewed interest in the use of extracorporeal ultrafiltration (UF) therapy in acute decompensated heart failure (ADHF) where congestion is the primary reason for frequent hospital admissions. Enhanced removal of sodium, the main determinant of extracellular fluid volume, has long been considered an advantage of UF over diuretics and is often used to explain the observed sustainability of its beneficial effects [1, 2]. This concept is of utmost importance as congestion is believed to be an independent risk factor for adverse outcomes, and previous studies have suggested that decongestive therapy, if not associated with sodium removal, would have limited impact on the course and outcomes of patients with heart failure [3]. Herein, the pertinent physiologic mechanisms and available clinical data are briefly explored to evaluate the often cited advantage of UF therapy in more efficient extraction of sodium.

Mechanistic Considerations

Water and Sodium Removal – UF Therapy

UF is the mechanical process of removing fluid by virtue of a semipermeable membrane that acts as a sieve. The patient's blood is passed through hollow fibers where the transmembrane pressure shifts the plasma water out into the dialysate compartment to form the ultrafiltrate. As

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the water is removed, intravascular colloid osmotic pressure gradually increases and hydrostatic pressure decreases leading to inter-compartmental fluid shifts to refill the plasma. Therefore the key underlying mechanism of excess fluid extraction from the extravascular space by UF is indeed based on continuous intravascular volume contraction. During the UF process, small solutes such as sodium will be driven across the membrane along with the water (i.e., solvent drag phenomenon). The ratio of the ultrafiltrate content of sodium to the amount retained in plasma water (i.e., the sieving coefficient) is typically less than 1 as the negatively charged proteins in plasma hinder its transmembrane movement.

Water and Sodium Removal – Loop Diuretics

The $Na^+/K^+/2Cl^-$ cotransporter in the luminal membrane of the medullary thick ascending loop of Henle is impermeable to water. Therefore, it not only contributes to medullary hypertonicity through active absorption and accumulation of sodium but also forms the diluting segment of the nephron. Free water absorption takes place downstream in the water-permeable collecting duct (concentrating segment) due to significant hypertonicity of medulla. Loop diuretics selectively block the $Na^+/K^+/2Cl^-$ cotransporter. Therefore, not only do they enhance urinary sodium excretion but also significantly disturb free water absorption by virtue of diminished medullary hypertonicity. As sodium re-absorption continues to take place after the loop of Henle in the distal tubules, the end result of loop diuretic use is disproportionately higher free water excretion than the sodium, and production of 'hypotonic urine' that typically contains less than 100 mmol/l of sodium.

Conceptual Considerations

The notion of higher mass clearance of sodium by UF therapy is based on 3 assumptions: (1) UF is associated with equivalent or greater total fluid removal than medical therapy, (2) the urinary composition of electrolytes remains predictable and constant during both methods of therapy and (3) the urine sodium concentration in patients undergoing UF is comparable to those receiving diuretics.

Most experts agree on the validity of the first assumption. Studies of UF therapy in ADHF have convincingly shown that UF is at least as efficient as pharmacologic therapy in removal of fluid [1, 2]. It is still a matter of debate as what the optimal practical tools are for evaluation of decongestion; while weight is commonly used for monitoring of the patients, substantial discrepancy exists between weight loss and fluid removal during treatment of ADHF [4]. For example, in the Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure trial, although patients in the UF group had significantly higher total and net amount of fluid removed, their weight loss was found to be similar to that of diuretics (10.7 vs. 10.3 kg at 72 h, respectively, p = 0.34) [1].

Regarding urinary sodium composition, Verbrugge et al. [5] recently showed that patients receiving intravenous (IV) diuretics for treatment of ADHF will have a drop in their urinary sodium concentration with progressive decongestion while their urine volume, corrected for diuretic dose, remains stable. Although no study to date has explicitly addressed the variability of sodium excretion in patients treated with UF, based on the aforementioned physiologic mechanisms, it is conceivable that a similar decline in urinary sodium would be experienced with progressive decongestion and correction of the underlying total body sodium excess. The mechanistic basis for UF fluid removal from the venous pool leading to interstitial decongestion is progressive intravascular volume contraction. In support of this concept, a recent study by Mentz et al. [6] showed that contrary to what was suggested by earlier studies, UF therapy is associated with even more pronounced elevation in plasma renin activity compared with diuretics, possibly due to lowered intravascular volume and decreased intracellular chloride in macula densa triggering renin release. During UF therapy, the increase in filtration fraction (i.e., the ratio of glomerular filtration rate to renal blood flow) could lead to enhanced proximal tubular sodium reabsorption. Moreover, natriuretic peptide secretion is inhibited by intravascular volume reduction further lowering urinary sodium excretion. Therefore, urine sodium is expected to significantly drop in patients undergoing UF therapy.

Revisiting Available Data

The efficacy of UF in ADHF has frequently been evaluated through its impact on fluid removal and weight change, although the precise proportion of removed fluid (urine and ultrafiltrate) or their sodium content is rarely reported. The significant urinary dilution associated with UF therapy was recently shown in a randomized controlled trial of ADHF, where the urine sodium concentration in the UF arm was found to be less than one-third of those receiving medical therapy (26 vs. 85 mmol/l, respectively, $p < 0.05$) [7]. Consequently, the 2 groups experi-

enced comparable total sodium removal (1,168 vs. 1,216 mmol, p = NS total removed sodium per patient, and 85 vs. 91 mmol/l, p = NS sodium removed per liter of fluid, for diuretics and UF, respectively). These data clearly challenge the conventional assumption about UF's ability for higher mass clearance of sodium compared to medical therapy. Since the study was designed to target a pre-determined weight loss in both groups, it could be argued that the actual sodium removal by UF would have been higher if clinical decongestion (irrespective of urine or ultrafiltrate volumes) had been set as the goal. However, if these urinary composition findings are applied to the data from the landmark cardiorenal rescue study in acute decompensated heart failure (CARRESS-HF) trial, UF does not still show a clinically pertinent advantage in sodium removal compared to medical therapy as depicted in table 1 (i.e., <100 mmol difference over 4 days) [8]. These numbers are approximate as nearly half of the patients in the pharmacologic arm of the CARRESS-HF trial received metolazone in addition to loop diuretic while some of the patients in the UF arm also received IV diuretics (potentially enhancing urinary sodium excretion in both groups).

Conflicting results had been reported in a frequently cited study by Guazzi et al. [9] from early 1990s in which urinary sodium excretion increased after UF therapy primarily due to improved urine volume (i.e., from less than 1 liter to over 2 liters a day) rather than urinary sodium concentration (which increased only from 46 to 64 mmol/l). The findings of this study might not be applicable to the current practice of UF as only patients with stable heart failure (rather than ADHF) were included, angiotensin-converting enzyme inhibitors were stopped prior to initiation of study and most importantly diuretics were continued during UF therapy. Therefore, the increased urine volume and sodium could be explained by improvement in renal hemodynamics resulting in restored response to continued dose of diuretics. The study did not include a control group to compare the changes.

Table 1. Estimated sodium removal in CARRESS-HF trial

	Medical therapy	UF	
	urine	urine	ultrafiltrate
Day 1, liters	2.8	1.6	1.55
Day 2, liters	3.35	1.15	2.75
Day 3, liters	3.3	1.05	1.85
Day 4, liters	2.8	1.3	1.05
Total, liters	12.25	5.1	7.2
Sodium concentration, mmol*	85	26	138
Total sodium removal, mmol	1,041	133	994
Total sodium removal, mmol	1,041		1,127

Urine and ultrafiltrate volumes are approximate numbers extracted from online supplemental figure S3 (see www.karger.com/doi/10.1159/000448391) of Bart et al. [8].

* Adopted from Chung et al. [7].

Conclusion

The goal of this article is not to question the established efficacy of UF in decongestion nor is it to argue against its inherent ability to extract sodium-rich fluid. The purpose is to highlight a gap in knowledge regarding the magnitude of sodium removal by UF. Based on the limited data that is currently available, it is unlikely that the observed sustainability of UF benefits could be explained by its greater sodium extraction. The diminished urinary sodium concentration during UF process does not preclude the possibility of increased post-UF natriuresis due to lowered renal interstitial pressure and improved intrarenal hemodynamics. Clearly, we need serial measurements of urine sodium content rather than randomly performed single spot measurements for a more precise evaluation and comparison before an affirmative statement can be made. This non-invasive, inexpensive and readily available test can easily be incorporated into the design of the future studies.

The available data also question the common practice of withholding diuretics during UF therapy. Among major clinical trials of UF in ADHF so far, only continuous UF for congestive heart failure was designed to allow (and encourage) concomitant use of diuretics along with UF [10]. Dual decongestive therapy was not associated with higher rate of adverse outcomes such as worsening renal function, and UF-treated patients experienced more prolonged clinical stabilization and greater freedom from heart failure re-hospitalization.

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