Determinants of Platelet Activation in Human Essential Hypertension

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Abstract—Experimental data suggest that oxidative stress might be enhanced in hypertension and contribute to platelet activation. We hypothesized that both oxidative stress and platelet activation could be related to the clinical characteristics of hypertensive patients. The urinary excretion of 11-dehydrothromboxane (TX) B₂, reflecting in vivo platelet activation, was measured in 75 patients with mild to severe essential hypertension and 75 pair-matched, healthy controls. The urinary excretion of 8-iso-prostaglandin (PG) F₂α was determined as an index of in vivo lipid peroxidation. Urinary 11-dehydro-TXB₂ was significantly higher in essential hypertensives compared with controls. Although no statistically significant difference in urinary 8-iso-PGF₂α was observed between patients and controls, plasma vitamin C was lower and plasma homocysteine higher in hypertensive patients than in controls. Both urinary 11-dehydro-TXB₂ and 8-iso-PGF₂α were higher in patients with advanced hypertensive retinopathy compared with patients without retinopathy. Multivariate linear regression analysis identified urinary 8-iso-PGF₂α, plasma fibrinogen, homocysteine, and vitamin E as the only variables independently correlated with urinary 11-dehydro-TXB₂. Logistic regression analysis showed that high urinary 8-iso-PGF₂α, plasma fibrinogen, and homocysteine, as well as low plasma vitamin E, advanced retinopathy, elevated diastolic blood pressure, and the absence of antihypertensive treatment, were predictors of high urinary 11-dehydro-TXB₂. We demonstrated increased oxidative stress and persistent platelet activation in essential hypertensives with advanced vascular lesions. These findings might help identify hypertensive patients who are at increased risk of cardiovascular events and who might benefit from long-term antiplatelet therapy. (Hypertension. 2004;43:64-70.)

Key Words: hypertension, essential ■ platelets ■ thromboxanes ■ oxidative stress ■ urine

Large observational studies indicate that in human essential hypertension, cardiovascular morbidity and mortality are related to the severity of the hypertensive state and to the development of cardiac and vascular changes. However, the signals that allow alterations in blood pressure control to be translated into atherothrombotic complications have only partially been characterized. Increased oxidative stress might be implicated. This hypothesis is based on data from animal models of genetic hypertension, showing increased generation of oxygen free radicals within the vascular wall, associated with worsening of blood pressure control, alterations in vascular function, and progression of vascular lesions.1–3 Experimental data suggest that oxidative stress might be increased in human essential hypertension and could be responsible for altered endothelial function.4–6

Different risk factors for atherothrombosis, such as hypercholesterolemia,7 severe hyperhomocysteinemia,8 visceral obesity,9 and diabetes mellitus,10 have been shown to be associated with biochemical evidence of platelet activation, as assessed by measuring the urinary excretion of 11-dehydro-thromboxane (TX) B₂, a noninvasive index of platelet TXA₂ production. In these clinical conditions, oxidative stress was also found to be increased. Oxidative stress was quantified by measuring the urinary excretion of 8-iso-prostaglandin (PG) F₂α, an abundant F₂-isoprostane generated in vivo. F₂-isoprostanes are PG isomers generated nonenzymatically through free radical–catalyzed attack of esterified arachidonic acid in cell membranes and lipoproteins.11

To date, there is little direct evidence of persistent platelet activation and an increase in oxidative stress in human essential hypertension. Moreover, is not clear how platelet activation and oxidative stress might be related to the clinical characteristics of hypertensive patients or to metabolic alterations coexisting with hypertension.5,12 We tested the hypothesis that platelet activation occurs in vivo in human essential hypertension by comparing hypertensive patients and appropriate healthy controls. Then we analyzed which of the clinical characteristics and metabolic variables was indepen-
TABLE 1. Demographic and Biochemical Variables in Essential Hypertensive Patients and Pair-Matched, Normotensive, Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensives (n=75)</th>
<th>Controls (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, F/M</td>
<td>42/33</td>
<td>42/33</td>
</tr>
<tr>
<td>Age, y</td>
<td>52 (18–76)</td>
<td>48 (22–69)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0 (19.2–39.3)*</td>
<td>23.4 (17.3–31.6)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>145 (120–190)*</td>
<td>120 (90–135)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94 (65–115)*</td>
<td>80 (60–90)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.5 (3.6–9.5)</td>
<td>5.5 (3.5–7.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 (0.8–2.4)</td>
<td>1.5 (0.8–2.4)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 (0.5–4.0)</td>
<td>0.9 (0.5–4.3)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>80.4 (45.9–116.6)</td>
<td>78.6 (52.1–121.9)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.3 (4.2–6.9)</td>
<td>5.2 (4.1–6.5)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>324 (181–679)</td>
<td>299 (202–466)</td>
</tr>
<tr>
<td>Vitamin A, μmol/L</td>
<td>2.6 (0.3–4.8)</td>
<td>3.0 (0.3–6.7)</td>
</tr>
<tr>
<td>Vitamin C, μmol/L</td>
<td>30.6 (0.5–95.3)*</td>
<td>43.7 (0.5–128.8)</td>
</tr>
<tr>
<td>Vitamin E, μmol/L</td>
<td>28.3 (16.2–51.0)</td>
<td>30.1 (5.5–67.3)</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>13.0 (6.4–41.4)*</td>
<td>10.7 (6.2–22.5)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). SBP indicated systolic blood pressure and DBP, diastolic blood pressure.

*P<0.001 vs normotensive subjects.

and E were also determined. On the same day, blood pressure was measured, and a thorough clinical evaluation was completed. In all hypertensive patients, examinations of the heart and carotid and retinal arteries, as well as measurement of the urinary excretion of albumin, were performed to identify lesions of large and small vessels and target-organ damage. The study protocol was approved by the ethics committee of the medical center in Verona. All subjects gave their informed consent to take part in the study.

Clinical Investigations and Biochemical Analyses
Arterial blood pressure was measured with patients in the sitting position.13 Pulse pressure was calculated. Carotid arteries were studied with a bidimensional ultrasonograph. The extent of carotid artery involvement was evaluated by the presence of atheromatos plaques at the level of the carotid axes.

Echocardiography was used to evaluate left ventricular hypertrophy (LVH) according to the recommendations of the American Society of Echocardiography. Retinal arteries were studied by fundoscopy according to the Keith-Wagener-Barker classification.14 Body mass index (BMI, in kg/m²) was also calculated. Measurement of urinary 8-iso-PGF₂α and 11-excreted dehydro-TXB₂ metabolite was performed according to previously described procedures.15,16

Plasma concentrations of vitamins A, C, and E and total concentration of homocysteine in plasma were determined by high-performance liquid chromatography. Plasma fibrinogen concentration was determined by analyzing its enzymatic conversion to fibrin. Microalbuminuria was detected by nephelometric immunossay. Plasma glucose, lipids, and creatinine and urinary creatinine were determined with an automated analyzer.

Statistical Analysis
The Kruskal-Wallis test and Mann-Whitney test were used. The Spearman correlation coefficient (R) was calculated. The Bonferroni adjustment was applied. Multivariate linear regression analysis was performed by backward stepping. For the odds ratio estimates, multivariate logistic regression analysis was carried out (SPSS-11 statistical package). A value of P<0.05 was considered statistically significant.

An expanded Methods section can be found in an online supplement available at http://www.hypertensionaha.org.

Results
Platelet Activation and Oxidative Stress in Essential Hypertensive Patients and Normotensive Controls
The urinary excretion of 11-dehydro-TXB₂, was significantly enhanced in hypertensive patients, exceeding the 75th percentile of control values in 36 of 75 patients (Figure 1). The urinary excretion of 8-iso-PGF₂α excitation was not statistically different in hypertensive and normotensive subjects (Figure 1). The biochemical profile and anthropometric indices were different in the 2 study groups, because BMI and plasma homocysteine levels were higher and plasma vitamin C was lower in hypertensive patients than in controls (Table 1).

Determinants of Platelet Activation in Hypertensive Patients
We investigated whether lipid peroxidation, arterial pressure, antihypertensive treatment, additional risk factors, and the presence of cardiovascular damage independently contributed to platelet activation in subjects with essential hypertension.

We observed that 15 patients had advanced hypertensive retinopathy (grade 2 or 3), most of them also having carotid artery stenosis (n=13). Thirty percent of the patients had


dently correlated with urinary 11-dehydro-TXB₂, a biochemical marker of platelet activation, in hypertensive patients, testing the hypothesis that oxidative stress is a determinant of platelet activation. Therefore, we tried to define the metabolic variables and the clinical characteristics of the studied patients by referring to the 1999 World Health Organization (WHO) criteria for the diagnosis of hypertension and for the identification of cardiovascular risk. In addition, we took into account additional variables, such as antioxidant vitamins and antihypertensive treatment, that could have effects on the urinary excretion of 11-dehydro-TXB₂.

Methods

Subjects and Study Protocol
Seventy-five healthy, nonsmoking normotensive subjects were pair-matched for gender and age with 75 nonsmoking but otherwise unselected, essential hypertensive patients, classified according to the 1999 WHO criteria.13

Criteria for exclusion were as follows: (1) concomitant diabetes mellitus, defined according to the criteria of the American Diabetes Association; (2) any active inflammatory or neoplastic disease; (3) acute cardiac or cerebrovascular events; and (4) cigarette smoking. None of the subjects was permitted to take vitamins, nonsteroidal anti-inflammatory drugs, or antiplatelet agents for at least 14 days before the study.

Both patients and healthy controls maintained their usual dietary habits during the study. Hypertensive patients were either untreated or under long-term treatment with antihypertensive medication at the time of study. The baseline characteristics of hypertensive patients and normotensive controls are detailed in Table 1.

The urinary excretion of 8-iso-PGF₂α and 11-dehydro-TXB₂ was evaluated from overnight urine collections (from 8 PM to 8 AM). Blood samples were taken at 8 AM after overnight fasting on the same day of the first urine collection. Plasma glucose, total and HDL cholesterol, triglycerides, creatinine, and fibrinogen were determined. Plasma concentrations of homocysteine and vitamins A, C,
atherosclerotic lesions of the carotid arteries but no signs of stable hypertensive retinopathy. LVH was observed in 15 patients. Microalbuminuria was detectable in 17 patients. When patients were grouped according to the presence or absence of signs of atherosclerosis or hypertension-induced cardiovascular changes, we found that patients with advanced retinopathy, whether or not associated with atherosclerosis of the carotid arteries, LVH, or microalbuminuria, had higher urinary excretion of both 11-dehydro-TXB₂ and 8-iso-PGF₂α than did patients without retinopathy (Figure 2). This subgroup analysis also showed that plasma fibrinogen, but not any of the other study parameters, was higher in patients with carotid artery stenosis or hypertensive retinopathy (Table 2). No statistically significant differences were observed when subgroup analysis was performed according to the presence or absence of LVH or microalbuminuria (data not shown). Similarly, no differences were observed in the excretion rates of 11-dehydro-TXB₂ and 8-iso-PGF₂α when treated and untreated hypertensive patients were compared (data not shown). Bivariate regression analysis showed that only the urinary excretion of 11-dehydro-TXB₂ was significantly correlated with 8-iso-PGF₂α (R² = 0.42, P = 0.0002, n = 75). Using multivariate linear regression analysis, we found that in hypertensive patients the urinary excretion of 11-dehydro-TXB₂ was independently correlated with the urinary excretion of 8-iso-PGF₂α and with the plasma concentrations of fibrinogen, homocysteine, and vitamin E (Table 3).

Additional analyses of the data were carried out with multivariate logistic regression (Table 4). The test was performed by considering high and low urinary 11-dehydro-TXB₂ excretion rates as dependent categorical variables (ie, values above and below the 75th percentile of those recorded in normotensive subjects). High plasma fibrinogen and urinary 8-iso-PGF₂α and low plasma concentrations of vitamin E, as well as advanced retinopathy and diastolic blood pressure >90 mm Hg, were predictors of high urinary excretion of 11-dehydro-TXB₂ in hypertensive patients. The use of
antihypertensive treatment was a predictor of low urinary 11-dehydro-TXB₂. None of the other studied variables, including other signs of cardiovascular damage, was independently correlated with high or low urinary excretion of 11-dehydro-TXB₂. (Similar results were obtained when data were analyzed as continuous variables.) In a different analytical model in which retinopathy was not included, microalbuminuria, the biochemical marker of microvascular damage in hypertension, was a predictor of high urinary excretion of 11-dehydro-TXB₂ (P=0.018), together with all of the other categorical variables identified by the previous analysis (data not shown).

**Discussion**

Abundant evidence indicates that platelet activation, as assessed in vivo by measuring the urinary excretion of TXA₂ metabolites, can be detected in clinical conditions associated with increased cardiovascular risk or during acute ischemic coronary and cerebrovascular syndromes. However, relatively limited evidence concerning platelet activation in human essential hypertension is available so far. In fact, although no statistically significant differences were found in the urinary excretion of 2,3-dinor-TXB₂ between healthy normotensive controls and patients with mild to moderate essential hypertension, the excretion of 11-dehydro-TXB₂ was found to be increased in patients with renovascular hypertension and severe pregnancy-induced hypertension, as well as in hypertensive patients with peripheral arterial disease compared with appropriately matched normotensive subjects.

Data from the present study indicate that the median urinary excretion rate of 11-dehydro-TXB₂ is significantly higher in unselected hypertensive patients when compared with pair-matched, normotensive controls. However, the metabolite excretion rate in ≈50% of hypertensive patients did not exceed that measured in controls. A subgroup analysis allowed us to appreciate that differences in TX metabolite excretion were related to hypertension-induced vascular changes. Our findings, demonstrating that patients with more severe microvascular alterations have enhanced TXA₂ biosynthesis, offer a plausible explanation for the apparent inconsistency of previously published data. It is interesting to note that advanced hypertensive retinopathy is usually observed in a small percentage of patients with more severe hypertension and is associated with increased risk of thromboembolic events.

Increased oxidative stress might have been expected in human essential hypertension on the basis of available experimental data. In fact, generation of reactive oxygen species has been described to occur via increased NAD(P)H oxidase or reduced dismutase and nitric oxide synthase activity within the vasculature in genetic and experimental models of hyper-

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Vascular Lesions (n=37)</th>
<th>Carotid Artery Stenosis (n=23)</th>
<th>Retinopathy (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, F/M</td>
<td>21/16</td>
<td>13/10</td>
<td>8/7</td>
</tr>
<tr>
<td>Age, y</td>
<td>50 (18–68)</td>
<td>57 (41–74)†</td>
<td>54 (29–76)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7 (19.8–32.0)</td>
<td>26.9 (20.4–33.3)</td>
<td>27.3 (19.2–39.3)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>145 (120–165)</td>
<td>150 (130–190)</td>
<td>145 (130–185)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>90 (65–100)</td>
<td>100 (80–115)</td>
<td>90 (70–105)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.5 (3.6–7.5)</td>
<td>5.5 (4.0–7.7)</td>
<td>5.8 (4.7–9.5)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 (0.8–2.0)</td>
<td>1.5 (1.1–2.2)</td>
<td>1.4 (1.1–2.4)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 (0.5–4.0)</td>
<td>1.1 (0.7–2.7)</td>
<td>1.2 (0.6–2.3)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>80.4 (45.9–116.6)</td>
<td>76.9 (60.1–107.8)</td>
<td>83.0 (50.3–109.6)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.1 (4.2–6.9)</td>
<td>5.3 (4.3–6.3)</td>
<td>5.6 (4.4–6.6)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>286 (181–485)</td>
<td>364 (240–490)†</td>
<td>326 (243–679)†</td>
</tr>
<tr>
<td>Vitamin A, μmol/L</td>
<td>2.6 (0.3–4.8)</td>
<td>2.8 (0.3–4.3)</td>
<td>2.6 (1.0–4.6)</td>
</tr>
<tr>
<td>Vitamin C, μmol/L</td>
<td>31.5 (1.7–64.1)</td>
<td>27.5 (0.5–50.6)</td>
<td>30.1 (0.5–95.3)</td>
</tr>
<tr>
<td>Vitamin E, μmol/L</td>
<td>27.8 (16.2–39.2)</td>
<td>30.1 (20.8–41.7)</td>
<td>29.7 (20.6–51.0)</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>13.3 (6.4–41.4)</td>
<td>13.2 (6.6–38.0)</td>
<td>12.4 (8.0–24.5)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). Abbreviations are defined in text and the footnote to Table 1. *P<0.001 and †P<0.05 vs subjects without vascular lesions. The Bonferroni adjustment was applied.

**TABLE 3. Linear Regression Analysis in Which the Urinary Excretion of 11-Dehydro-TXB₂ Was the Dependent Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Coefficient β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma fibrinogen</td>
<td>75</td>
<td>1.584</td>
<td>0.415</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>75</td>
<td>14.667</td>
<td>5.026</td>
<td>0.005</td>
</tr>
<tr>
<td>Urinary 8-iso-PGF₁₂</td>
<td>75</td>
<td>0.935</td>
<td>0.356</td>
<td>0.011</td>
</tr>
<tr>
<td>Plasma vitamin E</td>
<td>75</td>
<td>−10.539</td>
<td>−0.213</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Adjusted for age, BMI, plasma cholesterol, triglycerides, glucose, vitamin C, vitamin A, LDL-HDL ratio, SBP, DBP, and pulse pressure. Abbreviations are defined in text and the footnote to Table 1.
tension. Increased oxidative stress was inferred in essential hypertensive patients by the demonstration that endothelial dysfunction was reversed by the infusion of vitamin C.

In the present study, we investigated oxidative stress by measuring the urinary excretion of 8-iso-PGF$_{2a}$, a validated index of in vivo lipid peroxidation. Urinary 8-iso-PGF$_{2a}$ has been shown to be increased in association with a variety of cardiovascular risk factors. The results of the present study indicate that essential hypertension is not associated per se with increased oxidative stress, and this is in agreement with the recent demonstration that the urinary excretion of 15-F(2t)-isoprostane is not increased in untreated mild-to-moderate essential hypertensive patients compared with normotensive controls.

However, we observed that patients with more advanced retinal changes did show increased lipid peroxidation when compared with patients with absent or early signs of retinopathy. Increased generation of superoxide anion within the vascular wall has been shown to be responsible for vascular remodeling, favoring the proliferation of smooth muscle cells. Oxygen free radicals also induce a prothrombotic phenotype in endothelial cells and induce platelet activation. However, the association of lipid peroxidation with the severity of hypertension-induced microvascular lesions does not necessarily imply a cause-effect relation, because increased oxidative stress might accompany or be a consequence of the development of hypertension-induced vascular changes.

Our group of unselected hypertensive patients had a higher BMI and plasma concentration of homocysteine and a lower concentration of vitamin C compared with normotensive controls, consistent with previous observations. We also found that plasma fibrinogen was higher in patients with advanced retinopathy or carotid atherosclerotic lesions, also consistent with an earlier report. To investigate whether these metabolic changes were related to the increase in TXA$_2$ biosynthesis, we performed multivariate regression analyses. Thus, we took into account all of the variables used to define the cardiovascular risk profile of hypertensive patients, as well as additional variables associated with increased cardiovascular risk and potentially related to lipid peroxidation, such as plasma levels of fibrinogen, homocysteine, and antioxidant vitamins.

The observed correlation between the urinary excretion of 11-dehydro-TXB$_2$ and 8-iso-PGF$_{2a}$ and plasma vitamin E supports the hypothesis of a causal relation between increased oxidative stress and platelet activation in essential hypertensive patients. A similar positive correlation was found in patients with hypercholesterolemia, diabetes mellitus, visceral obesity, and homozgyous homocystinuria. In these clinical conditions, short-term supplementation with vitamin E was accompanied by a reduction in the urinary excretion of both 8-iso-PGF$_{2a}$ and 11-dehydro-TXB$_2$, thus suggesting that biologic events related to increased lipid peroxidation contribute to persistent platelet activation. Interestingly, 8-iso-PGF$_{2a}$ and possibly other isoeicosanoids, appears to mediate, at least in part,
the effects of oxidant stress on platelet activation and vascular injury. In fact, 8-iso-PGF₃α exhibits biologic activities both in vitro and in vivo. It is a vasoconstrictor, a mitogen for vascular smooth muscle cells, and a trigger of platelet adhesion and aggregation.⁶⁻⁻²⁹

A mild increase in plasma homocysteine has been identified as a risk factor for atherothrombosis in a number of observational studies.°° The noxious effects of homocysteine on the cardiovascular system have been attributed, at least in part, to its pro-oxidant activity and consequent reduction in nitric oxide bioactivity.⁴¹ Severe hyperhomocysteinemia is associated with biochemical evidence of increased oxidative stress and platelet activation.⁶ The present findings indicate that even a mild elevation in plasma homocysteina is an independent predictor of platelet activation.

Elevated plasma fibrinogen is a predictor of cardiovascular morbidity⁶² and is associated with the extent of vascular lesions in hypertensive patients.⁴³ Fibrinogen is a coagulation factor and an acute-phase reactive protein. Plasma fibrinogen is related to interleukin-6 and C-reactive protein in subjects at risk for cardiovascular events.⁴⁴ It can be considered an index of the underlying inflammatory process that might accompany vascular changes and trigger platelet activation in the setting of arterial hypertension.⁴⁴

We also observed that platelet activation was lower when blood pressure was normal or in the presence of antihypertensive treatment, consistent with the well-defined relations between hypertension and its treatment with cardiovascular events.⁴° Interestingly, we found that the inverse correlation between antihypertensive treatment and urinary 11-dehydro-TXB₂ is independent of blood pressure levels, thus suggesting that specific antihypertensive drugs might have favorable effects on platelet activation in vivo. However, a properly designed intervention study is necessary to test this hypothesis.

Perspectives

In conclusion, we obtained biochemical evidence of increased TXA₂ biosynthesis in essential hypertensive patients and observed that both platelet activation and increased oxidative stress are associated with the presence of hypertension-related microvascular changes. In this setting, platelet activation is related to increased oxidative stress and is also related to increased plasma fibrinogen, as well as to subtle changes in homocysteina metabolism. These findings might help identify hypertensive patients who are at increased risk for cardiovascular events and who might benefit from long-term treatment with antiplatelet agents.

Acknowledgments

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References


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