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

Maurizio D Guazzi, Piergiuseppe Agostoni, Battista Perego, Gianfranco Lauri, Alessandro Salvioni, Francesco Giraldi, Marco Matturri, Marco Guazzi, Giancarlo Marenzi

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 homeostatic 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.

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La constance du milieu intérieur est la condition d'une existence libre et indépendante.
Patients and methods

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 frusenide 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 in 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 constant 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 dialyser (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 Gambo System (Land, 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 hematocrit increased to 50%. The mean volume of fluid removed by this method was 3122 ml.

Table 1 Demographic and clinical characteristics in 22 patients

<table>
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<th>Patient No</th>
<th>Age (yr) and sex</th>
<th>Aetiology</th>
<th>NYHA class</th>
<th>Clinical data</th>
<th>Prior treatment</th>
<th>Current treatment (mg/day)</th>
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*Stopped 5 days before study.

ACEI, angiotensin-converting enzyme inhibitors; CAD, coronary artery disease; D, digoxin; F, frusenide; IDC, idiopathic dilated cardiomyopathy; I, inotropic preparations; LAN, long acting nitrates; NYHA, New York Heart Association functional class; PO, peripheral oedema; PE, plural effusion.
HAEMODYNAMIC VARIABLES
Haemodynamic variables were measured with a number 8 flow directed triple lumen thermomodulation 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 thermomodulation 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 chromatography25 (Kontron Instruments, Milan, Italy); plasma renin activity by radioimmunoassay26 (Technogenetics, Milan, Italy), and aldosterone by radioimmunoassay27 (Sorin, Saluggia, Italy). We used samples of arterial blood28 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 from the changes in the haematocrit (HCT), according to the following formula:

\[ PV_{	ext{ACT}} = \frac{100}{100 - \text{HCT pre}} \times \frac{\text{HCT post}}{\text{HCT post}} \]

This method assumes that no erythrocytes have been gained or lost.29 Measured haematocrits were corrected for trapped plasma volume and converted to whole body haematocrit.30

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.

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⁻¹.

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
UF, extracorporeal (ml)
Ultrafiltrate
Blood
Renal perfusion
sodium
Creatinine
2
Figure
intervals
hours
later.
PRA,
activity (PRA),
at baseline (B),
and
immediately after ultraltrafiltration (UF),
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; \( \Delta \ P < 0.01 v \) UF.

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 ultraltrafiltration (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
creatine 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 ultraltrafiltration
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:
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

![Graph](http://heart.bmj.com/)

(fig 2). Ulrafiltration 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Immediately after UF</th>
<th>24 h after UF</th>
<th>48 h after UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>76 (15)</td>
<td>71 (14)**</td>
<td>71 (14)**</td>
<td>71 (15)**</td>
</tr>
<tr>
<td>Serum sodium concentration (mmol/l)</td>
<td>139 (5)</td>
<td>142 (12)</td>
<td>141 (5)**</td>
<td>141 (3)**</td>
</tr>
<tr>
<td>Diuresis (ml/24h)</td>
<td>852 (692)</td>
<td>2132 (1181)**</td>
<td>1727 (755)**</td>
<td>126 (103)**</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24h)</td>
<td>39 (48)</td>
<td>137 (97)**</td>
<td>126 (103)**</td>
<td></td>
</tr>
<tr>
<td>Blood urea (mmol/l)</td>
<td>52 (29)</td>
<td>55 (28)**</td>
<td>54 (30)</td>
<td>49 (30)**</td>
</tr>
<tr>
<td>Serum creatinine concentration (mmol/l)</td>
<td>248 (177)</td>
<td>265 (177)**</td>
<td>229 (177)</td>
<td>221 (177)**</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>19 (5)</td>
<td>46.3 (13)**</td>
<td>44.2 (6)**</td>
<td></td>
</tr>
<tr>
<td>Renal perfusion pressure (mm Hg)</td>
<td>74 (26)</td>
<td>81 (19)**</td>
<td>78 (16)*</td>
<td>78 (15)*</td>
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<tr>
<td>Ultrafiltrate (ml)</td>
<td></td>
<td>3122 (1199)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UF, extracorporeal ultrafiltration; *P < 0.05; **P < 0.01; *** P < 0.001 v baseline.

Table 3 Correlations of baseline (BL) hormone values and their variations 24 hours after ultrafiltration \( \Delta 24 \) 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.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Noradrenaline</th>
<th>Plasma renin activity</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>( \Delta 24 ) h</td>
<td>BL ( \Delta 24 ) h</td>
<td>BL ( \Delta 24 ) h</td>
</tr>
<tr>
<td>Cardiac index:</td>
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<tr>
<td>( \Delta 24 ) h</td>
<td>0.43</td>
<td>-0.19</td>
<td>-0.05</td>
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<td>Mean arterial pressure:</td>
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<td>( \Delta 24 ) h</td>
<td>-0.25</td>
<td>-0.27</td>
<td>-0.25</td>
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<tr>
<td>Systemic vascular resistance:</td>
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<tr>
<td>( \Delta 24 ) h</td>
<td>-0.32</td>
<td>0.38</td>
<td>-0.42</td>
</tr>
<tr>
<td>Diuresis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta 24 ) h</td>
<td>0.58*</td>
<td>0.52*</td>
<td>0.36</td>
</tr>
<tr>
<td>Plasma volume:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% ( \Delta 24 ) h</td>
<td>0.65*</td>
<td>0.58*</td>
<td>0.68*</td>
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<tr>
<td>Diuresis:</td>
<td>0.66**</td>
<td>-0.70**</td>
<td>-0.45**</td>
</tr>
<tr>
<td>% ( \Delta 24 ) h</td>
<td>0.04</td>
<td>0.02</td>
<td>-0.04</td>
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<tr>
<td>Plasma renin activity:</td>
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<tr>
<td>( \Delta 24 ) h</td>
<td>-0.84***</td>
<td>-0.84***</td>
<td>-0.83**</td>
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<td>Aldosterone:</td>
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<tr>
<td>( \Delta 24 ) h</td>
<td>1</td>
<td>-0.81***</td>
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</table>

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 homeostatic response. 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. 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 oncotic actively proteins, age, and capillary and venous hydrostatic pressures) affecting intravascular volume balance 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. It 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. 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 adjustment 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, 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 caused by reduction in diastolic volume and pressure and wall tension), or lungs (resolution of lung congestion) and modulation of baroreceptor sensitivity, sympathetic activity, and secretion of renin and aldosterone by increased release of atrial natriuretic peptides or arginine vasopressin. 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 neuroendocrine system seemed to accumulate than is needed for receptor activity.

The lungs and kidneys play a fundamental role in removing noradrenaline from the blood. Relief of lung congestion improves fractional extraction. 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%. In congestive heart failure congestion and hyperperfusion of the kidneys are largely responsible for raising noradrenaline. In dogs clearance of noradrenaline depends on blood flow and a severe reduction of flow volume of noradrenaline from the kidneys. 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 fluid and salt retention and the renal 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.

40 Laragh JH. Artrial natriuretic hormone, the renin-angiotensin axis, and blood pressure-electrolyte homeostasis. Hypertension 1985;5:1-40.