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Vasopressin administration facilitates fluid removal during hemodialysis

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Inadequate secretion of vasopressin during fluid removal by hemodialysis may contribute to the cardiovascular instability that complicates this therapy and administration of exogenous hormone, by supporting arterial pressure, may facilitate volume removal. To test this, we measured plasma vasopressin in patients with end-stage renal disease (ESRD) during hemodialysis and found that despite significant fluid removal, plasma vasopressin concentration did not increase. We further found that ESRD did not alter the endogenous removal rate of plasma vasopressin and that plasma hormone is not dialyzed. Finally, in a randomized, double-blinded, placebo-controlled trial in 22 hypertensive patients, we examined the effect of a constant infusion of a non-pressor dose of vasopressin on the arterial pressure response during a hemodialysis in which the target fluid loss was increased by 0.5 kg over the baseline prescription. We found that arterial pressure was more stable in the patients receiving vasopressin and that while only one patient (9%) in the vasopressin group had a symptomatic hypotensive episode, 64% of the patients receiving placebo had such an episode ($P = 0.024$). Moreover, increased fluid removal was achieved only in the vasopressin group (520 ± 90 ml vs 64 ± 130 ml, $P = 0.01$). Thus, administration of non-pressor doses of vasopressin to hypertensive subjects improves cardiovascular stability during hemodialysis and allows increased removal of excess extracellular fluid. Inadequate vasopressin secretion during hemodialysis-induced fluid removal is a likely contributor to the intradialytic hypotension that limits fluid removal.

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In patients with end-stage renal disease (ESRD) treated with hemodialysis, removal of excess extracellular fluid during the relatively short period of a typical dialysis session frequently leads to symptomatic decreases in arterial pressure.[1] In addition to its directly deleterious effects, intradialytic hypotension and/or attempts to prevent it hinder normalization of the extracellular fluid, leaving many patients chronically volume-expanded.[2] In turn, volume expansion is a major cause of hypertension in patients on hemodialysis.[3–5] As in the general population, hypertension in patients with ESRD on hemodialysis is associated with high rates of cardiovascular diseases[6–8] and reduced lifespan.[9–11] Thus, the mechanisms of and therapy for intradialytic hypotension are of great interest.

Fluid removal during hemodialysis fails to elicit the systemic vasoconstriction expected for acute decreases of blood volume.[12–16] In some forms of hypotension without appropriate vasoconstriction or with frank vasodilation, we recently found that the plasma concentration of arginine vasopressin (vasopressin) was inappropriately low.[17,18] In such conditions, administration of exogenous hormone at doses that are not pressor in healthy subjects quickly restored blood pressure. Several reports suggest that volume removal during hemodialysis does not increase plasma vasopressin in patients with ESRD[19–25] and thus we postulated that non-pressor doses of exogenous hormone may maintain arterial pressure during hemodialysis-mediated fluid removal. To test this hypothesis, we examined the effects of ESRD and of hemodialysis on plasma vasopressin and the effect of hormone administration on the arterial pressure response to fluid removal during hemodialysis.

RESULTS

Effect of hemodialysis on the concentration of endogenous plasma vasopressin

To determine whether routine volume removal during hemodialysis increased plasma vasopressin, its concentration was measured in patients with ESRD during a standard hemodialysis treatment. The average weight of the patients decreased from 66.6 ± 5.0 kg before dialysis to 63.6 ± 5.0 kg after treatment ($P < 0.01$; $n = 10$), a reduction of 4.5%. Systolic arterial pressure also decreased during hemodialysis, averaging 144 ± 7 mm Hg at the start of the treatment and

123 ± 7 mm Hg at its completion ($P < 0.01$). Mean plasma vasopressin concentration was 3.1 ± 0.7 pg/ml before dialysis; 2.3 ± 0.8 and 4.1 ± 1.0 after one- and two-thirds of the procedure, respectively; and 5.0 ± 1.5 pg/ml at its conclusion. Analysis of variance revealed that plasma vasopressin concentration did not change significantly.

Effect of vasopressin administration on its plasma concentration in patients with ESRD and controls

To determine whether the disappearance rate of vasopressin in plasma is altered in renal failure, a constant intravenous infusion of hormone (0.3 mU kg^{-1} min^{-1}) was administered to healthy control subjects and to patients with ESRD. Figure 1 shows the mean plasma vasopressin concentrations as well as the systolic arterial pressures in the two groups of subjects during infusion of the hormone. Mean vasopressin plasma concentrations did not differ significantly between groups. In both normal subjects and in patients with ESRD, systolic arterial pressure was not significantly changed by the infusion of vasopressin.

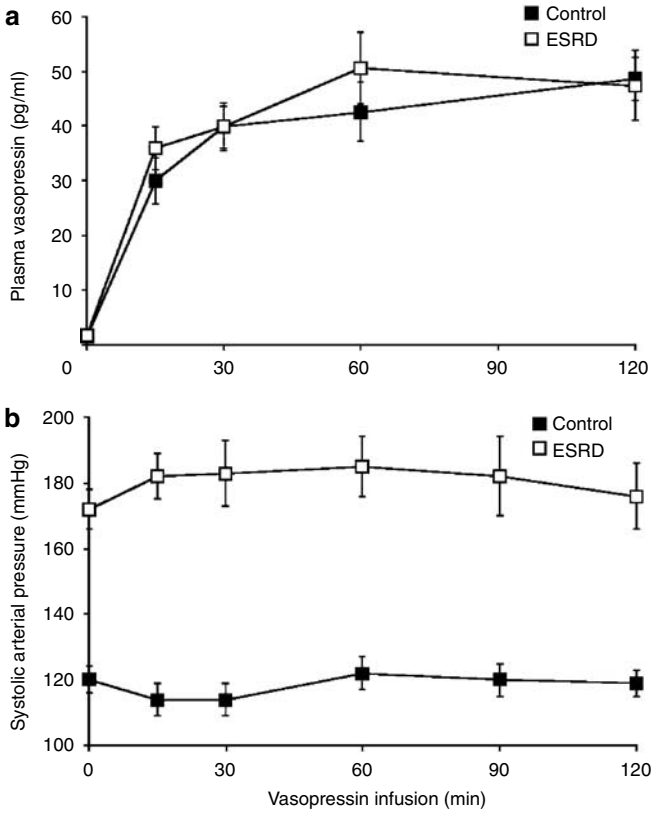

Figure 1 | Infusion of exogenous vasopressin to normal controls and patients with ESRD. (**a**) Plasma vasopressin concentrations and (**b**) systolic arterial pressure during vasopressin infusion. Vasopressin was administered to normal subjects (■; $n = 4$) and to patients with ESRD on a day off dialysis ($n = 4$). (**a**) Plasma vasopressin significantly increased in both groups ($P < 0.001$) and there were no significant differences between them. (**b**) Systolic arterial pressure was not significantly changed by vasopressin in controls or patients with ESRD.

Effect of hemodialysis on plasma vasopressin concentration during constant infusion of hormone

To determine whether hemodialysis removes vasopressin from plasma, we examined the effect of the procedure on the steady-state plasma concentration of hormone during a constant infusion. To obtain a stable plasma concentration, vasopressin (0.3 mU kg^{-1} min^{-1}) was infused to patients with ESRD for ~1 h prior to hemodiaylsis and the infusion continued during 2 h of treatment. Mean plasma concentration of hormone at the start of the treatment was 47 ± 6 pg/ml and it was 54 ± 6 pg/ml at 1 h and 52 ± 9 pg/ml at 2 h of dialysis ($n = 8$); analysis of variance showed that hemodialysis had no significant effect on the plasma vasopressin concentration.

Effect of vasopressin administration during increased hemodialysis-induced fluid removal

To determine whether exogenous vasopressin may improve blood pressure stability during hemodialysis-mediated fluid removal, the hormone was administered during a hemodialysis in which the target for weight reduction was increased by 0.5 kg beyond the baseline prescription to 'remove the weight gained since the last treatment.' On the day of study, subjects were randomized to receive, in double-blind fashion, vasopressin (0.3 mU kg^{-1} min^{-1}) or placebo during the dialysis. Table 1 shows the patient characteristics and important parameters of the dialysis session. The table also shows that the weight gained since the last treatment ('baseline prescription') and, therefore, the 'study target fluid loss' (baseline prescription plus 0.5 kg) did not differ significantly between the two groups. The total ultrafiltration and the weight lost achieved during the hemodialysis were also similar in the two groups.

The systolic arterial pressure in the two groups of patients during dialysis (Figure 2) was not significantly different (Table 2). However, systolic arterial pressure in the group that received vasopressin was significantly more stable: When compared to the placebo group, the maximum drop from the overall systolic pressure was smaller (16 ± 2 vs 34 ± 5 mm Hg, $P = 0.008$) and the lowest systolic pressure was higher

Table 1 | Patient characteristics and dialysis parameters

	Placebo (n=11)	Vasopressin (n=11)	P-value
Age (years)	60.8 ± 2.0	55.1 ± 2.5	0.09
Gender (female:male)	1:10	2:9	0.56
Patients with diabetes	57%	38%	0.48
Number of antihypertensive medications/patient	2.5 ± 0.3	3.1 ± 0.4	0.33
Weight loss previous six dialysis (kg)	3.0 ± 0.4	2.9 ± 0.6	0.82
Baseline prescribed fluid loss[a] (kg)	2.9 ± 0.3	2.5 ± 0.4	0.40
Study target fluid loss[b] (kg)	3.4 ± 0.3	3.0 ± 0.4	0.37
Ultrafiltration achieved (l)	3.1 ± 0.5	3.0 ± 0.5	0.21
Weight lost (kg)	3.0 ± 0.8	3.2 ± 0.6	0.79

[a]Baseline prescribed fluid loss was determined by the weight gained since the last treatment.
[b]Study target fluid loss was defined as the baseline prescribed fluid loss plus 0.5 kg.

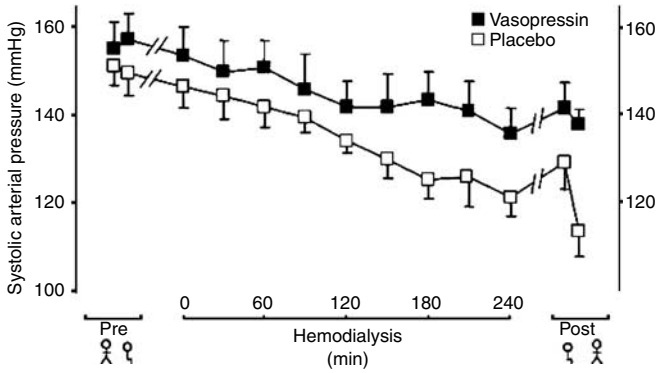

Figure 2 | Systolic arterial pressure in patients receiving placebo (□) or vasopressin (■) during the study dialysis. Systolic arterial pressures before and during dialysis were not significantly different between the two groups. As detailed in the text, however, the group of patients receiving vasopressin had a significantly more stable arterial pressure during the treatment. $N = 11$ in each group.

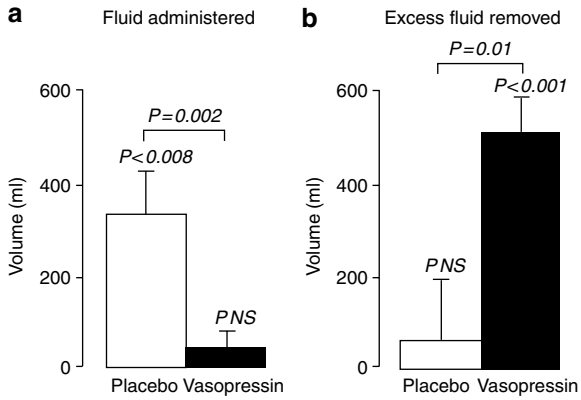

Figure 3 | Fluid administered and removed during hemodialysis. (**a**) Volume administered for pressure support and (**b**) excess fluid removed during the study hemodialysis. (**a**) Patients in the placebo group received 373 ± 79 ml ($P < 0.01$) of normal saline for pressure support while patients in the vasopressin group received a non-significant amount of fluid (45 ± 45 ml; $P < 0.01$ vs the placebo group). (**b**) Whereas the volume of extra fluid removed during the dialysis above the baseline prescription was not significant in the placebo group (64 ± 130 ml), patients in the vasopressin group had 520 ± 90 ml of additional fluid removed ($P < 0.001$; $P < 0.02$ vs placebo group).

Table 2 | Hemodynamic parameters on day of study

	Placebo (n=11)	Vasopressin (n=11)	P
Mean SAP during dialysis (mm Hg)	136 ± 4	146 ± 6	0.18
Mean hear rate during dialysis (beats/min)	79 ± 5	69 ± 4	0.16
Maximal SAP drop from mean (mm Hg)	34 ± 5	16 ± 2	0.008
Lowest SAP (mm Hg)	114 ± 5	133 ± 6	0.023
Patients with symptomatic hypotensive episode	64%	9%	0.024

P, P-value; SAP, systolic arterial pressure.

(133 ± 6 vs 114 ± 5, $P = 0.023$). In addition, increasing the target volume for fluid removal resulted in a symptomatic hypotensive episode in seven of the 11 patients receiving placebo but only in one of the eleven patients receiving vasopressin (64 vs 9%, $P = 0.024$).

In response to arterial pressure changes during dialysis and patient's symptoms, the nurse conducting the dialysis administered to patients in the placebo group 373 ± 79 ml of normal saline for pressure support ($P = 0.008$), but a non-significant amount of saline to those receiving vasopressin (45 ± 45 ml; $P = 0.002$ vs placebo; Figure 3a).

Finally, while the volume of extra fluid removed during the dialysis above the baseline prescription was not significant in the placebo group (64 ± 130 ml), patients in the vasopressin group attained the study's goal for additional fluid removal (520 ± 90 ml; $P < 0.001$; $P = 0.01$ vs placebo; Figure 3b). After the hemodialysis session, all patients were managed per routine. No patient reported orthostatic symptoms between the end of the study and the following dialysis.

Arterial pressure after hemodialysis and vasopressin infusion

To examine whether increased fluid removal with vasopressin would be associated with increased hypotension postdialysis, arterial pressure was recorded after the treatment in six hypertensive patients in a crossover trial. Figure 4 shows the

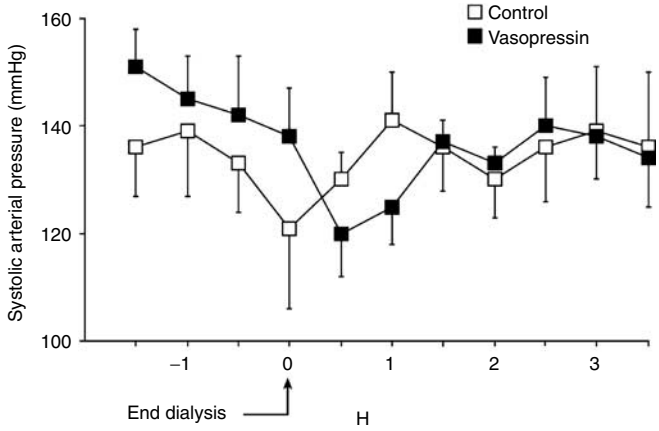

Figure 4 | Systolic arterial pressure after hemodialysis and vasopressin infusion. Systolic arterial pressure is shown before and after termination of hemodialysis during two treatments in six patients. A control hemodialysis to remove weight gained is compared to a treatment in which vasopressin was infused and the fluid removed averaged 0.5 kg above control.

mean arterial pressures during completion of two hemodialysis treatments. In one standard control treatment without vasopressin, fluid removal was targeted to dry weight. In the other hemodialysis, vasopressin was infused and additional fluid was removed, on average 0.5 kg greater than during the control day. As shown, the lowest mean systolic arterial pressures during the period of observation were identical (120 mm Hg) but whereas it occurred at the end of hemodialysis during the standard treatment, on the day of vasopressin infusion it occurred 30 min after the treatment, a time by which most of the exogenous vasopressin in plasma

should be metabolized.[15] Only one patient experienced lightheadedness, once during standard hemodialysis and once during vasopressin-facilitated fluid removal. Thus, when compared to a standard hemodialysis, the incidence of symptomatic hypotension was not increased by greater fluid removal during hemodialysis with vasopressin.

DISCUSSION

During hemodialysis, excess extracellular fluid is removed by ultrafiltration until the patient is returned to his or her 'dry weight.' However, 'dry weight' is empirically assigned to that weight at which symptomatic decreases in blood pressure are very likely to occur if further volume is removed.[1,2] Even in the presence of expanded extracellular fluid volume (i.e., edema), fluid removal by hemodialysis frequently causes hypotension, a complication that has beleaguered hemodialysis therapy since its inception. Thus, paradoxically, to avoid hypotension during hemodialysis, patients at their 'dry weight' are often volume expanded[2] and consequently hypertensive between dialysis treatments.[4,5]

Reduction of extracellular fluid volume during hemodialysis often fails to elicit the systemic vasoconstriction[12–16] that normally occurs when fluid is removed by ultrafiltration without hemodialysis.[12,14] We recently found that an important pathogenetic factor in some forms of hypotension without vasoconstriction is an inappropriately low concentration of plasma vasopressin (reviewed in Landry and Oliver[26]). As is well known, in addition to osmolarity, the secretion of vasopressin is under baroreflex control and decreases in blood volume activate the baroreflex-triggered secretion of vasopressin, increasing its plasma concentration.[27] In the setting of a decrease in blood volume, vasopressin contributes to blood pressure maintenance.[28]

During a standard hemodialysis treatment, plasma volume typically decreases 10–20%,[23,25] a change that should suffice to induce vasopressin secretion[27] and increase its concentration in plasma. However, confirming the observations of others,[19–25] we found that volume removal during hemodialysis does not increase plasma vasopressin.

Because the effect of renal failure on the clearance of plasma vasopressin was unresolved,[29,30] we sought to exclude the possibility that changes in plasma vasopressin during hemodialysis could be masked by increased hormone catabolism in renal failure. Thus, we infused vasopressin to normal subjects and patients with ESRD and followed plasma levels. We found that the plasma concentrations achieved were similar in the two groups of subjects, suggesting that that end-stage renal failure does not significantly alter the clearance of plasma vasopressin.

Next, we aimed to exclude the possibility that vasopressin could be removed from plasma by hemodialysis. Hence, we infused hormone to patients with ESRD and after achieving a steady plasma concentration, hemodialysis was begun. We found that hemodialysis did not significantly alter the concentration of vasopressin. This suggests that vasopressin, although not protein bound, is nonetheless not effectively removed by hemodialysis from plasma, likely due to its molecular weight >1000 Da.

The findings that vasopressin catabolism is not increased in patients with ESRD and that the hormone is not significantly lost through the dialysis membrane, led us to conclude that extracellular fluid removal during hemodialysis does not increase vasopressin secretion. Several mechanisms may account for the failure to secrete vasopressin during hemodialysis-mediated extracellular fluid removal. First of all, there is a substantial decrease in the plasma osmolarity during standard hemodialysis[31] and it is possible that, in a reversal of the well documented baroreflex modulation of the osmotic set-point for vasopressin secretion,[27] decreases in osmolarity could inhibit baroreflex-mediated vasopressin secretion. However, the rise in plasma vasopressin following hemorrhage was found to be unaffected by hypo-osmolality.[32] Another intriguing possibility is that the increased nitric oxide synthesis that occurs during hemodialysis[33] may inhibit vasopressin secretion.[34] Finally, autonomic dysfunction due to uremia is frequently listed as a potential cause of blood pressure instability during hemodialysis[1] and it is possible that it may contribute to the impaired baroreflex-mediated vasopressin secretion. Additional work is needed to distinguish between these alternatives.

Of note is that the dose of vasopressin infused in this study ($0.3\,\mathrm{mU\,kg^{-1}\,min^{-1}}$) increased its plasma concentration to a steady value of ~ 45 pg/ml but failed to increase arterial pressure in healthy subjects (as reported previously[35–37]) or in patients with ESRD. However, similar concentrations are seen during modest hemorrhage[32] or hypotension[38] and in these circumstances, the hormone becomes critical for the maintenance of blood pressure.[18,28]

Hence, we examined whether administration of exogenous hormone during hemodialysis in patients with ESRD may prevent development of hypotensive episodes, thus allowing a more complete correction of their volume expansion. To do this, we administered vasopressin during a hemodialysis session in which the amount of fluid to be removed was increased slightly above the clinically indicated value. In as much as ESRD patients maintained on hemodialysis who have an elevated arterial pressure are more likely to have expansion of the extracellular fluid volume,[4,5] patients with hypertension between dialysis treatments were selected to examine this hypothesis.

We found that when the amount of extracellular fluid to be removed by hemodialysis was increased by 17% above the baseline prescription, vasopressin administration markedly improved the stability of the systolic arterial pressure when compared to controls. Patients receiving placebo had significantly more hypotensive episodes were given greater amounts of saline by the nurse conducting the treatment and could not attain the target fluid loss. This suggests that, as extracellular fluid volume was decreased by dialysis, exogenous vasopressin contributed to the maintenance of their arterial pressure.

Taken together, our results suggest that, at least in some patients, inadequate vasopressin secretion contributes to the cardiovascular instability that complicates hemodialysis and that administration of exogenous hormone at doses that do not raise arterial pressure improves cardiovascular stability during hemodialysis-induced fluid removal. Hypotension during hemodialysis may be, like other states of vasodilatory hypotension, characterized by a deficiency of vasopressin and exquisite sensitivity to hormone replacement.[26] Detailed studies are required to delineate the etiology of the secretory defect and the potential contribution of binding proteins to vasopressin metabolism.

Clinical outcome trials are needed to determine whether prevention of intradialytic hypotension with vasopressin may improve chronic control of extracellular fluid volume in patients with ESRD. This, needless to say, could reduce the high incidence of hypertension in these patients, a maneuver with potentially considerable impact on their cardiovascular morbidity[6–8] and lifespan.[9–11] Of note, recent studies suggest that decreasing the rate of fluid removal by extending the duration of hemodialysis improves hemodynamic stability and diminishes chronic hypertension, likely because extracellular fluid volume is better controlled.[39,40] Replacement with non-pressor doses of vasopressin during hemodialysis may provide an additional therapeutic tool to attain this goal.

MATERIALS AND METHODS

Patients

Studies were performed at the Acute Dialysis Unit of the New York Presbyterian Hospital and at the Columbia University Dialysis Center, both located at Columbia University Medical Center. All patients gave informed consent to participate in the studies, which were approved by the Institutional Review Board of Columbia University. The study adhered to the Declaration of the Helsinki Principles.

For all studies, except when indicated in the specific protocols, any patient that had ESRD and was maintained on hemodialysis was a candidate for study. Exclusion criteria for all patients were as follows: (1) active vascular disease, including angina, claudication, transient ischemic events, ischemic colitis, and Raynaud's disease; (2) a history of prolonged QT syndrome; (3) a history of orthostatic hypotension or frequent episodes of intra-dialytic hypotension; (4) a systolic blood pressure greater than 200 mm Hg and/or a diastolic blood pressure greater than 100 mm Hg; and (5) a history of, or clinical evidence of, congestive heart failure.

All patients were studied at regularly scheduled dialysis sessions and all management decisions were left to the health care personnel managing the treatment. Patients underwent conventional hemodialysis with hollow fiber high flux polysulfone dialyzers on volumetric dialysis machines (Cobe Centrysystem 3, Gambro Renal Care Products, Inc., Lakewood, CO, USA). Dialysis time was $\sim$4 h. Blood flow was 300–400 ml/min and dialysate was delivered at 600 ml/min. The dialysis bath contained potassium, 2 mEq/l; calcium, 2.5 mEq/l; magnesium, 0.75 mEq/l; and bicarbonate, 40 mEq/l. In those patients who were prescribed dialysate sodium modeling and/or reduced dialysate temperature (35–37°C) prior to the study, the parameters of these interventions were held constant throughout the study. Ultrafiltration was performed at a constant rate based on the target weight loss for that dialysis session. Oscillometric blood pressure and heart rate measurements were taken at 15–30 min intervals per routine at the dialysis center.

Plasma vasopressin concentration

Vasopressin in plasma was determined as previously described.[17]

Study protocols

Effect of hemodialysis on the concentration of endogenous plasma vasopressin. Ten patients with ESRD had samples of venous blood collected during a standard hemodialysis treatment for determination of plasma vasopressin. Vasopressin was measured before starting the treatment, twice during it and at its conclusion.

Effect of vasopressin administration on its plasma concentration in patients with ESRD and in controls. Because the effect of exogenous vasopressin on the arterial pressure of patients with ESRD was unknown and these patients are frequently afflicted with hypertension, in addition to the exclusion criteria detailed above, subjects selected for this protocol were required to have a normal arterial pressure ($<$140 mm Hg systolic pressure). Four healthy normal volunteers and four patients with ESRD maintained on hemodialysis received an infusion of vasopressin while blood samples were collected for determination of the hormone concentration in plasma. 8-arginine vasopressin (American Pharmaceutical Partners, Schaumberg, IL, USA) in normal saline was administered through an antecubital intravenous line at a rate of 0.3 mU kg^{-1} min^{-1} for 2 h.

Effect of hemodialysis on plasma vasopressin concentration during constant infusion of hormone. Eight patients with ESRD received an intravenous infusion of vasopressin (of 0.3 mU kg^{-1} min^{-1}) begun $\sim$1 h prior the start of a routine hemodialysis and continued during the first 2 h of treatment. Blood samples were collected for determination of vasopressin in plasma at the beginning and after 1 and 2 h of dialysis.

Effect of vasopressin administration during increased hemodialysis-induced fluid removal. A unique group of 22 patients with ESRD was selected to study the effect on the arterial pressure of an infusion of vasopressin during a hemodialysis treatment during which the target weight reduction specified by the standard dialysis prescription – to remove the weight gained – was increased by 0.5 kg. In addition to the exclusion criteria detailed above for all patients, subjects included in this protocol had the following additional inclusion criteria: (a) hypertension (defined by a systolic arterial pressure greater than 140 mm Hg or a requirement for antihypertensive medications to maintain a lower systolic arterial pressure); (b) no hypotensive episode during the three hemodialysis treatments of the week preceding the study; and (c) the predialysis weight on the day of study within $\pm$1 kg of the mean predialysis weight of the previous three sessions. Patients were studied 2 days after the previous dialysis, a requirement that excluded the first hemodialysis treatment following the week-end.

The protocol was a randomized, double-blinded, placebo-controlled trial comparing the effect of vasopressin (0.3 mU kg^{-1} min^{-1}) in normal saline vs the same volume of normal saline alone on the incidence and magnitude of systolic hypotension and hypotensive symptoms elicited by the 0.5 kg increase in weight reduction. The infusion solutions were prepared by a researcher uninvolved with the hemodialysis treatment and patient care. The solutions were physically indistinguishable and the nurse conducting the dialysis, although aware of the study, was blinded to the

intervention. Otherwise, the hemodialysis routine was unchanged and managed exclusively by the health care personnel performing the treatment. Symptomatic hypotension was identified by the nurse conducting the dialysis treatment (criteria included a sudden drop in systolic arterial pressure associated with one or more of the following: lightheadedness, dizziness, cramping, nausea, and vomiting) and managed per routine with administration of normal saline and/or a decrease in ultrafiltration rate.

Arterial pressure after hemodialysis. To ascertain the arterial pressure response after the completion of hemodialysis and the discontinuation of the vasopressin infusion, six patients with hypertension as defined above were provided with ambulatory blood pressure monitors (Spacelabs, model 90217) and instructed to maintain their usual routine while wearing the pressure monitor for up to 4 h posthemodialysis. In a non-blinded crossover design, arterial pressure was recorded after two hemodialysis treatments with starting treatment assignment randomized to avoid an order effect. In a standard treatment, fluid removal was prescribed to be the targeted dry weight (as defined above). In the other hemodialysis, vasopressin was infused ($0.3\,\mathrm{mU\,kg^{-1}\,min^{-1}}$) and additional fluid removed averaged 0.5 kg beyond the control day fluid removal.

Statistical analyses

Analyses were performed using Statistical Package for the Social Sciences, version 12.0. Comparisons between treatment arms were made by independent samples *t*-test. Analysis of time trends for continuous variables was performed using analysis of variance. All values are expressed as mean $\pm$ s.e. unless otherwise stated. *P*-values of less than 0.05 (two-tailed) were considered statistically significant.

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