# Pathophysiological mechanisms of urbanisation-related hypertension and the sodium pressor response in black Zimbabweans

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**Abstract** **This study examined the role of endothelin (ET), the thromboxane $A_2$ ($TXA_2$)-prostacyclin ($PGI_2$) ratio ($TXA_2/PGI_2$), plasma renin activity (PRA) and urinary aldosterone excretion (ALDO) in urban hypertensive patients and in the sodium pressor response in normotensives. Twenty-seven urban hypertensive patients and the same number of normotensive controls were studied on baseline diet, after 5 days of sodium restriction and after 5 days of sodium loading. Mean arterial blood pressure, plasma and ET values, PRA, $TXA_2/PGI_2$ and ALDO were assessed on each diet.**

**The results showed that baseline PRA was suppressed in the hypertensive patients; this indicates that urbanisation-related hypertension is of the low renin type. ET levels and $TXA_2/PGI_2$ were higher in hypertensive than in normotenisve subjects, suggesting an association between high blood pressure and these factors. Although the baseline PRA in hypertensives was suppressed, urinary ALDO was no different from that in the normotensive controls where PRA was normal. In addition, sodium restriction did not increase PRA in hypertensive subjects while it more than doubled it in the controls. However, ALDO in hypertensive patients increased to levels that were no different from those in the normotensive subjects. Sodium loading increased blood pressure, ET values and $TXA_2/PGI_2$ indicating an association between the latter two factors and the sodium pressor response in those with hypertension. ALDO decreased to similar levels on sodium loading in the two groups. This decrease in ALDO was accompanied by suppression of PRA only in normotensive subjects.**

**In conclusion, the low-renin-activity urban hypertensives we studied had increased baseline ET levels and $TXA_2/PGI_2$. The observed pressor response was accompanied by increases in these two factors. This suggests an important role for the two factors in this form of hypertension and the sodium response in normotensives.**

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Vascular endothelial cells play a significant role in the control of blood pressure. They secrete vasoconstrictors like endothelin (ET)[1] and vasodilators like nitric oxide[2] and prostacyclin ($PGI_2$). Circulating $PGI_2$, an antithrombogenic vasodilator[3], is decreased in some forms of hypertension, particularly in mild essential hypertension[4] and in pregnancy-induced hypertension.[5] Thromboxane $A_2$ ($TXA_2$), mostly from activated thrombocytes, causes vasoconstriction and platelet aggregation.[6] Impairment of the synthesis and/or release of these two substances, particularly the reduction of $PGI_2$ synthesis, could lead to high blood pressure and also predisposes the subjects to increased thrombogenic phenomena. In this context, Minuz *et al.*[4,5] have reported suppression of $PGI_2$ in patients with mild essential hypertension and pregnancy-induced hypertension. In these two reports, $TXA_2$ was normal and resulted in a higher ratio of $TXA_2$ to $PGI_2$ in the patients than in matched normotensive controls.

ET has been shown to be elevated in essential hypertension[7,8] and to increase blood pressure when infused in humans.[9] The observed blood pressure can be increased by two mechanisms; vasoconstriction that leads to increased total peripheral resistance[9] and sodium retention stimulated by aldosterone secretion from the zona glomerulosa cells of the adrenal cortex.[10,11] It is possible that this latter action on the adrenal cortex is synergistic with the actions of the renin angiotensin system if stimulated.

A number of studies, mostly from Africa, have reported higher blood pressures and hypertension prevalences in urban than in rural environments.[12-15] An increased dietary sodium/potassium ratio was positively correlated with blood pressures in these studies. We have previously reported that young Zimbabwean men are sensitive to acute dietary sodium loading.[16] In addition, older urban and rural normotensive subjects have recently been shown to exhibit sodium pressor sensitivity.[17] The response of urban hypertensive patients to dietary sodium has, however, not been reported in developing countries.

A common pathway in the pathogenesis of high blood pressure and different forms of essential hypertension has not yet been discovered. It appears conceivable that elevated $TXA_2/PGI_2$ and ET levels already reported in other forms of hypertension, may play such a role in the pathophysiology of hypertension in urbanised subjects. In addition, these hormonal mechanisms could mediate sodium pressor sensitivity which has been implicated in urbanisation-related hypertension.

The purpose of this study was to examine the role of plasma renin activity (PRA), urinary aldosterone (ALDO), $TXA_2/PGI_2$ and ET in urban hypertensive patients and in the sodium pressor response in normotensive subjects.

## Methods

Two groups participated in this study. These consisted of 27 newly diagnosed hypertensive patients and 27 normotensive controls. Both men and women were included in similar numbers.

### Selection of urban hypertensive patients

Fifteen hypertensive men, identified from a blood pressure survey at Turnall Industries in Harare, volunteered and constituted the group of urban hypertensive men. Immediately after commencing the study, 1 subject withdrew leaving a total of 14 men who completed the study. Hypertensive women in the study were identified from a blood pressure survey which was part of Intersalt 1986.[18] The first 15 hypertensives to volunteer were

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considered for this study. On the first day of the study, 2 women did not turn up for baseline measurements and were immediately disqualified; this left 13 women to complete the study. Both groups of hypertensive subjects had resided in the urban environment for at least 5 years before this study.

### Selection of urban normotensive subjects

Twenty-seven normotensive men and women were matched for age with the hypertensive patients. Fourteen men and 13 women were recruited from subjects who were identified as normotensive in a blood pressure survey of all general workers at a teaching hospital in Harare. Some of the people in this study had participated in the Intersalt 1986 study. In addition, both groups of normotensives had resided in the urban environment for at least 5 years before this study.

### Laboratory measurements

Blood pressure was measured by means of a random zero sphygmomanometer according to the protocol used in Intersalt 1986[18] and then daily throughout the study. The subjects relaxed in chairs for 5 minutes before the heart rate and blood pressure were measured twice, 5 minutes apart. Sodium and potassium levels were measured by means of flame photometry. ET levels were measured from plasma after extraction, with radioimmunoassay kits supplied by Amersham International, United Kingdom.

$TXA_2$ and $PGI_2$ were measured by means of radioimmunoassay of their stable metabolites from 24-hour urine samples. Before the assay was carried out, a solid phase extraction procedure was performed for both prostaglandins according to the method described by Powell and by means of SEP-PAK C18 for column chromatography.[19] PRA and urinary ALDO were also measured by means of radio-immunoassay.

## Experimental protocol

Subjects had their blood pressures measured at least three times before the study. Initial blood pressure recordings were generally high compared with those taken on the second or third occasion. These spuriously high pressures were mostly the result of anxiety on the part of subjects, who were unfamiliar with the researcher or the procedures. Observations taken after repeated measurements tended to approximate the actual prevailing blood pressures. The subjects were accommodated in the University of Zimbabwe dormitories for the entire duration of the study.

On the first day, the subjects had baseline measurements taken. These included blood pressure measurements by one investigator using the random zero sphygomomanometer throughout the study, blood sampling and a 24-hour urine collection. After these baseline measurements, the subjects started on a low-salt diet that provided 40 mEq $Na^+$ per day for 5 days after which measurements similar to those under baseline conditions were done.

Subjects were then allowed free access to salt and any food they wished for 2 days and could at this stage visit their families. After this rest period they were served a high-salt diet that provided 300 mEq $Na^+$ per day for 5 days after which measurements similar to those done while on the low-salt diet were taken.

## Statistical analysis

Differences in these continuous variables reported were sought by means of Student's *t*-test. The sample size was adequate to identify statistically significant differences.

## Results

### Baseline measurements

The mean arterial pressure was 125 ± 3 mmHg in hypertensive patients compared with 89 ± 2 mmHg in the normotensive controls. The mean plasma ET level was 13 ± 2 pg/ml in the hypertensives compared with 8 ± 0,84 pg/ml in the normotensives. $TXA_2/PGI_2$ was 2,7 ± 0,2 in the hypertensives and 1,3 ± 0,1 in normotensives. Mean arterial pressure, ET, PRA and ALDO, and $TXA_2/PGI_2$ were all significantly higher in the hypertensive patients than in the normotensive controls. PRA was 1,6 ± 0,1 pmol angiotensin I/h/ml in hypertensives which was less than the 2 ± 0,2 in normotensives. ALDO was 27 ± 2 µmol/24 hours in hypertensives and 26 ± 2 in normotensives. ALDO excretion from 24-hour urine collections was similar in the two groups despite lower PRA in the hypertensive group (Table I).

### Sodium pressor response in normotensive patients

The mean arterial pressure increased from 83 ± 2 mmHg on a low-salt to 91 ± 2 mmHg on a high-salt diet. This sodium pressor response was accompanied by an increase in ET from 8 ± 0,84 pg/ml to 13 ± 1,36 pg/ml. PRA and ALDO were 4,8 ± 5 pmol angiotensin I/h/ml and 61 ± 3 µmol/24 h respectively on sodium restriction. These decreased to 1 ± 0,2 pmol angiotensin I/h/ml and 30 ± 2 µmol/24 h respectively in response to dietary sodium loading (Table I). $TXA_2/PGI_2$ did not change throughout the study.

**TABLE I.**
**Mean arterial blood pressure, PRA, 24-hour ALDO and sodium/potassium, plasma ET and thromboxane $TXA_2$ to $PGI_2$ prostacyclin changes on baseline, low salt and high salt diets. Mean ± standard error of the means are given for baseline, low-salt and high-salt diets**

| | Normotensives | | | Hypertensives | | |
|---|---|---|---|---|---|---|
| | Baseline | Low salt | High salt | Baseline | Low salt | High salt |
| Urinary $Na^+/K^+$ | 3,3 ± 0,3 | 0,6 ± 0,3 | 4,6 ± 0,4† | 3,4 ± 0,3 | 0,8 ± 0,2 | 4,1 ± 0,3† |
| MABP (mmHg) | 89 ± 2* | 83 ± 2 | 91 ± 2† | 125 ± 3 | 116 ± 3 | 127 ± 3† |
| PRA (pmol Ang I/h/ml) | 2 ± 0,2* | 4,8 ± 0,5 | 1 ± 0,2† | 1,6 ± 0,1 | 1,6 ± 0,1 | 1,1 ± 0,1 |
| Urinary ALDO (µmol/24 h) | 26 ± 2 | 61 ± 3 | 30 ± 2† | 27 ± 2 | 60 ± 10 | 39 ± 7† |
| ET (pg/ml) | 9 ± 0,7* | 8 ± 0,8 | 13 ± 1† | 19 ± 2 | 13 ± 2 | 24 ± 3† |
| $TXA_2/PGI_2$ | 1,3 ± 0,1* | 1,3 ± 0,1 | 1,4 ± 0,1 | 2,7 ± 0,2 | 2,8 ± 0,2 | 3,9 ± 2† |

*Significant difference ($P < 0,05$) between baseline hypertensives and normotensives.
†Significant difference ($P < 0,05$) between low salt and high salt in hypertensives or in normotensives.
MABP = mean arterial blood pressure.

### Sodium pressor response in hypertensive patients

The mean arterial pressure increased from 116 ± 3 mmHg on sodium restriction to 127 ± 3 mmHg on increasing dietary salt. ET increased from 13 ± 2 pg/ml to 24 ± 3 pg/ml during this pressor response. $TXA_2/PGI_2$ increased from 2,8 ± 0,2 on low salt to 3,9 ± 0,2 on increasing salt intake. ALDO was 60 ± 10 µmol/24 h on sodium restriction and decreased to 39 ± 7 on sodium loading. PRA did not change significantly throughout the study.

## Discussion

Our study examined the roles of ET and $TXA_2/PGI_2$ in urbanisation-related hypertension and the sodium pressor response. We report three important findings. Firstly, urbanisation-related hypertension as manifested in these subjects exhibits low PRA. Secondly, $TXA_2/PGI_2$ and ET levels were higher in urbanisation-related hypertensives than in normotensive urban controls which is consistent with findings in other forms of essential hypertension.[4,5] Thirdly, the sodium pressor sensitivity which is characteristic of most black essential hypertensive patients[20] was observed in both normotensives and hypertensives. This pressor sensitivity appears to be mediated by increased ET and an increased $TXA_2/PGI_2$ in the hypertensive patients, but only by increased ET in the normotensive controls. Elevated $TXA_2/PGI_2$ appears to be an additional mechanism leading to increased blood pressure in the hypertensives subjected to increased dietary salt intake.

The higher baseline levels of ET and $TXA_2/PGI_2$ in the hypertensive patients than in normotensive controls support an important role for these factors in urbanisation-related hypertension. Essential hypertension is a very heterogeneous disease and is associated with conditions like obesity, diabetes mellitus and pregnancy as well as urbanisation.

ET has already been shown to be elevated in essential hypertensives.[8] ET increases blood pressure by increasing vascular smooth muscle contraction and consequently increasing resistance.[9] This 21-amino acid residue peptide stimulates aldosterone secretion from the adrenal cortex independently of angiotensin II, which leads to sodium retention and an increase in blood pressure. The higher level of this peptide in urban hypertensive patients may be a cause or effect of hypertension. Results from our study support a causal role for this hormone. When the patients moved from low salt to high salt there was a significant increase in blood pressure, demonstrating sodium pressor sensitivity. This pressor sensitivity was accompanied by a significant increase in ET. Therefore, it appears that the increase in ET may contribute to the observed increase in blood pressure at least in the short term. The pressor response in the normotensives was also accompanied by increased ET. Although the concentration of ET was lower in the normotensive than in the hypertensive subjects during the pressor response, the causal role of this hormone in the observed blood pressure increase cannot be ruled out. This ET in sodium pressor relationship can be extrapolated from support to the possible long-term development of hypertension.

Baseline PRA was suppressed in the hypertensive patients compared with the normotensive controls. As expected, sodium restriction lowered blood pressure in both normotensives and hypertensives. PRA remained unchanged in the latter, although it more than doubled in the former. Baseline ALDO was similar in the two groups despite suppressed PRA in the hypertensive group. Furthermore, during sodium restriction, 24-hour ALDO excretion more than doubled in both groups of subjects. It appears that there has been a novel finding of increased ALDO excretion without increased PRA, the mechanism of which is not obvious, but which could be ET. During the same procedure, in hypertensives ET decreased to levels still higher than the baseline in normotensives. It is therefore conceivable that in the absence of normal PRA, other humoral agents, including increased ET, may act as an alternative mechanism for the stimulation of ALDO secretion.

A depressed circulating level of $PGI_2$ has been demonstrated in pregnancy-induced hypertension and in mild essential hypertension.[4,5] Increased $TXA_2/PGI_2$ due to decreased $PGI_2$ with normal $TXA_2$, may act as a synergistic mechanism in the blood pressure increase in hypertensives. $TXA_2$ from activated thrombocytes was reported to be normal, despite the elevated $TXA_2/PGI_2$ ratio in these patients. In our study, this ratio was much higher in the hypertensive patients than in the normotensive controls under baseline conditions. The ratio decreased significantly in the hypertensives on LS and returned to normal on sodium loading. These changes in the ratio mirrored the changes in ET and blood pressure on manipulation of blood pressure. However, the ratio did not change significantly throughout the study in the normotensive controls.

We conclude that both ET and the $TXA_2/PGI_2$ ratio are increased in urbanisation-related hypertension compared with normotensive controls. It is plausible that the two factors may act synergistically to increase blood pressure in these patients. This is supported by the demonstration of a significant increase in both factors in sodium pressor sensitivity.

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