Adrenal Function in Patients With Chronic Renal Failure

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• **Previous studies have reported divergent findings on the function of the hypothalamic-pituitary-adrenal axis in patients with chronic renal failure (CRF). The low-dose adrenocorticotropin (ACTH) test offers the possibility of unmasking adrenal dysfunction, which might remain undiscovered using the ACTH test with the standard 250-μg dose. Furthermore, the choice of renal replacement therapy (either hemodialysis or continuous ambulatory peritoneal dialysis [CAPD]) might have an impact on adrenal function. To investigate these possibilities, ACTH tests were performed with three different doses (ie, 1, 5, and 250 μg) in 14 CRF patients and in seven healthy controls. Seven of the CRF patients were receiving chronic hemodialysis and seven were receiving CAPD. Basal plasma concentrations of cortisol were comparable in the three groups tested (5.3 ± 0.4 μg/dL in the controls, 6.6 ± 0.7 μg/dL in the hemodialysis patients, and 7.9 ± 1.0 μg/dL in the CAPD patients), whereas basal ACTH concentrations were significantly elevated in the CRF patients (28.5 ± 3.8 pg/mL in the hemodialysis patients and 33.0 ± 6.0 pg/mL in the CAPD patients) when compared with normal controls (17.0 ± 1.4 pg/mL; $P < 0.05$). All three doses of ACTH resulted in a rapid increase of plasma cortisol concentrations that was comparable in all three groups. In the hemodialysis patients, a trend toward a diminished response to the lowest dose of 1 μg was noticed. We conclude, therefore, that adrenal response to ACTH in various doses is unaffected in CRF independent of whether hemodialysis or CAPD is chosen for renal replacement therapy.**

INDEX WORDS: Adrenal function; adrenocorticotropin test; hemodialysis; CAPD.

SEVERAL alterations of hypothalamic-pituitary-adrenal (HPA) axis function have been described in patients with chronic renal failure (CRF). However, many studies have reported normal findings. Basal plasma cortisol concentrations have been found to be normal or elevated, but the diurnal variation was always preserved.[1-5] Dexamethasone suppression of plasma cortisol concentration was normal in some[6] and blunted in other studies,[2,4,7] and a shortened half-life (t/2) and increased metabolic clearance rate of dexamethasone have been reported.[8] A uniform finding was the normal cortisol response to exogenously administered adrenocorticotropin (ACTH) in the standard dose of 250 μg.[1,4,6]

In a previous investigation using corticotropin-releasing hormone (CRH) stimulation of pituitary ACTH and adrenal cortisol release in patients with CRF on chronic hemodialysis (CHD), we speculated that some mild impairment of adrenal function might exist since normal plasma cortisol concentrations were achieved only in the event of significantly elevated plasma ACTH concentrations.[9] In addition, Ramirez et al[10] found elevated ACTH concentrations in hemodialysis patients with a prolonged cortisol response to CRH-stimulated ACTH release. In contrast, Siamopoulos et al[11] described a blunted ACTH response to CRH in hemodialysis patients but a normal response in continuous ambulatory peritoneal dialysis (CAPD) patients.[11]

The establishment of the low-dose ACTH stimulation test[12,13] offered the possibility of testing the hypothesis that subtle alterations of the pituitary-adrenal axis in CRF patients might be unmasked by use of lower and thus more physiologic ACTH concentrations. In addition, the influence of the modality of renal replacement therapy (ie, CHD or CAPD) on the HPA axis was evaluated. For this purpose, adrenal function was tested in 14 patients with end-stage renal failure (seven patients receiving CHD and seven patients receiving CAPD) using the ACTH test with the standard 250-μg dose as well as low doses of 5 μg and 1 μg, and the results were compared with those in healthy controls.

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Received May 23, 1997; accepted in revised form February 6, 1998.

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0272-6386/98/3201-0006$3.00/0

PATIENTS AND METHODS

The ACTH test was performed in seven CHD patients, seven CAPD patients, and seven age- and weight-matched healthy controls (Table 1) at all three doses (1 μg, 5 μg, and 250 μg) in a randomized order. A minimum 1-week interval was required between the tests. Informed consent was obtained from all patients. The protocol was approved by the Human Ethics Committee of the University of Vienna. The tests were performed in males only. For the benefit of a quiescent HPA axis, all tests were performed at 5 PM and all subjects had fasted at least 4 hours. In the hemodialysis patients, the tests were performed before starting hemodialysis, ie, 2 days after the last hemodialysis. Patients had received renal replacement therapy for 3 to 180 months. Patients who had undergone renal transplantation, who had received glucocorticoids as immunosuppressive therapy, or who had diabetes mellitus were excluded from the study. The underlying diseases were chronic glomerulonephritis in two patients; membranoproliferative glomerulonephritis, nephrectomy, and polycystic kidney disease each in one patient; and small kidneys of unknown etiology in the remaining patients. Therapy included multivitamin preparations, iron and erythropoietin, antihypertensive drugs, diuretics, lipid-lowering agents, acetylsalicylic acid, phosphate binders, H_2 antagonists, and proton pump inhibitors.

Doses of 1 μg, 5 μg, or 250 μg ACTH (Synachten, Ciba-Geigy, Vienna, Austria) were injected as an intravenous bolus and blood samples for determination of cortisol were drawn at −15, 0, 15, 30, 60, 90, and 120 minutes. Cortisol was measured as described previously.[14] Blood samples for determination of basal ACTH concentrations were drawn at −15 and 0 minutes; the samples were placed in prechilled EDTA tubes, immediately centrifuged, and stored at −20°C until assayed by a commercially available radioimmunoassay (Nichols Institute, San Juan Capistrano, CA).

Statistical Analysis

Data are expressed as mean values ± SEM. Statistical evaluation was completed using one-way ANOVA for comparison of delta max (peak concentration − basal concentration) between the three groups and the three doses. Student's *t*-tests with the Bonferroni correction were performed for comparison of the basal values. $P < 0.05$ was considered significant.

Table 1. Patient Characteristics

	Controls (n = 7)	CHD Patients (n = 7)	CAPD Patients (n = 7)
Age (yr)	39.6 ± 4.2	49.0 ± 6.2	43.5 ± 4.8
Body mass index	25.3 ± 2.0	23.9 ± 1.4	24.2 ± 1.9
Basal ACTH concentration (pg/mL)	17.0 ± 1.4	28.5 ± 3.8*	33.0 ± 6.0*
Basal cortisol concentration (μg/dL)	5.3 ± 0.4	6.6 ± 0.7	7.9 ± 1.0

NOTE. Data are given as mean values ± SEM.
*$P < 0.05$.

RESULTS

Basal plasma cortisol concentrations were comparable in the three groups tested (5.3 ± 0.4 μg/dL in the controls, 6.6 ± 0.7 μg/dL in the hemodialysis patients, and 7.9 ± 1.0 μg/dL in the CAPD patients). In contrast, basal plasma ACTH concentrations were significantly elevated in the CRF patients compared with the healthy controls (17.0 ± 1.4 pg/mL in the controls, 28.5 ± 3.8 pg/mL in the hemodialysis patients [$P < 0.05$], and 33.0 ± 6.0 in the CAPD patients [$P < 0.05$]).

The administration of 1 μg, 5 μg, and 250 μg resulted in a prompt increase of serum cortisol concentrations in all subjects (Fig 1). Peak levels were reached in all three groups tested by 30 minutes after 1 μg ACTH, by 60 minutes after 5 μg ACTH, and by 120 minutes after 250 μg ACTH. Adrenal responses to exogenously administered ACTH (expressed as delta max = peak concentration − basal concentration) were comparable in the three different groups. A trend toward a diminished cortisol release to 1 μg ACTH was observed in the hemodialysis patients (Fig 2).

DISCUSSION

Assessment of adrenal function has been performed for years by intravenous administration of a standard dose of 250 μg ACTH and measurement of plasma cortisol concentrations at 30 and/or 60 minutes.[15,16] The criteria for intact adrenal function included the attainment of a plasma cortisol concentration of more than 18 μg/dL or 20 μg/dL, or an increment of at least 7 μg/dL above the basal value. While the suggestion of using lower ACTH doses than the clearly supramaximal dose of 250 μg was made more than a decade ago,[17,18] it has only recently been shown that adrenal dysfunction can be detected with low doses of ACTH in cases in which the standard dose revealed normal adrenal function.[12,13,19] The clinical relevance of this finding is considerable and applicable to the large number of patients receiving glucocorticoids either topically (mainly an inhalant for asthma),[20] systemically for autoimmune diseases, or after cranial or pituitary surgery.[21]

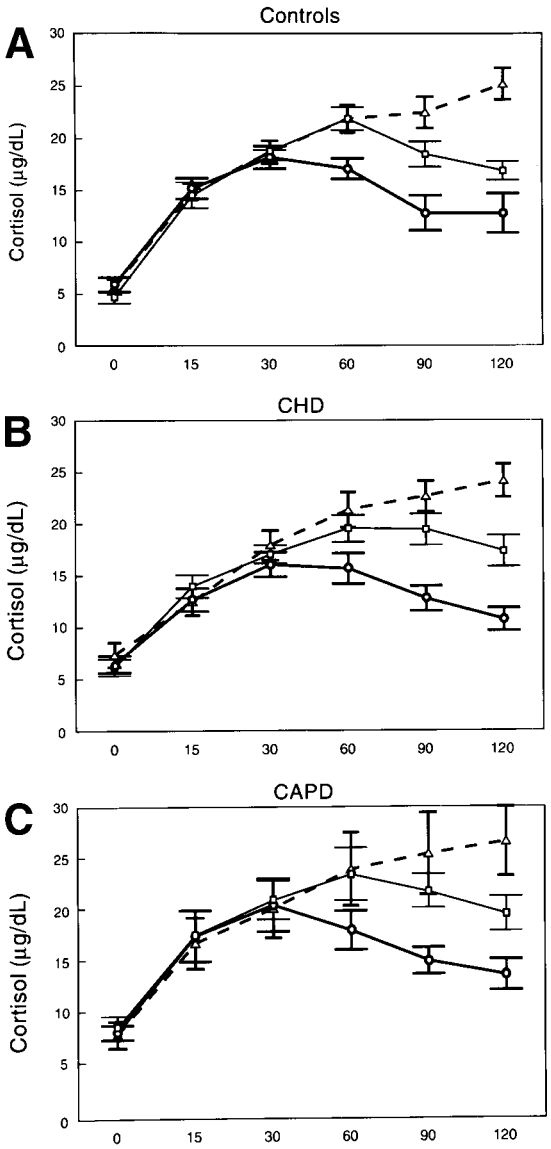

Fig 1. Mean plasma cortisol concentrations in response to 1 µg ACTH (heavy solid line; open circles), 5 µg ACTH (light solid line; open squares), and 250 µg ACTH (broken line; open triangles) in control subjects (A), in patients receiving CHD (B), and in patients receiving CAPD (C).

To enhance the chance of detecting subtle adrenal dysfunction in CRF patients, we therefore optimized the investigative setting by using low ACTH doses and comparing them with the test in the standard dose. In addition, testing at a time of relatively low adrenal activity (ie, in the late afternoon) further increases the chance of uncovering subtle differences in adrenal function since similar peak cortisol concentrations are obtained in the morning and afternoon. Thus, due to the lower basal afternoon concentrations, the hormonal response or cortisol increment is greater in the afternoon. Furthermore, tests were performed only in males to avoid interference of alterations due to the menstrual cycle. Nevertheless, comparable adrenal responses to all three ACTH doses in CRF patients and normal controls were observed. It is interesting to note, however, that although basal cortisol concentrations were comparable in the three groups tested, plasma ACTH concentrations were elevated in CRF patients irrespective of the modality of treatment of the end-stage renal disease.

It is surprising that neither changes of cortisol metabolism due to renal insufficiency, the effects of uremic toxins on the HPA axis, nor the modality of renal replacement therapy alters cortisol response to ACTH in patients with end-stage renal failure. Thus, in general, glucocorticoid replacement therapy in CRF patients does not appear to be necessary under everyday circumstances and only a minority of patients might benefit from glucocorticoids in stressful situations, such as major surgery. It should be emphasized, however, that patients with a history of kidney transplantation or glucocorticoid therapy in immunosuppressive doses were excluded from the study. Nevertheless, a trend to impaired adrenal function was observed at the lowest ACTH dose, which can be expected to produce ACTH concentrations comparable to those achieved in physiologic or pathophysiologic stress condi-

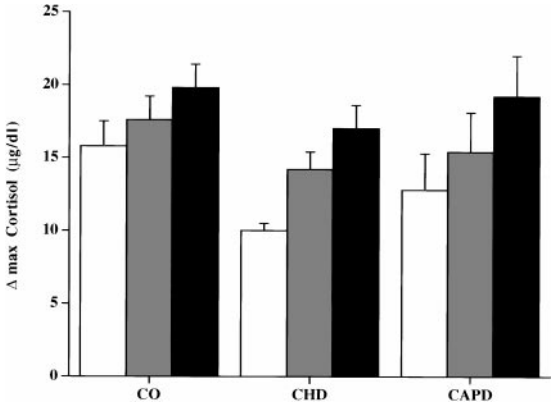

Fig 2. Mean cortisol responses expressed as delta max to 1 µg ACTH (open bars), 5 µg ACTH (shaded bars), and 250 µg ACTH (solid bars) in healthy control subjects (CO), in patients receiving CHD, and in patients receiving CAPD.

tions. Thus, the possibility of adrenal insufficiency in severe stress should be considered in CRF patients performing worse than expected.

In summary, the low-dose ACTH test elicited a normal adrenal response in a well-selected group of patients with CRF who were receiving hemodialysis or CAPD. This finding suggests that neither renal insufficiency itself nor the modality of renal replacement therapy has a major implication on adrenal function.

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