Sodium-Lithium Countertransport and Cardiorenal Abnormalities in Essential Hypertension

Romano Nosadini, Andrea Semplicini, Paola Fioretto, Luigi Lusiani, Roberto Trevisan, Valter Donadon, Giorgio Zanette, Gian Luigi Nicolosi, Vittorio Dall'Aglio, Domenico Zanuttini, and GianCarlo Viberti

The rate of red blood cell sodium-lithium countertransport is elevated only in a subgroup of patients with essential hypertension. We have therefore compared renal and cardiac function and morphology in two groups of hypertensive patients with high (n=23) or normal (n=22) sodium-lithium countertransport (mean±SEM: 0.61±0.10 versus 0.29±0.07 mmol/l red blood cells·hr). The two groups were similar in age, sex distribution, body mass index, smoking habit, duration of hypertension, and actual levels of untreated blood pressure. Hypertensive patients with elevated sodium-lithium countertransport activity showed elevated glomerular filtration rate (118±2 versus 109±2 ml/min·1.73 m²; p<0.001), albumin excretion rate (23±3 versus 14±2 μg/min; p<0.001), larger kidney volume (250±15 versus 203±13 ml·1.73 m²; p<0.01), lower lithium clearance rate (26.7±0.3 versus 28.9±0.3 ml/min·1.73 m²; p<0.01), and higher total body exchangeable sodium (2,716±33 versus 2,485±41 mmol·1.73 m²; p<0.01). Left ventricular mass index (139±6 versus 119±6 g/m²; p<0.05), relative wall thickness (0.39±0.05 versus 0.29±0.04 cm; p<0.001), and left posterior wall plus intraventricular septum thickness (2.02±0.04 versus 1.76±0.03 cm; p<0.05) were also higher in patients with high sodium-lithium countertransport. Hypertensive patients with normal sodium-lithium countertransport had renal and cardiac parameters similar to those of a normotensive control group (n=21) except for a higher glomerular filtration rate and left ventricular mass index. Finally hypertensive patients with elevated rates of sodium-lithium countertransport had significantly higher plasma triglyceride levels and lower plasma concentrations of high density lipoprotein cholesterol. Thus renal and cardiac hypertrophy, lipid abnormalities, and altered kidney function are prominent features of hypertensive patients with higher sodium-lithium countertransport. (Hypertension 1991;18:191-198)

The rate of red blood cell (RBC) sodium-lithium (Na⁺-Li⁺) countertransport has been reported to be elevated in patients with essential hypertension and not in patients with secondary hypertension.1-3 This elevated activity is believed to be a preclinical marker for essential hypertension in that it is found in first-degree relatives of hypertensive subjects and in normotensive teenage sons of two hypertensive parents.4,5 It has been suggested that Na⁺-Li⁺ countertransport is a mode of operation of the cell membrane sodium-hydrogen (Na⁺-H⁺) exchanger,6-7 and patients with essential hypertension have been found to have high activity of Na⁺-H⁺ antiport.2 Whether Na⁺-H⁺ antiport or Na⁺-Li⁺ countertransport are causally related to hypertension or simply epiphenomena arising from other alterations remains, however, unresolved.1,2 There is considerable overlap of Na⁺-Li⁺ countertransport values between normotensive and hypertensive subjects with approximately 50% of hypertensive patients showing normal Na⁺-Li⁺ countertransport activity.8 Genetic studies have confirmed the association between Na⁺-Li⁺ countertransport activity and hypertension providing evidence for a major locus

From the Department of Internal Medicine (R.N., P.F.), Patologia Medica I*, and the Department of Clinical Medicine (A.S., L.L., R.T.), Policlinico Universitario, Università di Padova; the Centro Antidiabetico e Divisione Cardiologica (V.D., G.Z., G.L.N., V.D., D.Z.), Ospedale di Pordenone, Padova, Italy; and the Unit for Metabolic Medicine (G.V.), UMDS, Guy's Hospital, London, UK Partially supported by grants N. 880193604 and N. 880038704 from the Italian National Research Council (CNR) and by the Imperial Chemical Industry Medical Department. Address for correspondence: R. Nosadini, MD, Patologia Medica I*, Policlinico Universitario, Via Giustiniani, 2-35128 Padova, Italy. Received January 30, 1990; accepted in revised form April 19, 1991.
Patients with essential hypertension free of clinical overt complications, who were attending the outpatient clinic of the Department of Internal Medicine, University of Padova, and Ospedale Civile of Porlezza, Italy, were asked to take part in the study if they met the following selection criteria: age below 40 years, body mass index below 25 kg/m², duration of hypertension less than 3 years, absence of clinical proteinuria with albumin excretion rates have been associated with greater frequency of coronary heart and peripheral vascular disease, and hypertensive subjects with proteinuria have been reported to have an increased mortality rate. Glomerular hyperfiltration in insulin-dependent diabetic patients is believed to be a forerunner of subsequent renal damage.

To gain further insights into the nature of the association between Na⁺-Li⁺ countertransport and arterial hypertension we studied renal and cardiac function and morphology in patients with recently diagnosed essential hypertension and different levels of Na⁺-Li⁺ countertransport activity.

Methods

Patients with essential hypertension free of clinical overt complications, who were attending the outpatient clinic of the Department of Internal Medicine, University of Padova, and Ospedale Civile of Porlezza, Italy, were asked to take part in the study if they met the following selection criteria: age below 40 years, body mass index below 25 kg/m², duration of hypertension less than 3 years, absence of clinical proteinuria (negative Albustix test, Albustix Ames Miles, Cavenago, Milan, Italy), normal serum creatinine, and absence of diabetes or impaired glucose tolerance as assessed by an abbreviated 75-g glucose tolerance test (baseline and 2-hour blood glucose concentrations). Cases of secondary hypertension have been excluded by a complete medical workup that included a 12-lead electrocardiogram.

Na⁺-Li⁺ countertransport was measured in 45 consecutive patients who met the selection criteria. For the purpose of comparison, patients were divided into two groups with Na⁺-Li⁺ countertransport below or above the upper limit of the normal range in our laboratory (0.11–0.41 mmol/l RBC * hr; n=35 normotensive subjects with negative family history of hypertension). Twenty-two patients had Na⁺-Li⁺ countertransport within the normal range (0.29±0.07 mmol/l RBC * hr) (group H₁), and 23 patients had Na⁺-Li⁺ countertransport above the upper limit of the normal range (0.61±0.10 mmol/l RBC * hr) (group H₂). These two groups were similar for sex, age, body mass index, duration of hypertension, and actual blood pressure levels. A group of 21 normotensive healthy subjects matched for age, sex, and body mass index served as control (Table 1). All subjects gave informed consent to the study, which was approved by the Ethical Committee of the University of Padova.

Patient groups and the control group were of European origin with normal renal, liver, and endocrine function and were following an isocaloric diet containing 55% carbohydrate, 25% fat, and 20% protein with approximately 150-200 mmol/day sodium chloride. Smoking habit was assessed from medical history.

Patients were admitted to a metabolic ward a week before the study; all antihypertensive medications had been discontinued for at least a week before admission. No patient was taking amiloride or oral contraceptives. Studies were carried out during the last 2–3 days of admission in the hypertensive patients and on an outpatient basis in the normotensive control subjects.

Blood pressure (diastolic phase V) was measured, with the participant in a sitting position after a 10-minute rest to the nearest 2 mm Hg, using a Hawksley random zero sphygmomanometer (12×35 mm cuff) (Hawksley and Sons, Lancing, UK), and hypertension was defined as a blood pressure of 145 mm Hg or greater systolic or 90 mm Hg or higher diastolic, or both, in the absence of antihypertensive treatment.

Sodium-Lithium Countertransport in Red Blood Cells

A fasting blood sample was taken into a 20 ml heparin-treated syringe for measurement of Na⁺-Li⁺ countertransport in Li⁺-loaded RBC, according to the method of Canessa et al. Na⁺-Li⁺ countertransport was calculated from the difference between Li⁺ efflux in Na⁺ and Mg⁺ media. Li⁺ concentration in the efflux media was measured after 1, 30, and 60 minutes, and efflux rate (mmol/l RBC * hr) was calculated from the slope of regression line of Li⁺ concentration versus time. The lithium concentration in the efflux media was determined by atomic emission spectrophotometry at 670.8 nm (2880 Perkin Elmer Equipment, Perkin-Elmer Corp., Norwalk, Conn.) against standard solutions containing 10 to 100 µM lithium made up in the same buffer. In our laboratory the variability over time of Na⁺-Li⁺ countertransport in healthy individuals is 9.2% (n=6 measured in triplicate on 10 different occasions over a 2-month period), and the interassay coefficient of
TABLE 1. Clinical Features of Subjects

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Normotensive control subjects</th>
<th>Hypertensive patients (H1)</th>
<th>Hypertensive patients (H2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, sex</td>
<td>10 F/11 M</td>
<td>10 F/12 M</td>
<td>11 F/12 M</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>31±2</td>
<td>30±2</td>
<td>31±2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.2±0.4</td>
<td>22.9±0.3</td>
<td>23.1±0.3</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119±3</td>
<td>160±2*</td>
<td>161±3*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78±2</td>
<td>97±3*</td>
<td>98±2*</td>
</tr>
<tr>
<td>Duration of antihypertensive treatment (yr)</td>
<td>...</td>
<td>1.3±0.2</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>30</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Na⁺-Li⁺ countertransport activity in RBC (mmol/1 RBC-hr)</td>
<td>0.26±0.07</td>
<td>0.29±0.07</td>
<td>0.61±0.10</td>
</tr>
<tr>
<td></td>
<td>(0.11-0.4)</td>
<td>(0.15-0.41)</td>
<td>(0.47-0.86)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.1±0.3</td>
<td>5.0±0.3</td>
<td>5.3±0.2</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/l)</td>
<td>1.35±0.02</td>
<td>1.13±0.05</td>
<td>1.07±0.03†</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
<td>1.6±0.2*†</td>
</tr>
</tbody>
</table>

Data are mean±SEM. H1, hypertensive patients with normal Na⁺-Li⁺ countertransport; H2, hypertensive patients with high Na⁺-Li⁺ countertransport; RBC, red blood cells; HDL, high density lipoprotein.

Variation is 7.1% (n=5 measured in triplicate in five different assays).

Renal Function Measurements

Glomerular filtration rate (GFR) (clearance of ⁵¹Cr-EDTA), lithium clearance (600 mg lithium carbonate per os given the evening before the test), and sodium excretion rate were measured simultaneously during steady-state water diuresis as previously described.²⁵ After 2-hour tracer equilibration, urine was collected for four 30-minute periods. Blood was drawn at the midpoint of each urine collection. Patients were supine throughout the study, standing only to void. ⁵¹Cr-EDTA in plasma and urine was measured in a well-type scintillation gamma counter (Packard Instruments, Milano, Italy). Na⁺ and Li⁺ were measured in plasma and urine by atomic emission spectrophotometry (2880 Perkin Elmer) at 589 nm and at 670.8 nm, respectively, in a medium containing cesium chloride (7.5 mmol/l) to reduce ionization. Recovery of lithium was found to be 102±4% (mean±SD) in a range of concentrations between 0.4 and 150 mmol/l. Further details are provided elsewhere.²⁵ Li⁺ and Na⁺ clearances were calculated according to standard formulas. Proximal sodium reabsorption (PRNa) was calculated from the fractional Li⁺ reabsorption as follows:

\[
PRNa = PNa \cdot GFR \cdot FRLi
\]

where \(PNa\) is plasma sodium and

\[
FRLi = 1 - (V/GFR) \times (Uli/Pli)
\]

where \(Uli/Pli\) is the urine-to-plasma ratio of lithium, and \(V\) is the urine flow.

Total exchangeable sodium was measured by radioisotope dilution technique using ²⁴Na.²⁶ A dose of approximately 60 μCi of ²⁴Na was given orally after an overnight fast, and urine was collected during the subsequent 24-hour period. During the last hour, four blood samples (two at the beginning and two at the end of this period) were obtained for determination of sodium-specific activity. ²⁴Na in plasma and urine was measured in a well-type scintillation gamma counter (Packard).

Timed overnight urine collections for urinary albumin measurement²⁷ were performed at least four times over a period of 6 months preceding the study. The mean of all values for each patient was used for calculations.

Ultrasound Studies

Kidney volumes were measured by ultrasound techniques.²⁸ The volume of both kidneys was measured, and the mean of the two values was used for calculations. Each subject was submitted to a two-dimensional derived/M-mode echocardiographic study with a mechanical 2.5 MHz probe and a commercially available instrumentation (Escarad 81, OTE Biomedica, Milano, Italy). According to the criteria of the American Society of Echocardiography,²⁹ the following parameters relative to the left ventricle were obtained, each as an average of at least three measurements: 1) left ventricular end-diastolic dimension (LVDD), 2) left ventricular end-systolic dimension (LVSD), 3) left ventricular diastolic posterior wall thickness (LVPW), and 4) interventricular septum thickness (IVS).

From these measurements, left ventricular mass index (LVMI) was calculated according to the Devereux formula.³⁰
Serum Measurements

Fasting serum was separated and stored at 4°C for determination of lipids within 5 days. High density lipoproteins (HDL) were separated by ultracentrifugation. Concentrations of cholesterol and triglycerides were measured by enzymatic colorimetric techniques.

Statistical Analysis

Values of albumin excretion rate and lipid concentrations were log transformed before analysis. Differences among groups were tested by analysis of variance. If a significant difference was found, differences between individual groups were tested by unpaired Student's t test (unless otherwise stated) with Bonferroni correction for multiple comparisons. The \( \chi^2 \) analysis was used to compare prevalence among groups. Results are expressed as mean±SEM unless otherwise stated.

Results

The two groups of hypertensive patients had similar age, sex distribution, body mass index, blood pressure, and duration of antihypertensive treatment (Table 1). GFR was higher in H2 patients than in H1 patients (118±2 versus 109±2 ml·min\(^{-1}\)·1.73 m\(^{-2}\); \( p<0.001 \)) who in turn had higher GFR than the control group (99±2 ml·min\(^{-1}\)·1.73 m\(^{-2}\); \( p<0.01 \)). Mean kidney volume was larger in H2 (250±12 ml/1.73 m\(^{-2}\)) compared with H1 (207±13 ml·1.73 m\(^{-2}\); \( p<0.01 \)) and control subjects (172±9 ml·1.73 m\(^{-2}\); \( p<0.01 \)) whose values did not differ from H1 patients (Figure 1). Lithium clearance was significantly lower in H2 than in H1 patients \( (p<0.01) \) and in control subjects \( (p<0.001) \) (Figure 2). The calculated rate of proximal tubule sodium reabsorption was therefore higher in H2 (73.4±0.7%) than in H1 patients (71.0±0.3%; \( p<0.01 \)) or in control subjects (69.6±0.4%; \( p<0.01 \)).

Plasma sodium concentrations (H2 141±2 versus H1 142±2 versus control 141±2 mmol/l) and sodium excretion rates (H2 127±11; H1 138±12; control, 119±15 mmol·min\(^{-1}\)·1.73 m\(^{-2}\)) were similar in the three groups. The volume of sodium pool was significantly greater in H2 patients than in H1 \( (p<0.01) \) or control subjects \( (p<0.01) \) (Figure 2).

Urinary albumin excretion rate was significantly elevated in H2 patients (mean 24, range 5–42 \( \mu g/min \)) compared with H1 patients (mean 14, range 4–28 \( \mu g/min \); \( p<0.01 \)) or control subjects (mean 10, range 3–19 \( \mu g/min \); \( p<0.001 \)) (Figure 1).

All control subjects had albumin excretion rates lower than 20 \( \mu g/min \), whereas 57% of H2 \( (p<0.01 \) H1 versus control) and 18% of H1 patients \( (p<0.05 \) H1 versus control) \( (p<0.05 \) H2 versus H2) showed an albumin excretion rate in the microalbuminuric range \( (i.e., >20<200 \mu g/min) \).

Mean and individual values of echocardiographic variables are given in Figure 3. Both H1 and H2 groups showed higher LVM/I, (LVPW+IVS)/LVDd ratio, and LVPW+IVS/LVDd sum than control subjects. However H2 patients also had significantly higher values than H1 patients.

Fasting serum cholesterol concentration was similar in the three groups of patients (H2, 5.3±0.2; H1, 5.0±0.3; and control, 5.1±0.3 mmol/l), but HDL cholesterol concentration was lower in H2 patients \( (1.07±0.03 \text{ mmol/l}) \) than in the control subjects \( (1.35±0.02; \ p<0.05) \). H1 patients had an HDL cholesterol level of \( 1.13±0.05 \text{ mmol/l} \), which was not significantly different from that of control subjects and H2 patients. Serum triglyceride concentration
was significantly higher in $H_2$ patients ($1.6\pm0.2$ mmol/l) than in $H_1$ patients ($1.2\pm0.1; p<0.01$) or in control subjects ($1.2\pm0.1; p<0.01$) (Table 1).

**Discussion**

Our study shows that functional and anatomic abnormalities of the kidney and of the heart, as well as abnormalities of plasma lipids, are prominent features of patients with essential hypertension and increased RBC $Na^+-Li^+$ countertransport. These findings support the view that these patients are at higher risk of renal and cardiovascular complications developing than hypertensive patients with normal $Na^+-Li^+$ countertransport.

Increased albumin excretion rate has been reported in some patients with hypertension, but no study so far has established a link with an increased $Na^+-Li^+$ countertransport activity. Recently an over-activity of $Na^+-Li^+$ countertransport has been reported in insulin-dependent diabetic patients with overt proteinuria or microalbuminuria or with glomerular hyperfiltration. Microalbuminuria, a common finding among our hypertensive patients with high $Na^+-Li^+$ countertransport, has been shown to be predictive not only of overt renal disease in insulin-dependent diabetic patients, but also of coronary heart and peripheral vascular disease in non-insulin-dependent diabetic as well as in nondiabetic subjects. Glomerular hyperfiltration has also been claimed to be a predictor of subsequent renal damage, and it is of interest that the hyperten-
sive patients with high Na\(^+\)-Li\(^+\) countertransport displayed the highest GFR values. A correlation between Na\(^+\)-Li\(^+\) countertransport and GFR has been shown in patients with insulin-dependent diabetes mellitus and, more recently, glomerular hyperfiltration was found to be associated with increased LVMI in patients with essential hypertension.

According to our data, left ventricular wall thickness and LVMI are also increased in hypertensive patients with high Na\(^+\)-Li\(^+\) countertransport compared with hypertensive patients with normal Na\(^+\)-Li\(^+\) countertransport despite comparable blood pressure and duration of hypertension. An association between raised Na\(^+\)-Li\(^+\) countertransport and electrocardiographic cardiac hypertrophy in hypertensive patients has also recently been reported by Yap et al. Cardiac hypertrophy has been shown to be associated with an increased risk of cardiac morbidity and mortality. Furthermore hypertensive patients with high Na\(^+\)-Li\(^+\) countertransport have a significantly greater frequency of positive family history for hypertension and cardiovascular diseases than hypertensive subjects with normal Na\(^+\)-Li\(^+\) countertransport. Thus, it can be suggested that an increased Na\(^+\)-Li\(^+\) countertransport may be regarded as a risk factor for renal and cardiovascular complications developing in essential hypertension. This latter view is eventually further supported by the evidence in the present study and in previous reports that abnormalities in plasma lipids are evident among patients with high Na\(^+\)-Li\(^+\) countertransport. The patients with high rates of Na\(^+\)-Li\(^+\) countertransport also showed nephromegaly, increased sodium reabsorption rate, and sodium pool volume, suggesting renal sodium retention.

We estimated proximal tubular sodium reabsorption using the lithium clearance. Although widely used as a marker of proximal tubule reabsorption, this technique may not precisely reflect the proximal reabsorption of sodium in that some reabsorption of Li\(^+\) seems to occur downstream from the proximal tubule in the renal cortical ascending limb. However, recently we found a good correlation between two estimates of proximal tubule Na\(^+\) reabsorption rate: the Li\(^+\) clearance and the maximal water clearance (free water clearance during forced diuresis).

Significant correlations between lithium clearance and rates of Na\(^+\)-Li\(^+\) countertransport have been reported by some authors in young patients with essential hypertension and in the offspring of hypertensive patients but have not been confirmed by other workers. The discrepancies between these studies could be accounted for, at least in part, by differences in age, race, and clinical characteristics of the patients studied. Although caution must be used in the interpretation of lithium clearance, our findings support the view that hypertensive patients with high Na\(^+\)-Li\(^+\) countertransport reabsorb more sodium, which could explain their expanded sodium pool. Consistent with our results are the data of Redgrave et al., who recently reported that patients with non-modulating hypertension, who have an impaired capacity to handle a sodium load, have a high Na\(^+\)-Li\(^+\) countertransport activity.

A number of environmental factors including body weight, serum lipids, gender, age, race, pregnancy, and thyroid disorders have been associated with the rates of RBC Na\(^+\)-Li\(^+\) countertransport. In our study the two groups of hypertensive patients were comparable for many of these variables; we excluded pregnancy and thyroid disease, but interestingly an association was found between low HDL cholesterol levels and higher plasma triglyceride concentrations and high Na\(^+\)-Li\(^+\) countertransport.

The present study links a disturbance of cell membrane transport of sodium in a subset of hypertensive patients to renal and cardiac abnormalities that may have a genetic basis.

Recently Devereux reported that echocardiographically determined left ventricular mass is higher in normotensive offspring of hypertensive parents than normotensive offspring of control subjects, suggesting that the mechanisms leading to left ventricular hypertrophy are active before the elevation of blood pressure and may be genetically determined. Moreover in the spontaneously hypertensive rat, a genetic model of arterial hypertension, organ, in particular cardiac, hypertrophy has been found to precede the development of hypertension.

The pathogenetic nature of the link between elevated Na\(^+\)-Li\(^+\) countertransport activity and the renal and cardiac abnormalities remains at the present obscure. It has been suggested that Na\(^+\)-Li\(^+\) countertransport activity reflects a mode of operation of the cell's membrane Na\(^+\)-H\(^+\) antiport. The activity of this exchanger system is involved in the regulation of renal proximal tubular sodium reabsorption, smooth muscle cell contractility, intracellular pH, and cell growth and replication.

A widespread high activity of the Na\(^+\)-Li\(^+\) countertransport could therefore contribute to the organomegaly and renal functional abnormalities we have described in a subset of hypertensive patients with elevated Na\(^+\)-Li\(^+\) countertransport activity. In addition to hemodynamic factors, a disturbance of trophic mechanisms may therefore contribute to explaining the renal and cardiac complications of essential hypertension.

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