Renin-Angiotensin-Aldosterone System in Primary Hyperparathyroidism Before and After Surgery

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Twenty consecutive unselected patients with proven primary hyperparathyroidism (PH), 26 essential hypertensive (EH) patients, and 13 normotensives were studied. Blood pressure (BP) and, under constant salt intake, plasma renin activity (PRA), parathyroid hormone (PTH), urinary and plasma sodium, potassium, aldosterone (ALD), creatinine, total calcium, and phosphate were measured. Patients with PH were also studied 1 and 6 months after successful surgery. In patients with PH, systolic and diastolic BP was significantly lower ($P < .001$) than in EH patients and higher ($P < .005$) than in controls. Eight patients with PH (40%) had BP levels greater than 140/90 mm Hg. PTH and plasma and urinary calcium in patients with PH were significantly ($P < .01$) higher than in controls, while PRA, ALD, phosphate, potassium, and sodium were superimposable in the three groups. PTH in patients with PH was weakly correlated with PRA (positively) and with plasma potassium (negatively) and was not associated with ALD, calcium, sodium, and BP levels. Surgery was followed by a significant reduction ($P < .01$) in PTH, calcium, and urinary phosphate and an increase ($P < .02$) in plasma phosphate, potassium, and sodium, whereas PRA, ALD, urinary potassium and sodium, and BP showed no change. In hypertensive patients with PH, PTH, PRA, and plasma and urinary ALD, calcium, and sodium did not differ from the values in normotensive PH patients, and variations in these humoral parameters after surgery were comparable in the two groups. In conclusion, our results show that hypertension is frequently associated with PH. However, the present data raise doubts about the assumption of a renin-mediated causal relationship between hyperparathyroidism and high BP. Indeed, as a unique finding in favor of the hypothesis of a stimulating role of PTH in renin secretion, we observed only a weak relation between PTH and PRA. Thus, unknown and/or unassessed factors related to parathyroid disease cannot be ruled out to explain the hypertension observed in some patients with PH.

IN VITRO STUDIES[1-3] show that parathyroid hormone 1-34 (PTH 1-34) exerts a direct stimulating effect on renin secretion, probably through inhibition of calcium influx. Similarly, in animals[4,5] and in humans[6,7] acute PTH (1-34) infusion significantly increases plasma renin activity (PRA) without affecting blood pressure (BP) and plasma calcium. In contrast, chronic continuous PTH infusion results in hypertension and an increase in plasma calcium in normal subjects.[8] In primary hyperparathyroidism (PH), a condition of chronic abnormal PTH secretion, the relationship between PTH and the renin-angiotensin-aldosterone (RAA) system has been a matter of debate in the past and is still an unsolved point. Some investigators have reported RAA system activation in hypertensive patients with PH, which is reversible after surgery,[7,9,10] while others have found no alteration of the RAA system in patients with PH, whether normotensive or hypertensive.[11-13]

For this reason, we conducted a prospective study in 20 unselected patients with PH by evaluating RAA system function during constant sodium intake before and after surgery.

SUBJECTS AND METHODS

Subjects

Twenty consecutive unselected untreated patients with PH were studied. Oral contraceptive use and hormone replacement therapy also constituted exclusion criteria. The diagnosis of PH was made on the basis of elevated serum total and 24-hour urine calcium and high intact PTH (1-84) levels confirmed by histological examination and by normalization of plasma calcium and PTH after surgery. Thirteen normal subjects and 26 untreated essential hypertensive (EH) patients were also included as controls. The study was approved by the local ethics committee, and all patients provided informed consent to the experimental design.

Experimental Protocol

The patients (all outpatients) were requested to follow a normocaloric diet with constant sodium (80 to 100 mmol/d) and potassium (60 to 80 mmol/d) intake for 2 weeks before the study. They also discontinued all medications for at least 15 days prior to the study, especially antihypertensive, to avoid any ongoing effect on BP and/or an influence on the RAA system. The experiment involved measurement of BP in the morning in fasted patients who had been seated for at least 15 minutes in a quiet room. BP was recorded by a mercury sphygmomanometer using the guidelines of the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.[14] An indwelling cannula was then inserted (between 7:30 and 8:30 AM) into a forearm vein; after 30 minutes, blood samples were taken for measurement of PTH, total calcium, phosphate, creatinine, PRA, aldosterone (ALD), cortisol, sodium, and potassium. Twenty-four-hour urine collection was performed for calcium, phosphate, creatinine, ALD, sodium, and potassium evaluation. This protocol was repeated 1 and 6 months after surgery.

Hormone Assays

Intact PTH (1-84), PRA, ALD, and cortisol levels were measured by specific radioimmunoassays (PTH, Nichols Institute Diagnostics, San Juan Capistrano, CA; PRA and ALD, Sorin Biomedica, Italy; cortisol, Radim, Rome, Italy).

Statistical Analysis

The results are expressed as the mean ± SEM. Statistical analysis was performed using Student's paired and unpaired t tests. Linear regression analysis was used to determine the relation between variables. A P level .05 indicated statistical significance.

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Table 1. Clinical Data for Patients With PH or EH and Controls

Variable	Patients		Controls
	PH	EH	
No. of subjects	20	26	13
Age, yr (range)	60.8 (38-74)	58.8 (27-71)	56.3 (44-73)
Sex	17F	23F	11F
Creatinine clearance (mL/min)	87.0 ± 4.2	89.8 ± 4.0	92.2 ± 4.0
Systolic BP (mm Hg)	136.6 ± 3.3	155.9 ± 3.1†	121.6 ± 3.9*
Diastolic BP (mm Hg)	84.4 ± 2.2	97.7 ± 1.6†	78.3 ± 2.1

Abbreviation: F, female.
*$P < .005$ *v* PH.
†$P < .001$ *v* PH.

RESULTS

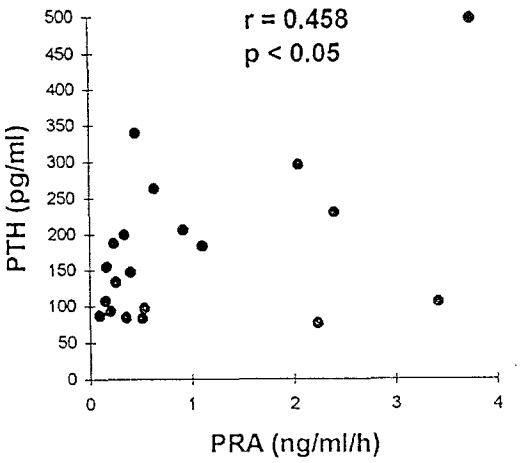
Patients with PH did not significantly differ from EH patients and controls in age, sex, and renal function. Systolic and diastolic BP in PH patients was significantly lower than in EH patients and higher than in controls (Table 1). Eight of 20 patients with PH (40%) had a BP greater than 140/90 mm Hg, which was significantly higher than in normotensive patients with PH (systolic BP, 151.5 ± 3.0 *v* 126.6 ± 2.3 mm Hg, $P < .0001$; diastolic BP, 92.2 ± 3.3 *v* 79.1 ± 1.6 mm Hg, $P < .001$).

PTH and plasma and urinary calcium in patients with PH were significantly higher than in controls, while PRA, ALD, phosphate, potassium, and sodium were superimposable in the three groups (Table 2).

Before surgery, PTH levels in PH patients correlated positively with PRA and negatively with plasma potassium (Fig 1) and were not associated with plasma or urinary ALD, calcium, sodium, and BP values. No correlation was found between plasma calcium and these parameters.

The removal of the parathyroid gland was followed by a significant reduction in PTH ($P < .006$), plasma ($P < .001$) and urinary ($P < .01$) calcium, and urinary phosphate ($P < .01$) and by an increase in plasma phosphate ($P < .02$), potassium ($P < .02$), and sodium ($P < .03$). PRA, ALD, urinary potassium and sodium, and BP showed no significant change after surgery (Table 3). PTH and plasma calcium did not correlate with BP, PRA, plasma and urinary ALD, sodium, and potassium.

Finally, no difference in PTH, PRA, plasma and urinary ALD, calcium, and sodium was observed in hypertensive versus normotensive PH patients, and variations in these humoral parameters after surgery were comparable in the two groups (data not shown).



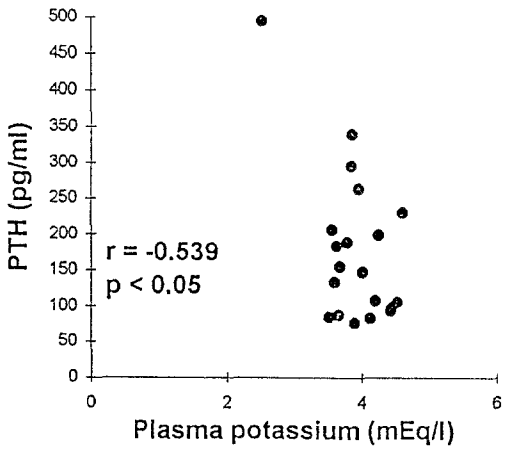


Fig 1. Correlations between PTH and PRA and plasma potassium in PH patients before surgery.

Table 2. Humoral Data for Patients With PH or EH and Controls (mean ± SEM)

Parameter	PH (n = 20)	Controls (n = 13)	EH (n = 26)
PTH (pg/mL)	178.1 ± 23.8	26.6 ± 3.3†	
Plasma calcium (mg/dL)	10.8 ± 0.3	9.2 ± 0.2†	
Urinary calcium (mg/24 h)	341.2 ± 65.7	170.0 ± 18.5*	
Plasma phosphate (mg/dL)	2.6 ± 0.3	3.2 ± 0.7	
Urinary phosphate (mg/24 h)	669 ± 77.7	580.0 ± 64.0	
PRA (ng/mL/h)	1.01 ± 0.25	0.92 ± 0.1	0.91 ± 0.17
Plasma ALD (ng/dL)	19.2 ± 6.1	13.9 ± 1.8	18.9 ± 2.9
Urinary ALD (μg/24 h)	19.5 ± 5.1	12.7 ± 2.0	16.3 ± 6.0
Plasma potassium (mEq/L)	3.9 ± 0.1	4.0 ± 0.3	4.1 ± 0.2
Urinary potassium (mEq/24 h)	53.8 ± 4.6	46.2 ± 4.6	51.2 ± 3.7
Plasma sodium (mEq/L)	141.8 ± 0.7	140.1 ± 0.8	140.6 ± 0.2
Urinary sodium (mEq/24 h)	119.6 ± 9.8	116.0 ± 8.9	121.8 ± 10.4

*$P < .01$ *v* PH.
†$P < .001$ *v* PH.

Table 3. Humoral and Hemodynamic Parameters for PH Patients Before and 1 and 6 Months After Surgery

Parameter	Before	1 Month	6 Months
PRA (ng/mL/h)	1.01 ± 0.25	0.81 ± 0.21	1.10 ± 0.32
Plasma ALD (ng/dL)	19.2 ± 6.1	14.1 ± 2.2	28.5 ± 4.8
Urinary ALD (μg/24 h)	19.5 ± 5.1	14.5 ± 1.9	17.0 ± 1.7
Plasma cortisol (nmol/L)	286 ± 36	262 ± 21	309 ± 38
Urinary potassium (mEq/24 h)	53.8 ± 4.6	39.2 ± 5.7	60.9 ± 5.8
Urinary sodium (mEq/24 h)	119.6 ± 9.8	83.1 ± 16.8	126.1 ± 14.1
Systolic BP (mm Hg)	136.6 ± 3.3	134.8 ± 4.2	135.9 ± 6.0
Diastolic BP (mm Hg)	84.4 ± 2.2	84.6 ± 2.1	83.4 ± 4.7

DISCUSSION

In isolated perfused[1] and nonfiltering[2] rat kidney, PTH shows renin-stimulating properties via specific receptors, independently of baroreceptors, macula densa, and prostaglandins. In addition, it has been reported that in isolated rabbit glomeruli and superfused dispersed rat juxtaglomerular cells,[3] the direct renin-stimulating action of PTH (1-34) is mediated through inhibition of calcium influx. Accordingly, in pentobarbital-anesthetized dogs[4,5] and in humans,[6,7] PTH (1-34) infusion significantly increased PRA without modifying BP and plasma calcium.

However, in chronic conditions such as PH, the relationship between PTH and the RAA system is controversial. Some investigators found RAA system activation especially in hypertensive patients, which was reversible after surgical correction of hyperparathyroidism.[7,9,10] In contrast, others reported no variation in the RAA system in patients with hyperparathyroidism, whether normotensive or hypertensive.[11-13] There are several explanations for this discrepancy. First, the definition of RAA system activation is questionable in many cases,[7,9,10] since values for PRA were not compared versus controls and/or EH patients. Second, it is difficult to attribute the postsurgery variation in PRA exclusively to a normalization of PTH without specifying the corresponding sodium urinary excretion.[7,9-13] In the present study, we compared PRA in PH patients versus normal subjects and EH patients, observing no activation of the RAA system, in accordance with other reports.[11-13] We found a positive association between PTH and PRA and a negative association between PTH and plasma potassium. However, these relations were weak, probably conditioned by the behavior of single cases, and are consequently devoid of biological meaning, especially since PTH was not associated with plasma and urinary ALD or with BP. Finally, our patients maintained a controlled sodium intake for 2 weeks prior to venous sampling both before and after surgery, so the natriuresis results are comparable. In these conditions, PRA and ALD were similar in PH patients versus EH patients and controls and did not change after removal of the parathyroid adenoma. In addition, patients with PH and hypertension showed PRA and ALD levels similar to those of normotensive PH patients, and variations in these humoral parameters after surgery were comparable in the two groups. Our data agree with the finding that saralasin (an angiotensin II competitive inhibitor) fails to decrease BP in patients with PH, suggesting that the hypertension associated with hyperparathyroidism does not involve the RAA system.[15] Finally, in accordance with findings from other studies,[12,13,16,17] BP did not change after correction of the hyperparathyroidism in either normotensive or hypertensive PH patients.

In conclusion, our data show that hypertension is a common feature in patients with PH. However, the present results do not allow the assumption of a renin-mediated causal relationship between hyperparathyroidism and high BP values. Indeed, as a unique finding in favor of the hypothesis of a stimulating role for PTH in renin secretion, we observed only a weak relation between PTH and PRA. Thus, unknown and/or unassessed factors related to parathyroid disease should be taken into account to explain the hypertension observed in some patients with PH.

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