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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The Pathophysiological Role of Interstitial Sodium in Heart Failure

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ABSTRACT

The current understanding of heart failure (HF) does not fully explain the spectrum of HF symptoms. Most HF hospitalizations are related to sodium (Na^+) and fluid retention resulting from neurohumoral up-regulation. Recent insights suggest that Na^+ is not distributed in the body solely as a free cation, but that it is also bound to large interstitial glycosaminoglycan (GAG) networks in different tissues, which have an important regulatory function. In HF, high Na^+ intake and neurohumoral alterations disrupt GAG structure, leading to loss of the interstitial buffer capacity and disproportionate interstitial fluid accumulation. Moreover, a diminished endothelial GAG network (the endothelial glycocalyx) results in increased vascular resistance and disturbed endothelial nitric oxide production. New imaging modalities can help evaluate interstitial Na^+ and endothelial glycocalyx integrity. Furthermore, several therapies have been proven to stabilize interstitial GAG networks. Hence, a better appreciation of this new Na^+ "compartment" might improve current management of HF. (J Am Coll Cardiol 2015;65:378–88) © 2015 by the American College of Cardiology Foundation.

Approximately 90% of heart failure (HF) hospitalizations are associated with signs and symptoms of sodium (Na^+) and fluid excess, which are associated with disease progression and a worse prognosis (1,2). Traditionally, the primary abnormality in HF was understood to be Na^+ handling, whereby water movement passively follows Na^+ to keep osmolality in balance. Due to neurohumoral up-regulation and increased arginine vasopressin (AVP) production, the kidneys are not capable of adjusting Na^+ excretion to Na^+ intake. The resulting imbalance leads to Na^+ accumulation, followed by interstitial and intravascular volume retention, and, eventually, to edema and increased cardiac filling pressures (3). However, before admission for acute decompensated heart failure (ADHF), patients display a wide spectrum of weight changes, with <50% gaining substantial weight (>1 kg) (4). Moreover, although a significant increase in cardiac filling pressure is consistently observed days before an ADHF admission, a broad range of plasma volumes has been observed in ADHF patients (5,6). Finally, total body Na^+ levels were found to be increased in observational studies of HF from >60 years ago (7). Interestingly, this increase was found in patients both with overt peripheral edema and without edema (8,9). Important changes in total body Na^+ occur over extended periods of time, even in healthy individuals on a stable Na^+ diet, and are not accompanied by changes in total body water

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(TBW) (10,11). Therefore, the classic idea of simultaneous Na^+ and fluid retention may not always be true as an explanation for fluid overload and increased cardiac filling pressures in ADHF.

Recent evidence has demonstrated that a large part of total body Na^+ is bound to glycosaminoglycan (GAG) networks in the interstitium; these GAG networks function as Na^+ buffers and play an important role in fluid homeostasis and endothelial function. This review aims to provide insight in the important physiological role of interstitial Na^+ bound to GAGs in preserving Na^+ and fluid regulation, as well as endothelial function. A better understanding of the contributory role of interstitial Na^+ across the spectrum of HF presentations may shed light on a novel therapeutic target that has otherwise been overlooked.

THE BODY TIGHTLY REGULATES SODIUM AND WATER BALANCE

A typical Western diet contains approximately 12 g of salt (Na^+ chloride) per day, which is equivalent to the approximately 4.5 g (approximately 200 mmol) of Na^+ that is almost completely absorbed in the gastrointestinal system. The plasma Na^+ concentration and osmolality start to rise 30 to 60 min after an oral Na^+ load (12). Because the body tightly regulates osmolality through osmoreceptors in the hypothalamus, a rise of even a few milliosmoles per liter in plasma osmolality results in retention of free water through stimulation of thirst and AVP release. Baroreceptors in the large (aortic arch, carotid sinus) and small vasculature (pulmonary vasculature, renal afferent arteriole) subsequently sense a rise in TBW to modulate urinary Na^+ and water excretion. From the plasma, Na^+ is freely filtered in the renal glomerulus. Because tubular Na^+ reabsorption exceeds 99%, only a tiny fraction of Na^+ is excreted in the urine. In normal circumstances, extrarenal Na^+ loss from skin (sweat) and from the gastrointestinal tract (feces) is negligible. Nevertheless, because relatively small changes in Na^+ excretion by the kidneys can lead to marked alterations in TBW (13), this tiny fraction of renal Na^+ excretion is highly regulated to mimic dietary intake.

SODIUM BUFFERING BY GLYCOSAMINOGLYCANS

On the basis of intracellular and extracellular Na^+ concentrations, approximately 65% of total body Na^+ is assumed to reside in the extracellular fluid (plasma fluid and interstitial fluid), whereas only 5% to 10% is found in the intracellular fluid (13). The remaining 25% of total body Na^+ is sequestered in bone as Na^+ apatites and is not readily exchangeable, in contrast to Na^+ in the extracellular and intracellular fluid compartments.

Contemporary evidence indicates that Na^+ cations are largely bound to negative biopolymers, called glycosaminoglycans (GAGs) (14,15). GAGs are linear polymers of disaccharide units with variable lengths that are modified by sulfation and/or acetylation and/or deacetylation. Thus, all GAGs have negative charges in the form of carboxyl and/or sulfate groups (**Central Illustration**) (16). Multiple GAG chains can anchor to a linear linking protein, forming a large brush-shaped proteoglycan that contains numerous anionic charges. They are connected via intramolecular hydrogen bonds to form a compact macromolecule (17). The extremely polyanionic nature of these macromolecules leads to electrostatic interactions between their negatively charged surfaces, such as collagen fibrils, proteins, and positive electrolytes, thus creating a network with a high oncotic pressure. In vitro studies have observed that the interaction with Na^+, the most abundant cation of the extracellular compartment, is favored over other ions and proteins (18). Consequently, a large amount of Na^+ is bound to GAGs, creating a microenvironment of hypertonic Na^+ concentration (19). However, the dense network exhibits a low compliance, secondary to its strong elastic and tensile force, thereby "pressing" fluid out. Importantly, disruption of bonds within GAGs or alterations in bound molecules will have significant structural and functional consequences for the proteoglycans (20,21).

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

AVP = arginine vasopressin

eGC = endothelial glycocalyx

EnNaC = endothelial sodium channel

GAG = glycosaminoglycan

HF = heart failure

Na^+ = sodium

NO = nitric oxide

TBW = total body water

VEGF-C = vascular endothelial growth factor C

INTERSTITIAL SODIUM

SODIUM ACCUMULATES DYNAMICALLY IN INTERSTITIAL GLYCOSAMINOGLYCAN NETWORKS. The interstitium connects and supports tissues while serving as a transport medium for nutrients, waste products, and signaling molecules. GAGs are the main constituents of the interstitium of various tissues (22–24). Together with collagen and/or elastin fibers, they comprise the solid phase and determine the structure and compliance of the interstitium (22,25). Because 1 GAG macromolecule can bind a large quantity of Na^+ cations, the interstitium can accumulate or buffer a high amount of Na^+ (**Figure 1A**) (26). Data from long-term balance studies in humans have confirmed that considerable amounts of Na^+ accumulate in the interstitium, particularly in skin and muscle tissue, without compensatory water retention or changes in plasma Na^+ concentration (11,27,28). Kopp et al.