Abstract: **755**

Dermal interstitial alterations in patients with heart failure and reduced ejection fraction are associated with volume status

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Background: The occurrence of edema is poorly correlated with cardiac filling pressure in heart failure patients with reduced ejection fraction (HFrEF). Other factors than increased capillary hydrostatic pressure might also determine the occurence of extracellular edema. Large networks of glycosaminoglycans (GAGs) in the interstitium help to regulate water homeostasis. Factors present in HFrEF might increase GAG density and sulphation, leading to interstitial GAG-network dysfunction and fluid accumulation.

Objectives: The aims of this study are to demonstrate in HFrEF patients 1) that interstitial GAG density is increased, 2) that GAG-networks can become dysfunctional contributing to interstitial fluid accumulation and the clinical presentation of edema, and 3) that there is a link between GAG dysfunction and the renin-angiotensin-aldosterone system (RAAS).

Methods: Two punch biopsies of the skin of the lower leg were obtained in healthy subjects (n=18) and HFrEF patients (n=29, Left ventricular ejection fraction 32±10%). Alcian blue staining and immunostaining for the angiotensin II type 1 receptor was performed. After obtaining tissue water content (TWC), total interstitial GAG (Uronic Acid (UA)) and sulphated GAG (sGAG) density were quantified with ELISA techniques. A venous blood sample, clinical investigation and echocardiography were simultaneously obtained.

Results: Significant higher interstitial GAG density and sulphation was observed in HFrEF patients compared to healthy controls (UA: 13.1±4.2 vs 9.6±1.6 mg/mg ; $p<0.0001$; sGAG 15.9±5.9 vs 10.1±1.2 mg/mg; $p=0.0021$) and in HFrEF patients with versus without presence of lower extremity edema (Table 1). In healthy subjects TWC was stable over a range of interstitial GAG density. In contrast, there was a strong correlation between TWC and UA in HFrEF patients (Figure 1A.). Expression of the angiotensin II type 1 receptor is found on dermal cells responsible for GAG synthesis. Moreover, use of ACE-inhbitors/ARB is associated with significantly lower levels of interstitial GAGs in HFrEF patients (Figure 1B and C).

Conclusion: Interstitial GAG concentration is increased in HFrEF patients compared to healthy control subjects, and correlated with tissue water content and clinical signs of volume overload. Expression of the angiotensin II type 1 receptor was demonstrated on dermal cells. ACE-inhibitors/ARB use is associated with lower levels of interstitial GAGs. A better appreciation of the interstitial compartment might improve current management of volume overload in HF.

	HFrEF without edema (n=13)	HFrEF with edema (n=16)	p-value
Skin biopsy - TWC (ml/mg)	4.0±0.9	6.5±3.0	0.001

- sGAG (ug/mg)	13.3±3.1	17.9±6.8	0.057
- UA (ug/mg)	10.9±2.5	14.8±4.5	0.010

sGAG: sulphated GAG, TWC: Tissue water content; UA: uronic acid