VIEWPOINT

The Sodium Paradox in Decompensated Heart Failure

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The maladaptive handling of sodium is central to the pathophysiology of heart failure (HF).[1] Two key observations shape our perception of sodium in HF. Sodium homeostasis is impaired in HF, promoting its accumulation, as patients with HF are believed not to be able to excrete it in adequate quantities. Sodium excess is associated with edema and pulmonary congestion; experimental exposure of patients with HF to a sodium chloride (NaCl) load led to its retention and the development of congestion.[1,2] This perspective follows logical reasoning: in a decompensated patient, sodium restriction should prevent further accumulation of this electrolyte (and water), thereby facilitating decongestion, but it often fails to do so.

Sodium Is Needed to Eliminate Sodium and Water

There are some fundamental considerations that contradict this traditional paradigm. First, the kidney controls body fluid space volume primarily by kidney electrolyte (sodium and chloride) handling. There is a positive relationship between natriuresis and urine output, making sodium a critical cofactor in effective urine excretion. Second, loop diuretics act primarily through sodium-dependent mechanisms. Third, sodium and chloride are closely linked in our body and are regulators of intravascular tonicity (influencing water movement across a semipermeable membrane), renin-angiotensin-aldosterone system (RAAS) activity, and diuresis.

Moreover, pathophysiological considerations suggest that sodium, through various mechanisms including modulation of the RAAS, intraglomerular hypertension, and glomerular perfusion, may help preserve kidney function. However, these assumptions remain theoretical.

Together, these insights suggest that, rather than always being deleterious, sodium availability to the kidney and its proper handling may be important for effective decongestion. The concept of using sodium to eliminate sodium thus challenges conventional wisdom and demands reexamination in light of emerging clinical data.

The Benefit of Sodium and Chloride Supplementation During Decongestion

Considering the previously mentioned caveats, various findings indicate that NaCl supplementation in conjunction with diuretics may provide decongestive benefits in decompensated HF, challenging the traditional approach of sodium restriction. The evolving understanding of the role of sodium in HF is reflected in the recent relaxation of sodium restriction recommendations presented in the European Society of Cardiology Heart Failure Association document.[1]

Previous research indicated that limiting sodium intake significantly reduced the natriuretic response to furosemide, contributing to the drug's diuretic tolerance, even in healthy individuals.[3] On the other hand, in animal models of shock, hypertonic saline infusion has been reported to improve central hemodynamics, visceral flow, and urine output.[4] Moreover, salt supplementation suppresses the neurohormonal drive, a core mechanism in the pathophysiology of HF and sodium avidity.

All these observations set the stage for early attempts to use NaCl supplementation in HF. Real-world data on the use of hypertonic saline in patients with diuretic-refractory HF demonstrated that the approach may be associated with increased diuretic efficiency (and weight loss), clinical and metabolic improvement without adverse effects. A meta-analysis of randomized clinical trials (RCTs) reported potential benefits of combining hypertonic saline with furosemide, including increased diuresis, natriuresis, and improvements in clinical end points, compared with furosemide alone.[5]

In the open-label TARGET-1 and TARGET-2 trials, patients with decompensated HF received Reprieve System therapy (an automated fluid management system), which was used in addition to diuretics.[6] The system continuously monitored urine output and returned a matched volume of 0.9% NaCl intravenously to maintain a set fluid balance (eg, 100 mL/hour net negative). With this approach, patients had significantly higher urine output (approximately 6 L/day) during the continuous infusion of NaCl compared to the day before (approximately 2 L/day) and after (approximately 2 L/day) system support.[6] Two insights can be derived from this small, uncontrolled study. First, contrary to traditional dogma, patients with decompensated HF were able to excrete the sodium (and water) they were continuously exposed to. Moreover, they maintained a negative sodium-water balance despite (or perhaps in response to) the NaCl supplementation. Second, they appeared to excrete sodium and volume more effectively when supported by NaCl infusion.

However, based on these data, it was impossible to determine whether the observed effects of infusion stemmed directly from the NaCl compensation, from a volume-related benefit, or both. The prospective, randomized SOLVRED-AHF trial was designed to answer this question.[7] In this mechanistic study, patients with HF were assigned to receive an isotonic infusion during decongestion: 0.9% NaCl (to prevent sodium and volume depletion) or 5% glucose (to prevent volume depletion only). The NaCl infusion outperformed glucose across all primary end points: the NaCl group showed significantly higher diuresis, natriuresis, and lower diuretic demand. This effect was driven by lower sodium avidity, inhibition of proximal tubular sodium reabsorption (without compensatory distal reabsorption), and lower aldosterone levels.[7] We are currently awaiting the detailed results of the randomized FASTR trial, which is expected to provide further data on the utility of NaCl for decongestion.

In the SALT-HF trial, a short-term infusion of NaCl combined with diuretics did not alter urine output within the first 3 hours in ambu-

latory decompensated patients.[8] This may reflect the fact that a 3-hour observation window is insufficient to detect a meaningful physiological response to supplementation. It is plausible that a certain time interval is required to restore sodium deficits and achieve adequate intravascular and tubular sodium availability before downstream physiological mechanisms can be effectively engaged. Importantly, patients allocated to NaCl infusion had a significantly higher (approximately −0.5 kg) weight decrease on day 7.

Although available data may support the hypothesis that NaCl supplementation can enhance decongestion, the relevant question is whether such an intervention translates into improvement in important clinical end points. Although residual congestion has been associated with adverse outcomes, this does not imply that enhancing short-term diuretic response will necessarily translate into improved prognosis; such an assumption would represent reverse causal reasoning rather than evidence of a true outcome-modifying effect. There is no evidence that improving diuretic response per se leads to better clinical outcomes. In contrast, data from large RCTs (PUSH-AHF, ADVOR) indicate that even effective decongestion (despite improving surrogate markers) does not translate into a reduction in hard clinical outcomes, such as all-cause mortality or HF rehospitalization.[9,10]

Conclusions

Although there is no definitive evidence supporting the hypothesis, an increasing number of studies suggest that controlled NaCl supplementation may facilitate decongestion in patients with HF. However, it is important to note that most of the data come from relatively small, mechanistic studies, which inherently limit their external validity and generalizability. On the other hand, it is crucial to recognize that our understanding of the current sodium paradigm largely stems from outdated observational studies completed before the broad adoption of neurohormonal blockade, highlighting a significant limitation. As a result, it may be necessary to reassess our perspective on the roles of sodium and chloride in HF, especially in light of findings regarding the effects of guideline-directed medical therapy on sodium avidity and water-sodium balance.

Although administering salt to a fluid-overloaded patient may seem counterintuitive, physiological foundations and preliminary, hypothesis-generating data justify further investigation in adequately powered randomized trials. NaCl, when administered in a controlled manner, could enhance diuresis and counteract harmful RAAS activation. Thus, our understanding of sodium chloride in HF is likely to evolve, and the sodium restriction paradigm may need to be reevaluated in further well-designed studies.

ARTICLE INFORMATION

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