Effects of Brief Coronary Occlusion and Reperfusion on Porcine Coronary Artery Reactivity

John P. Headrick, PhD, Debra A. Angello, MD, and Robert M. Berne, MD

The loss of coronary vasodilator reserve after ischemia-reperfusion may be due to endothelial injury, and this vascular dysfunction may contribute to functional alterations observed after ischemia. To determine whether endothelial dysfunction occurs after relatively brief periods of moderate low-flow ischemia in vivo, open-chest swine were subjected to 15 minutes of critical, subtotal left anterior descending coronary artery occlusion (80%) followed by 60 minutes of reperfusion. Serial measurements of regional coronary flow were made with the radiolabeled microsphere technique. After 60 minutes of reperfusion, the left anterior descending coronary artery was excised together with a section of the normally perfused left circumflex coronary artery to examine in vitro the relaxations to the endothelium-dependent dilators ADP and bradykinin and to the endothelial-independent dilators sodium nitroprusside and adenosine. Contractions to serotonin in quiescent rings were also examined. Endocardial and transmural blood flows recovered to preocclusion levels within 60 minutes of reperfusion, as did the epicardial-to-endocardial ratio. Vascular responses in isolated, reperfused left anterior descending coronary artery rings were significantly different from responses in control left circumflex coronary artery rings. Endothelium-dependent relaxations to adenosine diphosphate and bradykinin were significantly depressed in the left anterior descending coronary artery rings compared with left circumflex coronary artery rings (p<0.05). Serotonin-induced contractions were significantly greater in occluded-reperfused left anterior descending than in left circumflex coronary arteries (p<0.05). Relaxations to adenosine and sodium nitroprusside were not significantly different between the two groups. These data indicate that very brief periods of subtotal coronary occlusion in vivo can induce significant endothelial dysfunction. Although this was not associated with depressed recovery of coronary flow on reperfusion, this abnormality may play a role in postischemic myocardial dysfunction. (Circulation 1990;82:2163–2169)

Brief periods of coronary occlusion can result in sustained contractile dysfunction (myocardial stunning).1,2 Similarly, coronary occlusion-reperfusion also reduces coronary vasodilator reserve and vascular reactivity in some preparations,3–5 and it is possible that this reduced vascular reactivity and coronary flow may partially contribute to myocardial stunning.6 The endothelium is important in mediating vascular responses to endogenous and exogenous vasoactive compounds,7 and it has been recently demonstrated that the endothelium of coronary vessels is functionally sensitive to occlusion-reperfusion.4,5,8 Although it is clear that relatively prolonged periods (20–60 minutes) of occlusion-reperfusion can alter the reactivity of coronary arteries, it has not been determined whether brief ischemic episodes of moderate severity result in significant endothelial dysfunction. Interestingly, in vitro studies indicate that very brief periods of ischemia can produce significant degrees of functional vascular injury.9,10 Although endothelial dysfunction may occur after various periods of occlusion-reperfusion, it is not clear if this has any significant effect on coronary blood flow, and possibly contractile function, on reperfusion. The purpose of the present study was to determine whether a brief (15 minutes) period of moderate low-flow ischemia (80% occlusion) followed by 60 minutes of reperfusion would result in significant endothelial dysfunction, evident as a diminished vasodilator response to endothelium-dependent vasodilators.
Methods

Experimental Preparation

Adult domestic swine (35–50 kg) were premedicated with xylazine 2 mg/kg i.m. and ketamine hydrochloride 10 mg/kg i.m., and were then anesthetized with an intravenous infusion of ketamine 10 mg/kg/hr and morphine sulfate 1 mg/kg/hr. The pigs were intubated and ventilated with a volume-controlled ventilator, and arterial Po2 was maintained at 100 mm Hg. Lidocaine 2 mg/kg i.v. was administered to control ventricular arrhythmias. Experiments were terminated when ventricular fibrillation occurred, and the pig was not immediately defibrillated. A midline sternotomy was performed, and the heart was suspended in a pericardial cradle. Fluid-filled catheters were placed in the right femoral artery and vein, and the left atrium. A segment of the proximal third of the left anterior descending coronary artery (LAD) was dissected free and a hydraulic occluder was located around the vessel, distal to an ultrasonic flow probe. The electrocardiogram, arterial pressure, and LAD coronary flow signals were amplified and recorded continuously on a strip-chart recorder. Gamma-emitter–labeled microspheres suspended in saline with Tween-80 were used to measure regional coronary blood flow as described by Heymann et al.11 Approximately 2×10⁶ microspheres (10±1 μm, 15 μCi, 0.6 mBq) were suspended in 2 ml saline, agitated, and injected into the left atrium in conjunction with a timed femoral artery withdrawal.

To determine whether myocardial infarction occurred, triphenyl tetrazolium chloride (TTC) tissue staining was performed at the end of each experiment. All samples from ischemic and normal regions showed no evidence of infarction.

Experimental Protocol

A total of nine pigs were examined. A 30-minute baseline period was allowed after instrumentation during which myocardial blood flow was determined by using the microsphere technique. After this baseline period, a 15-minute subtotal LAD occlusion (20–25% control flow) was performed, guided by the ultrasonic flow probe readings. To document the flow reduction, microspheres were injected into the left atrium after 10 minutes of occlusion. At the end of the 15-minute subtotal occlusion period, LAD flow was returned to preoclusion flow levels by gradually releasing the occluder, thereby attenuating the reactive hyperemia normally associated with reperfusion. Hemodynamic data were obtained during the baseline period, occlusion period, and at 60 minutes after reperfusion. After 60 minutes of reperfusion, a final microsphere injection was made. Immediately after the 60 minutes of reperfusion, the pigs were exsanguinated and the hearts were removed. A 2–3-cm segment of the LAD was excised from the region between 1.5 and 4 cm distal to the instrumentation, together with a corresponding segment of the normally perfused left circumflex coronary artery (Cx).

The resultant average distance of ring segments from the site of occlusion and instrumentation was between 2 and 3 cm, allowing sufficient separation to exclude possible instrumentation-related damage.4,5 The segments were immediately placed in ice-cold modified Krebs bicarbonate buffer of the following composition (mM): NaCl 118, KCl 4.7, MgSO4 1.2, KH2PO4 1.2, CaCl2 2.5, NaHCO3 25, glucose 11.0, and EDTA 0.03. Immediately after arterial dissection, representative tissue samples (5–10 g) were taken from the ischemic region (distal to the occluder and away from the diagonal branches of the LAD) and from the corresponding nonischemic region in the posterior left ventricular wall. The tissue samples were stained with TTC and then frozen for subsequent well counting of microsphere activity.

Analysis

Tissue and arterial blood reference samples were counted for microsphere activity in a NaI(Tl) well counter within 2 weeks after the experiment. Tissue samples were divided into thirds for measurement of epicardial, midwall, endocardial, and transmural blood flows. Corrections of high-energy downscatter into lower energy windows were performed by a computer interfaced with the well counter. Myocardial blood flows were determined at baseline, during occlusion, and at the end of the experiment.

Organ Chamber Protocol

Artery segments were cleansed of all loose connective tissue and flushed free of blood. Special care was taken not to touch the luminal surface. Four rings (4 mm wide) were cut from each vessel segment and mounted on stainless-steel hooks in 10-ml organ baths containing the previously mentioned buffer maintained at 37° C and gassed with 95% O2-5% CO2 (bath Po2, 542±19 mm Hg; Pco2, 29.5±3 mm Hg, pH 7.42±0.04). The rings were progressively stretched until the contractile response to 40 mM KCl was maximal (optimal resting tension). When this tension was attained, the rings were equilibrated for 20 minutes and a maximal contraction to 60 mM KCl was obtained. The rings were then washed several times and allowed to equilibrate for an additional 40 minutes before experimentation. During this period, the rings were incubated with 5×10⁻⁶ M indomethacin to inhibit synthesis of endogenous prostanoids. A total of four LAD and four Cx rings were examined from each pig.

After the 30-minute equilibration period, the rings were constricted with a submaximal dose (2 μM) of prostaglandin F₂α (PGF₂α) and dose-response curves were obtained according to the following two procedures: procedure A—relaxation to bradykinin (10⁻¹⁰ to 10⁻⁷ M), relaxation to adenosine (10⁻⁷ M to 10⁻³ M), and constriction to serotonin (3×10⁻⁹ to 3×10⁻⁶ M); and procedure B—relaxation to sodium nitroprusside (10⁻⁹ to 10⁻⁶ M), relaxation to ADP (10⁻⁸ to 3×10⁻⁵ M), and constriction to serotonin (3×10⁻⁹ to 3×10⁻⁶ M).
Two rings from each coronary artery (LAD and Cx) were subjected to procedure A, and two rings from each artery were subjected to procedure B. The dose-response curves for ADP were obtained in the presence of 5 μM 8-phenyltheophylline (10 minutes before ADP treatment) to inhibit direct smooth muscle relaxation by adenosine receptors. The constrictor responses to serotonin were examined in quiescent rings, whereas all relaxations were determined in rings constricted with 2 μM PGF₂α.

**Drugs**

The following drugs were used: adenosine, ADP, bradykinin, 5-hydroxytryptamine creatinine sulfate (serotonin), indomethacin, sodium nitroprusside, and 8-phenyltheophylline. All drugs were purchased from Sigma Chemical Co., St. Louis.

**Statistics**

Values are given as mean±SEM. Unless otherwise stated, n refers to the number of pigs used. Relaxations are expressed as percentages of the contraction produced by 2 μM PGF₂α. Contractile responses are expressed as percentages of the maximal contraction to 60 mM KCl. The negative log of the concentration of agonist producing 50% relaxation of PGF₂α-contracted vessels (IC₅₀) was determined from individual dose-response curves, and the values quoted represent the means of these individual values. The concentration of serotonin producing 50% of the maximal constriction to 60 mM KCl was calculated in a similar manner. Statistical comparisons between IC₅₀ values and maximal responses in different rings were made by using a one-way analysis of variance with significance being accepted for probability values of less than 0.05. The in vivo coronary flows and dose-response curves were analyzed by a two-way analysis of variance with Newman-Keuls. Significance was accepted for probability values of less than 0.05.

**Results**

**Coronary Hemodynamics During Occlusion-Reperfusion**

LAD occlusion was initiated to reduce LAD flow to approximately 20% of control flow. Endocardial flow in the ischemic LAD region decreased from a value of 0.68±0.1 ml/min/g during control perfusion to a value of 0.18±0.05 ml/min/g after 15 minutes of ischemia (Figure 1). Endocardial flow in the ischemic region increased to preocclusion values within 1 hour of reperfusion (Figure 1). The ratio of endocardial to epicardial flow decreased during ischemia in the ischemic region, and recovered to preischemic levels after 60 minutes of reperfusion (Figure 1). Transmural blood flows followed similar patterns (Figure 1). Endocardial and transmural flows in the nonischemic region before occlusion were similar to flows in the ischemic region before occlusion. Blood flow in the nonischemic region (endocardial, transmural, and endocardial-to-epicardial ratio) was unaffected by occlusion and reperfusion (Figure 1). Mean aortic pressure and heart rate both remained unchanged during the preocclusion, occlusion, and reperfusion periods (Table 1).

**Effects of Vasodilators and Serotonin in Isolated Vascular Rings**

There were no significant differences in the contractile characteristics of rings from Cx and LAD.

**TABLE 1. Coronary Hemodynamics During Occlusion-Reperfusion**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preocclusion</th>
<th>Occlusion</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>85±6</td>
<td>77±5</td>
<td>85±5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81±6</td>
<td>84±6</td>
<td>87±7</td>
</tr>
</tbody>
</table>

Aortic pressure and heart rate in pig hearts before coronary occlusion, after 15 minutes of occlusion, and after 1 hour of reperfusion. Values are given as mean±SEM (n=9). No significant differences were detected among the three periods (p>0.05).
TABLE 2. Contractile Characteristics of Porcine Circumflex and Left Anterior Descending Coronary Arteries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cx</th>
<th>LAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal tension (g)</td>
<td>7.8±0.4</td>
<td>8.0±0.4</td>
</tr>
<tr>
<td>60 nM KCl contraction (g)</td>
<td>9.1±0.7</td>
<td>9.0±0.6</td>
</tr>
<tr>
<td>2 μM prostaglandin F2α-induced response (g)</td>
<td>5.6±0.3</td>
<td>5.8±0.3</td>
</tr>
<tr>
<td>IC50 SNP (−log M)</td>
<td>7.3±0.1</td>
<td>7.4±0.1</td>
</tr>
<tr>
<td>Maximum SNP dilation (%)</td>
<td>120±8</td>
<td>122±7</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; Cx, circumflex coronary artery; SNP, sodium nitroprusside.

Vessels. Optimal resting tensions and KCl-mediated and PGF2α-mediated contractions for rings originating from the LAD or Cx were not significantly different (Table 2). The relaxation responses to adenosine were identical in occluded reperfused LAD rings and control Cx rings (Figure 2a and Table 3), as were the responses to sodium nitroprusside (Figure 2b and Table 3). The responses of LAD rings to ADP and bradykinin were significantly depressed compared with responses in Cx rings (p<0.05) (Figures 3 and 4 and Table 3). Constrictions to serotonin in quiescent rings were significantly greater in LAD rings than in Cx rings (p<0.05) (Figure 5 and Table 3). Table 3 shows that the IC50 for serotonin was significantly lower in LAD, whereas the IC50 for serotonin was significantly lower in LAD, indicating a shift of the dose-response curve to the right.

Discussion

The major finding of this study is that a relatively brief period of moderate low-flow ischemia produces a significant degree of endothelial dysfunction. Specifically, whereas endocardial and transmural blood flows returned to normal during 60 minutes of reperfusion of hearts subjected to 15 minutes of subtotal coronary occlusion (Figure 1), the responses of ischemic vessels to endothelium-dependent dilators (ADP and bradykinin), determined in vitro, were significantly reduced (p<0.05) (Figures 3 and 4). Similarly, the constrictor response to serotonin was significantly enhanced in the occluded reperfused vessels (Figure 5). Responses to endothelium-independent dilators (sodium nitroprusside and adenosine) were unaffected by occlusion/reperfusion (Figure 2, Table 3). This is the first study to demonstrate a significant functional abnormality in coronary endothelium after such a brief period of subtotal coronary occlusion in vivo. Our results therefore demonstrate a high sensitivity of the porcine coronary endothelium to events associated with partial coronary occlusion.

Loss of vascular reactivity to endothelium-dependent drugs after reperfusion may be due to several mechanisms. These include the depletion of endogenous stores of endothelium-derived relaxing factor (EDRF) or enhanced inactivation of EDRF, or both, reduced vascular smooth muscle responsiveness to EDRF, impaired PG12 release, or enhanced release of endothelial vasoconstrictors. Whichever mechanism is responsible, it is proposed that decreased endothelium-dependent dilation contributes to the no-reflow phenomenon observed after coronary occlusion and reperfusion. To examine the effects of a brief coronary occlusion on vascular reactivity, we studied vessels isolated from the in vivo preparation so that complete dose-response relations could be obtained in vitro. This allowed the selective blockade of prostanoid formation with indomethacin incubation and the selective blockade of indirect purinergic relaxation with 8-phenylthiothophylline during ADP infusion. The resting tensions, dilations to nitroprusside, and constrictions to potassium chloride are nearly identical in Cx and LAD coronary arteries (Table 2).

The results with bradykinin and ADP indicate that the endothelium-dependent mechanism of relaxation is significantly reduced in subtotally occluded/reper-
TABLE 3. Maximum Responses and IC\textsubscript{50} for Vasodilative Compounds in Left Anterior Descending and Circumflex Coronary Artery Rings

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cx</th>
<th>LAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>% Max Dilation</td>
<td>76±7</td>
</tr>
<tr>
<td></td>
<td>IC\textsubscript{50}</td>
<td>3.7±0.1</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>% Max Dilation</td>
<td>119±8</td>
</tr>
<tr>
<td></td>
<td>IC\textsubscript{50}</td>
<td>7.2±0.1</td>
</tr>
<tr>
<td>ADP</td>
<td>% Max Dilation</td>
<td>88±9</td>
</tr>
<tr>
<td></td>
<td>IC\textsubscript{50}</td>
<td>6.1±1</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>% Max Dilation</td>
<td>118±7</td>
</tr>
<tr>
<td></td>
<td>IC\textsubscript{50}</td>
<td>9.2±0.1</td>
</tr>
<tr>
<td>Serotonin</td>
<td>% Max Contraction</td>
<td>61±1</td>
</tr>
<tr>
<td></td>
<td>IC\textsubscript{50}</td>
<td>6.8±0.1</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; Cx, circumflex coronary artery.

*Indicates a significant difference between Cx and LAD values with p<0.05.

Values are given as mean±SEM (n=9, each data point representing the mean of 18 rings). Maximum dilations are expressed as a percentage of the contraction to 2 \textmu M prostaglandin (PG) F\textsubscript{2o}. Maximum contraction to serotonin is also expressed as a percentage of the contraction to 2 \textmu M PGF\textsubscript{2o}. IC\textsubscript{50} values are depicted as −log molar concentrations.

FIGURE 3. Dose-response curves for ADP relaxations in prostaglandin F\textsubscript{2o}-constricted circumflex (●) and left anterior descending coronary artery (○) rings. Curves were obtained in the presence of 8-phenyltheophylline (5 \textmu M). Relaxations are expressed as percentages of the contraction to 2 \textmu M prostaglandin F\textsubscript{2o}. Values are given as mean±SEM (n=9, with each data point being the mean of 18 rings). *Indicates significant differences between left anterior descending coronary artery and left circumflex coronary artery responses (p<0.05).

FIGURE 4. Dose-response curves for bradykinin relaxations in prostaglandin F\textsubscript{2o}-constricted circumflex (●) and left anterior descending coronary artery (○) rings. Values are given as mean±SEM (n=9, with each data point being the mean of 18 rings). *Indicates significant differences between left anterior descending coronary artery and left circumflex coronary artery responses (p<0.05).

to elicit comparable dilations in occluded and nonoccluded vessels indicates the reduction in responsiveness to bradykinin and ADP is not due to nonspecific smooth muscle damage. Both ADP and bradykinin stimulate release of EDRF\textsuperscript{7}; thus, the endothelial dysfunction may be due to reduced EDRF release from the endothelium, enhanced EDRF inactivation, or reduced smooth muscle responsiveness to EDRF. The third possibility is unlikely because sodium nitroprusside produced almost identical dilations in both ischemic and nonischemic vessels (Figure 2, Table 3), and sodium nitroprusside induces relaxations by stimulation of guanylate cy-
clase, as does EDRF.7 Specific changes in the functional coupling of EDRF receptors to smooth muscle guanylate cyclase cannot be excluded. Superoxide radicals produced during reperfusion13 may enhance the degradation of EDRF in reperfused vessels.15 Furthermore, endothelial cell damage sustained during reperfusion, possibly mediated by free radical formation and cell aggregation, may reduce receptor-mediated release of EDRF. Both these hypotheses can also explain the enhanced constrictor responses to serotonin observed in quiescent ischemic rings (Figure 5). Serotonin activates release of EDRF together with inducing constriction in quiescent rings. When the release of EDRF is reduced, the constrictor response to serotonin is enhanced.

Another possible mechanism worth mentioning is that of hypoxic damage or modulation of endothelial function during the occlusion period.16–18 Although it is possible that hypoxic damage does play a role, as opposed to ischemia/reperfusion, endothelium appears to be relatively resistant to anoxia,18 and the effects of hypoxia on endothelial responses appear to be totally reversible on reoxygenation.16,17 Thus, it is unclear whether hypoxia plays a significant role in the prolonged endothelial dysfunction observed in the present study. Furthermore, the damaging effects of hypoxia on cells appears to be energy dependent.18 Because endothelium and vascular smooth muscle exhibit very low basal energy and oxygen requirements, and flow was reduced to only approximately 20% of control levels, it is unlikely that hypoxic damage to endothelium or smooth muscle is significant in these vessels.

It is interesting that a recent study has observed functional coronary microvascular injury, in the absence of ultrastructural changes, in canine coronary vessels subjected to 15 minutes of total coronary occlusion.19 It was concluded from this study that even brief ischemia and reperfusion causes injury to coronary endothelium. The present study is consistent with this conclusion. Moreover, the present results demonstrate that even a brief period of subtotal occlusion can induce significant dysfunction. The mechanisms mediating injury in the present study and in the recent study of Dauber et al19 may be similar. Although underlying mechanisms were not immediately evident in this previous study, it was clear that endothelial dysfunction was present in the absence of morphological changes to the endothelium.

Whereas endothelial dysfunction was present in the subtotally occluded/reperfused vessels (Figure 3), there was no evidence of reduced recovery of coronary flow in vivo, the no-reflow phenomenon.20 Previous studies have shown that relatively prolonged periods of total coronary occlusion followed by reperfusion are detrimental to endothelial function and coronary vascular reactivity.3–5,8,20 It has been proposed that these changes are at least partially responsible for the loss of vasodilator reserve sometimes observed after ischemic episodes. Because there was no depression of coronary perfusion during reperfusion in the present study, it is concluded that the degree of endothelial dysfunction produced in this study (a 15–20% reduction of responses) is not sufficient to significantly reduce the ability of the myocardium to maintain adequate perfusion after occlusion/reperfusion, or that the endothelial dysfunction observed in the LAD segments is not representative of dysfunction in more distal small coronary vessels. These findings are somewhat contrary to several studies in canine hearts indicating that 10–15 minutes of total coronary occlusion results in impaired coronary perfusion.21–23 Similarly, a recent study has also demonstrated a significant endothelial dysfunction after as little as 15 minutes of total occlusion in the in situ canine heart.19 The results of the present study, however, may be indicative of major differences in collateral flow in canine and porcine hearts, and may also reflect differences in experimental conditions, that is, total versus subtotal occlusion. Indeed, in a recent study of coronary artery occlusion in porcine hearts,24 it was shown that more than 40 minutes of occlusion was required before significant reductions in resting coronary flow were observed on reperfusion.

If the dysfunction observed in isolated rings from the occluded vessels is indicative of damage to more distal coronary vessels, the present results suggest that the relative reactivity of coronary vessels to endothelium-dependent dilators is not critical to the maintenance of coronary tone after occlusion, that the myocardium possesses a sufficient dilator reserve to compensate for these changes, or both. In fact, the response of vessels to endothelium-independent dilators (adenosine and nitroprusside) are unaltered by occlusion/reperfusion (Figure 2), consistent with other recent studies.24 Thus, it may be that coronary perfusion after brief occlusion is modulated by endothelium-independent dilators such as adenosine,25,26 or that endothelium-independent and dependent mechanisms act in concert, that is, a reduction in one being compensated for by an increase in the other. This suggestion is supported by the observations that reduced coronary flow after prolonged ischemia is associated with reductions in both endothelium-dependent and independent dilations, whereas brief periods of ischemia do not alter coronary flow and endothelium-independent responses but do alter endothelium-dependent responses.23,24,27 A final possibility is that the endothelial damage observed in the LAD segments is not reflected globally throughout smaller distal coronary vessels. If this is the case, then total myocardial flow would not be expected to alter significantly. Furthermore, if this is the case, the present results and the results from the studies previously discussed would imply that endothelial damage progresses in a graded manner throughout the vasculature as the period of ischemia is prolonged, or the degree of ischemia enhanced. In either case, the present results show that coronary endothelium is highly susceptible to damage as a result of occlusion-reperfusion.
In summary, the present study indicates that relatively brief periods of partial coronary occlusion followed by reperfusion are capable of significantly reducing endothelium-dependent responses in porcine coronary arteries. Although we have not determined whether this endothelial dysfunction occurs throughout coronary vessels more distal to the site of occlusion, these results nevertheless indicate that the coronary endothelium is extremely sensitive to brief ischemic episodes. This form of endothelial dysfunction may play an important role in the pathogenesis of postischemic myocardial dysfunction.

References


Key Words • left anterior descending coronary artery • circumflex • endothelium • EDRF • ischemia • reperfusion
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