Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events

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Aims
There is growing need for the identification of novel non-invasive methodologies for the identification of individuals at risk for adverse cardiovascular (CV) events. We examined whether endothelial dysfunction, as detected by non-invasive peripheral arterial tonometry (EndoPAT), can predict late CV events.

Methods and results
Reactive hyperaemia (RH) was induced following upper arm occlusion of systolic blood pressure in 270 outpatients (54 ± 12 years, 48% female). The natural logarithmic scaled RH index (L_RHI) was calculated from the ratio between the digital pulse volume during RH and at baseline. The patients were followed for CV adverse events (AE: cardiac death, myocardial infarction, revascularization or cardiac hospitalization) during a 7-year follow-up (inter-quartile range = 4.4–8). Cox models were used to estimate the association of EndoPAT results with AE adjusted for age. During the follow-up, AE occurred in 86 patients (31%). Seven-year AE rate was 48% in patients with L_RHI < 0.4 vs. 28% in those with L_RHI ≥ 0.4 (P = 0.03). Additional univariate predictors of AE were advancing age (P = 0.02) and prior coronary bypass surgery (P = 0.01). The traditional Framingham risk score was not higher in patients with AE. Multivariate analysis identified L_RHI < 0.4 as an independent predictor of AE (P = 0.03).

Conclusion
A low RH signal detected by EndoPAT, consistent with endothelial dysfunction, was associated with higher AE rate during follow-up. L_RHI was an independent predictor of AE. Non-invasive assessment of peripheral vascular function may be useful for the identification of patients at risk for cardiac AEs.

Keywords
Endothelial function • Outcome • Peripheral arterial tonometry • Reactive hyperaemia

Background
Coronary heart disease is the leading cause of morbidity and mortality in most industrialized societies.1 In spite of comprehensive treatment and modification of conventional risk factors, there is still high incidence of cardiovascular (CV) events rate.2 Thus, there is a need to identify a more individualized functional risk profile in order to personalize treatment.3

It has been suggested that cardiac risk factors can cause impairment of coronary vasomotor function of both the epicardial arteries and the microcirculation,4–8 which is considered an important phase in atherogenesis.9–11 It has been demonstrated that coronary endothelial dysfunction in humans may be associated with myocardial ischaemia.12,13

Coronary endothelial dysfunction is considered an early stage of atherosclerosis14 and has been shown to be associated with an increased risk of ischaemic CV outcome events and stroke.15–18 Assessment of coronary microcirculatory vasomotor function (especially in patients without obstructive coronary artery disease) may therefore allow the identification of patients in the early stages of coronary atherosclerosis and at risk for CV events. However, one of the main obstacles in using peripheral endothelial function for individualized assessment of CV risk is the lack of standardization of these tests.19

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Measurement of peripheral vasodilator response as a measure for endothelial dysfunction is correlated with adverse outcome events.26 and measurements of this response using fingertip pulse amplitude tonometry (peripheral arterial tonometry-PAT) may emerge as a useful method for non-invasive assessment of vascular health.21,22 Impairment of pulse amplitude hyperemic response is associated with the presence of coronary artery endothelial dysfunction, and we have previously reported the correlation between abnormal PAT results and coronary microvascular endothelial dysfunction as detected by invasive evaluation of the coronary endothelial function.23 Reactive hyperaemia (RH) response (with PAT) as detected by the RH index (RHI) has recently been shown to be related to multiple traditional and metabolic risk factors.24 However, it is unknown whether this non-invasive approach can predict adverse CV outcome events beyond the traditional risk assessment.

The purpose of this study was to examine whether endothelial dysfunction, as detected by non-invasive PAT, may have a role in predicting late adverse CV events.

Methods

Patient selection
Between August 1999 and August 2007, 329 symptomatic outpatients (with unexplained chest pain (low-risk findings during stress testing) and/or the absence of new obstructive lesions by an invasive coronary angiogram) underwent evaluation of endothelial function using RH with non-invasive PAT at the centres for coronary physiology at Mayo Clinic in Rochester, MN, and in Tufts Medical Center in Boston, MA. Five patients were excluded from the current investigation on the basis of poor quality signal (n = 3) or lack of research authorization as required by Minnesota law (n = 2). In 54 patients (17%), the follow-up and phone interview could not be completed. The final study group consisted of 270 patients.

Reactive hyperaemia by peripheral arterial tonometry
All vasoactive medications were discontinued at least 24 h prior to testing.

Peripheral arterial tonometry signals were obtained using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel), which has been validated and used previously to assess peripheral arterial tone in other populations.25–27 Specially designed finger probes were placed on the middle finger of each subject’s hand. These probes comprised a system of inflatable latex air cuffs connected by pneumatic tubes to an inflating device controlled through a computer algorithm. A constant counter pressure (pre-determined by baseline measurements of this response using fingertip pulse amplitude tonometry-PAT) may emerge as a useful method for non-invasive assessment of vascular health.21,22 Impairment of pulse amplitude hyperemic response is associated with the presence of coronary artery endothelial dysfunction, and we have previously reported the correlation between abnormal PAT results and coronary microvascular endothelial dysfunction as detected by invasive evaluation of the coronary endothelial function.23 Reactive hyperaemia (RH) response (with PAT) as detected by the RH index (RHI) has recently been shown to be related to multiple traditional and metabolic risk factors.24 However, it is unknown whether this non-invasive approach can predict adverse CV outcome events beyond the traditional risk assessment.

The purpose of this study was to examine whether endothelial dysfunction, as detected by non-invasive PAT, may have a role in predicting late adverse CV events.

Endothelial function was measured via an RH–PAT index. The RH–PAT set-up has been previously described.22,24,26 An RH protocol consists of a 5 min baseline measurement, after which a blood pressure cuff on the test arm was inflated to 60 mmHg above baseline systolic blood pressure or at least 200 mmHg for 5 min. Occlusion of pulsatile arterial flow was confirmed by the reduction of the PAT tracing to zero. After 5 min, the cuff was deflated, and the PAT tracing was recorded for a further 6 min. The ratio of the PAT signal after cuff release compared with baseline was calculated through a computer algorithm automatically normalizing for baseline signal and indexed to the contra lateral arm. The calculated ratio reflects the RHI.

The natural logarithmic scaled RHI (L_RHI) was calculated from the same ratio between the digital pulse volume during RH and at baseline.

Assessment of clinical status and outcome events
Vital status was determined by review of medical records, social security death index, and reviews of death certificates supplemented by a phone interview to determine patients’ clinical status and occurrence of CV outcome events since PAT examination date. Clinical data were determined by an investigator blinded to PAT data. The following clinical parameters were assessed.

Baseline characteristics
Baseline characteristics including risk factors status during the week in which PAT was performed: (i) Hypertension (blood pressure of >140/90 or treatment with anti-hypertensive medications), (ii) diabetes mellitus (patient history and/or treatment with insulin or oral hypoglycaemic agents), (iii) family history of coronary artery disease in first-degree relatives <55 (male) or <65 (female) years of age, (iv) hyperlipidaemia (total serum cholesterol level >240 mg/dL or treatment with lipid-lowering drugs), (v) smoking history (previous or current cigarette smoking), (vi) coronary artery disease, which was defined as diameter stenosis >50% diagnosed by coronary angiography or documented prior myocardial infarction (MI) [defined according to standard definition (serum cardiac biomarker elevation with symptoms of ischaemia and/or ECG changes indicative of new ischaemia/infarction)], (vii) angiographically diagnosed peripheral vascular disease, and (viii) patient medications at baseline.

We also collected the arterial blood pressure measurements and lipid profile (total, HDL and LDL cholesterol and level of triglycerides, all expressed in mg/dL) at the time of PAT study. The data from the risk factors in conjunction with the level of total and HDL cholesterol and the systolic blood pressure were then used to calculate the Framingham risk score (FRS) which presented as 10 years risk (in per cent).

Assessment of subsequent interventions and outcome events during follow-up
Analysis of the patient medical records which were supplemented by phone interview (as mentioned above) was performed to detect the occurrence of any of the following outcome events: (i) all-cause death, (ii) CV death (all death not known to be definitely non-CV), (iii) MI, (iv) percutaneous coronary intervention, (v) coronary artery bypass grafting, (vi) diagnosed ischaemic or haemorrhagic stroke or transient ischaemic attack (TIA). All cerebrovascular events were confirmed by neurologists to meet the criteria for stroke or TIA through appropriate combination of medical history, examination, and/or neuroimaging, and (vii) hospitalization for any cardiac cause, defined as hospitalization for any of the following symptoms: chest pain, dyspnoea, palpitations, or syncope. The number of cardiac hospitalizations...
during follow-up period was also recorded. The combined endpoint of cardiac adverse event (AE) was defined as the occurrence of CV death, MI, revascularization, or cardiac hospitalization.

Death certificates were reviewed to verify the date and cause of all death events occurred during the follow-up period.

Statistical analysis
The statistical analysis was performed by an independent observer (R.J.L.). Continuous variables are summarized as mean ± SD, unless otherwise specified. Discrete variables are summarized as frequency (percentage). Kaplan–Meier methods were used to estimate survival and event-free survival rates. Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios with corresponding 95% confidence intervals and P-values. Multiple Cox regression models were computed to estimate the partial effect of L_RHI. Three covariate sets were investigated: (1) age, (2) age and prior CABG, (3) the FRS (modelled as a three-degree-of-freedom spline). Sets 1 and 2 were chosen because they were significantly associated with AE. However, both gave similar results. The FRS was chosen for clinical relevance (and incorporates age into its calculation).

The best cut-off points for the PAT results for predicting future outcomes was identified and P-values were adjusted for the multiple tests done to identify the cut-off point.30 The ability of the cut-point to discriminate between high- and low-risk patients was estimated by a modified c-index statistic,31 similar to the traditional area under the ROC curve, but specifically for time-to-event endpoints which preclude ROC calculations.

One thousand bootstrap samples were created to estimate the optimism in the estimated association between L_RHI and follow-up AE. The optimism measure indicates how much better the model (or cut-point) works in the data set on which it was derived vs. other similar data sets. In each bootstrap sample, the best cut-off for L_RHI was determined as in the observed sample. The optimism measure was subtracted from the observed estimate to get a corrected measure of the effect. The same standard error was used to generate confidence intervals about the corrected point estimate, and a Wald test was used to calculate a corrected P-value.

Results
As mentioned above, a detailed follow-up including a telephone interview was completed in 270 patients (83%). Baseline characteristics are presented in Table 1. There were missing laboratory data on the following parameters: creatinine (n = 4), total and HDL cholesterol (n = 39), triglycerides (n = 38), LDL cholesterol (n = 31), systolic BP (n = 12), diastolic BP (n = 14).

Analysis of reactive hyperaemia–peripheral arterial tonometry
Reactive hyperaemia index was calculated from the ratio of the digital pulse volume during RH and baseline in 270 patients, and the mean (natural logarithmic) L_RHI was 0.5 ± 0.4 (range −0.7 to 1.8).

Clinical outcome
Patients were followed for a mean follow-up of 5.8 years (median = 5.8 years, IQR 4.4, 8.0) during which 98 patients had an AE. Adverse event as defined (CV death/MI/revascularization or CV hospitalization) occurred in 86 patients.

Nine patients died during follow-up: three died from a definite CV cause (two patients who died of MI and one patient due to heart failure). Eight patients experienced MI during the follow-up period (and two of them died later as mentioned above). Twenty-eight patients underwent a coronary revascularization procedure (18 percutaneous intervention and 10 coronary artery bypass surgery). Definite stroke was diagnosed in 10 patients. Sixty-nine patients overall were hospitalized for a cardiac cause during the follow-up period. Careful assessment of all cardiac hospitalizations identified exacerbation of chest pain (angina) and suspected acute coronary syndrome as the most frequent admission diagnosis (in >90% of cases).

Outcome events in relation to peripheral arterial tonometry results
Adverse event rates differed according to RH-PAT results, as patients with lower L_RHI had higher event rates during the follow-up period, and the most useful cut-off point was with an L_RHI of 0.4. The difference was due to CV death events which occurred only in the group with an L_RHI < 0.4, but especially

Table 1 Baseline characteristics of 270 patients undergoing reactive hyperaemia–peripheral arterial tonometry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>53.7 ± 12.4 years</td>
</tr>
<tr>
<td>Females</td>
<td>130 (48%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>123 (46%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (11.9%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>60 (22%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>178 (66%)</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>75 (28%)</td>
</tr>
<tr>
<td>Proven peripheral vascular disease</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean ± SD)</td>
<td>30.5 ± 6.6</td>
</tr>
<tr>
<td>10 years Framingham risk in % (range)</td>
<td>7.2 ± 6.65 (1–53)</td>
</tr>
<tr>
<td>History of prior myocardial infarction</td>
<td>37 (14%)</td>
</tr>
<tr>
<td>Known coronary artery disease (previous MI or revascularization)</td>
<td>43 (16%)</td>
</tr>
<tr>
<td>Discharge medications</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>117 (44%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>107 (40%)</td>
</tr>
<tr>
<td>Anti-platelet medications</td>
<td>126 (47%)</td>
</tr>
<tr>
<td>ACE-inhibitors or ARBs</td>
<td>123 (46%)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>169 (63%)</td>
</tr>
<tr>
<td>Nitrites</td>
<td>119 (44%)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL) (mean ± SD)</td>
<td>182 ± 41</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL) (mean ± SD)</td>
<td>51 ± 18</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL) (mean ± SD)</td>
<td>103 ± 34</td>
</tr>
<tr>
<td>Triglycerides (mg/dL) (mean ± SD)</td>
<td>147 ± 109</td>
</tr>
<tr>
<td>Systolic BP in mmHg (mean ± SD) (range)</td>
<td>126 ± 18 (90–190)</td>
</tr>
<tr>
<td>Diastolic BP in mmHg (mean ± SD) (range)</td>
<td>76 ± 11 (50–109)</td>
</tr>
<tr>
<td>Mean L_RHI</td>
<td>0.5 ± 0.4</td>
</tr>
</tbody>
</table>
due to a significantly higher rate (>50% increased rate) of CV hospitalizations (Table 2). Patients with L_RHI < 0.4 were not only more likely to be hospitalized but were more likely to experience repeated hospitalizations. Thus, the total number of hospitalizations during the follow-up period was significantly higher in patients with L_RHI < 0.4, with an incidence estimate of 0.19/year (135 hospitalizations during a total of 718.8 follow-up years in this group), when compared with 0.05/year (overall 44 hospitalizations during a total of 826.4 follow-up years) in the group with L_RHI ≥ 0.4.

The estimated 7-year AE rate was 48% in patients with L_RHI < 0.4 vs. 28% of patients with L_RHI ≥ 0.4 (P = 0.032; c-index = 0.57; corrected c-index = 0.55) and the Kaplan–Meier curves continued to separate during the follow-up period (Figure 1).

MI, revascularization, and stroke rates were not significantly higher in the patient group with L_RHI < 0.4. The comparison of the significance of this cut-point vs. others to differentiate patients by risk of AE is shown in Figure 2 as the relation between the (inverted) P-values and the L_RHI.

**Table 2** Estimated 7 years clinical cardiac adverse event rates in patients undergoing reactive hyperaemia–peripheral arterial tonometry in relation to natural logarithmic scaled reactive hyperaemia index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with L_RHI &lt; 0.4 (n = 130)</th>
<th>Patients with L_RHI ≥ 0.4 (n = 140)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>3.9%</td>
<td>0.0%</td>
<td>∞ (1.32, ∞)</td>
<td>0.032</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.4%</td>
<td>3.7%</td>
<td>1.06 (0.27, 4.27)</td>
<td>0.93</td>
</tr>
<tr>
<td>Revascularization</td>
<td>12.7%</td>
<td>11.4%</td>
<td>1.21 (0.55, 2.65)</td>
<td>0.64</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.3%</td>
<td>3.1%</td>
<td>1.6 (0.45, 5.68)</td>
<td>0.46</td>
</tr>
<tr>
<td>CV hospitalizations</td>
<td>30.5%</td>
<td>18.7%</td>
<td>2.06 (1.26, 3.38)</td>
<td>0.018*</td>
</tr>
<tr>
<td>AE</td>
<td>48%</td>
<td>28%</td>
<td>1.83 (1.18, 2.81)</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

*P-values adjusted for the multiple tests done to identify the optimal cut-point.

Most baseline characteristics were not different between the two groups. The mean FRS was also similar in both groups (Table 3).

Multivariate analysis showed that, for the observed data set, L_RHI < 0.4 was independently associated with increased AE rate (HR = 1.79, 95% CI 1.16–2.76, P = 0.008) during follow-up and identified advancing age as a predictor of AE (HR = 1.2, 95% CI 1.013–1.45, P = 0.035). L_RHI remained an independent predictor of AE even when included in a model with the FRS (HR = 1.68, 95% CI 1.02–2.78, P = 0.043) (Table 4).

**Discussion**

The main finding of our study was that low RH value derived from the EndoPAT signal was associated with a higher incidence of AEs during the follow-up period and especially was predictive of significant symptoms (mostly chest pain) during follow-up, requiring repeated hospitalizations for suspected acute coronary syndrome. The combined endpoint of CV death, MI, revascularization, and CV hospitalizations was not only more frequent during follow-up in

**Figure 1** Cardiovascular adverse events: a combination of cardiac death/myocardial infarction/coronary revascularization and cardiac hospitalizations in patients with and without low L_RHI (<0.4).

**Figure 2** Plot of the (inverted) P-values vs. the L_RHI cut-points comparing the usefulness of the cut-point of L_RHI 0.4 vs. other cut-points to risk stratify patients for adverse events.
Nitric oxide has been shown to be an important factor contributing to the augmentation of the PAT pulse amplitude after ischaemia, and administration of an endothelial nitric oxide inhibitor blunted the hyperaemic response as detected by PAT. Hence, the hyperaemic response detected by PAT reflects endothelial function.

Coronary endothelial dysfunction as evaluated by invasive methods predict CV events and stroke and correlate with abnormal PAT results and coronary endothelial dysfunction as detected by the invasive evaluation of coronary endothelial function. Brachial artery flow-mediated dilation was also shown recently to predict future adverse outcome events in patients with diagnosed obstructive coronary artery disease. The current study shows that PAT has a similar predictive power. Overall, PAT is becoming a useful method to evaluate vascular health in various disease states. For example, PAT detected improved endothelial function following treatment with enhanced external counter pulsation in patients with refractory angina pectoris. Abnormal endothelial function by PAT was also shown to be prevalent in adolescents with type 1 diabetes mellitus. Thus, the concept of using a non-invasive method to evaluate endothelial function in an office based manner is an appealing concept in primary (or secondary) prevention. The potential significance of the assessment of endothelial function is underscored by previous studies that demonstrated that lack of improvement of endothelial function by conventional therapy is associated with CV events. Therefore, the non-invasive evaluation of endothelial function may serve as a clinical tool, not only for prediction of events but also for the assessment of therapy. While the main limitation of peripheral endothelial testing was reproducibility of the results, PAT may have improved reproducibility, especially because of ongoing monitoring allowing for complete arterial occlusion and indexing the RH score to the contralateral arm.

Our finding that PAT results were predictive of outcome events beyond the traditional FRS is encouraging given the established predictive value of the FRS. However, in selected groups such as young adults and females, the FRS may have a lower predictive value, and its usefulness for risk stratification in the individual patient may still be limited. Thus, there is a dire need for better risk prediction tools, and individualized evaluation of endothelial dysfunction may allow a more personalized risk assessment. PAT may therefore be an important risk stratification tool in addition to the traditional FRS.

Study limitations

The study may be influenced by selection bias as the patients referred for tertiary centres may be a selected group, perhaps with more significant symptoms but with less overt obstructive coronary disease. The inclusion of patients with known coronary occlusion and indexing the RH score to the contralateral arm.

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artery disease may have increased the likelihood for future events but the L_RHI remained an independent predictor of events even when adjusted to the presence of known coronary artery disease. Additionally, we have not been able to demonstrate an independent role of PAT in the prediction of MI alone, and subsequent CV hospitalizations were the most common AEs. Nonetheless, in symptomatic patients with non-obstructive coronary artery disease, repeated cardiac hospitalizations may be a marker of other CV AEs, especially in women, and the events may be a result of coronary microvascular dysfunction or endothelial dysfunction.\textsuperscript{44,45} Moreover, CV hospitalizations for acute coronary syndromes are also a significant endpoint because they are associated with significant costs (average cost of $16,842 per hospitalization in the USA during 2006).\textsuperscript{46} This is especially important given the significant higher incidence of repeated hospitalizations observed among patients with a low L_RHI.

**Conclusions**

In conclusion, a low RH signal as detected by the EndoPAT, and consistent with endothelial dysfunction, was associated with higher AE rate during follow-up. L_RHI was an independent predictor of AE beyond the traditional FRS. Non-invasive assessment of peripheral vascular function in addition to the FRS may be useful for individualized identification of patients at risk for cardiac AEs.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** A.L. is a member of the advisory board of Itamar Medical. All other authors have no conflicts of interest to disclose.

**References**


CARDIOVASCULAR FLASHLIGHT

Contrast echocardiography guidance for alcohol septal ablation of hypertrophic obstructive cardiomyopathy

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A 63-year-old man was admitted due to worsening dyspnoea and faintness related to hypertrophic obstructive cardiomyopathy. Resting left ventricular outflow tract obstruction on echocardiography was 100 mmHg. Angiography showed normal coronary arteries, with one main septal perforator artery suitable for alcohol ablation (Panel A, black arrow). After installation of a 0.014 in. wire, a 1.5 mm over-the-wire angioplasty balloon was placed and inflated (Panel B, black arrow). Injection of the echographic contrast agent (Sonovue®, Bracco Imaging) through the catheter showed that the septal artery supplied a myocardial area distal to the subaortic bulge, extending to the tricuspid subvalvular apparatus (Panel C, white arrow). Thus, ablation of this septal artery was given up. Careful review of the baseline angiogram showed the presence of another small, hardly visible, septal perforator artery, 1 cm proximal to the previous one (Panel A, white arrow). It was catheterized by a wire and a balloon was installed (Panel D, white arrow). Contrast injection opacified the septal bulge (Panel E), confirming that it was the target vessel for ablation. Two millilitres of pure ethanol were infused over a period of 15 min. Immediate haemodynamic result was good, with disappearance of either resting or provoked left ventricular outflow tract gradient. Clinical outcome was uneventful.

Alcohol septal ablation has emerged as an effective method to treat symptomatic hypertrophic obstructive cardiomyopathy refractory to medical therapy. However, questions about its acute and long-term safety are still pending. Guidance of the procedure by contrast echocardiography can avoid acute complications which cannot be anticipated by angiography.

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