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RESEARCH ARTICLE

Diuretic response and effects of diuretic omission in ambulatory heart failure patients on chronic low-dose loop diuretic therapy

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Aims To study loop diuretic response and effect of loop diuretic omission in ambulatory heart failure (HF) patients on chronic low-dose loop diuretics.

Methods and results Urine collections were performed on two consecutive days in 40 ambulatory HF patients with 40–80 mg furosemide (day 1 with loop diuretic; day 2 without loop diuretic). Three phases were collected each day: (i) first 6 h; (ii) rest of the day; and (iii) night. On the day of loop diuretic intake, the total natriuresis was 125.9 (86.9–155.0) mmol/24 h and urine output was 1650 (1380–2025) mL/24 h. There was a clear loop diuretic response with a natriuresis of 9.4 (6.7–15.9) mmol/h and a urine output of 117 (83–167) mL/h during the first 6 h, followed by a significant drop in natriuresis and urine output during the rest of the day [2.6 (1.8–4.8) mmol/h and 55 (33–71) mL/h] and night [2.2 (1.6–3.5) mmol/h and 44 (34–73) mL/h]. On day 2, after loop diuretic omission, the natriuresis and urine output remained similarly low the entire day, resulting in a 50% reduction in natriuresis [55.1 (33.5–77.7) mmol/24 h; $P < 0.001$] and a 31% reduction in urine output [1035 (875–1425) mL/24 h; $P < 0.001$] compared with the day of loop diuretic intake.

Conclusion Patients with HF on chronic loop diuretic treatment still have a clear diuretic response phase, while loop diuretic omission leads to a significant drop in natriuresis and urine output, arguing against routine cessation of low-dose loop diuretics.

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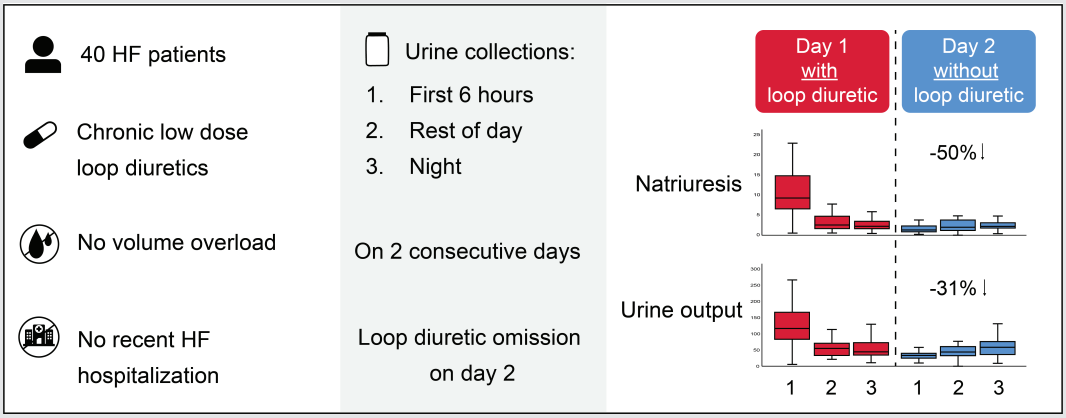
Graphical Abstract



In 40 heart failure (HF) patients on chronic low-dose loop diuretic therapy, phased urine collections were performed with and without loop diuretic. Despite long-term therapy, patients still had a clear loop diuretic response with a peak natriuresis and diuresis during the first 6 hours after loop diuretic intake. In contrast, loop diuretic omission on the subsequent day led to a 50% reduction in natriuresis and 31% reduction in diuresis.

Keywords Loop diuretics • Heart failure • Diuretic response • Natriuresis • Urine output

Introduction

Loop diuretics are a cornerstone treatment of congestion in heart failure (HF).[1] A high proportion of HF patients are prescribed diuretics during their disease course and often these drugs are continued as a part of their chronic treatment to prevent recurrence of congestion. In recent years, there has been increasing interest in the effects of deprescribing in chronic stable HF patients.[2–5] Loop diuretics have not consistently been shown to improve outcomes[6] and might interfere with up-titration of guideline-directed medical therapy.[7] Hence, an attempt to stop loop diuretics might be worthwhile. However, there are little and conflicting data on the success of loop diuretic withdrawal[4,8] and the effects on renal sodium handling are insufficiently understood. In an acute setting, administration of intravenous loop diuretics induces a steep increase in natriuresis and urine output, followed by a sodium retention phase during the rest of the day.[6] If this still holds true in HF patients taking loop diuretics chronically is unknown. In addition, there are no data on the effects of loop diuretic omission on natriuresis. Therefore, the objectives of this study were to investigate the different phases of natriuresis and urine output in ambulatory stable HF patients during low-dose loop diuretic intake and loop diuretic omission.

Methods

Study population

Patients were prospectively enrolled in the outpatient HF clinic of a single tertiary care centre between January 2019 and March 2020. Patients were eligible if they (i) were 18 years or older, (ii) had a diagnosis of HF >6 months, (iii) received a stable loop diuretic dose of 40–80 mg of furosemide (equivalent to 1-2 mg of bumetanide) once daily for >1 month, and (iv) were on a stable dose of guideline-directed medical therapy for at least 3 months. Patients were excluded if they had a HF hospitalization in the prior 3 months or if they had clinical signs of volume overload (oedema/ascites/pleural effusion). In addition, a small number of HF patients without the need for chronic loop diuretic use, who met all other inclusion and exclusion criteria, were enrolled as an exploratory comparator group. The study was approved by the institutional review board (18/0078U) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The manuscript was drafted according to the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies.[9]

Baseline data

All patients had a standard baseline evaluation consisting of medical history, clinical examination, blood sampling, an electrocardiogram, and a comprehensive transthoracic echocardiogram (*Figure 1*). Blood sampling was performed on the day before patients started the urine collections. The EVEREST congestion score[10] was calculated at baseline. All echocardiograms were performed according to the recommendations of the American Society of Echocardiography guidelines[11] with a Philips EPIQ 5 machine (Philips Healthcare, Andover, MA, USA) by an experienced sonographer independent of the study. Measurements were averaged from three consecutive cycles. Diastolic dysfunction was graded via an integrated approach as suggested by recent recommendations.[12] Right ventricular dysfunction was defined as a tricuspid annular plane systolic excursion <1.7 cm. Right atrial

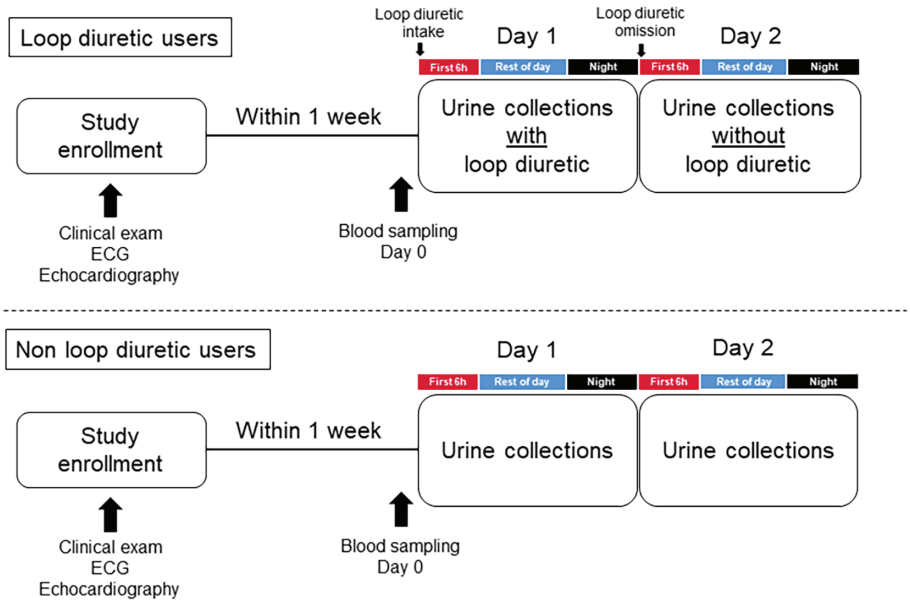


Figure 1 Study timeline. ECG, electrocardiogram.

pressure (RAP) was assessed with vena cava diameter >2.1 cm or <50% collapsibility indicating RAP >5 mmHg.

Urine collection

Within 1 week after the baseline evaluation, patients performed urine collections on two consecutive days. Urine was collected in three distinct phases every day (*Graphical abstract*). Immediately after their first morning void, patients took their loop diuretic and collected urine in the first container during the first 6 h, which coincides with the duration of the loop diuretic effect. The rest of the day, urine was collected in a second container until bedtime. All urine voids during the night, including the morning void on the subsequent day, were collected in a third container. On the second day, patients omitted their loop diuretic and performed the same sequence of urine collections, while continuing all other medication. Patients without the need for loop diuretics performed similar urine collections on two consecutive days. To ensure correct performance of the procedure, patients had to note the start and stop time on a standardized sheet. Urinary volume, sodium and creatinine were measured for each urine collection. To correct for differences in time windows, urine output and natriuresis were then recalculated as mL per hour and mmol per hour. Glomerular filtration rate (GFR) was calculated as creatinine clearance using the urine collection of the first day as the baseline reference.

A food diary, containing all ingested foods and drinks, was recorded by the patients on a fill-in sheet during the entire 48 h study protocol. Patients were asked to have an identical diet on the two consecutive days. The Belgian national nutrition database (Nubel®) was used to calculate sodium and fluid intake for each day separately afterwards.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation if normally distributed, or median (25th–75th percentile) otherwise. Categorical variables are noted as number (percentage). Categorical baseline variables were compared with Fisher's exact test. Continuous baseline variables were compared with Student's *t*-test or Mann–Whitney U test as appropriate. The difference in natriuresis and urine output between the day of diuretic intake and the day of diuretic omission was compared with Wilcoxon's signed rank test and compared with patients without loop diuretics using the Mann–Whitney U test. Then, the difference in natriuresis and urine output was calculated as percentage of the day of diuretic intake for patients on chronic loop diuretics. Univariate linear regression between the natriuresis and urine output difference and baseline variables was performed. Subsequently all variables with $P < 0.100$ were included in a multivariate analysis. For patients not needing loop diuretics, all urinary measures were averaged over the two consecutive days. The natriuresis and urine output across the different phases of the two consecutive days for patients with loop diuretics were compared using Friedman's test with post-hoc analysis with a Bonferroni correction for multiple testing. Patients with and without chronic loop diuretic use were compared using repeated measures ANOVA and post-hoc analysis with a Bonferroni correction for multiple testing. An interaction term between time and loop diuretic usage was added to the model to study differences in time patterns of natriuresis and urine output between patients with and without loop diuretic use on both days. Significance level was set at two-tailed $P < 0.05$. Statistical analysis was performed with SPSS Statistics version 25 (IBM, BM Corp., Armonk, NY, USA) and Stata 12.0 (Stata Corp., College Station, TX, USA).

Results

Study population

Between January 2019 and March 2020, 112 HF patients taking 40–80 mg furosemide daily and 26 HF patients not needing loop diuretics were approached for inclusion (online supplementary

Table 1 Study participants characteristics

	Loop diuretic (n = 40)	No loop diuretic (n = 10)	P-value
Age (years)	73 ± 8	68 ± 6	0.074
Male sex	27 (67.5%)	7 (70.0%)	1.000
Comorbidities			
Arterial hypertension	20 (50.0%)	3 (30.0%)	0.308
Diabetes	13 (32.5%)	2 (20.0%)	0.702
Dyslipidaemia	20 (50.0%)	4 (40.0%)	0.728
Coronary artery disease	13 (32.5%)	9 (90.0%)	**0.003**
Atrial fibrillation	28 (70.0%)	3 (30.0%)	**0.030**
Stroke	2 (5.0%)	1 (10.0%)	0.496
Peripheral artery disease	6 (15.0%)	1 (10.0%)	1.000
COPD	8 (20.0%)	0	0.184
Ischaemic aetiology	12 (30.0%)	9 (90.0%)	**0.001**
Duration of heart failure (years)	7.0 (2.5–11.1)	6.1 (3.9–10.9)	0.942
NYHA class			**0.001**
I	0	4 (40.0%)	
II	30 (75.0%)	6 (60.0%)	
III	10 (25.0%)	0	
EVEREST congestion score	4 (3–4)	1 (1–2)	**<0.001**
Physical exam			
Systolic blood pressure (mmHg)	123 ± 21	115 ± 15	0.244
Diastolic blood pressure (mmHg)	68 ± 10	64 ± 11	0.328
Heart rate (bpm)	72 ± 15	62 ± 9	**0.047**
BMI (kg/m^2)	26.9 ± 5.5	29.3 ± 5.5	0.223
Laboratory analysis			
Sodium (mmol/L)	140 ± 3	140 ± 4	0.705
Creatinine (mg/dL)	1.60 ± 0.55	1.19 ± 0.19	**0.027**
Urea (mg/dL)	81 ± 38	43 ± 18	**0.003**
GFR (mL/min)	51 ± 23	75 ± 26	**0.005**
NT-proBNP (pg/mL)	1377 (721–2402)	379 (282–467)	**0.001**
Echocardiography			
LVEF (%)	41 ± 10	33 ± 8	**0.020**
LVEF <40%	20 (50%)	9 (90%)	**0.031**
LVEDV (mL)	160 ± 68	198 ± 79	0.136
Diastolic dysfunction grade >1	21 (52.5%)	1 (10.0%)	**0.029**
RV dysfunction	14 (35.0%)	3 (30.0%)	1.000
TR gradient (mmHg)	29 ± 10	19 ± 7	**0.008**
RAP >5 mmHg	18 (45.0%)	0	**0.009**
Loop diuretic			
Dose (mg furosemide equivalent dose)	40 (40–40)	0	
Duration (years)	3.5 (1.3–9.5)		
Molecule			
Bumetanide	37 (92.5%)		
Furosemide	3 (7.5%)		
Therapy			
Thiazide	7 (17.5%)	0	0.319
ACE inhibitor/ARB	17 (42.5%)	4 (40.0%)	1.000
ARNI	18 (45.0%)	5 (50.0%)	1.000
Beta blocker	38 (95.0%)	10 (100%)	1.000
MRA	33 (82.5%)	9 (90.0%)	1.000
Antiplatelet	9 (21.0%)	8 (80.0%)	**0.001**
Anticoagulation	27 (67.5%)	2 (20.0%)	**0.011**
Statin	20 (50.0%)	9 (90.0%)	**0.031**
CRT	24 (60.0%)	5 (50.0%)	0.723
ICD	18 (45.0%)	9 (90.0%)	**0.014**
Sodium intake (mmol)[a]	107 ± 5	119 ± 19	0.398

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAP, right atrial pressure; RV, right ventricle; TR, tricuspid regurgitation.

[a]Sodium intake was calculated as the reported intake averaged over the 2-day study period.

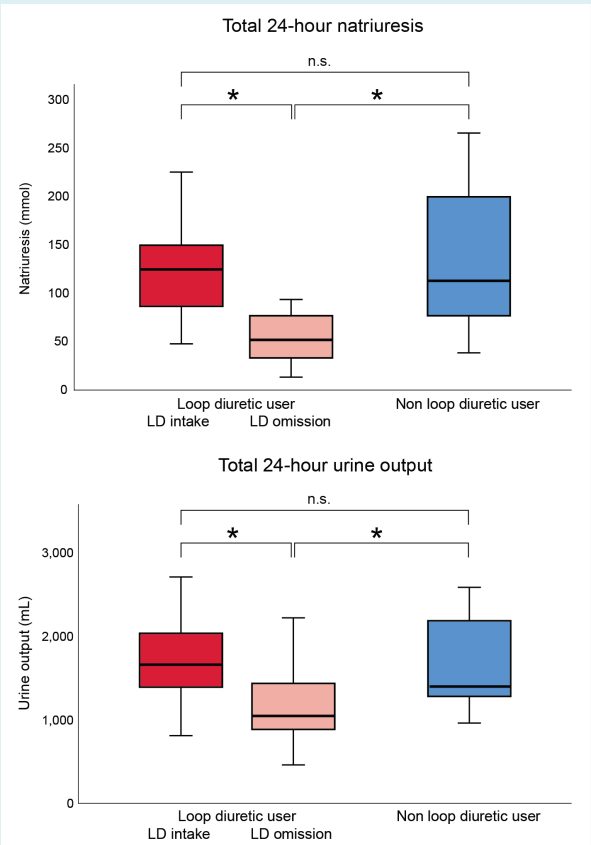


Figure 2 Total 24 h natriuresis and urine output. LD, loop diuretic. *$P < 0.05$.

Figure S1). Eighty patients found the study too laborious or did not understand the study procedure sufficiently to participate. Of the 58 patients included in the study, two patients did not return the urine samples and six patients were excluded due to incorrect performance of the urine collections, rendering a study population of 40 patients on loop diuretics and 10 patients not needing loop diuretics. Baseline characteristics of the final study population are displayed in *Table 1*. Patients on chronic loop diuretics had less ischaemic heart disease, more history of atrial fibrillation, a higher heart rate and worse GFR compared with patients not needing loop diuretics. Of note, EVEREST congestion score was higher, echocardiographic signs of elevated left and right-sided filling pressures were more frequent and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was higher in patients on chronic loop diuretics. There were no differences in these parameters of congestion and GFR between patients with a left ventricular ejection fraction (LVEF) <40% and LVEF ≥40% (online supplementary *Table S1*).

Sodium and fluid retention in patients on chronic loop diuretics

In HF patients on chronic loop diuretics, natriuresis [125.9 (86.9–155.0) vs. 55.1 (33.5–77.7) mmol/24 h, $P < 0.001$] and urine output [1650 (1380–2025) vs. 1035 (875–1425) mL/24 h, $P < 0.001$] were significantly lower on the day of diuretic omission (*Figure 2*). This corresponded to a reduction in natriuresis of 50.2 ± 23.2% and urine output of 30.5 ± 20.6% compared with the day of loop diuretic intake. The reduction in natriuresis and urine output was similar between patients with LVEF <40% vs. LVEF ≥40% (online supplementary *Figure S2*). Only two patients (5%) did not have a lower natriuresis. The only univariate variable associated with the magnitude of natriuresis reduction was thiazide use (*Table 2*), which was no longer significant in the multivariate analysis. None of the other clinical or echocardiographic variables, including GFR, NT-proBNP levels or dosage of neurohormonal blockers, were associated with the magnitude of natriuresis reduction. There were no univariate or multivariate variables that were associated with the magnitude of urine output reduction (*Table 3*). The calculated sodium intake (109 ± 37 mmol vs. 104 ± 35 mmol; $P = 0.416$) and water intake (2309 ± 571 mL vs. 2285 ± 615 mL; $P = 0.802$) were comparable on both days, as was the GFR (51 ± 23 mL/min vs. 50 ± 25 mL/min; $P = 0.761$).

Natriuresis and urine output profile in patients on chronic loop diuretics

The distinct collection phases of natriuresis and urine output for the two consecutive days are displayed in *Figure 3*. After loop diuretic administration, a natriuresis of 9.4 (6.7–15.9) mmol/h and a urine output of 117 (83–167) mL/h during the first 6 h were recorded. Subsequently, there was a drop in both natriuresis and urine output to 2.6 (1.8–4.8) mmol/h and 55 (33–71) mL/h, respectively, during the rest of the day, and 2.2 (1.6–3.5) mmol/h and 44 (34–73) mL/h during the night. The next morning, after loop diuretic omission, the natriuresis was 1.4 (0.9–2.3) mmol/h and urine output 33 (25–40) mL/h the first 6 h, 2.1 (1.2–3.9) mmol/h and 44 (33–61) mL/h the rest of the day, and 2.3 (1.8–3.4) mmol/h and 59 (36–76) mL/h during the night. Both natriuresis ($P < 0.001$) and urine output ($P < 0.001$) were significantly higher during the first 6 h after loop diuretic intake compared with all other phases of both days. The absolute natriuresis (expressed as total mmol, and thus not indexed per hour) and urine output (total mL) showed similar findings (online supplementary *Figure S3*).

Comparison between patients with and without loop diuretic need

Patients not needing loop diuretics had an averaged natriuresis of 113.1 (77.1–200.1) mmol/24 h, which was similar to patients on chronic loop diuretics on the day of loop diuretic intake [125.9 (86.9–155.0) mmol/24 h; $P = 1.000$], but significantly higher than the natriuresis on the day of loop diuretic omission [55.1 (33.5–77.7) mmol/24 h; $P < 0.001$] (*Figure 2*). The averaged total urine output for patients not needing loop diuretics was 1388 (1270–2175) mL/24 h, again similar to patients on chronic loop diuretics on the day of loop diuretic intake [1650 (1380–2025) mL/24 h; $P = 0.558$], but higher compared with the day of loop diuretic omission [1035 (875–1425) mL/24 h;

Table 2 Univariate and multivariate regression analysis for percentage of natriuresis reduction after loop diuretic omission

Parameter	Univariate predictors		Multivariate predictors	
	Standardized beta	*P*-value	Standardized beta	*P*-value
Age (years)	−0.138	0.397		
Male sex	−0.120	0.463		
Diabetes	−0.193	0.233		
Atrial fibrillation	−0.084	0.608		
NYHA class	0.167	0.302		
EVEREST congestion score	0.178	0.272		
Duration of heart failure (years)	0.134	0.409		
Duration of loop diuretic use (years)	0.199	0.218		
Furosemide equivalent dose (mg)	0.077	0.638		
Thiazide	−0.337	**0.033**	−0.297	0.073
ACE-inhibitor/ARB/ARNI (% of target dose)	−0.078	0.633		
ARNI	−0.073	0.653		
Beta-blocker (% of target dose)	−0.182	0.260		
MRA	0.035	0.831		
BMI (kg/m^2)	−0.099	0.542		
Heart rate (bpm)	0.137	0.401		
Systolic blood pressure (mmHg)	0.128	0.432		
Diastolic blood pressure (mmHg)	0.048	0.766		
Serum creatinine (mg/dL)	0.052	0.751		
GFR (mL/min)	−0.240	0.136		
Log NT-proBNP (pg/mL)	0.188	0.245		
Diastolic dysfunction grade >1	0.143	0.377		
TR gradient (mmHg)	0.285	**0.092**	0.242	0.142
Estimated RAP >5 mmHg	0.251	0.118		
RV dysfunction	0.207	0.201		
24 h urinary sodium day 1 (mmol)	0.157	0.334		

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAP, right atrial pressure; RV, right ventricle; TR, tricuspid regurgitation.

$P = 0.027$]. In patients not needing loop diuretics, there was no difference in hourly natriuresis across the different collection phases ($P = 0.108$). The different phases of natriuresis and urine output of the two consecutive days comparing patients on chronic loop diuretics and those without are displayed in *Figure 4*. On the day of loop diuretic intake, natriuresis and urine output were higher in patients on chronic loop diuretics during the first 6 h after intake of the loop diuretic, but lower during the rest of the day and night. On the day of loop diuretic omission both natriuresis and urine output were lower in patients on chronic loop diuretics during the entire day. Of note, despite these absolute differences, the time pattern did not differ between patient groups ($P = 0.230$ for natriuresis and $P = 0.827$ for urine output) on day 2. For absolute natriuresis and urine output, findings were again similar (online supplementary *Figure S4*).

Discussion

The results of this pivotal prospective observational study in contemporary optimally treated HF patients indicate that (i) ambulatory stable HF patients in need of chronic low-dose loop diuretic therapy still have a clear loop diuretic response with high natriuresis and high urine output, followed by a significant drop in both during the rest of the day and night; (ii) loop diuretic omission leads to a 50% drop in natriuresis and a 31% drop in urine output; (iii) the observed reduction in natriuresis and urine output seems to relate to the omission of the diuretic more than to the underlying clinical or cardiac status; (iv) although the small exploratory group of HF patients without the need for loop diuretic use has a similar total natriuresis and urine output, there is a clear difference in time pattern on the day of loop diuretic intake. In contrast, on the day of loop diuretic omission, time patterns become similar, while the total natriuresis is lower.

This is the first study to investigate the ambulatory loop diuretic response profile in chronic stable HF patients on contemporary optimal HF therapies. Despite long-term use, even low-dose loop diuretics continue to significantly increase natriuresis and urine output. A subsequent significant drop in natriuresis and urine output was noted the remaining day and night corresponding to the previously described post-diuretic sodium retention in acute

Table 3 Univariate and multivariate regression analysis for percentage of urine output reduction after loop diuretic omission

Parameter	Univariate predictors		Multivariate predictors	
	Standardized beta	*P*-value	Standardized beta	*P*-value
Age (years)	−0.087	0.593		
Male sex	−0.069	0.671		
Diabetes	−0.075	0.645		
Atrial fibrillation	−0.111	0.497		
NYHA class	−0.020	0.901		
EVEREST congestion score	−0.073	0.651		
Duration of heart failure (years)	0.117	0.473		
Duration of loop diuretic use (years)	0.192	0.236		
Furosemide equivalent dose (mg)	0.057	0.725		
Thiazide	−0.232	0.149		
ACE-inhibitor/ARB/ARNI (% of target dose)	−0.076	0.641		
ARNI	−0.090	0.583		
Beta-blocker (% of target dose)	−0.188	0.244		
MRA	0.266	**0.097**	0.260	0.095
BMI (kg/m^2)	0.065	0.689		
Heart rate (bpm)	0.089	0.587		
Systolic blood pressure (mmHg)	0.109	0.504		
Diastolic blood pressure (mmHg)	−0.076	0.641		
Serum creatinine (mg/dL)	−0.008	0.961		
GFR (mL/min)	−0.179	0.268		
Log NT-proBNP (pg/mL)	0.034	0.834		
Diastolic dysfunction grade >1	−0.059	0.717		
TR gradient (mmHg)	0.162	0.345		
Estimated RAP >5 mmHg	0.272	**0.089**	0.267	0.088
RV dysfunction	0.008	0.960		
24 h urine output day 1 (mL)	−0.006	0.971		

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAP, right atrial pressure; RV, right ventricle; TR, tricuspid regurgitation.

HF patients.[13] While other studies using intravenous loop diuretics have shown similar effects, they have only been performed in a very small number of study participants of whom none had HF or previous use of loop diuretics, and the post-diuretic natriuresis was not studied beyond 24 h.[13,14] Of note, the data of our study clearly illustrate that loop diuretic omission extends the post-diuretic sodium retention beyond 24 h, resulting in a 50% reduction in natriuresis and a 31% reduction in urine output. This also indicates that clinical estimation of the need for chronic loop diuretic maintenance was correct in our study population. Indeed, patients on chronic loop diuretics needed these drugs to enhance natriuresis, while patients not needing loop diuretics succeeded to achieve a similar natriuresis without.

Renal sodium avidity is very high in patients with HF and ongoing congestion with different contributing mechanisms.[15] Indeed, venous congestion and reduced renal blood flow leading to higher filtration fraction, a lower number of functionally active nephrons and neurohormonal activation, all contribute to impaired natriuresis. Loop diuretics overcome a part of this avidity by blocking the sodium reabsorption at the loop of Henle and thus increasing natriuresis and total urine output. However, long-term use of loop diuretics can lead to hypertrophy of distal tubular segments and increased distal sodium reabsorption, reducing diuretic response.[16] The remaining mild signs of congestion as well as the adaptations to chronic utilization might contribute to increased and prolonged sodium retention in case of loop diuretic omission.

Importantly, median NT-proBNP levels in patients on chronic loop diuretic therapy were 1377 pg/mL, which is comparable to patients in recent HF drug trials,[17–19] and a high proportion of patients had echocardiographic evidence of elevated filling pressures, clearly indicating that our patient population had an increased risk for adverse outcomes related to ongoing subclinical congestion warranting chronic diuretic utilization. Indeed, in a recent small cross-over trial, stopping neurohormonal blockers and diuretics in stable HF patients already led to increased signs of congestion after 48 h.[5] Furthermore, withdrawal of long-term loop diuretic treatment was only successful in 50% of clinically stable elderly patients in a small randomized trial.[8] Of note, only 50% of the patients had HF as an indication for loop diuretics and phenotyping was poor. In contrast, in the ReBIC-1 (Rede Brasileira

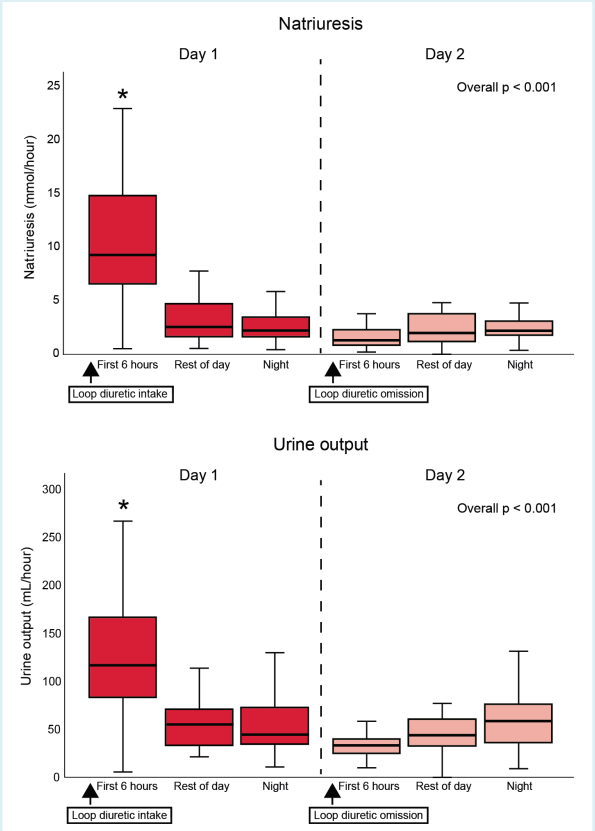


Figure 3 Natriuresis and urine output profile in heart failure patients on chronic loop diuretic therapy. *$P < 0.05$ compared with all other collections.

de Estudos em Insuficiencia Cardıaca) trial, which studied patients with a lower median NT-proBNP (652 pg/mL) and low loop diuretic dosage (40–80 mg furosemide equivalent dose), loop diuretic therapy could be stopped without increased dyspnoea nor increased need for furosemide reuse after 30 days.[4] However, our data suggest that low-dose loop diuretic omission in stable HF patients on optimal medical background therapy without clinical signs of congestion but with elevated NT-proBNP does pose a risk of increased sodium and water retention.

Interestingly, commonly used clinical signs of congestion, NT-proBNP and echocardiographic variables associated with increased filling pressures could not predict the magnitude of natriuresis reduction after loop diuretic omission. In a study investigating the value of routine investigations to predict the success of loop diuretic down-titration in 50 HF patients, neither of these same variables were predictive of down-titration success.[20] As such, predicting renal response to loop diuretic omission remains difficult, and probably relates to the complex cardiorenal physiology in HF with congestion itself as well as chronic loop diuretic utilization to be related to the observed sodium and fluid retention. Therefore, in the absence of good predictors, a trial of loop diuretic withdrawal should probably only be attempted in stable patients with HF with reduced ejection fraction, mild symptoms, low NT-proBNP and on optimized guideline-directed medical therapy as these would most resemble the population of the ReBIC-1 trial. Although urinary sodium is an attractive target to assess sodium avidity and has gained attention in predicting diuretic response in acute HF,[21] there are currently no data on its value in predicting success of loop diuretic withdrawal. Of note, other HF therapies, such as angiotensin receptor–neprilysin inhibitors (ARNI) and sodium–glucose co-transporter 2 (SGLT2) inhibitors, might have a significant impact on the pattern of natriuresis and urine output. In a post-hoc analysis of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, the use of ARNI was associated with more loop diuretic dose reductions and fewer dose increases compared with enalapril[22], which suggests that switching from angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to ARNI might reduce sodium avidity and increase the success of loop diuretic withdrawal. However, in patients needing loop diuretics in our study, ARNI use was not correlated with the magnitude of sodium retention after loop diuretic omission. In addition, SGLT2 inhibitors block glucose and sodium reabsorption in the proximal tubule and might thus enhance natriuresis. However, results of recent studies on the effects of SGTL2 inhibitors on natriuresis are conflicting[23–26] and if SGLT2 inhibitors increase feasibility of loop diuretic withdrawal is unknown. While the use of acetazolamide might result in a better natriuretic response in patients with acute HF, it is currently unknown if chronic acetazolamide therapy might reduce the need for chronic loop diuretic therapy.[27]

Finally, glomerular filtration and natriuresis show diurnal variations in healthy subjects, peaking during the middle of the day with a dip during the night.[28] Both HF and loop diuretics disturb this physiological circadian variation as corroborated in our study. HF patients without loop diuretic therapy showed a different pattern with a fairly stable natriuresis over 24 h but a dip in natriuresis during the first 6 h of the day. This distinct ‘HF pattern’ might reflect fluctuations in neurohormonal activation, the effect of medication and/or haemodynamic fluctuations due to body position (upright vs. recumbent). In addition, patients on chronic loop diuretics showed another pattern with a peak natriuretic response after looop diuretic intake and a dip during the rest of the day and night. Interestingly, diuretic omission led to a pattern similar to those not taking loop diuretics, albeit lower in absolute numbers.

Clinical perspective

The finding of a prolonged sodium retention phase after loop diuretic omission argues against prescribing loop diuretics at a lower frequency than once daily in HF patients and also against routine cessation of loop diuretics. When a trial of loop diuretic withdrawal is considered, it should be performed cautiously, especially in patients with persistently elevated NT-proBNP with close monitoring to tackle sodium and fluid retention early. Additionally, the potential effects on diuresis and natriuresis of new HF drugs like ARNI, SGLT2 inhibitors, vericiguat and omecamtiv mecarbil need further investigation.

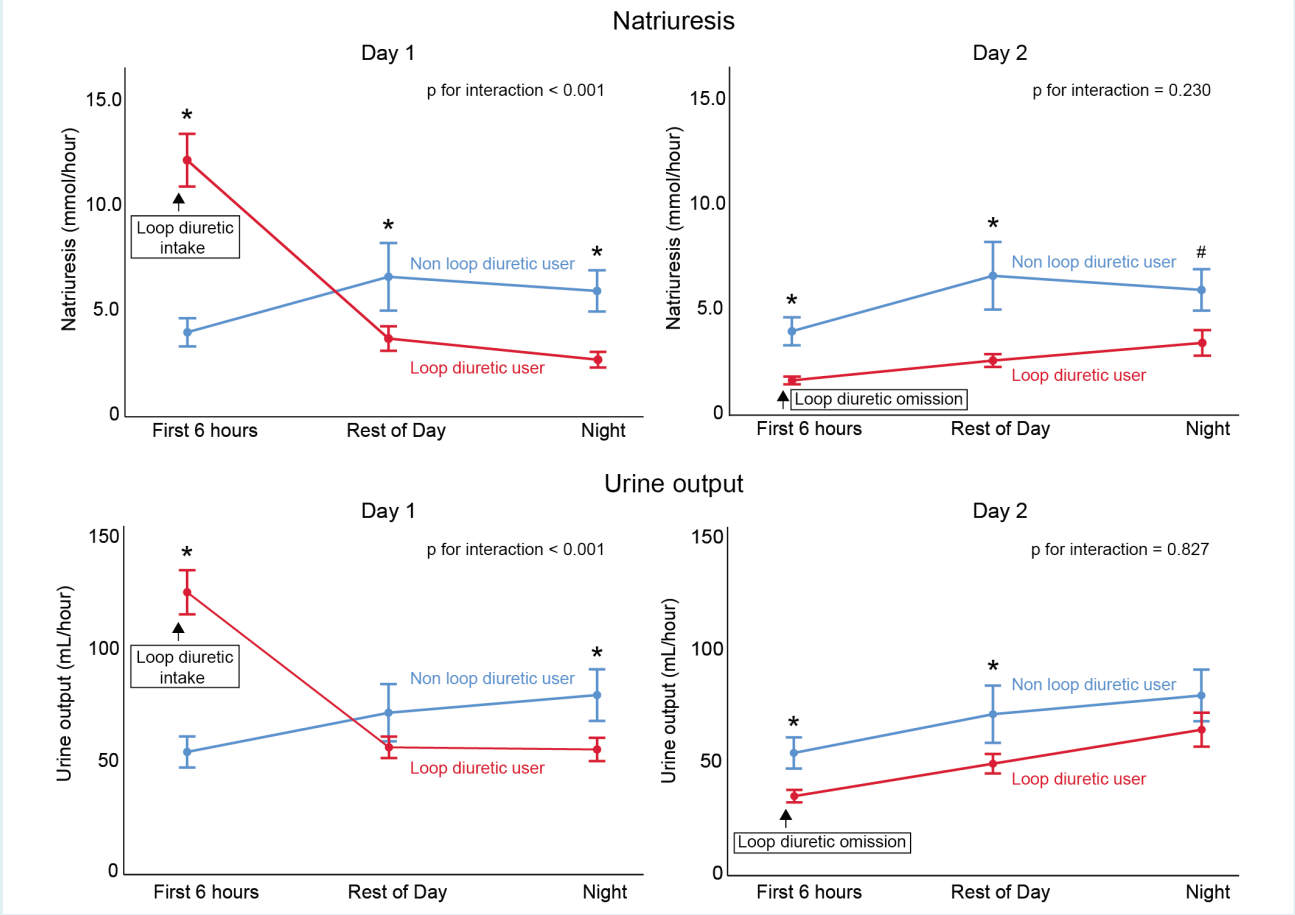


Figure 4 Natriuresis and urine output profile in heart failure patients with and without chronic loop diuretics. Bars represent mean ± standard error. *P*-values for between-group (loop diuretic user vs. non loop diuretic user) differences: $^{*}P < 0.05$; $^{\#}P = 0.06$. *P* for interaction represents the significance of group-time interaction.

Limitations

This study was subject to certain limitations. First, the study was performed in ambulatory patients, who collected urine at home without supervision. However, to account for this, only patients with sufficient understanding during screening were included and all patients noted the exact hours of collection on a standardized form to ensure correct performance of the procedure. Patients who violated the procedure were excluded. Second, the inclusion criteria specified a rather low loop diuretic dose to ensure a homogeneous patient population. Third, the study sample size was small, inherent to mechanistic studies that require complex patient handling like phased urine collections, which also limits the possibilities to perform subgroup analyses. Fourth, we did not collect urine beyond 48 h after loop diuretic intake. Whether the low natriuresis and low urine output state would persist after this period remains unknown. Fifth, the effects of diuretic omission on clinical, echocardiographic and biochemical parameters was not studied. Last, as none of the study participants used the longer acting torsemide, the results cannot be extrapolated to torsemide users.

Conclusion

Ambulatory HF patients on low-dose chronic loop diuretic therapy continue to have a diuretic response phase, followed by a period of low natriuresis and urine output during the rest of the day. Diuretic omission results in a 50% reduction in natriuresis and a 31% reduction in urine output.

Supplementary Information

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

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