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Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study

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Aims To evaluate the clinical, biohumoral, and haemodynamic effects of ultrafiltration vs. intravenous diuretics in patients with decompensated heart failure (HF). Signs and symptoms of volume overload are often present in these patients and standard therapy consists primarily of intravenous diuretics. Increasing evidence suggests that ultrafiltration can be an effective alternative treatment.

Methods and results Thirty patients with decompensated HF were randomly assigned to diuretics or ultrafiltration. Haemodynamic variables, including several novel parameters indicating the overall performance of the cardiovascular system, were continuously assessed with the Pressure Recording Analytical Method before, during, at the end of treatment (EoT) and 36 h after completing treatment. Aldosterone and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels were also measured. Patients treated with ultrafiltration had a more pronounced reduction in signs and symptoms of HF at EoT compared with baseline, and a significant decrease in plasma aldosterone (0.24 ± 0.25 vs. 0.86 ± 1.04 nmol/L; $P < 0.001$) and NT-proBNP levels (2823 ± 2474 vs. 5063 ± 3811 ng/L; $P < 0.001$) compared with the diuretic group. The ultrafiltration group showed a significant improvement (% of baseline) in a number of haemodynamic parameters, including stroke volume index ($114.0 \pm 11.7\%$; $P < 0.001$), cardiac index ($123.0 \pm 20.8\%$; $P < 0.001$), cardiac power output ($114.0 \pm 13.8\%$; $P < 0.001$), dP/dt_{max} ($129.5 \pm 19.9\%$; $P < 0.001$), and cardiac cycle efficiency (0.24 ± 0.54 vs. -0.14 ± 0.50 units; $P < 0.05$), and a significant reduction in systemic vascular resistance 36 h after the treatment ($88.0 \pm 10.9\%$; $P < 0.001$), which was not observed in the diuretic group.

Conclusions In patients with advanced HF, ultrafiltration facilitates a greater clinical improvement compared with diuretic infusion by ameliorating haemodynamics (assessed using a minimally invasive methodology) without a marked increase in aldosterone or NT-proBNP levels.

Keywords Ultrafiltration • Diuretic therapy • Minimally invasive monitoring • Haemodynamic • Heart failure

Introduction

Most patients hospitalized for decompensated heart failure (HF) show signs and symptoms of volume overload[1,2] primarily due to an abnormal haemodynamic and neurohormonal status.

Standard therapy for decompensated HF consists predominantly of intravenous loop diuretics and vasodilators,[3] however, concerns

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about the safety and therapeutic efficacy of diuretic-based treatment strategies have been raised.[4–9]

Moreover, increasing evidence suggests that ultrafiltration, a mechanical strategy to reduce volume overload, can be an effective alternative treatment for patients with acute HF, and should not be limited to those unresponsive to diuretic therapy.[4,5]

The Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated (UNLOAD) congestive HF trial recently demonstrated that early ultrafiltration safely provides greater weight and fluid loss during the acute phase, and reduces 90-day resource utilization for HF compared with diuretics in patients with moderate HF, independently of the presence of renal dysfunction.[10]

Previous studies, conducted by means of pulmonary artery catheterization, showed an improvement in 'classic' haemodynamic variables in HF patients treated with ultrafiltration, but not in those treated with diuretics.[11] Moreover, our group recently reported on the usefulness of ultrafiltration treatment in acute decompensated HF, as inferred by the trend of haemodynamic variables assessed with a minimally invasive method.[12]

However, the mechanisms explaining the different impact of these two methods of fluid removal on clinical benefit as well as other haemodynamic variables related to the overall performance of the cardiovascular system have not yet been adequately explored.

The aim of this randomized controlled trial was to evaluate the clinical, biohumoral, and haemodynamic effects of ultrafiltration compared with standard intravenous diuretic therapy in patients with acutely decompensated HF and over-hydration. Haemodynamic changes determined by the two methods of fluid removal were assessed by the Pressure Recording Analytical Method (PRAM).[13,14]

Methods

The ULTRADISCO (ULTRAfiltration vs. DIureticS in deCOmpensated HF) study is a prospective, randomized, open label, single-centre study comparing early ultrafiltration with intravenous diuretics in patients hospitalized with HF and signs of hypervolaemia. The study protocol was in agreement with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained from all patients before enrolment.

Study population

All patients admitted to the Cardiac Step-Down Unit at the University of Florence, Italy, with a diagnosis of decompensated HF, were eligible to participate. Patients were at least 18 years old and were randomized upon admission after a clinical assessment. Admission criteria were peripheral oedema $\geq 2+$ and at least one of the following: (i) pulmonary rales or cracklings; (ii) dyspnoea, paroxysmal nocturnal dyspnoea, orthopnoea or tachypnoea; (iii) third heart sound; (iv) jugular venous distension; (v) positive hepato-jugular reflux; (vi) maximal pulmonary pressure values >50 mmHg, measured by two-dimensional echocardiogram; or (vii) radiographic pleural effusions. Patients were excluded for (i) severe valvular stenosis; (ii) acute coronary syndrome; (iii) serum creatinine >3 mg/dL; (iv) systolic blood pressure ≤ 80 mmHg; (v) haematocrit $>45\%$; (vi) poor venous access; (vii) vasoactive drug and/or >60 mg intravenous diuretic use before trial entry; (viii) severe comorbidities; or (ix) contraindication to unfractionated heparin administration.

According to these criteria, 30 patients with a primary diagnosis of decompensated HF and over-hydration (mean age $\pm$ SD, 69.1 $\pm$ 16.2 years) with New York Heart Association (NYHA) functional class III or IV status were randomized to receive continuous diuretic infusion (15 patients) or ultrafiltration (15 patients). A treatment duration of at least 36 h was predicted for all patients enrolled.

Pre-treatment phase

All patients underwent a physical examination with particular emphasis on the signs and symptoms of HF. A clinical score was obtained for each patient by assigning one point for the presence of each sign and symptom listed in the inclusion criteria. All patients underwent an electrocardiogram, echocardiogram, complete blood count, blood chemistry, and assessment of partial thromboplastin time. Aldosterone and pro-B-type natriuretic peptide (NT-proBNP) plasma levels were also assessed.

Beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers were continued throughout the study as tolerated.

Following radial artery cannulation, PRAM monitoring (MostCare®, Vytech, Padova, Italy) was started 1 h before the initiation of treatment. Arterial waveform was recorded at 1000 Hz and data stored electronically. The PRAM technique requires neither calibration nor pre-estimated measurement of patient parameters (such as gender, age, or anthropometric data). The haemodynamic variables obtained beat to beat by this monitoring system were: systolic, diastolic, dicrotic, and mean arterial blood pressures (mmHg); heart rate (HR, beats per minute); cardiac output index (CI; L/min/m^2); stroke volume index (SVI; mL/m^2); cardiac power output (CPO; Watts); dP/dt_{max} (mmHg/ms);[12] cardiac cycle efficiency (CCE; units);[15,16] and systemic vascular resistance index (SVRI; dyne $\times$ sec $\times$ m^2/cm^5).

Haemodynamic data from each patient were evaluated, for a mean duration of 20 min before starting the treatment as well as around each phase during the entire study. At these times, the morphology of the arterial waves was carefully checked by the attendant physician in order to detect arterial waves showing an over- or under-dumping phenomenon, and to optimize arterial waveform with correct adjustment of both the transducer and line extensions.[17,18]

Treatment phase: ultrafiltration

In patients randomized to ultrafiltration, intravenous access for blood withdrawal and return was obtained using a standard femoral vein catheter connected to the PRISMA™ System (HOSPAL-GAMBRO DASCO, Medolla, Italy). Ultrafiltration was performed by the predilution technique using an M 100 PRESET PRISMA filter and a blood flow rate of 150 mL/h. Continuous renal replacement therapy was performed using the slow continuous ultrafiltration technique. Unfractionated heparin was used as anticoagulant to maintain a partial thromboplastin time of between 65 and 85 s. Ultrafiltration was started at a rate of fluid removal ranging from a minimum of 100 to a maximum of 300 mL/h. The rate of fluid removal was adjusted according to systolic arterial blood pressure (SAP) values: for SAP <100 mmHg the rate of fluid removal was 100 mL/h; for SAP >100 mmHg and ≤ 110 mmHg the rate of removal was 200 mL/h; and for SAP >110 mmHg the rate of removal was 300 mL/h. In 13 patients, the rate of fluid removal was 100 mL/h and in the remaining two patients it was 200 mL/h.

The duration of ultrafiltration treatment differed according to the clinical condition of the patient. Data were collected every 6 h

during ultrafiltration, at the end of treatment (EoT), and then 12 and 36 h after treatment discontinuation. Ultrafiltration was discontinued when the patient's clinical score was reduced by at least one-third with respect to its initial value or when either a reduction in systolic blood pressure or an increase in heart rate >15% was observed. During ultrafiltration treatment, intravenous diuretic therapy was not administered and patients requiring intravenous inotropes (dobutamine, dopamine or levosimendan) for worsening HF were considered to have failed treatment. However, none of the patients enrolled in the present study required any of these drugs.

Treatment phase: diuretics

Patients randomized to intravenous diuretic therapy received a continuous infusion of furosemide at an initial dose of 250 mg/24 h. The diuretic dose was gradually reduced when the patient's clinical score decreased by at least one-third with respect to its initial value, or an increase of >0.5 mg/dL in plasma creatinine levels was detected or when either a reduction in systolic blood pressure or an increase in heart rate >15% was observed. The diuretic dose was increased to 500 mg/24 h if the initial dose level was not sufficient to achieve a negative fluid balance >2000 mL/day. Only two patients required 500 mg/day as the first dose. During diuretic treatment, patients requiring intravenous inotropes for worsening HF were considered to be treatment failures. However, none of the patients in this group required these drugs.

In both treatment groups, all patients underwent assessment of aldosterone and NT-proBNP levels and underwent a transthoracic two-dimensional echocardiogram every 24 h. Physical examinations (including body weight and fluid loss), complete blood count, blood chemistry, and arterial blood gas evaluations were done every 6 h. Haemodynamic parameters were recorded continuously.

Post-treatment phase (after the end of ultrafiltration or diuretic infusion)

Oral administration of diuretics was started at the minimum dose required to maintain a daily negative fluid balance; NT-proBNP levels, fluid balance, and diuresis were measured every 24 h. Blood chemistry and the physical examination with clinical score were repeated every 6 h. Thirty-six hours after the end of ultrafiltration or diuretic infusion, the PRAM assessment was stopped.

Statistical analysis

Data were stored in a dedicated database and analysed with SPSS 13.0 for Windows statistical software (SPSS Inc, Chicago, IL). Statistical significance was fixed at $P < 0.05$. To minimize inter-individual variability, only parameters, which can vary within a narrow range (pH, PaO_2, HCO_3^-, lactate, electrolytes and creatinine) are reported as absolute values; other variables which are prone to marked individual variations [body weight, arterial blood pressures, haemodynamic parameters (heart rate, SVI, CI, CPO, SVRI, dP/dt_{max}), NT-proBNP, and aldosterone] were normalized as a percentage of baseline (for each patient, baseline values = 100%). These values were used to construct figures. In particular, for CCE, which can assume both positive and negative values, absolute differences from baseline were considered.

Data are reported as frequencies (percentages) and mean ± SD or median (25th to 75th percentile), and compared with Fisher's exact test and the Student's *t*-test or Mann–Whitney *U* test, respectively. All continuous data were tested for normality by means of the one-sample Kolmogorov–Smirnov test, and analysed with parametric or non-parametric tests, as appropriate. Notably, all of the variables recorded by PRAM at each study point (for 20 min) were normally distributed; we therefore used the arithmetic mean to describe these values at each time point during the study. Comparisons were performed between baseline values (absolute or normalized, see above), EoT, and 36 h after treatment was discontinued (Post 36). Values were also compared between the two treatments at each of these time points.

Throughout the study period, linear regression analyses were performed to investigate trends. Moreover, the trend for each treatment was investigated by means of repeated measures two-way analysis of variance; interactions between variables were investigated by means of ANCOVA.

Our goal was to achieve a 10% increase in CI (with a SD ± 0.5 L/min/m^2) and a 12% increase in CPO (with a SD ± 0.14 Watt) in at least one of the two treatments. We therefore estimated that we needed to enrol 20 patients per treatment group. In fact, at an alpha error level of 5% and a statistical power of 80%, the sample size required was 22 patients for CI and 19 for CPO. However, the study was limited to 15 patients per treatment group, because the statistical power was largely satisfied for the majority of target variables namely weight loss, SVI, CI, CPO, dP/dt_{max}, NT-proBNP and aldosterone: all at least 90%.

Results

Baseline data did not differ between the two treatment groups as shown in *Table 1*. The median length of treatment was 46 (25th to 75th percentile, 39–71) h in the ultrafiltration group and 57 (25th to 75th percentile, 48–85) h in the diuretic group (P = ns). Five patients in the ultrafiltration group (33.3%) and 9 (60%) in the diuretic group (P = ns) required more than 60 h of treatment. In both treatment groups, body weight was significantly decreased compared with baseline values, but weight loss in the ultrafiltration group at Post 36 was greater ($P = 0.001$) (*Table 2* and *Figure 1*). At Post 36, the ultrafiltration group had a greater cumulative fluid loss compared with the diuretic group (9.7 ± 2.9 vs. 7.8 ± 2.0 L, respectively, $P = 0.047$) (*Figure 1*).

Changes in clinical, biohumoral and haemodynamic variables are listed in *Table 2* and summarized in *Table 3*. With respect to plasma levels of creatinine and haemoglobin, no differences were detected between baseline and Post 36 values in either group, between the two groups, or in the trends throughout the study. Mean plasma creatinine levels at baseline were 2.22 mg/dL in the ultrafiltration group and 1.86 mg/dL in the diuretic group. Similarly, blood gas analysis data (pH, lactate, PaO_2, HCO_3^-) as well as serum sodium and potassium concentrations did not differ between groups during the study (data not shown).

In the ultrafiltration group, NT-proBNP levels decreased significantly from 5063 ± 3811 pg/mL at baseline to 2823 ± 2474 pg/mL at EoT, and 1797 ± 1327 pg/mL at Post 36 (both $P < 0.001$), whereas levels remained essentially unchanged in the diuretic group (6707 ± 3597 pg/mL at baseline, 5104 ± 2522 pg/mL at EoT, and 5271 ± 3251 pg/mL at Post 36). Aldosterone levels showed a similar trend; 0.86 ± 1.04 nmol/l at baseline, 0.24 ± 0.25 at EoT, and 0.25 ± 0.23 nmol/l at Post 36 in the ultrafiltration group (both $P < 0.001$), and 0.73 ± 0.87 to 0.78 ± 0.49 nmol/l at EoT and 0.80 ± 0.46 nmol/l at Post 36 (P = ns) in the diuretic group.

No significant changes were observed in systolic, diastolic, or mean arterial blood pressures in the ultrafiltration group during

Table 1 Baseline clinical characteristics of patients

Characteristic	Ultrafiltration group ($n = 15$)	Diuretic group ($n = 15$)
Age (years)	72.4 ± 14.1	65.8 ± 18.4
Male	13 (87)	13 (87)
History of hypertension	3 (20.0)	9 (60.0)
Coronary artery disease	9 (60.0)	9 (60.0)
Chronic obstructive pulmonary disease	7 (46.7)	4 (26.7)
Diabetes Mellitus	6 (40.0)	9 (60.0)
Prior HF	15 (100)	15 (100)
Ischaemic/non-ischaemic aetiology	9/6 (60/40)	9/6 (60/40)
Left ventricular ejection fraction*	34 ± 19.9	30 ± 13.4
Signs and symptoms		
Third heart sound	4 (26.7)	3 (20.0)
Jugular venous distension	12 (80.0)	12 (80.0)
Pulmonary rales	12 (80.0)	9 (60.0)
Peripheral oedema	15 (100)	15 (100)
Dyspnoea or tachypnoea	11 (73.3)	6 (40.0)
Positive hepato-jugular reflux	11 (73.3)	6 (40.0)
Pulmonary artery pressure >50 mmHg[a]	3 (20.0)	2 (13.3)
Pleural effusion	8 (53.3)	4 (26.7)
Ascites	7 (46.7)	5 (33.3)
Diaphoresis	3 (20.0)	1 (6.7)
Weariness	6 (40.0)	5 (33.3)
Hepatomegaly	9 (60.0)	9 (60.0)
Laboratory measurements		
Serum sodium	136 ± 7.9	138 ± 5.1
Serum potassium	4.2 ± 0.6	4.3 ± 0.9
Medications		
ACE-I/ARB	13 (86.7)	12 (80)
Beta-blockers	10 (66.7)	11 (73.3)
Aldosterone antagonists	0 (0)	1 (6.7)
Loop diuretics	15 (100)	15 (100)

Percentage values are represented in parenthesis. For all comparison between the two treatments, P = n.s.
[a]Measured by means of transthoracic echocardiography.

or after treatment. Conversely, all these pressure values showed a significant decrease 36 h post-diuretic treatment compared with baseline (*Table 2*). Moreover, the decrease in mean blood pressure was significantly more relevant in the diuretic infusion group compared with the ultrafiltration group at both the EoT ($P = 0.014$) and at Post 36 ($P = 0.046$).

With regard to dicrotic blood pressure, we observed a significant decrease in both treatment groups at both EoT and Post 36, with respect to baseline values (*Table 2*).

A significant increase in HR was observed in the diuretic group at Post 36, whereas no change in HR occurred in the ultrafiltration group (*Table 2*). We observed significantly higher HR values in the diuretic infusion group than in the ultrafiltration group ($P < 0.001$) at Post 36 (92.7 ± 10.2 vs. 76.6 ± 4.7 beats/min, respectively).

Both SVI and CI improved significantly in the ultrafiltration group at the EoT and at Post 36 with respect to baseline values. Conversely, in the diuretic group there was a significant decrease in SVI or CI at Post 36 compared with baseline values. Significant differences were detected between the two treatments, at both EoT ($P = 0.013$ for SVI and $P = 0.014$ for CI) and at Post 36 ($P < 0.001$ for both SVI and CI) (*Table 2*).

A significant difference between the slopes for both SVI ($P = 0.011$) and CI ($P = 0.005$) was observed in the two treatment groups, as shown in *Figure 2*. Cardiac power output and dP/dt_{max} increased significantly in the ultrafiltration group ($P < 0.001$) both at the EoT and at Post 36 (*Table 2*) (*Figures 2* and *3*). In the diuretic infusion group, CPO decreased slightly and the dP/dt_{max} decreased significantly at both EoT ($P = 0.003$) and Post 36 ($P = 0.002$) compared with baseline. A significant difference ($P < 0.001$) in CPO and dP/dt_{max} between the two groups at both EoT and Post 36 was observed. The slopes between the two treatments were significantly different only with respect to dP/dt_{max} ($P < 0.001$).

Cardiac cycle efficiency improved in the ultrafiltration group at both EoT (0.27 ± 0.30-unit increase, $P = 0.003$) and at Post 36 ($P = 0.005$) compared with baseline (*Figure 3*). No significant variations were observed in the diuretic group compared with baseline (*Table 2*). In the comparison between the two groups, we observed a significant difference ($P = 0.036$) only at Post 36. The slopes between the two treatment groups were significantly different ($P = 0.012$, *Figure 3*).

Systemic vascular resistance index showed a significant decrease at Post 36 compared with baseline in the ultrafiltration group ($P < 0.001$). No significant difference in LVEF values was observed between baseline and either EoT or Post 36. Neither local nor systemic complications were observed in either group. In particular, no significant decrease in haemoglobin levels was observed in the ultrafiltration group between baseline and both the EoT and Post 36 values (*Table 2*).

Two-way ANOVA for repeated measures, after adjustment for baseline values, detected statistically significant differences between treatments for all variables investigated, except for systolic and dicrotic blood pressures. Significant intra-group differences were detected during the study for weight ($P < 0.001$), fluid balance ($P < 0.001$), dicrotic blood pressure ($P < 0.001$), HR ($P < 0.001$), SVRI ($P < 0.001$), NT-proBNP ($P < 0.001$), aldosterone ($P < 0.001$) and the signs and symptoms score ($P < 0.001$).

A significant interaction (treatment × phase) was found for dicrotic blood pressure [$P = 0.045$, HR ($P < 0.001$), CI ($P = 0.001$), dP/dt_{max} ($P < 0.001$), SVRI ($P < 0.001$), aldosterone ($P < 0.001$) and the signs and symptoms score ($P = 0.002$)].

Discussion

ULTRADISCO is a randomized study comparing the effects of ultrafiltration vs. diuretic therapy on clinical, biohumoral and haemodynamic variables in decompensated HF patients with hyper-hydration. In the present study, haemodynamic parameters were assessed with PRAM, a minimally invasive method that can

Table 2 Clinical, biohumoral and haemodynamic data for patients in the ultrafiltration and diuretic therapy groups

	Baseline (absolute values)	End of treatment (% baseline unless otherwise specified)	*P* baseline vs. EoT	Post 36 h (% baseline unless otherwise specified)	*P* baseline vs. post 36 h
Weight (kg)	*74.4 ± 11.6*	*92.7 ± 3.9*	*<0.001*	*90.9 ± 1.7*	*<0.001*
	83.4 ± 19.3	93.3 ± 2.8	<0.001	93.1 ± 1.8	<0.001
Between groups *P*	n.s.	n.s.		0.001	
Fluid loss (% body weight)	*0%*	*12.5 ± 4.0*	*<0.001*	*14.9 ± 2.4*	*<0.001*
	0%	10.7 ± 4.4	<0.001	12.5 ± 3.6	<0.001
Between groups *P*		n.s.		0.032	
Systolic ABP	*121.3 ± 16.6*	*105.9 ± 16.3*	*n.s.*	*100.0 ± 15.8*	*n.s.*
	118.0 ± 22.9	97.9 ± 18.0	n.s.	93.1 ± 11.0	0.029
Between groups *P*	n.s.	n.s.		n.s.	
Diastolic ABP	*64.6 ± 7.9*	*101.2 ± 12.9*	*n.s.*	*97.3 ± 18.7*	*n.s.*
	66.4 ± 13.0	93.7 ± 14.8	n.s.	85.0 ± 14.55	0.001
Between groups *P*	n.s.	n.s.		0.048	
Mean ABP	*84.6 ± 17.4*	*100.5 ± 9.1*	*n.s.*	*98.3 ± 15.0*	*n.s.*
	85.7 ± 17.8	89.5 ± 14.4	0.014	87.8 ± 13.4	0.003
Between groups *P*	n.s.	0.014		0.046	
Dicrotic ABP	*82.0 ± 12.9*	*91.9 ± 12.5*	*n.s.*	*90.6 ± 9.5*	*n.s.*
	74.5 ± 19.3	92.9 ± 9.5	0.012	89.0 ± 9.4	<0.001
Between groups *P*	n.s.	n.s.		n.s.	
HR (beats/min)	*76.9 ± 8.8*	*99.8 ± 10.0*	*n.s.*	*100.7 ± 2.7*	*n.s.*
	83.1 ± 19.5	101.2 ± 9.5	n.s.	111.5 ± 9.9	<0.001
Between groups *P*	n.s.	n.s.		*P* < 0.001	
SVI	*29.5 ± 10.5*	*113.6 ± 11.7*	*<0.001*	*114.6 ± 14.2*	*<0.001*
	27.8 ± 9.6	92.7 ± 30.1	n.s.	82.2 ± 25.9	0.019
Between groups *P*	n.s.	0.013		<0.001	
CI	*2.06 ± 0.48*	*122.9 ± 20.8*	*<0.001*	*127.2 ± 15.6*	*<0.001*
	2.24 ± 0.88	103.9 ± 20.3	n.s.	83.6 ± 16.1	0.001
Between groups *P*	n.s.	0.014		*P* < 0.001	
CPO	*0.67 ± 0.12*	*113.6 ± 13.8*	*0.002*	*117.3 ± 15.5*	*<0.001*
	0.79 ± 0.27	89.3 ± 18.9	0.046	89.9 ± 27.4	n.s.
Between groups *P*	n.s.	*P* < 0.001		0.001	
dP/dt_{max}	*1.02 ± 0.43*	*129.5 ± 19.9*	*<0.001*	*123.6 ± 24.4*	*0.001*
	0.92 ± 0.29	81.6 ± 19.6	0.003	090.9 ± 9.5	0.002
Between groups *P*	n.s.	*P* < 0.001		*P* < 0.001	
SVRI	*2921 ± 598*	*99.8 ± 7.8*	*n.s.*	*88.1 ± 10.9*	*<0.001*
	2809 ± 830	100.0 ± 14.9	1	98.9 ± 20.6	n.s.
Between groups *P*	n.s.	n.s.		n.s.	
CCE	*−0.14 ± 0.50*	*0.27 ± 0.30*	*0.005*	*0.32 ± 0.33*	*0.003*
	−0.34 ± 0.26	0.15 ± 0.34	n.s.	0.00 ± 0.46	1
Between groups *P*	n.s.	n.s. (absolute Δ from baseline)		0.036 (absolute Δ from baseline)	
NT-proBNP	*5063 ± 3811*	*45.0 ± 30.3*	*<0.001*	*35.5 ± 25.1*	*<0.001*
	6707 ± 3597	78.9 ± 50.0	n.s.	78.6 ± 45.6	n.s.
Between groups *P*	n.s.	n.s.		0.004	
Aldosterone	*0.86 ± 1.04*	*32.3 ± 22.3*	*<0.001*	*28.4 ± 23.4*	*<0.001*
	0.73 ± 0.87	106.8 ± 52.1	n.s.	109.8 ± 45.9	0.422
Between groups *P*	n.s.	*P* < 0.001		*P* < 0.001	
Haemoglobin (absolute values)	*11.2 ± 1.3*	*10.4 ± 1.4*	*0.12*	*11.0 ± 1.2*	*0.644*
	11.6 ± 1.4	11.5 ± 1.0	0.835	11.3 ± 1.4	0.562

Continued

Table 2 *Continued*

	Baseline (absolute values)	End of treatment (% baseline unless otherwise specified)	*P* baseline vs. EoT	Post 36 h (% baseline unless otherwise specified)	*P* baseline vs. post 36 h
Between groups *P*	n.s.	0.019		n.s.	
Creatinine (absolute values)	*2.22 ± 0.75*	*2.05 ± 0.93*	*n.s.*	*1.67 ± 0.74*	*0.039*
	1.86 ± 0.63	1.83 ± 0.61	n.s.	1.93 ± 0.62	n.s.
Between groups *P*	n.s.	n.s.		n.s.	
NYHA class (absolute values) (mean ± SD)	*3.7 ± 0.50*	*2.3 ± 0.61*	*<0.001*	*2.0 ± 0.50*	*<0.001*
	3.5 ± 0.53	2.6 ± 0.76	<0.001	2.4 ± 0.52	<0.001
Between groups *P*	n.s.	n.s.		0.037	
NYHA class frequency (%)					
I		*2 (13.3)*		*2 (13.3)*	
		0		0	
II		*8 (53.3)*		*11 (73.3)*	
		8 (53.3)		9 (60.0)	
			<0.001		*<0.001*
III	*5 (33.3%)*	*5 (33.3)*	0.003	*2 (13.3)*	<0.001
	7 (46.7%)	5 (33.3)		6 (40.0)	
IV	*10 (66.7%)*	*0*			
	8 (53.3%)	2 (13.3)			
Between groups *P*	n.s.	n.s.		n.s.	
Signs and symptoms score (absolute values)	*6.75 ± 2.76*	*3.33 ± 0.58*	*<0.001*	*3.50 ± 1.00*	*<0.001*
	5.17 ± 1.75	3.50 ± 2.17	0.031	3.83 ± 1.83	0.049
Between groups *P*	n.s.	n.s.		n.s.	

Italic, ultrafiltration group; plain. intravenous diuretic group. ABP, arterial blood pressure.

calculate CO and other variables related to the overall performance of the cardiovascular system.[13,14]

In agreement with previous studies,[10,11] our data showed that fluid removal using either ultrafiltration or diuretics resulted in a significant improvement in the symptoms of congestion, but the clinical improvement observed in patients treated with ultrafiltration was greater than that observed in those treated with diuretic infusion. In the present study ultrafiltration was performed independently of the presence of renal dysfunction, which is at variance with the HF guidelines of the European Society of Cardiology.[19] Until now the use of ultrafiltration has been limited for mainly technical reasons, however, recent technological advances in the new devices and the results of the UNLOAD trial have encouraged the wider use of ultrafiltration in these patients. Moreover, our findings show that the fluid removal obtained with ultrafiltration in the acute phase had more beneficial effects on biohumoral variables, namely aldosterone and NT-proBNP, and haemodynamic variables compared with the diuretic infusion.[20]

Patients treated with ultrafiltration had a greater reduction in plasma levels of NT-proBNP and aldosterone than patients treated with diuretic therapy.[21] Unlike diuretics, ultrafiltration does not stimulate macula densa-mediated neurohormonal activation or produce prolonged intravascular hypovolaemia, this is because well-conducted ultrafiltration removes fluid from the blood at the same rate at which fluid is reabsorbed from the oedematous interstitium.[22–24] This reduction in neurohormonal activation is crucial for interrupting the vicious cycle, which maintains and worsens fluid retention in HF patients.[25] This finding can explain, at least in part, the greater clinical improvement observed in the ultrafiltration group both during treatment and soon after its discontinuation, as previously reported.[5,11,21,26,27]

In a recent pilot study,[12] our group demonstrated the beneficial effects of ultrafiltration on the overall performance of the cardiovascular system, measured by means of PRAM, in patients with decompensated HF. However, the pilot study did not allow a definitive conclusion about whether the possible beneficial effects observed in patients treated with ultrafiltration were due to fluid removal *per se* or if the benefits could be specifically ascribed to ultrafiltration treatment. In order to evaluate the latter issue, we compared the effects of ultrafiltration and diuretics on haemodynamic variables in the present study using the aforementioned minimally invasive PRAM method.

The differences in haemodynamic parameters observed in the two treatment groups deserve further consideration. Concerning arterial pressure values, the continuous beat-by-beat monitoring of systemic arterial pressure showed that systolic, diastolic, and

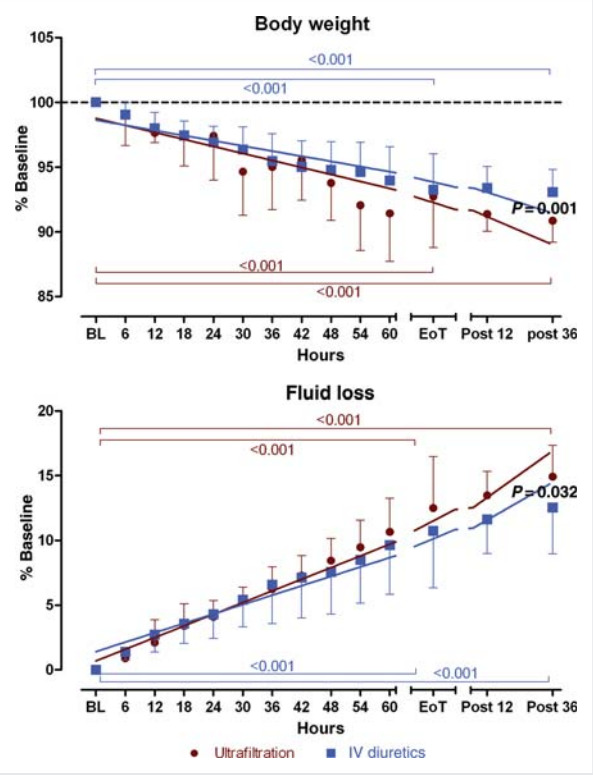

Figure 1 Trends over time in body weight and fluid balance for patients in the ultrafiltration and diuretic therapy groups.

Table 3 Summary of the effects of ultrafiltration and diuretics on the variables analysed

	Ultrafiltration	Intravenous diuretics
Systolic blood pressure	↔	↓
Diastolic blood pressure	↔	↓
Mean blood pressure	↔	↓
Dicrotic blood pressure	↔	↓
Heart rate	↔	↑↑
Stroke volume index	↑↑	↓
Cardiac index	↑↑	↓↓
Cardiac power output	↑↑	↔
dP/dt_{max}	↑↑	↓↓
Systemic vascular resistance	↓↓	↔
Cardiac cycle efficiency	↑↑	↔
NT-proBNP	↓↓	↔
Aldosterone	↓↓	↔
Creatinine	↓	↔
Sign and symptom score	↓↓	↓

↑↑ No significant changes.
↓ or ↓↓ Significant decrease: $P < 0.05$ or $P < 0.01$, respectively.
↔ Significant increase: $P < 0.01$.

mean arterial pressures remained unchanged during and after ultrafiltration, as previously reported;[4,5,22] however, these parameters decreased significantly during and after the diuretic infusion, suggesting greater haemodynamic stability with the use of ultrafiltration, which is particularly important in advanced HF. The results observed in the ultrafiltration group can be explained by a plasma refilling rate sufficient to prevent hypovolaemia, this finding can be ascribed, at least in part, to our decision to perform ultrafiltration at a low rate of fluid removal, ranging from 100 and 300 mL/h.[22,28]

Ultrafiltration is a mechanical method of sodium and water removal, with adjustable volumes and rates that allow optimal preservation of systemic volaemia, whereas intravenous diuretic administration can reduce circulating blood volume in a less predictable way because of inter-individual variability in response to these drugs. Some investigators have reported that intravascular hypovolaemia is persistent during intravenous diuretic infusion, and that the decrease in systemic arterial pressures observed with this therapy can occur as a consequence of this phenomenon.[29,30] Similarly, we can speculate that the significant increase in heart rate observed in the diuretic infusion group, but not in the ultrafiltration group, can be ascribed to hypovolaemia and to the consequent neurohormonal activation[10,18] more frequently associated with the use of diuretics.

In our study population, both SVI and CI showed an early and significant increase during and after ultrafiltration, and a significant decrease after diuretic infusion. The increase in SVI in the ultrafiltration group in turn also determined an early increase in CI without any effects on heart rate, which did not show any significant change as previously reported.[22]

In our study population, SVRI only decreased significantly in the ultrafiltration group. The SVRI reduction in this group of patients can be explained, at least in part, by the increase in SVI as well as by removal of neurohumoral metabolites such as norepinephrine from the blood by ultrafiltration.[21] Moreover, we also observed a significant increase in CPO only in the ultrafiltration group. Cardiac power output is a novel haemodynamic parameter obtained from the product of cardiac output and mean arterial blood pressure, it therefore represents an integrative measure of cardiac hydraulic pumping ability, and can be considered a direct indicator of overall cardiac function and a powerful predictor of prognosis in HF patients.[31,32] The increase in CPO observed in our patients can mostly be ascribed to the increase in cardiac output, since the mean arterial pressure values were unchanged. Similarly, the observed decrease in CPO in the diuretic infusion group can be ascribed to the reductions in cardiac output and mean arterial pressure recorded in this group of patients.

We detected a significant increase in dP/dt_{max} only during and after ultrafiltration. It is not fully understood why fluid removal

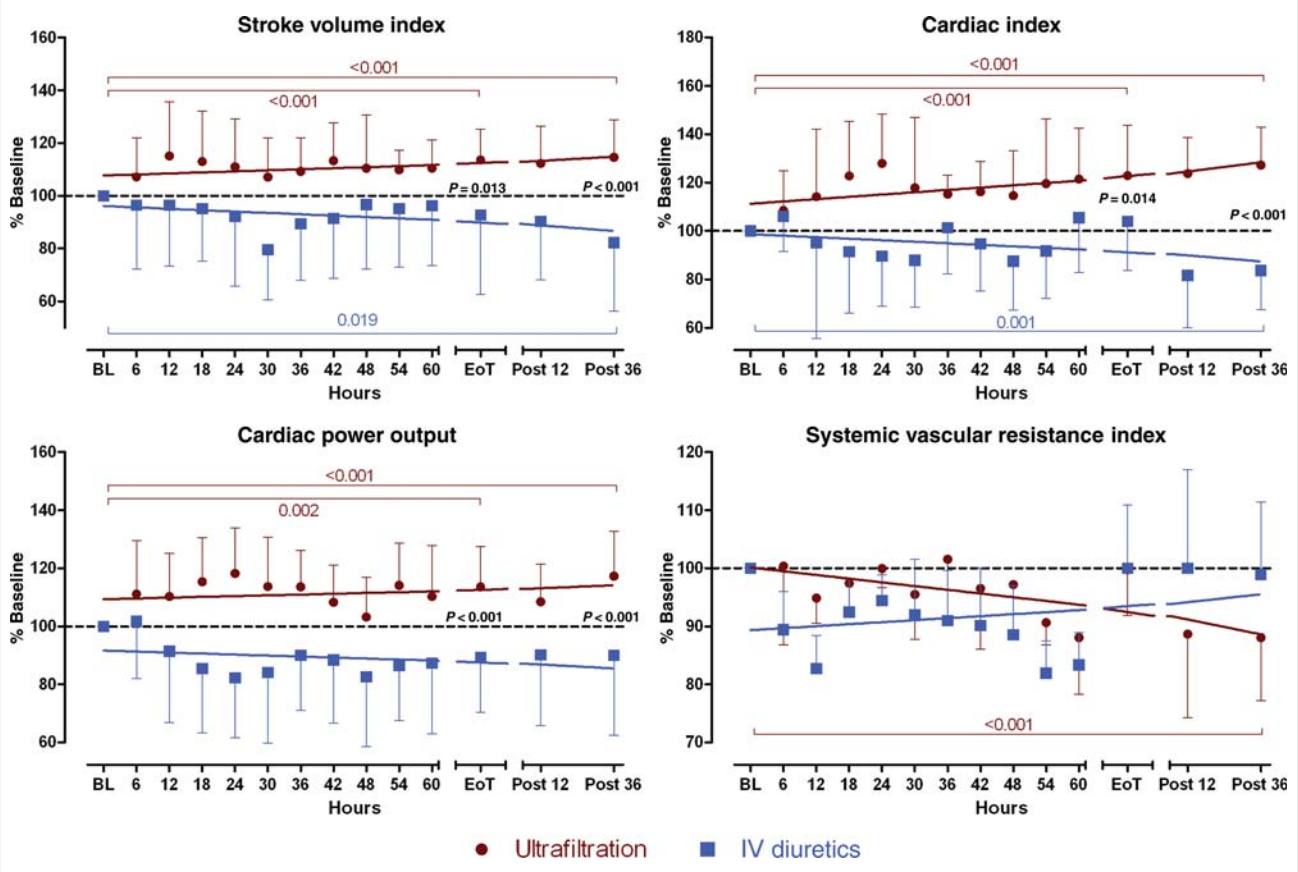

Figure 2 Trends over time in haemodynamic variables for patients in the ultrafiltration and diuretic therapy groups.

with ultrafiltration results in an increase in dP/dt_{max}, which is an index of myocardial contractility related to the interaction between the isovolumetric phase of the contraction and the arterial stiffness.[33] We hypothesize that the mechanism underlying the improvement induced by ultrafiltration may extend beyond simple salt and water removal. Ultrafiltration membranes allow the passage of small macromolecules with molecular weights up to 20,000 Da. Investigators have suggested that the removal of cytokines with myocardial depressant properties, including tumor necrosis factor-alpha and other inflammatory cytokines, may improve myocardial contractility. Previous studies have shown that such molecules are removed from the blood during ultrafiltration and can be found in the ultrafiltrate.[34–36]

It is possible that dP/dt_{max} improved because ultrafiltration was also able to reduce myocardial oedema. This hypothesis, as previously suggested by other authors,[37,38] needs to be further evaluated and could be an interesting issue for future studies.

We observed a significant increase in CCE in both treatment groups; however CCE was significantly higher at Post 36 in the ultrafiltration group than in the diuretic infusion group. Cardiac cycle efficiency represents the ratio between haemodynamic work performed by the heart and energy expenditure;[15,16] thus, an increase in CCE reflects a reduction in energy used by the cardiovascular system to maintain the same haemodynamic balance. The increase in CCE observed in both groups can be interpreted as an improvement in ventricular–arterial coupling due to fluid removal, independently of the method used. The more pronounced increase in CCE in the ultrafiltration group could be ascribed to the numerous favourable haemodynamic effects observed in this group of patients.

A limitation of this study is that patients were enrolled in a single centre, and thus only a small sample size was obtained, although the haemodynamic variables analysed had a statistical power higher than 80%. Another limitation is that our results only apply to the acute phase of HF management, since long-term outcome was not assessed. Moreover, in the present study we did not investigate the possible association between the beneficial clinical effects of ultrafiltration and improved haemodynamic and neurohormonal status. Further studies need to be performed to evaluate this issue.

In conclusion, our study shows that in patients with advanced HF and signs and symptoms of over-hydration, ultrafiltration may represent a more beneficial method of fluid removal than diuretic infusion, since its effects go beyond clinical improvement by ameliorating haemodynamic status without a marked increase in aldosterone or NT-proBNP levels.

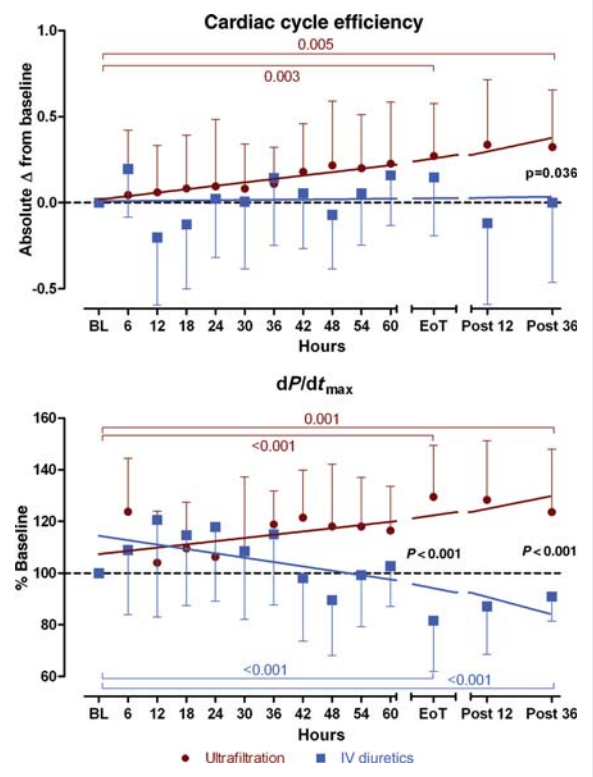

Figure 3 Trends over time in cardiac cycle efficiency and d*P*/dt_{max} for patients in the ultrafiltration and diuretic therapy groups.

Conflict of interest: none declared.

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