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Evaluation of the effectiveness of diuretic treatment using the RenalGuard system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment

Authors: Paweł Siwołowski, Piotr Gajewski, Mateusz Sokolski, Robert Zymliński, Mateusz Guzik, Joanna Szachniewicz, Piotr Ponikowski

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[ORIGINAL ARTICLE]

Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment — preliminary study

[Short title: **Treatment using the RenalGuard® system in ADHF**]

Paweł Siwołowski, Piotr Gajewski, Mateusz Sokolski, Robert Zymliński, Mateusz Guzik,
Joanna Szachniewicz, Piotr Ponikowski

Department of Cardiology, Institute of Heart Diseases, University Hospital, Wrocław, Poland

Address for correspondence: Paweł Siwołowski, Department of Cardiology, Institute of Heart Diseases, University Hospital, ul. Borowska 213, 50–556 Wrocław, Poland, tel: +48 608378555, e-mail: patiks@yahoo.com

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Abstract.

Background: *The aim of the study was to analyze the potential relationship between the diuretic response, the clinical profile and the concentrations of selected biochemical markers and to identify a group of patients who will benefit from a new form of therapy combining standard diuretic therapy with the use of a RenalGuard® system.*

Methods: *This is a retrospective study of 19 patients (mean age 67 ± 10 years, 95% men) hospitalized due to acute decompensated heart failure (ADHF, NYHA class III–IV, BP $125 \pm 14/73 \pm 16$ mmHg, eGFR 58 ± 24) with persistent overhydration despite standard therapy. A targeted comparative analysis of selected clinical and biochemical parameters was performed to determine the parameters associated with a better diuretic response [good diuretic responders (GDR) group].*

Results: *The good diuretic responders group had significantly lower levels of creatinine (1.23 ± 0.4 vs. 1.69 ± 0.35 , $p = 0.025$) magnesium 0.70 ± 0.14 vs. 0.83 ± 0.09 , $p = 0.030$) and blood urea nitrogen (BUN, 28 ± 11 vs. 39 ± 10 , $p = 0.045$). Additionally, in GDR group a statistically significant greater ability to dilute urine in the 12th and 24th hour of therapy was found.*

Conclusions: *The results of the study indicate the potential use of the RenalGuard® system in combination with standard intravenous diuretic therapy for controlled dehydration in the treatment of a selected group of patients with ADHF. It is advisable to identify the detailed mechanisms of GDR and characterize this group of patients more precisely.*

Keywords: **acute heart failure, decongestion, diuretic response, spot urine analysis, biomarkers**

INTRODUCTION

Despite a robust body of knowledge on heart failure pathogenesis and treatment, exacerbation of heart failure symptoms remains one of the main causes of hospitalization in hospital wards in patients over 65 years of age and is still related to high mortality and frequency of rehospitalizations [1]. In-hospital mortality among patients hospitalized due to acute heart failure (AHF) ranges from 4 to 10%, and the incidence of death and re-hospitalization exceeds 45% in a one-year follow-up. The most common form of clinical manifestation in patients with acute heart failure (50–70% of cases) is the so-called acute decompensated heart failure (ADHF). Initial clinical evaluation of patients with decompensated heart failure allows for easy identification of four different hemodynamic profiles, including the largest group of patients with symptoms of overhydration, without reduced peripheral perfusion, i.e., the so-called “wet-warm” profile [2].

Regardless of the cause of decompensation, one of the basic goals in treating patients with acute decompensated heart failure and symptoms of fluid overload is the rapid and safe elimination of overhydration using, among others, loop diuretics. It is known that excessive increase in the volume of the extravascular space is, alongside hyponatremia and increased blood urea nitrogen (BUN), one of the most important factors of poor prognosis in patients with decompensated heart failure. The associated chronic activation of many neurohormonal factors (mainly the renin-angiotensin-aldosterone system or vasopressin), in the group of patients treated for chronic heart failure, causes a gradual decrease in the effectiveness of standard pharmacological treatment, and as a consequence leading to partial or complete resistance to diuretic treatment and progressive overhydration.

The first-line treatment option for exacerbation of chronic heart failure symptoms in patients with symptoms of congestion and overhydration remains loop diuretics, often in combination with vasodilators [1, 3–5]. The main goal of diuretic therapy is to remove excess fluid from the body. First, excess fluid is removed from the intravascular space and then a volume of fluid is moved from the extravascular space to the vessels of the vascular bed at a rate known as plasma refill rate (PRR). From a clinical point of view, the key element for the safety and effectiveness of diuretic therapy is the ability to achieve a stable, fully controlled rate of excess fluid movement from the extravascular space to the vascular bed. If the rate of excess fluid removal from the intravascular space is too fast in relation to the plasma refill rate, excessive emptying of the intravascular space may occur, resulting in a decrease in cardiac output and decreased renal perfusion, which leads to the activation of a number of renal and extrarenal mechanisms of sodium and water retention in the body and, consequently, to the development of diuretic resistance [6, 7]. There are also no clear guidelines on the optimal dosing of diuretics, monitoring their efficacy and safety in terms of the risk of excessive diuretic effect (excessive dehydration), kidney damage and worsening of long-term prognosis. This is an extremely relevant clinical problem because deterioration of renal function during hospitalization due to exacerbation of heart failure symptoms is very common and has a significant impact on prognosis. As does chronic kidney disease coexisting with heart failure, which is an independent factor of poor prognosis in patients with acute heart failure [8]. Moreover, it should be considered that the use of furosemide in treatment of patients hospitalized in intensive care units is associated with a significant risk of acute kidney damage [9]. There is therefore still a need to develop new, safe and effective methods

for eliminating overhydration and monitoring diuretic therapy in patients with acute heart failure.

Aim of the study

The aim of the study was to assess the use of a loop diuretic (furosemide) in combination with the method of controlled dehydration using the RenalGuard® system in patients with ADHF and concomitant chronic kidney disease, hospitalized due to ADHF, and to attempt to identify a group of patients who will derive significantly greater benefit from this form of therapy, based on the analysis of the potential relationship between the diuretic response and the clinical profile of these patients and the concentrations of selected biochemical markers.

METHODS

The analysis was performed based on a prospective, single-center study conducted in patients hospitalized in the 4th Military Clinical Hospital in Wrocław due to ADHF.

The study involved a non-randomized, retrospective analysis of the therapy of 19 patients hospitalized due to ADHF [NYHA class III–IV, BP $125 \pm 14/73 \pm 16$ mmHg, estimated glomerular filtration rate (eGFR) 58 ± 24] with persistent symptoms of overhydration despite standard therapy based on the use of an intravenous loop diuretic. The study was conducted with the approval of the local Bioethics Committee of the Lower Silesian Chamber of Physicians and the Bioethics Committee at the Medical University of Wrocław (opinion No. KB — 210/2019) and in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All patients gave their written informed consent to participate in the study before being included in the study.

The most important inclusion criteria for the study included:

- 1) Primary diagnosis of acute heart failure as the cause of hospitalization.
- 2) Clinical signs of overhydration (despite standard treatment of acute heart failure with intravenous furosemide), which included: persistent dyspnea at rest or with minimal physical effort at screening and recruitment, basal crackles, peripheral edema $\geq +1$ (on a scale 0–3 +) on physical examination and radiological evidence of pulmonary congestion on plane chest X-ray.

- 3) Elevated natriuretic peptide levels: B-type natriuretic peptide (BNP) ≥ 500 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 2000 pg/mL; in patients ≥ 75 years of age or with current atrial fibrillation (at the time of inclusion), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL.
- 4) Systolic blood pressure ≥ 100 mmHg at the start and end of the screening test.
- 5) Previous chronic kidney disease defined as an eGFR between presentation and enrollment to the study ≥ 25 and < 90 mL/min/1.73 m², calculated using the MDRD equation.

The exclusion criteria included mainly:

- 1) Total urine output < 200 mL or average urine rate < 50 mL/hour in the Diuretic Challenge.
- 2) Patient is managed on, or there is a plan to manage on, renal replacement therapy (RRT) such as ultrafiltration, hemofiltration or dialysis.
- 3) Dyspnea due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), which may interfere with the ability to interpret the primary cause of dyspnea.
- 4) Patients with blood pressure > 180 mmHg at the time of enrollment or persistent heart rate > 130 bpm.
- 5) Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis.

The intravenous administration of a loop diuretic recommended by the current European Society of Cardiology (ESC) guidelines in the treatment of patients with acute heart failure was combined with the use of the RenalGuard® system, which operates by administering 0.9% saline solution by intravenous infusion in an amount proportional to the continuously measured volume of urine obtained per hour. The loop diuretic (furosemide) was administered in an individual dose for each patient, determined by the treating physician, necessary to ensure a time-planned negative fluid balance value.

Patients treated with intravenous furosemide during the first 24 hours of hospitalization, underwent a therapy combining intravenous furosemide with the use of the RenalGuard® system and the fluid loss limit (FLL) determined by the treating physician for the next 24 hours. The RenalGuard® system infusion catheter was connected to the patient

via a peripheral venous access, and a urine reservoir placed on the device scale was connected to a standard Foley catheter placed in the patient's bladder for continuous monitoring of urine output. At the beginning of therapy, all patients received 40 mg of furosemide as an intravenous bolus. In the first hour of therapy, hydration was continued in a 1:1 ratio to the obtained diuretic effect (matched fluid balance phase), and then the desired fluid balance was set (desired fluid balance phase) at -100 mL/h. (Fig. 1) Subsequent doses of furosemide and the drug administration regimen (intravenous bolus or continuous intravenous infusion) were determined based on the assessment of the patient's clinical condition in order to achieve the assumed negative fluid balance. The study lasted up to 24 hours or until the assumed fluid loss was achieved, indicating the achievement of euvolemia, as assessed by the study doctor. In all patients, the symptoms of heart failure and diuretic effect were assessed, blood and urine were collected for laboratory assessment of selected biochemical parameters and biomarkers such as creatinine, eGFR, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), endothelin-1 (ET-1), kidney injury molecule-1 (KIM-1) at specific time intervals during therapy, at discharge and during 30-day follow-up, as well as the relationship between the diuretic response and the sodium ions and creatinine levels in urine.

Statistical analysis

Normally distributed continuous variables were described by means \pm standard deviation, non-normally distributed variables were described by medians with (upper and lower quartiles), categorical variables were given as counts and percentages. The normality of the distribution was tested using the Shapiro–Wilk test. The statistical significance of differences between time points was assessed using the paired samples t-test or the Wilcoxon test. Differences between the good and poor diuretic response groups were assessed using the unpaired t test or the Mann–Whitney test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATISTICA 13 software (StatSoft Poland, Kraków, Poland).

RESULTS

The clinical characteristics of the study population are summarized in Table 1. The vast majority of the study group were men (95%), the mean age was 67 ± 10 years. Immediately before enrollment to the study, 16 patients (84%) presented with symptoms of

heart failure in NYHA class IV, the remaining patients were in NYHA class III. The mean systolic blood pressure on admission was 125 ± 14 mmHg, NTproBNP level was 4492 (2662–6806) pg/mL, and hospitalization time 14 ± 9 days.

Diuretic effect

The mean duration of the Renal Guard® therapy in the analyzed group of patients was 25 ± 1 hours. The diuretic response during therapy expressed in milliliters (mL) was assessed per 40 mg of furosemide, obtaining a median for the entire study population of 933 mL/40 mg (Tab. 2).

Based on the median obtained in this way, the study population was divided into two groups:

1. Those patients who achieved a better diuretic effect and clinical response during the therapy were called “good diuretic responders” (GDR).
2. Those patients who achieved a worse diuretic effect and had less benefit from the therapy were called “worse diuretic responders” (WDR) (Tab. 3).

Biochemical parameters

In the next stage, a targeted comparative analysis of selected clinical and biochemical parameters was performed for the first time in both groups to determine in detail the parameters associated with a better diuretic response and the greatest clinical benefit after the applied therapy. In the GDR group, significantly lower levels of creatinine, magnesium and BUN were found (Tab. 4).

Moreover, the analysis of electrolyte levels in spot urine samples collected at specific time intervals of therapy revealed no significant differences of sodium and chloride ions concentrations at the beginning, in the 1st, 6th, and 12th hour and after the end of therapy (Fig. 2).

The relationships between the diuretic response and the concentrations of sodium ions and creatinine in urine used as markers of the kidney's ability to dilute urine (uCreat in baseline to uCreat in subsequent timepoints) and the relationships between natriuresis and urine dilution (water excretion) defined as uNa/uCreat were also analyzed in the studied patient population. In the GDR group, a statistically significant greater ability to dilute urine

was found in the 12th and 24th hour of therapy, with no differences in uNa/uCreat concentration values (Fig. 3).

It is also worth noting the significantly lower total dose of the loop diuretic used to achieve the expected diuretic effect. In the assessment of clinical symptoms, patients from the GDR group were characterized by less severe symptoms of overhydration, such as jugular venous pressure (JVP), pulmonary congestion or peripheral edema (Fig. 4).

DISCUSSION

Overhydration, with or without signs of hypoperfusion, is a major cause of hospitalization in patients with ADHF, regardless of the geographic region [10]. From a historical point of view, the first alternative method of dehydration to loop diuretics in patients with ADHF and signs of overhydration was continuous venovenous ultrafiltration [11, 12]. The randomized UNLOAD trial, which evaluated the clinical effect of ultrafiltration versus standard diuretic therapy in the treatment of acute heart failure, demonstrated greater net weight loss and fluid loss within 48 hours and a lower rate of rehospitalization due to heart failure symptoms at 90-day follow-up [13]. In contrast to previous clinical trials, a study published in 2012 highlighted for the first time a significant limitation of the use of this method, namely the risk of exacerbation of chronic kidney disease in a group of patients treated with ultrafiltration who had a significant increase in urea nitrogen and creatinine levels [14]. In the study by Vazir et al. [15], the saturation of central venous blood was analyzed during ultrafiltration and an increase in venous oxygen tension and a decrease in creatinine concentration were observed in the first phase of dehydration. After obtaining 2 liters of removed fluid volume, a decrease in CvO₂ and deterioration of renal function were noted. The authors of the study suggest that the deterioration of renal function may be related to transient changes in cardiac output occurring during ultrafiltration. The above observation may be of significant importance in the context of the safety of controlled dehydration using the RenalGuard® system, because in the study group there was no significant variability of CvO₂ during the therapy; $49 \pm 12\%$ at baseline, $57 \pm 8\%$ after 6 hours and $54 \pm 14\%$ after 24 hours ($p = 0.1$).

To date, a number of clinical trials have been conducted using the RenalGuard® system, proving its efficacy in preventing post-contrast nephropathy, including in the group of patients with chronic kidney disease undergoing urgent or planned percutaneous coronary

revascularization procedures [16–19]. Based on a previously conducted analysis of the safety and efficacy of the RenalGuard® system in treating patients with ADHF, the procedure was well tolerated and none of the patients had any infections or other complications related to the procedure, either during or after the treatment phase. All patients noted significant improvement in heart failure symptoms. The primary efficacy endpoint in preventing excessive fluid loss — actual fluid loss not exceeding the target fluid loss after completion of RenalGuard® therapy — was met in all 19 (100%) patients. During the 30-day follow-up, no deaths or serious adverse events were reported in the study population. Maintaining venous volume expansion and renal perfusion pressure may have additional nephroprotective effects [20].

The authors of a consensus statement by the Heart Failure Association of the European Society of Cardiology published in 2021 drew attention to the need to profile patients with heart failure in the context of making therapeutic decisions depending on the coexistence of factors such as heart rate (below 60 bpm or above 70 bpm, atrial fibrillation, symptomatic hypotension, eGFR below 30 or above 30 mL/min, hyperkalemia and clinical symptoms of overhydration [21]. Currently, many authors also emphasize the role of sodium and chloride ions in the pathophysiology of water and electrolyte metabolism disorders in the course of acute heart failure and the assessment of their concentrations in spot urine samples as predictors of response to diuretic therapy and independent factors allowing the identification of high-risk patients in the course of ADHF episodes [22–25]. Researchers are also focusing on explaining the interrelationship between urinary sodium and creatinine concentrations and the response to standard diuretic therapy, which is measured by the ability to dilute urine. [26, 27]. In the analyzed population, a significantly greater ability to dilute urine was found in the group of patients who were characterized by a better diuretic response (GDR).

It is interesting to note that higher urinary sodium concentrations were observed between groups at subsequent time points, in the group with a better overall diuretic response, but no significant differences were found when the correlation between natriuresis and urine dilution (sodium concentration corrected for urine creatinine concentration) was taken into account, which is consistent with the fact that natriuresis is a strong factor determining the diuretic response. Patients with a better diuretic response showed a greater ability to dilute urine at later time points (> 12 hours) despite the same natriuresis. Despite differences in diuretic response, no significant differences were found in the serum concentrations of renal damage markers such as Cystatin or Kim-1. However, a trend towards higher endothelin

concentrations was observed at subsequent time points in patients with better response to treatment, which may support increased activation of this system as a compensatory mechanism in response to increased urine production by the kidneys (fluid loss).

CONCLUSIONS

The results of the study indicate the potential use of the RenalGuard® system in the treatment of a selected group of patients with ADHF and symptoms of overhydration, in combination with standard intravenous diuretic therapy for controlled dehydration. Based on the analysis of selected biochemical parameters, a correlation was demonstrated between the concentrations of creatinine, urea nitrogen (BUN), magnesium in serum and the diuretic response of patients undergoing therapy with the RenalGuard® system. Some differences in sodium and chloride ions concentrations in urine samples collected at specific time intervals were also observed, but they were statistically insignificant. Limitations of the study resulting from the small size of the study population, single-center cohort and retrospective analysis prevented precise determination of the clinical profile of the group of patients with ADHF who could be expected to have a good diuretic response without an increased risk of glomerular filtration deterioration secondary to concomitant chronic kidney disease.

Further work to determine the precise hemodynamic and biochemical profile of a larger population of patients with the optimal effect after this form of therapy may improve the future efficacy and safety of renal replacement therapies, currently widely used in cardiac intensive care units in patients treated for ADHF.

Data availability statement: All patients gave their written informed consent to participate in the study before being included in the study.

Ethics statement: The study was conducted with the approval of the local Bioethics Committee of the Lower Silesian Chamber of Physicians and the Bioethics Committee at the Medical University of Wrocław (opinion No. KB — 210/2019) and in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Conflict of interest: None declared.

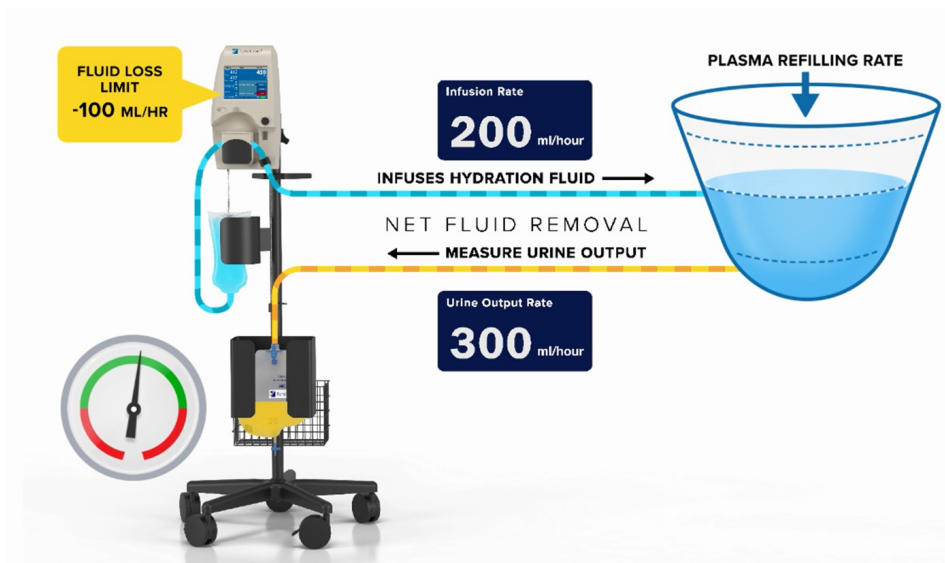
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A



B

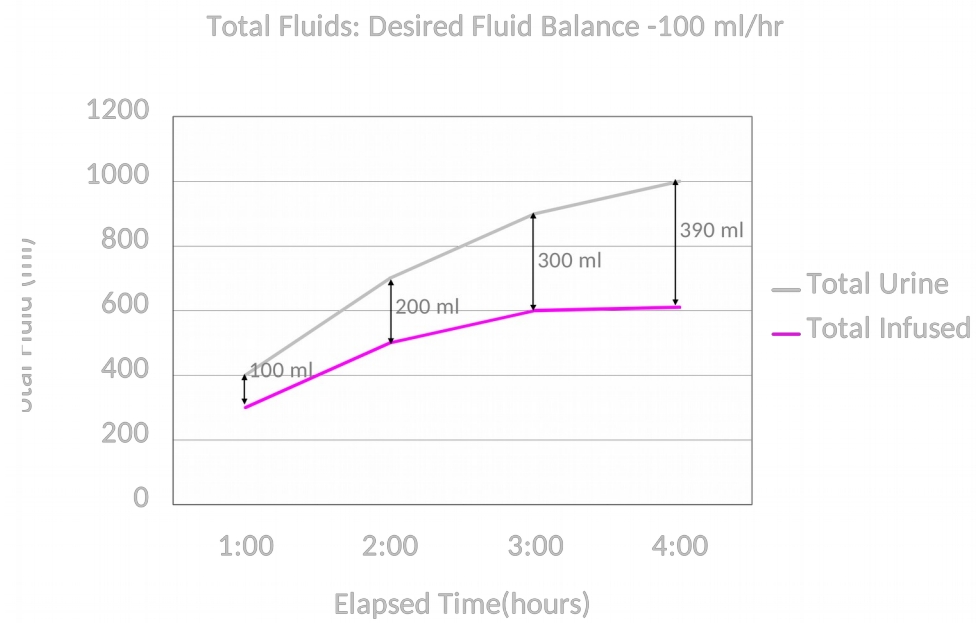
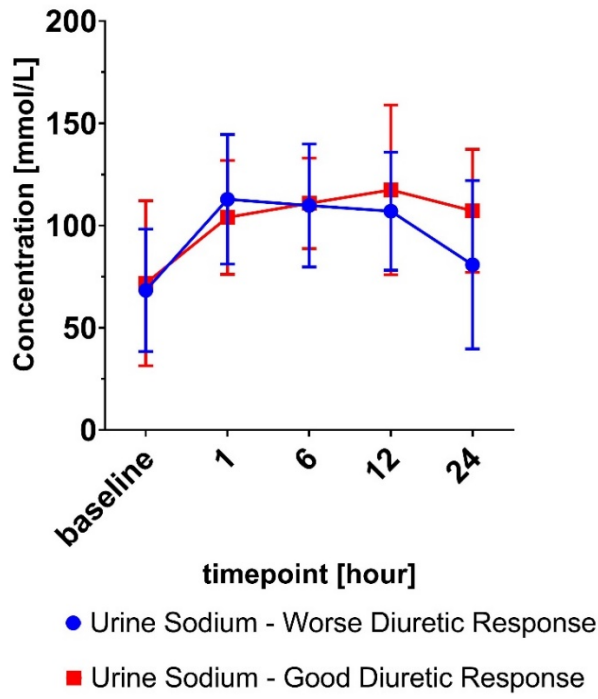


Figure 1A, B. Diagram of the RenalGuard® system

A



B

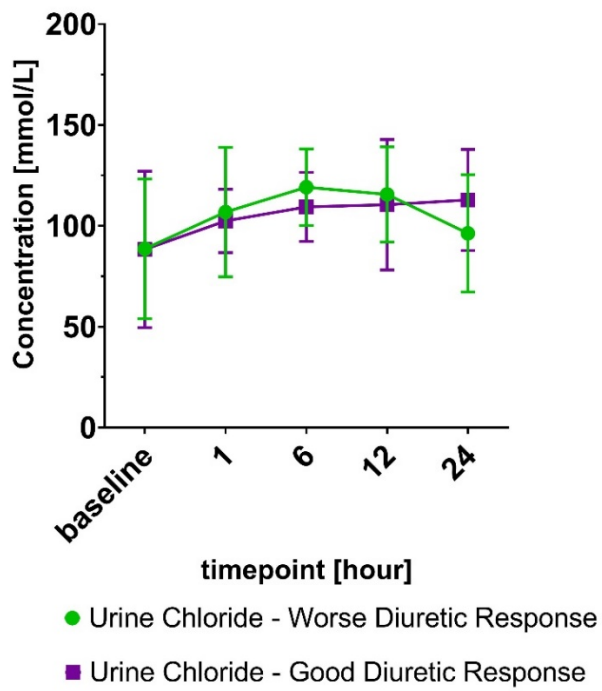


Figure 2A, B. Sodium and chloride urine concentration

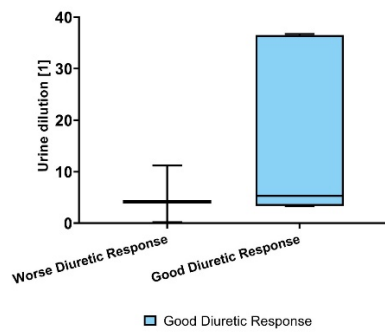
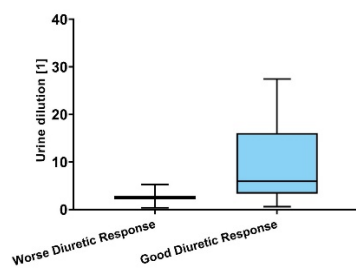
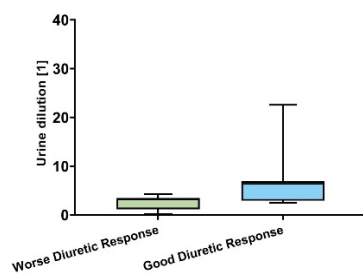
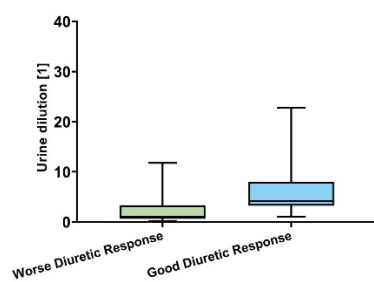
A**B****C****D**

Figure 3. Urine dilution 1 h (A); Urine dilution 6 h (B); urine dilution 12 h (C); urine dilution 24 h (D)

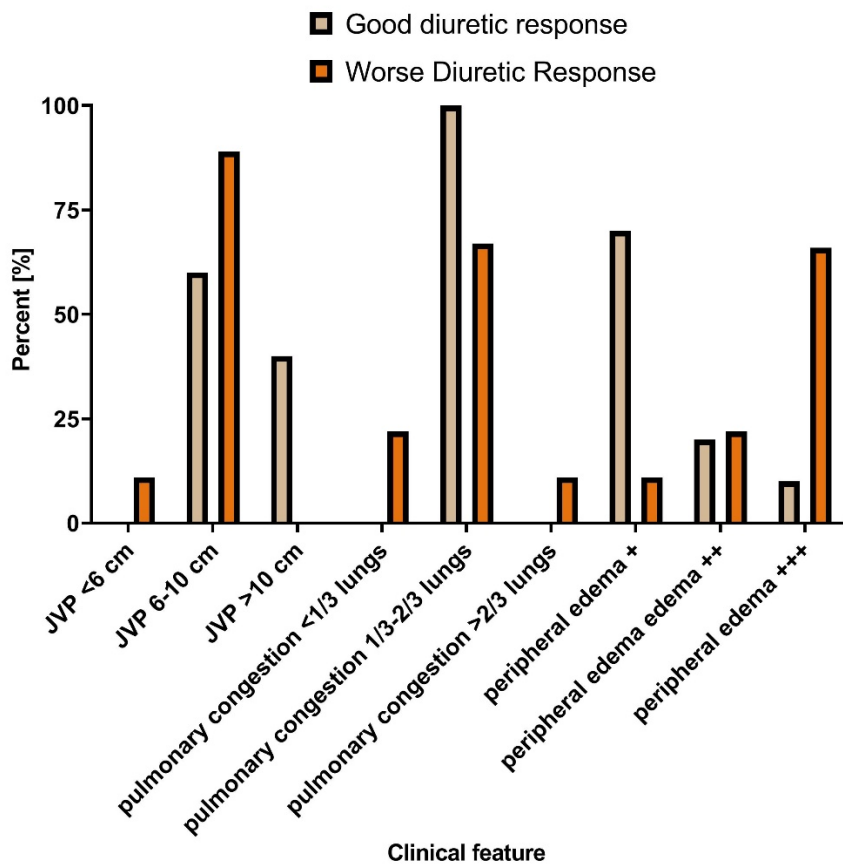


Figure 4. Clinical feature

Table 1. Clinical characteristics of the population

Variable		Good diuretic response	Worse diuretic response	P-value
Patients, n	19	10	9	
Age, years	67 ± 10	66 ± 13	69 ± 7	0.806
Male sex, n [%]	18 (95)	9 (90)	9 (100)	0.48
NYHA class I/II/III/IV before inclusion	0/0/3/16	0/0/1/9	0/0/2/7	0.465
Left ventricular ejection fraction [%]	34 ± 15	32 ± 13	37 ± 17	0.743
Acute heart failure <i>de novo</i> [%]	8 (42)	3(30)	5(55)	0.259
Ischaemic aetiology of heart failure [%]	8 (42)	6(60)	2(22)	0.958
Days in hospital before inclusion	2 ± 1			
LOS (days)	14 ± 9.4	12.6 ± 9.3	15.7 ± 9.9	0.391
Signs and symptoms				
Patient's self-reported weight gain [kg]	8.6 ± 5.8			
Congestion at admission < 1/3 / 1/3–2/3 / > 2/3 [%]	2 (11)/16 (84)/1 (5)			
Peripheral oedema + / ++ / +++ [%]	8 (42)/3 (16)/8 (42)			
JVP < 6/6–12/> 12 [cm]	1 (5)/14 (74)/4 (21)			
Heart rate at baseline (bpm)	76 ± 15	74 ± 15	78 ± 16	0.713
Systolic blood pressure at admission (mmHg)	125 ± 14	125 ± 11	125 ± 18	0.967
Central venous oxygen saturation [%]	49 ± 12			

Treatment before admission					
Furosemide dose before hospitalisation [mg]	80 [40–160]				
Baseline laboratory parameters					
Haemoglobin [g/dL]	12.9 ± 1.3	13.1 ± 1.56	12.6 ± 1.08		0.513
White blood count [10 ⁹ /L]	6.7 ± 1.6	6.8 ± 1.33	6.7 ± 2.01		1.000
PLT [10 ⁹ /L]	164 ± 54	170 ± 54	159 ± 57		0.838
AST [IU/L]	32 ± 15	34 ± 16	30 ± 14		0.595
ALT [IU/L]	29 ± 21	33 ± 24	25 ± 17		0.743
Bilirubin [mg/dL]	1.6 ± 0.6	1.5 ± 0.5	1.7 ± 0.7		0.513
Albumin [mg/dL]	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.3		0.462
Sodium [mmol/L]	138 ± 4	138 ± 3.7	137 ± 4.3		0.870
Potassium [mmol/L]	4.1 ± 0.5	4.1 ± 0.5	4.0 ± 0.4		0.653
Serum osmolality [mmol/L]	277 ± 9				
Creatinine [mg/dL]	1.45 ± 0.4	1.23 ± 0.4	1.69 ± 0.35		0.025
eGFR baseline [mL/min/1.73 m ²]	57 ± 23	68 ± 25	47 ± 14		0.079
BUN [mg/dL]	33 ± 12	28 ± 11	39 ± 10		0.045
NTproBNP [pg/mL]	4492 (2662–5806)	3684 (2635–5624)	5389 (4695–6448)		0.066
Urine sodium [mmol/L]	70 ± 45	73 ± 43	66 ± 49		0.563
Urine chloride [mmol/L]	88 ± 32	103 ± 32	72 ± 24		0.120
Urine creatinine [mg/dL]	98 ± 54	120 ± 55	73 ± 43		0.230

ALT — alanine aminotransferase; AST — Aspartate Aminotransferase; bpm — beats per minute; BUN — blood urea nitrogen; eGFR — estimated glomerular filtration rate; JVP — jugular venous pressure; LOS — length of stay; NT-proBNP — N-terminal pro B-type natriuretic peptide); PLT — platelets

Table 2. Diuretic response during therapy (per 40 mg of furosemide)

	Nvalid	Mean	Median	Lower quartile	Upper quartile	SD
Diuretic response mL/40 mg	19	1043,860	933,3333	700,0000	1400,000	508,3625

SD — standard deviation

Table 3. Two groups based on the median for the entire population: 933 mL/40 mg

	Good diuretic response 1	Nvalid	Mean	Median	Lower quartile	Upper quartile	SD
Good diuretic response mL/40 mg	1,00	9	1448,148	1400,000	1066,667	1900,000	426,2599
Worse diuretic response mL/40 mg	0,00	10	680,0000	725,0000	600,0000	800,0000	211,6659

SD — standard deviation

Table 4. Biochemical parameters — comparison

Variable	Good diuretic response	Worse diuretic response	P-value
	GDR	WDR	
Creatinine [mg/dL]	1.23 ± 0.4	1.69 ± 0.35	0.025
BUN [mg/dL]	28 ± 11	39 ± 10	0.045
Magnesium [mg/dL]	0.70 ± 0.14	0.83 ± 0.09	0.030
Cystatin C [mg/dL]	1.36 ± 0.5	1.85 ± 0.6	0.112
NGAL [ng/mL]	21.38 ± 17.16	19.61 ± 21.81	0.755
ET-1 [pg/mL]	13.97 ± 9.77	71.02 ± 169.25	0.134
KIM-1 [pg/mL]	140.67 ± 25.45	1177.25 ± 2716.97	0.404

BUN — blood urea nitrogen; ET-1 — endothelin-1; KIM-1 — kidney injury molecule-1; NGAL — neutrophil gelatinase-associated lipocalin