Kidney International, Vol. 18 (1980), pp. 480–488

Role of osmolality in blood pressure stability after dialysis and ultrafiltration

William L. Henrich, Terry D. Woodard, Jon D. Blachley, Celso Gomez-Sanchez, William Pettinger, and Robert E. Cronin

Department of Internal Medicine, Veterans Administration Medical Center and The University of Texas, Southwestern Medical School, Dallas, Texas

Role of osmolality in blood pressure stability after dialysis and ultrafiltration. To clarify the mechanisms involved in the stability of blood pressure during ultrafiltration (UF) alone versus regular dialysis, this study systematically examined the importance of changes in serum potassium, osmolality, and plasma norepinephrine during several dialysis maneuvers. Six stable, normotensive chronic dialysis patients were subjected to a uniform 2 to 3% decrease in body weight during the 2 hours of each dialysis maneuver. Supine to upright mean blood pressure (MBP) decreased (90 to 75 mm Hg, $P < 0.05$), and three patients became symptomatic after weight loss during regular dialysis, but orthostatic blood pressure was stable (89 to 86 mm Hg, NS) and the patients were asymptomatic after UF and weight loss. Isokalemic regular dialysis did not afford hemodynamic stability, as orthostatic MBP declined (85 to 56 mm Hg, $P < 0.02$), and four of the patients again were symptomatic after standing. A continuous hypertonic mannitol (25%) infusion during the 2-hour dialysis, however, kept osmolality from decreasing and was associated with a stable orthostatic MBP (89 to 83 mm Hg, NS). A continuous infusion of isotonic mannitol (5%) given in a volume five times that of the hypertonic mannitol failed to prevent orthostatic hypotension (89 to 60 mm Hg, $P < 0.005$). Plasma norepinephrine concentrations were high in these patients and increased only modestly after weight loss. These results implicate constant plasma osmolality as a critical protective factor of blood pressure during UF and further demonstrate that changes in blood pressure may be dissociated from changes in both serum potassium and plasma norepinephrine concentration.

Rôle de l'osmolalité dans la stabilité de la pression artérielle après dialyse et ultrafiltration. Afin de clarifier les mécanismes impliqués dans la stabilité de la pression artérielle au cours de l'ultrafiltration (UF) seule par comparaison avec la dialyse habituelle ce travail évalue systématiquement l'importance des modifications de la kaliémie, de l'osmolalité et de la norépinéphrine plasmatique au cours de plusieurs tactiques de dialyse. Six sujets stables, normotendus, en hémodialyse chronique ont subi une diminution de poids corporel de 2 à 3% au cours des 2 heures de chaque tactique de dialyse. La pression artérielle moyenne a diminué de la position couchée à la position debout (de 90 à 75 mm Hg, $P < 0,05$) et trois patients sont devenus symptomatiques après la perte de poids au cours de la dialyse habituelle. Par contre la pression artérielle orthostatique a été stable (89 à 86 mm Hg, NS) et les malades ont été asymptomatiques après UF. La dialyse habituelle isokaliémique n'a pas déterminé de stabilité hémodynamique, la pression artérielle moyenne orthostatique a diminué (85 à 56 mm Hg, $P < 0,02$) et quatre malades ont été à nouveau symptomatiques quand ils se sont levés. Cependant quand une perfusion continue de mannitol hypertonique (25%) pendant les deux heures de la dialyse a empêché la baisse de l'osmolalité la pression artérielle moyenne orthostatique a été stable (89 à 83 mm Hg, NS). Une perfusion continue de mannitol isotonique (5%) apportant un volume cinq fois celui du mannitol hypertonique n'a pas empêché l'hypotention orthostatique (89 à 60 mm Hg, $P < 0,005$). Les concentrations plasmatiques de norépinéphrine étaient élevées chez ces malades et n'ont que peu augmenté après la perte de poids. Ces résultats impliquent qu'une osmolalité plasmatique constante est un facteur protecteur critique pour la pression artérielle au cours de UF et ils démontrent, de plus, que les modifications de la pression artérielle peuvent être dissociées des modifications du potassium plasmatique et de la concentration de norépinéphrine.

Received for publication October 8, 1979
and in revised form March 18, 1980

0085-2538/80/0018-0480 $01.80

Hypotension occurring during weight removal in patients on hemodialysis is a frequent and perplexing clinical problem, and is a significant cause of morbidity in dialyzed patients. Several possible mechanisms by which hemodialysis may provoke hypotension include rapid volume depletion, and sudden declines in either serum potassium, plasma norepinephrine, or plasma osmolality. Autonomic neuropathy is frequent in dialysis patients [1, 2], and hypokalemia may further impair protective circulatory reflexes needed to avoid hypotension [3, 4]. Similarly, a decline in norepinephrine concentration is reported to occur during dialysis [5], an effect that could impede a normal maximal increase in peripheral vascular resistance in response to a fall in blood pressure. Finally, a decline in osmolality may compound hypotension by enhancing hypovolemia or via an effect on resistance vessels [6, 7].

Dialysis ultrafiltration is a process in which hydrostatic pressure exerted across a dialysis membrane is utilized to cause fluid removal in a manner similar to regular hemodialysis, except that no dialysate is allowed to circulate during the procedure [5]. This maneuver results in improved tolerance to weight removal in dialysis patients [7, 8]. Despite these observations, the exact mechanisms responsible for this blood pressure protection remain uncertain. In contrast to regular hemodialysis, ultrafiltration alone causes no changes in serum potassium or osmolality, but the degree to which these factors influence the stability of blood pressure during rapid weight loss is unclear. Moreover, the importance of circulating plasma norepinephrine concentration in ultrafiltration is still speculative.

Therefore, in an effort to determine why blood pressure remains stable during fluid removal in ultrafiltration, we systematically studied six stable chronic hemodialysis patients during five different dialysis maneuvers: regular dialysis, ultrafiltration alone, isokalemic regular dialysis, continuous hypertonic mannitol infusion, and finally, continuous isotonic mannitol infusion. The results implicate the maintenance of a constant plasma osmolality as the primary blood pressure protective factor during ultrafiltration, and further suggest that this protective effect is independent of changes in serum potassium or plasma norepinephrine concentration.

Methods

Six stable hemodialysis patients with their native kidneys were used in each aspect of the study. Each patient was normotensive and took no antihypertensive medications for at least 6 months prior to study. Interdialytic weight gains did not exceed 4% of body weight in these patients. Informed consent was obtained from each patient prior to entry into the study. All patients were male with a mean age of 59 ± (SEM) 2 years and had been on chronic dialysis three times per week for a mean of 40 ± 9 months. The etiology of renal failure in the patients was polycystic kidney disease in three, analgesic nephropathy in one, and nephrosclerosis in two. The six study patients were selected from a dialysis population of 42 patients on the basis of normal responses to both an amyl nitrate inhalation test [10] and a standard Valsalva maneuver [11]. Forced expiration against 40 mm Hg for 10 to 12 sec was used as the standard strain. An insufficient autonomic response was defined if both the arterial pressure overshoot and bradycardia were absent after release of the strain. The results of these studies are depicted in Table 1. Thus, these patients were specially selected in order to exclude autonomic insufficiency and hypertensive medications as variables that could influence the hemodynamic responses to the dialysis protocols.

Table 1. Autonomic function tests

Patient	Amyl nitrate			Valsalva	
	ΔHR[a]	ΔBP[b]	ΔHR/ΔBP	Bradycardia	AP overshoot
1	6	6	1.00	+	+
2	20	30	0.67	+	+
3	18	19	0.95	+	+
4	24	23	1.04	+	+
5	20	23	0.87	+	+
6	15	15	1.00	+	+
Mean	17	19	0.92		
± SEM	2.5	3.3	0.06		

[a] ΔHR denotes increase in heart rate.
[b] ΔBP denotes decrease in mean blood pressure.

For each of the five maneuvers listed below, the patients were studied on their regular beginning-of-the-week dialysis day (either Monday or Tuesday). In each protocol, the same dialyzer (Travenol Hollow Fiber 1.3 m^2; Travenol Laboratories, Deerfield, Illinois) and delivery system (Drake-Willock single patient proportioning unit; Drake-Willock, Inc., Portland, Oregon) was used.

An identical protocol was followed during each dialysis maneuver. The protocol was as follows: After being weighed, the patients remained recumbent for 15 min. after insertion of needles for standard dialysis. Supine blood pressure, heart rate, and blood samples (plasma electrolytes, osmolality, and plasma norepinephrine) were obtained. The patients then stood for 5 to 7 min, and blood pressure, heart-rate, and blood samples for norepinephrine were again obtained. Following these premaneuver measurements, the patients remained recumbent for 2 hours, during which time 2 to 3% of body weight was removed by each dialysis maneuver. After 2 hours of the dialysis procedure, the blood pump was stopped, and blood pressure, heart rate, and blood work (electrolytes, osmolality, and norepinephrine) were again performed in the supine position. The patients then stood, and weight, blood pressure, and heart rate were noted. Symptoms of postural hypotension were also recorded, as blood (plasma norepinephrine only) was again sampled. The patients did not eat or drink during the 2-hour study period. After completion of each dialysis protocol, a regular dialysis was resumed for 3 to 4 hours as per the patient's usual routine.

Five different maneuvers were performed as follows:

I. Regular dialysis. Standard hemodialysis with sufficient negative pressure to reduce body weight by 2.5% was performed.

II. Ultrafiltration alone. The same protocol as listed above was used except that the dialysis machine was placed in bypass, and dialysate was not circulated through the dialyzer.

III. Isokalemic dialysis. Each patient had a serum potassium measured during the predialysis blood sampling, and sufficient potassium was added to the dialysate mixture to increase the concentration to that of the patient's serum. Constant electrocardiographic monitoring was performed during the 2 hours of dialysis, and serum potassium was sampled every 30 min. Following the completion of the 2-hour protocol, 3 to 4 hours of regular dialysis with a low potassium bath was undertaken.

IV. Hypertonic mannitol. Twenty-five percent hypertonic mannitol in a dose of 0.16 g/kg/hr was evenly infused with a Sage pump (Sage Instruments Inc., White Plains, New York) into the venous return line throughout the 2-hour protocol period. This dose will yield a constant plasma osmolality during a 6-hour dialysis procedure [12]. Plasma for osmolality was sampled every 15 min. to verify that osmolality did not vary during the infusion.

V. Isotonic mannitol. In these studies, 5% isotonic mannitol was evenly infused into the venous return line over the 2-hour protocol period. The volume of isotonic mannitol infused was exactly five times the volume infused during the hypertonic mannitol study, so that although the concentration of mannitol given in the two protocols (IV and V) was different, the absolute amount was the same.

No patients experienced any deleterious effects from any aspect of the study, although (as mentioned in the Results sections) dizziness and nausea occurred in some patients after standing and weight loss.

Electrolyte determinations were performed by flame photometry, and urea nitrogen, plasma proteins, and creatinine were done by an autoanalyzer. Plasma osmolality was measured by freezing-point depression (Advanced Instruments, Inc., New Highlands, Massachusetts). All samples for catecholamines measurements were collected on ice in chilled tubes containing glutathione, immediately separated by cold centrifugation, and frozen at −70° C. Plasma catecholamines were analyzed by a radioenzymatic methodology previously described [13]. Briefly, this method involves enzymetric *o*-methylation of the catechol hydroxy and separation of metabolites by thin layer chromatography and scintillation counting. The mean normal supine value for norepinephrine with this methodology in 42 normotensive subjects was 172 ± 10 pg/ml; the mean for norepinephrine value after standing for 5 min. was 377 ± 21 pg/ml.

Statistics were performed using Student's t test when comparing pre to post or supine to upright values in any given patient. Analysis of variance [14] was used when results from different groups of dialysis protocols were compared. Data are presented as the means ± SEM, and a P value of < 0.05 was considered significant.

Results

Changes in body weight during the dialysis maneuvers (Table 2). Body weight declined comparably and significantly during the 2 hours of each of the dialysis maneuvers. Pre and post maneuver weights were also similar for each of the maneuvers, and the percent decrease in body weight in each maneuver was also statistically similar, with a range of −2.13% (isotonic mannitol) to −3.2% (ultrafiltration only). Thus, the magnitude of weight loss was similar in each of the procedures.

Changes in blood chemistries during dialysis maneuvers (Table 3 and Fig. 1). Changes in plasma osmolality, urea nitrogen, creatinine, and serum potassium and sodium are depicted in Table 3. During regular dialysis a significant 7% decrease in osmolality (from 308 ± 6 to 288 ± 7 mosm/kg H_2O, $P < 0.001$) and serum potassium (from 4.9 to 0.3 to 3.9 ± 0.2 mEq/liter, $P < 0.005$) occurred in the 2 hours of the protocol. In contrast, ultrafiltration induced no significant alteration in either osmolality (309 ± 6

Table 2. Changes in body weight during the dialysis maneuvers

Dialysis maneuvers	Premaneuver weight *kg*	Weight after 2 hr *kg*	*P*	Decrease in weight *%*
I. Regular dialysis	79.3 ± 6.0	77.3 ± 6	<.001	2.5%
II. Ultrafiltration only	79.6 ± 6.0	77.0 ± 6	<.001	3.2%
III. Isokalemic dialysis	79.8 ± 6.0	77.9 ± 6	<.005	2.6%
IV. Hypertonic mannitol	79.7 ± 7.0	77.7 ± 6	<.01	2.6%
V. Isotonic mannitol	79.8 ± 7.0	78.1 ± 7	<.001	2.13%

Table 3. Changes in blood chemistries during dialysis maneuver[a]

	Regular dialysis			Ultrafiltration			Isokalemic dialysis			Hypertonic mannitol			Isotonic mannitol		
	Pre	*P*	After 2 hr	Pre	*P*	After 2 hr	Pre	*P*	After 2 hr	Pre	*P*	After 2 hr	Pre	*P*	After 2 hr
Plasma osmolality, *mOsm/kg H_2O*	308 ±6	<0.001	288 ±7	309 ±6	NS	306 ±6	308 ±7	<0.005	296 ±5	301 ±6	NS	298 ±5	306 ±5	<0.005	290 ±3
Serum potassium, *mEq/liter*	4.9 ±0.3	<0.005	3.9 ±0.2	5.0 ±0.2	NS	5.2 ±0.3	5.1 ±0.3	NS	5.0 ±0.3	5.3 ±0.2	<0.001	4.0 ±0.3	5.2 ±0.3	<0.001	4.0 ±0.2
Serum sodium, *mEq/liter*	139 ±2	NS	137 ±2	138 ±2	NS	136 ±2	137 ±2	<0.001	132 ±2	131 ±3	NS	132 ±3	137 ±3	NS	134 ±2
BUN, *mg/dl*	77 ±13	<0.02	44 ±4	79 ±11	NS	74 ±8	87 ±6	<0.001	58 ±5	83 ±10	<0.001	56 ±10	71 ±2	<0.001	45 ±2
Serum creatinine, *mg/dl*	13.6 ±1.0	<0.01	10.8 ±1.2	14.7 ±1.7	NS	14.10 ±1.3	17 ±1	<0.005	12 ±1	17 ±1	<0.001	11 ±1	15.1 ±1.1	<0.001	10 ±1

[a] Values are the means ± SEM. Pre is predialysis, and after 2 hr means at conclusion of weight loss.

to 306 ± 6 mOsm/kg H_2O, NS) or potassium (5.0 ± 0.2 to 5.2 ± 0.3 mEq/liter, NS).

The possibility that this maintenance of potassium and osmolality that occurred in ultrafiltration was responsible for improved blood pressure during rapid weight loss (vide infra) was further investigated in the next two series of studies. In the first, dialysate potassium concentration was increased to that of the predialysis serum. In these studies (isokalemic dialysis, Table 3), serum potassium was held constant (5.1 ± 0.3 to 5.0 ± 0.3 mEq/liter, NS) during the 2-hour dialysis as plasma osmolality was allowed to decrease 4% (from 308 ± 7 to 296 ± 5 mOsm/kg H_2O, $P < 0.005$). To isolate the effect of constant osmolality as a potential blood pressure protective factor during dialysis, we infused hypertonic mannitol (25%; 0.16 g/kg/hr) during the 2 hours of dialysis; plasma osmolality was checked every 15 min to detect any fluctuations in osmolality (Fig. 1). In these studies (hypertonic mannitol), plasma osmolality was maintained constant during the 2 hours of dialysis (301 ± 6 to 298 ± 5 mOsm/kg

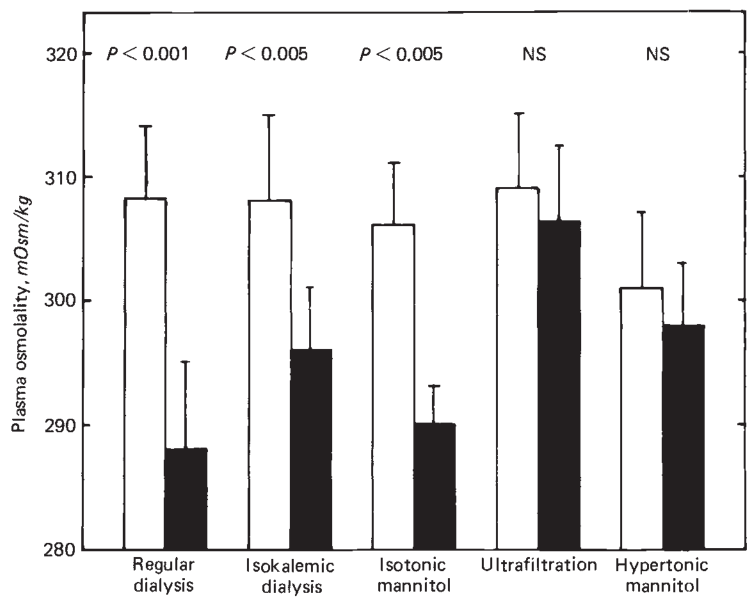

Fig. 1. *Pre and post maneuver plasma osmolality.* A significant decrease in plasma osmolality occurred after 2 hours of regular dialysis, isokalemic dialysis, and isotonic mannitol dialysis. Plasma osmolality was stable after 2 hours of ultrafiltration and hypertonic mannitol. *Open bars* denote premaneuver; *closed bars,* after 2 hours.

Table 4. Changes in blood pressure and heart rate during each dialysis maneuver[a]

Mean blood pressure, *mm Hg*														
RD			UF			ISOK+			HMAN			IMAN		
Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr
Premaneuver														
92 ±7	NS	97 ±5	88 ±4	NS	91 ±5	88 ±3	NS	85 ±3	89 ±3	NS	89.4 ±2.7	92 ±4	NS	95 ±3
After 2 hr														
90 ±6	<0.05	75 ±13	89 ±5	NS	86 ±7	85 ±5	<0.02	56 ±10	89 ±3	NS	83 ±6	87 ±6	<0.005	69 ±6

[a] Values are means ± SEM. Abbreviations used are: RD, regular dialysis; UF, ultrafiltration; ISOK+, isokalemic dialysis; HMAN, hypertonic mannitol; IMAN, isotonic mannitol; Sup, supine; Upr, upright.

H_2O, NS) as plasma potassium was allowed to decrease (5.3 ± 0.2 to 4.0 ± 0.3 mEq/liter, $P < 0.001$). The insignificant decreases in plasma osmolality in the hypertonic mannitol group and the ultrafiltration group (a 1% decrease in plasma osmolality) were significantly less than that observed either in the regular dialysis group (−7%, $P < 0.05$) or the isokalemic group (−4%, $P < 0.05$).

In the final dialysis maneuver, studies in which isotonic mannitol (5%) was infused evenly over the 2-hour protocol were performed. The volume of isotonic mannitol infused was five times that infused during the hypertonic mannitol studies for each patient, so that each patient received the identical amount of mannitol that was previously infused, but at a different concentration. In this group of experiments, plasma osmolality declined 5.2% (306 ± 5 to 290 ± 3 mOsm/kg H_2O, $P < 0.005$) and serum potassium (5.2 ± 0.3 to 4.0 ± 0.2 mEq/liter, $P < 0.001$) again fell during the 2 hours of dialysis and the constant infusion.

Changes in blood pressure and heart rate during each dialysis maneuver (Table 4 and Fig. 2). Supine and upright blood pressures were comparable prior to each dialysis protocol, as no clear directional changes in blood pressure were observed with assumption of the upright position. Following weight loss, supine blood pressure was not significantly dif-

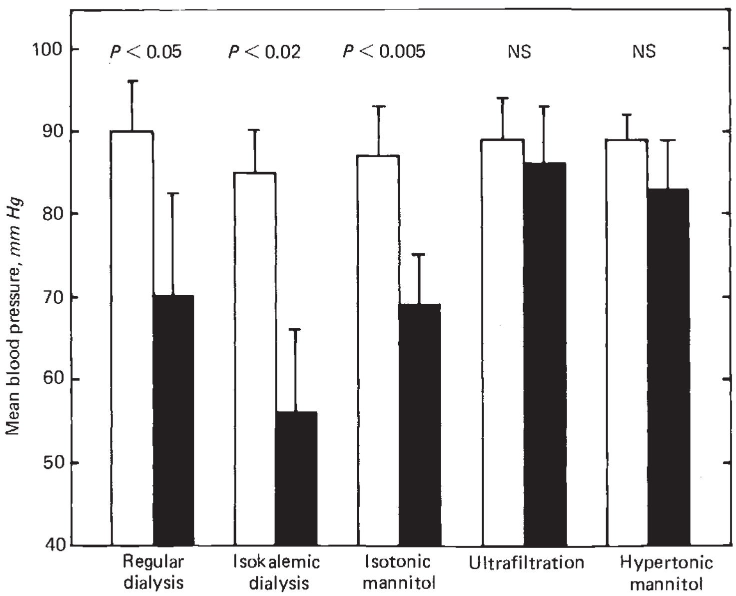

Fig. 2. *Orthostatic blood pressure change after weight loss.* Orthostatic mean blood pressure decreased significantly following regular dialysis, isokalemic dialysis, and isotonic mannitol dialysis. No significant decrease in mean blood pressure occurred after ultrafiltration and hypertonic mannitol dialysis. *Open bars* denote supine position; *closed bars,* upright position.

Table 4. *(continued)*

Heart rate, *beats/min*														
RD			UF			ISOK+			HMAN			IMAN		
Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr
							Premaneuver							
86 ±6	<0.05	93 ±5	87 ±6	<0.05	93 ±6	85 ±5	<0.05	90 ±5	78 ±6	<0.005	93 ±8	79 ±5	<0.005	88 ±6
							After 2 hr							
88 ±6	<0.05	107 ±6	77 ±6	<0.05	93 ±9	96 ±5	<0.025	110 ±6	83 ±5	<0.001	102 ±6	83 ±4	<0.01	105 ±5

ferent than supine or upright premaneuver pressure. On assumption of the upright posture following weight loss, however, impressive differences in blood pressure were noted. Mean blood pressure fell from 90 ± 6 to 75 ± 13 mm Hg ($P < 0.05$) in the regular dialysis group, and three of the patients became symptomatic (dizziness in two and nausea and dizziness in one) when upright. In striking contrast, after ultrafiltration alone and a body weight loss of 3.2%, mean blood pressure was well maintained (89 ± 5 supine vs. 86 ± 7 mm Hg upright, NS). Moreover, none of the latter patients were symptomatic when upright.

The possibility that isokalemia during ultrafiltration contributed to this protective effect on orthostatic pressure was next examined in studies in which the serum potassium was maintained constant and osmolality allowed to fall (isokalemic dialysis). After the 2 hours of dialysis and a 2.6% body weight loss, however, orthostatic mean blood pressure fell markedly from 85 ± 5 to 56 ± 10 mm Hg ($P < 0.02$). Moreover, four of the six patients again became symptomatic on standing. This result suggested that factors other than isokalemia were responsible for the blood pressure protection observed during ultrafiltration.

In the next series of studies, hypertonic mannitol (25%) was infused to achieve constant plasma osmolality. In contrast to the isokalemic and regular dialysis maneuvers, mean blood pressure did not fall after a 2.6% weight loss and standing (89 ± 3 to 83 ± 6 mm Hg, MS). The maintenance of constant plasma osmolality or the addition of a constant infusion of volume could have explained this result. Therefore, in the final series of studies, isotonic mannitol (5%) was infused to provide the same amount of mannitol as infused during the hypertonic mannitol studies. In this final group of experiments, plasma osmolality was thus allowed to decline 5.2%. After a 2.13% weight loss and the isotonic mannitol infusion, mean blood pressure again fell from 87 ± 6 to 69 ± 6 mm Hg, $P < 0.005$. To estimate changes in plasma volume during the hypertonic and isotonic mannitol infusion studies, we made comparisons of pre and post maneuver hematocrits and plasma proteins. A comparable increase in hematocrit occurred after both hypertonic mannitol (from 27.2 ± 2 to 29.2 ± 2%, $P < 0.025$) and isotonic mannitol (from 28 ± 3 to 29.3 ± 2.0%, $P < 0.02$) studies. Similarly, the increases in plasma proteins following hypertonic mannitol (7.0 ± 0.8 to 7.5 ± 0.2 mg/dl, $P < 0.05$) and isotonic mannitol (6.9 ± 0.2 to 7.6 ± 0.14 mg/dl, $P < 0.005$) were also comparable. Thus, the decrement in estimated plasma volume was comparable during these two protocols.

In all protocols, standing resulted in a significant increase in heart rate both before and after the dialysis maneuvers.

Changes in plasma norepinephrine (Table 5). Baseline plasma norepinephrine concentrations were noted to be high in the dialysis patients, a finding noted in previous investigations [15, 16]. During regular dialysis and ultrafiltration, plasma norepinephrine moderately increased after weight loss and orthostatic challenge. No significant differences in post maneuver upright norepinephrine concentrations, however, were noted in the two groups (regular dialysis, 991 ± 237, vs. ultrafiltration, 1032 ± 218 pg/ml, NS), and the magnitude of increase was similar in both groups. During the isokalemic dialysis maneuver, norepinephrine again increased significantly on standing (from 512 ± 155 to 675 ± 162 pg/ml), $p < 0.005$), but mean blood pressure fell (from 85 ± 5 to 56 ± 10, $P < 0.02$). This result clearly suggested that although baseline levels are high, directional changes in plasma norepinephrine of the

Table 5. Changes in plasma norepinephrine during dialysis maneuver[a]

Regular dialysis			Ultrafiltration			Isokalemic dialysis			Hypertonic mannitol			Isotonic mannitol		
Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr	Sup	*P*	Upr
Premaneuver norepinephrine, pg/ml														
687		756	736		890	602		624	688		630	766		1070
±78		±83	±93		±141	±110		±98	±96		±120	±174		±226
	NS			NS			NS			NS			<0.02	
2-hour norepinephrine, pg/ml														
627		991	814		1032	512		675	711		757	625		785
±88		±237	±158		±218	±63		±66	±134		±173	±108		±119
	NS			<0.025			<0.005			NS			<0.001	

[a] Values are the means ± SEM. Sup denotes supine position; Upr, upright position.

magnitude observed in this study do not prevent decreases in mean blood pressure. In the hypertonic mannitol dialysis, mean pressure was maintained after standing and weight loss (89 ± 3 to 83 ± 6 mm Hg, NS), and no change occurred in plasma norepinephrine (711 ± 134 to 757 ± 173 pg/ml, NS). Finally, following the isotonic mannitol infusion dialysis, assumption of the upright posture produced a fall in mean blood pressure (87 ± 6 to 69 ± 6 mm Hg, $P < 0.005$) as plasma norepinephrine again increased modestly (625 ± 108 to 785 ± 119 pg/ml, $P < 0.001$). No consistant abnormalities of epinephrine or dopamine were observed in any of the protocols.

Discussion

There are many potential reasons for hypotension to occur during hemodialysis. Rapid weight removal with depletion of the circulating plasma volume is of primary importance in many instances of dialysis hypotension [17]. Autonomic insufficiency, however, is a common finding in dialyzed patients and may prohibit the normal function of protective reflexes that are activated during hypotensive stress [1, 2, 10, 18]. Further, hypokalemia is a therapeutic goal of dialysis but potentially may exacerbate autonomic insufficiency [3, 4], thereby compounding any tendency to hypotension. Moreover, a fall in plasma osmolality also occurs routinely during regular dialysis, favoring a greater intracellular movement of water, thus compounding hypovolemia. Finally, the importance of catecholamines in the stress response to hypotension induced in dialysis is unclear. Plasma norepinephrine concentrations have been previously noted to be high in dialysis patients [15], but questions as to the ability (and the importance) of catecholamines to increase during dialysis remain unsettled [5].

Ultrafiltration is a dialysis technique, first described by Alwall and Herner [19], that has been associated with maintenance of blood pressure despite sudden, profound weight loss, even in patients with a tendancy to develop hypotension on regular dialysis [6, 7]. This procedure differs from regular dialysis in that dialysate flow is absent and, thus, only ultrafiltration of the plasma occurs; plasma osmolality remains constant during the weight loss because dialysis is not occurring. A series of recent investigations performed by Bergström and Wehle et al have shown ultrafiltration to be a practical method of fluid removal in dialysis patients prone to hypotension [6, 8]. These investigators have previously used a high dialysate sodium bath to demonstrate that plasma osmolality may play a role in the stability of blood pressure during ultrafiltration [8]. A recent preliminary report, however, suggests that constant osmolality is of less protective importance [20]. Thus, the purpose of the present investigations was to focus on the potential protective features of ultrafiltration by elucidating the relationship between blood pressure and changes in osmolality and determining the importance of changes in serum potassium and plasma norepinephrine during the maneuver. Additionally, the further influence of upright posture on blood pressure was incorporated into each dialysis protocol as a practical means of assessing stability. To obviate as many variables as possible and in contrast to previous investigations in this area [2, 7], we specifically selected six stable normotensive patients with normal autonomic testing and without prior episodes of hypotension on dialysis. None of the patients were on antihypertensive medicines, and all were studied at the beginning of the dialysis week.

In the first series of studies, the patients underwent a 2.5 to 3.0% weight loss over a 2-hour period, first on regular dialysis and then on ultrafiltration alone. Supine blood pressures after these first two procedures and after weight loss were comparable, but with the added stimulus of standing, important differences were noted. Mean blood pressure fell significantly after the regular dilaysis procedure (Table 4 and Fig. 2) and three of the six patients became symptomatic. In contrast, after ultrafiltration orthostatic blood pressure did not fall, and importantly, none of the patients were symptomatic. Thus, these initial two maneuvers confirm the prior experience with ultrafiltration [6], although the importance of the upright posture had not been previously systematically studied.

In the next series of investigations, potassium was added to the dialysate so that serum potassium remained unchanged throughout the 2-hour course of the procedure as weight decreased. This maneuver failed to maintain blood pressure after standing, and four of the six patients again became symptomatic during the orthostatic maneuver. Thus, a stable serum potassium was insufficient as an isolated factor to account for the hemodynamic stability observed with ultrafiltration. Plasma norepinephrine concentration was observed to increase significantly on standing, but the magnitude of the increase was statistically no different than in the previous two procedures.

To investigate the importance of a constant osmolality as a protective factor of blood pressure during ultrafiltration, we infused hypertonic mannitol (25%) in a dose previously associated with a stable osmolality during dialysis [12]. This method of providing a constant osmolality was selected to allow for the incorporation of a volume control in a subsequent protocol (isotonic mannitol studies, vide infra). In marked contrast to the results in the isokalemic dialysis maneuver, no orthostatic decrease in blood pressure occurred in the patients after a 2.6% decrease in body weight, and none of the patients became symptomatic after standing. These results were thus comparable to those observed during ultrafiltration alone, and occurred despite a fall in serum potassium and no significant increase in catecholamines. Moreover, the insignificant decrease (1%) in plasma osmolality was comparable to the decrease during ultrafiltration (1%) and was significantly less than the decrease in osmolality with regular (7%) and isokalemic (4%) dialysis. The infusion of hypertonic mannitol, however, not only produced a constant osmolality, but also provided expansion of the circulating plasma volume. Therefore, a final group of studies was performed in which the volume given in the hypertonic mannitol studies was matched with isotonic mannitol (5%), thereby allowing osmolality to decline (by 5.2%). In this final group of studies, blood pressure again fell after a 2.13% decrease in body weight and the isotonic volume infusion. Importantly, increases in hematocrit and plasma proteins were comparable after the mannitol infusion maneuvers, suggesting comparable decrements in estimated plasma volume. Thus, the results from all of the dialysis groups would suggest that an important mechanism by which blood pressure is protected in ultrafiltration is via an effect of osmolality on vascular reactivity, lending support to the earlier conclusions made by Bergström [6]. The studies with hypertonic and isotonic mannitol do not conclusively exclude, however, an additional effect of osmolality on extracellular fluid volume distribution, for the precise amount of volume flux during these procedures is unknown. Clearly, however, maintenance of osmolality (no more than a 1% decrease) afforded the greatest protection of blood pressure as pressure still decreased following isotonic volume repletion in the context of rapid weight loss on dialysis. Interestingly, studies in experimental animals suggest that sudden declines in osmolality (concomitant with decrements in potassium and magnesium) produce an increase in cardiac output, a modest decline in peripheral vascular resistance, and a resultant increase in blood pressure [21, 22]. Thus, the present results and those of Wehle et al [8] are compatible with an effect of declining osmolality to reduce peripheral vascular resistance, although this is a subject worthy of further investigation.

The present results clearly demonstrate that changes in serum potassium may be dissociated from changes in blood pressure during weight loss and dialysis, provided no cardiac arrythmias occur. Thus, blood pressure was maintained despite a fall in serum potassium in one maneuver (hypertonic mannitol), but fell when potassium was unchanged in another (isokalemic dialysis).

Plasma norepinephrine concentration was again noted to be high in these dialysis patients, but the modest increases in catecholamines did not prevent an orthostatic fall in blood pressure ($>$ 10 mm Hg) in the isokalemic and isotonic mannitol groups. These increases in catecholamines may in part simply be a secondary increase and reflect the degree of hypotension to which the patients were subjected. The added stimulus of upright posture in these studies, however, demonstrates that plasma norepinephrine is able to moderately increase during the dialysis procedures, a finding not previously observed.

Summary. The ultrafiltration procedure affords orthostatic blood pressure stability during rapid weight removal when compared with regular dialysis. Maintenance of constant plasma osmolality appears to be the major protective reason for this stability, probably via an effect on peripheral vascular resistance. The acute changes in blood pressure that occur in dialysis may be dissociated from acute changes in serum potassium concentration. Last, although plasma norepinephrine concentrations are high in dialysis patients, the magnitude of further increases in norepinephrine concentrations observed in these studies would appear to be insufficient to protect blood pressure during the stress of rapid weight removal and standing.

Acknowledgments

An abstract of this work was presented at and appeared in Proceedings of the American Society of Nephrology, 12th Annual Meeting, 1979. This research was supported by funds supplied by Organon Teknika Corporation, Travenol Laboratories and NIH Grant 1R01HL 23670-01. Technical assistance was provided by Mr. A. Sofranko, M. Henry, and W. Stephenson, and secretarial assistance was provided by Ms. S. Moody.

Reprint requests to Dr. William L. Henrich, General Medical Research 111G1, VA Medical Center, 4500 South Lancaster Road, Dallas, Texas 75216, USA

References

1. Ewing DJ, Winney R: Autonomic function in patients with chronic renal failure on intermittent hemodialysis. *Nephron* 15:424-429, 1975
2. Lilley JJ, Golden J, Stone RA: Adrenergic regulation of blood pressure in chronic renal failure. *J Clin Invest* 57:1190-1200, 1976
3. Biglieri EG, McIlroy MB: Abnormalities of renal function and circulatory reflexes in primary aldosteronism. *Circulation* 33:78-86, 1966
4. Fukuchi S, Hanata M, Takahashi H, Demura H, Goto K: The relationship between vascular reactivity and extracellular potassium. *Tohoku J Exp Med* 85:181-191, 1965
5. Zucchelli P, Catizone L, Delgi Esposti E, Furasoli M, Ligabue A, Zuccala A: Influence of ultrafiltration on plasma renin activity and adrenergic system. *Nephron* 21:317-324, 1978
6. Bergström J: Ultrafiltration without dialysis for removal of fluid and solutes in uremia. *Clin Nephrol* 9:156-164, 1978
7. Raja RM, Kramer MS, Rosenbaum JL: Use of mannitol in hemodialysis. *Dial Transpl* 5:32-40, 1976
8. Wehle B, Asaba H, Castenfors J, Fürst P, Grahn A, Gunnarson B, Shaldon S, Bergström J: The influence of dialysis fluid composition on the blood pressure response during dialysis. *Clin Nephrol* 10:62-66, 1978
9. Wehle B, Asaba H, Castenfors J, Fürst P, Gunnarson B, Shaldon S, Bergström J: Hemodynamic changes during sequential ultrafiltration and dialysis. *Kidney Int* 15:411-418, 1979
10. Kersh ES, Kronfield SJ, Unger A, Popper RW, Canter S, Lohn K: Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypotension. *N Engl J Med* 290:650-653, 1974
11. Sharpey-Schafer EP: Effects of Valsalva's maneuver on the normal and failing circulation. *Br Med J* 1:693-695, 1955
12. Rodrigo R, Shideman J, McHigh R, Buselmeir T, Kjellstrand C: Osmolality changes during hemodialysis. *Ann Intern Med* 86:554-561, 1977
13. Passon PG, Peuler PD: A simplified radiometric assay for plasma norepinephrine and epinephrine. *Ann Biochem* 51:618-631, 1973
14. Scheffe H. *The Analysis of Variance*. John Wiley and Sons, Inc., New York, NY, 1959
15. Henrich WL, Katz FH, Molinoff PB, Schrier RW: Competitive effects of hypokalemia and volume depletion on plasma renin activity aldosterone, and catecholamine concentrations in hemodialysis patients. *Kidney Int* 12:279-284, 1977
16. Atuk NO, Westerveldt FB, Peach M: Altered catecholamine metabolism, plasma renin activity and hypertension in renal failure (abst). *Int Congr Nephrol*, Florence, 1975, p. 475
17. Nolph KD: Chronic peritoneal dialysis in a patient with diabetes mellitus and heart disease. *Kidney Int* 15:698-708, 1979
18. Rubin LJ, Gutman RA: Hypotension during hemodialysis. *Kidney* 11:21-24, 1978
19. Alwall N, Herner B: On the artificial kidney. *Acta Med Scand* 132:572-586, 1948
20. Hampl H, Paeprer H, Unger V, Fischer C, Kessel M, Cambi V: Hemodynamic studies, acid-base and osmolality in the intra-individual study of different hemodialysis procedures (abst). *Proc Trans Soc Artif Organs* 3:15, 1979
21. Haddy FJ, Scott JB: Mechanism of the acute pressor action of hypokalemia, hypomagnesemia, and hypo-osmolality. *Am Heart J* 85:655-661, 1973
22. Emerson TE, Jr., Scott JB, Haddy FJ: Effects of acute multiple changes in plasma electrolyte levels on dog blood pressure. *Am J Physiol* 218:234-240, 1970