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RESEARCH ARTICLE

Sodium loading in ambulatory patients with heart failure with reduced ejection fraction: Mechanistic insights into sodium handling

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Aims Sodium restriction was not associated with improved outcomes in heart failure patients in recent trials. The skin might act as a sodium buffer, potentially explaining tolerance to fluctuations in sodium intake without volume overload, but this is insufficiently understood. Therefore, we studied the handling of an increased sodium load in patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results Twenty-one ambulatory, stable HFrEF patients and 10 healthy controls underwent a 2-week run-in phase, followed by a 4-week period of daily 1.2 g (51 mmol) sodium intake increment. Clinical, echocardiographic, 24-h urine collection, and bioelectrical impedance data were collected every 2 weeks. Blood volume, skin sodium content, and skin glycosaminoglycan content were assessed before and after sodium loading. Sodium loading did not significantly affect weight, blood pressure, congestion score, N-terminal pro-brain natriuretic peptide, echocardiographic indices of congestion, or total body water in HFrEF (all $p > 0.09$). There was no change in total blood volume (4748 ml vs. 4885 ml; $p = 0.327$). Natriuresis increased from 150 mmol/24 h to 173 mmol/24 h ($p = 0.024$), while plasma renin decreased from 286 to 88 μU/L ($p = 0.002$). There were no significant changes in skin sodium content, total glycosaminoglycan content, or sulfated glycosaminoglycan content (all $p > 0.265$). Healthy controls had no change in volume status, but a higher increase in natriuresis without any change in renin.

Conclusions Selected HFrEF patients can tolerate sodium loading, with increased renal sodium excretion and decreased neurohormonal activation.

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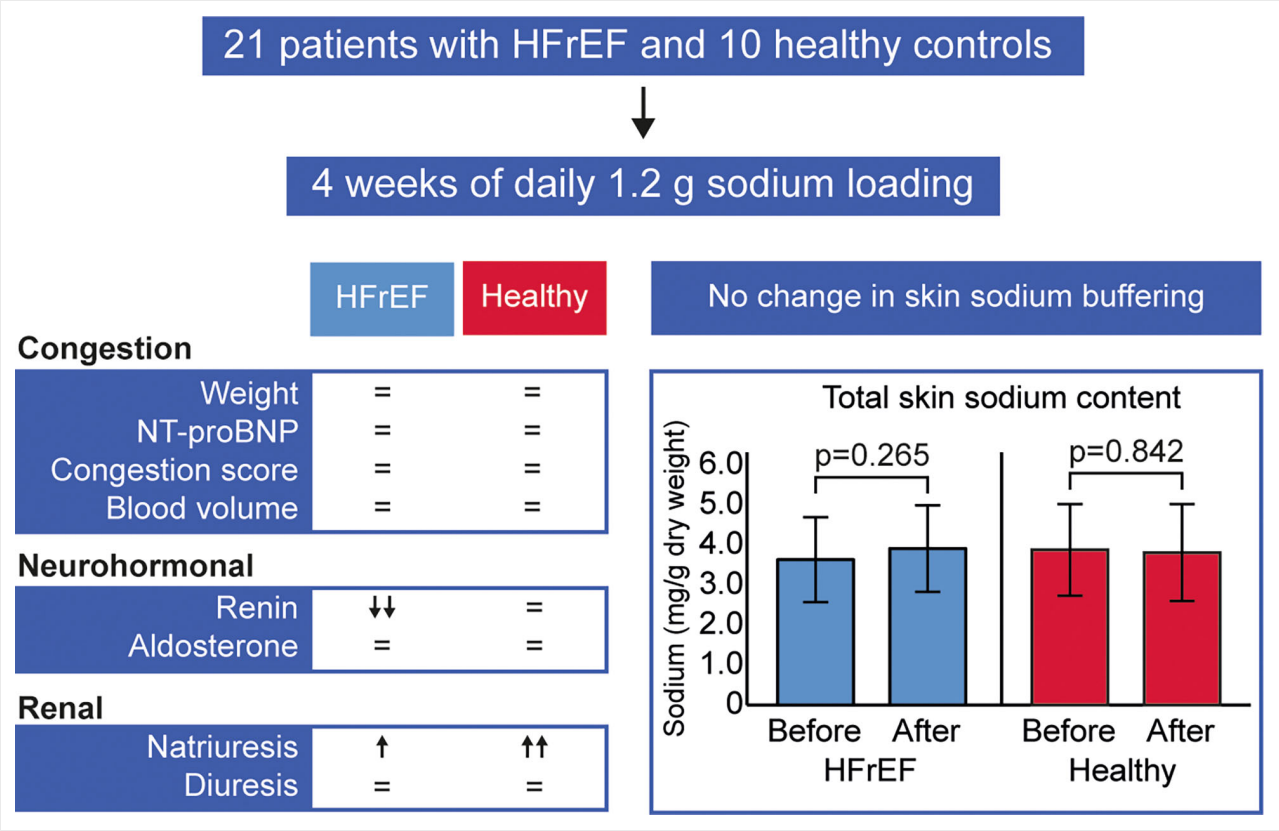
Graphical Abstract



Summary of study findings. HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Keywords Sodium restriction • Heart failure • Sodium load • Glycosaminoglycan • Skin • Neurohormonal activation

Introduction

Historically, sodium restriction has been an essential part of heart failure (HF) treatment for decades. Neurohormonal activation increases sodium avidity, rendering patients with HF susceptible to volume overload.[1] Indeed, untreated patients with mild HF without signs of volume overload, have a reduced ability to excrete a sodium load and abnormal cardiac and haemodynamic adaptations compared to healthy controls.[2] However, conflicting evidence has emerged regarding the impact of sodium restriction on clinical outcomes, especially in ambulatory HF patients.[3] The recent Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF) failed to show any benefit of long-term restriction of sodium intake to <1.5 g per day on clinical endpoints within 12 months.[4] Moreover, two independent meta-analyses reported no significant advantages of sodium restriction on clinical outcomes and conflicting evidence regarding quality of life.[5,6] These findings challenge the notion that higher sodium intake invariably leads to increased extracellular volume in stable HF patients on guideline-directed medical therapy (GDMT). Therefore, current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines only recommend to avoid excessive sodium intake in stage C HF (Class 2a),[7] while European Society of Cardiology guidelines only advise to avoid salt intake >5.0 g per day (≈2.0 g of sodium per day).[8]

New insights in human sodium handling might help to explain these paradoxical data. The skin has been identified as a sodium buffer, where negatively loaded glycosaminoglycans can bind and store sodium.[9,10] As such, sodium and its osmotic properties can be excluded from the extracellular space, thereby avoiding volume overload. Notably, alterations in the sodium buffering capacities of the skin have been observed in patients with HF with reduced ejection fraction (HFrEF).[11]

However, whether stable ambulatory HFrEF patients on GDMT tolerate an excess sodium load and what the potential role of these skin buffers is, remains unknown. Therefore, this mechanistic

study investigated the effects of sodium loading on clinical parameters, haemodynamics, renal sodium handling and skin sodium buffering capacities in ambulatory patients with HFrEF on GDMT and compared them with age-matched healthy controls.

Methods

Patients

The study included ambulatory stable patients with HFrEF and age-matched healthy controls. Inclusion criteria for patients with HFrEF comprised a left ventricular ejection fraction (LVEF) ≤40%, stable use of GDMT for at least 3 months, and a maximum daily dose of 40 mg furosemide or equivalent loop diuretic, which should have been stable for at least 1 month. Healthy controls were eligible if they were >60 years old, had an LVEF ≥50%, were not taking any neurohormonal blockers (beta-blockers, renin–angiotensin–aldosterone system [RAAS] inhibitors, mineralocorticoid receptor antagonists, or sodium–glucose cotransporter 2 inhibitors), and had a N-terminal pro-brain natriuretic peptide (NT-proBNP) <125 ng/L. Exclusion criteria included HF with New York Heart Association (NYHA) class III–IV symptoms, estimated glomerular filtration rate <30 ml/min/m^2, clinical signs of congestion, severe valvular heart disease defined according to recent guidelines,[12] or right ventricular dysfunction (tricuspid annular plane systolic excursion <17 mm). The study protocol was approved by the local institution's ethics committee (19/0033U), and all participants provided written informed consent. The study was registered on ClinicalTrials.gov (NCT04226755) and adhered to the principles of the Declaration of Helsinki.

Sodium loading protocol

The study protocol commenced with a 2-week run-in phase without sodium loading (online supplementary *Figure S1*). Following the run-in phase, patients were instructed to take one 1 g sodium chloride (NaCl) tablet (Fagron, Nazareth, Belgium) three times daily with meals, corresponding to a daily increase of 1.2 g or 51 mmol of sodium. Tablets were provided by the investigators at each visit. No specific dietary restrictions were imposed during any phase of the study and participants were strongly encouraged to not change their normal diet pattern at any moment. The sodium loading regimen was continued for 4 weeks. At the end of the study, patients were requested to return any remaining tablets to evaluate overall adherence.

Study procedures

Participants underwent four study visits: baseline, end of the run-in phase, after 2 weeks of sodium loading, and after 4 weeks of sodium loading. At each visit, clinical parameters including weight, blood pressure, and the EVEREST congestion score[13] were recorded. Patient thirst was assessed using a visual analogue scale. Blood samples were collected to measure serum creatinine, sodium, NT-proBNP (Elecsys, Roche, Rotkreuz, Switzerland), renin and aldosterone (both Immunodiagnostic Systems assay, Tyne & Wear, UK). Additionally, patients performed a 24-h urine collection at home before each visit. Standardized echocardiography was conducted at each visit with a Philips EPIQ 6 machine and the patient lying in left lateral position by the same single trained investigator. Images were stored as DICOM files. Analysis was done off-line by a single independent investigator using Enterprise Imaging version 8.1.2 (Agfa Healthcare, Mortsel, Belgium) with measurements done according to current American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.[14] There was blinding towards the patient's identity and visit number. Left ventricular volumes and ejection fraction were assessed in 2D with the Simpson's biplane mode. All measurements were averaged over three consecutive cardiac cycles. Diastolic dysfunction was graded according to current guidelines.[15] Body fluid status was assessed using bioelectrical impedance analysis with the BioScan 920-II device (Maltron International Ltd, Rayleigh, UK), measuring total body water and extracellular water. Detailed procedures are provided in the online supplementary material.

Skin sodium and glycosaminoglycan analysis

Two skin biopsies with a diameter of 6 mm were taken at the end of the run-in phase and two more biopsies at the end of the sodium loading period. The biopsies were obtained from the inner calf after topical anaesthesia (see online supplementary *Methods*). Glycosaminoglycans were evaluated following lyophilization (VirTis Freezemobile). Glycosaminoglycan molecules consist of disaccharide units composed of a uronic acid (UA) and hexosamine, with variable length and sulfation modifications. The total UA, representing the total glycosaminoglycan content, was analysed using the carbazole test. The sulfated glycosaminoglycan content (sGAG), representing the total content of sulfated glycosaminoglycans, was analysed using the 1,9-dimethylmethylene blue (DMMB) assay. Both UA and sGAG are expressed as μg per mg of dry defatted weight (μg/mgDW). Skin sodium content was measured using inductively coupled plasma optical emission spectrometry after digesting the samples with nitric acid (HNO_3). Results are reported as mg per g of dry weight (mg/gDW).

Nuclear blood volume measurements

Total blood volume and plasma volume were assessed at the end of the run-in phase and at the end of the sodium loading period using the technetium (^{99}Tc)-radio-labelled red blood cell dilution technique, following the guidelines of the International Committee for Standardization in Haematology.[16] Venous blood samples were labelled with ^{99}Tc in the nuclear laboratory and then re-injected into the patients. Subsequently, 5 ml venous blood samples were collected at 10-min intervals over a period of 30 min. Radioactivity was measured using an automated counter (Veenstra/Comecer, Joure, The Netherlands). Blood volume was calculated as the zero-time volume of distribution of the radiolabelled red blood cells, obtained through semilogarithmic extrapolation of the measured values. Plasma volume was derived from the measured blood volume and venous haematocrit, corrected for the trapped plasma and mean body haematocrit.

Statistical analysis

Continuous variables are presented as mean ± standard deviation if normally distributed, or as median (25th–75th percentile) otherwise. Categorical variables are reported as number (percentage). Variables collected at each visit were compared using repeated measures ANOVA, Friedman's test, or Chi-square test as appropriate. Total blood volume, plasma volume, skin sodium content, total UA, and sGAG were compared using a paired *t*-test if normally distributed or a Wilcoxon signed-rank test otherwise. Study adherence was calculated as the ratio of effectively taken salt tablets to the number of intended

salt tablets, expressed as a percentage. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Results

Study population

Between June 2020 and April 2022, a total of 21 patients with HFrEF and 10 age-matched healthy controls were included in the study. Two patients with HFrEF discontinued the sodium loading experiment due to excessive nausea after ingestion of the salt tablets and were excluded, as they used the tablets for less than 1 week. Additionally, one patient with HFrEF withdrew from the study due to a newly diagnosed cancer during the run-in phase and was also excluded from the analysis. Baseline characteristics of the remaining 18 patients and 10 healthy controls are summarized in *Table 1*. Patients with HFrEF had a mean age of 66 ± 8 years, longstanding HF, low congestion scores, and relatively low NT-proBNP levels. The majority of patients were classified as NYHA class II, and renal function was well preserved. GDMT was adequately implemented and only one-third of them were taking loop diuretics. Healthy controls had a similar age, few comorbidities, and normal baseline renal function.

Table 1 Baseline characteristics

	HFrEF ($n = 18$)	Healthy controls ($n = 10$)
Age (years)	66 ± 8	67 ± 6
Female sex	2 (11.1%)	3 (33%)
Duration of heart failure (months)	48 (25–71)	–
LVEF (%)	35 (31–39)	56 (54–58)
Ischemic aetiology	18 (100%)	–
BMI (kg/m^2)	28.7 ± 4.6	27.1 ± 2.7
NYHA class		
I	4 (22.2%)	10 (100%)
II	14 (77.8%)	0
EVEREST congestion score	2 (1–3)	1 (0–2)
Blood pressure (mmHg)		
Systolic	116 ± 18	142 ± 14
Diastolic	68 ± 6	88 ± 12
Heart rate (bpm)	57 ± 8	66 ± 7
Comorbidities		
Hypertension	7 (38.9%)	0
Diabetes	4 (22.2%)	0
Dyslipidaemia	12 (66.7%)	5 (50.0%)
Myocardial infarction	13 (72.2%)	0
Stroke	0	0
Atrial fibrillation	5 (27.8%)	0
Peripheral artery disease	1 (5.6%)	0
COPD	2 (11.1%)	0
Lab		
Sodium (mmol/L)	140 ± 2	140 ± 3
Creatinine (mg/dl)	1.15 (1.04–1.37)	0.90 (0.74–1.07)
eGFR (ml/min/1.73 m^2)	68 (51–74)	84 (74–87)
NT-proBNP (ng/L)	431 (275–961)	69 (53–104)
Medication		
ACE inhibitor/ARB/ARNI	17 (94.4%)	0
Beta-blocker	18 (100%)	0
MRA	18 (100%)	0
SGLT2 inhibitor	2 (11.1%)	0
Ivabradine	1 (5.6%)	0
Loop diuretic	6 (33.3%)	0
Antiplatelet	11 (61.1%)	1 (10.0%)
Anticoagulation	8 (44.4%)	0

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium–glucose cotransporter 2.

Congestion parameters

During the run-in phase, all measurements assessing congestion remained stable. In patients with HFrEF, sodium loading did not result in significant changes in weight or EVEREST congestion scores (*Table 2*) and systolic blood pressure was also not affected. The diastolic blood pressure marginally increased (68 ± 6 mmHg at baseline vs. 67 ± 6 mmHg at the end of the run-in phase vs. 70 ± 5 mmHg after 2 weeks of sodium loading vs. 70 ± 6 mmHg after 4 weeks of sodium loading; $p = 0.030$). There was no significant change in left ventricular volumes or in the diastolic dysfunction parameter E/e', but a slight numerical increase in the tricuspid regurgitation gradient was observed (20 [15–23] mmHg at baseline vs. 20 [18–23] mmHg at the end of the run-in phase vs. 24 [19–26] mmHg after 2 weeks of sodium loading vs. 22 [18–25] mmHg after 4 weeks of sodium loading; $p = 0.064$). However, the grading of diastolic dysfunction remained consistent throughout the experiment and NT-proBNP levels did not show significant changes. Furthermore, both total body water and extracellular water remained stable during sodium loading. Notably, sodium loading did not have a significant effect on thirst. These parameters did also not exhibit significant changes in healthy controls, except for a slight decrease in systolic blood pressure (*Table 3*).

Blood volumes

In patients with HFrEF, the baseline total blood volume was 4748 (4442–5132) ml, with a plasma volume of 2735 (2547–3032) ml. After sodium loading, these values did not change significantly, with a final total blood volume of 4885 (4342–5304) ml ($p = 0.327$) and a plasma volume of 2904 (2234–3253) ml ($p = 0.231$) (*Figure 1*). Similarly, no significant change in total blood volume (4718 [3896–5481] vs. 4627 [4172–5080] ml; $p = 0.959$) or plasma volume (2666 [2307–3127] vs. 2691 [2296–2949] ml; $p = 0.959$) was found in healthy controls.

Neurohormonal activation

In patients with HFrEF, plasma renin levels were elevated at baseline but gradually decreased during sodium loading (286 [25–550] μU/L at baseline vs. 255 [38–550] μU/L at the end of the

Table 2 Clinical variables in patients with heart failure with reduced ejection fraction

	Baseline	End of run-in	2 weeks sodium loading	4 weeks sodium loading	*p*-value
Clinical					
Weight (kg)	87.3 ± 14.3	87.1 ± 14.2	87.7 ± 14.0	87.3 ± 14.1	0.090
Systolic blood pressure (mmHg)	116 ± 18	115 ± 13	118 ± 11	120 ± 13	0.263
Diastolic blood pressure (mmHg)	68 ± 6	67 ± 6	70 ± 5	70 ± 6	**0.030**
Heart rate (bpm)	57 ± 8	58 ± 10	60 ± 9	60 ± 8	0.442
EVEREST congestion score	2 (1–3)	2 (1–4)	2 (1–4)	2 (1–3)	0.075
Thirst scale (%)	22 (15–52)	29 (8–47)	31 (14–48)	29 (14–53)	0.526
Echocardiography					
LVEDVi (ml/m^2)	111 (98–128)	113 (104–130)	114 (98–127)	115 (104–129)	0.083
LVEF (%)	35 (31–39)	35 (31–38)	35 (31–40)	35 (30–41)	0.801
E/e′	10 (7–16)	9 (7–17)	11 (8–15)	10 (8–16)	0.559
LAVi (ml/m^2)	35 (26–41)	32 (25–42)	34 (27–43)	34 (29–46)	0.644
TRG (mmHg), 2 missing	20 (15–23)	20 (18–23)	24 (19–26)	22 (18–25)	0.064
Diastolic dysfunction					0.572
Grade 1	14 (77.8%)	15 (83.3%)	14 (77.8%)	15 (83.3%)	
Grade 2	1 (5.6%)	0	1 (5.6%)	0	
Grade 3	0	0	0	0	
Undetermined	3 (16.7%)	3 (16.7%)	3 (16.7%)	3 (16.7%)	
Bioelectrical impedance					
Total body water (L)	46.87 (41.76–50.53)	43.65 (39.51–49.64)	46.76 (42.13–48.51)	44.41 (41.29–48.40)	0.780
Extracellular water (L)	20.53 (18.07–21.44)	19.84 (17.31–21.15)	20.73 (18.41–22.20)	20.04 (17.93–21.78)	0.103
Neurohormones					
NT-proBNP (pg/ml)	431 (275–961)	554 (284–860)	663 (255–1045)	513 (278–885)	0.768
Renin (μU/ml)	286 (25–550)	255 (38–550)	116 (25–358)	88 (19–362)	**0.002**
Aldosterone (ng/L)	96 (37–163)	124 (37–187)	91 (37–157)	74 (37–132)	0.313

LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; TRG, tricuspid regurgitation gradient.

run-in phase vs. 116 [25–358] μU/L after 2 weeks of sodium loading vs. 88 [19–362] μU/L after 4 weeks of sodium loading; $p = 0.002$) (*Table 2*). Plasma aldosterone levels did not show significant changes. In healthy controls, there were no notable changes in renin or aldosterone levels (*Table 3*).

Renal response

Total urine output did not show significant changes in both patients with HFrEF and healthy controls (*Figure 2*). However, natriuresis increased during sodium loading in patients with HFrEF (150 ± 55 mmol/24 h at baseline vs. 151 ± 53 mmol/24 h at the end of the run-in phase vs. 177 ± 57 mmol/24 h after 2 weeks of sodium loading vs. 173 ± 58 mmol/24 h after 4 weeks of sodium loading; $p = 0.024$). Similarly, there was a numerical larger increase in natriuresis in healthy controls (154 ± 63 mmol/24 h at baseline vs. 170 ± 48 mmol/24 h at the end of the run-in phase vs. 184 ± 70 mmol/24 h after 2 weeks of sodium loading vs. 212 ± 85 mmol/24 h after 4 weeks of sodium loading; $p = 0.100$).

Skin biopsies

The results of the skin biopsy analyses are presented in *Figure 3*. In patients with HFrEF, total UA levels were 14.76 ± 2.81 μg/mgDW at baseline and 15.45 ± 2.67 μg/mgDW after 4 weeks of sodium loading ($p = 0.415$). There were also no significant differences in sGAG levels (5.83 ± 0.86 vs. 5.86 ± 1.14 μg/mgDW; $p = 0.880$). Skin sodium content was 3.64 ± 1.06 mg/gDW at baseline and 3.91 ± 1.08 mg/gDW after 4 weeks of sodium loading ($p = 0.265$). In healthy controls, the absolute values were similar, with no significant differences in total UA (12.78 ± 1.60 vs. 13.52 ± 2.45 μg/mgDW; $p = 0.437$), sGAG (5.76 ± 0.85 vs. 6.08 ± 0.65 μg/mgDW; $p = 0.154$), or skin sodium content (3.88 ± 1.14 vs. 3.81 ± 1.21 mg/gDW; $p = 0.842$).

Study adherence

Adherence to the salt tablets was high, with a median adherence rate of 99% (range: 91–100%) in patients with HFrEF and 99% (range: 92–100%) in healthy controls.

Discussion

The objective of this mechanistic study was to specifically investigate sodium handling in ambulatory euvolaemic HFrEF patients on GDMT and age-matched controls by significantly increasing sodium intake with 1.2 g (51 mmol) per day for 4 weeks. Patients with HFrEF tolerated this prolonged increase of sodium intake without signs and symptoms of HF, congestion or blood volume increase. Additionally, such an increase of sodium intake led to a significant

Table 3 Clinical variables in healthy controls

	Baseline	End of run-in	2 weeks sodium loading	4 weeks sodium loading	*p*-value
Clinical					
Weight (kg)	80.9 ± 11.1	80.5 ± 11.3	81.0 ± 11.4	80.8 ± 11.2	0.195
Systolic blood pressure (mmHg)	142 ± 14	138 ± 12	135 ± 15	137 ± 13	**0.008**
Diastolic blood pressure (mmHg)	88 ± 12	88 ± 9	88 ± 10	88 ± 7	0.940
Heart rate (bpm)	66 ± 7	67 ± 6	69 ± 12	67 ± 5	0.825
EVEREST congestion score	1 (0–2)	1 (0–1)	0 (0–2)	0 (0–1)	0.846
Thirst scale (%)	18 (2–41)	18 (2–30)	18 (5–43)	19 (3–44)	0.407
Echocardiography					
LVEDVi (ml/m^2)	68 (63–72)	64 (61–73)	69 (64–73)	64 (59–74)	0.564
LVEF (%)	56 (53–58)	56 (53–58)	54 (53–58)	54 (53–58)	0.923
E/e′	7 (6–10)	6 (5–8)	7 (6–10)	8 (6–9)	0.062
LAVi (ml/m^2)	27 (21–30)	25 (20–30)	27 (23–32)	26 (21–29)	0.207
TRG (mmHg)	19 (17–24)	19 (15–22)	18 (15–22)	17 (14–18)	0.552
Diastolic dysfunction	0	0	0	0	
Grade 1					
Grade 2					
Grade 3					
Undetermined					
Bioelectrical impedance					
Total body water (L)	39.45 (35.34–45.61)	39.62 (36.04–44.35)	39.13 (34.98–46.12)	39.69 (34.86–44.99)	0.668
Extracellular water (L)	17.39 (15.89–20.54)	17.56 (16.13–19.74)	17.35 (15.99–20.84)	17.50 (16.18–20.14)	0.840
Neurohormones					
NT-proBNP (pg/ml)	69 (53–104)	55 (50–83)	58 (50–93)	52 (50–111)	0.153
Renin (μU/ml)	15 (7–22)	16 (9–22)	11 (9–18)	12 (7–20)	0.178
Aldosterone (ng/L)	78 (38–97)	76 (39–95)	52 (37–104)	69 (48–94)	0.378

LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; TRG, tricuspid regurgitation gradient.

decrease in residual neurohumoral activation. While there was no increase in thirst or diuresis, a significant increase in natriuresis was observed. Finally, no changes in sodium skin buffering were noted (*Graphical Abstract*). Therefore, these data suggest that stable HFrEF patients can tolerate increased sodium intake for at least up to 4 weeks.

The baseline sodium intake of both patients with HFrEF and healthy controls was around 150 mmol (or 3.5 g) per day based upon the 24-h natriuresis, which is consistent with recent epidemiological data for the Western population reporting a daily sodium intake of 3.3–5.0 g.[17,18] Of note, this also illustrates that the patients in the current study poorly adhered to dietary sodium restrictions as there was no difference with healthy controls, but nevertheless they had no congestion. Observational studies have reported low adherence rates to sodium intake recommendations in HF patients, with only one in four patients adhering to a sodium intake of less than 2 g per day.[19,20] Additionally, we previously reported sodium intakes of up to 4.7 g per day without development of congestion during 30 weeks of follow-up.[21] Importantly, while daily sodium intake was increased by 1.2 g (51 mmol) – representing a 34% increase – none of the patients experienced symptoms or signs of congestion within the 4-week follow-up period. This was further supported by stable NT-proBNP levels, total body water and total blood volume throughout the study. These findings suggest that stable HFrEF patients are able to compensate for the increased sodium load and can maintain fluid balance without intra- or extravascular volume expansion.

In addition, these findings could have important implications for changing dietary restrictions in HFrEF patients. Allowing patients to increase their daily intake of sodium by 1.2 g (or salt by 3 g) implies a significant change and might help improving their quality of life.

We corroborated our previous finding that ambulatory chronic HFrEF patients without signs and symptoms of congestion on GDMT still demonstrate a residual rise in renin which is partially linked to the intake of RAAS inhibitors but also indicative of ongoing neurohumoral activation.[22] Renin is released from the afferent arteriole in response to three main stimuli: (1) decreased arterial blood pressure sensed by baroreceptor cells in the afferent arteriolar vessel wall, (2) decreased chloride concentrations in macula densa cells lining the renal tubules at the end of Henle's loop, and (3) sympathetic nerve system activation.[23,24] As a result of a higher chloride reabsorption in macula densa cells, inhibition of renin release by a high salt intake would be expected. Indeed, previous studies have demonstrated that a high salt diet can reduce neurohormonal activation in experimental canine HF models[25] and HF patients.[2,22,26–28] Intriguingly, this also indicates that the RAAS in HFrEF patients on GDMT remains appropriately responsive

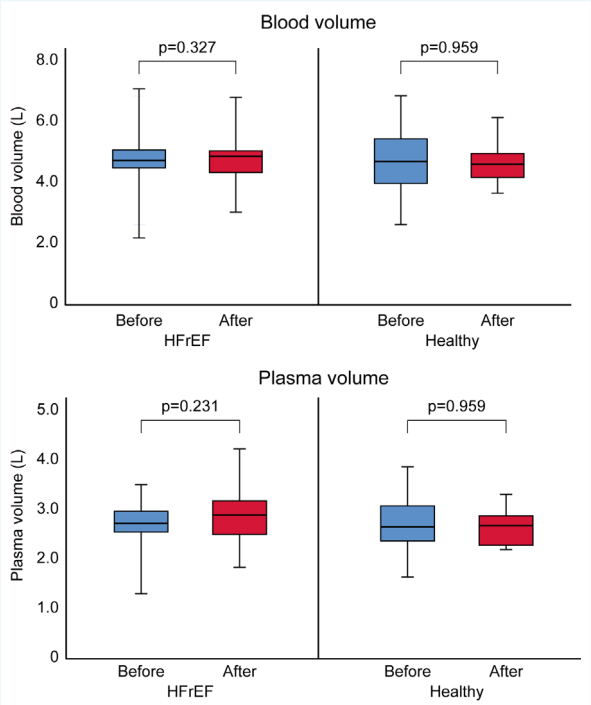


Figure 1 Blood and plasma volumes before and after sodium loading. HFrEF, heart failure with reduced ejection fraction.

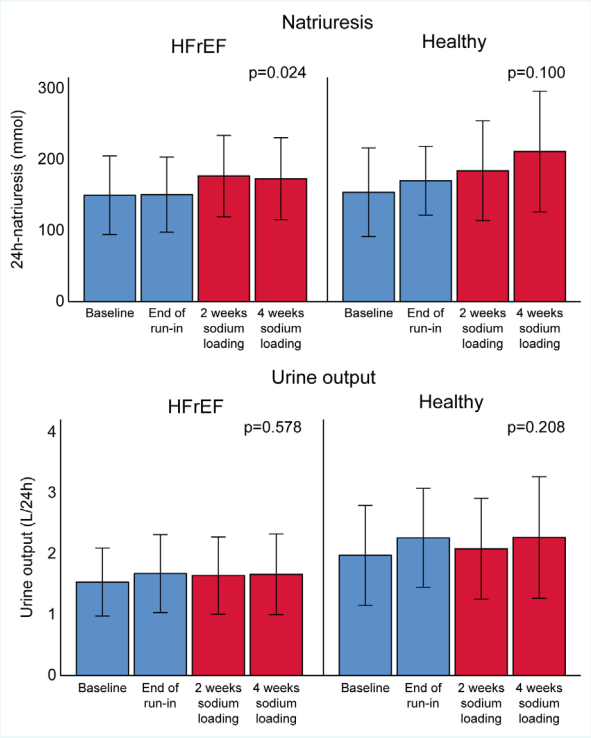


Figure 2 Twenty-four-hour natriuresis and urine output. Bars represent mean with standard deviation. HFrEF, heart failure with reduced ejection fraction.

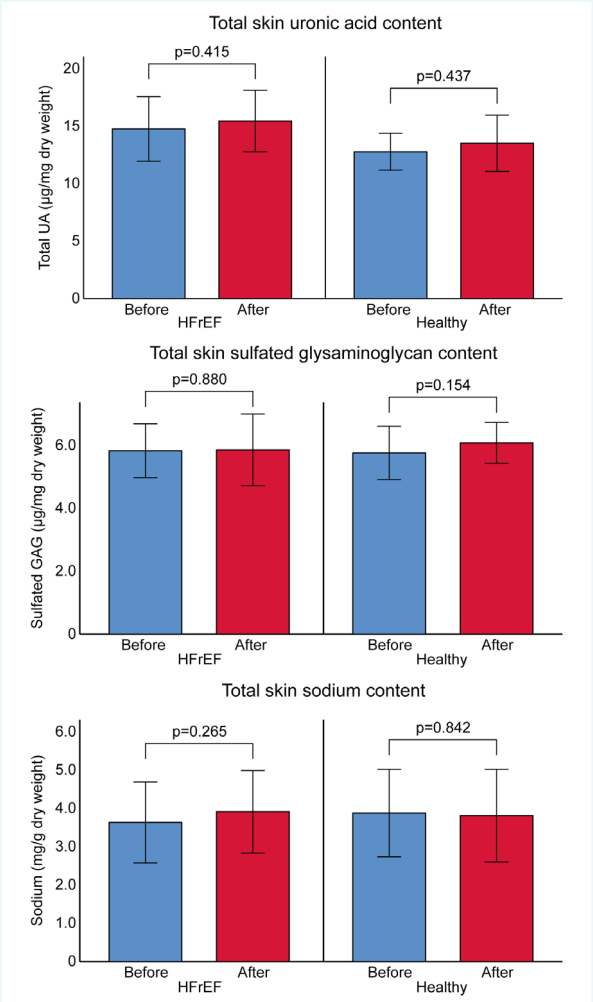


Figure 3 Skin glycosaminoglycan and sodium content before and after sodium loading. Bars represent mean with standard deviation. GAG, glycosaminoglycan; HFrEF, heart failure with reduced ejection fraction; UA, uronic acid.

to changes in salt loading as other variables like blood pressure or GDMT have not been changed during the study. Importantly, changes in renin were occurring without any obvious change in effective circulatory volume.

The increased sodium load was not coinciding with an increase in thirst or diuresis and at least partly compensated by an increase in natriuresis in HFrEF patients. Although the increase was less than expected in patients with HFrEF compared to healthy controls (25 mmol vs. 58 mmol increase), no definitive conclusions can be drawn. Urine collections are prone to collection errors and 'physiological' day-by-day variations in natriuresis can be substantial. In theory, HFrEF patients could have decreased their dietary sodium intake during the sodium loading phase but patients did not report any change in their diet, and also thirst was unaffected.

Emerging evidence has supported the presence of non-osmotic sodium buffering mechanisms in the skin, cartilage, bone and muscles.[10] This mechanism involves the binding of positively charged

sodium molecules to glycosaminoglycans, which are abundant linear polymers in the interstitium with a negative charge. This interaction allows sodium to be stored in the body without concurrent water retention, effectively acting as a reservoir. In patients with HFrEF (especially in decompensated states), an increased glycosaminoglycan skin content has been confirmed by skin biopsies and the glycosaminoglycan content correlated with tissue water and signs of volume overload.[11] In the current study, the baseline glycosaminoglycan content in the skin was comparable between patients with HFrEF and healthy controls. After 4 weeks of sodium loading, there were no significant changes observed in the glycosaminoglycan content in either group. Similarly, the skin sodium content was similar between patients and healthy controls, and there was no significant change after sodium loading. Of note, a previous study investigating the effects of sodium loading on blood pressure and skin sodium buffering in 48 healthy subjects reported a significant increase in skin sodium content after administering a much larger salt load (200 mmol daily) for 7 days.[29] However, these participants were considerably younger (mean age 30 ± 2 years) and were placed on a low sodium diet (70 mmol/day) prior to the intervention. Furthermore, the observed increase in skin sodium content was consistent only in men, with a mean increase of 0.25 mg/g of wet weight. In contrast, our study involved older participants with HFrEF, representing a different population with distinct characteristics. Therefore, the smaller salt load used in the current study might have been insufficient to induce detectable changes in only skin sodium content. Furthermore, recent data have questioned the concept of non-osmotic buffering and suggested changes in sodium content are merely a reflection of changed tissue architecture.[30]

This study has certain limitations. First, it was an open-label study, which could have influenced the dietary behaviour of the patients although we did not find evidence pointing in that direction and patients were instructed to not change their diet. Second, the study was non-randomized due to logistical constraints. During the study design, a randomized double-blind cross-over design was considered, but because this would necessitate skin biopsies at three different time points, this was not deemed feasible. Alternatively, a randomized design with an intervention and a control group was also considered. However, this would require a higher number of participants and because a difficult recruitment was anticipated, this study design was also not deemed feasible. Third, the study included a highly selected group of patients with HFrEF, limiting the generalizability of the results. Fourth, the 4-week duration of the salt loading intervention may not capture the longer-term effects. Fifth, it is difficult to disentangle whether changes in neurohormonal activation are related to sodium or chloride administration. Finally, our findings should not be expanded to NYHA class III or IV patients as previous studies have suggested a specific benefit of sodium restriction in this population.[31]

Conclusion

Selected HFrEF patients tolerate a prolonged and significant increase of sodium intake without signs and symptoms of congestion or blood volume increase. The increased sodium intake led to reduced neurohumoral activation and a significant increase in natriuresis. Further studies are needed to explore the long-term effects of sodium loading.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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