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PLASMA RENIN ACTIVITY IN NORMAL HEALTHY VOLUNTEERS : EFFECT OF PHYSIOLOGICAL VARIABLES

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Abstract: Plasma renin activity was determined in hundred normal subjects of either sex (M=65, F=35, age range 2 - 70 yr) using Angiotensin-I test kits. The effect of various physiological variables viz, age, sex, posture and salt intake was determined. The basal values for PRA ranged from 1.19 ± 0.09 ng/ml/hr for males and 1.02±0.12 ng/ml/hr for females in erect posture. In contrast high basal supine PRA was noticed in subjects on low salt diet, which showed a signficant increase in erect posture. A marked decrease in PRA with advancing age in both the sexes with significantly low values at higher age range was noticed. Captopril produced an insignificant effect on PRA and BP in salt replete supine state, whereas in salt deplete state there was a significant rise in both the parameters.

Key words: plasma renin activity physiological variables captopril

INTRODUCTION

The function of renin-angiotensin system in various physiological and pathological conditions has unveiled it to be an elegant, complex and vital homeostatic system. Development of radioimmunoassay (RIA) for its components, renin, Ang-I (PRA) and Ang-II has helped in understanding the pathogenesis of hypertension and in the diagnosis of secondary hypertension due to renovascular disease (1, 2). There are a number of reports available in the literature on PRA levels in normal subjects (3-5). However, limited information is there on PRA in Indian population (6,7) with none reporting the effect of physiological variables. Since PRA is influenced to a great extent by the ethnic and dietetic factors, it becomes imperative to set the normal range which could be compared with those obtained in various pathological states. We report PRA in different sex and age groups and the effect of change in posture and salt intake in normal healthy subjects. The effect of captopril administration on PRA in normal and salt depleted state has also been studied.

METHODS

Normal healthy volunteers (n=100) of either sex (M=65, F=35, age range 2-70 yr) were included in the study. All subjects were free from any organic illness and drugs including contraceptives known to affect the renin-angiotensin system. Blood pressure in every volunteer was below 140/90 mm Hg on at least two occasions prior to blood sampling. Blood samples (10 ml) were drawn in an upright posture from the peripheral vein and collected in chilled tubes containing potassium EDTA (0.1 ml). Plasma was separated in a refrigerated centrifuge and stored at 10°C till assay. In

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another series of experiments blood samples and blood pressure were taken in a supine position, and again after 30-40 min of assuming an erect posture. In order to find out the effect of low salt intake (< 2gm/day) on PRA, the blood samples were drawn before and after low salt diet for 3 days. The effect of captopril on PRA was studied under normal and low salt states. The blood samples were taken in the basal state and after 30-45 min following captopril (50 mg orally) administration. Sampling was always carried out in the morning between 9-10 am. Twenty four hr urine samples were collected for measuring Na^+ and K^+ levels.

RIA of Angiotensin-I : Estimation of Ang-I was carried out by RIA, based on the two-step method of Haber et al (4)using commercial kits from Pharmacia (Uppsala, Sweden). In the first step, Ang-I is generated by the action of renin on angiotensinogen in the plasma samples treated with acid inhibitor mixture (to block the conversion of generated Ang-I to Ang-II) and incubated for one hr at 37°C (pH 5.8-6.0). In the second step, Ang-I in the sample or in the standards is allowed to compete with a fixed amount of labelled Ang-I for the binding sites of Ang-I antibodies. Free and bound Ang-I are separated by adsorption on dextran-coated charcoal mixture and radioactivity of the supernatant counted in a γ - scintillation counter. The amount of Ang-I generated was calculated from the standard curve obtained by plotting the different concentrations of standards and percentage binding. Plasma renin activity was represented as Ang-I generated ml/hr.

RESULTS

Performance characterisitics of RIA for PRA: The sensitivity of PRA assay was 0.2 ng/ml/hr. The intrassay and interassay variations were 7.12% and 9.42% respectively. The percentage recovery of added Ang-I was 112.7%. The mean plasma renin activity in normotensive healthy males (n=65) and females (n=35) in the erect posture was 1.19 ± 0.09 ng/ml/hr and 1.02 ± 0.12 ng/ml/hr respectively. Although the values in female volunteers appeared to be lower than in males, the difference was, however, not statistically significant (P>0.05).

Effect of change of posture : In volunteers on normal salt intake (n=20), supine PRA was 0.83±0.44 ng/ml/hr. On assuming erect posture, the PRA values increased to 1.26±0.02 ng/ml/hr (P>0.05). In contrast, a high basal supine PRA was noticed in volunteers on low salt intake which significantly increased in erect posture (Table I).

Variation due to age and sex: The PRA ranged from 0.9-1.8 ng/ml/hr in the age group of 2-10 yr. The values were marginally high in volunteers belonging to the age range of 20-40 yrs. A significant decrease in PRA was observed in the higher age group of 50-70 yr. However, comparison of values obtained in either sex in the same age range revealed no significant difference (Table II).

TABLE I : Effect of posture on PRA in volunteers on normal and restricted salt intake.

	n	Supine PRA (ng/ml/hr)	Erect PRA (ng/ml/hr)	24 hr Urinary sodium (meq/l)
Normal salt intake	20	0.83 ± 0.44	1.26 ± 0.02	169.2 ± 106
Restricted salt intake	20	3.20 ± 0.93*	8.6 ± 2.1*	82.6 ± 6.8

P<0.05* (v/s normal salt intake group) P>0.05* (v/s supine value).

Effect of low salt intake The basal PRA in volunteers on low salt intake (n=20) was 3.12±0.81 ng/ml/hr which was signficantly higher than 0.81 ± 0.24 ng/ml/hr observed in the group on the normal salt intake. Captopril administration caused a marginal increase to 1.3±0.45 ng/ml/hr in salt replete state whereas a signficant rise to 17.0 ± 5.9 ng/ml/hr was noted in salt-deplete state (P<0.01).

TABLE II: Effect of age on PRA in normal volunteers.

Age Range (yrs)	Males		Females	
	n	PRA (ng/ml/hr) mean±SE	n	PRA (ng/ml/hr) mean±SE
2-10	4	1.52±0.21	2	1.30±0.40
20-30	8	1.87±0.19	2	1.50±0.30
30-40	20	1.50±0.18	10	1.51±0.27
40-50	18	1.00±0.71	12	0.91±0.15
50-70	15	0.56±0.14*	9	0.46±0.13*

*P<0.05 (Comparison with values of 2-10, 20-30 and 30-40 yr, Student "t" test).

DISCUSSION

The PRA values ranged widely (0.2-3.0 ng/ml/hr) in normal, healthy volunteers as reported by others. However, Boyd et al (3) found a low range of the 0.54-0.65 ng/ml/hr while Sealey et al (8) reported values in the range of 1.4-6.3 ng/ml/hr. Similarly in 28 normal Indian subjects, Sagar et al (7) reported 0.18-1.65 ng/ml/hr and Deshpande et al (6) reported a higher range of 0.3-3.8 ng/ml/hr.

The renin sodium profile constructed from the values of sodium excretion and renin activity observed in 100 normal volunteers showed no significant correlation between the two parameters in majority, however in 20 subjects with low salt intake the renin activity was always inversely correlated. The difference in age of the study populations, which is reported to influence the PRA (9) could be a factor responsible for such large variations in PRA.

Mean supine PRA in normal salt intake group showed a marginal increase after 30 min of assuming upright posture. However, an Indian study on 28 normal subjects, reported 3 fold increase from the basal value after 1 hr (7) and some western reports have also shown a significant rise after 3-4 hrs of ambulation (4).

It is well known that assumption of the upright posture increases sympathetic nerve activity and produces renal arteriolar constriction leading to rise in PRA. The response is shown to be superimposed by the diurnal rhythm of PRA, as greater increase in PRA to change in posture has been observed/in forenoon than in afternoon (10,11). The significant rise in PRA observed by the previous workers could be because of the sampling carried out comparatively in early hours of the day. The stimulating effect of sympathetic nervous system on renin release is to a large extent determined by the availability of mobilizable renin stores (5). The insignificant effect of posture may not be on account of limited renin stores as the same subjects when on low salt intake showed further rise in PRA on assuming erect posture. The results suggest that hyponatremia becomes an additional factor contributing to the sympathetic overactivity for renin release during erect posture to maintain BP.

No significant difference in PRA was observed in either sex, though males showed apparently high values. A marked decrease in PRA with advancing age in both the sexes ($P<0.05$) with significantly low values at higher age range was observed. Such age dependent relationship with plasma renin activity in normal subjects has been reported by others (5,12). Since in normotensive subjects with advancing age physical work capacity and exercise induced tachycardia decrease, which is less supressible by the beta blockade (13), it is possible that a decreased sympathetic nervous system activity in the elderly may be responsible for the low PRA.

Similarly captopril produced an insignificant effect on both BP and PRA in salt replete supine state suggesting insignificant role of RAS in BP homeostasis

in the sodium replete state. The finding is supported by a study showing insignificant rise in PRA following an intravenous bolus of teprotide (1 mg/kg) in subjects on a salt intake of 150 meq/day (14). Further, there was a significant rise in PRA and fall in BP in the salt deplete state as reported by others (15). The significant rise in PRA is because of three factors working together viz (i) hyponatremia, (ii) fall in BP, (iii) ineffective short feedback loop in absence of Ang-II formation. The significant hypotensive effect of captopril is suggestive of an important role of RAS in hyponatremic state.

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