Erythrocyte Na⁺,K⁺ Cotransport and Na⁺,K⁺ Pump in Black and Caucasian Hypertensive Patients

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SUMMARY Alterations in red blood cell (RBC) Na⁺,K⁺ pump and in Na⁺,K⁺ cotransport (CoT) have been described in essential hypertension (EH). We examined pump and CoT in 50 normotensive (NT) subjects and 58 EH subjects subdivided by race and family history of hypertension (+ FH). RBCs were preloaded with Na⁺ to obtain intracellular levels of 25 mM/liter cells by using the p-chloromercuribenzenesulfonic acid (pCMBS) method. Na⁺ and K⁺ efflux rates into a magnesium-sucrose medium were quantitated in the presence of ouabain and ouabain plus furosemide to define pump and CoT activity respectively. Mean intracellular Na⁺ content was higher (p < 0.05) in black NT and HT subjects compared to Caucasians. Mean RBC CoT was lower in black EH compared to NT and compared to Caucasian NT and HT subjects. Conversely, Caucasian HT patients had higher mean CoT than NT subjects. Subdivision into + FH revealed very little effect of + FH on CoT in black NT and HT subjects. In Caucasian NT and HT subjects with + FH, mean CoT was significantly reduced (<0.3 mM/liter cells/hr) compared to those without + FH. A subgroup of Caucasian EH subjects displayed high CoT (>0.6 mM/liter cells/hr); a + FH had little impact on the high CoT group. There was no correlation between RBC CoT activity and age, sex, severity of hypertension, urinary sodium excretion, and plasma aldosterone. There was a positive correlation (r = +0.47; p < 0.01) between CoT and upright plasma renin activity. In 11 EH patients, reductions in blood pressure by antihypertensive agents did not consistently alter RBC CoT activity. Mean Na⁺ efflux by the RBC Na⁺,K⁺ pump measured in washed cells at Vmax was not different in RBCs from black and Caucasian NT and HT subjects. Since CoT function is normally low in RBCs from both black NT and EH subjects, the CoT assay may not be useful as a screening test to identify hypertensive-prone black NT subjects. In Caucasian subjects with a + FH, the assay might have utility as a screening procedure if further evidence links this assay to the pathophysiology of EH. (Hypertension 6: 536-544, 1984)

KEY WORDS • Na⁺,K⁺ cotransport • Na⁺,K⁺ pump • sodium • hypertension • erythrocyte • renin • race

A reduction in the erythrocyte Na⁺,K⁺ cotransport system has been described in patients with essential hypertension. Garay and co-workers first noted reduced erythrocyte net sodium-to-potassium flux ratios in essential hypertension. Subsequently, Dagher and Garay reported reduced outward Na⁺ and K⁺ cotransport in the erythrocytes from white patients with essential hypertension and in normotensive offspring from families with essential hypertension. Confirmation of a reduced red blood cell (RBC) Na⁺,K⁺ cotransport in the essential hypertensive population has not been uniform. One investigation noted reduced inward cotransport of ⁸⁶Rb, a substitute for potassium, in about 75% of the patients with essential hypertension. Another study, however, detected reduced cotransport in less than half of the patients. Other studies that used modified methodology to quantitate the furosemide-sensitive erythrocyte cotransport system were unable to detect any abnormality in this transport pathway in Caucasian subjects with essential hypertension. Recently, Adragna et al. reported elevated erythrocyte Na⁺,K⁺ cotransport in Caucasian subjects with essential hypertension and in normotensive offspring with a family history of hypertension.

These inconsistent findings in erythrocyte Na⁺,K⁺ cotransport in essential hypertension may be due to differences in RBC assay methodology. More importantly, they may reflect genetic, geographic, racial, or clinical differences in the hypertensive populations sampled. In a study by Davidson et al. in Capetown, South Africa, that included black, Caucasian, and racially mixed patients with essential hypertension, mean cotransport activity was lower in hypertensive patients as compared to controls of the same ethnic group. Hennessy and Ober described a lower capacity for K⁺ transport in erythrocytes from black patients with essential hypertension as compared to matched...
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Caucasian subjects. A higher percentage of K\(^+\) transport was dependent on ouabain-sensitive mechanisms, which suggested reduced ouabain-insensitive transport capacity.

Measurements of the activity of the Na, K pump in peripheral cells in essential hypertension have also yielded variable findings. Wambach et al.\(^{14}\) found elevated erythrocyte Na\(^+\),K\(^+\)-ATPase activity in hypertensive subjects, and Garay et al.\(^{15}\) noted higher ouabain-sensitive Na\(^+\) efflux rates in RBCs from patients with essential hypertension. Some studies have reported no difference in RBC pump activity between normotensive and hypertensive subjects.\(^{9,16}\) and others have found reduced ouabain-sensitive Na\(^+\) transport in erythrocytes from patients with essential hypertension.\(^{17}\) Two studies have suggested differences in pump activity between black and white normotensive and hypertensive subjects. Ouabain-sensitive rubidium uptake was reported to be lower in RBCs from black vs white normotensive subjects.\(^{18}\) Reduced ouabain-sensitive Na\(^+\) efflux rate constants were found in black Africans with essential hypertension.\(^{19}\) A recent study\(^{20}\) reported a higher sodium passive permeability in RBCs in white hypertensive patients but not in blacks.

Our present study examined outward erythrocyte Na\(^+\),K\(^+\) cotransport and Na\(^+\),K\(^+\) pump activity in a well-characterized population of black and Caucasian subjects with essential hypertension and a matched normotensive population. The relationship of these Na\(^+\) transport pathways to a family history of hypertension (+ FH) and to demographic and biochemical factors was analyzed.

Patients and Methods

We studied 58 patients with essential hypertension and 47 normotensive subjects in the Hypertension Clinics, Center for Health Sciences, UCLA School of Medicine, and the VA Medical Center, Sepulveda, California. Of the 58 with essential hypertension, 20 were black and 38 were Caucasian; of the 47 normotensive subjects, 18 were black and 29 were Caucasian. Approximately one-third of the normotensive and hypertensive subjects were female. Patients with essential hypertension ranged in age from 25 to 37 years, and normotensive subjects from 22 to 63 years. Secondary forms of hypertension were excluded by a family history of hypertension and related complications in first-degree relatives. Patients were on ad libitum sodium and potassium intakes. A 24-hour urine was collected for sodium, potassium, and creatinine. The day before each clinic visit. Samples for RBC transport assay were obtained in the morning with patients in the sitting position, and samples were collected on ice.

The assay is a modification of that described by Dagher and Garay\(^{4}\) to measure outward Na\(^+\) and K\(^+\) CoT. Fresh venous blood was collected in tubes containing sodium heparin (Organon, West Orange, New Jersey) and centrifuged at 4000 g at 4°C for 10 minutes; the plasma and buffy coat were then aspirated. The RBCs were washed twice at 4°C with approximately 10 volumes of cold 110 mM MgCl\(_2\) and recentrifuged. The RBCs were then loaded with Na\(^+\) and choline and depleted of internal K\(^+\) by the pCMBS (2,5-chloromercuribenzene sulphonate) method. The packed RBCs (4 ml) were suspended in the sodium-choline-loading solution at 4% hematocrit that contained (mM): 55 NaCl, 3 KCl, 150 choline chloride, 2.5 Na phosphate, 1 MgCl\(_2\), 1 ethyleneglycol-bis-(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), and 0.02 pCMBS at pH 7.2 and 4°C. The cells were incubated for 20 hours at 4°C in a slow-speed shaker. After centrifugation and complete removal of the supernatant, cells were resuspended for 1 hour at 37°C in a recovery medium containing (mM): 150 NaCl, 1 MgCl\(_2\), 5.4 Na phosphate, 4 cysteine, 2 adenine, 3 inosine, 1 EGTA, 10 glucose, and Tris buffer to adjust pH to 7.2. After centrifugation and removal of supernatant, cells were washed five times in cold 110 mM MgCl\(_2\) and resuspended in the same solution to obtain an approximately 50% hematocrit. Aliquots were taken for measurement of hematocrit and intracellular Na\(^+\) and K\(^+\). The internal cation composition was determined in triplicate from addition of the cell suspension to a 1/50 dilution in distilled water. To measure wet and dry weight of RBCs, 100 µl of packed RBCs (50% suspension) was weighed before and after 24 hours at 80°C. Measurements of percent water content were made on fresh cells and after pCMBS-loading of cells.

For cation flux studies, 1 ml of cells (4% to 5% final hematocrit) was added to tubes containing a Na-free, K-free Mg succrose medium (75 mM MgCl\(_2\), 85 mM sucrose, and 10 mM MOPS-Tris at pH 7.2 at 37°C). Fluxes were examined under three conditions with this medium and the following additions: KCl 5 mM, ouabain 0.1 mM, and ouabain 0.1 mM plus furosemide 1.0 mM. Aliquots (2 ml) of the above three suspensions were transferred to smaller tubes; tubes containing KCl alone and those containing ouabain alone were incubated at 37°C for 1 hour to measure the ouabain-sensitive fluxes. Separate tubes containing ouabain alone and ouabain plus furosemide were incubated for 3 hours with continuous agitation for measurement of cotransport. To stop the reaction, tubes were trans-
fered to 4°C for 1 minute, then centrifuged at 6000 g for 5 minutes. The supernatant was taken for measurement of Na+ and K+ content by atomic absorption spectrophotometry (Perkin Elmer 5000). Standards for Na and K in water ranged from 10 to 150 μM, and measurements were made without added ionization suppressor as no difference in readings was noted in solutions with and without the suppressor.

The cation efflux rate was calculated in millimoles per liter of cells per hour by dividing the regression slope relating cation efflux to time and was corrected for concentration by the final hematocrit of the Mg sucrose RBC suspension. The furosemide-sensitive efflux (cotransport) rate was derived from differences between values in the absence and presence of 1.0 mM furosemide. Ouabain-sensitive efflux (pump) was derived from differences between values obtained in the absence and presence of ouabain (0.1 mM). Ouabain- and furosemide-insensitive Na+ and K+ efflux (passive permeability) was expressed as a rate constant.

Blood samples for plasma renin activity and aldosterone were obtained from the antecubital vein with the patient upright. Plasma renin activity was measured by radioimmunoassay of the angiotensin I generated at 37°C for an hour. Assay sensitivity was 0.2 ng/ml/hr, and interassay coefficient of variation was 6%. Aldosterone was measured on extracted plasma by the radioimmunoassay method of Mayes et al.

Cysteine, adenine, inosine, EGTA, ouabain, and Tris were all ACS grade purchased from Sigma Chemical Company (St. Louis, Missouri). KCI, NaCl, and MgCl2 were purchased from Mallinckrodt, Inc. (St. Louis, Missouri). Furosemide was a gift from Hoechst Roussel Pharmaceuticals, Inc. (Somerville, New Jersey).

**Results**

The mean age and blood pressure level of the normotensive subjects and the patients with essential hypertension are depicted in Table 1. The differences in blood pressure were not significant between black and Caucasian patients. The range of urinary sodium excretion in the group with essential hypertension was 76 to 266 mEq per 24 hours.

**Intracellular Cation Concentration**

Mean intracellular sodium concentration was significantly (p < 0.05) higher in fresh erythrocytes from black compared to Caucasian patients with essential hypertension (Table 2). There was a difference in erythrocyte intracellular sodium between black and Caucasian normotensive subjects, but the values did not reach significance. Intracellular potassium content in fresh erythrocytes did not differ significantly among the four study groups (Table 2). Red cells were sodium-loaded by the pCMBS method to attain intracellular sodium concentrations as shown in Table 2. Mean concentrations were not different among the four study groups.

**Furosemide-Sensitive Sodium and Potassium Efflux**

Figure 1 depicts furosemide-sensitive Na+ and K+ efflux (cotransport) rates in erythrocytes from black and Caucasian subjects. Caucasian patients with essential hypertension displayed a significantly (p < 0.05) higher mean Na+ and K+ efflux rate compared to sodium efflux rate in black and Caucasian subjects. Caucasian patients with essential hypertension demonstrated a difference in erythrocyte Na+ and K+ efflux rate that was significantly (p < 0.05) lower than that of black normotensive subjects. Mean values for the rates of potassium efflux compared to sodium efflux rate were higher in the four study groups (Figure 1). These findings were not due to changes in erythrocyte water content after pCMBS loading. The variation in mean percent water content
in cells in Caucasian normotensive subjects before (64.2% ± 0.3% wt/wt) and after pCMBS (65.5% ± 0.4% wt/wt) and in black normotensive subjects before (62.5 ± 0.6% wt/wt) and after pCMBS (63.9% ± 0.5%) was minimal. Studies in cell water content in the hypertensive subjects also showed minimal changes after pCMBS treatment and no differences between blacks and Caucasians. The higher cotransport values for $K^+$ were most prominent in black normotensive and hypertensive subjects, which suggested an alteration in the coupling ratio between furosemide-sensitive $Na^+$ and $K^+$ efflux in this group.

Figure 2 depicts furosemide-sensitive $Na^+$ efflux (cotransport) in erythrocytes from the normotensive black and Caucasian subjects subdivided by family history of hypertension. The scatter diagram and mean ± SEM levels of furosemide-sensitive $Na^+$ efflux rate (cotransport) in erythrocytes from black and Caucasian normotensive (NT) subjects and those with essential hypertension (EH) subdivided by family history of hypertension.
and hypertensive populations subdivided by race and a positive (+FH) or negative family history of hypertension (−FH). Caucasian normotensive and hypertensive subjects with +FH had significantly (p < 0.05) lower mean Na⁺ cotransport compared to normotensive and hypertensive subjects with −FH (Figure 2). Nine of the 40 Caucasian hypertensive patients actually had elevated values for Na⁺ cotransport that were greater than 0.6 mM/liter cells/hr. A +FH did not have as great an effect on those hypertensive patients with high cotransport; the incidence of this observation was almost equal in those with +FH and −FH.

A +FH had less effect on mean values of erythrocyte Na⁺ cotransport in black normotensive and hypertensive subjects. Although mean Na⁺ cotransport was lower in black subjects with +FH, the differences were not significant compared to those with −FH. In 77% of black subjects, cotransport values for Na⁺ efflux were 0.3 mM/liter cells/hr or less. Mean values for red cell K⁺ cotransport showed patterns similar to those for Na⁺ when compared by race and family history of hypertension.

Ouabain-Sensitive Sodium Efflux

Figure 3 shows mean ouabain-sensitive Na⁺ efflux (pump) in erythrocytes from normotensive and hypertensive black and Caucasian subjects. Values depict a stimulated rate for Na⁺ efflux as cells were Na⁺-loaded by the pCMBS method to values approximating 25 mM/liter cells with an external K⁺ concentration of 5 mM. There was no significant difference between values for ouabain-sensitive Na⁺ efflux between normotensive and hypertensive subjects and no differences between blacks and Caucasians. Of the 58 patients with essential hypertension, only three had a value for ouabain-sensitive Na⁺ efflux below 3.0 mM/liter cells/hr.

Ouabain- and Furosemide-Insensitive Sodium and Potassium Efflux

The mean rate constants for the passive permeability of Na⁺ in RBCs from normotensive subjects (0.030 ± 0.008 hr⁻¹) and hypertensive subjects (0.034 ± 0.010 hr⁻¹) were not significantly different. Passive permeability for K⁺ was also not different in the two groups (0.015 ± 0.002 vs 0.011 ± 0.003 hr⁻¹).

Clinical Correlations

Blood Pressure, Age, Sex, and Duration of Hypertension

Mean arterial pressure ranged from 94 to 143 mm Hg. Values did not correlate with erythrocyte furosemide-sensitive Na⁺ efflux (cotransport) or with ouabain-sensitive Na⁺ efflux (pump) in patients with essential hypertension. Additionally, there was no relationship between age, sex, or duration of hypertension and the measured erythrocyte transport pathways.

Urinary Sodium Excretion

Mean urinary sodium excretion in hypertensive patients on an ad libitum sodium intake was 159 ± 16 mEq per 24 hours with a range from 76 to 266 mEq. No correlation was found between sodium excretion and erythrocyte Na⁺ transport through the cotransport or pump pathways in either black or Caucasian hypertensive subjects.

Plasma Renin Activity and Aldosterone

In the patients with essential hypertension, plasma renin activity determined after ad libitum sodium intake and 3 hours of upright posture demonstrated a mean value of 1.89 ± 0.2 ng/ml/hr with a range from 0.25 to 6.0 ng/ml/hr. There was a positive correlation between furosemide-sensitive Na⁺ efflux (cotransport) and plasma renin levels (r = + 0.47; p < 0.01) for these hypertensive patients (Figure 4). This correlation did not relate to patient age or race. No correlation was found between plasma renin and erythrocyte ouabain-sensitive Na⁺ efflux (pump). Mean upright plasma aldosterone level in normotensive subjects was 9.2 ± 1.8 ng/dl and in essential hypertensive subjects was 11.2 ng/dl ± 1.5. Individual aldosterone levels did not correlate with either furosemide- or ouabain-sensitive erythrocyte Na⁺ efflux in normotensive or hypertensive subjects.

Effect of Blood Pressure Reduction on Sodium Cotransport

The effect of blood pressure reduction on RBC furosemide-sensitive Na⁺ efflux (cotransport) was examined at 1 and 3 weeks in 11 patients with essential hypertension who were treated with either a thiazide diuretic or an angiotensin-converting enzyme inhibitor. Mean arterial pressure fell significantly (p < 0.01) from 115.4 ± 1.5 to 102 ± 1.3 mm Hg (Figure 5). Most
subjects had no consistent change in Na\(^+\) cotransport rate after blood pressure reduction, although three patients with low Na\(^+\) cotransport showed an increase in activity on treatment with angiotensin-converting-enzyme inhibitor. The increase in Na\(^+\) cotransport appeared greater than could be explained by the inter-assay coefficient of variation for Na\(^+\) cotransport, which ranged from 11% to 24% in 10 control subjects sampled over time.

**Discussion**

This study describes a major difference in Na\(^+\) and K\(^+\) transport rates through the ouabain-insensitive pathways in erythrocytes from black compared to Caucasian patients with essential hypertension. Black hypertensive patients had a consistently lower rate of erythrocyte furosemide-sensitive Na\(^+\) and K\(^+\) efflux (cotransport) as compared to Caucasian hypertensive patients. This was a uniform finding in that most black hypertensive patients had Na\(^+\) cotransport values less than 0.35 mM/liter cells/hr. Additionally, a family history of hypertension had less influence on erythrocyte Na\(^+\) and K\(^+\) cotransport function in black normotensive and hypertensive subjects compared to Caucasians. Since ouabain-sensitive erythrocyte Na\(^+\) efflux (pump) was normal in black subjects, the lower rate of Na\(^+\) efflux through the cotransport pathway may explain the higher level of intracellular Na\(^+\) concentration seen in black normotensive and hypertensive individuals. Whether these Na\(^+\) transport abnormalities could potentially relate to the higher prevalence of hypertension, average higher diastolic blood pressure levels, and higher rate of complications in the American black population compared to Caucasians remains to be resolved.

In the 20 black patients with essential hypertension in this study there was only a weak inverse correlation (\(r = -0.34, p < 0.02\)) between Na\(^+\) cotransport and intracellular sodium levels. A larger population sampling may be necessary to verify or exclude this relationship. It should be noted, however, that studies on normal human RBCs have shown that the cotransport pathway may not affect net Na\(^+\) fluxes.

Garay et al. reported that red cell Na\(^+\), K\(^+\) cotransport was less than 0.25 mM/liter cells/hr in 72% of normotensive Ivory Coast blacks. Cotransport values were virtually absent to very low in all hypertensive subjects sampled from this population, which has a very high incidence of hypertension. In a study from Capetown, South Africa, Davidson et al. reported lower levels of RBC cotransport expressed as the mean value of Na\(^+\) plus K\(^+\) efflux in black, Caucasian, and racially mixed hypertensive patients compared to normotensive subjects. They did note a large overlap of values among study groups and could not detect an environmental influence on RBC cotransport activity. A low total K\(^+\) efflux in RBCs from hypertensive blacks was reported in Nigerian subjects by Aderounmu et al. Hennessy and Ober also noted lower total K\(^+\) transport capacity in erythrocytes from black
patients with essential hypertension and further suggested that this occurred through reductions in the ouabain-insensitive transport pathways. Canessa et al. have recently reported in a well-designed study that the maximum velocity (Vmax) for K⁺ cotransport in erythrocytes from hypertensive blacks and their juvenile offspring was significantly reduced compared to values in Caucasian subjects. Although assay methods and patient selection varied somewhat in most of the above studies and in our present study, they do indicate one or more alterations of ouabain-insensitive Na⁺ and K⁺ transport in erythrocytes from black subjects with essential hypertension. Some investigators have detected a stronger familial aggregation of ouabain-insensitive RBC transport abnormalities in hypertensive blacks than our results have indicated.

Caucasians with essential hypertension not only display higher mean levels of furosemide-sensitive erythrocyte Na⁺ and K⁺ efflux (cotransport) compared to those in blacks, but also had a much greater range of distribution of RBC cotransport levels. Hypertensive Caucasians with −FH almost uniformly had Na⁺ cotransport values greater than 0.3 mM/liter cells/hr, and a substantial percentage had values higher than 0.6 mM/liter cells/hr. Caucasian subjects with +FH showed a downward shift of the distribution of RBC cotransport function; 12 of 14 normotensive subjects and 12 of the 23 hypertensive patients displayed values less than 0.3 mM/liter cells/hr. Thus, +FH had more effect on the distribution of RBC cotransport levels in Caucasian normotensive and hypertensive subjects than was the case in blacks. There was, however, a group of hypertensive Caucasians but not normotensive subjects who displayed Na⁺ RBC cotransport values above 0.6 mM/liter cells/hr; this was observed both in individuals with +FH and −FH. Previous investigations of RBC cotransport in Caucasians with essential hypertension have described low, normal, or elevated values. These discordant observations in the Caucasian hypertensive population may be partly explained by differences in RBC transport methodology. Procedures such as ²²Na or rubidium influx into RBCs may not detect the same furosemide-sensitive cotransport pathway abnormalities as studies examining Na⁺ efflux rates because of differences in internal and external apparent Km for Na⁺ through this pathway. Several investigators have used different levels of intracellular Na⁺ that included fresh cells and cells loaded to approximately 25 or 50 mmol Na⁺/liter cells. Differences in the apparent Km for intracellular Na⁺ through the cotransport pathway are best detected in RBCs from hypertensive patients examined at higher intracellular Na⁺ levels.

An equally plausible explanation for the variable findings of cotransport activity in Caucasian subjects may relate to a genetic polymorphism for expression of this transport process in Caucasians. Thus, investigators who examined only a small sample of hypertensive Caucasians may not have seen the full range of RBC cotransport variability in this population. Our finding of a higher mean RBC cotransport in American Caucasians with hypertension compared to those who were normotensive agrees with the observations of Adragna et al., especially in those with −FH. These investigators also noted high cotransport in RBCs from normotensive subjects of hypertensive parents. As they did not examine family history in the established hypertensive group, it remains uncertain whether our observation of lower cotransport in this group is in accord with their studies. Garay and co-workers have consistently noted reduced RBC cotransport in a significant percentage of hypertensive Caucasians from Paris, France. Using the same assay methodology as Garay et al., we found that approximately 40% of our Caucasian hypertensive subjects had RBC Na⁺ cotransport values below 0.3 mM/liter cells/hr; most of these patients had a +FH. It is possible that this heterogeneity of RBC cotransport function in hypertensive Caucasians reflects different degrees of gene expression of transport abnormalities in subgroups. Some hypertensive patients with a strong +FH might show markedly reduced cotransport activity, and another group with less familial aggregation of hypertension might display consistently elevated levels. Intracellular Na⁺ levels in Caucasians did not correlate with cotransport activity, that is, the low cotransport group did not have a higher intracellular Na⁺ compared to the high cotransport group.

Our study also examined if nongenetic factors including demographic and biochemical indices influence RBC Na⁺ and K⁺ cotransport. There was no consistent relationship between patient age, sex, level of blood pressure, and duration of hypertension and RBC cotransport activity in essential hypertension. Urinary excretion of sodium was used to determine sodium balance and as an estimate of salt intake. Although no correlation was found between sodium excretion and RBC cotransport in our hypertensive population, a better controlled long-term dietary sodium protocol is required to definitively examine this relationship. Morgan et al. demonstrated that a high sodium intake decreased RBC ²²Na efflux rates and increased blood pressure in male hypertensive patients. Ambrosioni et al. observed that low salt diet in labile hypertensive patients reduced lymphocyte intracellular sodium concentrations and that acute salt loading restored intracellular levels. Both studies suggest that sodium intake may affect cellular cation transport functions.

Our present study does demonstrate that a sodium-dependent hormonal system, the renin-angiotensin system, may be related to RBC cotransport function. A positive correlation between plasma renin activity and RBC cotransport was noted in our hypertensive subjects. As no studies on the effect of angiotensin II on RBC cotransport activity have been described, no direct cause-effect relationship can be proposed at this time. Both patient age and race are factors known to influence renin levels. The age of our hypertensive subjects did not correlate with cotransport activity, so this variable does not explain this observation. Although the number of black hypertensive subjects stud-
ied was small, just as many Caucasian as black hypertensive subjects had low renin levels. Thus, differences in renin levels between black and Caucasian hypertensive subjects could not entirely explain the renin and cotransport correlation. A positive correlation between incremental renin response and another ouabain-insensitive transport pathway, the sodium-lithium cotransporter, has been described by Brugnara et al. in RBCs from hypertensive subjects. Despite this relationship with renin, we observed no correlation between plasma aldosterone and RBC cotransport.

Studies of the ouabain-sensitive Na+,K+-ATPase pump in RBCs and white cells from hypertensive subjects have also yielded variable results. Actual increases in RBC pump activity have been described in patients with essential hypertension as well as normal levels and reduced levels. Experiments showing that hypertensive plasma inhibits pump activity in normotensive cells and in isolated Na+,K+-ATPase preparations suggest a circulating pump inhibitor. We found no differences in ouabain-sensitive Na+ efflux rates in RBCs from black and Caucasian normotensive and hypertensive subjects. Our method washed the RBCs, measured cells at high internal Na+ concentrations, and used pCMBS that might bind to the RBC pump. These results, therefore, may not be directly comparable to other studies, but do indicate that RBC Na+ efflux through the ouabain-sensitive pathway was normal in hypertensive individuals as studied under these conditions of near maximal transport capacity. No relationship was noted between RBC pump activity and +FH or between other clinical and biochemical indices examined.

Several hypertensive patients including six with low RBC Na+ cotransport activity were followed during antihypertensive therapy with thiazide diuretics or an angiotensin-converting enzyme inhibitor to the endpoint of a 10% or greater fall in mean arterial pressure from baseline. Three patients with low RBC Na+ cotransport had improved transport function after treatment with an angiotensin-converting-enzyme inhibitor. The other subjects had either inconsistent or unchanged cotransport function during this period. One other study noted no differences in RBC cotransport between untreated and hypertensive patients treated with various antihypertensive agents. It is uncertain whether that study examined prospectively in the same patients the effects of blood pressure reduction on RBC cotransport before and during therapy.

Acknowledgment
We thank Pamela Joyce for preparing this manuscript.

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Hypertension. 1984;6:536-544
doi: 10.1161/01.HYP.6.4.536

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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