

## Plasma aldosterone concentrations in chronic renal disease

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**Plasma aldosterone concentrations in chronic renal disease.** The disagreement in the literature concerning the role of aldosterone in the maintenance of potassium homeostasis in chronic renal disease might be partially explained by differences in plasma renin activity (PRA) among individual patients. Therefore, a study was done in 28 selected patients with varying degrees of renal insufficiency whose serum potassium and PRA concentrations were within the normal range. The results indicate that at comparable serum potassium and PRA concentrations, plasma aldosterone is in most instances elevated when creatinine clearance is lower than 50% of normal.

**Concentrations plasmatiques d'aldostérone au cours de l'insuffisance rénale chronique.** Les désaccords de la littérature au sujet du rôle de l'aldostérone dans le maintien de l'homéostasie du potassium dans l'insuffisance rénale chronique peuvent être partiellement expliqués par les différences entre individus en ce qui concerne l'activité rénine plasmatique (PRA). Par conséquent une étude a été réalisée chez 28 malades sélectionnés ayant des degrés divers d'insuffisance rénale et dont les concentrations de potassium sérique et les niveaux de PRA étaient dans l'éventail des valeurs normales. Les résultats indiquent que, à concentration de potassium sérique et PRA semblables, l'aldostérone plasmatique est dans la plupart des cas élevée quand la clairance de la créatinine est inférieure à 50% des valeurs normales.

Despite progressive loss of functioning nephrons, patients with chronic renal insufficiency usually show a serum potassium concentration that is within normal limits, even up to a far-advanced stage of illness. When function decreases, the kidneys continue to excrete the same amount of potassium, because the kidney is able to elevate the fractional excretion. If it is true that all of the filtered potassium is reabsorbed in the proximal tubule, then the increased excretion must be the result of increased tubular secretion [1]. Only in far-advanced renal insufficiency does increased potassium excretion by the gut contribute appreciably to total potassium homeostasis [2, 3]. Experimental work in rats has suggested that aldosterone is not the most important factor in this adaptive process of the kidney, although the presence of aldosterone is essential in the rat, as well as in man [4]. In chronic renal disease, normal aldosterone excretion and plasma concentrations have been reported, which supports the conclusion that there is "no evidence that increased aldosterone secretion is part of the adaption required to maintain potassium homeostasis" [4, 5]. In a recent study [6],

markedly increased plasma aldosterone concentrations were found, but only in patients with creatinine clearances below 12 ml/min. Because aldosterone secretion is also under the regulatory influence of the sodium balance via the renin-angiotensin system, abnormalities can only be detected if this factor is also taken into account. The present study shows that, when potassium intake and plasma renin activity are within the normal range, plasma aldosterone concentrations are increased in proportion to the degree of renal failure.

### Methods

Twenty-eight patients were selected from a group of 39 with various degrees of renal failure on the basis of normal serum potassium (4.0 to 5.0 mmoles/liter) and plasma renin activity (PRA) (200 to 700 fmoles/liter/sec). The patients did not use any medication except sodium bicarbonate, aluminum hydroxide, calcium carbonate, and vitamin D supplements. The diagnoses are listed in Table 1. The patients were assigned to three groups according to the degree of renal failure; that is, group 2 had creatinine clearances between 21 and 70 ml/min; group 3, between 11 and 20 ml/min; and group 4, between 3 and 10 ml/min. Twenty-two healthy volunteers serving as controls (group 1) were kept on normal diet. Blood samples were collected at 9 A.M. after the subjects had been in the upright position for at least half an hour. Twenty-four-hour urine for analysis was collected during the day before investigation. Potassium and sodium were measured by flame photometry. Renal function was assessed by calculating the 24-hour creatinine clearance. PRA (fmoles/liter/sec) was determined radioimmunologically according to a modification of the method described by Haber (incubation of undiluted plasma for 1 hr at 37° C and at a pH of 5.6, followed by deproteinization of the plasma with 4 N ammonia/acetone (1:9) [7]. After 2.0 ml of plasma was extracted with dichloromethane and purified on Sephadex LH 20 columns (1.0 × 50 cm), plasma aldosterone (PALDO, pmoles/liter) was assayed by radioimmunoassay with the radioassay buffer as the mobile phase, as described by Nowaczynski et al [8].

For statistical evaluation, analysis of variance and Student's *t* test were used. For correlations, Spearman's ranking test was used.

### Results

The mean values for the four groups are listed in Table 2. There were no differences in serum potassium concentrations. The urine potassium excretion was slightly higher in the controls than it was in the patients, due to the difference in diet.

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**Table 1.** Diagnosis in the three groups of patients with renal failure

Diagnosis	Group 2	Group 3	Group 4	Total
Polycystic disease	4	2	3	9
Interstitial nephritis	3	3	4	10
Medullary cystic disease				1
Glomerulonephritis	7	3	4	8
<i>Total</i>	14	8	11	28

Urinary potassium was lower in group 4 than it was in groups 2 and 3. This difference may at least partly be due to an increased potassium excretion by the gut and probably also reflects a lower potassium intake. Sodium excretion was slightly lower in group 4. Mean PRA was somewhat low in groups 3 and 4, but within the limits set by the range of our normal control group. Mean PALDO was higher than normal in all patients with decreased renal function and strikingly elevated in group 4, even in the presence of a slightly reduced urinary potassium load. Statistical differences ( $P < 0.01$ ) were found between both the log PALDO values and the log PALDO/log PRA ratio for group 1 vs. groups 2, 3, and 4, group 2 vs. 4, and group 3 vs. 4. Only the values of groups 2 and 3 did not differ significantly. Figure 1 gives the individual values for log PALDO/log PRA, plotted against the creatinine clearance, illustrating that below creatinine clearances of 50 ml/min log PALDO/log PRA is elevated in most instances proportionally to the degree of renal failure ( $r = 0.54$ ,  $P < 0.007$ ). Figure 1 also shows that not all patients with severe renal insufficiency had an elevated PALDO. The two patients in group 4 with the lowest log PALDO/log PRA ratio both suffered from glomerulonephritis, but the other patients with this disease had elevated values.

### Discussion

The role of aldosterone in patients with renal insufficiency was formerly assessed from the aldosterone secretion or excretion rate. Urine aldosterone determinations may have some value in patients with moderate renal insufficiency [1], but when aldosterone clearance is depressed in severe renal failure these methods will not reflect circulating plasma concentrations [6, 10]. Plasma concentrations are therefore indispensable if the role of aldosterone is to be evaluated.

Because aldosterone secretion is strongly influenced by PRA, the role of aldosterone can only be evaluated properly if this factor is taken into account. Weidmann et al [11] reported normal values for PRA and PALDO in patients with creatinine clearances ranging from 9.5 to 55.8 ml/min and a normal serum potassium concentration. Closer inspection of their data shows, however, that PRA was low normal and PALDO was in the high normal range, which means that the PALDO/PRA ratio was elevated. Berl et al [6] found a high PALDO in patients with creatinine clearances below 11 ml/min and normal serum potassium. Their series comprises only two patients within the moderately impaired range (creatinine clearance, 25 and 33 ml/min) who had a normal PALDO. Reubi, Weidmann, and Glück [12] recently reported an inverse relationship between PALDO and the GFR, but their group of patients showed a wide range of PRA values.

Most patients in our study, who were selected on the basis of normal PRA and serum potassium concentrations, had increased PALDO concentrations, even in half of group 2 whose

renal function was only moderately decreased. More severe degrees of renal failure were accompanied by a progressive rise in PALDO and log PALDO/log PRA ratio (Fig. 1). That this phenomenon has not been observed previously, except in patients with far advanced renal disease, is explained by the interference of PRA levels.

Because we found an elevated plasma aldosterone concentration in patients with renal insufficiency whose PRA and serum potassium were normal, it seems likely that aldosterone is involved in the maintenance of a normal serum potassium level by increased fractional excretion. Although low aldosterone concentrations do not usually lead to hyperkalemia in subjects with normal renal function, the necessity for the presence of this hormone in chronic renal failure in man is illustrated by the well-documented syndrome of hyporeninemic hypoaldosteronism [1, 13].

The role of aldosterone in the adaptation of potassium metabolism in renal insufficiency is still not clear, however. In the adrenalectomized rat this adaptive process remains intact, only if a physiologic amount of aldosterone is provided [4]. Among patients with renal disease, at least four different patterns may be found: patients with normal serum potassium, with and without increased PALDO, patients in whom both serum potassium and PALDO are elevated, and patients without increased PALDO despite elevated serum potassium. As illustrated in Fig. 1, two of our patients with severe renal failure and normal PRA and serum potassium did not show an elevated PALDO. On the other hand, some patients with advanced renal failure may show an inability of the kidney to increase the potassium excretion, despite adequate levels of endogenous or exogenous mineralocorticoids [14, 15]. We observed a hyperkalemic patient with normal PRA (440 fmoles/liter/sec) and a very high PALDO level (6000 pmoles/liter), in whom infusion of aldosterone had no additional effect on potassium excretion (unpublished observation). Thus, in our group of patients with renal failure and normal serum potassium, PALDO tended to be elevated, although exceptions were noticed.

An explanation of these differences may be the renal tubular function in relation to the decrease of GFR. The more the tubular function is affected, the higher PALDO may be required to make the tubule excrete the desired amount of potassium. Because 21 of the 28 patients in the present study suffered from tubulointerstitial diseases, the results may not be applicable to all types of chronic renal disease, although the 7 patients with glomerulonephritis as a group could not be clearly distinguished from the rest.

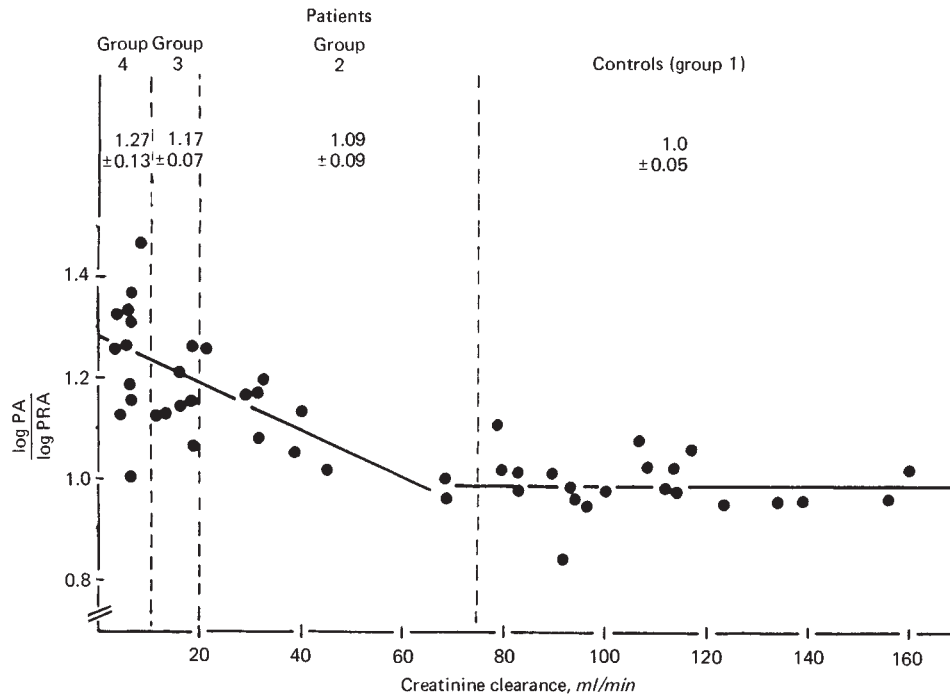
It is not clear how a decreased renal function induces increased PALDO levels. Because more than 80% of aldosterone is metabolized in the liver, renal function does not influence PALDO by way of the metabolic clearance rate. In acute potassium-loading experiments in normal subjects, a serum potassium and PALDO elevation have been found [17]. In chronic-loading studies, PALDO elevations have only been found when dietary potassium was increased to at least 200 mmoles/day [18]. In this latter study, marked increases in renal potassium excretion were present with no detectable change in plasma potassium. It is therefore not unexpected that in slowly progressive renal failure adaptation takes place without detectable changes in plasma potassium levels.

**Conclusion.** In our group of patients with renal failure

**Table 2.** Biochemical data of the controls (group 1) and the patients with renal failure (groups 2-4)<sup>a</sup>

Group	N	Male	Female	Age	CCR ml/min	Serum K mEq/liter	Urinary K		Urinary Na		Log PRA	Log PALDO	Log PA/ Log PRA
							mEq/24 hr		mEq/24 hr				
1	22	15	7	29 ± 8	78-160	4.3 (3.9-4.9)	80 ± 26	166 ± 47	2.70 ± 0.15	(2.32-2.88)	2.67 ± 0.21	1.00 ± 0.05	
2	9	5	4	38 ± 8	21-70	4.3 (4.0-4.8)	58 ± 20	101 ± 53	2.70 ± 0.10	(2.56-2.88)	2.95 ± 0.22	1.09 ± 0.09	
3	8	6	2	40 ± 11	11-20	4.3 (4.0-4.8)	51 ± 17	139 ± 51	2.55 ± 0.18	(2.30-2.69)	3.01 ± 0.27	1.17 ± 0.07	
4	11	6	5	41 ± 14	3-10	4.4 (3.9-4.9)	32 ± 16	95 ± 54	2.60 ± 0.04	(2.38-2.85)	3.32 ± 0.37	1.27 ± 0.13	

<sup>a</sup> Values with ± sign are means ± SEM. Parentheses contain the range. PRA was measured in fmoles/liter/sec; and PALDO, in pmoles/liter in upright position.



**Fig. 1.** Relation between  $\log \text{PALDO}/\log \text{PRA}$  and creatinine clearance. For the patient group,  $r = 0.54$  ( $P < 0.007$ ).

predominantly but not exclusively due to interstitial diseases, but with normal serum potassium and normal PRA, an elevated plasma aldosterone concentration is found, not only in severe, but also in moderate renal failure.

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