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Influence of continuous ambulatory peritoneal dialysis on the autonomic nervous system

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The stabilization of systemic blood pressure is one of the most challenging tasks in the management of uremic patients. Continuous ambulatory peritoneal dialysis (CAPD) is associated with the development of hypotension in some patients [1–3]. Several pathogenetic mechanisms may be responsible for this type of dialysis-associated hypotension. Several authors have reported on the presence of autonomic dysfunction in uremic patients [4–8], and it has been postulated as a cause of hemodialysis-induced hypotension [4–8].

However, Marquez-Julio et al [3] have suggested that hypotension in CAPD patients may be due to the combined effect of an increased removal of sodium chloride and water and the loss of large concentrations of vasoconstrictive substances.

In recent years, CAPD has been performed in a rapidly increasing number of diabetic patients with endstage renal disease [9]. It is well known that autonomic neuropathy is a long-term complication of diabetes mellitus [10–12].

The present study was undertaken first, to clarify whether or not hypotension in nondiabetic and diabetic CAPD patients is related to autonomic neuropathy and second, to see whether or not a functional lesion of the autonomic nervous system may be induced by peritoneal dialysis "per se."

Methods

Patients. Our CAPD program began November 1979 and since that time, 23 patients have been trained in this technique. Only two of them had been on in-center intermittent peritoneal dialysis prior to beginning CAPD; the others chose CAPD as their initial form of treatment. Peritoneal access was achieved via a straight in-dwelling Tenckhoff catheter in all patients. Two types of dialysis solution (2-liter plastic bags) were used. Both solutions were warmed to body temperature and contained: lactate 35 mEq/liter, calcium 3.5 mEq/liter, magnesium 1.5 mEq/liter, chloride 102 mEq/liter, and sodium, 132 mEq/liter. They differed only in their glucose concentrations (1.5 or 4.25 g/dl, respectively). In all patients four to five exchanges were performed daily, 7 days a week. For the purpose of the study, 14 patients already on CAPD for at least 3 months (nine males and five females), with an age range of 45 to 73 years (mean, 61 years), comprising four diabetic and ten nondiabetic patients, were selected. Informed consent was obtained from all the individuals. None had undergone bilateral nephrectomy. There was no clinical evidence of edema, increased jugular venous pressure, or cardiac failure in any of the patients. None had clinical peritonitis and none experienced symptomatic postural hypotension during the study. Underlying renal diseases included hypertensive nephroangiosclerosis (four patients), glomerulonephritis (five patients), diabetic glomerulosclerosis (four patients), and pyelonephritis (one patient). At the time of the study all patients continued their usual ambulatory activity and diet (approximately 100 mEq/day sodium, 60 mEq/day potassium, 1.1 to 1.2 g/kg/day protein, 30 to 35/kg/day calories). In the hypertensive patients all forms of antihypertensive medications were discontinued at least 15 days prior to the study. In the diabetic patients the amounts of insulin required were determined with the patient active and performing self-care to maintain blood sugar between 80 and 180 mg/dl immediately before an exchange. Fifteen age- and sex-matched healthy normal subjects (10 males and 5 females) aged between 41 and 71 years (mean age, 60 years) were studied as controls.

Protocol. The first day on dialysis began at 7 A.M. when patients filled the peritoneal cavity with 2 liters of the solution with 1.5 g/dl glucose. At 10 A.M. (dwell-time = 3 hr), after 2 hr resting supine, arterial blood pressure (BP; Arteriosonde Roche 1217) and heart rate (HR) were measured, and blood was taken for measurement of plasma renin activity (PRA) and plasma noradrenaline (NA). Subsequently a 7-min postural test with determination of BP, HR, and NA was performed. On the same morning all patients performed a Valsalva maneuver, cold pressor test, and diving reflex. At the end of the study the volume of dialysate removed was measured.

The second day out of dialysis began at 8 A.M. when the peritoneal cavity was drained and maintained empty for the following 36 hr. Between 9 and 10 A.M., 1 hr after interruption of the dialysis, the patients received a dose of ^{22}Na.

On the third day, 24 hr after the administration of ^{22}Na, blood for determination of exchangeable sodium (NaE) was taken and the same protocol as day 1 was performed.

Techniques. Mean arterial pressure (MAP) was calculated as diastolic BP plus one-third pulse pressure. The NA assay was performed according to the fluorimetric method of Renzini, Brunori, and Valori [13]. PRA was measured according to the angiotensin I radioimmunoassay method [14]. Briefly, renin activity expressed as nanograms per milliliters per hour refers

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Table 1. Comparison of several parameters evaluated in control subjects, nondiabetic and diabetic CAPD patients[a]

	No. of patients	MAP supine *mm Hg*	HR supine *beats/min*	PRA supine *ng/ml/hr* A_I	NA supine *ng/liter*	NA upright *ng/liter*	Δ NA %	Δ MAP *mm Hg*
Control subjects	15	91 ± 2.1	67 ± 1.3	0.59 ± 0.06	178 ± 23	346 ± 39	99.4 ± 17	4.7 ± 1.6
		$P < 0.001$	$P < 0.01$	P = NS	$P < 0.001$	$P < 0.005$	P = NS	P = NS
Nondiabetic CAPD patients	10	120 ± 7.1	73 ± 2.2	2.52 ± 1.55	380 ± 54	633 ± 88	95.6 ± 16.2	8.5 ± 2.5
Control subjects	15	91 ± 2.1	67 ± 1.3	0.59 ± 0.06	178 ± 23	346 ± 39	99.4 ± 17	4.7 ± 1.6
		$P < 0.01$	$P < 0.01$	P = NS	P = NS	P = NS	$P < 0.05$	P = NS
Diabetic CAPD patients	4	111 ± 8.1	87 ± 7.0	0.79 ± 0.45	337 ± 132	538 ± 250	48.1 ± 20.3	−15.5 ± 10.7

Abbreviations and symbols: Δ NA% = [(NA upright − NA supine)/(NA supine)] × 100; Δ MAP = MAP upright − MAP supine; PRA, plasma renin activity; HR, heart rate; NA, noradrenaline; MAP, mean arterial pressure; A_I, angiotensin I.

[a] Data are expressed as means ± SEM.

to the ability of plasma to form angiotensin I from endogenous renin substrate during incubation of the sample at pH 6.5 for 2 hr at 37°C. NaE was evaluated by the isotope dilution technique as previously described [15]. The NaE of an individual patient was standardized by expressing it as milliequivalents per kilograms of the lean body mass (LBM). LBM was estimated following the method recommended by Durnin [16]. Using the Valsalva maneuver, the subject was studied supine and trained to maintain an expiratory pressure of 40 mm Hg for 13 sec by blowing through a mouthpiece attached to an aneroid manometer. HR was registered continuously throughout and for 30 sec after release of the strain on ECG at a chart speed of 25 mm/sec. The result was expressed as the ratio between the shortest R-R interval in phase 3 and the longest R-R interval in phase 4 (Valsalva ratio). The maneuver was repeated three times and the highest ratio accepted. During the cold pressor test, after a control period of 10 min, the patients plunged their right hands into a pan containing equal parts of water and ice at a temperature of 0 to 2°C for 2 min. In the control period and during the test, BP was measured at 1-min intervals. The results were expressed as the difference between the mean resting values of systolic and diastolic BP and the highest value obtained during the maneuver. For the diving test, the subjects were seated for 5 min and breathed without hyperventilating. They then bent forward so that their faces were 3 to 4 cm over a basin with water at 18°C. After a signal the patients lowered their faces until immerged in water up to the ears. They were instructed not to take a maximal inspiration or to perform a Valsalva maneuver. Facial immersion was continued for as long as tolerated. Before and during the test HR was monitored with an ECG. The results were expressed as the difference between resting HR (the average of five R-R intervals immediately preceding the test) and the maximum bradycardia during the maneuver. The test was performed three times, at 5-min intervals, and the complex with the lowest HR during apneic face immersion was accepted.

Statistics. Group means are presented with SEM as the index of dispersion. Mann-Whitney's Rank sum test and Wilcoxon's paired signed rank test were used to compare the differences in mean values. Due to the low number of patients, changes within the diabetic group were evaluated with the Student's t test, following a preliminary inspection of data by Bartlett's test to verify the homogeneity of the variances. Simple linear regression analysis was used for testing the relation between two variables.

Results

Out of dialysis

Nondiabetic CAPD patients versus controls. As shown in Table 1, the nondiabetic patients had mean values of supine MAP, HR, NA, and upright NA significantly higher than the matched-controls. On the contrary the percent increase of NA and the MAP changes on standing were similar in the two groups. The mean value of PRA was higher in the nondiabetic subjects than in the control patients, but the difference was not significant owing to a large overlap of individual values. The Valsalva ratio (Fig. 1) was significantly higher in the controls than in the uremic patients ($P < 0.01$). The mean drop in HR in response to the diving reflex, performed in eight patients, was also significantly higher in the controls than in the nondiabetic patients ($P < 0.01$). On the contrary, the average increase in systolic and diastolic BP in response to the cold pressor test was similar in the two groups.

Diabetic CAPD patients versus controls (Table 1). Mean values of supine MAP and HR in the diabetic patients were significantly higher than in the control subjects. The mean values of PRA and supine and upright NA were numerically higher, although not statistically significant, in the diabetic than in the control subjects. On standing, the diabetic patients showed a decrease in MAP despite the increase observed in the control subjects, with a percent increase of NA significantly lower in the former than in the latter group ($P < 0.05$). All the diabetic patients showed a pathological response to both the Valsalva maneuver and the diving reflex and the response of diastolic BP to the cold pressor test was also significantly different in the two groups ($P < 0.01$, Fig. 1).

Nondiabetic versus diabetic patients. The only significant differences found between the nondiabetic and the diabetic patients are shown in Fig. 2. On standing, MAP fell in the diabetics and increased in the nondiabetics, with a percent increase of NA significantly higher in the latter than in the former group ($P < 0.05$). Mean values differed significantly between the nondiabetic and the diabetic patients in the responses to the Valsalva maneuver and in the diastolic BP changes due to the cold pressor test. There was no relationship between MAP changes in the response to the postural test and

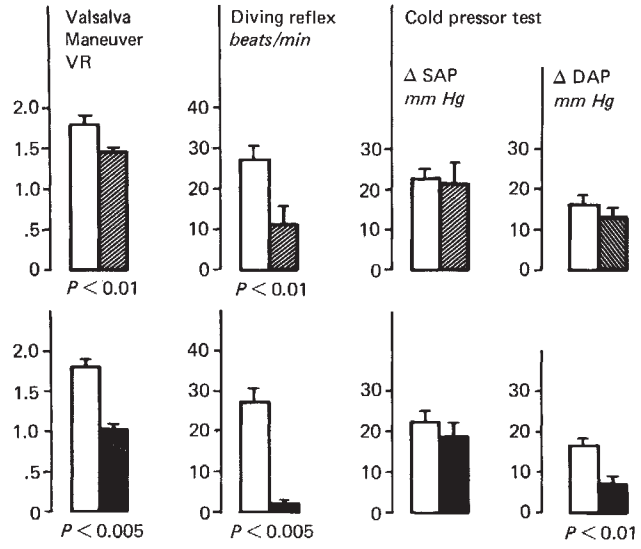

Fig. 1. *Comparison of responses* (upper panel) *to functional tests between controls* (open squares) *and nondiabetic CAPD patients* (shaded squares). Comparison of responses *(lower panel)* to functional tests between controls *(open squares)* and diabetic CAPD patients *(closed squares)* is shown. Data are the means ± SEM. Δ SAP and Δ DAP represent the changes induced by the cold pressor test in systolic and diastolic arterial pressure, respectively. VR represents the Valsalva ratio.

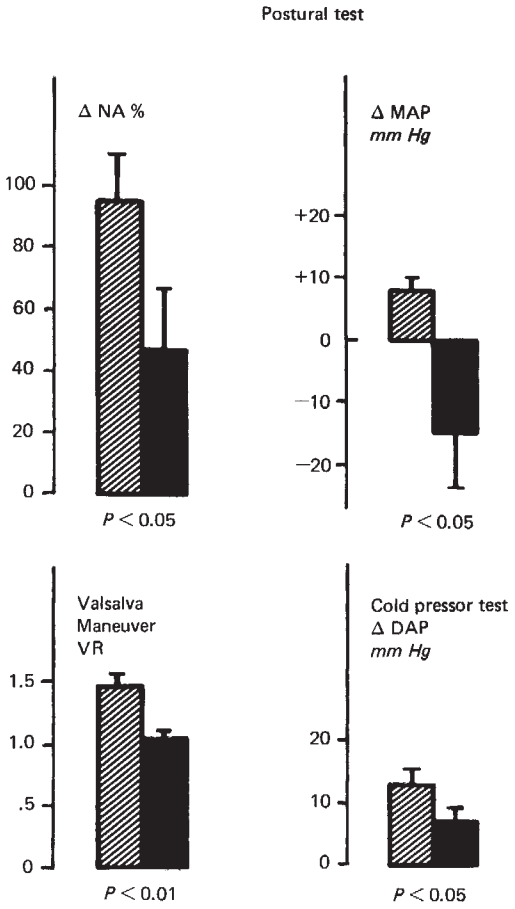

Fig. 2. *Comparison of responses to postural test* (upper panel), *Valsalva maneuver and cold pressor test* (lower panel) *in nondiabetic* (shaded squares) *and diabetic* (closed squares) *CAPD patients*. Data are the means ± SEM. Abbreviations and symbols: Δ NA%, percent increase of noradrenaline due to postural test; Δ MAP, changes in mean arterial pressure due to postural test; VR, Valsalva ratio; Δ DAP, changes in diastolic arterial pressure due to cold pressor test.

NaE, PRA, age, and duration of CAPD treatment, in either group.

On dialysis

Nondiabetic CAPD patients. As shown in Table 2, 3 hr of dialysis induced a significant increase in supine NA ($P < 0.05$) whereas it produced a statistically insignificant increase in supine HR and PRA. Moreover, no significant differences were found either in NA percent increment (from 95.6 ± 16.2 to 121.1 ± 44.8) and MAP changes (from 8.5 ± 2.5 to 7.6 ± 3.8) induced by the postural test, or in systolic (from 21.8 ± 4.6 to 19.5 ± 4.3 mm Hg) and diastolic BP changes (13.3 ± 2.7 to 10.9 ± 2.7 mm Hg) induced by the cold pressor test (Fig. 3). Dialysis did not induce a variation in the HR response to the Valsalva maneuver (from 1.45 ± 0.06 to 1.48 ± 0.08) or to the diving reflex (from −11.2 ± 4.5 to −8.6 ± 2.8 beats/min).

Diabetic CAPD patients (Table 2). In these patients supine MAP, HR, PRA, and NA were unmodified by dialysis. Three diabetic patients, who had had a drop in MAP in response to the postural test out of dialysis, showed a collapse in response to the postural and cold pressor tests during dialysis (Fig. 4). One of these patients had a subnormal NaE value. On the contrary the HR response to the Valsalva maneuver (1.08 ± 0.01 vs. 1.09 ± 0.02) and the diving reflex (−2.0 ± 0.7 vs. −3.7 ± 0.4 beats/min) was unmodified by dialysis. The volume of dialysate drained was similar in the diabetic and nondiabetic CAPD patients (2372 ± 96 vs. 2345 ± 112 ml, P = NS).

Discussion

The means of the supine to standing increments in noradrenaline and mean arterial pressure in our nondiabetic uremic patients were not significantly different from our control subjects. Furthermore, the response to the cold pressor test, which activates efferent sympathetic pathways [17], was similar in CAPD and control subjects. On the contrary, cardiovascular response to the Valsalva maneuver and the diving reflex was impaired in some of our nondiabetic uremic patients. Other authors [5, 6] have reported abnormalities in Valsalva ratio in uremic patients and concluded that their patients had impaired autonomic function. Nevertheless, an abnormal Valsalva maneuver may occur in subjects without abnormality of the sympathetic system [18] but with alteration of vagal heart control [19] and/or other diseases [20]. An alteration of parasympathetic function seems to be present in our patients because the responses to the diving reflex, an effective and simple test for evaluating vagal function [21, 22], were abnormal.

In summary, these data suggest a substantial integrity of the sympathetic nervous system in nondiabetic CAPD patients. Nevertheless, a parasympathetic dysfunction is present in some of these subjects in agreement with previous observations in hemodialysis patients [23, 24].

Abnormalities of adrenergic physiology were found to be significant in the subpopulation of diabetic CAPD patients. A

Table 2. Effect of 3 hr of dialysis on several parameters in ten nondiabetic and four diabetic CAPD patients[a]

	MAP supine *mm Hg*	HR supine *beats/min*	PRA supine *ng/ml/hr* A_I	NA supine *ng/liter*
Nondiabetic				
Out of dialysis	120 ± 7.1	73 ± 2.2	2.52 ± 1.55	380 ± 54
	P = NS	P = NS	P = NS	$P < 0.05$
On dialysis	117 ± 7.1	76 ± 2.3	3.34 ± 2.02	525 ± 80
Diabetic				
Out of dialysis	111 ± 8.1	87 ± 7.0	0.79 ± 0.45	337 ± 132
	P = NS	P = NS	P = NS	P = NS
On dialysis	117 ± 10.3	92 ± 3.3	0.70 ± 0.39	398 ± 180

Abbreviations: MAP, mean arterial pressure; HR, heart rate; PRA, plasma renin activity; NA, noradrenaline; A_I, angiotensin I.
[a] Data are expressed as means ± SEM.

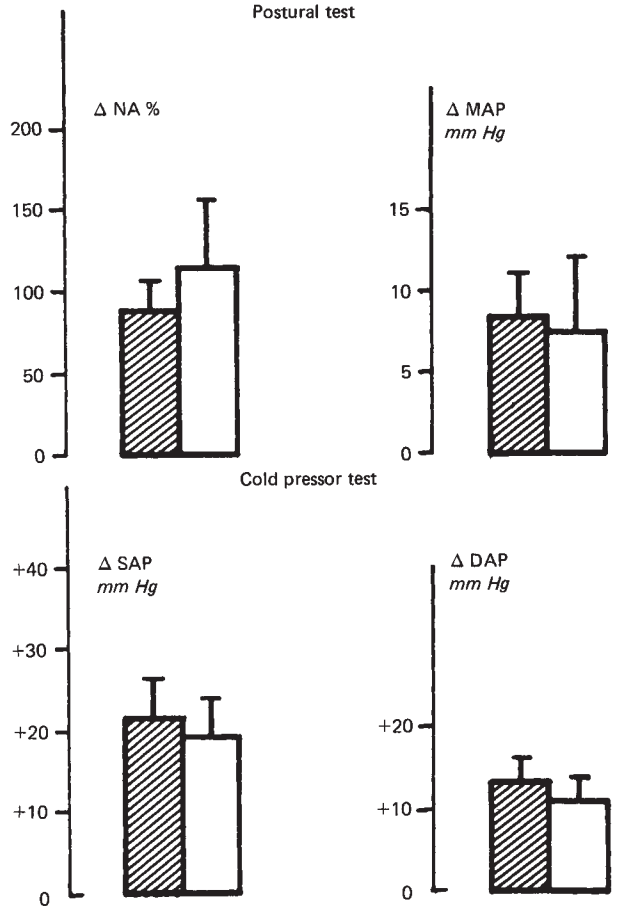

Fig. 3. *Comparison between responses of nondiabetic patients to functional tests performed both out of* (shaded squares) *and during* (open squares) *dialysis.* Data are presented as means ± SEM. Abbreviations and symbols: Δ NA%, percent increment in noradrenaline due to postural test; Δ MAP, changes in mean arterial pressure due to postural test; Δ SAP, changes in systolic arterial pressure due to cold pressor test; Δ DAP, changes in diastolic arterial pressure due to cold pressor test.

blunted noradrenaline response to standing and a decrease of mean arterial pressure in response to the postural test were consistent with the presence of subclinical adrenergic neuropathy in these patients. Moreover, a parasympathetic impairment was present in all our diabetic CAPD patients as proved by the abnormal response of heart rate to the diving reflex. Functional abnormalities of the autonomic nervous system in long-term diabetes are well known [10–12], and it seems reasonable to conclude that sympathetic dysfunction in our diabetic CAPD patients was due to diabetes rather than to uremia.

Peritoneal dialysis did not seem to affect sympathetic function in nondiabetic CAPD patients. In fact the response to functional tests performed either before and during dialysis were similar in these patients. However, supine noradrenaline was significantly higher during dialysis. This increased peripheral noradrenaline during CAPD may reflect a higher sympathetic drive required to stabilize constant systemic arterial pressure in the face of a decrease in cardiac output. In fact other authors [25, 26] have reported a reduction in venous return with a decrease in stroke volume and cardiac output during peritoneal dialysis. Either an increase in inferior vena caval pressure due to increased abdominal pressure [25] or a plasma volume contraction due to fluid loss induced by peritoneal dialysis [26] have been implicated in these hemodynamic changes. The observation that the sympathetic system of these patients is able to maintain a stable arterial pressure level on standing despite the decrease in cardiac output due to both the dialysis and the upright posture, by greater increases in sympathetic activity, is consistent with the integrity of this system.

Three out of the four diabetic patients had a collapse when the postural and cold pressor tests were performed during dialysis. We believe that the impaired adrenergic system of these patients was incapable of producing the maximum effort required by the double stimulus of dialysis and postural or cold pressor tests and showed the paradoxical response as described by Lovallo and Zeiner [27].

Moreover, chronic dehydration may have been a concomitant factor in the collapse of the diabetic patient with low NaE.

In conclusion, there is no evidence that sympathetic failure affects circulatory reflexes in nondiabetic CAPD patients. In diabetic patients a slight dysfunction is found. Peritoneal dialysis does not produce a functional lesion of the sympathetic nervous system in nondiabetic patients, but it could be a concomitant factor in intradialytic hypotension of diabetic patients.

Summary. Several authors have found postural hypotension in patients on CAPD. Autonomic system dysfunction could be a cause of postural hypotension. To verify the hypothesis that

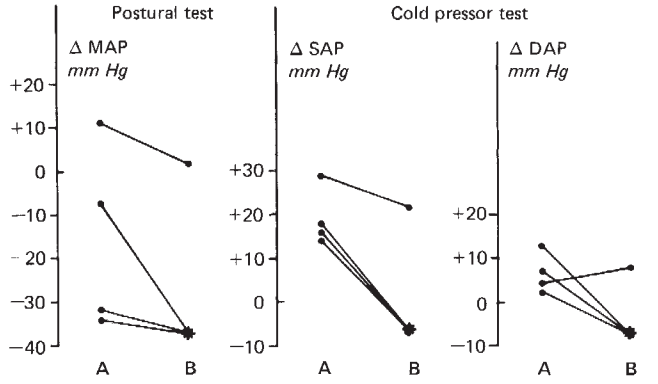

Fig. 4. *Individual values in diabetic CAPD patients of mean arterial pressure changes* (Δ MAP) *induced by postural test and systolic and diastolic arterial pressure changes* (Δ SAP/Δ DAP) *induced by cold pressor test, performed both out of dialysis* (**A**) *and during dialysis* (**B**). *Asterisk* refers to collapse.

CAPD could interfere with sympathetic activity, we studied 14 uremic patients on CAPD. In all the patients plasma noradrenaline in the recumbent and upright positions was measured and the Valsalva maneuver, diving reflex, and cold pressor test were performed. This protocol was carried out both during dialysis and after interruption of CAPD for 2 days. Out of dialysis, the nondiabetic patients showed a substantial integrity of sympathetic function. A blunted noradrenaline response to standing and a decrease of arterial pressure in response to the postural test were present in the diabetic patients. The dialysis did not affect either the responses to functional tests or the humoral parameters evaluated in the nondiabetic patients, while three out of the four diabetic patients had a collapse during the postural and cold pressor tests. These results seem to indicate that a sympathetic dysfunction is present only in diabetic patients. Peritoneal dialysis does not alter sympathetic function in nondiabetic patients but could be a concomitant factor in intradialytic hypotension of diabetic patients.

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