Br Heart J 1994;72:534–539

Apparent paradox of neurohumoral axis inhibition after body fluid volume depletion in patients with chronic congestive heart failure and water retention

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Abstract

***Background*—Hypovolaemia stimulates the sympathoadrenal and renin systems and water retention. It has been proposed that in congestive heart failure reduction of cardiac output and any associated decrease in blood pressure cause underfilling of the arterial compartment, which promotes and perpetuates neurohumoral activation and the retention of fluid. This study examined whether an intravascular volume deficit accounts for patterns that largely exceed the limits of a homoeostatic response, which are sometimes seen in advanced congestive heart failure.**

***Methods and Results*—In 22 patients with congestive heart failure and water retention the body fluid mass was reduced by ultrafiltration and the neurohumoral reaction was monitored. A Diafilter, which was part of an external venous circuit was regulated to produce 500 ml/hour of ultrafiltrate (mean (SD) 3122 (1199) ml) until right atrial pressure was reduced to 50% of baseline. Haemodynamic variables, plasma renin activity, noradrenaline, and aldosterone were measured before and within 48 hours of ultrafiltration. After ultrafiltration, which produced a 20% reduction of plasma volume and a moderate decrease in cardiac output and blood pressure (consistent with a diminished degree of filling of the arterial compartment), there was an obvious decrease in noradrenaline, plasma renin activity, and aldosterone. In the next 48 hours plasma volume, cardiac output, and blood pressure recovered; the neurohumoral axis was depressed; and there was a striking enhancement of water and sodium excretion with resolution of the peripheral oedema and organ congestion. The neurohumoral changes and haemodynamic changes were not related. There were significant correlations between the neurohumoral changes and increase in urinary output and sodium excretion.**

***Conclusions*—In advanced congestive heart failure arterial underfilling was not the main mechanism for activating the neurohumoral axis and retaining fluid. Because a decrease in circulating hormones was associated with reabsorption of extravascular fluid it is likely that hypoperfusion and/or congestion of organs, such as the kidney and lung, reduce the clearance of circulating noradrenaline and help to keep plasma concentrations of renin and aldosterone raised. A positive feedback loop between fluid retention and plasma hormone concentrations may be responsible for progression of congestive heart failure.**

(*Br Heart J* 1994;72:534–539)

La constance du milieu intérieur est la condition d'une existence libre et indépendente.

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Accepted for publication 1 June 1994

A decrease in the volume of body fluid leads to reduced excretion of salt and water and activation of the sympatho-adrenal and renin-aldosterone systems. Bleeding,[2] pharmacological diuresis[3 4] and, possibly, cardiac insufficiency[5 6] activate this defence reaction. In heart failure retention of water and salt and neurohumoral stimulation can greatly exceed the limits of a homoeostatic response.[7] To explain this, Peters coined the term "effective blood volume",[8] which was subsequently identified as the state of filling of the arterial compartment.[4] According to these concepts, a reduction of the output of the heart and any decrease of blood pressure in heart failure can be regarded as an intravascular volume deficit,[9] and the neurohumoral reaction would be perpetuated if the haemodynamic disorder persisted. Clinical studies of frusemide and ultrafiltration accord with this view. Acute volume depletion by intravenous frusemide or ultrafiltration,[10–13] in patients with congestive cardiac failure was associated with increased systemic vascular resistance and reduced cardiac output and blood pressure (consistent with hypovolaemia) and an additional increase in plasma noradrenaline, renin, and aldosterone.[14–19] However, two points should be considered: frusemide stimulates the renin system independently of volume depletion[16] (the associated increase in plasma noradrenaline may be, at least in part, mediated through facilitation of the neurotransmitter release by angiotensin II[20 21]) and in patients with heart failure and congestion ultrafiltration reduced rather than increased concentrations of circulating hormones. So does vascular underfilling alone account for the striking neurohumoral activation and fluid retention that occur in the more advanced stages of the disease?

This question prompted us to perform a 48 hour follow up study of patients with congestive heart failure and fluid retention who had ultrafiltration alone.

Patients and methods

PATIENTS

We studied 22 patients with congestive heart failure admitted to the Institute of Cardiology, University of Milan (table 1). They had dyspnoea on moderate exertion or at rest (New York Heart Association class III or IV) with dependent oedema, lung congestion on chest *x* ray, and pleural effusion in some cases. Twenty patients were in sinus rhythm and two had chronic atrial fibrillation. Mean (SD) urinary output in 24 hours was 852 (692) ml. Cardiac failure was caused by ischaemic heart disease in 14 and primary dilated cardiomyopathy in eight. These 16 men and six women gave their written consent to the investigation after being given detailed information on the procedure and its possible clinical benefits. The protocol was approved by the hospital ethics committee.

STUDY DESIGN

After admission, each patient was confined to bed and was treated with his or her usual outpatient doses of frusemide and digoxin by mouth: the doses were kept constant for an individual patient throughout the trial. Angiotensin converting enzyme inhibitors or inotropic drugs other than digitalis were gradually withdrawn during the first 5 days of hospital stay.

Patients were eligible for the study if they had had no exacerbation of symptoms within 2 weeks of hospital admission and ACE inhibitors and inotropic preparations were withdrawn in hospital. Patients whose clinical condition deteriorated for any reason during run-in were immediately withdrawn from the trial.

Ultrafiltration was performed when body weight, renal function, sodium and water excretion, and serum sodium and potassium concentration had remained steady for 4 days. This took about 10 days.

None of these patients was included in our previous studies.[11 19 22 23] Haemodynamic and hormonal variables and plasma volume were assessed before, immediately after ultrafiltration, and 24 and 48 hours later. Patients were familiarised with the laboratory and its staff; measurements were carried out in an air conditioned room adjacent to the coronary care unit, at 22°C, after an overnight fast. Tea, coffee, cigarettes and alcohol were not taken in the last 12 hours. Patients had had a stable heart rate, blood pressure, pulmonary artery wedge pressure and cardiac output for at least an hour before the study started. After the baseline measurements were taken the external venous circuit was attached and ultrafiltration was started. Haemodynamic variables were measured every 30 minutes during ultrafiltration and those recorded immediately before and immediately after the procedure were compared. For the next 48 hours the patients remained in bed without any change in treatment. Every 24 hours urine was collected and the haematocrit, serum electrolytes and creatinine, blood urea nitrogen, creatinine clearance, and hormone concentrations were measured.

ULTRAFILTRATION

We used a D20 SF Amicon diafilter (Danvers, Massachusetts, USA), which allows filtration of plasma water and solutes < 50 000 D.[11] The filter was part of an external circuit, connecting the right femoral vein with an antecubital vein. Flow was driven by a Gambro System (Lund, Sweden) AK peristaltic pump which was set to produce ultrafiltrate at a rate of 500 ml/hour. Veins were cannulated with haemodialysis catheters (Becton Dickinson, Sandy, Utah). Ultrafiltration was continued until the mean right atrial pressure had been reduced to 50% of baseline or until the haematocrit increased to 50%. The mean volume of fluid removed by this method was 3122 ml

Table 1 Demographic and clinical characteristics in 22 patients

Patient No	*Age (yr) and sex*	*Aetiology*	*NYHA class*	*Clinical data*		*Prior treatment*				*Current treatment (mg/day)*	
				PO	*PE*	*D*	*ACEI*	*I*	*LAN*	*D*	*F*
1	58 M	CAD	IV	Yes	Yes	Yes	No	Yes*	No	0.25	180
2	64 M	CAD	IV	Yes	No	Yes	Yes*	No	Yes*	0·25	160
3	67 F	CAD	IV	Yes	No	No	No	Yes*	No	—	100
4	77 M	IDC	IV	Yes	Yes	Yes	Yes*	Yes*	No	0·25	250
5	47 M	CAD	IV	Yes	No	Yes	No	No	Yes*	0.125	100
6	57 F	IDC	IV	Yes	No	Yes	No	No	No	0·25	500
7	66 M	CAD	IV	Yes	Yes	Yes	Yes*	No	No	0.125	200
8	42 M	CAD	IV	Yes	Yes	Yes	No	Yes*	No	0.50	140
9	51 M	IDC	IV	Yes	No	No	No	No	Yes*	—	300
10	59 M	IDC	IV	Yes	No	Yes	Yes*	No	No	0·125	160
11	72 M	CAD	IV	Yes	No	Yes	No	No	Yes*	0·125	500
12	64 F	IDC	IV	Yes	Yes	Yes	No	Yes*	No	0.25	180
13	65 M	CAD	IV	Yes	No	Yes	No	No	No	0·25	100
14	65 M	IDC	IV	Yes	No	Yes	Yes*	No	Yes*	0·25	160
15	73 F	IDC	IV	Yes	No	No	No	Yes*	No	—	120
16	62 M	CAD	IV	Yes	No	No	No	Yes*	No	—	300
17	64 M	CAD	IV	Yes	No	Yes	No	No	No	0·25	120
18	67 M	CAD	IV	Yes	No	Yes	No	No	Yes*	0·25	120
19	79 M	IDC	III	Yes	Yes	Yes	Yes*	No	No	0·25	140
20	67 F	CAD	III	Yes	No	Yes	No	No	No	0·25	160
21	48 M	CAD	IV	Yes	No	Yes	No	Yes*	No	0.25	80
22	70 F	CAD	IV	Yes	No	Yes	Yes*	No	No	0·125	1000

*Stopped 5 days before study.
ACEI, angiotensin-converting enzyme inhibitors; CAD, coronary artery disease; D, digoxin; F, frusemide; IDC, idiopathic dilated cardiomyopathy; I, inotropic preparations; LAN, long acting nitrates; NYHA, New York Heart Association functional class; PO, peripheral oedema; PE, plural effusion.

(range 1000–5000 ml). When the procedure was complete the filtering circuit was removed.

HAEMODYNAMIC VARIABLES

Haemodynamic variables were measured with a number 8 flow directed triple lumen thermodilution catheter introduced percutaneously into a subclavian vein and advanced to the pulmonary artery or to the wedge position. Right atrial pressure was measured at the proximal port of the catheter. A short catheter was introduced into a brachial artery to measure systemic arterial pressure. Pressures were determined with Hewlett Packard (Waltham, Massachusetts) strain gauge transducers (model 1286 B) and recorded on a Hewlett Packard 8-channel recorder (model 1064 C). Cardiac output was measured by the thermodilution method with an Edwards (Santa Ana, California) cardiac output computer (9520 A); the mean of three measurements was taken for each time point. Systemic vascular resistance was calculated from the ratio of the driving pressure through the systemic circuit (mean arterial pressure minus mean right atrial pressure) and cardiac output. The driving pressure through the systemic circuit was also used as an index of the renal perfusion pressure.[24]

HUMORAL AND PLASMA VOLUME TESTS

Measurements of hormones in all samples from a single patient were obtained in the same assay: noradrenaline by high performance liquid chromatography[25] (Kontron Instruments, Milan, Italy); plasma renin activity by radioimmunoassay[26] (Technogenetics, Milan, Italy), and aldosterone by radioimmunoassay[27] (Sorin, Saluggio, Italy). We used samples of arterial blood[28] that were cooled immediately and stored at −20°C. The normal plasma values (SD) in the supine position in our laboratory are: noradrenaline 0·911 (0·031) nmol/l, aldosterone 2·52 (0·7) nmol/l, plasma renin activity 0·029 (0·009) nmol/l/h. The intra-assay variations are 4%, 7%, and 6% respectively.

Microhaematocrits were determined in triplicate at each period and the percentage changes in plasma volume (PV) were calculated[29] from the changes in the haematocrit (HCT), according to the following formula:

$$PV_{HCT} = \frac{100}{(100 - HCT\ pre)} \times \frac{100(HCT\ pre - HCT\ post)}{HCT\ post}$$

This method assumes that no erythrocytes have been gained or lost.[30] Measured haematocrits were corrected for trapped plasma volume and converted to whole body haematocrit.[31]

STATISTICAL ANALYSIS

Changes from before to after ultrafiltration were assessed by repeated measures of analysis of variance. Analysis of two variable linear regression was used to compare each circulating hormone and selected variables that might have been related to the degree of filling of the arterial compartment: cardiac index, systemic arterial pressure and resistance, plasma volume, and urinary output. We used multiple regression analysis to compare the fluid removed and circulating noradrenaline at baseline with changes in noradrenaline soon after the procedure.

Data are expressed as mean (SD). We regarded a P value of $< 0·05$ as significant.

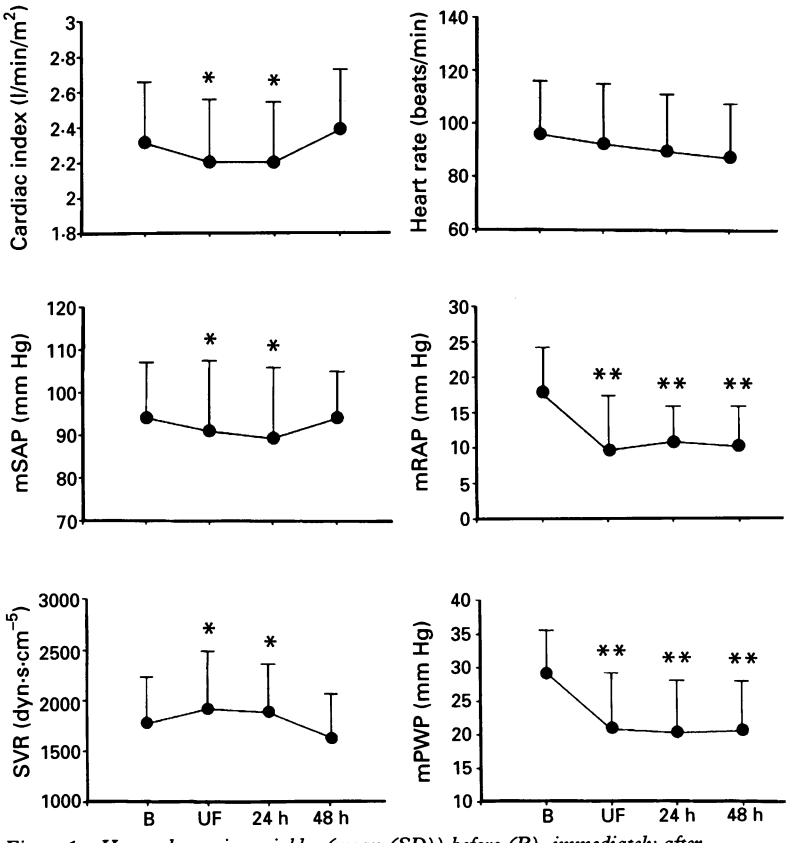

*Figure 1 Haemodynamic variables (mean (SD)) before (B), immediately after ultrafiltration (UF), and 24 and 48 hours later. mSAP, mean systemic arterial pressure; mRAP, mean right atrial pressure; SVR, systemic vascular resistance; mPWP, mean pulmonary wedge pressure. *P < 0·05 v baseline; **P < 0·01 v baseline.*

Results

VALUES AT BASELINE AND AFTER ULTRAFILTRATION

Haemodynamic variables

The mean cardiac index was 2·35 l/min/m² at baseline, decreased to 2·15 l/min/m² ($P < 0·05$ *v* baseline) soon after filtration and at 24 h, and returned to baseline in the next 24 h (fig 1). Changes in cardiac index were caused by changes in stroke volume; heart rate did not vary significantly from baseline at any time. The corresponding values for mean systemic arterial pressure were 94, 91, 89, 94 mm Hg; and those for systemic vascular resistance were 1774, 1923, 1892, 1650 dyn.s.cm⁻⁵.

Immediately after ultrafiltration mean pulmonary wedge pressure decreased by 29% and right atrial pressure decreased by 46%. Both variables remained unchanged in the next two days.

Noradrenaline, renin, aldosterone, and plasma volume

At baseline plasma noradrenaline, renin activity, and aldosterone were strikingly raised

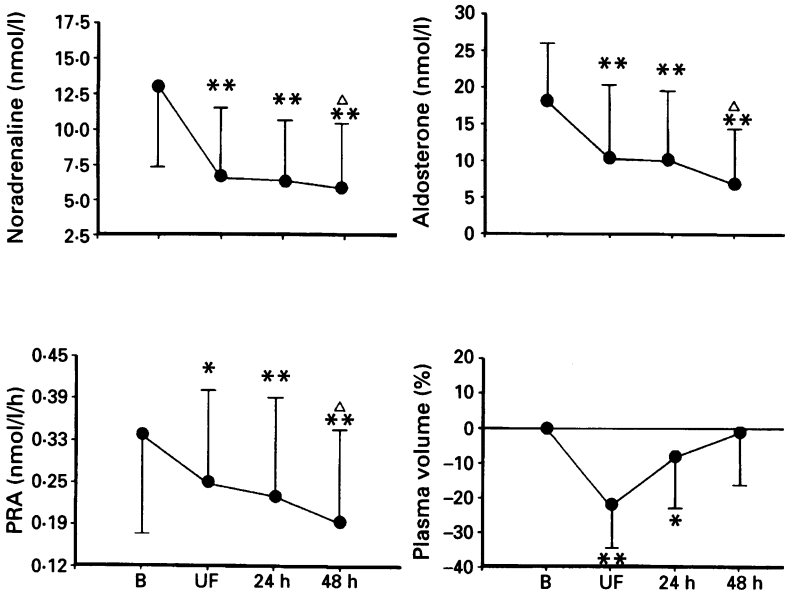

*Figure 2 Values (mean (SD)) of circulating noradrenaline, aldosterone, plasma renin activity (PRA), at baseline (B), immediately after ultrafiltration (UF), and 24 and 48 hours later. Mean percentage changes from baseline of plasma volume (PV) at the same intervals are also reported. *P < 0·05 v baseline; **P < 0·01 v baseline; Δ P < 0·01 v UF.*

Table 2 Sodium and water metabolism and renal function (mean (SD))

Variable	*Baseline*	*Immediately after UF*	*24 h after UF*	*48 h after UF*
Body weight (kg)	76 (15)	71 (14)***	71 (14)***	71 (15)***
Serum sodium concentration (mmol/l)	139 (5)	142 (12)	141 (5)**	141 (3)**
Diuresis (ml/24h)	852 (692)		2132 (1181)***	1727 (753)***
Urinary sodium excretion (mmol/24h)	39 (48)		137 (97)***	126 (103)***
Blood urea (μmol/l)	52 (29)	55 (28)***	54 (30)	49 (30)**
Serum creatinine concentration (μmol/l)	248 (177)	265 (177)**	239 (177)	221 (177)**
Creatinine clearance (ml/min)	19 (5)		46·3 (13)**	44·2 (6)***
Renal perfusion pressure (mm Hg)	74 (26)	81 (19)**	78 (16)*	78 (15)**
Ultrafiltrate (ml)		3122 (1199)		

UF, extracorporeal ultrafiltration; *P < 0·05; **P < 0·01; *** P < 0·001 *v* baseline.

(fig 2). Ultrafiltration elicited an immediate significant fall of each of them by 52, 28, and 46% of baseline, respectively. In the next two days we recorded a further significant decrease in these variables. Plasma volume was reduced by 22% immediately after the procedure and by 10% 24 hours later; it fully recovered in the next 24 hours.

Sodium and water metabolism and renal function

Mean baseline 24 h urinary output was 852 (692) ml and mean body weight was 76 kg (table 2). The day after ultrafiltration (mean 3122 ml of plasma water) diuresis increased by 150% and urinary sodium excretion by 251% of baseline, body weight decreased by 5·1 kg, creatinine clearance increased by 142% and serum sodium, urea nitrogen, and creatinine concentrations were unchanged. At 48 hours diuresis and output of sodium were 102% and 233% respectively higher than at baseline; body weight was 5 kg less; creatinine clearance was 131% higher; urea nitrogen and creatinine concentrations were 6% and 10% lower, respectively. Renal perfusion pressure was 9% higher soon after ultrafiltration and 6% higher in the two subsequent 24 hour periods.

Correlations with noradrenaline, renin, and aldosterone

We correlated hormone values at baseline with each other and with the corresponding values for other selected variables that may be related to filling of the arterial compartment[4]: cardiac index, mean systemic arterial pressure, systemic vascular resistance, plasma volume, urinary output (table 3). Noradrenaline and renin were positively related to each other but not to aldosterone, cardiac index, arterial pressure and systemic vascular resistance; noradrenaline and renin were inversely related to urinary output. Twenty four hours after ultrafiltration the changes in noradrenaline

Table 3 Correlations of baseline (BL) hormone values and their variations 24 hours after ultrafiltration Δ 24 h) with each other and with corresponding values of other selected variables that may be involved in the regulation of filling of the arterial compartment.

	Noradrenaline		*Plasma renin activity*		*Aldosterone*	
Measurement	*BL*	*Δ 24 h*	*BL*	*Δ 24 h*	*BL*	*Δ 24 h*
Cardiac index:						
BL	0·43	−0·19	0·05	−0·16	−0·35	0·12
Δ 24 h	0·25	−0·27	0·25	−0·36	−0·11	0·02
Mean arterial pressure:						
BL	−0·32	0·38	−0·42	0·40	−0·21	−0·14
Δ 24 h	0·31	−0·25	−0·37	−0·25	0·35	0·16
Systemic vascular resistance:						
BL	0·58*	0·52*	0·36	0·40	0·44	0·30
Δ 24 h	0·65*	0·58*	0·68**	0·57*	0·29	0·26
Diuresis:						
BL	−0·79**	0·69**	−0·63**	0·45*	−0·37	0·02
Δ 24 h	0·66***	−0·70**	0·45*	−0·53**	−0·18	−0·12
Plasma volume:						
% Δ 24 h	0·06	0·02	0·04	0·07	0·28	0·22
Noradrenaline:						
BL	1	−0·84***	0·85***	−0.64**	0·30	0·02
Δ 24 h	−0·84***	1	−0·83***	0·60**	−0·15	0·15
Plasma renin activity:						
BL			1	−0·81***	0·36	0·06
Δ 24 h			−0·81***	1	−0·13	0·04
Aldosterone:						
BL					1	−0·24
Δ 24 h					−0·24	1

Correlation coefficients were obtained by linear regression analysis:
*P < 0·05; **P < 0·01; ***P < 0·001

and renin were related to each other and to changes in systemic vascular resistance and urinary output; they were not related to changes in aldosterone, cardiac index, arterial pressure, and plasma volume. Changes of plasma volume did not correlate with the amount of fluid withdrawn. There was a positive significant correlation ($P < 0.001$) between changes in plasma noradrenaline with ultrafiltration and the combination of the amount of fluid removed and the circulating concentration of noradrenaline at baseline.

Discussion

Patients in this study had accumulation of fluid associated with striking activation of the neurohumoral axis. In these patients water and salt retention and hormonal stimulation greatly exceeded the limits of a homoeostatic response.[7]

Ultrafiltration removed a mean volume of 3122 ml of plasma water at a rate of 500 ml/h. This loss of fluid, which equals or exceeds in quantity the entire normal plasma water compartment, must have been offset by entry of fluid from the interstitial space. In other studies removal of 3 kg of fluid during regular haemodialysis led to a sharp 20% decrease in plasma volume.[32,33] We obtained similar results as judged by the haematocrit method; the only blood loss in our patients was the small amount taken for hormone determinations. The complexity of the interactions among the variables (magnitude and direction of osmotically active solutes and oncotically active proteins, age, and capillary and venous hydrostatic pressures) affecting intravascular volume balance[30] may explain why changes in plasma volume were unrelated to the amount of ultrafiltrate.

Decreased plasma volume, right atrial pressure, cardiac index, and mean arterial pressure and raised systemic vascular resistance immediately after ultrafiltration were consistent with some degree of intravascular volume deprivation. The circulating volume was probably restored in the next 48 hours, as shown by recovery of cardiac index, plasma volume, and blood pressure. Paradoxically, during this interval we found that water and sodium excretion were enhanced and the neurohumoral axis was further depressed. It is reasonable to ask whether reducing pressure volume by 20%, right atrial pressure to 10 mm Hg, and mean arterial pressure to 90 mm Hg is sufficient to provoke neuroendocrine activation. It is significant, however, that the response was exactly the opposite of a classic defence reaction to volume depletion. This may suggest that at this stage of the disease the defence mechanisms were exhausted or that factors other than hypovolaemia were maintaining water retention and neurohumoral overactivity.

Baseline noradrenaline and renin concentrations correlated with each other, as expected from the feedback loops linking the renin system with the adrenergic nervous system and noradrenaline.[34-36] The correlation of their changes after ultrafiltration with each other suggests that the interrelation of the two variables persisted after body fluid was reduced. A tentative interpretation is that renin helped to modulate aldosterone secretion and that noradrenaline facilitated the release of renin. Noradrenaline may be viewed as the initiator of the hormonal adjustments to withdrawal of fluid. The mechanisms that cause circulating concentrations of noradrenaline to decrease with ultrafiltration are probably manifold and not easily explored. The combination of the volume of ultrafiltrate removed and the baseline concentration of noradrenaline correlated with changes in the circulating catecholamine soon after the procedure. It is possible that noradrenaline was filtered from the blood and the concentration decreased because extracellular fluid entered the circulating compartment. This interpretation, however, does not accord with the increase in plasma noradrenaline after ultrafiltration in patients with congestive heart failure and without water retention,[19] or with the continuing decrease in noradrenaline concentration that occurred in the two days after ultrafiltration in our patients. Other mechanisms are reactivation of reflex inhibitory stimuli originating from periphery, heart (greater ventricular shortening[37] caused by reduction in diastolic volume and pressure and wall tension), or lungs[38] (resolution of lung congestion) and modulation of baroreceptor sensitivity, sympathetic activity, and secretion of renin and aldosterone by effects on atrial natriuretic peptides or arginine vasopressin.[4,6,39-41] However, the lack of association between plasma concentrations of noradrenaline and cardiovascular function is not consistent with these interpretations. In fact, in these patients who had a fifteenfold higher concentration of circulating noradrenaline than normal a reduction of more than 50% did not have important circulatory consequences. A similar decrease of sympathetic firing would probably produce very different effects. At this stage of the disease more of the neurotransmitter seems to accumulate than is needed for receptor activity.[39]

The lungs and kidneys play a fundamental role in removing noradrenaline from the blood. Relief of lung congestion improves fractional extraction.[42] Outflow of the neurotransmitter from the kidneys accounts for nearly 25% of the total spillover to plasma in healthy subjects and the kidneys extract 35–55%.[42] In congestive heart failure congestion and hypoperfusion of the kidneys are largely responsible for raising noradrenaline. In dogs clearance of noradrenaline depends on blood flow and a severe reduction of flow results in a spillover of noradrenaline from the kidneys.[42] We did not measure renal plasma flow; none the less, the increased output of urine, sodium excretion, creatinine clearance, and renal perfusion pressure after fluid withdrawal were consistent with improved renal haemodynamics and enhanced sodium concentration in the macula densa. These changes probably increased the clearance of

noradrenaline and reduced the release of renin and aldosterone.

We suggest that in patients with water retention in heart failure, withdrawal of intravascular fluid by ultrafiltration and the consequent reabsorption of a corresponding amount from the extravascular space, reduces the concentrations of circulating hormones by various mechanisms and increases the output of water and sodium by the kidneys. This in turn, as shown by a strong correlation between the increase in diuresis and decrease in hormone concentrations, further decreases hormones in the blood. Removal of fluid by ultrafiltration may interrupt a positive feedback loop between salt and water retention and activation of the neurohumoral axis.

It is unlikely that vascular underfilling perpetuates the stimulation of the neurohumoral axis and accumulation of fluid at all stages of congestive heart failure. In more advanced stages organs such as the kidneys and lungs may play a fundamental part in keeping circulating concentrations of hormones high; the positive feedback loop between fluid and salt retention and the humoral axis seems to be a mechanism responsible for progression of congestive heart failure.

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