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Current and Birth Weights Exert Independent Influences on Nocturnal Pressure-Natriuresis Relationships in Normotensive Children

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Abstract—The objective was to study the impact of birth weight on the relationship between ambulatory blood pressure and urinary sodium excretion in children and adolescents The study included 134 healthy children (61 boys), all Caucasians, who were born at term after a normotensive pregnancy For each subject, a 24-hour ambulatory blood pressure monitoring and a complete urine collection were simultaneously performed according to the protocols designed Average ambulatory blood pressure (BP) and the urinary excretion rates for sodium, potassium, and creatinine were calculated separately for 24-hour, awake, and sleep periods defined by a mini-diary The excretion rate of sodium during sleep time was positively correlated with ambulatory systolic BP, such a positive relationship was not found for waking hours Consequently, the impact of birth weight on the relationship between blood pressure and the urinary sodium excretion rate was analyzed during sleeping hours Stepwise multiple regression analysis shows that although current weight was the strongest predictor for the sodium excretion rate during sleep ($P< 001$), there was also an independent significant direct relationship for birth weight ($P< 04$) after controlling for age, sex, and the average of systolic BP during sleep Adjusted for current weight, a significant difference in the regression slopes relating urinary sodium excretion rate and systolic BP during sleep exists between children in the lowest (<3 100 kg) and the highest tertiles (>3 500 kg) of birth weight ($P< 02$) Differences in sodium excretion rates, adjusted for current weight, between the two extreme tertiles of birth weight became significant at the highest systolic BP ($P< 04$) The children who had the lowest birth weight tended to excrete less sodium during sleep The results of the present study show a blunted pressure natriuresis curve in children and adolescents with the lowest birth weight Whether this abnormal renal sodium handling may be present as an initial or as an intermediate mechanism leading to higher BP values must be assessed in additional studies **(*Hypertension*. 1998;31[part 2]:546-551.)**

Key Words: birth weight ■ ambulatory blood pressure ■ sodium excretion ■ children

The crucial influences in producing adverse cardiovascular disease risk profiles may be the interactions among fetal development, as indexed by birth weight, genetic background, and environmental factors later in life Recently, a number of studies have found an inverse relationship between birth weight and blood pressure (BP) levels in both adults and children,[1-4] and this relationship becomes more evident throughout one's lifetime [5] There seems to be evidence that hypertension and the distribution of BP within the population are partially programmed in intrauterine life Postnatal exposure to environmental factors may then modify the prenatal BP setting [6] The interaction between fetal and environmental factors, however, remains poorly understood

There already exists a well documented connection between BP levels and salt intake [7,8] In essential hypertension, some observations and experiments have led to the hypothesis that a restricted ability to excrete sodium is one initiating factor in the development of hypertension [9] A sustained restraint on sodium excretion tends to trigger volume expansion, which itself stimulates a sustained activation of compensatory volume-adjusting mechanisms It is the persistent presence of the compensatory mechanisms that causes a rise in BP, thereby helping to overcome the kidney's inability to excrete sodium An abnormal pressure-natriuresis relationship could provide one pathway by which an impaired ability to excrete sodium would lead to hypertension [9]

As birth weight, hypertension, and dietary sodium intake are all common indicators of a population's health, any association between these factors is of great interest Investigations that gather such data can contribute to understanding how mechanisms acting during early life can contribute to the development of high BP later in life The present research was undertaken to study the impact of birth weight on the relationship between ambulatory BP and urinary sodium excretion in children and adolescents

Methods

Selection of Participants

One hundred and forty-nine children (69 boys) from 3 to 19 years of age were included in the present study All children had been selected

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from the pediatric outpatient clinic of the General Hospital of the University of Valencia, Spain, which the children attended for the purpose of routine health maintenance Systemic and renal disease were discounted through physical examination, serum biochemistry, and urinalysis All children included were born at term (>37 weeks) after a normotensive pregnancy The gestational age and the birth weight were obtained from routine obstetrical records Subjects were divided into tertiles by birth weight lowest tertile, <3 1 kg, middle tertile, 3 1 to 3 5 kg, and highest tertile, >3 5 kg Informed consent was obtained from the children and their parents The study was approved by the Committee for the Protection of Human Subjects of the General Hospital, University of Valencia, Spain

For each subject, 24-hour ambulatory BP monitoring and a complete urine collection were simultaneously performed according to the protocols described below

BP Measurements

Office and ambulatory measurements were performed following a previously published protocol [10] Briefly, on the day of the monitoring, nurses measured the BP of the subject, in the sitting position, three times consecutively using a mercury sphygmomanometer after a rest of at least 5 minutes Korotkoff phase I was used for systolic blood pressure (SBP) and phase IV was used for diastolic blood pressure (DBP) for children younger than 13 years of age, and phase V was used for children older than 13 years of age [11] The mean of the three measurements was considered the office BP

An ambulatory BP monitoring was performed using a SpaceLabs model 90207 monitor (SpaceLabs, Inc) weighing 340 g (including batteries) This device uses an oscillometric method with a deflation rate of 8 mm Hg/s The proper cuff was selected from among the three sizes supplied by the manufacturer (10×13, 13×24, and 24×32 cm) according to the subject's arm length, the cuff, which was placed on the nondominant arm, extended completely around the arm, and the bladder width covered at least two-thirds of the upper arm The accuracy of the monitor was tested on each subject under resting conditions at the beginning of the monitoring period

Ambulatory BP monitoring was performed during a regular school day with normal recreational activities, although the children were instructed not to engage in vigorous physical exercise or contact sports on monitoring days Recording began between 8 30 and 9 00 AM The reading frequency was programmed every 20 minutes from 6 00 AM to 12 00 midnight and every 30 minutes from 12 00 midnight to 6 00 AM The relatives of the participants were required to keep a mini-diary, recording what time the children went to sleep and when they awoke

Readings were automatically rejected when 1) SBP>220 mm Hg or <70 mm Hg, and 2) DBP>140 mm Hg or <40 mm Hg Whenever a reading could not be successfully completed, the measurement was automatically repeated after 2 minutes while retaining the preestablished sequence Nonedited recordings, in which more than 30% of the measurements were erroneous, were excluded from the analysis The average of the total number of readings obtained during each monitoring session was 61±3

Three different time periods were defined for this study 24-hour, awake-time, and sleep-time The 24-hour period included all valid readings performed during the monitoring Both awake-time and sleep-time were defined according to the mini-diary, in which bedtime and awakening times were annotated by the subject or his relatives Sleep-time was identified from the subject's mini-diary as the time between retiring at night and standing up in the morning Awake-time was defined as the remainder of the day The following parameters were calculated for each subject total number of readings and mean SBP and mean DBP during the 24-hour, awake-time, and sleep-time periods

Urinary Electrolyte Measurements

On the day of the ambulatory BP monitoring (ABPM), the subjects collected a timed, 24-hour urine specimen in two containers, one for awake-time and one for sleep-time use All urine produced during waking hours, including the last urine before retiring, was collected in the awake-time bottle Urine passed during sleep-time and upon rising was collected in the sleep-time container Urine volume was measured, and aliquots of urine were taken from both samples to measure urinary electrolyte and creatinine levels the day after collection Sodium and potassium concentrations in the urine were determined by flame-photometry, and creatinine concentration was measured by an automated enzymatic method (Technicon Autoanalyzer, Technicon Instruments) The sodium, potassium, and creatinine excretions were expressed per minute for the whole day, the awake period, and the sleep period

Possible under-collection or over-collection of urine during the 24-hour period was evaluated using standardized creatinine excretion for body weight estimates Creatinine excretion was well within the accepted normal range for age according to a previous study [12]

TABLE 1. General Characteristics, Office and Ambulatory Blood Pressure in the Study Population (n=134)

Parameter	Average	SD
Age (yr)	10 0	3 5
Weight (kg)	43 1	17 4
Height (m)	1 41	0 22
Body mass index (kg/m^2)	20 8	4 9
Birth weight (kg)	3 4	0 65
Office blood pressure		
SBP (mm Hg)	105 1	25 1
DBP (mm Hg)	57 5	6 9
Ambulatory blood pressure		
24-hour		
SBP (mm Hg)	108 9	9 1
DBP (mm Hg)	63 9	4 8
Awake-time		
SBP (mm Hg)	112 6	9 5
DBP (mm Hg)	67 8	5 1
Sleep-time		
SBP (mm Hg)	99 6	9 7
DBP (mm Hg)	54 9	6 1

Awake-time and sleep-time for each individual subject was calculated using a mini-diary

Statistical Analysis

An association within two parameters was assessed by Pearson correlation coefficient Multiple linear regression analysis was calculated in which urinary sodium excretion per minute during sleep-time was the dependent variable and age, sex, current weight, birth weight, and the average of sleep SBP were the independent variables The regression slopes relating urinary sodium excretion and SBP during sleep within lower and higher tertiles of birth weight were evaluated by a formal test for interaction (covariance analysis) by adjusting for current weight The covariant per SBP of the differences in sodium excretion per minute and per current weight during awake and sleep periods within lower and higher tertiles of birth weight was evaluated using a multiple analysis of variance

Results

General Characteristics of the Study Population

One hundred and thirty-four children (61 boys and 73 girls), all Caucasians, who fulfilled the inclusion criteria were included in the analysis The general characteristics of the study population are shown in Table 1

TABLE 2. Urinary Electrolyte Measurements (n=134)

Parameter	24-hour	Awake-time	Sleep-time
Duration (hr min)	24 00±00 00	14 56±00 55	09 03±00 55
Volume (mL/min)	0 67±0 34	0 71±0 42	0 61±0 39*
Creatinine (μg/min)	420 9±31 1	414 0±33 2	437 2±35 6
Sodium (μmol/min)	105 3±4 5	114 6±5 7	88 9±5 7*
Potassium (μmol/min)	32 1±1 1	40 1±1 6	19 4±1 2*
Sodium/potassium ratio	3 39±0 11	2 95±0 10	5 27±0 25*

The values are expressed as mean±standard error Awake-time and sleep-time for each individual subject was calculated using a mini-diary

*$P<$ 001 denotes a significant difference between awake-time and sleep-time

BP Measurements

The mean values of SBP and DBP for both office and ambulatory BP for 24-hour, awake-time, and sleep-time measurements are shown in Table 1 Reflecting circadian rhythmicity, the SBP and DBP during awake-time were higher than those measured during sleep-time

An inverse relationship between birth weight and all ambulatory BP values was observed The correlation coefficients between birth weight and means of ambulatory BP were as follows 24-hour SBP ($r=-0$ 11, $P=$ 23), 24-hour DBP ($r=0$ 04, $P=$ 69), awake-time SBP ($r=-0$ 13, $P=$ 13), awake-time DBP ($r=-0$ 03, $P=$ 72), sleep-time SBP ($r=-0$ 08, $P=$ 71), sleep-time DBP ($r=0$ 04, $P=$ 70) Although the correlation coefficients were low, the strongest relationship was observed between birth weight and SBP In contrast, a significant positive correlation emerged between ambulatory SBP with age (24-hour $r=0$ 51, $P=$.0002, awake-time $r=0$ 53, $P=$ 0001, sleep-time $r=0$ 37, $P=$ 004), current weight (24-hour $r=$0.27, $P=$ 002, awake-time $r=0$ 25, $P=$ 004, sleep-time $r=0$ 21, $P=$ 018), and body mass index (24-hour $r=0$ 23, $P=$ 01, awake-time $r=0$ 22, $P=$ 01, sleep-time $r=0$ 20, $P=$ 02)

Urinary Measurements

In the study population, the total sodium excretion was 151 7±6 5 mmol for the 24-hour and 47 7±3 0 mmol for the sleep-time periods A significant positive correlation between these variables ($r=0$ 67, $P<$ 001) was observed The values for creatinine and urinary electrolyte excretion, expressed per minute, are shown in Table 2 Awake-time urine was collected for an average of 14 56±0 55 hours and sleep-time urine was collected for an average of 09 03±0 55 hours Creatinine excretion remained constant during both awake and sleep periods In contrast, urinary volume, sodium, and potassium excretion rates were significantly higher during the awake period than they were during sleep The awake/sleep ratio for the sodium excretion rate was 1 61±0 09 The sodium/potassium ratio increased significantly during sleep

A univariant relationship between ambulatory BP values and selected variables with urinary sodium excretion rates per minute for the 24-hour, awake, and sleep periods is shown in Table 3 Regardless of the time period considered, a significant positive correlation between sodium excretion and age, current weight, and body mass index was observed There is also a positive correlation between sodium excretion rate during sleep and birth weight The excretion rate of sodium during the 24-hour and sleep-time periods was positively correlated with ambulatory SBP, such a positive relationship was not found for waking hours (Table 3)

TABLE 3. Correlation Coefficients Between Urinary Sodium Excretion per Minute and General Characteristics and Blood Pressure in the Study Population (n=134)

	Sodium (μmol/min)		
Parameter	24-hour	Awake-time	Sleep-time
Age (yr)	0 48†	0 45†	0 29†
Current weight (kg)	0 57†	0 49†	0 44†
Body mass index (kg/m^2)	0 42†	0 34†	0 37†
Birth weight (kg)	0 16	0 07	0 24†
24-hour SBP (mm Hg)	0 21*	0 15	0 21*
24-hour DBP (mm Hg)	−0 07	−0 12	0 04
Awake SBP (mm Hg)	0 19*	0 14	0 20*
Awake DBP (mm Hg)	−0 09	−0 14	0 03
Sleep SBP (mm Hg)	0 18*	0 11	0 19*
Sleep DBP (mm Hg)	−0 08	−0 10	−0 01

Awake-time and sleep-time for each individual subject was calculated using a mini-diary

*$P<$ 05, †$P<$ 01

Birth Weight, BP, and Urinary Sodium Excretion During Sleep

The impact of birth weight on the relationship between BP and the urinary sodium excretion rate during sleeping hours was analyzed Stepwise multiple linear regression analysis was used to assess the impact of other variables on the association between the birth weight and the urinary sodium excretion rate Although current weight was the strongest predictor for the sodium excretion rate during sleep, there was also an independent significant direct relationship between birth weight and urinary sodium excretion after controlling for age, sex, and the average of SBP during sleep (Table 4)

Adjusted for current weight, the regression slopes and their corresponding 95% confidence interval, relating the urinary sodium excretion rate and SBP during sleep in the lowest (<3 100 kg) and the highest tertiles (>3 500 kg) of birth weight are shown in Fig 1 The children who had the lowest birth weight tended to excrete less sodium during sleep The differences in sodium excretion rates between the two groups became significant when sleep SBP increases (Fig 1) As

TABLE 4. Relationship Between Urinary Sodium Excretion During Sleep with Other Selected Variables Estimated by Stepwise Multiple Regression Analysis (n=134)

Variables	Beta	P	R^2
Step 1			
Current body weight (kg)	1 637	< 001	
			0 194
Step 2			
Current body weight (kg)	1 525	< 001	
Birth weight (kg)	17 185	< 035	
			0 222

Other variables included in the analysis were age, sex, and average of sleep SBP

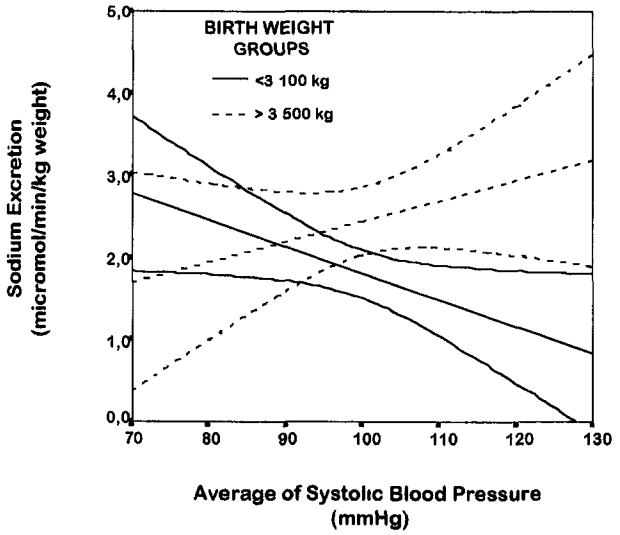

Figure 1. Regression slopes and their corresponding 95% confidence intervals, showing urinary sodium excretion rate, adjusted for current weight, and SBP during sleep in the lowest (<3 100 kg) and the highest tertiles (>3 500 kg) of birth weight There is a significant difference between the slopes (covariance analysis, $P < 02$)

sleep-time SBP increases, the urinary sodium excretion rate, adjusted for current weight, seems to be blunted among children in the lowest birth weight group when compared to those in the highest (MANOVA, $P< 04$) (Fig 2A) Furthermore, a lower sodium excretion rate during sleep in children in the lowest birth weight tertile was not compensated for during waking hours (Fig 2B)

Discussion

It has been extensively documented over the last several years that the population distribution of BP is partially programmed in intrauterine life (reviewed in ref 4) Postnatal exposure to lifestyles and to environmental factors seems to modify the prenatal BP setting, however One of the main environmental factors influencing BP values is sodium consumption,[8] and abnormal sodium-handling[9] may be a contributing factor to the development of essential hypertension In the present study, while simultaneously measuring ambulatory BP and urinary sodium excretion, we examined whether the pressure-natriuresis curve is influenced by birth weight In children and adolescents, birth weight seems to influence the pressure-natriuresis curve during sleep The sodium excretion rate of children with the lowest birth weight was lower than that observed in the highest birth weight group at the same level of BP

This observed difference in sodium excretion among children in the extreme tertiles of birth weight could not been explained by differences in gestational age, maternal BP, and current weight Gestational age and maternal BP do not seem to be determinants in the observed difference in sodium excretion because all subjects included were born at term, after a normotensive pregnancy Current weight has a significant positive correlation with sodium excretion ($r=0$ 44, $P< 01$) and with birth weight ($r=0$ 19, $P< 03$) If current weight is, to some extent, an intermediate variable between sodium excretion and birth weight, the sodium excretion rate was expressed per kilogram of current weight to avoid the effect of this potentially confounding variable After adjusting for current weight, difference in the sodium excretion rate during sleep remained significant between children in the extreme tertiles of birth weight

The relationship between BP values and sodium excretion, and the impact birth weight has on this relationship, was analyzed during sleeping hours During this time, but not during waking hours, SBP and the sodium excretion rate were positively correlated This difference could not be attributed to methodological problems in urine collection because creatinine excretion was constant throughout the 24 hours, as would be expected for complete collections During sleep, the balance between sodium-retaining and sodium-conserving mechanisms favors sodium excretion, so the pressure-natriuresis relationship probably becomes evident only at night [13,14]

Sodium excretion depends on papillary flow, which is not believed to be efficiently self-regulating, changing according to arterial pressure [15] An elevation in BP may result in an increased hydrostatic pressure within the vasa recta capillaries and the renal interstitium resulting in so-called pressure natriuresis [16] Sympathetic tone and other hormonal regulatory systems, such as the renin-angiotensin-aldosterone system, modulate the basic effect of arterial pressure on sodium excretion [17] Reduced activity in these modulating mechanisms

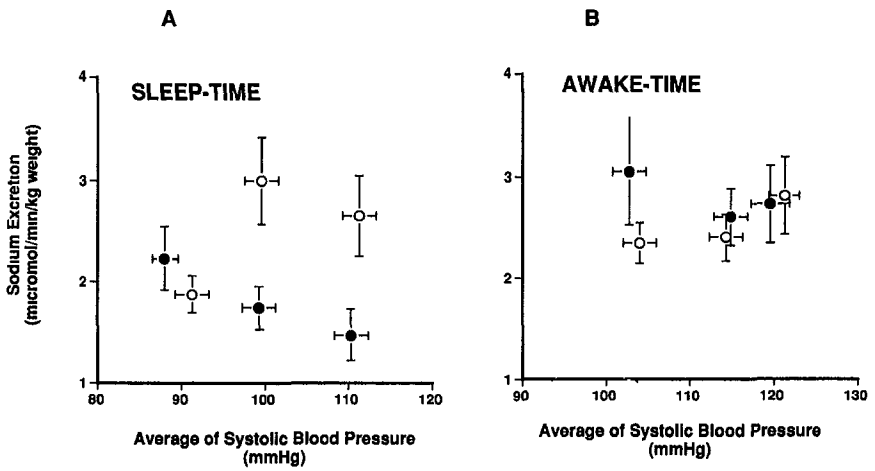

Figure 2. Urinary sodium excretion rate, adjusted for current weight, at different SBP values during sleep-time (A) and awake-time (B), in the two extreme tertiles of birth weight (lowest birth weight, <3 100 kg [●], and highest birth weight, >3 500 kg [○]) Urinary sodium excretion during sleep was blunted in children in the lowest birth weight group when compared to those in the highest birth weight group (MANOVA, $P < 04$) The lower sodium excretion rate during sleep in children in the lowest birth weight tertile was not compensated for during waking hours

at night, in a prolonged supine position, is substantiated by our data There is an increment in the sodium/potassium ratio, which allows overnight urinary sodium to reflect, in part, the pressure-natriuresis relationship

According to the pressure-natriuresis hypothesis for essential hypertension formulated by Guyton et al,[18] a diminished ability for sodium handling in the kidney leads to expanded extracellular volume Thus, BP rises, allowing the kidney to excrete excess sodium and restore the normal extracellular fluid volume Given the data in the present study, we have formulated a hypothesis to explain the association between birth weight and high BP values in children and adolescents A lesser ability to excrete sodium might be present in subjects with lower birth weight and could predispose them to a progressive rise in BP levels throughout life Abnormalities in sodium excretion have been observed in subjects who are prone to develop hypertension, such as healthy normotensive black adolescents,[19] young normotensive offspring of patients with essential hypertension,[20] and rats with hereditary hypertension [21]

The abnormal sodium-handling observed in normotensive children with lower birth weight, together with lifelong salt intake and the decreased ability to excrete sodium with age,[22] may contribute to an increase of BP values and to the inverse relationship between birth weight and BP values that becomes more evident throughout life [5] The mechanisms resulting in abnormal sodium-handling in children with the lowest birth weight, although still not fully explained, may be related to those implicated in the hypotheses advanced to explain why birth weight influences BP values A number of mechanisms could link a compromised intrauterine environment to reduced fetal growth and higher BP values An adverse environment during critical periods may lead to permanent changes in the body's structure, physiology, and metabolism, of these, reduced renal mass[23] and hormonal imprinting of cardiovascular and cerebral tissues during fetal life[24] have received the most attention

It has been argued that a reduced number of nephrons is one of the mechanisms responsible for the impact of low birth weight on BP values [25] Sixty percent of the nephron population develops in the third trimester,[26] and severe intrauterine retardation in human fetuses has been shown to exert a profound effect on renal development [27] A reduced number of nephrons produces an impairment in the capacity of the kidney to excrete sodium by the kidney A reduced number of nephrons by itself, however, does not explain the relationship between birth weight and BP described in the absence of intrauterine growth retardation

Increased fetal exposure to maternal glucocorticoids exerts organizational effects or imprinting patterns of response on vascular structures and cerebral tissue that persist throughout life [24] Reinforcing this, lower arterial compliance in subjects who were small at birth has been recently reported [28] Glucocorticoids in the maternal circulation are normally prevented from gaining access to the fetus by a placental enzyme, 11-beta-hydroxysteroid dehydrogenase, which catalyzes the rapidly metabolized cortisol and corticosteroid into inactive products Studies conducted in rats demonstrated a low activity level of this enzyme in newborn animals that have a large placenta but a low birth weight [29] Furthermore, the administration of low doses of dexamethasone to pregnant rats leads to persistently raised BP in the offspring [30] Hormonal imprinting may lead to reduced sodium excretion ability by predisposing the kidney to a higher vascular resistance, a situation characteristic in prehypertensive stages [31 32]

The finding of our study is important with regard to the development of high BP values and may be appropriate for the identification of high risk groups, an important public issue due to its potential for hypertension prevention It must be borne in mind that current weight is still one of the main determinants of BP values Indeed, the subjects with the highest risk for developing hypertension are those with the lowest birth weight and a higher current weight [33] Consequently, given our data, we believe the opportunity to implement dietary salt restrictions should be explored Any interpretation of our results, however, must take into account the cross-sectional design of the study Further research is needed to determine whether directly manipulating salt intake in this high risk group of children will result in a reduction of the BP rise rate

In summary, this study seeks to advance the knowledge of the mechanisms implicated in the inverse relationship between birth weight and BP values during life Our study shows that normotensive children in the lower birth weight tertile may have a restricted ability to excrete sodium Further studies are needed to assess the impact of abnormal renal sodium-handling on BP later in life An appreciation of the determinants of BP in the early years of life could provide clues for the prevention of hypertension

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