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Mechanisms of autonomic nervous system dysfunction in uremia

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Mechanisms of autonomic nervous system dysfunction in uremia. Autonomic nervous system (ANS) function was evaluated in 60 normal subjects, 21 predialysis patients, 16 dialysis patients, and 15 patients with chronic illnesses and normal renal function by Valsalva ratio, hand-grip exercise, and response to orthostasis. Blood levels of norepinephrine (NE) and the response to NE infusion were also evaluated. Valsalva ratio was normal in patients with chronic illness and significantly reduced ($P < 0.01$) in both dialysis and predialysis patients; this abnormality was more marked in the latter. During upright posture, mean blood pressure (MBP) decreased significantly in predialysis but not in dialysis patients. During hand-grip exercise, the increment of heart rate was significantly reduced ($P < 0.01$) in the patients with uremia and this abnormality appeared related to the disturbance in Valsalva ratio. Plasma NE in predialysis (35 ± 3.6 ng/dl) was higher ($P < 0.01$) than it was in dialysis patients (24 ± 3 ng/dl), normal subjects (21 ± 1 ng/dl) and in those with chronic illness (21 ± 3 ng/dl). The magnitude of rise in plasma NE in response to orthostasis was greater ($P < 0.01$) in predialysis (60 ± 7 ng/dl) than it was in dialysis patients (30 ± 5 ng/dl) and normal subjects (28 ± 2 ng/dl). NE infusion produced smaller ($P < 0.05$) changes in MBP and heart rate in predialysis than it did in dialysis patients and in normals. These data indicate that disturbances of ANS function are common in uremia and that they are more extensive in predialysis than in dialysis patients. Taken together, the results are consistent with the notion that the mechanisms for these derangements are multifactorial. Reduced end-organ response to NE appears to be a major factor underlying these abnormalities in predialysis patients; derangements in the parasympathetic nervous system and/or disturbances in cardiac function may also be involved.

Mécanismes du dysfonctionnement du système nerveux autonome au cours de l'urémie. Le fonctionnement du système nerveux autonome (ANS) a été évalué chez 60 sujets normaux, 21 malades avant l'institution de la dialyse, 16 malades en dialyse et 15 malades atteints d'affections chroniques mais avec une fonction rénale normale, par le rapport de Valsalva, l'épreuve du serrement de main et la réponse à l'orthostatisme. Les concentrations plasmatiques de norépinéphrine (NE) et la réponse à la perfusion de NE ont aussi été évaluées. Le rapport de Valsalva était normal chez les malades atteints d'affections chroniques et significativement réduit ($P < 0,01$) chez les malades dialysés et avant la dialyse. L'anomalie était plus importante chez ces derniers. Au cours de la position debout, la pression sanguine moyenne (MBP) a diminué de facon significative chez les malades avant la dialyse, mais pas chez les malades dialysés. Au cours de l'épreuve du serrement de main l'augmentation du rythme cardiaque a été significativement diminuée ($P < 0,01$) chez les malades urémiques et cette anomalie paraît en rapport avec la modification du rapport de Valsalva. La NE plasmatique était plus élevée ($P < 0,01$) chez les malades avant la phase de dialyse (35 ± 3,6 ng/dl) que chez les malades dialysés (24 ± 3 ng/dl), les sujets normaux (21 ± 1 ng/dl) et les sujets atteints d'affections chroniques (21 ± 3 ng/dl). L'amplitude de l'augmentation de NE du plasma en réponse à l'orthostatisme était plus importante ($P < 0,01$) chez les malades avant dialyse (60 ± 7 ng/dl) que chez les malades dialysés (30 ± 5 ng/dl) et les sujets normaux (28 ± 2 ng/dl). La perfusion de NE a produit des modifications plus faibles ($P < 0,05$) de MBP et du rythme cardiaque chez les malades avant dialyse que chez les malades dialysés et les sujets normaux. Ces résultats indiquent que les désordres de fonctionnement de ANS sont fréquents dans l'urémie et qu'ils sont plus importants chez les malades à la phase prédialytique que chez les malades dialysés. Dans leur ensemble ces résultats sont en accord avec la notion selon laquelle les mécanismes de ces désordres sont multifonctionnels. La diminution de la réponse à NE de l'organe cible paraît être un facteur majeur de ces anomalies chez les malades avant la dialyse. Des altérations du système parasympathique et/ou des désordres de la fonction cardiaque pourraient aussi être impliqués.

Several abnormalities of autonomic nervous system (ANS) function have been noted in patients with end-stage renal failure, and these include defective function of sweat glands [1, 2], abnormal response to the Valsalva maneuver [3, 4], reduced baroreceptor sensitivity [5, 6], reduced elevation in blood pressure in response to sustained hand-grip exercise [4], and nonvolume responsive hypotension during hemodialysis [7]. The pathogenesis of these disturbances and the localization of the lesion responsible for them along the baroreceptor reflex arc are, as yet, not clear, however.

Some investigators [8] postulated, on the basis of an abnormal amyl nitrate inhalation test (a functional index of the entire baroreceptor reflex arc) and of a normal cold pressor test (a proposed index of the efferent pathway) that the lesion may reside in the baroreceptors. Others, have found, on the other hand, that plasma norepinephrine (NE) levels are elevated in patients with renal failure. The association of elevated levels of NE and ANS dysfunction could suggest end-organ resistance to the action of NE. In addition, patients with advanced renal failure have marked anemia and suffer from a state of chronic illness; the role of these factors in the genesis of ANS dysfunction in uremia have not been examined. The present study was undertaken in 138 subjects in an attempt to investigate the factors responsible for the genesis of the dysfunction of the ANS in patients with advanced chronic renal failure.

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Methods

A total of 112 subjects, including 60 normal volunteers, 37 patients with chronic uremia, and 15 patients with chronic illness but normal renal function, were studied for evaluation of ANS function. Patients with diabetes mellitus, congestive heart failure, and those receiving medication that may affect the autonomic nervous system were excluded from the study. Other studies were carried out in an additional 10 patients with essential hypertension for the evaluation of pressor response to NE infusion and in an additional 16 patients on maintenance hemodialysis for the examination of the effect of dialysis procedure on blood levels of catecholamines as detailed below. The nature of the research was explained to all participants, and an informed consent was obtained prior to the study.

Among the normal persons, there were 41 males and 19 females, with their ages ranging between 18 and 52 (35.0 ± 1) years. They were selected from the medical and the paramedical personnel of the Los Angeles County-University of Southern California Medical Center. The 37 uremic patients were made up of two groups: *(1)* 21 patients with creatinine clearances of less than 8 ml/min and who were not treated with dialysis (referred to hereafter as "predialysis" patients). Among them were 12 males and 9 females (age range, 19 to 62 [40 ± 3] years). These patients were ambulatory before admission to the hospital for evaluation and preparation for dialysis. *(2)* The other group was 16 patients treated with chronic maintenance hemodialysis for 0.5 to 10 (4.5 ± 0.9) years. They received 4 to 5 hours of hemodialysis three times a week. Among them were 11 males and 5 females (age range, 21 to 60 [38 ± 3] years). All patients were at home and came to the Center three times a week for dialysis. The studies in the patients were carried out on the day when they did not receive dialysis therapy.

The causes of the renal failure in the 37 patients were chronic glomerulonephritis in 11, malignant hypertension in 7, obstructive uropathy in 4, pyelonephritis in 3, polycystic kidney disease in 2, interstitial nephritis in 1, medullary cystic disease in 1, and the cause was unknown in 8 patients. All patients with chronic uremia received a diet containing 40 to 60 g of protein and 100 mEq of sodium per day, and all antihypertensive medications were discontinued at least 2 weeks prior to the study. The concentrations of various compounds in the blood of predialysis and dialysis patients were: urea, 118 ± 11 and 88 ± 9 mg/dl, $P < 0.05$; creatinine, 13.7 ± 1.0 and 17.9 ± 1.2 mg/dl, $P < 0.02$; sodium 136 ± 2 and 139 ± 1 mEq/liter, NS; potassium, 4.6 ± 0.3 and 5.3 ± 0.3 mEq/liter, NS; calcium, 8.0 ± 0.3 and 8.9 ± 0.3 mg/dl, $P < 0.05$; phosphorus, 5.9 ± 0.4 and 5.0 ± 0.5 mEq/liter, NS; magnesium, 2.5 ± 0.2 and 2.7 ± 0.2 mg/dl, NS, respectively.

The 15 patients with chronic illness and normal renal function were all males, and their ages ranged between 22 and 63 (43 ± 3) years. Eleven were recruited from the medical outpatient clinic, and 4 were at the hospital at the time of the study. Creatinine clearance was 85 to 160 (113 ± 57) ml/min, and hematocrit was 19.0 to 44.7% (39.6 ± 1.9%). Four patients had rheumatoid arthritis, 5 Hodgkin's disease, 2 chronic obstructive pulmonary disease, 1 sarcoidosis, 1 gout, 1 scleromyxedema, and 1 chronic peptic ulcer.

All normal subjects and those with chronic illness were asked to obtain complete urine collection during the 24 hours preceding the study for the measurements of sodium excretion in order to judge their sodium intake. Both the normal subjects and the patients were asked to fast overnight and to avoid coffee, tea, coca-cola, chocolate, and smoking for at least 12 hours before the study. In the morning of the study, the subjects remained in the supine position for 1 hour and were connected to an electrocardiograph. Thirty minutes before the start of the study, a needle connected to a heparin lock was inserted into a forearm vein. Blood pressure and heart rate were measured, and blood samples were obtained for the determination of plasma norepinephrine (NE), epinephrine (E) and plasma renin activity (PRA) after resting supine for 1 hour. While still in the supine position and after instruction on the use of the hand-grip dynamometer, the subjects gripped the instrument maximally with their hand for a few seconds. The highest value of three grip contractions was taken as the maximum voluntary contraction (MVC). Hand-grip was then maintained steadily at 30% MVC to the end-point of tiring. Heart rate and blood pressure were measured, and blood samples were obtained at the end-point of the sustained hand grip. Fifteen minutes later and while the subjects were still supine, they performed the Valsalva maneuver at an expiratory pressure of 40 mm Hg for 12 sec while blowing through a mouthpiece connected to a mercury manometer. The Valsalva maneuver was repeated three times. Heart rate was continuously recorded throughout the maneuver and for 60 sec after its completion. The heart rate response to the Valsalva maneuver was expressed as the Valsalva ratio [9]. This is defined as the ratio between the longest R-R interval (msec) during the release phase and the shortest R-R interval during the strain phase of the maneuver. The value selected was the best of the three attempts. The subjects were asked not to take deep inspiration before the Valsalva maneuver because we found that the Valsalva ratio was significantly ($P < 0.01$) lower when the maneuver is performed following a deep inspiration (1.77 ± 0.05) than during normal respiration (1.99 ± 0.06).

The effects of orthostasis were examined 15 min after the Valsalva maneuver. Blood pressure, heart rate, P_{NE}, P_E, and PRA were measured after 10 min of passive standing and after an additional 50 min of ambulation.

To determine the vascular responsiveness to NE, we infused the agonist into 5 of the predialysis and 6 of the dialysis patients, 10 normal subjects, and 10 patients with essential hypertension. The subjects were kept resting in the supine position for 1 hour, and an indwelling i.v. catheter was inserted into a forearm vein at least 30 min before starting the NE infusion. L-Norepinephrine (Levophed bitartrate; Winthrop Laboratory, New York) was infused at a rate delivering increasing amounts of 20, 50, and 100 ng/kg/min with each rate given for 10 min. Blood pressure and heart rate were measured before and at the end of each rate of the infusion.

The effects of a standard 4-hour hemodialysis on blood pressure, heart rate, plasma catecholamine, and PRA were examined in an additional 16 patients. This group included 10 males and 6 females whose ages ranged between 23 and 54 (36 ± 3) years.

In all studies, blood pressure was measured with an automatic recorder (Physiometric SRII, Sphygmetrics, Woodland Hills, California), and each data point is the average of three consecutive measurements. Mean blood pressure was calculated as the sum of diastolic blood pressure and one-third of pulse pressure.

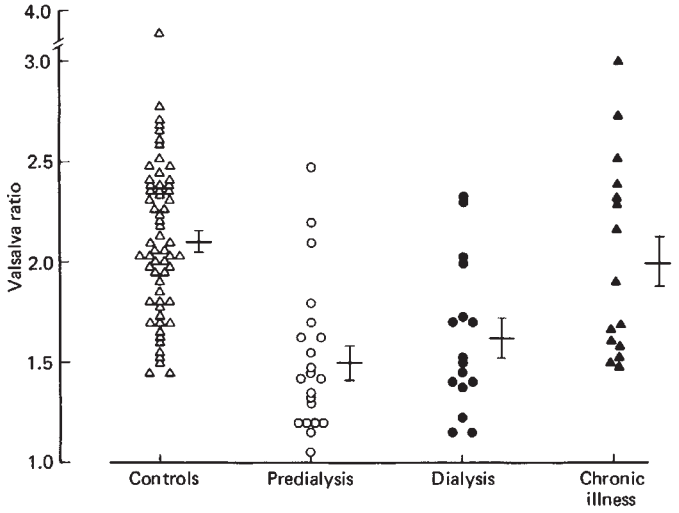

Fig. 1. *Valsalva ratio, that is, the ratio between the longest RR interval during the release phase and the shortest RR interval during the strain phase of the Valsalva maneuver, in 60 normal subjects, 21 predialysis patients, 16 patients on maintenance hemodialysis, and 15 patients with chronic illnesses but with normal renal function.* The brackets denote the means ± SEM.

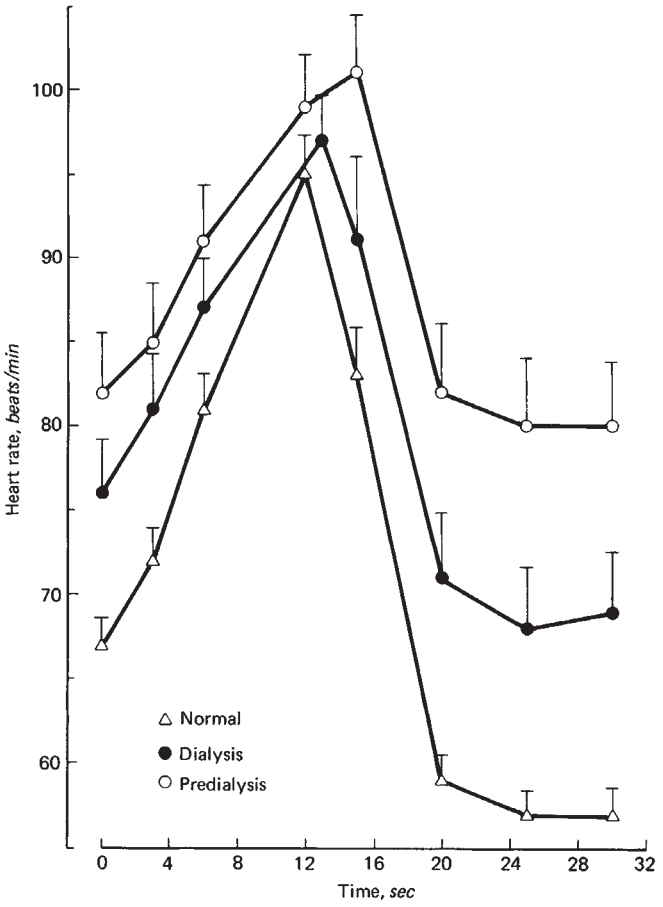

Fig. 2. *Heart rate before and during the Valsalva maneuver in normal subjects and predialysis and dialysis patients.* During the release phase, heart rate was significantly lower ($P < 0.01$) in normal subjects than it was in the two groups of uremic patients, and it was lower in dialysis ($P < 0.05$) than in predialysis patients. Data are presented as means ± SEM.

Heart rate was determined from electrocardiographic tracings.

Plasma renin activity (PRA) was measured by the radioimmunoassay method of Sealey, Gerten-Banes, and Laragh [10], with the antiserum provided by Endocrine Sciences (Tarzana, California), the ^{125}I-angiotensin I (^{125}I-AI) from New England Nuclear (Boston, Massachusetts), and the AI standard provided by Cal Biomed (San Diego, California). The interassay coefficient of variability for PRA was 7.3% (for 40 consecutive determinations).

Plasma catecholamines were measured in duplicate by the radioenzymatic method of DaPrada and Zurcher [11]; the enzyme catechol-o-methyl transferase was prepared according to the method of Axelrod and Tomchick [12], and ^{3}H-methyl-s-adenosine-methionine (New England Nuclear, Boston, Massachusetts) was used as a methyl donor. The sensitivity of this method is 1 pg for NE and E. This method is highly specific. Among physiologic substances, only epinin and 3-4 dihydroxyphenyl-glycol showed minimal interference. Mean coefficient of intraassay and control plasma variations in 78 unselected consecutive determinations with this method were 5.1% and 12.1% for P_{NE}, 5.7 and 10.1% for P_E. Sodium and potassium were determined by flame photometry (Instrumentation Laboratories) and creatinine by Technicon Autoanalyzer. The statistical evaluations of the data were made by one-way analysis of variance (Anova) for comparison between means, by the Tukey-HSD multiple comparisons, by unpaired and paired Student's *t* test and by linear regression analysis. Values are expressed as the means ± SEM.

Results

The values of the Valsalva ratio in all subjects are given in Fig. 1. The Valsalva ratio was significantly lower ($P < 0.01$) in both the predialysis (1.51 ± SEM 0.08) and dialysis patients (1.62 ± 0.09) than control subjects (2.10 ± 0.05) and those with chronic illness (2.00 ± 0.13). The ratio was not different among the predialysis and the dialysis patients. Even though there was considerable overlap between groups, almost half of the predialysis (52%) and of the dialysis (44%) patients had values of Valsalva ratio lower than the lowest value seen in normal subjects or in those with chronic illness. The difference in the Valsalva ratio was mainly due to significantly different falls in pulse rate (as determined by RR intervals) during the release phase of the Valsalva maneuver (Fig. 2). The highest heart rate achieved during the strain phase was not different between the three groups; although the change in heart rate from baseline values was smaller in the uremic patients. During the release phase, the lowest heart rate was 57 ± 1 beats/min in the normal subjects, 80 ± 4 beats/min in the predialysis ($P < 0.01$) and 68 ± 4 beats/min in the dialysis patients ($P < 0.01$). The values were significantly lower ($P < 0.05$) in dialysis than they were in predialysis patients.

To determine whether there is a relationship between the abnormality in the Valsalva ratio and the anemia of uremia, we compared the hematocrit of the patients with overtly low Valsalva ratio with those who had ratio within the normal range. Predialysis patients with Valsalva ratio of 1.25 ± 0.04 had hematocrits of 15.8 to 37.3% (22.5 ± 2.6%), and those with Valsalva ratio of 1.80 ± 0.11 had hematocrits of 18.8 to 29.1% (22.8 ± 1.5%). Among the dialysis patients, the hematocrit was

16.8 to 32.9% (23.9 ± 2.4%) with a Valsalva ratio of 1.31 ± 0.05 and 19.4 to 38.8% (24.9 ± 2.5%) with a Valsalva ratio of 1.87 ± 0.10. Furthermore, there was no significant correlation between the individual values of the Valsalva ratio and the hematocrit for the entire uremic population.

There was no correlation between the mean blood pressure (BP) and the Valsalva ratio. Among the predialysis patients, 8 had a normal mean BP (84 ± 4 mm Hg) with a Valsalva ratio of 1.54 ± 0.17 and 13 were hypertensive (113 ± 5 mm Hg) with a Valsalva ratio of 1.50 ± 0.08. Similarly, the Valsalva ratio in the 10 normotensive (88 ± 4 mm Hg) dialysis patients was 1.67 ± 0.11 and 1.53 ± 0.18 in the 6 hypertensive (108 ± 2 mm Hg) ones. Finally, half of the uremic patients who had overtly low Valsalva ratio were hypertensive.

During hand-grip exercise, mean BP and heart rate increased significantly ($P < 0.01$, paired analysis) in all four groups of patients studied, but the magnitude of the changes between the different groups was different (Table 1). The increment in blood pressure in normal subjects (28 ± 1 mm Hg) was significantly ($P < 0.01$) higher than the predialysis (15 ± 3 mm Hg) and the dialysis (21 ± 2 mm Hg) patients but not different from those with chronic illness (25 ± 3 mm Hg). In 7 of 20 (35%) predialysis patients and in 2 of 16 (13%) dialysis patients, the change in blood pressure was lower than the lowest value observed in normal subjects (Fig. 3). The increment in heart rate in normal subjects (21 ± 1 beats/min) was significantly higher ($P < 0.01$) than predialysis (11 ± 2 beats/min) and dialysis (10 ± 2 beats/min) patients and those with chronic illness (13 ± 2 beats/min). In 16 of 36 (44%) uremic patients, the increment in heart rate was lower than the lowest value observed in normal subjects (Fig. 4). Only in 4 of 15 patients (27%) with chronic illness was the change in heart rate below the normal range. It is of interest that 8 of 11 predialysis (73%) and 5 of 7 dialysis (71%) patients who had low Valsalva ratio also had an abnormal heart rate response to the hand-grip exercise.

The values for mean BP, heart rate, P_{NE}, P_E, and PRA during the supine position and the effect of orthostatic stress on these parameters in all subjects are given in Table 1.

The mean BP in predialysis (100 ± 4 mm Hg) and dialysis patients (95 ± 4 mm Hg) was significantly greater ($P < 0.01$) than it was in controls (81 ± 1 mm Hg). The heart rate in predialysis (80 ± 3 beats/min) and dialysis patients (79 ± 3 beats/min) was also significantly higher ($P < 0.01$) than it was in controls (64 ± 1 beats/min) or in those with chronic illness (67 ± 2 beats/min). The concentrations of P_{NE} in predialysis patients (35 ± 4 ng/dl) were significantly higher ($P < 0.01$) than they were in dialysis patients (24 ± 3 ng/dl), controls (21 ± 1 ng/dl) and in those with chronic illness (21 ± 3 ng/dl). Similarly, P_E levels in predialysis patients (3.3 ± 0.6 ng/dl) were significantly greater ($P < 0.05$) than they were in dialysis patients (2.1 ± 0.4 ng/dl), controls (2.5 ± 0.2 ng/dl) and in those with chronic illness (2.1 ± 0.4 ng/dl). PRA in predialysis (3.4 ± 0.6 ng/ml/hr) and in dialysis patients (3.2 ± 0.6 ng/ml/hr) was significantly higher ($P < 0.01$) than in controls (1.3 ± 0.1 ng/ml/hr) and in patients with chronic illness (1.6 ± 0.2 ng/ml/hr).

Urine sodium excretion during the 24 hr preceding the study was 159 ± 8 (range, 59 to 277 mEq/24 hr) in controls and 157 ± 15 (range, 85 to 250 mEq/24 hr) in patients with chronic illness. No systematic attempt was made to determine sodium excretion in uremic patients because of their renal failure.

There was a modest fall in the mean BP after standing and ambulation in normal subjects and those with chronic illness, but the change was significant only in the normal controls. Dialysis patients did not have a decrease in BP during these maneuvers. But, a marked and significant ($P < 0.01$) decrease in the mean BP occurred in the predialysis patients; it fell by 15 ± 4 and 15 ± 3 mm Hg after 10 and 60 min of ambulation, respectively. The concentration of P_{NE} increased significantly in all four groups. But, the magnitude of rise in P_{NE} after 60 min of ambulation in the predialysis patients (60 ± 7 ng/dl) was significantly ($P < 0.01$) higher than that in normal subjects (28 ± 2 ng/dl) dialysis patients (30 ± 5 ng/dl) and those with chronic illness (37 ± 5 ng/dl). The increments in heart rate after orthostasis were not different among the four groups of subjects. Both P_E and PRA increased significantly with orthostasis in all subjects and the magnitude of the increments were not different among the four groups studied.

The effect of hemodialysis on mean BP, heart rate, P_{NE}, P_E and PRA in 16 additional dialysis patients, studied in the supine position, are shown in Table 2. There were no significant changes in these parameters except for significant decrease in body weight and in the plasma concentration of sodium and potassium.

The changes in mean BP and heart rate during the NE infusion in normal subjects, predialysis, and dialysis patients, and in those with essential hypertension and normal renal function are shown in Fig. 5. There was a dose-response relationship between the changes in both mean BP and heart rate and the amount of NE infused. In the predialysis patients, the changes in mean BP with 20, 50, 100 ng/kg/min of NE were −3.4 ± 1.5, +4.2 ± 2.6, and +13.2 ± 2.9 mm Hg, values significantly ($P < 0.05$) lower than those observed in normal subjects (+2.3 ± 1.9, +11.4 ± 2.7 and +23.0 ± 4.7 mm Hg) and in those with essential hypertension and normal renal function (+8.4 ± 2.2, +17.3 ± 1.7, +31.5 ± 2.5 mm Hg). The changes in the latter groups were significantly ($P < 0.01$) greater than they were in normal controls. The changes in mean BP in the dialysis patients were (+3.8 ± 1.1, +9.3 ± 1.1, +17.0 ± 1.5 mm Hg), not different than they were in normal subjects. Similarly, the decrements in heart rate were significantly smaller ($P < 0.05$) in the predialysis patients (−2.0 ± 0.7, −3.2 ± 2.2, and −4.4 ± 3.3 beats/min) than they were in dialysis patients (−3.0 ± 2.4, −9.0 ± 3.8, −13.0 ± 4.3 beats/min), normal subjects (−4.0 ± 1.4, −8.9 ± 1.6, −12.0 ± 1.8 beats/min), and in those with essential hypertension (−7.4 ± 1.9, −12.2 ± 2.0, −12.8 ± 2.4 beats/min). There was no significant difference in the changes in heart rate between the dialysis patients and normal subjects.

Discussion

Although dysfunctions in the autonomic nervous system (ANS) have been previously reported in patients treated with maintenance dialysis [3–8], similar abnormalities have not been documented in patients prior to treatment with dialysis. Furthermore, the mechanisms responsible for the dysfunction in the ANS in uremia have not, as yet, been elucidated. We have evaluated ANS function in predialysis and dialysis patients, determined the blood levels of catecholamines, and examined the reactivity of the target organs to norepinephrine (NE) in an effort to understand the genesis and the pathways involved in the derangement of the autonomic nervous function in uremia.

Table 1. Mean blood pressure, heart rate, plasma levels of norepinephrine, epinephrine, and plasma renin activity during supine position, hand-grip exercise, and orthostasis[a]

			Mean blood pressure *mm Hg*				Heart rate *beats/min*			
					Standing				Standing	
	N	Age *yr*	Supine	Hand-grip exercise	10 min	50 min	Supine	Hand-grip exercise	10 min	50 min
Normal subjects	60	35 ± 1	81 ± 1	109 ± 2[b]	76 ± 1[b]	76 ± 1[b]	64 ± 1	84 ± 2[b]	85 ± 2[b]	85 ± 2[b]
Patients with chronic illness and normal renal function	15	43 ± 3	85 ± 3	109 ± 5[b]	82 ± 4	81 ± 4	67 ± 2	80 ± 2[b]	87 ± 4[b]	89 ± 4[b]
Predialysis patients	21	40 ± 3	100 ± 4[c]	115 ± 6[b]	84 ± 5[b,c]	85 ± 4[b,c]	80 ± 3[c]	90 ± 3[b]	98 ± 4[b,c]	100 ± 4[b,c]
Dialysis patients	16	38 ± 3	95 ± 3[c]	117 ± 5[b]	94 ± 5[c]	93 ± 5[c]	79 ± 3[c]	88 ± 3[b]	98 ± 4[b,c]	96 ± 5[b,c]
One-way Anova		NS	<0.01	NS	<0.01	<0.01	<0.01	NS	<0.01	<0.01

[a] Data are presented as the means ± SEM.
[b] $P < 0.01$, compared with values in the supine position (Student's paired *t* test).
[c] $P < 0.01$, compared with values in the normal subjects (by Tukey-HSD multiple comparisons).

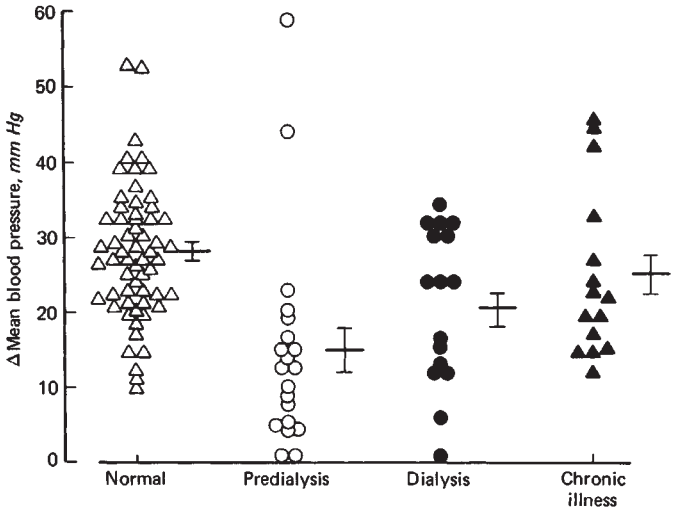

Fig. 3. *Changes in mean blood pressure in normal subjects, in predialysis and dialysis patients, and in patients with chronic illnesses but with normal renal function in response to sustained hand-grip exercise at one third of maximum voluntary contraction.* The increment in mean blood pressure was significantly lower ($P < 0.01$) in the two groups of uremic patients. The brackets denote the mean ± SEM.

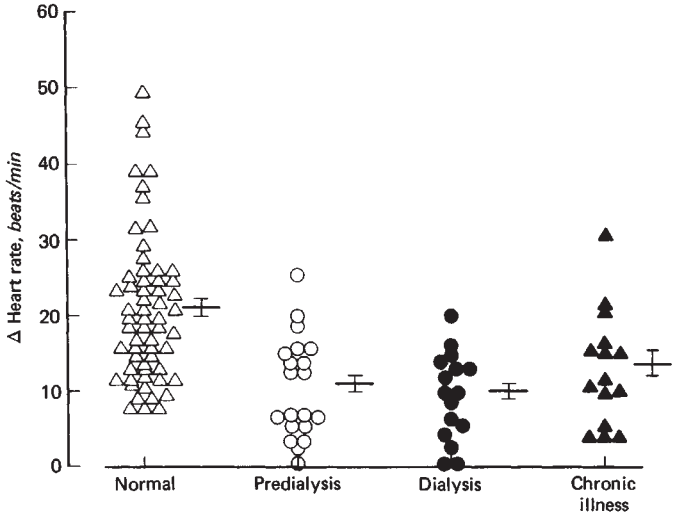

Fig. 4. *Changes in heart rate in normal subjects, in predialysis and dialysis patients, and in patients with chronic illnesses but with normal renal function in response to sustained hand-grip exercise at one third of maximum voluntary contraction.* The increment in heart rate was significantly lower ($P < 0.01$) in the two groups of uremic patients. The brackets denote mean ± SEM.

The results of our studies demonstrate that a large number of predialysis and dialysis patients had dysfunction of ANS. These included abnormal Valsalva ratio, abnormal response to hand-grip tests, and abnormal fall in blood pressure (BP) during orthostasis. The disturbances appear to be related to uremia itself or to some of its consequences rather than to the state of chronic illness, because patients with other chronic disease, but normal renal function, did not have such abnormalities.

Two findings in our data indicate that some of these abnormalities are more extensive in the predialysis patients. First, the abnormal response of blood pressure during the hand-grip exercise was more frequent among the predialysis patients. Second, the majority of the predialysis patients (67%) displayed orthostatic hypotension whereas the response to upright posture in the dialysis patients was not different from normal subjects.

It is plausible that the anemia of uremia and the presence or absence of hypertension may affect the function of the ANS. Our data do not support either of these notions. First, the abnormal Valsalva ratio and the abnormal response to hand-grip exercise were not related to the magnitude of the anemia. Second, many of the uremic patients had abnormal heart rate response but normal BP response to hand-grip exercise. Third, the response to orthostasis was abnormal in the predialysis patients and normal in the dialysis patients despite no significant difference in hematocrit. Finally, the abnormalities in the function of ANS did not correlate with the presence or absence of an elevated mean BP.

The abnormality in heart rate response during the Valsalva maneuver was more pronounced during the release phase of the test in both the predialysis and dialysis patients. During this phase, an increase in systemic arterial pressure occurs, which is

Table 1. (Continued)

Plasma norepinephrine *ng/dl*				Plasma epinephrine *ng/dl*				Plasma renin activity *ng/ml/hr*			
		Standing				Standing				Standing	
Supine	Hand-grip exercise	10 min	50 min	Supine	Hand-grip exericse	10 min	50 min	Supine	Hand-grip exercise	10 min	50 min
21 ± 1	29 ± 2[b]	47 ± 3[b]	48 ± 2[b]	2.5 ± 0.2	3.8 ± 5[b]	4.4 ± 0.4[b]	4.9 ± 0.4[b]	1.3 ± 0.1	1.7 ± 0.2[b]	2.0 ± 0.3[b]	2.4 ± 0.2[b]
21 ± 3	24 ± 3[b]	52 ± 6[b]	57 ± 7[b]	2.1 ± 0.4	3.2 ± 0.7[b]	4.2 ± 0.7[b]	5.3 ± 1.1[b]	1.6 ± 0.2	2.1 ± 0.3[b]	2.6 ± 0.4[b]	3.7 ± 0.6[b]
35 ± 4[c]	42 ± 5[b,c]	73 ± 7[b,c]	97 ± 9[b,c]	3.3 ± 0.6[c]	4.2 ± 0.7[b]	6.5 ± 1.2[b]	7.1 ± 1.1[b,c]	3.4 ± 0.6[c]	3.9 ± 0.6[b,c]	4.1 ± 0.6[b,c]	4.8 ± 0.9[b,c]
24 ± 3	29 ± 3[b]	53 ± 7[b]	55 ± 5[b]	2.1 ± 0.4	3.2 ± 0.5[b]	4.0 ± 1.0[b]	5.0 ± 1.2[b]	3.2 ± 0.6[c]	4.2 ± 0.7[b,c]	4.6 ± 0.8[b,c]	5.0 ± 1.0[b,c]
<0.01	<0.01	<0.01	<0.01	<0.05	NS	NS	<0.05	<0.01	<0.01	<0.01	<0.01

Table 2. Effect of a single hemodialysis on mean blood pressure, heart rate, plasma norepinephrine, epinephrine, plasma renin activity, body weight, and plasma concentration of sodium and potassium in 16 patients[a]

	Mean BP *mm Hg*	Heart rate *beats/min*	P_{NE} *ng/dl*	P_E *ng/dl*	PRA *ng/ml/hr*	Body wt *kg*	S_{Na} *mEq/liter*	S_K *mEq/liter*
Before dialysis	101 ± 4	73 ± 4	25 ± 5	7.9 ± 2.0	4.0 ± 1.2	69 ± 4	137 ± 1	5.3 ± 0.1
After dialysis	98 ± 4	81 ± 4	27 ± 4	6.3 ± 1.0	6.6 ± 2.5	67 ± 3	133 ± 1	3.9 ± 0.1
P	NS	NS	NS	NS	NS	<0.01	<0.01	<0.01

[a] Data are the means ± SEM. These patients are not among the patients included in Table 1. Abbreviations are defined as follows: BP, blood pressure; P, plasma concentration; NE, norepinephrine; E, epinephrine; PRA, plasma renin activity; S, serum concentration; Na, sodium; K, potassium.

sensed by the baroreceptors in the aortic arch and carotid arteries, subsequently leading to reflex bradycardia [13, 14]. The increase in BP is due to an increase in cardiac output secondary to enhanced venous return and to increased peripheral vascular resistance produced by augmented sympathetic tone [13–16]. The abnormal response in heart rate during the release phase could be due to failure of the BP to rise secondary to an inappropriate change in peripheral vascular resistance, derangement in the vagal pathway, and/or disturbance in cardiac function.

We did not use invasive techniques to monitor arterial pressure during the Valsalva maneuver, but others have shown that dialysis patients display a blunted arterial-pressure overshoot during the release phase of the test [7]. The more pronounced abnormality in heart rate response during the release phase of the Valsalva in the predialysis patients could be, at least partially, due to a greater impairment in arterial pressure response during this phase. This impairment could be secondary to a resistance to the action of NE on blood vessels.

The demonstration in the dialysis patients that an elevation in BP with the infusion of NE produced a normal fall in heart rate suggests that the abnormal response in heart rate during the release phase of the Valsalva maneuver may be due to a failure of arterial pressure to rise in this phase of the test. It should be emphasized, however, that abnormalities in the vagus pathways could also be responsible for the abnormal response in heart rate both in the predialysis and dialysis patients. Support for this idea is found in the results of hand-grip test as discussed below.

The hand-grip exercise is associated with an increase in heart rate, cardiac output, and arterial pressure [18–20]. The pressor response is believed to be mediated by cardiac acceleration [18], but even when heart rate fails to increase during the test, the pressor response occurs most probably due to increased peripheral vascular resistance [20]. Although the mechanisms for these hemodynamic responses are not fully elucidated, a participation of the sympathetic and parasympathetic nervous systems has been proposed [18, 20]. Certain data suggest that the change in heart rate is due to parasympathetic inhibition (vagus release) [20], and that the increased peripheral resistance is secondary to enhanced sympathetic activity [20]. The observation in our study that the majority of the patients who displayed an abnormal response of heart rate during the hand-grip exercise have also an abnormal Valsalva ratio is consistent with the notion that a disturbance in the vagus pathways is present in uremic patients. Furthermore, the demonstration that 35% of the predialysis patients, but only 13% of the dialysis patients, had abnormal pressor response (despite similar incidence of deranged heart rate response) suggests that a disturbance in sympathetic activity is more predominant in the predialysis patients. This proposal is consistent with the finding of peripheral resistance to NE infusion in the predialysis patients.

The maintenance of arterial pressure during orthostasis is dependent on the ability to augment peripheral vascular resistance [21, 22]. Our data clearly demonstrate that the majority of the predialysis patients displayed marked postural hypotension (Δ mean BP > 12 mm Hg), whereas the changes in BP were not different from that in normal subjects in the dialysis patients. The reason for this difference is most probably due to target-organ resistance to NE present only in the predialysis patients. Our data do not necessarily imply that orthostatic hypoten-

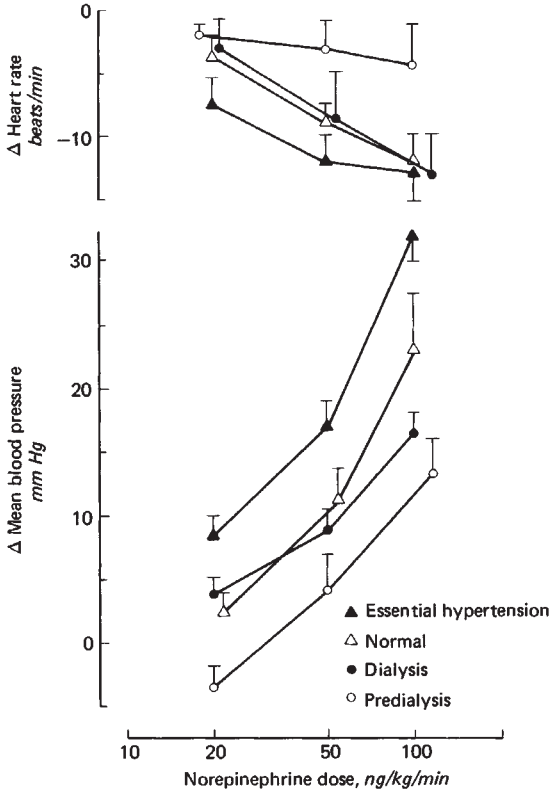

Fig. 5. *Changes in mean blood pressure and heart rate during norepinephrine infusion at progressive doses of 20, 50, 100 ng/kg/min in 10 normal subjects, 5 of the predialysis, and 6 of the dialysis patients included in Table 1 and in 10 patients with essential hypertension and normal renal function.* Each infusion rate was given for 10 min. The changes in mean blood pressure and heart rate were significantly ($P < 0.01$) lower in dialysis but not in predialysis patients, then in normal subjects.

sion due to autonomic nerve dysfunction is not encountered in dialysis patients but would suggest that such a problem is not frequent. It is our opinion that if orthostatic hypotension is noticed in a dialysis patient, a vigorous search for causes other than uremic ANS dysfunction should be undertaken.

Our data do not provide information on the mechanism of the resistance to the action of NE in the predialysis patients. Because the resistance improves or disappears with dialysis therapy it is tempting to speculate that dialyzable material is responsible for the phenomenon. It is also possible that occupation and/or down regulation of the α-receptors of the vascular smooth muscle due to elevated level of P_{NE} plays a role in decrease response to the agonist.

It is of interest that the blood levels of NE are elevated in the predialysis patients and are normal in the dialysis subjects. Atuck et al [23] also found elevated blood levels of NE in predialysis patients. The mechanisms for elevation in blood levels of NE in uremia are not clear. Several factors could be contributory, including decreased renal clearance, diminished degradation secondary to reduced catechol-o-methyl transferase activity [23], reduced reuptake of the agonist from the sympathetic neurons end-terminals [24], or increased release of the hormone. The presence of resistance to the action of NE results in hemodynamic consequences that would dictate an increased need for the agonist and would result in the stimulation of its release. The normalization of the blood levels of NE in our dialysis patients is most probably secondary to an improvement or a disappearance of the resistance to the action of the hormone rather than to its loss during dialysis. Indeed, our observation that blood levels of NE do not decrease during the dialysis procedure is consistent with this postulate. Others have also found that the dialysis procedure does not lower blood levels of NE [25] whereas Lake et al [26] reported an increase in these levels during dialysis.

The normal basal concentrations of P_{NE} found in our dialysis patients are in agreement with the results of Lake et al [26] and at variance with those of others [27–29]. The reasons for this discrepancy are not obvious. It may be due to different methodology or to variable degrees in the improvement of the resistance to the action of NE. This improvement may be influenced by the efficacy of the dialysis treatment and its duration. Thus, patients receiving inadequate dialysis or treated for shorter periods of time may not have sufficient improvement in the resistance to the action of the agonist and, thus, would still have elevated levels of NE.

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