FUNCTIONAL RENAL INVOLVEMENT IN NORMOTENSIVE PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS

Impaired Sodium Excretion during Isotonic Saline Infusion

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An intravenous infusion of 2,000 ml isotonic saline was performed in 8 normotensive, normoreninemic patients with progressive systemic sclerosis. None of them had clinical evidence of renal disease. Total and proximal fractional excretion of sodium was reduced when compared with that of 8 normal subjects. No correlation was found with para-aminohippurate (PAH) clearance values. Two years after this study was done, 4 patients developed arterial hypertension; interestingly, plasma renin activity remained within the normal range. Reduced sodium excretion is suggested as having a pathogenetic role in the hypertension of progressive systemic sclerosis.

Since the report by Moore and Sheehan (1), increasing evidence has been obtained that renal involvement is a very important feature of progressive systemic sclerosis (PSS) or scleroderma and is one of the most prominent causes of death in the affected patients (2–6).

It is also well known that arterial hypertension, often in its malignant form, is a manifestation of renal involvement in PSS (4).

Hyperreninemia has been frequently reported in PSS hypertensive patients (7–9). It has been suggested that renin not only causes hypertension through angiotensin activation, but it also promotes vasoconstriction and vascular damage, which further leads to the malignant phase of hypertension and rapidly progressive renal failure (10–13). Conversely, sodium metabolism, which is intimately related to hypertension in renal diseases, has received little attention in PSS.

To investigate the possible role of an early derangement of renal handling of sodium in PSS, a group of normoreninemic patients with scleroderma who had neither hypertension nor clinical evidence of renal disease was studied by means of an acute isotonic saline infusion in maximal water diuresis.

PATIENTS AND METHODS

Eight patients (5 women and 3 men aged 18–65 years) afflicted with PSS were studied. The criteria for diagnosis of PSS were defined as the presence of diffuse skin induration (diffuse scleroderma), Raynaud's phenomenon, and esophageal and pulmonary involvement as assessed by radiology. None had CREST syndrome. The duration of symptoms ranged from 6 to 41 years.

At the time of our study, none of these patients had a diastolic pressure above 80 mmHg or a systolic blood pressure above 140 mmHg; in all of them cardiac index and plasma renin activity (PRA) were within the normal range. PRA was determined by radioimmunoassay of generated angiotensin I (14) in blood samples collected both in supine and standing positions.

No evidence of renal damage was present, as evaluated by urinalysis, creatinine clearance, BUN values, concentration, and acidification tests performed according to the standard procedures (15). A urinary osmolality of more than 800 mOsm/kg water and a urine pH of less than 5.3 units were considered the normal limits for concentration and acidification studies (15).

All drugs (griseofulvin, vasodilators, and nonsteroidal antiinflammatory compounds) were discontinued at least 15 days prior to the study.

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Eight normal subjects were used as controls. Both patients and controls were kept on a constant diet containing 150 mEq of Na^+ and Cl^- prior to the study.

After an overnight fast, 10 mg of deoxycorticosterone acetate were injected intramuscularly. Then a hypotonic maximal diuresis was induced by giving 20 ml/kg of tap water and maintained by additional amounts of water equal to the urinary losses. When urinary osmolality was below 70 mOsm/kg water, 2,000 ml of isotonic saline were infused intravenously over 150 minutes, and five clearance periods were obtained, during which the different patterns of Na^+ transport along the nephron were calculated according to Seldin and Rector (16).

Before and after the saline infusion, inuline and PAH clearances were performed according to Roe (17) and Smith (18). In plasma and urine, sodium and potassium concentrations were determined by atomic absorption spectrophotometer (Perkin-Elmer model 370); chloride levels were assessed by titrimetic method (Oxford titrator) and osmolality by freezing point depression with Halmikro-Osmometer.

The urine pH was evaluated by means of pH-meter (Radiometer-Copenhagen).

RESULTS

In all patients, inulin clearances were above 90 ml/minute. PAH clearances were within the normal range (550–650 ml/minute) in 3 patients and below 350 ml/minute in 5 patients, with the filtration fraction (FF) ranging 0.17 to 0.31.

Table 1 shows the results of volume expansion in the group of sclerodermic patients compared with controls. The values are expressed as mean ± SEM.

The urine output and fractional excretion of sodium (FE_{Na}) were significantly reduced in PSS patients (Table 1). Proximal fractional excretion of sodium (PFE_{Na}) appeared even more significantly depressed in the same group of patients (Table 1).

Free water clearance (C_{H_2O}), an indirect estimation of sodium reabsorption in the ascending limb of Henle's loop, was lower in PSS patients than in controls (Table 1). However, when C_{H_2O} values were corrected by distal delivery of sodium, using the chloride clearance (16), no difference was evident.

Distal sodium reabsorption, roughly estimated by fractional excretion of potassium (FE_K), did not show any significant difference.

The mean values of total sodium excretion during the infusion of a solution containing 308 mEq of Na^+ were significantly lower in patients with PSS than in controls (40.95 ± 7.58 and 107.62 ± 20.07 mEq, respectively; $t = 3.107$, $P < 0.01$).

After this study was performed, a reliable followup was obtained in all 8 patients for 2 years. Up to now, 4 of the 8 patients have developed hypertension, and repeated testing of PRA levels on these patients receiving a constant diet containing 150 mEq of Na^+ and Cl^- have been within normal limits (Table 2).

Table 2 summarizes each patient's values of PAH clearance and PRA determinations before the saline infusion, the sodium retention as a percentage of

Table 1. The effect of saline load in 8 PSS patients and 8 normal subjects

	V/GFR × 100†		C_{H_2O}/GFR × 100‡		FE_{Na} %§		PFE_{Na} %¶	
Periods*	PSS	Control	PSS	Control	PSS	Control	PSS	Control
Basal	3.58 ± 0.98	3.04 ± 0.52	1.62 ± 1.04	0.95 ± 0.44	1.02 ± 0.27	1.30 ± 0.24	3.31 ± 1.22	2.71 ± 0.55
t	0.485		0.584		0.775		0.448	
P	NS		NS		NS		NS	
First	7.55 ± 1.05	11.22 ± 1.84	5.07 ± 0.88	7.25 ± 1.35	1.20 ± 0.21	5.30 ± 2.63	6.70 ± 1.05	13.23 ± 2.73
t	1.733		1.353		2.495		2.232	
P	NS		NS		<0.025		<0.05	
Second	9.15 ± 1.48	13.77 ± 1.04	6.91 ± 1.30	10.03 ± 0.90	1.43 ± 0.31	3.94 ± 0.80	8.74 ± 1.56	14.61 ± 0.97
t	2.559		1.974		2.925		3.195	
P	<0.025		NS		<0.01		<0.01	
Third	9.61 ± 1.41	14.74 ± 0.58	6.84 ± 1.05	11.02 ± 0.53	1.81 ± 0.43	5.54 ± 0.83	9.05 ± 1.17	17.22 ± 1.22
t	3.367		3.556		3.990		4.833	
P	<0.005		<0.005		<0.005		<0.001	
Fourth	8.57 ± 1.51	15.62 ± 0.43	5.97 ± 1.38	11.65 ± 0.29	2.45 ± 0.51	6.06 ± 2.24	8.83 ± 1.67	18.44 ± 2.30
t	4.496		4.030		1.571		3.381	
P	<0.001		<0.001		NS		<0.005	
Fifth	10.36 ± 1.88	16.22 ± 0.82	7.37 ± 1.35	11.69 ± 0.60	2.15 ± 0.42	4.89 ± 0.98	10.05 ± 1.72	17.28 ± 1.41
t	2.856		3.847		2.570		3.251	
P	<0.02		<0.005		<0.025		<0.01	

* Values expressed are mean ± SEM.
† V/GFR = urine volume per minute/glomerular filtration rate.
‡ C_{H_2O} = free water clearance.
§ FE_{Na} = fractional excretion of sodium.
¶ PFE_{Na} = proximal fractional excretion of sodium.

Table 2. Functional and clinical data in 8 PSS patients

Name	Sex	Cl_{PAH} (ml/min)*	Sodium retention†	PRA‡		Subsequent development of hypertension	PRA, after 2 years	
				Supine§	Standing¶		Supine	Standing
BM	F	305	82.49	1.90	3.30	Yes	2.05	4.18
DA	M	585	80.10	2.00	3.06	Yes	1.83	3.02
DM	M	610	94.97	2.10	3.60	No		
LF	M	340	89.33	0.93	2.13	No		
SA	F	315	83.72	1.30	3.40	Yes	2.00	3.10
SL	F	325	78.64	2.26	3.46	No		
TA	F	345	98.05	0.70	1.00	Yes	1.44	2.80
VA	F	650	86.36	0.30	0.60	No		

* Cl_{PAH} = para-aminohippurate clearance.
† As a percentage of sodium infused during the test time.
‡ PRA = plasma renin activity.
§ Normal range 0.2–2.7 ng/ml/hour.
¶ Normal range 1.5–5.6 ng/ml/hour.

sodium infused, and the subsequent development of hypertension. No correlation was found among these parameters.

DISCUSSION

It has been suggested that the intrarenal vascular changes might play a predominant role in the pathogenesis of hyperreninemia in progressive systemic sclerosis (4,5,7). Indeed, in sclerodermic patients with severe hypertension or renal failure, high renin levels are often observed (7–9), and there is strong evidence that the renin–angiotensin system may play a significant pathogenetic role in the acceleration of renal damage (10–12).

Nevertheless, during preclinical renal involvement in PSS, the role of hyperreninemia in causing high blood pressure is at present still debatable, and in nonmalignant hypertension high values of PRA are not usually found (10,19–21).

Moreover, vascular renal lesions such as hyaline sclerosis, intimal fibrosis, and fibrinoid degeneration have been described before any increase in serum renin level (14).

In a group of normoreninemic sclerodermic patients with normal blood pressure, we found an inadequate natriuretic response to saline infusion, both in those with normal and those with reduced PAH clearance. This early renal sodium retention, which is evident in spite of the absence of clinical signs of renal damage, has been observed years before the development of arterial hypertension.

Our results are consistent with the view that sodium retention probably takes place before renin–angiotensin system activation, and therefore it should be considered the prominent underlying pathogenetic mechanism of nonmalignant hypertension in scleroderma. Such a metabolic disorder is not regularly correlated with PAH clearance values, which are usually considered an early index of renal involvement in PSS (22), and might represent the first appearance of abnormal renal function in this disease.

The impaired natriuresis in our patients seems to be due to an exaggerated sodium reabsorption in the proximal tubule. The various factors affecting water and solute reabsorption in the proximal tubule include glomerulotubular balance, peritubular capillary forces, sympathetic nerve activity, and some unidentified natriuretic factor(s), presumably hormonal, that inhibit sodium or chloride reabsorption or both at one or several nephron sites and increased sodium excretion (23,24).

Our data do not indicate which of these factors are mainly involved in our patients. Moreover, since sodium reabsorption was not correlated with PAH clearance or filtration fraction, such hemodynamic parameters do not seem to be responsible for the impaired natriuresis.

Conversely, it cannot be excluded that a lack of activity of some natriuretic substances (such as natriuretic hormone or third factor (25), prostaglandins, kallikrein, kinins, and dopamine) may be implicated in the pathogenesis of sodium retention.

Plasma renin levels remained within the normal range in our patients, regardless of the eventual development of benign hypertension in 50% of them.

It has been suggested that in the preclinical stages of renal disease in PSS sodium retention might cause inhibition of renin release in spite of renal underperfusion, which could be the case in the 4 patients who

developed mild hypertension. On the contrary, the renin release, which is increased in the great majority of PSS patients with malignant or accelerated hypertension, seems to become independent of the degree of sodium retention owing to the severe renal vascular disease (21).

This study in scleroderma patients with normal arterial pressure demonstrates inadequate sodium excretion after saline infusion. Further studies in the early phase of hypertension in scleroderma may determine whether our data support the hypothesis that renal alterations can cause hypertension through an inadequate sodium and water excretion (26).

REFERENCES

1. Moore HC, Sheean HL: The kidney of scleroderma. Lancet 1:68–70, 1952
2. Rodnan GP, Schreiner GE, Black RL: Renal involvement in the progressive systemic sclerosis (generalized scleroderma). Am J Med 23:445–462, 1957
3. Medsger TA Jr, Masi AT, Rodnan GP, Denedek TG, Robinson H: Survival with systemic sclerosis (scleroderma): a life-table analysis of clinical and demographic factors in 309 patients. Ann Intern Med 75:369–376, 1971
4. Cannon PJ, Hassar M, Case DB, Casarella WJ, Sommers SC, LeRoy EC: The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. Medicine 53:1–46, 1974
5. Oliver JA, Cannon PJ: The kidney in scleroderma. Nephron 18:141–150, 1977
6. LeRoy EC, Fleischmann RM: The management of renal scleroderma: experience with dialysis, nephrectomy and transplantation. Am J Med 64:974–978, 1978
7. Stone RA, Tisher CC, Hawkins HK, Robinson RR: Juxtaglomerular hyperplasia and hyperreninemia in progressive systemic sclerosis complicated by acute renal failure. Am J Med 56:119–123, 1974
8. Abe T, Mori I, Morimoto C, Hara M, Yamosaki K, Homma M: Plasma renin activity levels in patients with systemic sclerosis (abstract). XIV International Congress of Rheumatology. 1977, p 158
9. Chetlin SM, Shapiro AP, Rodnan GP, Medsger TA, Tolchin SF, Leb DE: Plasma renin activity in progressive systemic sclerosis (abstract). XIV International Congress of Rheumatology. 1977, p 158
10. Gavras H, Gavras I, Cannon PJ, Brunner HR, Laragh JH: Is elevated plasma renin activity of prognostic importance in progressive systemic sclerosis? Arch Intern Med 137:1554–1558, 1977
11. Markenson JA, Sherman RL: Renal involvement in progressive systemic sclerosis: prolonged survival with aggressive antihypertensive management. Arthritis Rheum 22:1132–1134, 1979
12. Lopez-Ovejero JA, Saal SD, D'Angelo W, Cheigh JS, Stenzel KH, Laragh JH: Reversal of vascular and renal crisis of scleroderma by oral angiotensin-converting-enzyme blockade. N Engl J Med 300:1417–1419, 1979
13. Walker WG, Solez K: Renal involvement in disorders of connective tissue, Strauss and Welt's Diseases of the Kidney. Edited by LE Earley, CW Gottschalk. Boston, Little Brown, 1979, p 1259
14. Haber E, Koerner T, Page LB, Kliman B, Purnode A: Application of radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J Clin Endocrinol 29:1349–1355, 1969
15. Kassirer JP, Gennari FJ: Laboratory evaluation of renal function, Strauss and Welt's Diseases of the Kidney. Edited by LE Earley, CW Gottschalk. Boston, Little Brown, 1979, p 41
16. Seldin DW, Rector FC Jr: Evaluation of clearance methods for the localization of site of action of diuretics, Modern Diuretic Therapy in the Treatment of Cardiovascular and Renal Disease. Edited by AF Lant, GM Wilson. Amsterdam, Excerpta Medica, 1973, p 97
17. Roe JN, Epstein JH, Goldstein NP: A photometric method for the determination of inulin in plasma and urine. J Biol Chem 178:839–845, 1949
18. Smith HW, Finkelstein N, Aliminosa L, Crawford B, Graber M: The renal clearance of substituted hippuric acid derivatives and other aromatic acid in dog and man. J Clin Invest 24:388–404, 1945
19. Fleischmajer R, Gould AB: Serum renin and renin substrate levels in scleroderma. Proc Soc Exp Biol Med 150:374–379, 1975
20. Kovalchik MT, Guggenheim SJ, Silverman MH, Robertson JS, Steigerwald JC: The kidney in progressive systemic sclerosis: a prospective study. Ann Intern Med 89:881–887, 1978
21. Kahaleh MB, LeRoy EC: Progressive systemic sclerosis: kidney involvement. Clin Rheum Dis 5:167–184, 1979
22. Urai L, Nagy Z, Szinay G, Wiltner W: Renal function in scleroderma. Br Med J 2:1264–1266, 1958
23. Reinech HJ, Stein JH: Renal regulation of extracellular fluid volume, Sodium and Water Homeostasis. Edited by BM Brenner, JH Stein. New York, Churchill Livingstone, 1978, p 24
24. Lassiter WE: Disorders of sodium metabolism, Strauss and Welt's Diseases of the Kidney. Edited by LE Earley, CW Gottschalk. Boston, Little Brown, 1974, p 1522
25. De Wardener HE: Natriuretic hormone. Clin Sci Mol Med 53:1–8, 1977
26. Coleman TG, Guyton AC, Cowley AW Jr, Young DB, Declue JW, Cevese A: Renal abnormalities that do and do not cause hypertension. Proceedings VI International Congress of Nephrology, Basel, Karger, 1976, pp 266–273