Erythrocyte Water, Na⁺-K⁺ Cotransport, and Forearm Vascular Function in Humans

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SUMMARY We examined the relationships between erythrocyte (RBC) composition (Na⁺, K⁺, and water content) and ouabain-insensitive transports (Na⁺-K⁺ cotransport, Li⁺-Na⁺ countertransport) and forearm vascular hemodynamics under standardized basal conditions and during vasoconstriction (intra-arterial infusion of graded doses of norepinephrine and angiotensin II) and vasodilation (intra-arterial phenolamine and postischemic exercise). RBC water content correlated positively and significantly (r = 0.53, p = 0.001) with minimum forearm vascular resistance, a measure of vascular structural change, and negatively with maximum forearm blood flow (r = —0.55, p < 0.001). Similar correlations with forearm vascular resistance and blood flow were observed under all experimental conditions. RBC Na⁺-K⁺ cotransport correlated positively and significantly (r = 0.43, p = 0.01) with the change in forearm blood flow produced by phentolamine, a functional measure of α-adrenergic tone, and was as strong an independent predictor of phentolamine-induced blood flow change as was arterial norepinephrine concentration. RBC Na⁺-K⁺ cotransport was also significantly positively correlated with residual forearm blood flow and resistance after phenolamine administration, where nonadrenergic influences predominate. RBC water correlated negatively with Li⁺-Na⁺ countertransport (r = —0.33, p < 0.05) and Na⁺-K⁺ cotransport (r = —0.44, p < 0.01). We propose that RBC water is a marker for a vascular structural property that contributes to vascular reactivity. RBC Na⁺-K⁺ cotransport seems to relate most strongly to the sympathetically mediated control of forearm blood flow and may also be linked to the intrinsic myogenic tone of the forearm vasculature. Li⁺-Na⁺ countertransport is not significantly correlated with vascular hemodynamic measures but may, along with Na⁺-K⁺ cotransport, relate to the control of cell composition. (Hypertension 12: 199-205, 1988)

KEY WORDS • erythrocytes • cell water • sodium-potassium cotransport • lithium-sodium countertransport • vascular structure • vascular reactivity • norepinephrine • angiotensin II

NUMEROUS studies have linked variations in red blood cell (RBC) cation composition1,2 and transmembrane transport3-6 to human hypertension, but RBC disorders have not yet convincingly been related to organ-scale pathophysiological mechanisms capable of initiating or sustaining hypertension. Some investigators have hypothesized that RBC membranes share transport functions with other specific cell types, such as kidney proximal tubular cells7,8 or vascular smooth muscle cells (VSMCs),9 while others argue that changes in RBCs reflect a widespread membrane defect induced either by circulating factors10,11 or variations of membrane structure.12 While it is not possible to measure cellular ion composition and transmembrane transport directly in relevant effector cells in humans, examination of the relation of cardiovascular functions to RBC characteristics offers one approach to the search for clues to pathophysiological mechanisms.1,2,8,13-15

Subjects and Methods

Twenty-four men with mild essential hypertension and 18 age-matched and weight-matched normotensive volunteers were recruited by public advertisement. All were in good health, and except for hypertension, none had any known cardiovascular, endocrine, renal, or liver disease. Medications were discontinued in the hypertensive subjects 3 weeks before study. After an explanation of the details of the protocol, each subject read and signed an informed consent previously approved by the Human Use Committee of the University of Michigan, Ann Arbor, MI, USA.
Physiological Measurements

Arterial pressure was measured directly from a 20-gauge plastic catheter in the left brachial artery using a Hewlett-Packard 1290A quartz transducer, 4568C polygraph, and 1308A oscilloscope (Andover, MA, USA) and a Gould TA-600 thermal recorder (Cleveland, OH, USA). Mean arterial pressure (MAP) was determined by electronic integration of the brachial artery pulse-wave form.

Forearm blood flow (FBF) was measured by mercury-in-Silastic strain-gauge, venous occlusion plethysmography using a Hokanson EC-4 plethysmograph (Issaquah, WA, USA) and a Hokanson E-10 rapid cuff inflator. After forearm volume was determined by water displacement, the left forearm was supported above the level of the heart with the strain gauge encircling the forearm approximately 7 cm below the olecranon. Sixty seconds before each FBF measurement, a child-sized cuff encircling the wrist was inflated to above systolic blood pressure to exclude the hand circulation. The venous conglobating cuff on the upper arm was then rapidly inflated to 40 to 50 mm Hg for 10 to 15 seconds and deflated for 3 to 5 seconds. FBF (in ml/dl of forearm volume/min) was determined in four inflation-deflation cycles by dividing the mean vertical deflection/minute by the 1% electrical calibration signal. Forearm vascular resistance (FVR) was calculated as MAP/FBF and expressed in arbitrary units. Maximal FBF was determined after 10 minutes of ischemic forearm exercise as the mean of six flow curves obtained in the 60 to 90 seconds immediately following the ischemic period.

Pharmacological Studies

After a stable (± 10%) baseline FBF was documented, norepinephrine was infused into the left brachial artery in sequential doses of 1.25, 5.0, 20.0, 80.0, 160.0, 240.0 ng/dl forearm volume/min for 4 minutes at each dose. MAP and FBF were measured during the fourth minute of each infusion. Fifteen to 30 minutes after the intra-arterial NE infusion was concluded, baseline FBF was again measured and angiotensin II (Ang II) was infused into the brachial artery in sequential doses of 0.125, 0.5, 2.0, 8.0, 16.0, and 24.0 ng/dl forearm volume/min for 4 minutes at each dose. Measurements of MAP and FBF were made during the fourth minute of each dose. Following the intra-arterial Ang II infusion, a stable baseline flow was again established, phentolamine (12 μg/dl forearm volume) was infused for 10 minutes, and measurements of MAP and FBF were obtained during the last minute.

RBC Measurements

For RBC measurements, 20 ml of whole blood was collected from the arterial catheter in a heparinized syringe. Two 400-μl aliquots were transferred to preweighed Beckman microfuge tubes and centrifuged for 5 minutes at 9000 g in a Beckman Microfuge B (Palo Alto, CA, USA). The supernatants and upper layer of cells were aspirated and discarded, and the cell pellets were weighed and then dried for 48 hours at 90 °C, cooled in a desiccator, and reweighed. Cell water was calculated from the wet and dry weights and expressed as percent weight/weight. No correction was made for trapped extracellular fluid. The coefficient of variation of the measurement was 1.0% as calculated by the following formula: coefficient of variation = \( \sqrt{\text{d}^2 / 2N} \), where \( d \) is the difference between paired measurements and \( N \) is the number of pairs.

RBC cation contents were determined in 5% trichloroacetic acid lysates of 200-μl aliquots of washed packed RBCs assayed for Na\(^+\) and K\(^+\) concentrations on a Perkin-Elmer Model 2380 atomic absorption spectrophotometer (Perkin-Elmer, Norwalk, CT, USA) using bracketed trichloroacetic acid standards.

Li\(^+\)-Na\(^+\) countertransport was determined by the method of Canessa et al.\(^3\) with minor modifications.\(^16\) Briefly, 5 ml aliquots of washed packed RBCs were loaded with Li\(^+\) by incubation for 3 hours at 37 °C in a Tris–morpbinopranosulphonic acid–buffered 150 mM LiCl solution. Li\(^+\)-Na\(^+\) countertransport was then determined as the difference in Li\(^+\) efflux into Na\(^+\)-rich and Na\(^+\)-free media. The technical error of this assay is about 8%.\(^17\)

Na\(^+\)-K\(^+\) cotransport was defined as bumetanide-sensitive Na\(^+\) efflux from cells loaded to equimolar concentrations of Na\(^+\) and K\(^+\) by the nystatin technique.\(^16\) Following Na\(^+\) loading, the cell water content was assessed gravimetrically as already described, and cotransport measurements were excluded from analysis if final cell water was greater than 3% above fresh cell water. The error of the cotransport measurement is about 18%.\(^17\)

Statistical Methods

Data were stored on the Michigan Terminal System of the University of Michigan and analyzed using the MIDAS statistics package. Descriptive statistics are expressed as means ± SE. Relationships between variables were examined by simple and partial correlation and by multiple linear regression. Group differences were assessed by unpaired t test. Significance was accepted at the 0.05 level.

Results

A total of 42 men completed the forearm vascular and RBC transport studies. Analysis is limited to the 36 whites as race has an important impact on RBC transport.\(^16\) Characteristics of the study population are shown in Table 1. The groups were matched well for age, weight, and height. Except for blood pressure, only arterial plasma norepinephrine was significantly different between the groups. RBC contents and ouabain-insensitive fluxes did not differ significantly between hypertensive and normotensive subjects.
TABLE 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=15)</th>
<th>Hypertensive (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33±2</td>
<td>37±2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181±2</td>
<td>179±2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.2±4.5</td>
<td>98.6±5.9</td>
</tr>
<tr>
<td>Forearm volume (ml)</td>
<td>1328±60</td>
<td>1355±54</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122±4</td>
<td>144±3*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78±3</td>
<td>100±2*</td>
</tr>
<tr>
<td>Baseline NEa (pg/ml)</td>
<td>134±12</td>
<td>209±24†</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.8±0.6</td>
<td>42.5±0.5</td>
</tr>
<tr>
<td>RBC contents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺ (mmol/L cells)</td>
<td>7.9±0.4</td>
<td>7.5±0.4</td>
</tr>
<tr>
<td>K⁺ (mmol/L cells)</td>
<td>85.0±1.7</td>
<td>90.2±2.1</td>
</tr>
<tr>
<td>H₂O (% wt/wt)</td>
<td>63.3±0.5</td>
<td>64.0±0.3</td>
</tr>
<tr>
<td>Na⁺-K⁺ cotransport (mmol/L cells/hr)</td>
<td>0.543±0.065*</td>
<td>0.610±0.062</td>
</tr>
<tr>
<td>Na⁺-Li⁺ countertransport (mmol/L cells/hr)</td>
<td>0.332±0.039</td>
<td>0.338±0.029</td>
</tr>
</tbody>
</table>

Values are means ± SE. BP = blood pressure; NEa = arterial norepinephrine.
*p < 0.001, †p < 0.05, compared with normotensive subjects.
†n = 13.

RBC Na⁺, K⁺, and water content, Li⁺-Na⁺ countertransport, and Na⁺-K⁺ cotransport were first examined by simple regression for relationships to blood pressure and forearm hemodynamics in the normotensive and hypertensive subgroups and in the combined group. The most striking finding was the consistency of the positive correlation between RBC water content and FVR under all study conditions (Table 2). Of greatest interest is the correlation between RBC water content and minimum FVR, an index of vascular structure, which was present in both the hypertensive (r = 0.49, p < 0.03) and the normotensive (r = 0.56, p < 0.03) groups as well as in the combined group (Figure 1). As would be predicted from a change in structure, cell water content also correlated with resistance over the entire range of conditions studied. RBC water content also correlated inversely with maximal FBF in both hypertensive (r = -0.54, p < 0.02) and normotensive (r = -0.58, p < 0.03) groups and in the entire group (r = -0.55, p < 0.001) and again correlated similarly over the entire range of flows (see Table 2). Correlations of cell water with FBF and FVR in the hypertensive and normotensive subgroups were similar to those for the entire study group (see Table 2), as shown for the highest dose of norepinephrine infused (Figure 2). Cell water did not correlate significantly with blood pressure. Only weak and generally nonsignificant correlations between arterial blood pressure, FBF or FVR and RBC Na⁺ and K⁺ were found.

RBC Na⁺-K⁺ cotransport activity correlated most strongly with the change in FBF induced by phenotolamine (Figure 3) and with residual postphenotolamine FBF (r = 0.44, p < 0.01) and FVR (r = -0.53, p < 0.001). Subgroup analysis showed that these relationships were similar in normotensive

TABLE 2. Forearm Vascular Resistance and Blood Flow and Correlation Coefficients with RBC Water Content in 36 Subjects

<table>
<thead>
<tr>
<th>Conditions of measurement</th>
<th>FVR (arbitrary units)</th>
<th>FBF (ml/100 g tissue/min)</th>
<th>r</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postischemic exercise</td>
<td>2.1±0.1</td>
<td>52.3±1.9</td>
<td>0.53*</td>
<td>-0.55*</td>
</tr>
<tr>
<td>10-min phenotolamine</td>
<td>8.9±0.7</td>
<td>13.4±1.0</td>
<td>0.33†</td>
<td>-0.25</td>
</tr>
<tr>
<td>Baseline NEa</td>
<td>25.6±1.4</td>
<td>4.2±0.3</td>
<td>0.37†</td>
<td>-0.39†</td>
</tr>
<tr>
<td>i.a. NE infusion (ng/dl forearm volume/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>32.7±1.9</td>
<td>3.3±0.2</td>
<td>0.42‡</td>
<td>-0.41‡</td>
</tr>
<tr>
<td>5.0</td>
<td>39.8±2.0</td>
<td>2.6±0.1</td>
<td>0.35†</td>
<td>-0.42‡</td>
</tr>
<tr>
<td>20.0</td>
<td>46.7±2.5</td>
<td>2.2±0.1</td>
<td>0.36‡</td>
<td>-0.42‡</td>
</tr>
<tr>
<td>80.0</td>
<td>81.6±3.7</td>
<td>1.3±0.1</td>
<td>0.39†</td>
<td>-0.43‡</td>
</tr>
<tr>
<td>160.0</td>
<td>88.7±5.0</td>
<td>1.2±0.1</td>
<td>0.40‡</td>
<td>-0.52*</td>
</tr>
<tr>
<td>240.0</td>
<td>90.3±4.2</td>
<td>1.1±0.1</td>
<td>0.43‡</td>
<td>-0.55*</td>
</tr>
<tr>
<td>Baseline Ang II</td>
<td>26.3±1.2</td>
<td>3.9±0.2</td>
<td>0.31</td>
<td>-0.34†</td>
</tr>
<tr>
<td>i.a. Ang II infusion (ng/dl forearm volume/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125</td>
<td>31.5±1.6</td>
<td>3.3±0.2</td>
<td>0.37†</td>
<td>-0.44‡</td>
</tr>
<tr>
<td>0.5</td>
<td>38.8±1.8</td>
<td>2.7±0.1</td>
<td>0.48‡</td>
<td>-0.52*</td>
</tr>
<tr>
<td>2.0</td>
<td>45.8±1.8</td>
<td>2.3±0.1</td>
<td>0.36‡</td>
<td>-0.47‡</td>
</tr>
<tr>
<td>8.0</td>
<td>69.3±3.1</td>
<td>1.5±0.1</td>
<td>0.28</td>
<td>-0.40‡</td>
</tr>
<tr>
<td>16.0</td>
<td>78.7±3.8</td>
<td>1.4±0.1</td>
<td>0.33‡</td>
<td>-0.39†</td>
</tr>
<tr>
<td>24.0</td>
<td>87.3±4.3</td>
<td>1.3±0.1</td>
<td>0.26</td>
<td>-0.34‡</td>
</tr>
</tbody>
</table>

Results are means ± SEM. FVR = forearm vascular resistance; FBF = forearm blood flow; NE = norepinephrine.
*p < 0.005, †p < 0.05, ‡p < 0.01.
subjects \( r = 0.60, -0.60, -0.61 \), respectively; all \( p < 0.03 \) and hypertensive subjects \( r = 0.34, 0.33, -0.51 \), respectively; \( p < 0.15, 0.15, 0.02 \), respectively). The other major determinant of the phentolamine-induced change in FBF, arterial plasma norepinephrine, was similarly positively correlated \( r = 0.51, p < 0.005 \), and multiple linear regression demonstrated that both arterial norepinephrine (partial \( r = 0.57 \)) and RBC Na\(^+\)-K\(^+\) cotransport (partial \( r = 0.51 \)) were highly significant \( p < 0.005 \) correlates of the phentolamine-induced change in flow. Together these two factors accounted for 45% of the variability in the change in FBF.

Li\(^+\)-Na\(^+\) countertransport was weakly positively correlated with mean arterial blood pressure \( r = 0.28, p = 0.09 \), but it was not consistently related to forearm vascular resistance or flow. RBC water content was significantly inversely correlated with both Li\(^+\)-Na\(^+\) countertransport \( r = -0.33, p < 0.05 \) and Na\(^+\)-K\(^+\) cotransport \( r = -0.44, p < 0.01 \). Countertransport and cotransport were positively intercorrelated \( r = 0.36, p < 0.05 \).

Discussion

The primary new finding in the present study is the demonstration of a significant direct relationship between RBC water content and FVR. Calculated resistance expresses the relationship between blood pressure and flow, and in our data the basis of the link between RBC water and resistance clearly resides in a significant inverse correlation with FBF. Although we did not assess systemic hemodynamics in the present study, unpublished data from an earlier invasive hemodynamic study of normotensive, borderline, and mildly hypertensive men\(^{18}\) revealed a stronger, albeit nonsignificant, relationship between RBC water content and systemic flow, that is, cardiac index \( r = -0.21, p < 0.09, n = 65 \), than with total vascular resistance \( r = 0.07, p = 0.56 \). RBC water therefore seems to be a better marker of forearm than of systemic vascular resistance, and accordingly, RBC water content was not different between hypertensive and normotensive subjects in the present study.

Poiseuille's law, \( R = 8\pi n L/r^4 \), defines the important factors contributing to vascular resistance \( R \), namely, blood viscosity \( n \), vessel length \( L \), and radius \( r \). In our study, RBC water was not significantly correlated with hematocrit \( r = -0.05, p = 0.80 \), the primary determinant of whole-blood viscosity.\(^{19}\) Cell water content could be a marker for
cell deformability or aggregability, the two other cellular characteristics contributing to blood viscosity,19 or for the rheological properties of plasma, but we have no data on those factors. We think it unlikely that an effect on blood viscosity could explain the correlations between FVR and FBF and RBC water, as even major changes in whole-blood viscosity have no discernible effect on in vivo hemodynamics.20 Indeed, the demonstration of a significant correlation between RBC water and minimum FVR (maximal vasodilation) strongly suggests a vascular structural element as the basis of the observed cell water–resistance relationship.

Increased vascular resistance at maximal postischemic flow, a measure of vascular structural change, has been demonstrated repeatedly in borderline21 and mild hypertensive subjects.22 There is no evidence that vascular length is abnormal in hypertension, so increased minimum resistance has been attributed to diminished vascular luminal radius. As shown by Folkow,23 a structural compromise of luminal cross-sectional area should nonspecifically augment vascular reactivity to all vasoconstrictors and vasodilators. In support of the structural hypothesis, our laboratory has demonstrated that increased minimum FVR in hypertensive subjects is associated with a nonspecific increase in vascular reactivity to intra-arterial infusion of both norepinephrine and Ang II.24 As would be expected for a marker of vascular structural change, cell water also correlated with FVR at all degrees of vasoconstriction, independently of the vasoactive agent infused. Furthermore, cell water was not significantly correlated with differences in the apparent threshold sensitivity to intra-arterial infusion of either norepinephrine or Ang II (data not shown), again compatible with a relationship to a nonspecific vascular structural element.

In addition to cell contents, we measured two ouabain-insensitive modes of RBC cation transport, bumetanide-sensitive Na\(^+-\)K\(^+\) cotransport and Li\(^+-\)Na\(^+\) countertransport. Of greatest interest is the relationship of RBC Na\(^+-\)K\(^+\) cotransport to the alteration in forearm hemodynamics produced by intra-arterial infusion of phentolamine. The change in FBF and FVR produced by phentolamine represents the effect of withdrawal of sympathetic tone and was greater in hypertensive than in normotensive subjects, presumably reflecting increased sympathetic drive, as assessed by arterial plasma norepinephrine level, in the hypertensive subjects. However, we also observed a significant correlation between RBC Na\(^+-\)K\(^+\) cotransport and the change in FBF and a borderline significant correlation with resistance change produced by phentolamine that was independent of the effect of plasma norepinephrine. Since Na\(^+-\)K\(^+\) cotransport was not significantly correlated with minimum FVR \((r = 0.26, p = 0.14)\) or FBF \((r = -0.14, p = 0.44)\), the correlation observed cannot be ascribed to an effect of a structural change. Interestingly, RBC Na\(^+-\)K\(^+\) cotransport is also significantly correlated with residual FBF and FVR following intra-arterial phentolamine infusion, suggesting that cotransport activity may be related as well to nonsympathetic factors mediating myogenic tone, including both circulating substances and intrinsic properties of VSMCs. VSMCs9 and endothelial cells\(^{23}\) demonstrate a high level of loop diuretic-sensitive Na\(^+-\)K\(^+\) cotransport, and in VSMCs cotransport activity is inhibitable by norepinephrine.9 If quantitative variations in RBC Na\(^+-\)K\(^+\) cotransport reflect similar variations in smooth muscle cell membrane transport, Na\(^+-\)K\(^+\) cotransport could contribute to interindividual differences in vascular reactivity.

Li\(^+-\)Na\(^+\) countertransport, as we16, 18 and others13, 26–31 have previously reported, is positively, although in this study not significantly, correlated with blood pressure. We did not find a significant increase in countertransport activity in this group of hypertensive subjects, perhaps because weight, which may affect countertransport,28, 31–34 was well matched in our normotensive and hypertensive groups. We have previously reported a correlation between total vascular resistance and RBC Li\(^+-\)Na\(^+\) countertransport activity,18 but we did not observe any significant relationship between RBC countertransport and FVR over the wide range of conditions studied, perhaps because vascular structure differs between vascular beds. We continue to regard countertransport as a marker for the genetic component of risk for hypertension15 and interpret the present findings as evidence that the effector organ mediating the countertransport-related component of hypertension is more likely to be renal than vascular.8

Finally, the interrelationships of cell water with Li\(^+-\)Na\(^+\) countertransport and Na\(^+-\)K\(^+\) cotransport are of interest. Several investigators,16, 17, 35–37 although not all,38 have noted weak but significant positive correlations of cotransport and countertransport, but the cause of the relationship is unknown. Our current data support these previous findings, and we suggest that the interaction may reflect a codependence of both functions on cell water. Controlling for variations in cell water by partial correlational analysis reduced the significant positive correlation between RBC cotransport and countertransport \((r = 0.36, p < 0.05)\) to nonsignificance \((partial r = 0.08, p = NS)\), but since the contribution of these transport functions to the control of RBC water content is unknown, the basis for this apparent interaction cannot be ascertained in the present study. Circulating lipids have been found to be significantly related to RBC Li\(^+-\)Na\(^+\) countertransport34, 39 and Na\(^+-\)K\(^+\) cotransport,34 and alterations in membrane lipid composition may be the link between cell water content and transport function.

The present study has several limitations. First, the sample sizes are small, although we made an attempt to match normotensive and hypertensive
subjects carefully. Second, matching the groups for weight may have introduced a bias in the normotensive subjects, as we have found that when subjects are selected solely on blood pressure criteria, hypertensive subjects are usually heavier than comparable normotensive subjects. Because of the need to standardize FBF measurements to forearm volume, we elected in this study to match for weight. It will be of interest to determine if our observations can be extended to less rigorously selective normotensive subjects. Third, we relied wholly on correlative analyses in this study; therefore, we cannot directly address the question of the physiological mechanisms linking our observations in RBCs to those in blood vessels. Finally, five of the hypertensive subjects had been treated before the study. Although we withdrew all medications at least 3 weeks before performing our studies, residual drug effects could have contributed to our findings, although analysis of the data did not show any differences between treated and untreated subjects, and the relationships described in hypertensive subjects were also observed in normotensive subjects, in whom drug treatment is not an issue.

In 1952, Tobian and Binion suggested that “water-logged” vessels could compromise the vascular lumen and produce hypertension. Our data provide support for the concept that RBC water content is a marker for a structural vascular change that nonspecifically augments pressor responses to vasoconstrictors and vasodilators.

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