Erythrocyte Ion Fluxes in Essential Hypertensive Patients With Left Ventricular Hypertrophy

Alejandro de la Sierra, MD; Antonio Coca, MD; Juan Carlos Paré, MD; Miguel Sánchez, MD; Valentin Valls, MD; Alvaro Urbano-Márquez, MD

Background. Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in essential hypertension (EH). Several hemodynamic and nonhemodynamic factors have been involved in the development of LVH in hypertension, including abnormalities in cellular ion mobilization.

Methods and Results. We measured different ion transport systems in erythrocytes from 50 patients with EH classified as having or not having LVH measured by M-mode echocardiography. Thirty-two EH patients (64%) exhibited criteria of LVH, and 18 (36%) did not. When the two groups were compared, patients with LVH were older (44.7±1.4 versus 37.6±2.1 years; P<0.01) and exhibited higher rates of erythrocyte Na⁺-H⁺ exchange (9.8±4.1 versus 7.1±2.6 mmol·[L/cell]·[h]⁻¹; P<0.05) and higher intracellular Na⁺ content (8.5±1.3 versus 7.5±0.8 mmol/L per cell; P<0.01). Systolic and diastolic blood pressure values, as well as biochemical, hormonal, and other erythrocyte ion transport systems studied did not differ between EH with or without LVH. The results of a multiple linear regression analysis using left ventricular mass index (LVMI) as the dependent variable showed that Na⁺-H⁺ exchange and the maximal rate of the Na⁺-K⁺-Cl⁻ cotransport were the only two independently significant parameters associated with an increased LVMI.

Conclusions. The increased rate of the erythrocyte Na⁺-H⁺ exchange and the decreased maximal rate of the Na⁺-K⁺-Cl⁻ cotransport system are both associated with the presence of LVH in EH patients. These abnormalities of ion transport pathways tend to increase the intracellular Na⁺ content and may be involved in the pathogenesis of LVH in EH. (Circulation. 1993;88[part 1]:1628-1633.)

KEY WORDS • hypertension • hypertrophy • ions • sodium • potassium

Left ventricular hypertrophy (LVH) measured by echocardiography is exhibited by about one half of essential hypertensive (EH) patients1 and is thought to represent an index of the severity of hypertension. Previous studies have shown that echocardiographically detected LVH predicts cardiovascular complications during 5-year follow-up periods in hypertensive men.2 The severity of high blood pressure and the duration of the hypertensive disease are the major determinants of LVH. Nevertheless, the fact that not all EH patients exhibit LVH and that cardiac enlargement is detected in some normotensive subjects with a family history of hypertension suggests that nonhemodynamic factors must also be involved in the pathogenesis of LVH in hypertension.

In recent years, convincing evidence has been presented that alterations in the intracellular pool of ions, especially Na⁺ and Ca²⁺, may play a role in the pathogenesis of EH. Abnormalities of Na⁺ and Ca²⁺ transport pathways have been reported in red blood cells from EH patients and rats with primary hypertension.3-7 Several attempts have been made to correlate ion transport abnormalities with clinical aspects of hypertension, and some authors have reported that patients with an increased maximal rate of Na⁺-Li⁺ countertransport exhibit some differences in severity of high blood pressure,3 lipid profile,8 and plasma renin activity.5-6 With respect to LVH, Yap et al9 reported that patients with elevated Na⁺-Li⁺ countertransport showed a higher incidence of LVH (71%) measured by ECG (Sokolow-Lyon index) than hypertensive persons without this transport abnormality (19%). Likewise, Nosadini et al,10 using M-mode echocardiography, observed a significantly higher left ventricular mass index (LVMI) in patients with elevated erythrocyte Na⁺-Li⁺ countertransport.

On the basis of these previous considerations, we have conducted a prospective clinical study in EH patients to analyze clinical, biochemical, hormonal, and erythrocyte ion transport systems related to the presence of LVH in EH.

Methods

Patient Selection

Fifty consecutive EH patients of both sexes were selected from the Hypertension Unit of the Department of Internal Medicine, Hospital Clinic, Barcelona, Spain, from January through December 1991. These patients were between 18 and 55 years old and had an office diastolic blood pressure between 90 and 114 mm Hg in at least three repeated measurements. None of them had received antihypertensive therapy before their in-
clusion in the study. The diagnosis of EH was considered on the basis that no known cause of high blood pressure could be detected after complete clinical, biochemical, and radiological examination. None of the patients had renal impairment (serum creatinine >1.5 mg/dL), papilloedema, cardiac failure, or evidence of coronary heart disease (positive clinical history, ECG abnormalities, or positive exercise test). Patients with any severe concomitant pathological condition, alcohol intake >100 g of pure ethanol per day, pregnant women, or those taking contraceptive pills were excluded from the study.

All patients gave informed consent. The protocol was approved by the Ethics Committee of the Hospital Clinic and by the Spanish Health Authority Committee (Dirección General de Farmacia del Ministerio de Sanidad, Protocolo 91/93).

Echocardiographic Studies
Two-dimensional controlled M-mode echocardiograms were recorded in each patient in the partial left decubitus position after a rest of at least 10 minutes. All traced echocardiograms were read by two trained physicians. According to the criteria of the American Society of Echocardiography,11 the following parameters relative to the left ventricle were obtained, each as an average of at least three measurements: (1) left ventricular end-diastolic diameter, (2) left ventricular end-systolic diameter, (3) left ventricular diastolic posterior wall thickness, and (4) interventricular septum thickness. Left ventricular mass was determined by the Penn convention criteria12 and divided by the body surface area to calculate LVMI in grams per square meter. LVH was diagnosed if LVMI exceeded 110 g/m² in women and 130 g/m² in men.13 The relative wall thickness ratio was obtained by the standardized formula14-16: 2×posterior wall thickness/left ventricular end-diastolic diameter. Concentric hypertrophy was diagnosed if the patient had increased LVMI plus a relative wall thickness ratio ≥0.45. Eccentric hypertrophy was considered if this ratio was <0.45.

Laboratory Measurements
Biochemical and hormonal measurements. Biochemical measurements were performed by means of a Technicon Dax-72 autoanalyzer using standardized methodologies: hexokinase method for glucose, Trinder method for lipids, and Jaffé’s method for creatinine. Plasma renin activity, aldosterone, epinephrine, norepinephrine, and atrial natriuretic factor were measured by previously described methods.17

Ion transport measurements. A fasting blood sample was drawn into two 30-mL heparin-treated tubes and used immediately.

Simultaneous measurement of fluxes via Na⁺-K⁺ pump, Na⁺-K⁺-Cl⁻ cotransport, Na⁺-Li⁺ countertransport, and Na⁺ leak. Maximal efflux rates (Vmax) and intracellular Na⁺ concentrations required for half-maximal stimulation (K50%) of the Na⁺-K⁺ pump, Na⁺-K⁺-Cl⁻ cotransport, and Na⁺-Li⁺ countertransport were calculated by previously described methods.3-5 Briefly, red blood cells were washed twice with KCl 150 mmol/L, MOPS-Tris (pH 7.4) 10 mmol/L, and MgCl₂ 1 mmol/L. Four aliquots were prepared and suspended in four different loading media. A fifth aliquot was kept at its normal internal Na⁺ concentration and maintained at 4°C until flux measurements were made. The loading media were prepared by mixing suitable amounts of Na⁺ loading solution (in mmol/L, NaCl 140, sucrose 52, and MOPS-Tris 10) and K⁺ loading solution (KCl 140, sucrose 52, and MOPS-Tris 10). Nystatin (40 µg/mL) was added to each loading solution, and red blood cells were incubated for 20 minutes at 4°C. At the end of the loading period, the erythrocytes were washed four times at 37°C with the loading solutions, the nystatin being replaced by serum bovine albumin at a final concentration of 2 g/L. The internal Na⁺ content obtained by this procedure ranged from 2 to 80 mmol/L per cell, and internal pH was maintained at 7.3 to 7.4.

Red blood cells washed five times in cold MgCl₂ 110 mmol/L were resuspended (duplicates) at a final hematocrit of 5% in four different Na⁺-free media containing, in mmol/L, MgCl₂ 75, sucrose 85, MOPS-Tris 10, and glucose 10, plus the following additions (mmol/L): KCl 2 (medium 1); ouabain 0.1 (medium 2); ouabain 0.1 and bumetanide 0.02 (medium 3); and ouabain 0.1, bumetanide 0.02, and LiCl 10 (medium 4). They were incubated at 37°C for 30 minutes (medium 1) or 60 minutes (media 2, 3, and 4). Calculations of Vmax (in mmol·L⁻¹·cells·h⁻¹) and K50% (in mmol/L per cell) were performed using the following equation for Na⁺ efflux via Na⁺-K⁺ pump and via Na⁺-K⁺-Cl⁻ cotransport:

\[ V = \frac{V_{\text{max}}}{1 + \frac{K_{50}}{[\text{Na}^+]}} \]

\[ \text{where } V_{\text{max}} \text{ is the maximal rate of ouabain-sensitive or bumetanide-sensitive Na⁺ efflux and } K_{50} \text{ represents the apparent dissociation constant for internal Na⁺ (Na⁺i).} \]

For Na⁺-Li⁺ countertransport (Li⁺-stimulated Na⁺ efflux), the same equation was used without the exponent 3.

Na⁺ leak was expressed as the constant of permeability, calculated by dividing the ouabain bumetanide-resistant Na⁺ efflux in fresh cells by the internal Na⁺ content.

Measurement of the Na⁺-H⁺ exchange. Na⁺ influx via Na⁺-H⁺ exchange was determined in acid-loaded cells by use of a modified protocol described by Canessa et al.7 Briefly, erythrocytes were depleted of internal Na⁺ by the above-described loading procedure with nystatin. Two aliquots of cells were prepared and incubated for 60 minutes at 37°C in a medium containing (mmol/L) KCl 140, MgCl₂ 1, glucose 5, and MOPS-Tris 10 buffered at pH 7.4 (first aliquot) or pH 6 (second aliquot). The osmolality of these solutions was adjusted to 360 mOsm/L with the addition of sucrose. After 30 minutes of cell incubation, DIDS 250 µmol/L and acetazolamide 400 µmol/L were added to the incubation media to inhibit the erythrocyte Cl⁻/HCO₃⁻ anion exchanger and carbonic anhydrase. Finally, red blood cells washed in choline chloride 150 mmol/L were incubated (duplicates) for 30 minutes at 37°C in a flux medium containing (mmol/L) NaCl 140, MOPS-Tris 10 (pH 7.4), sucrose 30, MgCl₂ 1, glucose 5, ouabain 0.1, and bumetanide 0.02. The Na⁺ influx via Na⁺-H⁺ exchange was calculated by subtracting the influx of Na⁺ in normal pH cells (mean±SD, 7.3±0.2) from that obtained in acid-loaded cells (mean±SD, 6.2±0.1).
**Table 1. Differences in Clinical, Biochemical and Hormonal Parameters Between Hypertensive Patients With and Without Left Ventricular Hypertrophy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients With LVH</th>
<th>Patients Without LVH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.7±7.4</td>
<td>37.6±9.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>20/12</td>
<td>14/4</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>172.5±13.4</td>
<td>166.9±17.2</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>103.1±5.5</td>
<td>104.2±8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal exercise SBP, mm Hg</td>
<td>203.0±25.8</td>
<td>199.7±21.1</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal exercise DBP, mm Hg</td>
<td>121.6±11.1</td>
<td>117.2±10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>103.7±17.4</td>
<td>95.7±10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Total serum cholesterol, mg/dL</td>
<td>201.6±41.3</td>
<td>212.9±51.0</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>129.2±36.2</td>
<td>138.7±44.7</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.9±11.1</td>
<td>50.5±10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>122.7±77.2</td>
<td>128.1±67.3</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.99±0.17</td>
<td>1.02±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary Na+ excretion, mmol/24 h</td>
<td>127.5±78.5</td>
<td>122.4±78.5</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity, ng · (mL · h)⁻¹</td>
<td>0.47±0.33</td>
<td>0.56±0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>19.8±10.9</td>
<td>17.9±13.6</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial natriuretic factor, fmol/mL</td>
<td>14.7±6.5</td>
<td>12.4±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>42.7±41.9</td>
<td>32.1±40.2</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>216.4±91.7</td>
<td>193.3±97.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

**Measurement of the Ca²⁺ pump.** Maximal Sr²⁺ efflux rate (Vmax) and apparent dissociation constant for total internal Ca²⁺ (Ka) of the erythrocyte Ca²⁺ pump were calculated by previously described methods. Briefly, washed red blood cells were suspended in eight different Ringer media (in mmol/L, NaCl 75, KCl 75, MOPS-Tris 10, glucose 10, and MgCl₂ 0.2) with the addition of different concentrations of SrCl₂ (from 3 to 7 mmol/L) and CaCl₂ (from 0 to 1 mmol/L) and a fixed concentration of the calcium ionophore A-23187 (6 μmol/L). The erythrocytes were incubated for 15 minutes at 37°C, the ionophore was eliminated by washing cells four times in serum bovine albumin (10 g/L), and intracellular ATP was replaced with the addition of inosine 5 mmol/L, adenine 2 mmol/L, and Na₂HPO₄ 5 mmol/L. Final intracellular cation composition ranged from 0.2 to 4 mmol/L per cell for total internal Sr²⁺, and from 0.1 to 2.5 mmol/L per cell for total internal Ca²⁺. Red blood cells (duplicates) were then incubated in Ringer medium with MgCl₂ 1 mmol/L for 15 minutes at 37°C, and the Sr²⁺ content was measured in supernatants. The Sr²⁺ efflux was plotted as a function of total internal Sr²⁺ and Ca²⁺ contents, and the Vmax of Sr²⁺ efflux and the apparent dissociation constant for total internal Ca²⁺ (Ka) were calculated (see Reference 6 for details).

Normal values of all these parameters were obtained in 30 healthy, age-matched, normotensive subjects without family history of hypertension.

**Statistics.** Computer analyses were done using BMDP biomedical statistical software (BMDP Statistical Software, Berkeley, Calif). Student's t tests for continuous variables and χ² tests for dichotomous variables were used for univariate comparison between groups. Pearson's correlation coefficients were used to estimate the association between two continuous variables. A multiple linear regression analysis was done to identify variables independently associated with LVMI.

**Results.** Thirty-two EH patients (64%) fulfilled echocardiographic criteria of LVH (mean±SD of this group, 160.5±27 g/m²), and 18 (36%) did not (98.1±16 g/m²). Among EH patients with an increased LVMi, 10 had concentric LVH (relative wall thickness ratio >0.45), and 22 had eccentric LVH (relative wall thickness ratio <0.45). Only two patients without LVH had a relative wall thickness ratio >0.45, thus exhibiting echocardiographic signs of left ventricular remodeling.

Compared with patients without LVH, hypertensive patients with LVH were older (44.7±7.4 versus 37.6±9.2 years; P<.01) but did not present other clinical differences in terms of basal systolic (172.5±13.4 versus 166.9±17.2 mm Hg; P=NS) and diastolic blood pressure values (103.1±5.5 versus 104.2±8.3 mm Hg; P=NS) or those achieved at maximal exercise capacity (203±25.8 versus 199.7±21.1 mm Hg for SBP; P=NS and 121.6±11.1 versus 117.2±10.5 for DBP; P=NS). Likewise, biochemical and hormonal parameters (plasma fasting glucose, lipid profile, renal function, urinary Na⁺ excretion, plasma renin activity, plasma aldosterone, atrial natriuretic factor, or catecholamines) did not differ in the two groups of patients (Table 1).

No significant differences in kinetic parameters of ion transport systems were seen between patients with or
**TABLE 2. Differences in Intraerythrocyte Na⁺ Content and Kinetic Parameters of Ion Transport Systems Between Hypertensive Patients With and Without Left Ventricular Hypertrophy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients With LVH</th>
<th>Patients Without LVH</th>
<th>Normotensive Control Subjects</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraerythrocyte Na⁺ content, mmol/L per cell</td>
<td>8.5±1.3</td>
<td>7.5±0.8</td>
<td>6.9±1.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Na⁺ efflux via Na⁺-K⁺ pump</td>
<td>18.3±5.6</td>
<td>12.9±5.6</td>
<td>19.0±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>K⁺, mmol/L per cell</td>
<td>12.9±5.6</td>
<td>8.4±6.3</td>
<td>8.2±5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Vₓpt, mmol · (L · cells · h)⁻¹</td>
<td>8.8±1.9</td>
<td>0.33±0.13</td>
<td>0.38±0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Na⁺-K⁺-Cl⁻ cotransport</td>
<td>12.9±5.6</td>
<td>8.4±6.3</td>
<td>0.33±0.13</td>
<td>NS</td>
</tr>
<tr>
<td>K⁺, mmol/L per cell</td>
<td>12.9±6.2</td>
<td>5.9±2.4</td>
<td>20.3±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Vₓpt, mmol · (L · cells · h)⁻¹</td>
<td>0.62±0.31</td>
<td>0.21±0.05</td>
<td>0.21±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Na⁺ leak, 10⁻² · h⁻¹</td>
<td>19.0±4.0</td>
<td>19.3±4.6</td>
<td>17.9±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Na⁺ influx via Na⁺-H⁺ exchange, mmol · (L · cells · h)⁻¹</td>
<td>9.8±4.1</td>
<td>7.1±2.6</td>
<td>5.5±1.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Sr²⁺ efflux via Ca²⁺ pump</td>
<td>77.2±49.6</td>
<td>72.6±50.7</td>
<td>55.3±15.1</td>
<td>NS</td>
</tr>
<tr>
<td>KCa, μmol/L per cell</td>
<td>6.5±1.7</td>
<td>5.7±2.4</td>
<td>5.2±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Vₓpt, mmol · (L · cells · h)⁻¹</td>
<td>9.8±4.1</td>
<td>7.1±2.6</td>
<td>5.5±1.3</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; Kᵢ, concentration required for half-maximal stimulation; Vₓpt, maximal efflux ratio; KCa, apparent dissociation constant for total internal Ca²⁺.

*Comparison of essential hypertensive patients with and without LVH.

without LVH (Table 2), except that the Na⁺-H⁺ exchange was clearly elevated in patients with LVH (9.8±4.1 versus 7.1±2.6 mmol · [L · cells · h]⁻¹; P<.05) (Fig 1, top). In fact, erythrocyte Na⁺-H⁺ exchange was abnormal (higher than the 95% confidence limits of the control group of 8.2 mmol · [L · cells · h]⁻¹) in 20 patients (62.5%) with LVH and in only 4 hypertensive patients (22%) without LVH. In addition, as is shown in Fig 1, bottom, patients with LVH exhibited an increased intraerythrocyte Na⁺ content (8.5±1.3 versus 7.5±0.8 mmol/L per cell; P<.01).

Using LVMI as a dependent variable and the remaining clinical, biochemical, and hormonal parameters as well as ion transport determinations as independent variables, a linear correlation analysis was performed. The results of this analysis showed that age (r=0.45, P<.01) and erythrocyte Na⁺-H⁺ exchange (r=0.52, P<.001) were the only two parameters that significantly correlated with LVMI in the univariate analysis.

To account for possible interrelations between the variables analyzed, a stepwise multiple linear regression analysis was performed using LVMI as the dependent variable. The independent variables included in this analysis were those that had a correlation coefficient higher than ±0.23 (P<.1): age, systolic blood pressure, plasma fasting glucose, Na⁺,K⁺-ATPase (Vₓpt), Na⁺-K⁺-Cl⁻ cotransport (Vₓpt), and Na⁺-H⁺ exchange. The results of this analysis showed that after age was forced into the model, Na⁺-H⁺ exchange (r=.475 adjusted by age) and Vₓpt of the Na⁺-K⁺-Cl⁻ cotransport (r = −.287 adjusted by age and Na⁺-H⁺ exchange) were the only two significant parameters relating independently with LVMI (Fig 2, top and bottom).

**FIG 1. Plots showing (top) individual values of erythrocyte Na⁺-H⁺ exchange in mmol · (L · cells · h)⁻¹ in patients with and without left ventricular hypertrophy (LVH) and (bottom) individual values of intraerythrocyte Na⁺ content in mmol/L per cell in patients with and without left ventricular hypertrophy.**
In our study, both office blood pressure values and those achieved at maximal exercise capacity were not significantly different between patients with or without LVH. Moreover, there was no significant correlation between these blood pressure values and LVMI. Some authors have recently reported that average systolic and diastolic blood pressure values obtained by means of 24-hour ambulatory blood pressure monitoring correlated significantly with LVMI. Unfortunately, this measurement was not performed in our patients.

Among nonhemodynamic factors of LVH, the increased sympathetic activity and some renin-angiotensin-aldosterone-mediated actions may be involved in myocardial cell growth. However, this evidence is based on in vitro tissue culture studies. Both norepinephrine and angiotensin II stimulate protein biosynthesis and cell growth in the cardiac muscle. However, there is little evidence linking catecholamines and renin or aldosterone levels with the degree of LVH in hypertensive persons. In this sense, Bauwens et al showed a significant correlation of LVMI with plasma renin activity and aldosterone but not with urinary catecholamines. We were not able to reproduce these results. In fact, plasma renin activity, aldosterone, plasma catecholamines, and atrial natriuretic factor levels did not differ between hypertensive persons with or without LVH. Moreover, there was no significant relation between these hormonal measurements and LVMI.

The main finding of the present study is the demonstration of a close relation between LVH and sodium transport abnormalities. The increased Na+-H+ exchange and the decreased Na+-K+-Cl- cotransport activity were significantly correlated with LVMI. Moreover, patients with LVH showed an increased intraerythrocyte Na+ content and higher rates of Na+-H+ exchange. Ion transport abnormalities reported in the past 20 years have been implicated in the pathogenesis of EH. Some authors have postulated that these abnormalities may identify EH patients with special clinical features. With respect to LVH, Schmieder et al reported that sodium intake was a powerful determinant of the degree of LVH, and Inoue et al found a significant correlation between intracellular Na+ and Ca2+ content and LVMI in EH patients. Recent studies have reported that hypertensive persons with higher rates of erythrocyte Na+-Li+ countertransport more frequently exhibited LVH, determined either by ECG criteria or by direct echocardiographic measurement. The present study does not confirm a relation between erythrocyte Na+-Li+ countertransport and LVH, although a different assay of Na+-Li+ countertransport (Li+-stimulated Na+ efflux instead of Na+-stimulated Li+ efflux) was used in our study. However, we found that other abnormalities of intracellular Na+ mobilization, ie, an increased entry of Na+ via Na+-H+ exchange or a decreased extrusion by the Na+-K+-Cl- cotransport system, are associated with LVH in EH. There is clear evidence that there are population differences in the fraction of hypertensive patients exhibiting elevated Na+-Li+ countertransport. Blacks have lower values than whites, and black hypertensive patients do not exhibit significantly higher Na+-Li+ exchange than normotensive blacks. Nevertheless, both black and white hypertensive patients exhibit significant elevation of Na+-H+ exchange.
The hyperactivity of the Na⁺-H⁺ exchanger is known to produce a simultaneous net Na⁺ influx and H⁺ efflux from the cell. In different cell types, this transport system exhibits distinct characteristics that affect its sensitivity to amiloride and its analogues, the activation kinetics by Na⁺ and H⁺, and a variety of responses to intracellular messengers. It seems that at least two different subtypes of this transport system exist, the first involving nonepithelial cells and the basolateral domain of epithelial cells and the second involving the apical domain of polarized epithelial cells. In nonepithelial cells, such as circulating cells (platelets and probably erythrocytes) and myocardocytes, Na⁺-H⁺ exchange activity is enhanced by increases in cytosolic Ca²⁺ concentration and by the activation of the phospholipase C and protein kinase C pathway by vasoactive substances (angiotensin II) and growth factors (platelet-derived growth factor, epidermal growth factor). Furthermore, in myocardial and vascular smooth muscle cells, the increased Na⁺ entry via Na⁺-H⁺ exchange could lead to a rise in intracellular Ca²⁺ content through an inhibition of sarcolemmal Na⁺-Ca²⁺ exchange, thereby promoting increased contractility. Whether this abnormality is primary and genetically determined or secondary to the primary activation of intracellular messengers remains to be established.

In conclusion, our results suggest that the increased intraerythrocyte Na⁺ content observed in hypertensive patients exhibiting LVH could be related basically to both the hyperactivity of the Na⁺-H⁺ exchanger and the hypoactivity of the Na⁺-K⁺-Cl⁻ cotransport system. The lack of relation between blood pressure values and left ventricular mass in hypertensive patients strengthens the hypothesis that other factors than blood pressure are also involved in the development of LVH in EH. The enhancement of the Na⁺-H⁺ exchanger in erythrocytes of EH patients seems to be a good biological marker of myocardial hypertrophy.

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