Renin-sodium profile and renal prostaglandins in the pathogenesis of systemic arterial hypertension in blacks

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Thirteen black women with systemic (essential) arterial hypertension, age-matched with normotensives, were examined during two protocols inducing sodium depletion and sodium loading respectively. Changes in plasma renin activity (PRA), urinary aldosterone values and prostaglandin E_2 (PGE_2) and F_{2a} (PGF_{2a}) excretion were simultaneously assessed. Renin profiles, obtained by the plotting of PRA against the urinary excretion of sodium, showed a 62% prevalence of low-renin hypertension, the remaining 38% of the patients having normal-renin hypertension.

At basal level the hypertensives had suppressed renal synthesis of vasodilator PGE_2 and a non-significant increase in venopressor PGF_{2a}. This was reflected in the significant 32% decrease in the PGE_2/PGF_{2a} ratio. This finding was in keeping with their low-renin hypertension. During sodium depletion PG excretion was increased in both normotensive and hypertensive groups. The opposite effect was found during sodium loading.

The results of this study do not support a natriuretic role for renal PGE_2, but do support the hypothesis that there is decreased renal vasodepressor PGE_2 synthesis in black hypertensive patients.

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There is evidence that differences in renal physiology may play a role in the prevalence and severity of essential hypertension in blacks.[1,2] Renal haemodynamics play an important role in sodium homeostasis. With sodium restriction renal blood flow is reduced, while with sodium loading renal blood flow is increased and sodium excretion enhanced. Normally the change in renal blood flow is a reflection both of a change in the circulating renin-angiotensin system (RAS) as well as in the intrarenal RAS. Investigators have reported lower plasma renin activity levels relative to sodium excretion in clinical series of black (as opposed to white) hypertensives in the USA[3] and South Africa.[4] In addition, an impaired ability to excrete a sodium load has been reported.[5] The same authors reported that plasma aldosterone, urinary norepinephrine and prostaglandin (PG) E_2 values were comparable in both normotensive and hypertensive blacks during changes in sodium balance. These authors proposed that decreased renal production of dopamine might contribute to the sodium sensitivity typical in black hypertensives, and might also be a pathological factor in the development of hypertension in blacks. In addition, a number of hypotheses have been proposed to explain the cause(s) of sodium-sensitive systemic arterial hypertension in blacks.[6] Impairment of vascular vasodilatory negative feedback systems, such as the PG and kallikrein-kinin systems, operating to offset vasoconstrictive influences, are believed to be implicated in the pathogenesis of essential hypertension, particularly low-renin hypertension.[7-9] Renal PGs are involved in the mechanisms which regulate renin release and other renal vascular functions, such as renal blood flow, the adrenergic neuro-effector response or the tubulo-vascular feedback loop.[10] Furthermore, a close relationship between the renal PG and kallikrein-kinin systems in the kidney has been reported.[11] It has generally been accepted that a deficiency in the kallikrein-kinin system inhibits sodium excretion, causing the high rates of hypertension in blacks.[2,12-14]

The PGs have received comparatively little attention, but could nonetheless be related to black/white differences in blood pressure. The reported data so far are scarce and inconclusive.[5,15] Previous studies of urinary PGs as influenced by sodium balance have been complicated by problems with assay methodology, inclusion of male subjects, and/or failure to standardise daily fluid consumption and renin status.

The objectives of this study were to assess renal PG concentrations in black normotensives and hypertensives during consecutive changes of renin-sodium profile produced by sodium depletion and sodium loading.

Subjects and methods

The study was performed on 13 hypertensive black Zimbabwean women and 13 age-matched black normotensive women (Table I). The study protocol was approved by the Medical Ethics Committee of Parirenyatwa Hospital, Harare. All subjects gave written informed consent to participate in the study.

Table I. Demographic data and selection (means ± SD) of control subjects and hypertensive patients

	Normotensive	Hypertensive
No.	13	13
Age (yrs)	35 ± 1,29	39 ± 1,80
BMI	26 ± 1,22	28 ± 1,26
Systolic arterial pressure pressure (mmHg)	122 ± 3,36	164 ± 5,96*
Diastolic arterial pressure (mmHg)	73 ± 2,68	105 ± 4,08*
Mean arterial pressure (mmHg)	89 ± 2,70	125 ± 4,46*
Heart rate (min)	88 ± 2,84	88 ± 3,53
Creatinine clearance (ml/s)	1,87 ± 0,16	1,51 ± 0,12

BMI = body mass index (calculated as body weight; kg/height; m^2). Demographic data differences were NS.
* Difference significant compared with respective normotensives ($P< 0,001$).

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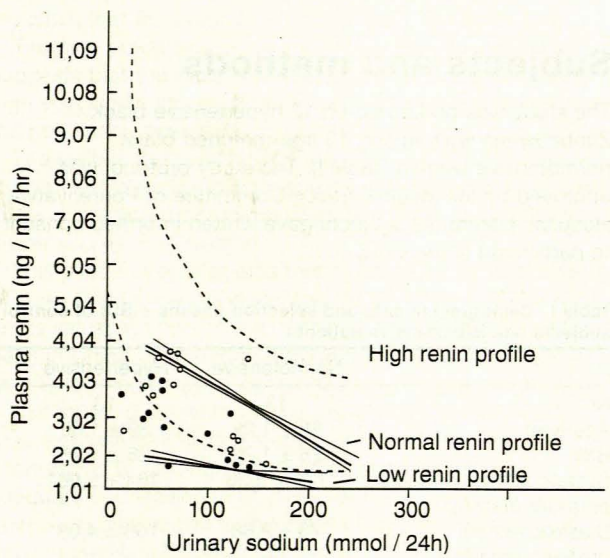
The diagnosis of essential hypertension was established on the basis of a history, a physical examination, blood chemistry studies, urinalysis, and rapid-sequence pyelography, which revealed no evidence of secondary forms of hypertension. The patients were newly diagnosed and untreated. They were classified according to the WHO classification as WHO grade I, with a systolic blood pressure greater than 160 mmHG and/or a diastolic blood pressure greater than 95 mmHG (fifth Korotkoff sound) found at least three times during a 1-month run-in period. All subjects were accommodated at the University Hostel for the duration of the experiment. Food that ensured a constant caloric intake, dietary NaCl and potassium content, was prescribed by a dietician and provided by the hospital. Details are described elsewhere.[16] Briefly, the subjects were provided with a low-sodium diet (less than 40 mmol sodium/day) for 5 days, followed by a high-sodium diet (300 mmol sodium/day) for another 5 days. The manipulation of dietary sodium intake was used to evaluate the effect of sodium-balance changes on the renin-angiotensin and PG status. Renal PGs were assessed in women, since striking variations in urinary PG excretion may result in men as a result of the entry of seminal PGs into the urine. Alcohol was prohibited during the study period. None of the subjects was a smoker. Blood pressure was measured in the sitting position with a random zero sphygmomanometer.

Blood samples were collected in the morning after 12 hours of fasting, before and at the end of each diet, after the subjects had been ambulatory for 2 hours.[17,18] Plasma renin activity was measured by radio-immuno-assay (RIA) by means of a commercially available kit (Phadebas Angiotensin I Test, Pharmacia Diagnostics, Sweden). The renin-sodium profile was based on a nomogram that had previously been constructed by defining a normal band that included 95% of the renin-sodium values of 106 normal white subjects (Fig. 1, shaded band).[16,17] Patients with renin-sodium profiles below the lower boundary of that band were classified as having a low profile, and those within the band as having a normal profile. None of the black subjects exhibited a high renin-sodium profile (above the upper boundary of that band).



Open circles indicate normotensives; closed circles indicate hypertensives. The normal range of the relation of ambulatory PRA to daily urinary sodium excretion in normotensives is indicated by the shaded band. The relations for subjects with normal and low renin profiles are defined by the regression lines and 95% confidence intervals. To convert values for plasma renin activity to ng/l/s divide by 3,6.

Fig. 1. Relationship between morning plasma renin activity and corresponding daily rate of sodium excretion in normotensive and hypertensive black women.

Twenty-four-hour urine samples were collected and refrigerated for determination of sodium, potassium, aldosterone and PG values before and at the end of each diet. Aldosterone and PG values were calculated by RIA (Amersham kits). Before RIA was carried out, a solid phase extraction procedure was performed for both PGE_2 and $PGF_{2\alpha}$, according to the method described by Powel;[19] SEP-PAK C^{18} was used for column chromatography. Sodium and potassium concentrations were determined by flame photometry. All data are presented as means ± SEM. Parameters were compared within the normotensive group and the hypertensive group and also between the two groups, by means of Student's *t*-test for both unpaired and paired observations.[20] Corrections for age were made during statistical analysis. Pearson's correlation coefficients were used to examine the relationship among changes in the variables. A *P*-value of less than 0,05 was considered significant.

Results

The results are presented in Tables I and II. They show that both normotensive and hypertensive groups were well balanced and comparable during low-Na and high-Na regimens. The two groups responded with a significant decrease in systolic arterial pressure during sodium restriction, and with an increase in both systolic and diastolic arterial pressure during sodium loading.

The normotensive black women had relatively low plasma renin activity (PRA) and a discrepancy between their low PRA and normal aldosterone excretion was evident. Sixty-two per cent of the hypertensives had low-renin hypertension and 38% normal-renin hypertension (Fig. 1). In spite of suppressed RASs, the two groups still responded to changes in sodium balance with an increase or a decrease in PRA during sodium restriction and sodium loading, respectively. PGE_2 excretion was low in both normotensive and hypertensive groups; this was in accordance with their low-renin status. PGE_2 excretion was significantly lower in the hypertensive group compared with the normotensives. The higher PGF_{2a} excretion in the hypertensives was not significant. The significantly decreased PGE_2 excretion and the trend toward increased PGF_{2a} excretion in the hypertensives was reflected in the significantly decreased PGE_2/PGF_{2a} ratio in this group ($P < 0,001$).

Linear regression analysis of pooled data (during normal-, low- and high-Na diets) in both groups showed no significant correlation between PRA and mean arterial pressure. PRA was inversely correlated with the Na^+/K^+ ratio ($r = -0,52$; $P < 0,01$). There was no significant correlation between urinary sodium excretion and that of both urinary PGE_2 and $PGF_{2\alpha}$. A good positive correlation between PGE_2 and PRA was found ($r = 0,61$; $P < 0,01$).

Table II. Effect of sodium status on arterial pressure, plasma renin activity, urinary aldosterone levels and prostaglandin excretion in 13 normotensive black women

Dietary sodium (mmol/24h)	SAP	DAP	MAP	Na^+/K^+	PRA	Aldo	PGE_2	$PGF_{2\alpha}$	$PGE_2/PGF_{2\alpha}$
Basal (120 - 150)	122 ± 3	73 ± 3	89 ± 3	2,97 ± 0,33	2,26 ± 0,27	27 ± 2,4	243 ± 11	428 ± 20	0,57 ± 0,02
Low Na^+ (less than 40)	108 ± 4*	68 ± 2	81 ± 2*	0,41 ± 0,05*	4,10 ± 0,59*	60 ± 3,6*	409 ± 15*	546 ± 22*	0,76 ± 0,03*
P-value	< 0,01	> 0,10	< 0,01	< 0,001	< 0,01	< 0,001	< 0,001	< 0,001	< 0,001
High Na^+ (300)	125 ± 3†	78 ± 2†	94 ± 2†	4,05 ± 0,29†	1,04 ± 0,07†	34 ± 2,4†	294 ± 25†	480 ± 22†	0,64 ± 0,04†
P-value	< 0,01	< 0,01	< 0,001	< 0,001	< 0,001	< 0,001	< 0,001	> 0,05	< 0,05

Data are presented as means ± SEM; SAP = systolic arterial pressure (mmHg); DAP = diastolic arterial pressure (mmHg); MAP = mean arterial pressure (mmHg); Na^+/K^+ (mmol/24h); PRA = plasma renin activity (ng/ml/h) (normal total range for the kit at daily sodium intake *ad lib* is 2,0 - 5,0 ng/ml/h); Aldo = aldosterone (μmol/24h); PGE_2 = prostaglandin E_2 (ng/24h); $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$ (ng/24h).
* Statistically significant compared with control basal value.
† Statistically significant compared with low-Na^+ diet.

Table III. Effect of sodium status on arterial pressure, plasma renin activity, urinary aldosterone levels and prostaglandin excretion in 13 hypertensive black women

Dietary sodium (mmol/24h)	SAP	DAP	MAP	Na^+/K^+	PRA	Aldo	PGE_2	$PGF_{2\alpha}$	$PGE_2/PGF_{2\alpha}$
Basal (120 - 150)	164 ± 5*	105 ± 4*	125 ± 4*	3,30 ± 0,40	1,70 ± 0,18	28 ± 1,9	166 ± 14*	450 ± 26	0,38 ± 0,02*
P-value	< 0,001	< 0,001	< 0,001	> 0,10	> 0,10	> 0,10	> 0,10	> 0,10	< 0,001
Low Na^+ (less than 40)	150 ± 5†	95 ± 4	113 ± 4†	0,48 ± 0,10†	2,22 ± 0,23	61 ± 2,1†	188 ± 16	435 ± 20	0,43 ± 0,02
P-value	= 0,05	> 0,1	< 0,05	< 0,001	> 0,10	< 0,001	> 0,10	> 0,10	> 0,10
High Na^+ (300)	165 ± 5‡	107 ± 4‡	126 ± 5‡	3,78 ± 0,69‡	1,18 ± 0,10‡	40 ± 1,8‡	164 ± 13	425 ± 20	0,38 ± 0,02
P-value	< 0,001	< 0,001	= 0,05	< 0,001	< 0,001	< 0,02	> 0,10	> 0,10	> 0,10

Data are presented as means ± SEM. See Table II for legend.
* Statistically significant compared with basal value of the normotensive group (Table II).
† Statistically significant compared with control value of the same group.
‡ Statistically significant compared with low-Na^+ diet of the same group.

Discussion

Urinary PGE_2 and $PGF_{2\alpha}$ appear to be derived predominantly from *de novo* intrarenal synthesis.[21] Numerous studies have used these measurements to evaluate the hypothesis that a deficiency of the known vasodilating and natriuretic effects of renal PGE_2 and/or an excess of the renal venoconstrictor $PGF_{2\alpha}$ might be of importance in causing systemic (essential) hypertension. Changes in urinary PGE_2 excretion during sodium loading are of interest in evaluating its possible role as a natriuretic substance. Stimulation of renal PG synthesis by sodium depletion or furosemide administration has been used to evaluate renal reserve for PG synthesis.[8] Considerable controversy about PG excretion in relation to dietary sodium intake has been reported. Some authors reported increased PGE_2 excretion after oral sodium loading in humans[23,24] or decreased PGE_2 excretion in response to furosemide administration.[9,25] The same authors[23-25] found low basal PG excretion in essential hypertensive patients and postulated that a deficiency of the renal vasodilator-natriuretic system (dopamine-PGS-kallikreins) is involved in the genesis of essential hypertension. In contrast to these observations, other studies[15,26] do not support the assumption that endogenous PGE_2 has a natriuretic action on the kidney. The results of the present study agree with this latter assumption and indicate that PGE_2 excretion increased when dietary sodium intake was reduced both in normotensives and in hypertensives, i.e. renal PGE_2 does not act as a diuretic. The reason for stimulation of renal PG synthesis by sodium depletion remains unresolved at present, but enhanced renin release may play some role, since it has been reported that the renin-angiotensin-aldosterone system (RAAS) is closely associated with PGs.[27] It has been suggested that PGs modulate the vasoconstrictive activity of angiotensin II and the renal sympathetic nervous system during salt depletion.[26] The increased concentrations of angiotensin II and antidiuretic hormone may enhance the mobilisation of arachidonic acid and thus the synthesis of PGs.[28] Plasma aldosterone, increased by sodium restriction (more distinctly than PRA), may increase PGE_2 excretion by activation of the renal kallikrein-kinin system.[21] The mechanism responsible for the decrease of PG production after high salt intake is also unclear. In addition to the suppressed RAAS, an effect of sodium chloride on PGE_2-9-ketoreductase, which is considered a mediator of salt intake-related PG-renin interaction,[29] might be considered.

In the present study, distinctly suppressed PGE_2 excretion was found in the hypertensive group; this agrees with the concept of decreased renal PG synthesis in hypertensive subjects[30,31] and points to a specific PG pattern in hypertensive patients of African origin which depends on their low-renin status. The present data are consistent with the suggestion that variations in dopamine and kallikrein in black people might contribute to a system that exhibits both sodium sensitivity and renal vasoconstriction.[14,32] This pattern is consistent with volume expansion and early nephrosclerosis in black hypertensive patients.

The present results do not support the theory of increased synthesis of renal venopressor $PGF_{2\alpha}$ in black hypertensive patients.

Further studies are necessary to confirm the possibility of ethnic pattern in renal PG synthesis.

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Duchenne and Becker muscular dystrophy prevalence in South Africa and molecular findings in 128 persons affected

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A genetic service for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) was initiated in Cape Town in 1987. Of the 143 DMD patients diagnosed during the period 1987-1992, 66 had a familial pattern of inheritance and 77 were apparently sporadic. Twenty BMD patients were identified, of whom 12 had other affected relatives and 8 were sporadic. Overall minimum prevalence rates of 1/100 000 for DMD and 1/755 000 for BMD were calculated. A markedly low DMD prevalence in the indigenous black population (1/250 000) contributed to the overall low DMD prevalence in South Africa when compared with that in the UK (1/40 000).

By means of molecular methods, the diagnosis in 42% of the affected DMD males was confirmed by detection of deletions in the dystrophin gene. Deletions were identified in 50% of Indian, white and mixed ancestry patients. In contrast, only 22% of blacks had identifiable deletions.

DMD appears to be underrepresented in the black population; the low deletion frequency in this group suggests that unique mutations not detectable by methods used in this study may be more frequent in these patients than in the other populations. The increased DMD frequency in Indians corroborates findings reported from the UK.

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Duchenne muscular dystrophy (DMD) is the most common heritable muscle disorder[1] and is transmitted as an X-linked recessive trait. Affected boys characteristically exhibit progressive muscle weakness and pseudohypertrophy of the calf muscles.[2] The disorder has an inexorable progressive clinical course culminating in death in the teenage years. A similar but milder condition, Becker muscular dystrophy (BMD), occurs less commonly. Those with this disorder are less severely affected and are usually able to procreate.[3]

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