

EDITORIAL

Regulation of Fluid Volume From the Outside

A Role of Glycosaminoglycans in the Skin Interstitium?

See Article by Nijst et al

Helge Wiig, MD, PhD

Few will argue against the central role of salt in fluid volume and blood pressure homeostasis—a role that has passed the test of time through classical studies linking blood pressure and Na^+ balance,¹ also placing the kidney in the very center of extracellular fluid volume and blood pressure homeostasis.² This fact notwithstanding, a role for other tissues like the interstitium, mostly in skin, has more recently been suggested in an increasing number of studies.³ Indeed, already Guyton et al⁴ proposed that strongly negatively charged mucopolysaccharides (now named glycosaminoglycans [GAGs]) could attract and thereby generate a higher density of cations, notably Na^+ , and that “tissue fluids, pressures, and gel” could influence overall regulation of circulation.⁵ There are 2 major types of GAGs, hyaluronan having 1 charge and sulfated GAGs having ≤ 3 charges per disaccharide unit.⁶ At physiological pH, GAGs have a net negative charge, thus attracting counterions. Although there existed data showing Na^+ accumulation in skin, thus challenging the commonly accepted sodium homeostasis principle,⁷ this challenge was brought to a new level by Titze et al who introduced a new paradigm with regard to salt handling in the body. In studies from humans, rats, and mice, they showed that Na^+ can be buffered in the body in kidney-independent reservoirs. This occurs without commensurate water retention, thereby making the Na^+ osmotically inactive by association with negatively charged GAGs and thereby invisible to the kidney. In a series of studies, they demonstrated that the skin acts as kidney-independent regulator of the release and storage of Na^+ , for example,⁸ making the interstitium and its extracellular matrix and gel phase an additional player in Na^+ homeostasis. Without questioning the undisputed role of the kidney, these studies also established the immune cells from the mononuclear phagocyte system, including macrophages and dendritic cells and lymphatics as regulators of body fluid volume and blood pressure^{8,9} and the interstitium/extracellular matrix and lymphatics of the skin as potential targets in body fluid homeostasis.

To investigate whether there is an association between GAGs in the skin interstitium and Na^+ and fluid homeostasis in heart failure, a condition characterized by Na^+ retention by the kidney and thereby an increase in total body sodium is, therefore, pertinent. In the present issue of *Circulation: Heart Failure*, Nijst et al¹⁰ present data suggesting that GAGs are involved when fluid accumulates, eventually resulting in an edema characteristic for heart failure. They studied patients with heart failure and reduced ejection fraction (HFrEF) and found that patient skin obtained from punch biopsies had 35% higher uronic acid content, representative for total GAGs, than healthy subjects. Sulfated GAGs with an elevated charge density and thereby capacity to attract (buffer) cations were 56% higher, and the sulphatation per disaccharide was increased in patients suggesting that the GAG

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pool had gained capacity for Na⁺ buffering in the HFrEF group. Apparently, the shift in the content of GAGs and the raised sulphatation was dependent on the development of edema because the content of uronic acid and sGAGs were not different in healthy and patients with HFrEF without edema. Interestingly, the GAGs were influenced by therapy targeting the renin-angiotensin-aldosterone system because blockers reduced the skin content of GAGs and their sulphatation. Taken together, their data from patients with HFrEF suggest that GAGs in the skin interstitium are active participants in interstitial fluid volume and sodium buffering in heart failure, in addition to their role in blood pressure regulation shown earlier.

As pointed out by the authors, the study is small and considered hypothesis generating and will have to be followed up by more comprehensive studies. They also point to the limitation that the control group is significantly younger than the HFrEF group but argue that their own and literature data do not support an association between age and GAG density, as well as tissue water, thus supporting their claim that age is not a confounder.

If we agree with Nijst et al¹⁰ that HFrEF results in increased skin GAG content and an increased degree of sulphatation, what is/are the stimulus/stimuli for this reaction? They have several suggestions, includ-

ing total body sodium, inflammation and oxidative stress, and local renin-angiotensin-aldosterone system activation (Figure). Signaling via total body Na⁺ would have to be via hormonal or neural mechanisms that may initially be triggered by local stretch because of interstitial fluid accumulation (see below). If, however, signaling occurred via local Na⁺ accumulation, this would represent a GAG response in line with that observed by Titze et al¹¹ during high salt intake shown to result in skin Na⁺ accumulation and increased buffering. Unfortunately, skin Na⁺ was not measured by Nijst et al.¹⁰ It is conceivable, however, that the Na⁺ content was higher expressed on a dry weight basis in the HFrEF group with increased GAG concentration than in controls because the increase was found in the group with edema only. This follows from the fact that edema represents accumulation of interstitial fluid that has a Na⁺ concentration similar to that of plasma even during high-salt conditions¹² and even when correcting for the reduced plasma Na⁺ in the HFrEF group. The (likely) low interstitial fluid Na⁺ concentration is probably not a driver for increased GAG content, but we cannot exclude that the increased skin Na⁺ content may have resulted in increased skin osmolality, again stimulating GAG increase. This might be determined experimentally by tissue osmometry.

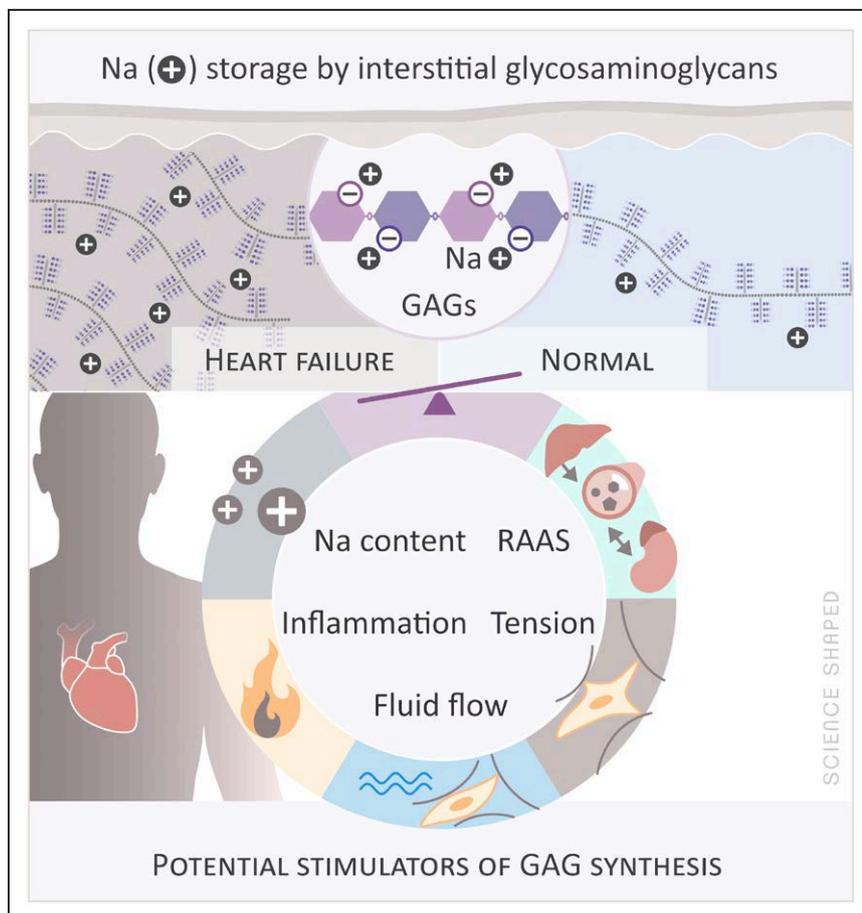


Figure. Heart failure results in increased production of glycosaminoglycans (GAGs), in particular sulfated GAGs.

Potential triggers of an increased GAG synthesis are shown. RAAS indicates renin-angiotensin-aldosterone system.

As discussed by Nijst et al, it is likely that the increased content of GAGs will be able to buffer more Na⁺ in the interstitium (Figure). It is moreover conceivable that the GAGs will change their structure, which will result in expansion of their network and thus an increased imbibition pressure and a more negative interstitial fluid pressure and thus to fluid filtration and accumulation. It is, however, not so likely that the GAGs will have an oncotic effect that promotes fluid filtration through an increase in the interstitial fluid oncotic pressure. Given that the interstitial fluid protein and Na⁺ concentration is similar in normal and high-salt diet,¹² the latter shown to increase skin GAGs, it is unlikely that the increase is seen by the capillary, where the determinants of filtration are the protein concentration in interstitial fluid as well as interstitial fluid pressure.

What might be the mediators influencing GAGs that high-salt diet and HFrEF have in common? In the study by Titze et al discussed above, it is likely that the extreme salt load used was contributing, whereas for Nijst et al, the tissue salt content was probably increased, although not to such an extreme extent. One factor that is not common is renin-angiotensin-aldosterone system involvement, which is expected to be low in the high-salt-intake studies but shown to be a potential contributor to increased GAG synthesis in the study by Nijst et al. If we look for potential GAG stimulation factors that heart failure and high-salt exposure have in common, inflammation is a likely candidate (Figure). It is well established that heart failure can result in a general inflammatory condition¹³ and that increased salt intake can have the same effect,¹⁴ both conditions capable of inducing increased GAG formation.¹⁵

One common factor as inducer of GAG formation not considered in the article by Nijst et al would be mechanical stretch. Heart failure, as well as tissue salt accumulation, will promote fluid accumulation in the interstitium that will result in stretching of extracellular collagen fibers mediated to fibroblasts thereby inducing GAG synthesis.¹⁵ That mechanotransduction might be a relevant factor is supported by the finding by Nijst et al that GAG accrual was observed only after edema developed. Another candidate biophysical factor is interstitial fluid flow. The high capillary pressure resulting from increased capillary filling pressure and increased Na⁺ ingestion will both result in enhanced capillary filtration and thereby interstitial flow, which has been shown to be a stimulator of interstitial matrix production, in particular, sulfated GAGs.¹⁶

It might, therefore, be that what we observe in skin in HFrEF, and increased sodium intake is an example of more general mechanism for storing excess Na⁺, as proposed by Bhavne and Neilson.¹⁶ Whereas high cell content tissues like muscle with a large intracellular relative to interstitial space can exchange Na⁺ for K⁺ or other intracellular osmolytes, tissues with a lower content of cells

like skin depend on osmotically active storage with interstitial GAGs or osmotically inactive storage with mineral matrix. Having demonstrated that interstitial GAGs are increased in patients with HFrEF, Nijst et al have established that such increase does not occur in situations of high sodium intake associated with blood pressure only, supporting the hypothesis that GAG increase is a general mechanism for handling Na⁺ excess in relatively cell-poor tissues like skin. An important implication of their studies is that the interstitium is emerging as a potential target in the management of fluid volume disturbances.

ARTICLE INFORMATION

Correspondence

Helge Wiig, MD, PhD, Department of Biomedicine, University of Bergen, Jonas Lies vei 91, N-5009 Bergen, Norway. E-mail helge.wiig@uib.no

Affiliation

Department of Biomedicine, University of Bergen, Norway.

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REFERENCES

- Guyton AC, Coleman TG, Cowley AW, Manning RD, Norman RA, Ferguson JD. A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. *Circ Res*. 1974;35:159–176.
- Coffman TM. The inextricable role of the kidney in hypertension. *J Clin Invest*. 2014;124:2341–2347. doi: 10.1172/JCI72274.
- Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. *Acta Physiol (Oxf)*. 2018;222.
- Guyton AC, Granger HJ, Taylor AE. Interstitial fluid pressure. *Physiol Rev*. 1971;51:527–563. doi: 10.1152/physrev.1971.51.3.527.
- Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. *Annu Rev Physiol*. 1972;34:13–46. doi: 10.1146/annurev.ph.34.030172.000305.
- Comper WD, Laurent TC. Physiological function of connective tissue polysaccharides. *Physiol Rev*. 1978;58:255–315. doi: 10.1152/physrev.1978.58.1.255.
- Ivanova LN, Archibasova VK, Shterental' ISh. [Sodium-depositing function of the skin in white rats]. *Fiziol Zh SSSR Im IM Sechenova*. 1978;64:358–363.
- Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, Park JK, Beck FX, Müller DN, Derer W, Goss J, Ziomber A, Dietsch P, Wagner H, van Rooijen N, Kurtz A, Hilgers KF, Alitalo K, Eckardt KU, Luft FC, Kerjaschki D, Titze J. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med*. 2009;15:545–552. doi: 10.1038/nm.1960.
- Wiig H, Schröder A, Neuhofer W, Jantsch J, Kopp C, Karlsen TV, Boschmann M, Goss J, Bry M, Rakova N, Dahlmann A, Brenner S, Tenstad O, Nurmi H, Mervaala E, Wagner H, Beck FX, Müller DN, Kerjaschki D, Luft FC, Harrison DG, Alitalo K, Titze J. Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. *J Clin Invest*. 2013;123:2803–2815. doi: 10.1172/JCI60113.
- Nijst P, Olinevich M, Hilkens P, Martens P, Dupont M, Tang WHW, Lambrechts I, Noben JP, Mullens W. Dermal interstitial alterations in patients with heart failure and reduced ejection fraction: a potential contributor to fluid accumulation? *Circ Heart Fail*. 2018;11:e004763. doi: 10.1161/CIRCHEARTFAILURE.117.004763.

11. Titze J, Shakibaei M, Schaffhuber M, Schulze-Tanzil G, Porst M, Schwind KH, Dietsch P, Hilgers KF. Glycosaminoglycan polymerization may enable osmotically inactive Na⁺ storage in the skin. *Am J Physiol Heart Circ Physiol*. 2004;287:H203–H208. doi: 10.1152/ajpheart.01237.2003.
12. Nikpey E, Karlsen TV, Rakova N, Titze JM, Tenstad O, Wiig H. High-salt diet causes osmotic gradients and hyperosmolality in skin without affecting interstitial fluid and lymph. *Hypertension*. 2017;69:660–668. doi: 10.1161/HYPERTENSIONAHA.116.08539.
13. Van Tassell BW, Toldo S, Mezzaroma E, Abbate A. Targeting interleukin-1 in heart disease. *Circulation*. 2013;128:1910–1923. doi: 10.1161/CIRCULATIONAHA.113.003199.
14. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, Muller DN, Hafler DA. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*. 2013;496:518–522. doi: 10.1038/nature11868.
15. Engebretsen KV, Lunde IG, Strand ME, Waehre A, Sjaastad I, Marstein HS, Skrbic B, Dahl CP, Askevold ET, Christensen G, Bjørnstad JL, Tønnessen T. Lumican is increased in experimental and clinical heart failure, and its production by cardiac fibroblasts is induced by mechanical and proinflammatory stimuli. *FEBS J*. 2013;280:2382–2398. doi: 10.1111/febs.12235.
16. Bhave G, Neilson EG. Body fluid dynamics: back to the future. *J Am Soc Nephrol*. 2011;22:2166–2181. doi: 10.1681/ASN.2011080865.

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