Abnormal Red Blood Cell Ion Transport and Hypertension

The People's Gas Company Study

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SUMMARY A population-based survey of 134 white men, recruited from the Chicago People's Gas Company labor force, was carried out to examine the association between sodium-lithium (Na-Li) countertransport and hypertension. Of the 134 participants in this industry-sponsored periodic health examination, 64 were normotensive and 70 were either taking antihypertensive medications or had a systolic pressure ≥ 140 or a diastolic pressure ≥ 90 mm Hg. The hypertensives were older and more overweight. Countertransport was significantly higher in hypertensives than in normotensives. Among the three subgroups of hypertensives — untreated borderline (140/90 to 160/95 mm Hg), untreated definite (over 160/95 mm Hg), and treated — an increase in countertransport was consistently observed, significant for the latter two groups. The relationship between countertransport and hypertension was independent of overweight, with countertransport being significantly related to both blood pressure and overweight. Altered ion transport may play an important role in the etiology and/or pathophysiology of hypertension. (Hypertension 5:363-367, 1983)

KEY WORDS • countertransport • sodium metabolism • blood pressure

RED blood cell sodium-dependent membrane processes are currently being studied in relation to the etiology and pathogenesis of hypertension.1-4 Previous case control studies have demonstrated a relationship between sodium-lithium (Na-Li) countertransport and hypertension.5-7,15-17 This report described the results of a population-based cross-sectional survey in employed white men relating levels of countertransport to the presence of hypertension.

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countertransport values; one was hypertensive and one
normotensive. Previous experience had demonstrated
that approximately 2% of the normal population have
countertransport values greater than twice the usual
average. The meaning of such extremely high values
is not yet understood. Inclusion of the data on these 23
persons did not change the outcome of the subsequent
analyses.

Laboratory Methods
Simultaneous analyses of red cell sodium concentra-
tion and the maximum velocity of Na-Li countertrans-
port were carried out. The washed cell technique was
used to determine red cell sodium concentration, as
previously described. The method of Canessa et al.1
with modifications was used to determine the maxi-
mal rate of Na-Li countertransport. Cells were washed
with 5 x volume of ice-cold 115 mmol/liter of MgCl2.
Previous work has shown these methods to be stable
in the same person over time. Technical error was
assumed to be 2.5% for the sodium concentration assay and 6.4% for
Na-Li countertransport. (Technical error was esti-
ated as error of blind duplicates analyzed in the same
batch: √Σd/2N. Expressed as a percent, it represents
the absolute error as a percentage of the sample
means).

Results
The characteristics of the study population are de-
scribed in table 1. All subgroups of hypertensives had
statistically significant differences compared to nor-
motensives for the following variables: age, weight,
and body mass index (BMI: weight in kilograms over
the square of height in meters). Serum potassium was
significantly lower in hypertensives on medications.
Hypertensives on medication had similar systolic and
diastolic pressure/treatment status was recorded. The difference be-
tween normotensives and untreated definite hyperten-
sives is significant at the p < 0.05 level; between
normotensives and treated hypertensives, at the p <
0.001 level. As noted above, treated hypertensives had
lower serum potassium levels. Within this group, a
sizable negative correlation existed between serum po-
kassium and countertransport (r = -0.335), but it is
only of borderline significance (p = 0.06). Red cell
sodium concentration was slightly higher among treat-
ed hypertensives, and lower among the untreated, rela-
tive to normotensives; only the difference between nor-
motensives and borderline hypertensives is statistically
significant.

Correlation analysis was undertaken, restricted to
the normotensives and the untreated hypertensives. In
this subgroup of 111 individuals, countertransport
positively and significantly related to diastolic blood
pressure (p < 0.001) (table 3). A significant positive
relationship between BMI and countertransport was
also observed. The anticipated relationships among
systolic and diastolic pressures, height, weight, age,
and BMI were observed.

Since overweight, as estimated by BMI, was signifi-
cantly related to both countertransport and blood pres-
sure, analysis of variance was performed for all 134
men to determine the independent relationship of
countertransport and BMI to diastolic blood pressure
and to assess interactions. The relationship between
countertransport and blood pressure/treatment status
remains highly significant after adjustment for BMI (p
= 0.003); BMI is also a significant and independent
covariate in this analysis (p = 0.013). No significant
interaction effect was detected.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives (n = 64)</th>
<th>All hypertensives (n = 70)</th>
<th>Untreated hypertensives</th>
<th>Treated hypertensives (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>124.8 ± 10.8</td>
<td>145.1 ± 15.3</td>
<td>137.2 ± 8.2</td>
<td>151.4 ± 15.1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.8 ± 5.5</td>
<td>93.1 ± 7.3</td>
<td>89.5 ± 2.4</td>
<td>98.4 ± 4.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.9 ± 12.3</td>
<td>90.6 ± 13.2</td>
<td>88.9 ± 12.7</td>
<td>90.8 ± 12.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.7 ± 6.6</td>
<td>173.9 ± 6.5</td>
<td>173.9 ± 5.5</td>
<td>173.7 ± 6.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 ± 3.2</td>
<td>29.9 ± 3.9</td>
<td>29.3 ± 3.8</td>
<td>30.0 ± 3.6</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>47.1 ± 9.5</td>
<td>51.9 ± 6.2</td>
<td>50.7 ± 5.5</td>
<td>51.5 ± 6.8</td>
</tr>
<tr>
<td>Serum Na (mmol/liter)</td>
<td>148.1 ± 6.2</td>
<td>146.8 ± 7.1</td>
<td>146.4 ± 5.4</td>
<td>146.6 ± 4.3</td>
</tr>
<tr>
<td>Serum K (mmol/liter)</td>
<td>4.7 ± 0.4</td>
<td>4.5 ± 0.6</td>
<td>4.6 ± 0.4</td>
<td>4.6 ± 0.4</td>
</tr>
</tbody>
</table>

BMI = body mass index. Values are means ± sd.
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Table 2. Red-Cell Sodium-Dependent Lithium Efflux in Normotensives and Hypertensives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives (n = 64)</th>
<th>All hypertensives (n = 70)</th>
<th>Untreated hypertensives</th>
<th>Treated hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na-Li</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counter-transport (µmol/LRBC/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC [Na], (mmol/LRBC)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| Normotensives |               | All | Untreated hypertensives | Treated hypertensives | |
|---------------|---------------|-----|-------------------------|-----------------------|
|               | (n = 64)      | (n = 70) | Borderline (n = 24) | Definite (n = 23) | |
| 4.9 ± 1.3     | 5.9 ± 2.1     | 5.0 ± 2.0 | 6.1 ± 1.9†         | 6.7 ± 2.0*         |

*p < 0.001, vs normotensives.
†p < 0.05, vs normotensives.

Values are means ± sd. RBC [Na] = red blood cell sodium concentration.

Discussion

The results of the present study confirm earlier findings of a direct relationship between countertransport and essential hypertension. The previous reports were generally based on clinical series or case-control studies of limited size. The present study drew all of its participants from a defined population; therefore, the full range of blood pressure was examined as it related to countertransport. Furthermore, the relatively large sample size allowed analysis of subgroups, i.e., treated and untreated hypertensives, as well as a correlation analysis that treated blood pressure as a continuous variable. It should be noted that all participants in this study were men; additional large-scale studies are needed to confirm these findings in women.

Of the variables considered in this study, BMI correlated significantly with both countertransport and blood pressure. While it is possible that abnormal sodium transport is one of the mechanisms linking obesity to hypertension, a highly significant relationship (p = 0.003) between countertransport and diastolic pressure was recorded with control for the confounding effect of adiposity. The increase in countertransport in treated hypertensives over those not using medication suggests that blood pressure level itself may not be the major or only mediating factor in the relationship between countertransport and hypertension. Two explanations of this finding are plausible. It is reasonable to assume that the treated hypertensives had more severe disease; certainly their blood pressure would have been higher had they not been on medication. In such people, it may be that countertransport reflects an aspect of hypertensive disease not fully reversed by treatment, such as peripheral resistance.

Also, in more severe hypertensives, abnormal sodium-dependent transport pathways in the cell or its organelles may alter calcium availability, which in turn may affect contractility in vascular smooth muscle. Alternatively, it is possible that drug treatment raises countertransport levels, e.g., as a response to reduced serum potassium. It would be of relevance in future studies to attempt to relate efflux levels to parameters reflecting possible physiologic mechanisms, such as peripheral resistance.

Several laboratories have reported abnormal Na-Li countertransport levels in hypertensives. Canessa

Table 3. Correlation Matrix: Normotensives and Untreated Hypertensives (n = 111)

<table>
<thead>
<tr>
<th>Na-Li counter-transport</th>
<th>RBC Na</th>
<th>Sys BP</th>
<th>Dias BP</th>
<th>Weight</th>
<th>Height</th>
<th>Age</th>
<th>Serum [Na]</th>
<th>Serum K</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na-Li</td>
<td>0.017</td>
<td>0.113</td>
<td>0.280†</td>
<td>0.148</td>
<td>-0.026</td>
<td>0.053</td>
<td>-0.076</td>
<td>0.010</td>
<td>0.205*</td>
</tr>
<tr>
<td>RBC [Na]</td>
<td>-0.044</td>
<td>-0.106</td>
<td>-0.123</td>
<td>-0.159</td>
<td>-0.066</td>
<td>-0.099</td>
<td>0.130</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Sys BP</td>
<td>-0.099†</td>
<td>0.207*</td>
<td>-0.084</td>
<td>0.125</td>
<td>0.078</td>
<td>-0.042</td>
<td>0.290†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dias BP</td>
<td>-0.213*</td>
<td>0.280*</td>
<td>0.044</td>
<td>0.208*</td>
<td>-0.060</td>
<td>0.087</td>
<td>0.290†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>-0.531†</td>
<td>0.047</td>
<td>-0.124</td>
<td>-0.160</td>
<td>0.869†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>-0.010</td>
<td>-0.109</td>
<td>-0.047</td>
<td>-0.106</td>
<td>0.046</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.090</td>
<td>-0.086</td>
<td>0.118</td>
<td></td>
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<tr>
<td>Serum Na</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.399†</td>
<td>-0.131</td>
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<tr>
<td>Serum K</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>-0.133</td>
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<td></td>
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<tr>
<td>BMI</td>
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</tbody>
</table>

BMI = body mass index; RBC = red blood cell.
* p < 0.05.
† p < 0.001.
et al.\textsuperscript{1} noted a 130\% increase in countertransport of hypertensives vs normotensives; the blood pressure differences between the two groups was greater than reported here, and the same was true for age. Canali, et al.\textsuperscript{15} apparently compared severe hypertensives to normotensives and noted a 50\% higher countertransport in the group with hypertension. Cusi et al.\textsuperscript{16} compared normotensives and a group of hypertensive patients (mean age 45 years), defined as hypertensive by three successive diastolic readings greater than 94 mm Hg, and found a 33\% increase in countertransport. Finally, Wood et al.\textsuperscript{17} in a study of familial patterns of countertransport noted a 105\% increase in adult hypertensives over controls; blood pressure levels were not given. In none of these four studies was the method of selection of participants described in relation to any general population; weight was reported in only one;\textsuperscript{12} treatment status was mentioned in only two of the studies.\textsuperscript{15, 17} In all four studies controls were generally said to be free of chronic disease, although no mention was made of psychiatric illness. It would appear that the study by Cusi et al. is most comparable to the one reported here in terms of blood pressure levels of hypertensives; the increase in countertransport is also very similar, e.g., 33\% and 20\% respectively. Apparently, differences between mean levels of countertransport in hypertensives and normotensives depend to a large extent on the selection of participants. By the same token, controlling for confounding variables, particularly overweight, is necessary to estimate the independent effect of the transport variables. Although a significant increase in mean countertransport was observed in hypertensives compared to normotensives, a large area of overlap exists. This may be due to heterogeneity among hypertensives, genetic and/or environmental in origin, as reported by both Canessa et al.\textsuperscript{28}{\textsuperscript{28}} and Cusi et al.\textsuperscript{38}{\textsuperscript{38}}

In a previous report by Canessa et al.,\textsuperscript{1} countertransport was not increased in a group of five patients with secondary hypertension. Mahoney et al.\textsuperscript{27} found no increase in the rate of ouabain insensitive Na influx in a group of patients with secondary hypertension. These findings suggest that the defect described in the present study applied only to blood pressure elevation in essential hypertension.

In the correlation analysis that excluded treated hypertensives, a significant relationship was observed between countertransport and diastolic blood pressure, but not systolic pressure. There is little reason to think that diastolic pressure is a more reliable estimate of the physiologic parameter of interest in hypertensive disease, unless perhaps it bears a closer relationship to peripheral resistance in this population with a mean age of 50 years. In a previous report by our group,\textsuperscript{29} a significant correlation between countertransport and systolic blood pressure was reported in children; the relationship persisted after controlling for weight, although it was not apparent with diastolic pressure. Systolic pressure is more reliably measured in children than diastolic pressure, and that may account for the apparent inconsistency. Alterations in red cell Na-K cotransport, sodium permeability, total sodium efflux, and sodium influx in hypertensives have all been described.\textsuperscript{11-14} Additional investigators have worked with leucocytes.\textsuperscript{29-31} Contradictory findings have been reported and the relationships among various assays are unclear.\textsuperscript{25, 26, 32-34} Rigorous sampling procedures that yield representative groups of participants have not always been applied and may have contributed to the lack of consistent results.

It appears that sodium transport studies can yield important new information about the pathophysiology of hypertension. Additional work is needed to relate the abnormalities that have been identified to the mechanism of blood pressure elevation, and to test the several hypotheses advanced based on the data currently available.

Acknowledgments

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