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Circulatory Response to Fluid Overload Removal by Extracorporeal Ultrafiltration in Refractory Congestive Heart Failure

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OBJECTIVES The goal of this study was to investigate the hemodynamic and circulatory adjustments to extracorporeal ultrafiltration (UF) in refractory congestive heart failure (rCHF).

BACKGROUND In rCHF, UF allows clinical improvement and restores diuretic efficacy. However, in the course of a UF session, patients are exposed to rapid variations of body fluid composition so that, as fluid is withdrawn from the intravascular compartment, hypotension or even shock could occur.

METHODS In 24 patients with rCHF undergoing UF, we measured, after every liter of plasma water removed, hemodynamics, blood gas analysis (in both systemic and pulmonary arteries), plasma volume changes (PV) and plasma refilling rate (PRR). The PV and PRR were calculated by considering hematocrit and ultrafiltrate volume.

RESULTS In all patients, UF was performed safely, without side effects or hemodynamic instability (ultrafiltrate = 4,880 ± 896 ml). Mean right atrial, pulmonary artery and wedge pressures progressively reduced during the procedure. Cardiac output increased at the end of the procedure and, to a greater extent, 24 h later, in relation to the increase of stroke volume. Heart rate and systemic vascular resistance did not increase, and other peripheral biochemical parameters did not worsen during UF. Intravascular volume remained stable throughout the entire duration of the procedure, indicating that a proportional volume of fluid was refilled from the congested parenchyma.

CONCLUSIONS In patients with rCHF, subtraction of plasma water by UF is associated with hemodynamic improvement. Fluid refilling from the overhydrated interstitium is the major compensatory mechanism for intravascular fluid removal, and hypotension does not occur when plasma refilling rate is adequate to prevent hypovolemia. (J Am Coll Cardiol 2001;38:963–8)
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Refractory congestive heart failure (rCHF) usually represents the end stage of heart failure in which hypotension and oliguria, leading to progressive generalized edema, occur. Refractory CHF is considered the end product of a vicious circle in which reduced cardiac output and impaired salt and water renal excretion have a negative impact on each other (1,2). As a consequence of progressive resistance to larger doses of diuretics, kidney replacement therapies have gained wide acceptance in the management of refractoriness. Among these, extracorporeal ultrafiltration (UF) is particularly helpful because it allows for sustained clinical improvement. Indeed, after UF, pulmonary and peripheral edema reduce, mechanical lung function improves, right atrial pressure and pulmonary wedge pressure decrease, neurohumoral activation is reset toward a more physiological condition and diuretic efficacy is restored (3–7).

In the course of a UF session, patients are exposed to rapid variations of body fluid composition. Since fluid is withdrawn from the intravascular compartment, blood volume falls during this process. The transient reduction of blood volume elicits compensatory mechanisms, namely the process of intravascular refill, which are aimed at minimizing this reduction (8). Refill from the overhydrated interstitium depends on fluid movement through the capillary walls, a result of hydrostatic and oncotic pressure gradient changes between the intravascular and the interstitial compartments (9). Cardiovascular reaction to transient hypovolemia is mainly mediated by the sympathetic and renin-angiotensin systems (1,10). Often, however, these mechanisms are already maximally utilized or even exhausted in rCHF, and, when the cardiovascular system fails to respond to hypovolemia, hypotension and shock progressively occur. The circulatory response of patients with rCHF undergoing UF is not completely understood. Although UF is considered a safe procedure and severely ill patients tolerate UF better than hemodialysis, a wide incidence rate of hypotension and treatment failure has been reported (11,12). This can be due to differences in the patients' clinical characteristics, technique utilized (venovenous vs. arterovenous circuit, ultrafiltration vs. hemofiltration, etc.) or amount and speed of fluid removal. All these factors can influence the circulatory responses to fluid subtraction and, finally, the clinical outcome of patients with rCHF.

We performed this study in order to investigate whether it is possible to preserve blood volume and hemodynamic

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Abbreviations and Acronyms

Ht	=	hematocrit
NYHA	=	New York Heart Association
PRR	=	plasma refilling rate
PV	=	plasma volume
rCHF	=	refractory congestive heart failure
UF	=	extracorporeal ultrafiltration

stability during UF through an adequate plasma refilling rate, in spite of the removal of large amounts of fluid.

METHODS

Study patients. The study included 24 patients (18 men and 6 women, mean age 64 ± 11 years) with rCHF (New York Heart Association [NYHA] functional class IV). Seventeen patients had ischemic heart disease, and seven patients had idiopathic dilated cardiomyopathy. All patients had symptoms of dyspnea with radiological evidence of pulmonary venous congestion and cardiomegaly, recent body weight gain (>5 kg in the last month), generalized edema and ingravescent oligoanuria. All patients were in the cardiac intensive care unit for treatment of heart failure at the time of the study. Long-term medications included digoxin (n = 11), diuretics (n = 24), angiotensin-converting enzyme inhibitors (n = 15), nitrates (n = 8) and amiodarone (n = 12). Short-term medications used for cardiac decompensation included dopamine (n = 16), dobutamine (n = 8) and amrinone (n = 2) in different combinations and doses. During the study period, medications were not changed. The ethical committee of our institution approved the study, and written informed consent was obtained from each patient after detailed explanation of the technique and the clinical and research purposes of the study were given.

Study protocol. Hemodynamic studies were performed in the morning after an overnight fast. All patients had a 7F triple lumen balloon flotation catheter for measurement of right atrial, pulmonary artery and pulmonary capillary wedge pressures. Mixed venous blood for gas analysis was obtained from the distal port of this catheter. Cardiac output was determined in triplicate by the thermodilution method. A radial artery catheter was used to measure arterial pressure and to obtain arterial blood for determinations of gases. After endovascular procedures, patients were allowed to rest quietly in the most comfortable position they could find for at least 1 h before arterial and mixed venous blood samplings and hemodynamic recordings were performed. Hemodynamic measures included heart rate, mean systemic blood pressure, mean right atrial pressure, mean pulmonary artery and wedge blood pressures and cardiac output. Derived data, namely stroke volume and systemic and pulmonary vascular resistances, were calculated with standard formulas. Blood samples were utilized to determine hemoglobin, P_{O_2}, P_{CO_2}, pH and hemoglobin saturation (IL482 and IL1306, Instrumentation Laboratories, Lexington, Massachusetts). Arterial-venous oxygen difference, oxygen consumption, oxygen delivery and oxygen extraction ratio were also obtained by using standard formulas (13). The changes in plasma volume (ΔPV) during UF were calculated from changes in hematocrit (Ht) according to the following formula (14): $\Delta PV = 100/(100 - Htpre) \times [100\ (Htpre - Htpost)]/Htpost$ where pre and post are the two time points considered. Plasma refilling rate (PRR, ml/min), which represents a measurement of the fluid volume transport from the interstitium to the intravascular space during ultrafiltration, is the ultrafiltrate volume/time, where time is the duration of ultrafiltration if ΔPV = 0. When PRR equals ultrafiltration rate, blood volume stability is preserved.

In all patients, hemodynamic data were obtained before UF and repeated after 1 L, 2 L, 3 L and 4 L of UF, at the end of the procedure and 24 h later. Hematocrit for ΔPV estimation was obtained for every liter of ultrafiltrate, up to the end of UF and 24 h later.

Ultrafiltration. Ultrafiltration treatment was performed by using a B. Braun-Carex Diapact CRRT peristaltic pump (Mirandola, Italy). During UF, blood is pumped through a filter (Renaflo HF700, Mirandola, Italy), which is inserted into an extracorporeal circuit connected to a double lumen Y-shaped catheter positioned in a femoral vein. A peristaltic pump was regulated to maintain a blood flow of 100 ml/min within the circuit. The flow velocity was never changed during the procedure. In all patients, the procedure was terminated when Ht was increased by 10% of baseline (more than 4 L of ultrafiltrate in all cases). A loading bolus of 5,000 IU of heparin was administered inside the circuit before allowing blood to pass into the filter, and then a continuous heparin infusion rate of 500 to 1,000 IU/h was maintained during the UF session.

Statistical analysis. All data are presented as mean ± SD. Changes during UF were assessed by repeated measures of analysis of variance, applying the post-hoc Dunnet adjustments. All statistical analyses were performed using the SPSS software package. A p value ≤ 0.05 was considered significant.

RESULTS

In all patients, the single session of UF was performed safely, without side effects or hemodynamic instability. The mean time duration of the procedure was 9 ± 3 h, and the total fluid volume removed was 4,880 ± 896 ml (range: 4,300 to 7,000 ml), which, in addition to the increase in urinary output induced by UF (2,6,15), resulted, 24 h after UF, in a reduction in body weight of 7.4 ± 1.8 kg. After UF, the stage of congestive heart failure (NYHA classification) improved in all patients; pulmonary edema was relieved; ascites and peripheral edema were significantly reduced, and the response to subsequent diuretic therapy was enhanced (the mean dose of furosemide was reduced from 380 ± 157 mg/day to 112 ± 70 mg/day from the day after UF).

Table 1. Blood Gas Analysis and Hemodynamic Data at Each of Examined Treatment Steps

		Before UF	1 L	2 L	3 L	4 L	After UF	24 h After UF
pH	A	7.44 ± 0.04	7.44 ± 0.04	7.43 ± 0.04	7.44 ± 0.03	7.44 ± 0.04	7.45 ± 0.05	7.47 ± 0.07*
	V	7.41 ± 0.04	7.41 ± 0.04	7.41 ± 0.05	7.42 ± 0.05	7.42 ± 0.04	7.42 ± 0.04	7.42 ± 0.04
P_{O_2} (mm Hg)	A	80 ± 15	81 ± 14	82 ± 14	82 ± 16	84 ± 16	86 ± 20*	87 ± 17*
	V	29 ± 5	28 ± 5	29 ± 5	30 ± 4	32 ± 4	34 ± 5*	35 ± 4*
P_{CO_2} (mm Hg)	A	35 ± 4	35 ± 4	34 ± 6	35 ± 7	34 ± 5	33 ± 7	33 ± 6
	V	41 ± 4	41 ± 4	40 ± 5	41 ± 5	41 ± 5	40 ± 5	40 ± 4
Sat O_2 (%)	A	95 ± 4	95 ± 5	95 ± 4	95 ± 6	96 ± 4	96 ± 3	97 ± 2*
	V	54 ± 12	54 ± 12	55 ± 13	57 ± 12	58 ± 12*	60 ± 13*	64 ± 10*
HR (beats/min)		82 ± 17	83 ± 16	82 ± 15	83 ± 16	81 ± 17	80 ± 15	80 ± 16
mSAP (mm Hg)		86 ± 16	84 ± 15	82 ± 14	84 ± 16	80 ± 18	78 ± 21	80 ± 18
mPAP (mm Hg)		39 ± 11	38 ± 10	38 ± 11	36 ± 12	34 ± 10*	34 ± 11*	30 ± 15*
SVR (dynes·s·cm^{-5})		1,676 ± 465	1,640 ± 430	1,682 ± 415	1,710 ± 515	1,699 ± 567	1,701 ± 795	1,319 ± 412*
PVR (dynes·s·cm^{-5})		324 ± 160	342 ± 173	365 ± 184	339 ± 165	344 ± 178	350 ± 188	264 ± 148*
V_{O_2} (ml/min/m^2)		127 ± 29	126 ± 30	128 ± 32	128 ± 36	127 ± 31	128 ± 33	132 ± 48*
D_{O_2} (ml/min/m^2)		311 ± 88	299 ± 97	310 ± 101	335 ± 105	327 ± 112	385 ± 105*	410 ± 134*
ER_{O_2} (%)		43 ± 14	42 ± 15	41 ± 15	38 ± 17	39 ± 16	33 ± 16*	32 ± 13*
a-v D_{O_2} (ml/dl)		7 ± 2	6.8 ± 2	6.7 ± 2	6.4 ± 2	6.2 ± 2*	5.9 ± 2*	5.5 ± 2*

Data are mean ± SD. *$p < 0.05$ vs. before UF.

A = arterial blood; a-v D_{O_2} = arterial-venous oxygen difference; D_{O_2} = oxygen delivery; ER_{O_2} = oxygen extraction ratio; HR = heart rate; mPAP = mean arterial pulmonary pressure; mSAP = mean systemic arterial pressure; PVR = pulmonary vascular resistances; SVR = systemic vascular resistances; UF = ultrafiltration; V = mixed venous blood; V_{O_2} = oxygen consumption.

During the procedure, as well as in the following 24 h, patients showed no changes in heart rate, mean systemic arterial pressure or systemic vascular resistance (Table 1). Mean right atrial pressure, pulmonary wedge pressure (Fig. 1) and pulmonary artery pressure (Table 1) progressively reduced. Right atrial and pulmonary wedge pressure reduction was parallel and on a one to one basis (Fig. 2). Cardiac output increased at the end of the procedure and, to a

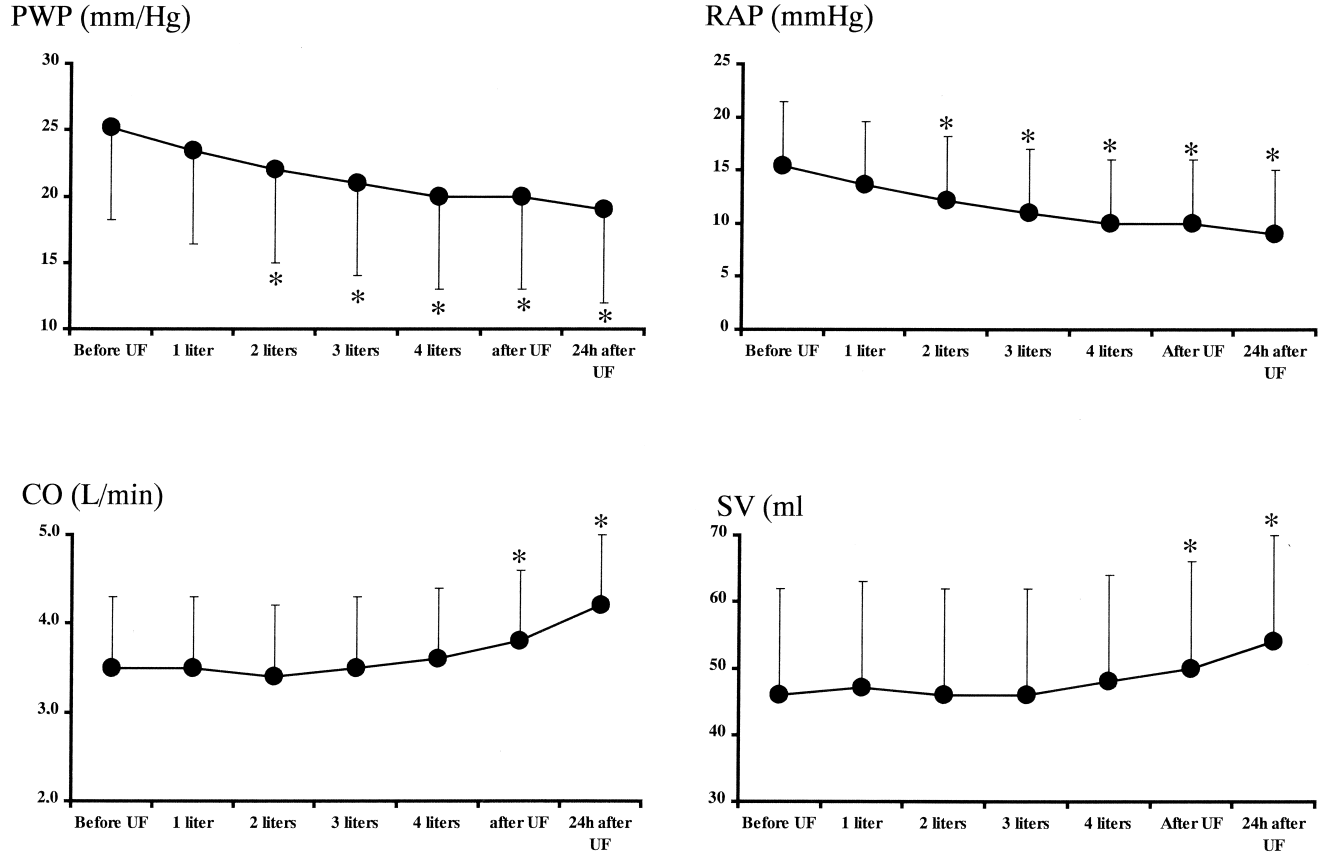

Figure 1. Mean pulmonary wedge pressure (PWP), mean right atrial pressure (RAP), cardiac output (CO) and stroke volume (SV) before, during and after extracorporeal ultrafiltration (UF). *$p < 0.01$ vs. before ultrafiltration.

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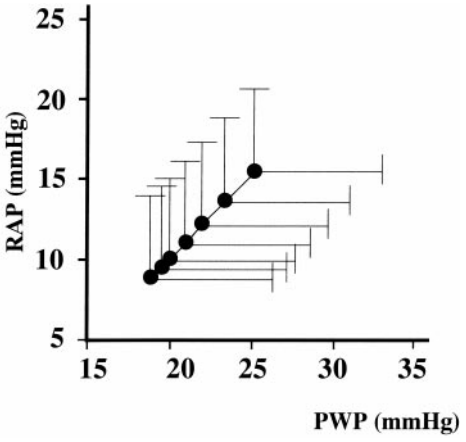

Figure 2. Right atrial pressure (RAP) versus pulmonary artery wedge pressure (PWP) during extracorporeal ultrafiltration. Symbols (mean **[black circle]** ± SD **[bar]**) are, from right to left, data obtained before ultrafiltration, after 1 L, 2 L, 3 L and 4 L of ultrafiltrate, at the end and 24 h after ultrafiltration. A 1 to 1 reduction of right and left atrial pressures suggests lowering of extracardiac constraint (see text).

greater extent, 24 h later in relation to the increase of stroke volume (Fig. 1). Table 1 also shows the derived hemodynamic and blood gas parameters at each of the examined steps. No change in all these parameters occurred during UF, whereas, at the end of the procedure and 24 h later, P_{O_2} and hemoglobin saturation increased. This was more relevant at the venous site.

Intravascular volume, as estimated by hematocrit values, remained stable throughout the entire time of the treatment despite the large amount of fluid removed (Fig. 3). This indicates that a proportional volume of fluid was refilled from the congested interstitium. Accordingly, it was possible to calculate the PRR, which progressively decreased during UF (Fig. 3).

DISCUSSION

Our study confirms that UF is effective in removing fluid in overhydrated patients with CHF. As previously demonstrated (3–6,15,16), the procedure induces improvement in respiratory function and relieves ascites and peripheral edema. The benefits are usually obtained in a very short time, particularly if compared with any other available therapeutic approach. Sometimes, however, prolonged UF treatment is required. It is known that, in most patients, diuretic responsivity can be regained; for instance, in this study, furosemide dosages were reduced by approximately 300% the day after UF. This is important because it allows for maintenance, and even improvement of, the clinical benefit achieved at the end of a single session of UF in the days and months that follow (17). Thus, by restoring diuresis and diuretic responsiveness, UF is able to interrupt, and then revert, the vicious circle that leads to refractoriness. Nevertheless, some concerns still exist in regard to the safety of the procedure, particularly in patients with impaired hemodynamic stability and poor cardiac functional reserve, such as those with rCHF.

Hemodynamic consequences of ultrafiltration. Our study demonstrates that withdrawal by UF of more than 4 L of plasma water over a period of a few hours can be safely performed without detrimental hemodynamic consequences. Indeed, during treatment, heart rate, systemic arterial pressure, cardiac output and systemic vascular resistances did not change, despite a progressive decline in ventricular filling pressures. Both cardiac output and stroke volume significantly increased at the end and, to a greater extent, 24 h after UF. This apparent paradox indicates that in rCHF, during UF, the heart is operating on the horizontal part of the ventricular function curve or that a reduction of the external work of the heart is occurring (18,19). Indeed, because right and left heart pressures reduce in a 1 to 1 fashion (Fig. 2) and not on a 1 to 3 basis, as usually happens when external cardiac constriction is absent (19,20), a reduction of the extracardiac constraint, acting on both sides of the heart, is likely. This extracardiac constraint might be due to increased lung water (6,16,17,21), pleural effusion and ascites (22). Thus, reduction in the filling pressure of both ventricles and improvement in cardiac performance purely reflect the reduction of intrathoracic pressure and the removal of its negative influence on the heart (19,23,24). Indeed, removal of the constraining effect exerted by the overhydrated lungs on the heart has been shown to reduce the ventricular filling pressures and improve diastolic properties of the heart, which means improved cardiac performance (18).

Blood gas changes induced by ultrafiltration. In addition to central hemodynamic parameters, we also investigated the possibility that, in reference to patients with rCHF, biochemical compensatory mechanisms are elicited in the periphery during UF. Before treatment, venous P_{O_2} and hemoglobin saturation, as well as oxygen delivery, were low, while oxygen extraction ratio and arterial-venous oxygen difference were increased when compared with normal subjects (13). This indicates that, when central hemodynamic impairment occurs and oxygen delivery to peripheral tissue reduces, activation of peripheral compensatory mechanisms, in order to increase oxygen extraction, takes place. During UF, all these parameters remained stable, suggesting either no further activation (because of hemodynamic stability) or the exhaustion of defensive homeostatic mechanisms. The lack of cardiac output and mean systemic arterial pressure worsening during the procedure did not allow us to speculate about the exhaustion of homeostatic mechanisms in rCHF. In contrast, at the end of the treatment, a trend toward normalization of all these variables, parallel with oxygen delivery increase, was observed; this implies that compensatory mechanisms are turned off by UF.

Blood volume adjustments during ultrafiltration. Because hemodynamic worsening does not take place during UF, refilling from the extravascular space is adequate to replace the removed intravascular fluid, and hypovolemia is prevented (14,25). Adequate refilling, as well as plasma volume changes, can be easily monitored through an Ht

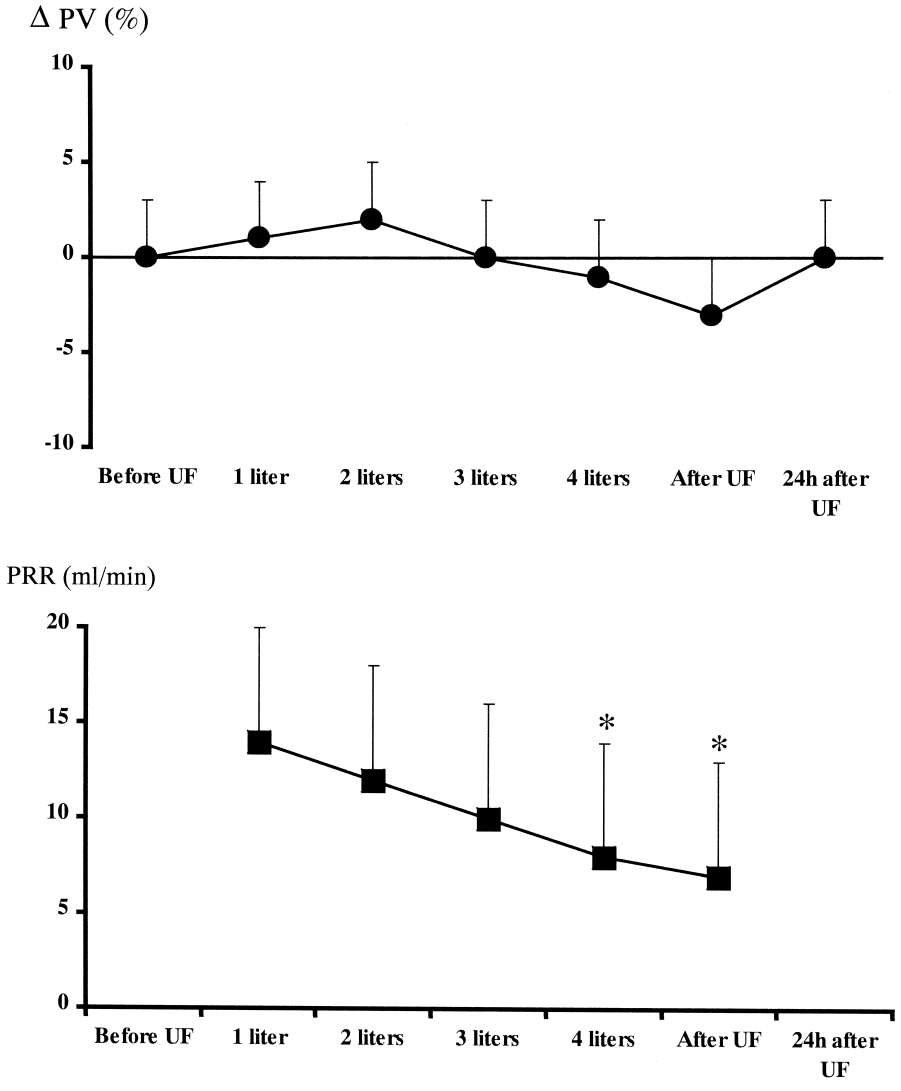

Figure 3. Percent changes in plasma volume (PV) **(upper)** and plasma refilling rate (PRR) **(lower)** during extracorporeal ultrafiltration (UF). *$p < 0.01$ vs. 1 L.

changes evaluation. In our study, and in others as well (6,25), Ht did not significantly change despite the large amount of fluid that was removed. This indicates a proportional shifting of water from the extravascular to the intravascular phase. If Ht increases, it may indicate either an insufficient refilling rate in order to compensate an excessively fast fluid withdrawal or the complete removal of the extravascular edema. In both cases, any further prolongation of the treatment, or of the same UF speed, would cause a possibly dangerous hypovolemia-related hypotension and a cardiac output reduction. Hemodynamic stability, due to plasma refilling, explains why the procedure can be performed in patients with cardiogenic shock as well (4,10); again, however, this is true only in the presence of an extravascular edema able to warrant a sufficient refilling. Average estimated refilling rate (Fig. 3) during UF progressively declined with time, suggesting that, as extravascular fluid volume is progressively removed, UF rate has to be reduced. As a consequence, a close monitoring of plasma volume changes is required during UF.

In conclusion, our data show that UF, when performed as a kidney replacement therapy for rCHF, is a safe and effective procedure that allows the patient to reach a rapid clinical and hemodynamic improvement. This is associated with intravascular volume stability, mainly due to adequate refilling of fluid from the overhydrated interstitium. However, monitoring of intravascular volume changes is mandatory in order to prevent hypovolemia-related hypotension; this can easily be performed through sequential measurements of the Ht fraction.

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