

Randomized Comparison of Vasodilator Effects of Iloprost versus Diltiazem on Flow and Pathologic Changes in Radial Arteries: Mid-term Angiographic Control Study of the Comparison of Vasodilators on Radial Artery Vasospasm



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ABSTRACT

Background: The increasing prevalence of routine radial artery (RA) use in coronary artery bypass grafting (CABG) has rendered the pharmacologic prevention of spasm of this artery a critical consideration in the early postoperative period and in the long-term outcome. In this study, we compared the effects of iloprost and diltiazem on vasospasm.

Methods: Seventy patients who underwent CABG with the RA were randomized into 2 groups, and the vasodilator effects of iloprost and diltiazem were studied prospectively. RA flow was measured with Doppler ultrasonography. Following harvesting, a 5-mm piece was removed from the RA distally for pathologic examination. In group B, diltiazem was infused before removing the RA, whereas in group A, iloprost infusion was initiated 5 days before surgery. At the end of a 2-year follow-up, each patient underwent coronary angiography.

Results: Doppler flow measurements made during harvesting revealed a statistically significant reduction in flow, and a pathologic examination of the RAs revealed significant luminal narrowing in group B. A 2-year angiographic follow-up revealed all of the RA grafts in group A to be patent.

Conclusions: Our evaluation of the results revealed the superior efficacy of iloprost over diltiazem in preventing RA spasm in the early period, and the 2-year angiographic findings showed that the use of iloprost produced superior mid-term patency.

INTRODUCTION

In coronary artery bypass grafting (CABG) surgery, the rates of long-term patency for grafts with arteries (particularly the left internal mammary artery, but also the radial artery [RA] and other arteries) have been $\geq 90\%$ [Barner 1998; Bhan 1999; Chanda 2000; Amano 2002; Manabe 2006].

In 1973, Carpentier et al [1973] reported that the RA could

be used as a graft source in CABG; however, the high rate of graft insufficiency caused by early vasospasm has long prevented the RA from being used for grafting in CABG [Velez 2001]. In 1990, Acar et al [1992] suggested that the RA could still be an alternative source of grafts and studied this issue. They demonstrated that the short-term patency rate of this graft is 93.5% when a calcium blocker and aspirin are used postoperatively [Barner 2002]. With this modification, the use of the RA in grafting has become more prevalent; however, the pharmacologic prophylaxis to use for postoperative RA vasospasm is still being debated. Our purpose in this prospective randomized study was to evaluate the effects of diltiazem, a calcium channel blocker, and iloprost, a synthetic prostaglandin I₂ analogue, on RA vasospasm via examining graft blood flow and investigating pathologic alterations.

MATERIALS AND METHODS

The RA has been used as a source of grafts in 70 patients who have undergone surgery for coronary artery disease between January 2002 and February 2004. The research staff was blinded in this study.

Our patients were randomized with the sealed-envelope technique into one of 2 groups, and the data were collated prospectively. The patients in group A began receiving iloprost as a prophylactic vasodilator agent 5 days before surgery, and the drug was infused during periods of 6 hours/day, beginning with a systemic dose of 0.5 ng/kg per minute and increasing at regular intervals up to 2.5 ng/kg per minute at each session. The procedure was repeated for 5 days according to the vasospastic disease protocol for iloprost [Scorza 2001]. The patients were queried about iloprost side effects (nausea, vomiting, abdominal pain, and head-neck pain) during electrocardiogram (ECG) monitoring during iloprost infusion. No important side effects were seen during this period. None of the patients in group A received any other vasodilator medication perioperatively or postoperatively unless an ischemic sign appeared. When ischemia did develop, nitroglycerin perfusion was added to the medications.

In group B, diltiazem was administered as the prophylactic vasodilator agent. Intravenous diltiazem was initiated at a dose of 1 mg/kg per minute following the induction of general anesthesia and was maintained until cardiopulmonary

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Table 1. Demographic Data and Patient Characteristics*

Parameters	Group A (Iloprost)	Group B (Diltiazem)	P
Age, y	52.33 ± 11.0	53.66 ± 10.30	NS
M/F sex, n	24/11	25/10	NS
Smoker, n	10	10	NS
No. of lesions	2.86 ± 0.64	2.73 ± 0.59	NS
No. of bypasses	3.53 ± 0.51	3.33 ± 0.72	NS
CPB time, min	78.66 ± 10.56	77.93 ± 10.85	NS
Extubation time, h	5.65 ± 2.47	6.01 ± 1.86	NS
ICU stay, h	18.4 ± 2.41	18.8 ± 2.76	NS
Hospital discharge time, d	5.2 ± 1.11	6.1 ± 1.06	NS
Blood pressure during flow, mm Hg			
Flow I	78.4 ± 10.6	81.1 ± 8.8	NS
Flow II	69.8 ± 9.7	67.9 ± 7.6	NS
Flow III	74.4 ± 8.8	76.6 ± 6.9	NS

*Data are expressed as the mean ± SD. NS indicates not statistically significant; CPB, cardiopulmonary bypass; ICU, intensive care unit.

bypass (CPB) was initiated. Diltiazem infusion was resumed following CPB and was maintained until the second postoperative day. Intravenous diltiazem infusion was then replaced with oral diltiazem at 180 mg/day, which was continued for 1 year.

Prior to RA harvesting, an Allen test was performed with a pulse oximeter to test whether the flow of the ulnar artery of the nondominant upper extremity was sufficient; values ≥10 seconds were regarded as positive. RA flow was measured intraoperatively by Doppler ultrasonography (Quantix/OR; Cardiosonix, Ra'anana, Israel). RA flow was measured before cutaneous incision, during harvesting prior to the distal dissection of the RA, and from the proximal side of the graft following CPB before closure of the sternum. After harvesting, 5-mm lengths were removed from the distal RA. All RAs were removed with their accompanying veins with the aid of microhemoclips for controlling side-branch hemorrhage. Electrocautery was not used during these procedures. The patients were heparinized for CABG with 300 U/kg heparin, and the RA was removed. In both groups, RAs were then suspended in a solution containing 2.5 mg nitroglycerin, 500 U heparin, 300 mL Ringer solution, and 30 mL blood.

Following preparation of the proper grafts, CABG was performed with the on-pump technique under normothermic conditions (35°C–36°C). The left internal mammary artery has primarily been anastomosed to the left anterior descending coronary artery. All RA grafts were anastomosed to either the circumflex artery or its branches. Beginning on the first postoperative day, antiplatelet therapy with either 100 mg/day aspirin or 75 mg/day clopidogrel was administered to the patients in both groups.

For the analysis of infarction or ischemia that could develop, 12-lead ECG and cardiac enzyme (troponin I, creatine kinase isoenzyme MB, serum glutamic-oxaloacetic transaminase [aspartate aminotransferase]) analyses were made 4 times within the first 24 hours after surgery, and these variables were again evaluated twice a day on the second, third, and fourth postoperative days, and once per day until discharge. All data were entered onto standardized forms. These data included the patient's age, sex, cardiac profile, preoperative risk factors, graft flow rates, surgical data, postoperative complications, and mortality. The patients were followed up in the outpatient clinic of the Department of Cardiovascular Surgery, and postdischarge data were added to these forms.

We excluded from the study patients with renal dysfunction, native circumflex artery stenosis of <70%, diffuse atherosclerosis of the native coronary artery, atherosclerosis of the RA, or a requirement for endarterectomy; patients in whom the RA was used as a composite graft (Y Tector or T Tector graft); patients with diabetes, a positive Allen test result, a possibility of a requirement for inotropic support, or a new attack of myocardial infarction within the previous 6 weeks; patients who underwent their operations under emergency conditions; patients >70 years of age; patients in whom a porcelain aorta was found; and patients in whom off-pump CABG and/or sequential anastomosis were performed.

This study has been performed with the approval of both the local ethics committee and the patients themselves; all patients signed related informed-consent forms prior to surgery.

Pathologic Analysis

The 5-mm length removed from the end of the RA was fixed in 10% formalin. The thickness of the vascular wall and the luminal diameter were measured and noted. The tissue was prepared, and the specimen was embedded into a paraffin block and dissected into pieces 4 μm thick, which were placed on 3 slides. Each slide was stained with hematoxylin-eosin and Masson trichrome, and smooth muscle and actin

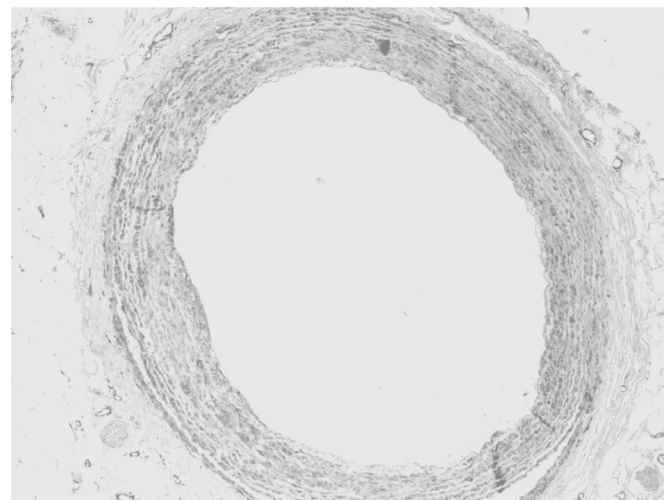


Figure 1. A pathologic specimen of group A.

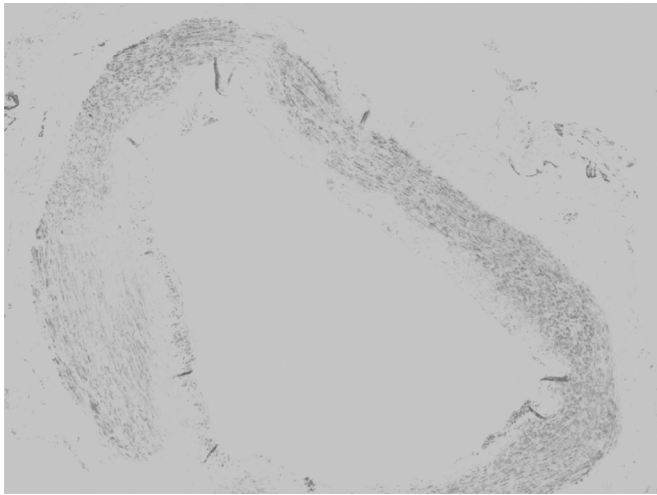


Figure 2. A pathologic specimen of group B.

structures were investigated both histochemically and immunohistochemically. The thickness of the media layer was investigated histochemically, whereas the muscular mass and the actin density were evaluated immunohistochemically. The luminal diameter and wall thickness of the RA were measured with micrometers during examination with a light microscope, and the results were recorded.

Statistical Analyses

Statistical analyses were performed with SPSS software (version 10.0; SPSS, Chicago, IL, USA). Descriptive data for continuous variables were summarized as the mean ± SD. The data in both groups were analyzed with the Student *t* test and paired Student *t* tests. A *P* level <.05 was regarded as statistically significant.

RESULTS

Table 1 summarizes the demographic data and patient characteristics for the 2 groups. No operative mortality occurred in either group, and no revision was made for any purpose (eg, hemorrhage). The alterations in flow rates and pathologic findings are displayed in Table 2. Prior to cutaneous incision,

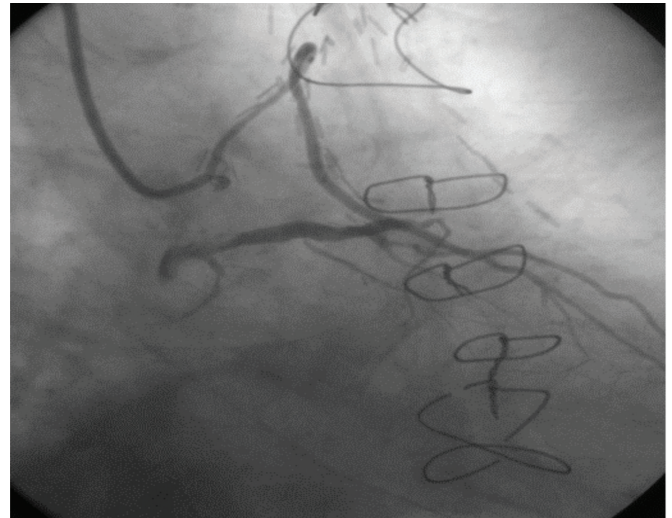


Figure 3. A patent radial artery graft from group A.

there were no significant differences between groups with respect to RA flow rates; however, measurements made prior to cutaneous incision and secondary measurements made in the same place after RA harvesting revealed that the flow rate was reduced significantly in group B compared with flow rate values prior to cutaneous incision. On the other hand, the reduction in flow rate in the second measurement was not statistically significant. In group A, the reduction in flow rate was 33% when the first and second measurements were compared, whereas the reduction in flow rate was 62% in group B. The third flow rate measurement performed at the proximal side of graft prior to closure of the sternum revealed that the reduction in flow rate from the first to the third measurement was 12% in group A and 40% in group B (*P* = .0001).

Figure 1 displays the pathologic examination of an RA specimen from group A, and Figure 2 displays the pathologic examination of an RA specimen from group B. Figure 2 shows the RA lumen in the group B specimen to be irregular, with a diffusely damaged elastic lamina. In addition, the increased staining for actin in the samples from group B indicates muscular spasm. The 2 groups were not significantly different regarding the mean external diameters of the pathologic RA

Table 2. Results for Flow Changes and Pathologic Findings*

Parameters	Group A (Iloprost)	Group B (Diltiazem)	<i>P</i>
Flow I (before skin incision), mL/min	20.73 ± 5.73	21.4 ± 6.86	NS
Flow II (after harvesting), mL/min	14.0 ± 5.37	8.13 ± 5.02	.005
Flow III (before sternal closure), mL/min	18.53 ± 5.09	12.93 ± 5.29	.006
RA diameter, mm	2.246 ± 0.344	2.080 ± 0.295	NS
RA lumen diameter, mm	1.70 ± 0.368	1.066 ± 0.463	.008
RA media size, mm	0.515 ± 0.196	0.465 ± 0.201	NS

*Data are presented as the mean ± SD. NS indicates not statistically significant; RA, radial artery.

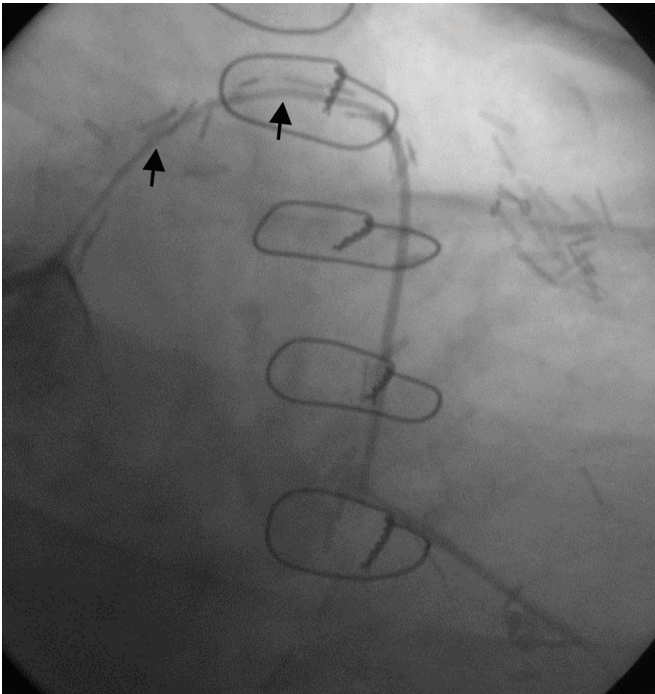


Figure 4. A string sign view of the radial artery from group B.

specimens; however, the 2 groups had significantly different luminal diameters. In group A, the mean luminal diameter was 1.70 ± 0.368 mm, whereas it was 1.066 ± 0.463 mm in group B ($P = .008$). The measurements of the medial layer revealed no significant difference between the groups with respect to mass and thickness. The postoperative ECGs indicated 3 patients in group A and 11 patients in group B with ST-segment elevations (≥ 2 mm). When we controlled the pathologic specimens of these patients, we found that the luminal diameters in these patients were below the group mean. In particular, the mean luminal diameter of the 11 patients in group B (0.865 ± 0.332 mm) was profoundly below the group mean (1.066 ± 0.463 mm; $P = .0004$). The ST elevations responded to nitroglycerin and heparin therapies in all patients. No angina or changes in cardiac enzyme changes were observed in these patients, and no hypoperfusion occurred in these patients. Coronary angiographic evaluations performed in the early period revealed that the grafts were open.

After the 2-year follow-ups, all patients underwent control coronary angiographic examinations. In group A, all RA grafts were patent, and no spastic segments were found (Figure 3). In contrast, total occlusion was found in the RA grafts of 3 patients (8.56%) in group B, and irregular and stenotic RA segments were found in 4 cases (11.43%) (Figure 4). When the pathologic specimens and clinical states of these cases were controlled, all of these cases in group B were found to be among the cases with ST changes in the early postoperative period. In group B, the mean luminal diameter in these 7 cases was 0.644 ± 0.441 mm, and the stenosis was statistically significant compared with the mean diameter of the group, which was 1.066 ± 0.463 mm ($P = .002$).

DISCUSSION

The outcomes of coronary artery surgery depend on the moderate- and long-term patency of the grafts. In this regard, vasospasm of the RA (which is an ideal graft morphologically) in the early period, development of the string sign, and the corresponding hypoperfusion syndrome arise as significant problems [Locker 2002]. In CABG operations performed with the RA, various vasoactive substances, such as perioperatively secreted catecholamines, endothelin that arises from the endothelium and causes contraction, norepinephrine, platelet-derived vasoconstrictors, and angiotensin II (which is the most important product of the renin-angiotensin system) play significant roles in early RA vasospasm [Velez 2001; Locker 2002; Manabe 2005].

Endogenous levels of catecholamines increase by 3- to 4-fold in response to CPB and remain elevated for 24 hours [Locker 2002]. Compared with the other grafts used in CABG, the RA musculature is more sensitive to the increase in catecholamine levels [Locker 2002]. Vasospasm also may be secondary to increased denervation during harvesting and to increased α -adrenoreceptors in response to denervation [Velez 2001; Locker 2002]. In our study, the difference between the first and second measurements of flow rate in both groups and its statistical significance appear to support these 2 theories. Because of the RA vasospasm that develops during harvesting, the technique used during this period has been modified from mechanical dilatation to hydrostatic dilatation in order to preserve endothelial functions [da Costa 1996; Kaufer 1997; Manabe 2005]. According to histologic studies, the elastic lamina of the RA has a single layer with multiple fenestrations [Kaufer 1997; Manabe 2005]. This morphology indicates that RA is sensitive to increased mechanical stress. Therefore, the spasm developing secondary to damage of the RA elastic lamina delays RA remodeling. The time-dependent RA dilatation is at the same time a part of the RA remodeling [Acar 1992]. We suggest that the vasodilatation developing in the early period in group A also preserves the elastic lamina during harvesting and contributes to early initiation of remodeling. RA has a thick media layer, approximately 1.7 times thicker than the media of the internal mammary artery, and is rich in smooth muscle cells [Acar 1991]. Our histopathologic examinations revealed thick media layers; however, the media layers in both groups were equivalent in thickness and did not contribute to the internal diameter of the lumen or to endothelial irregularity. Despite these facts, this high vasoconstriction rate cannot simply be attributed to morphologic alterations and receptor sensitivity [He 1997].

Receptors from different subgroups exist in the smooth muscle cells of the RA, and these findings may explain the increased RA contractility [He 1998]. In light of this consideration, Table 3 summarizes the drugs used for the treatment of early vasospasm of RA grafts [He 2000; Velez 2001; Manabe 2005] and their receptors [Manabe 2005]. Of these drugs, diltiazem is widely accepted and used for preventing vasospasm [Velez 2001; Manabe 2005]. Nevertheless, in vitro studies have indicated that the vasospasm-preventing effect

Table 3. Potency and Spectrum of Vasodilator Drugs*

Vasodilator Drugs	ET-I	PGF ₂	NOR	PHE	TBX-A ₂	5HT	ATII	KCl
Calcium antagonist								
Nifedipine	+++	-	+++	++	-	+/-	+/-	+++
Verapamil	++	-	++	-	-	+/-	+/-	++
Diltiazem	+/-	-	-	+/-	-	+/-	+/-	++
Nitrovasodilator								
Nitroglycerin	++	-	+++	-	+++	++	++	+++
Nitroprusside	-	-	-	++	-	-	-	++
PDE III inhibitor								
Papaverine	-	-	-	-	-	-	-	+++
Milrinone	-	-	-	+++	++	-	-	+/-
Olprinone	-	-	-	+	+	-	-	++
Potassium channel opener								
Nicorandil	++	-	-	++	++	-	-	++
α -Adrenoceptor antagonist								
Phenoxybenzamine	-	-	+++	+++	-	-	-	-
V-G solution								
	+++	-	++	++	-	+++	+++	+++
Iloprost	++	++	-	++	+++	+++	+++	+

*ET-I indicates endothelin 1; PGF₂, prostaglandin F₂; NOR, norepinephrine; PHE, phenylephrine; TBX-A₂, thromboxane A₂; 5HT, 5-hydroxytryptamine; ATII, angiotensin II; KCl, potassium chloride; PDE, phosphodiesterase; V-G solution: 5 mg verapamil, 2.5 mg nitroglycerin, 300 mL Ringer solution, 0.2 mL 8.4% NaHCO₃, and 500 U heparin; -, no effect; +/-, uncertain effect; +, not enough; ++, enough; +++, too much.

of diltiazem is still a matter of debate [He 2000; Manabe 2005]. Despite intensive clinical use of diltiazem, the problem of vasospasm in the early postoperative period is still being reported at a rate of 5% to 10% [Acar 1992; Velez 2001; Locker 2002; Lowe 2002]. Early RA spasm that does not resolve with this drug suggests variation in receptor type and sensitivity and indicates that the serotonin-related vasoconstriction is persistent [Moran 2001].

As indicated in Table 3, iloprost has inhibitory effects not only on serotonin receptors but also on all arterial system vasospasms via the substances and mechanisms indicated below [Drinda 2005]. In human and animal arterial preparations, iloprost inhibits vasospasm by inducing arachidonic acid (prostaglandin F₂), thromboxane A₂ and its analogue U46619, angiotensin I and II, phenylephrine-norepinephrine, and transmural neural stimulation [Manabe 2005].

When one considers that all of these receptors exist around the RA and are responsible for vasospasm [Manabe 2005], one realizes that serotonin-related vasospasm in particular is among the causes of string sign and hypoperfusion syndrome, and iloprost may be helpful in solving this problem [He 1997; Velez 2001; Manabe 2005]. The basic principles of this study arise from the effects of iloprost on (1) peripheral arterial vasospastic diseases and (2) vasoconstrictor receptors in animal experiments and in vitro studies [Kobzar 2001].

In this regard, the statistical difference in the first, second, and third flow rate measurements within groups and the results favoring iloprost render the principles of our study justifiable.

Besides its vasodilator effects, iloprost also aids in arterial remodeling via transmural neuronal stimulation. Furthermore, it has antiaggregant effects and reduces peripheral vascular resistance. It has natriuretic effects via increasing renal blood flow and has cytoprotective activity. Iloprost also reduces ectopic beats and therefore has reducing effects on fibrillation [Chanda 2000; Kobzar 2001]. Other than preventing RA vasospasm, the effects of iloprost mentioned above might reduce the side effects of CPB; however, such hypotheses require the support of future studies.

When the RA is used for stenoses of <70%, the patency rate is significantly reduced, and the increased intimal hyperplasia influences the survey results when it is used in diabetic patients [Deshpande 2000; Royse 2000; Nicolosi 2002; Manabe 2005]. Therefore, we have excluded both patients with a circumflex artery with <70% stenosis and diabetic patients in this study.

Despite all of these clinical results, RA graft spasm is frequently observed in postoperative angiography evaluations [Moran 2001; Lowe 2002]. In the 2-year coronary angiography examinations of our cases, all of the patients in group A had patent RA grafts, whereas group B had 3 cases of total occlusion and 4 cases with irregular stenosis.

The biological structure of the RA easily adapts to increased blood flow and prevents progressive graft stenosis or occlusion. In this regard, it is an ideal arterial graft with a graft patency close to that of the internal mammary artery. When the problem of early RA vasospasm is solved, graft patency may increase significantly.

Our intraoperative flow rate measurements, pathologic findings, and 2-year graft angiography results indicate that iloprost is a more effective vasodilator agent than diltiazem in preventing early RA vasospasm and increasing mid-term patency; however, further studies comparing iloprost with other agents used for this purpose are required.

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