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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

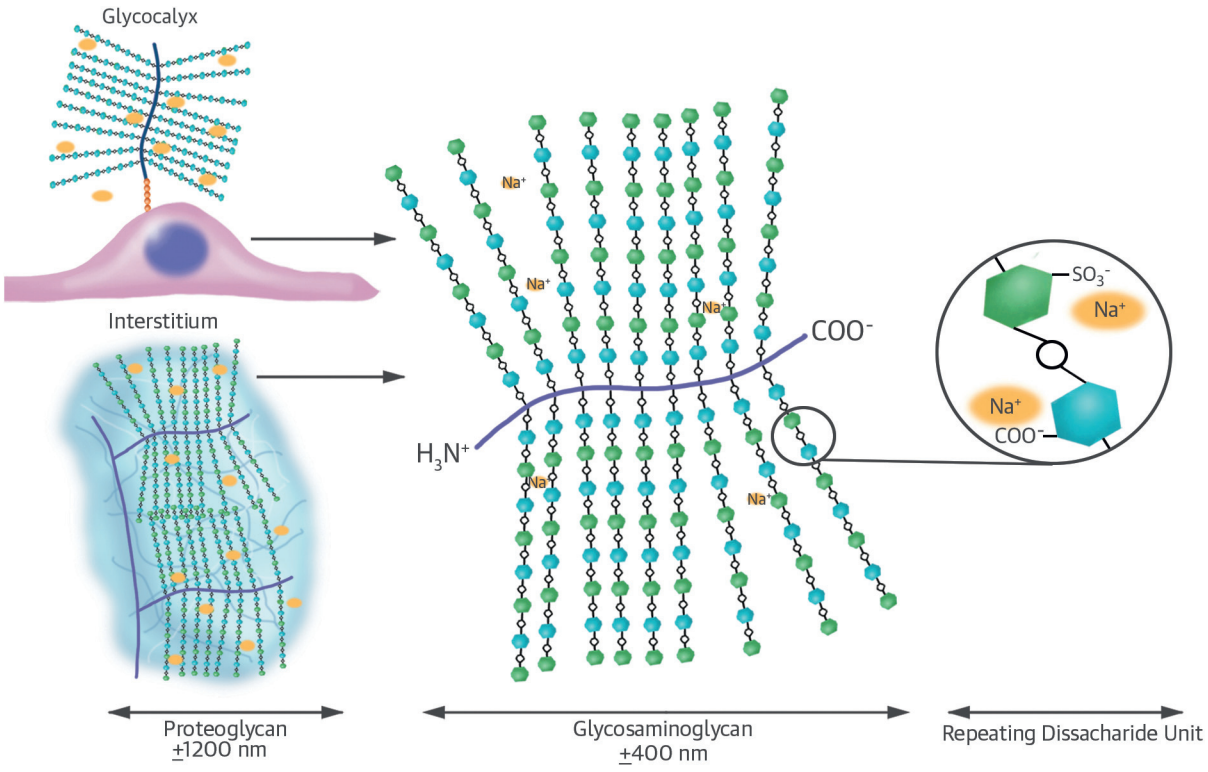
TBW = total body water

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.

CENTRAL ILLUSTRATION **Interstitial Sodium in Heart Failure: Proteoglycans and Glycosaminoglycans**



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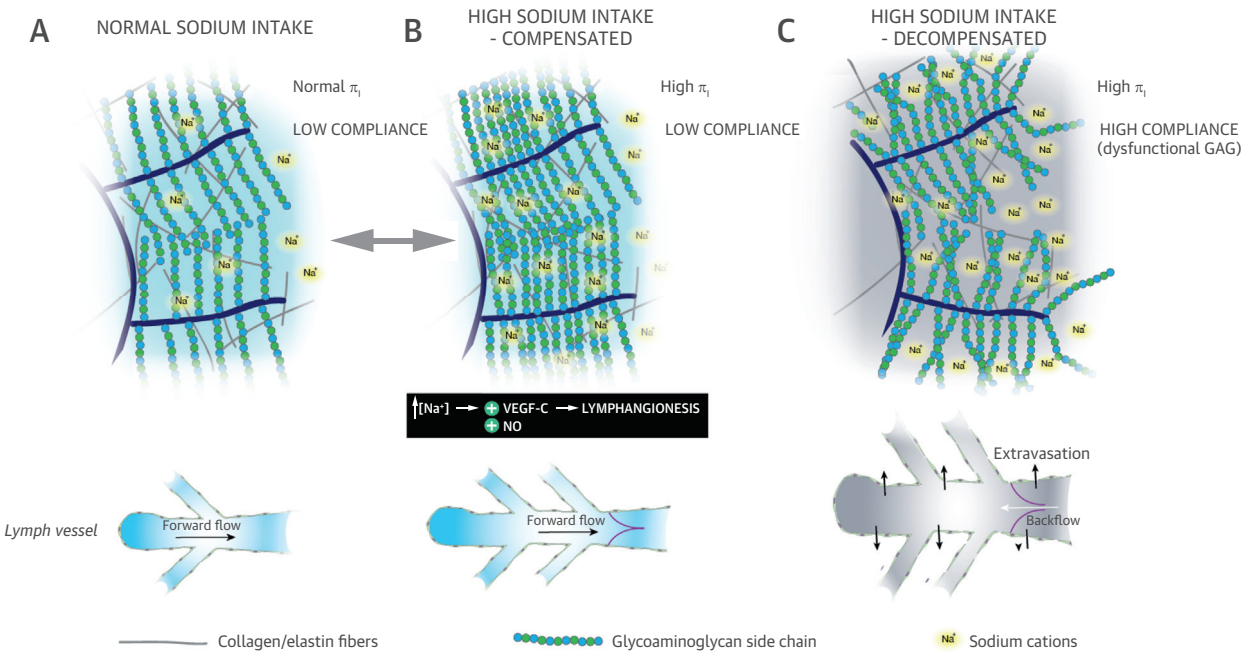
Proteoglycans are the major structural components of the interstitium of different tissues and the first endothelial layer (the endothelial glycocalyx). They consist of multiple glycosaminoglycans (GAGs) attached to a linking protein. GAGs are linear polymers of disaccharide units that are modified by sulfation and/or acetylation and/or deacetylation and have fixed negative charges in the form of carboxyl (COO^-) and sulfate (SO_3^-) groups. The polyanionic nature of the GAG network leads to electrostatic interactions with different molecules, particularly sodium (Na^+) cations.

recently quantified Na^+ concentrations in skin and muscle on the basis of ^{23}Na-magnetic resonance imaging spectroscopy. Their data suggested that, in contrast to a very stable plasma Na^+ concentration, the tissue Na^+ content in humans is highly variable, and that these variations are not accompanied by changes in tissue fluid content (15,29). As a consequence, in both normal circumstances and compensated HF states, interstitial GAG networks "smooth" fluctuations in plasma Na^+ concentrations, and therefore, conceal Na^+ ions from the pituitary osmoreceptors, preventing AVP release and thus preventing water retention. Moreover, because these secluded Na^+ cations do not reach the renal nephron, they also escape renal regulatory function and are more difficult to remove from the body.

In vitro studies have also shown that the interstitial GAG network can adapt to short periods of higher salt intake, because a high concentration of Na^+ cations changes the sulfation pattern and increases GAG charge density (17,30). High Na^+ concentrations also promote gene expression of GAG polymerization enzymes, which further increases GAG content, and thus, activates a positive feedback pathway to expand Na^+ storage capacity (**Figure 1B**) (10). In the reverse situation of salt scarcity, GAG polymerization and sulfation are reduced, and a subsequent reduction in the matrix is associated with gradual mobilization of Na^+ from tissue reservoirs (19).

However, if an excessively high Na^+ concentration in the GAG network is prolonged, the conformation of the macromolecules will eventually be altered, leading to a dysfunctional GAG network, which results in a loss of interstitial network integrity and buffering capacity (**Figure 1C**). The loss of interstitial buffering capacity may be especially important in salt-sensitive

FIGURE 1 The Interstitium



(A) The interstitium consists of a network of proteoglycans and collagen and/or elastin fibers that determine its compliance. Interstitial fluid is formed by transcapillary filtration of plasma fluid and is subsequently drained by many lymphatic vessels. **(B)** High dietary sodium (Na^+) intake leads to an interstitium with a large glycosaminoglycan (GAG) network, which can accumulate a higher concentration of Na^+ (and proteins), thus creating a higher interstitial oncotic pressure. A high interstitial sodium concentration acts as a positive stimulus for lymphangiogenesis through tissue vascular endothelial growth factor-C (VEGF-C) and nitrous oxide (NO) production. Due to the low interstitial compliance and increased lymphatic capacity, interstitial fluid is efficiently drained, and there is no interstitial fluid accumulation; however, interstitial oncotic pressure is high (compensated state). **(C)** When the conformation of the GAGs is altered, the GAG network becomes dysfunctional, and the interstitium enters a high-compliance state. Furthermore, high interstitial oncotic pressure (as with high salt intake) favors transcapillary filtration of interstitial fluid. In addition, due to widening of lymphatic vessels and disturbance of propagation coordination, lymphatic drainage becomes less efficient, leading to lymph extravasation. Therefore, in heart failure (HF), interstitial fluid can accumulate (decompensated state), even in patients with mildly elevated venous pressures.

hypertension and in neurohumoral activation in HF (31,32).

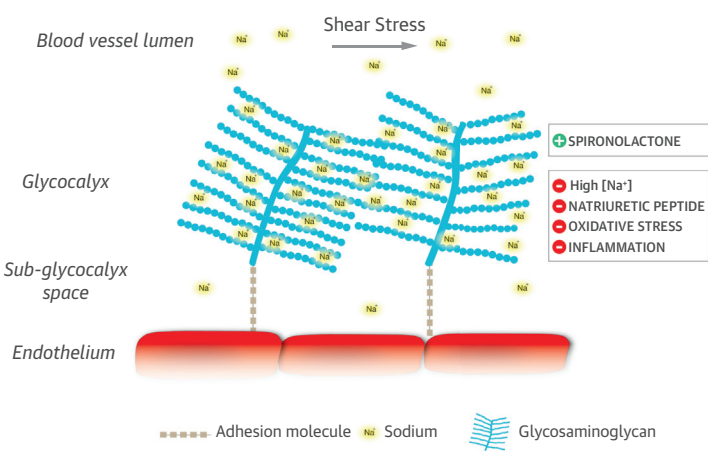
INTERSTITIAL FLUID TRANSPORT IS REGULATED BY INTERSTITIAL SODIUM MICROENVIRONMENTS. As stipulated previously, GAGs create a high osmotic pressure microenvironment (22). Therefore, subjects with a more dense interstitial GAG network—and consequently with a higher interstitial oncotic pressure (π_I)—will have more filtration of plasma fluid over the capillary membrane into the interstitium. However, the limited elastic properties (and thus, low compliance) of the interstitial GAG network prevent fluid accumulation (33,34). Small increases in interstitial fluid content lead to important increases in interstitial tensile stress. This forces interstitial fluid into the gaping lymphatic vessels. As fluid quickly drains into the systemic circulation, interstitial hydrostatic pressure remains low, and oncotic pressure remains high (compensated state) (**Figure 1B**). Moreover, subcutaneous tissue macrophages can sense high Na^+ concentrations and react by expressing tonicity enhancer binding protein (TonEBP) (19), which is a transcription factor that regulates the expression of osmoprotective genes in response to osmotic stress. Vascular endothelial growth factor C (VEGF-C), a potent inducer of lymphatic vessel formation and endothelial nitric oxide (NO) synthase expression, is 1 of the genes induced by the tonicity enhancer binding protein, further stimulating lymphangiogenesis (35,36). Higher VEGF-C levels and robust lymphatic vessel hyperplasia in the dermal interstitium have been found in response to high-salt feeding (37,38).

INTERSTITIAL EDEMA FORMATION DEPENDS ON INTERSTITIAL MATRIX COMPOSITION. Interstitial fluid accumulates when the rate of transudation from capillaries into the interstitium exceeds the rate at which the lymphatic system can efficiently drain the fluid. Venous pressure, more than arterial pressure, increases capillary hydrostatic pressure (13).

Therefore, increased central venous pressure and pulmonary capillary wedge pressure in HF promote interstitial fluid accumulation. In response, lymphatic capacity gradually increases, parallel to a rise in venous pressure, and only in higher ranges of venous pressures is the return of lymph to the great veins impeded (39,40). However, although patients with decompensated HF always present with elevated filling pressures (8), the occurrence of pulmonary and peripheral edema are correlated poorly with pulmonary capillary wedge pressure and central venous pressure, respectively (8,41,42). Other factors in addition to increased capillary pressure must play a more important role in determining the occurrence of edema.

As described by the Starling equation, high interstitial oncotic (π_I) pressures and low interstitial hydrostatic pressures promote transudation of plasma fluid into the interstitium, whereas low interstitial compliance opposes fluid accumulation. A prolonged, excessively high Na^+ concentration leads to a dense interstitial GAG network with the accumulation of Na^+ cations (high π_I) and an altered conformation of the GAG macromolecules, creating a dysfunctional GAG network. This may result in decreased tensile stress, and thus, a high compliance state of the interstitial matrix (**Figure 1C**). The combination of high interstitial oncotic pressure and high compliance facilitates fluid transudation (34). Importantly, spironolactone stabilizes altered GAGs, suggesting that unrestrained neurohumoral stimulation in HF further contributes to the dysfunction of the GAG network (43,44). Moreover, lymphatic vessel integrity is altered as lymph vessels start to widen, leading to leakage of lymph into the interstitium (**Figure 1C**) (40). Thus, when interstitial GAG networks become dysfunctional, even mildly elevated venous pressures in HF might lead to pulmonary congestion and peripheral edema (decompensation).

FIGURE 2 The Endothelial Glycocalyx



The endothelial glycocalyx (eGC) is a network of glycosaminoglycans (GAGs) connected to the underlying endothelium by adhesion molecules. It acts as a mechanotransducer and shields the underlying epithelium from blood cells. Moreover, due to the net negative charge, positively charged molecules, such as sodium (Na^+) and plasma-derived proteins, are concentrated inside the GAG network, creating a buffer and a high internal oncotic pressure. The eGC will be shed by inflammation, oxidative stress, natriuretic peptides, and high Na^+ concentration, whereas spironolactone has protective effects.

SODIUM AND ENDOTHELIAL FUNCTION

THE ENDOTHELIAL GLYCOSAMINOGLYCAN NETWORK CONTROLS ENDOTHELIAL FUNCTION. The endothelial glycocalyx (eGC) (the inner fragile layer of the endothelium), which is a highly specialized variant of interstitium, is composed of a network of membrane-bound and different types of soluble proteoglycans (mostly heparin sulfate) and glycoproteins that are connected to the endothelial cell membrane through adhesion molecules. A dynamic equilibrium exists between the eGC and flowing blood, which continuously affects the composition and thickness of the eGC (43,45). Both endothelium- and plasma-derived soluble molecules (e.g., albumin, proteins, ions) interact with this mesh (**Figure 2**) (46).

The eGC has multiple vasoprotective functions, and it shields the underlying apical side of the endothelium from the plasma. It reduces vascular permeability, restricts molecules from reaching the endothelium, and prevents interaction of platelets and leucocytes with endothelial cell adhesion molecules (47,48). Moreover, the endothelial GAG network acts as a Na^+ buffer by binding positively charged Na^+ cations (49). Na^+ reversibly binds and dissociates from eGC binding sites. As a result, the eGC buffer allows gradual passage of Na^+ from the blood into the space between the eGC and endothelium (50). Na^+ can subsequently enter the endothelial cell through apical endothelial Na^+ channels (EnNaCs), which are almost identical to epithelial Na^+ channels. Then, sodium-potassium adenosine triphosphatase (Na^+/K^+ -ATPase) pumps at the basolateral side will quickly try to restore cell homeostasis by creating a transcellular passage for Na^+ into the interstitium (13). However, most Na^+ is transported between endothelial cells along its electrochemical gradient via the paracellular pathway. Importantly, the eGC also acts as a mechanotransducer, transmitting shear stress signals into specific cell signaling processes in the

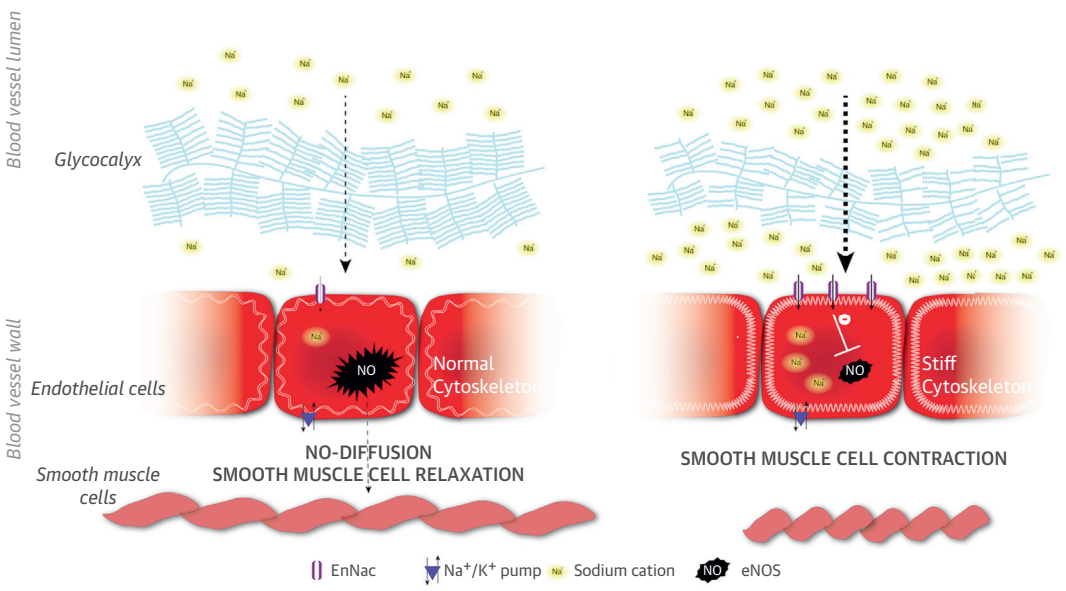
endothelial cell, and influencing NO production and cytoskeletal reorganization (45,51).

HIGH INTRAENDOTHELIAL SODIUM CONCENTRATION REDUCES NITRIC OXIDE PRODUCTION. Na^+ uptake in the endothelial cell is promoted if the abundance of EnNaC in the apical membrane increases and/or EnNaC channel activity is stimulated. This occurs when the plasma Na^+ concentration increases (**Figure 3**) (52). Furthermore, high concentrations of aldosterone (as observed in HF) trigger rapid membrane insertion of pre-formed EnNaC complexes residing in vesicles just beneath the plasma membrane (53). As a consequence, Na^+ uptake into endothelial cells is stimulated in HF patients, especially those on high-salt diets. Importantly, even minor elevations in Na^+ influx into the endothelial cell through EnNaCs have large consequences for endothelial stiffness and NO production (54,55). Recent atomic force microscopy studies have observed that the endothelial cell stiffens within minutes of an acute elevation of intraendothelial Na^+ concentrations (52). This acute endothelial cell reaction is mediated by interactions between EnNaCs and cytoskeletal proteins (actin) in the endothelial cell submembraneous cortical cytoskeleton (**Figure 3**) (56).

Na^+ entry via EnNaCs also reduces endothelial NO synthase activity via the PI3K/AKT signaling pathway (57–59). In addition, Na^+ up-regulates the endogenous inhibitor of NO synthase, which is asymmetrical dimethyl-L-arginine. Both result in decreased NO levels (a hallmark of endothelial dysfunction) and impair relaxation of the smooth muscle cells surrounding the vessels (52,60). This plays an important role in endothelial dysfunction, on top of the loss of mechanotransduction of shear stress when the eGC is diminished.

SODIUM AND NATRIURETIC PEPTIDES DISRUPT THE ENDOTHELIAL GLYCOCALYX. Prolonged plasma Na^+ concentrations in the high physiological range (>140 mmol/l) damage the eGC. In an original in vitro experiment, Oberleithner et al. showed that Na^+ overload changes the negatively charged sulfate residues in the eGC, which results in eGC dysfunction (43). Interestingly, spironolactone prevented these harmful effects of Na^+ on the eGC (43). Furthermore, it is well known the eGC can be severely damaged by inflammation, ischemia and/or reperfusion, oxidative stress, excessive shear stress, and enzymatic degradation, all of which are common in HF (45,61). Intriguingly, several animal studies have

FIGURE 3 Endothelial Dysfunction



Damage to the endothelial glycocalyx (eGC) leads to increased vascular permeability **(dotted arrow)**, diminished sodium (Na^+) buffer capacity, and disturbed mechanotransduction in response to shear stress. High Na^+ concentrations and high aldosterone concentration promote the abundance of endothelial sodium channels (EnNaCs) at the apical membrane of endothelial cells. Na^+ subsequently activates EnNaCs, altering endothelial cytoskeleton organization and stiffening the endothelial cell. High EnNaC activity and disturbed mechanotransduction influence smooth muscle cell contraction by impairing nitrous oxide (NO) production, a characteristic of endothelial dysfunction. eNOS = endothelial nitrous oxide synthase; Na^+/K^+ pump = sodium-potassium adenosine triphosphatase pump; NO = nitrous oxide.

demonstrated that the natriuretic peptides (atrial, brain, and C-type) disrupt the eGC (62,63). In an elegant in vivo model, physiological doses of natriuretic peptides were observed to lead to shedding of the eGC, as assessed by venous washout of glycocalyx constituents (syndecan [an endothelial proteoglycan] and heparin sulfate) and morphologically confirmed electron microscopic changes in eGC integrity (63).

Oberleithner et al. (43) further demonstrated that Na^+ overload leads to increased intracellular endothelial Na^+ concentrations. It is speculated that Na^+ will not be buffered when the eGC is damaged, and instead of a gradual presentation to the underlying endothelium, large amounts of Na^+ cations will reach the apical side of the endothelium and intercellular clefts at once. This enhances the activity of EnNaCs, which alters endothelial mechanical properties and function, and promotes paracellular Na^+ transport to the interstitial space, which contributes to interstitial fluid accumulation.

A DYSFUNCTIONAL ENDOTHELIAL GLYCOCALYX RESULTS IN VASCULAR DYSFUNCTION. In vitro experiments confirmed that inadequate responses to shear stress variations and impaired NO production are noticed when the eGC is disrupted (64). It is well known that, compared with healthy subjects, endothelium-dependent NO-mediated vasodilation is impaired in skeletal muscle and in the coronary and pulmonary circulations of patients with chronic HF (65–67). Overall, the lack of NO increases vascular smooth muscle tone and consequently increases vascular resistance (68). Increased arteriolar resistance results in increased cardiac afterload, which often characterizes ADHF. In this respect, multiple studies have observed that arterial stiffening significantly improves with dietary salt reduction (69,70). Furthermore, in vivo experiments have shown that high salt intake and deficient NO production also leads to a higher tone in the venous side of the vasculature (71–74). Importantly, the largest part of total blood volume—about three-fourths—resides in veins and venules (13). Similar to autonomic regulated venous constriction (75), a dysfunctional eGC might also contribute to the shift of fluid from the venous reservoir into the effective circulatory volume. Finally, when the eGC is disrupted, vascular permeability increases, and plasma fluid extravasation into the interstitium of different tissues is no longer impeded (76,77).

In conclusion, a dysfunctional eGC contributes to the increased cardiac filling pressures in HF patients, which may be an important contributor to decompensation, because it consistently precedes ADHF admissions (78,79).

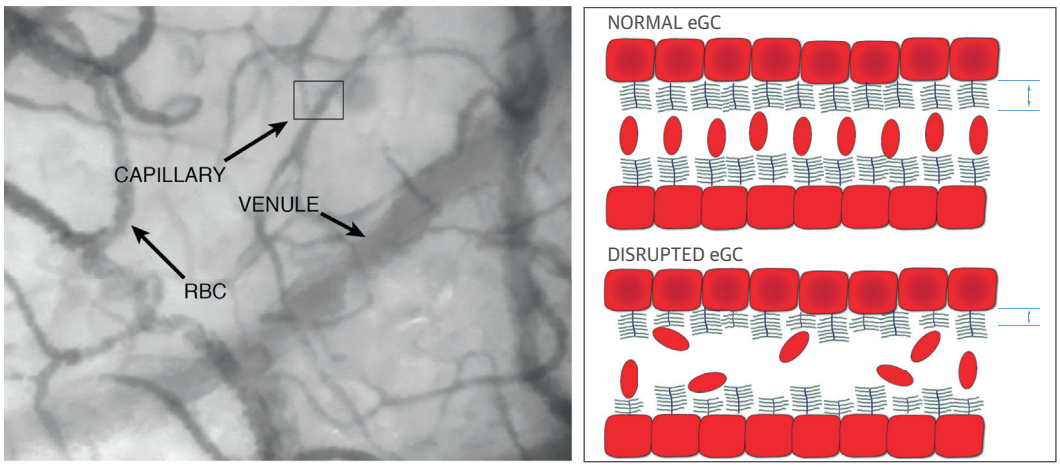
TARGETING INTERSTITIAL SODIUM IN HEART FAILURE

Current strategies assume enhanced Na^+ excretion with diuretics or antagonizing neurohumoral upregulation to effectively achieve Na^+ homeostasis at the level of the nephron. However, mortality and rehospitalization rates for HF remain tremendously high (1). Because the interstitial compartment also plays an important role in Na^+ and fluid homeostasis of the body, further understanding of this new "compartment" is of great interest. Moreover, preservation and restoration of normal GAG function in the interstitium, as well as in the eGC, could be interesting new strategies in HF management.

First, identifying dysfunctional interstitial GAG networks and a disrupted eGC may predict HF patients at a higher risk for decompensation. Because persistent signs of Na^+ and fluid overload in HF are important predictors of mortality and HF re-hospitalization, interstitial Na^+ content might be a good indicator to guide therapy and might be a new cardiovascular risk factor (80,81). A recently developed imaging technique, $^{23}Na^+$ magnetic resonance imaging, makes it possible to assess the Na^+ content of different tissues or in the whole body, and to monitor Na^+ evolution during therapy (15). Furthermore, there are currently several methods to determine eGC integrity, such as measurements of the products shed in plasma (e.g., syndecan or heparin sulfate) or visualization of the eGC with sidestream dark-field imaging (videomicroscopy). This technique makes it possible to directly visualize the microcirculation and to detect changes in glycocalyx volume on the basis of in vivo recordings of the sublingual microvasculature (**Figure 4**) (82–84).

Second, because the eGC plays an important protective role in the maintenance of a normal endothelial function and vascular permeability, stabilizing or restoring this specific GAG network is an interesting new therapeutic target. Preliminary data have shown that in the acute inflammatory and proteolytic situation of a myocardial infarction, hydrocortisone might help to sustain the vascular barrier function, and possibly, abrogate damage to the glycocalyx (85,86). A potential area of further research is to determine whether this strategy prevents eGC damage when high levels of natriuretic peptides circulate in ADHF. There is renewed interest in sulodexide, which is an old drug, in the fields of nephrology and vascular medicine. It is a mixture of naturally occurring GAG components (20% dermatan sulfate, 80% heparin sulfate) that can be given orally or

FIGURE 4 Sidestream Dark Field Videomicroscopy of the Microcirculation



Real-time image of the sublingual microvasculature obtained with a hand-held videomicroscope **(left panel)**. Moving red blood cells (RBCs) can be directly visualized in arterioles, capillaries, and venules. Differentiation is based on the vessel width and flow direction. Post hoc software analyses allow assessment of the integrity of the endothelial glycocalyx (eGC) based on the mean distance between RBCs and the vessel wall—and thus mean height of the eGC **(blue bars/arrows)**—and the appearance of the flow of RBCs in the capillaries (aligned and homogenously distributed along the capillary when the eGC functions properly vs. inhomogeneously distributed when the eGC is disrupted) **(right panel)** (82–84).

intravenously, and was originally used as an anticoagulant. After modification and reduction of its anticoagulant activity, sulodexide also restores the eGC (87,88). Various mechanisms could be responsible, such as its anti-inflammatory effects, its promotion of synthesis and sulfation of endogenous GAGs and proteoglycans, and its antiproliferative properties (89,90).

Dietary Na^+ reduction is currently a simple (and probably the most important) way to prevent endothelial dysfunction and the interstitial Na^+ accumulation that causes GAG dysfunction. Dietary intake is associated with a higher cardiovascular mortality and more ADHF events in stable HF patients (91,92). Furthermore, a reduction in Na^+ intake can lead to a significant decrease in plasma Na^+ (1.5 to 3.0 mmol/l) and possibly restore dysfunctional GAG networks (93). In this regard, a meticulous change in dietary Na^+ intake alone can reverse vascular endothelial dysfunction and improve vascular compliance (94,95).

When edema is present, current applied therapies in ADHF (loop diuretics and ultrafiltration) target free Na^+ cations and water in the plasma compartment. It is currently not clear how they influence interstitial Na^+ and GAGs. However, spironolactone has proven beneficial effects that extend beyond its natriuretic effect. Kopp et al. (29) observed that spironolactone induced a large reduction in tissue Na^+ in hypertensive subjects with high aldosterone levels. This recommendation could seem futile because mineralocorticoid receptor antagonists are currently part of general HF management. However, despite their widely demonstrated beneficial effects in patients with HF with reduced ejection fractions, mineralocorticoid receptor antagonists are significantly underused, especially during ADHF, when further mobilization of interstitial Na^+ may be essential (96,97). Spironolactone also protects the eGC and influences downstream negative endothelial consequences of Na^+ overload, because it diminishes EnNaC surface abundance and increases endothelial NO production in vitro (43,98).

CONCLUSIONS

The interstitium plays an important role in Na^+ and fluid homeostasis. Na^+ is distributed in the body as free cations and bound to networks of negatively charged biopolymers, GAGs, in the interstitium of different tissues. These interstitial GAG networks function as Na^+ buffers, regulating interstitial fluid accumulation, lymphatic vessel formation, and endothelial function. Long-term Na^+ overload and neurohumoral up-regulation in HF cause dysfunction of interstitial GAG networks, resulting in increased vascular resistance and permeability, as well as edema. Additional studies are needed to assess if

interstitial Na^+ content is more than just an amenable cardiovascular risk factor. Appraisal of this Na^+ compartment may provide new therapeutic strategies that target interstitial network dysfunction and eGC integrity, thereby reducing the burden of HF.

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