Retrograde cerebral perfusion provides negligible flow through brain capillaries in the pig

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Objectives: Although retrograde cerebral perfusion is being used clinically during aortic arch surgery, whether retrograde flow perfuses the brain effectively is still uncertain.

Methods: Fourteen pigs were cooled to 20°C with cardiopulmonary bypass and perfused retrogradely via the superior vena cava for 30 minutes: 7 underwent standard retrograde cerebral perfusion and 7 underwent retrograde perfusion with occlusion of the inferior vena cava. Antegrade and retrograde cerebral blood flow were calculated by quantitating fluorescent microspheres trapped in brain tissue after the animals were put to death; microspheres returning to the aortic arch, the inferior vena cava, and the descending aorta were also analyzed during retrograde cerebral perfusion.

Results: Antegrade cerebral blood flow was $16 \pm 7.7 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ before retrograde cerebral perfusion and $22 \pm 6.3 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ before perfusion with caval occlusion ($P = .14$). During retrograde perfusion, calculations based on the number of microspheres trapped in the brain showed negligible flows ($0.02 \pm 0.02 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ with retrograde cerebral perfusion and $0.04 \pm 0.02 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ with perfusion with caval occlusion; $P = .09$); only 0.01% and 0.02% of superior vena caval inflow, respectively. Less than 13% of retrograde superior vena caval inflow blood returned to the aortic arch with either technique. During retrograde cerebral perfusion, more than 90% of superior vena caval input was shunted to the inferior vena cava and was then recirculated, as indicated by rapid development of an equilibrium in microspheres between the superior and inferior venae cavae. With retrograde perfusion and inferior vena caval occlusion, less than 12% of inflow returned to the descending aorta and only 0.01% of microspheres.

Conclusions: The paucity of microspheres trapped within the brain indicates that retrograde cerebral perfusion, either alone or combined with inferior vena caval occlusion, does not provide sufficient cerebral capillary perfusion to confer any metabolic benefit. The slightly improved outcome previously reported with retrograde cerebral perfusion during prolonged circulatory arrest in this model may be a consequence of enhanced cooling resulting from perfusion of nonbrain capillaries and from venoarterial and venovenous shunting.

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Operations on the aortic arch and a variety of complex congenital abnormalities still are a great challenge for cardiac surgeons, in part because they require a period of interruption of normal antegrade cerebral blood flow. Profound hypothermic circulatory arrest (HCA) is the most commonly used technique for achieving operative exposure and simultaneously protecting the brain,^{1,2} but alternatives have been eagerly embraced because of the fairly stringent time limits imposed by HCA.

In recent years, a number of surgeons have enthusiastically adopted the use of retrograde cerebral perfusion (RCP) as a means of improving neurologic outcome after complex cardiovascular and aortic surgery, even though considerable uncertainty exists regarding both the efficacy and the safety of this technique.³⁻⁵ The appeal of RCP lies in its possible benefit both in reducing embolic injury and in prolonging the safe duration of HCA.⁶

In almost all of the clinical as well as experimental studies, the question of whether RCP provides adequate capillary perfusion to the brain has been raised. Several experimental studies, including one carried out in a nonhuman primate model, showed that RCP does not perfuse the brain because of massive venovenous shunting,⁷ but other studies using a variety of different techniques and animal models challenged this conclusion.^{8,9} Furthermore, several clinical and experimental studies have shown improved outcome when RCP was used.^{10,11}

The current study was carried out to demonstrate the pattern of flow to the brain during RCP in an established animal model suitable for comparisons of cerebral protection techniques. In this model, earlier studies had shown that RCP can remove particulate emboli from the brain if the inferior vena cava (IVC) is occluded¹² and that RCP can improve cerebral outcome when compared with prolonged HCA unless the head is packed in ice.¹³ The recent validation of the use of fluorescent microspheres—by comparison with the classic technique of quantitating organ blood flows with the use of radioactive microspheres—made direct studies of cerebral blood flow during retrograde perfusion possible.^{14*}

Materials and Methods

Fourteen juvenile Yorkshire pigs (Thomas D. Morris Inc, Reisterstown, Md), 3 to 4 months of age, weighing 28 to 35 kg, were assigned to one of two groups after cooling to a deep brain temperature of 20°C: 30 minutes of standard RCP (n = 7) or 30 minutes of RCP with occlusion of the IVC (RCP-O; n = 7).

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Preoperative Management

All animals received humane care in accordance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. The protocol for these experiments was approved by the Mount Sinai Institutional Animal Care and Use Committee.

Anesthesia and Hemodynamic Monitoring

Anesthesia was induced with ketamine hydrochloride (10 mg/kg intramuscularly) and muscular paralysis was maintained with pancuronium (0.1 mg/kg intravenously). After endotracheal intubation, the animals were maintained on positive-pressure ventilation with 100% oxygen; anesthesia was maintained with isoflurane (1%). Appropriate catheters were positioned in the femoral artery and vein to allow sampling and pressure monitoring, in the pulmonary artery for determination of cardiac output, and in the esophagus and rectum for temperature determinations. Sagittal sinus cannulation was undertaken as previously described, and epidural and deep brain temperatures were also monitored.¹² Systemic arterial, venous, and sagittal sinus blood samples were obtained to determine pH, PO_2 , PCO_2 , oxygen saturation, oxygen content, hematocrit, and hemoglobin (Ciba-Corning Diagnostic Corp, Medfield, Mass). Glucose and lactate were analyzed with a YSI 2300 Stat (Yellow Springs Instrument Co, Yellow Springs, Ohio).

Cardiopulmonary Bypass

Through a right thoracotomy in the fourth intercostal space, the heart and great vessels were exposed. After heparinization (300 IU/kg), the ascending aorta was cannulated with a 16F arterial cannula, the right atrial appendage with a single 24F atrial cannula, and nonpulsatile cardiopulmonary bypass (CPB) was initiated at a flow rate $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. A cannula was passed from the right superior pulmonary vein into the left ventricle to permit the decompression of the left side of the heart during CPB. A heat exchanger was used for core cooling, and surface cooling was achieved with a cooling blanket. A membrane oxygenator (VPCML Plus; Cobe Laboratories, Inc, Lakewood, Colo) was primed with 1 L of 0.9% sodium chloride, 1 unit 5% albumin, furosemide (1 mg/kg), heparin (5000 IU), and potassium chloride (1 mEq/kg). The pH was maintained, by alpha-stat principles, at 7.40 with an arterial PCO_2 of 35 to 40 mm Hg, uncorrected for temperature.

CPB with perfusion cooling was carried out for 45 minutes to attain a deep brain temperature of 20°C. Cardiac arrest was induced by adding potassium chloride (1 mEq/kg) to the perfusate, and topical cardiac cooling was then begun and maintained throughout the procedure. The ascending aorta was crossclamped just proximal to the aortic cannula.

Experimental Protocol

After the desired deep brain temperature of 20°C had been reached and microspheres had been injected for determination of antegrade cerebral blood flow, the aortic arch was isolated and all animals underwent a 30-minute interval of RCP or RCP-O. Preparations

for RCP involved inserting a 14F cannula into the superior vena cava (SVC), advancing it as cranially as possible, snaring it in place, and connecting it to the arterial line with a Y connector. The azygos and hemiazygos veins were ligated in both groups. In the RCP-O groups, the IVC was also snared and a 10F cannula was inserted into the descending aorta just distal to the second cross-clamp to permit collection of descending aortic return. Retrograde flow was slowly increased and regulated to achieve a pressure of 20 mm Hg in the sagittal sinus. In all animals, maintenance of adequate retrograde flow volume required infusion of 500 to 1000 mL of blood obtained from donor pigs. Perfusate returning from the upper body to the isolated aortic arch (and descending aorta in RCP-O) was drained to collecting chambers and measured for volume and for quantification of microspheres.

Antegrade Cerebral Blood Flow

Antegrade cerebral blood flow was measured with the use of fluorescent microspheres as described by us in previous studies.¹³ In brief, a bolus of approximately 0.8 to 1.2×10^6 microspheres $15 \pm 0.5 \mu\text{m}$ in diameter was injected and flushed with 5 mL of saline solution into a left ventricular catheter before CPB and into the arterial cannula before HCA. Blood reference samples were withdrawn from the femoral arterial line at a constant rate (2.91 mL/min) with a Harvard withdrawal pump (Harvard Apparatus, Inc, Holliston, Mass) beginning 10 seconds before microsphere injection and ending 110 seconds after injection. After the experiment, the animals were put to death with sodium pentobarbital (30 mg/kg) and potassium chloride (6 mEq/kg). In all 14 animals, the brain was removed, and fluorescent analysis was carried out by flow cytometry (Interactive Medical Technology, Cambridge, United Kingdom).

Cerebral blood flow was calculated by this equation: $\text{CBF (mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}) = (\text{Cerebral tissue counts} \times \text{Rate of withdrawal}) / (100 / [\text{Counts in reference sample} \times \text{Brain weight}])$.

Microsphere Injection for RCP

The venous and arterial lines of the CPB circuit were connected before the experiment. During preparation for RCP (eg, insertion of the cannula into the SVC), the reservoir of the CPB circuit was filled with donor blood and a bolus of 2 million microspheres was injected into the reservoir. The arterial and venous lines were clamped proximal and distal to the connecting line, and the pump was started for 5 minutes with normal flow rates (2.5 L/min), allowing mixing of the microspheres with the blood of the cardiomy reservoir. After 5 minutes, at the end of the RCP circuit preparation, the venous and arterial lines were opened, 1 mL of blood was withdrawn from the arterial line, and RCP inflow into the SVC was gradually increased until a sagittal sinus pressure of 20 mm Hg had been achieved. After 5 minutes of RCP, and for every 5-minute interval thereafter, 1-mL samples of blood were simultaneously withdrawn from the perfusate going into the SVC, from the “venous” return from the upper part of the body, collected in a chamber draining the isolated aortic arch, and also from a chamber draining the descending aorta during RCP-O. After its volume had been measured, the chamber with each “venous” collection was treated in a vortex for 1 minute, and 1 mL of blood was withdrawn for microsphere determination: each sample was analyzed in duplicate.

The blood was further processed for quantification of the microspheres as described previously (unpublished data).

Calculation of Flows During RCP

Since the number of microspheres in the SVC inflow was measured by sampling every 5 minutes during RCP, and both the flow rate into the SVC in each animal and the duration of RCP were also known, we were able to calculate total number of microspheres entering the brain for each animal: number of microspheres/milliliter $\times$ SVC flow rate $\times$ 30 minutes. After analyzing the brain, we knew the total number of microspheres trapped in its capillaries and thus could calculate the percent of microspheres traversing the cerebral capillary bed with great accuracy. Furthermore, we collected the entire quantity of blood during RCP that returned to the isolated aortic arch in both groups—and from the descending aorta during RCP-O—as well as sampling the microspheres every 5 minutes during RCP in this “venous” return. We were therefore able to determine the amount of blood passing through venoarterial shunts: microspheres not trapped by capillaries but returned to the aortic arch (or to the arch and descending aorta in the RCP-O group). Because we measured the total volume of blood coming out of the isolated arch, we could then calculate indirectly the amount of blood that was passing through noncerebral capillary beds: this is what remains when one subtracts the blood passing through cerebral capillary beds and the blood flowing through venoarterial shunts from the total amount of blood returning to the aortic arch. Figures 4 and 5 show the distribution of blood for each 100 mL of blood going into the SVC with RCP and RCP-O, respectively. Cerebral capillary blood flow per minute was also calculated: the total amount of blood going into the SVC/100 $\times$ percent of microspheres trapped in the brain is the capillary blood flow per 30 minutes; dividing this number by 30 yields the cerebral capillary blood flow per minute.

Statistical Analysis

Differences between groups were tested by means of the Wilcoxon test or *t* test, as appropriate, for single time points, and repeated-measures analysis of variance was used for multiple time points. The analyses were implemented with SAS programs (SAS Institute, Inc, Cary, NC) on a VAX computer (Digital Equipment Corporation, Maynard, Mass).

Results

Comparability of Experimental Groups

Physiologic data. The median weight of the animals in the RCP group was 30 kg (28–35 kg) and in the RCP-O group, 29 kg (28–33 kg) ($P = .34$ by Wilcoxon test). The median CPB cooling time in both groups was 47 minutes (44–49 minutes).

Deep brain temperature. Figure 1 shows average deep brain temperature during the interval of RCP. There was no updrift in temperature during the period of RCP, indicating that the perfusate was keeping the brain parenchyma uniformly cool.

Antegrade cerebral blood flow. Figure 2 displays antegrade CBF for the two experimental groups. As expected,

Figure 1. Direct measurement of deep brain temperatures in 14 pigs before and during 30 minutes of standard retrograde cerebral perfusion (RCP, $n = 7$) and retrograde perfusion with occlusion of the inferior vena cava (RCP-O, $n = 7$), as detailed in the text. CA, Circulatory arrest.

Figure 2. Antegrade cerebral blood flow (CBF), calculated by means of fluorescent microspheres, at baseline and at 20°C deep brain temperature in the groups before 30 minutes of standard retrograde cerebral perfusion (RCP) and retrograde perfusion with occlusion of the inferior vena cava (RCP-O). Antegrade flows were not significantly different between the groups. HCA, Hypothermic circulatory arrest.

CBF was comparable in the two groups at baseline temperatures and decreased significantly with cooling to 20°C in both groups: it was $16 \pm 7.7 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ before RCP and $22 \pm 6.3 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ before RCP-O ($P = .19$).

Ascending aorta blood saturation. The average saturation of the blood that returned to the aortic arch at each interval during RCP and RCP-O is shown in Figure 3. With both methods, there was a continuous decrease in oxygen saturation during retrograde perfusion, indicating that some

oxygen extraction was occurring. There were no significant differences between the RCP and RCP-O groups.

Cerebral Perfusion During RCP

Brain capillary perfusion. Only minimal numbers of microspheres were found in the brain after sacrifice, regardless of whether retrograde perfusion for 30 minutes was with standard RCP or RCP-O (Figures 4 and 5). Cerebral blood flow calculations revealed negligible flow through the brain

Figure 3. Saturation of blood returning to the aortic arch during retrograde perfusion: cerebral “venous” saturations. The falling saturations did not differ significantly whether or not the inferior vena cava was occluded during retrograde cerebral perfusion (abbreviations as in previous figures); low saturations indicate high extraction and imply low flow.

Figure 4. Flow distribution during conventional retrograde perfusion (RCP), calculated by means of the number of microspheres trapped in particular tissues and the volumes of blood collected in each location, as explained in detail in the text. For ease of understanding, the calculations were adjusted to express results with retrograde perfusion at a rate of 100 mL/min into the superior vena cava (SVC). IVC, Inferior vena cava; RA, right atrium.

with either method: $0.02 \pm 0.02 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ with RCP and $0.04 \pm 0.02 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ with RCP-O ($P = .09$). This was only 0.01% and 0.02% of SVC inflow, respectively, and only 0.1% of antegrade flow at this temper-

ature, which is presumably autoregulated according to metabolic requirements. Thus, true capillary perfusion of the brain is far below what is required to provide any significant metabolic benefit even in the presence of hypothermia.

Figure 5. Blood distribution during RCP-O, retrograde perfusion with occlusion of the inferior vena cava, calculated by means of the number of microspheres trapped in particular tissues and the volumes returned to each location. The calculations were adjusted to reflect results from retrograde perfusion at a flow rate of 100 mL/min into the superior vena cava (SVC).

Aortic arch return. The total volume of blood returning to the aortic arch was $10\% \pm 4.6\%$ in the RCP group and $12.8\% \pm 3.9\%$ in the RCP-O group: this reflects the total “venous” return from the upper part of the body during RCP or RCP-O, including the face, head, neck, and arms, as well as the brain. The small amount of aortic arch return indicates that the majority of blood infused into the SVC during RCP was not perfusing the upper part of the body at all. Analysis of the concentration of microspheres in the aortic arch return—0.8% and 1.1% of the total injected for RCP and RCP-O, respectively—indicates that a very small volume was passing through venoarterial or venovenous shunts in the upper part of the body during either RCP or RCP-O: most of the microspheres were extracted by capillaries in the brain or in other structures.

During RCP, 90% of SVC input was shunted to the IVC and was then recirculated: this was apparent from the rapid development of an equilibrium in microsphere concentration between the SVC and IVC. By subtracting the sum of the microspheres found in the IVC, aortic arch, and brain capillaries from the number initially infused, we can calculate the amount of perfusion of nonbrain capillaries. This was 9.2% of all SVC inflow in the RCP group.

With RCP-O, the total amount of blood returning to the descending aorta throughout the whole period of RCP was 540 ± 350 mL, 12% of total SVC inflow: only 0.01% of inflow microspheres returned to the descending aorta. Thus,

we calculate that 11.7% of total SVC inflow was taken up by nonbrain capillaries in the RCP-O group. As we have seen in previous studies, 75% of all SVC inflow volume was sequestered in the body, not returning to either the ascending or the descending aorta, and leading to total body as well as cerebral edema.¹²

Discussion

The data from this study show dramatically that RCP provides negligible flow through brain capillaries in a pig model. It confirms earlier work in baboons showing that most of the inflow into the SVC during RCP is shunted through low-resistance high-capacity venous beds.⁷ Our results are also in accord with the findings of Ye and associates,¹⁵ who showed that RCP via the SVC supplies limited dye to brain tissue: a large amount of dye is shunted into the IVC, even in the absence of noticeable valvular obstruction in the internal jugular veins.¹⁵ A study in human cadavers, in which latex was injected through the SVC, also showed that most of the SVC inflow is shunted through venovenous anastomoses.¹⁶ In the current study, even though the azygos and hemiazygos veins were both ligated before implementation of RCP, 90% of the SVC inflow during RCP was nevertheless shunted into the IVC and recirculated. The possible venovenous anastomoses responsible for this shunting were not identified during this experiment, but we believe that some anastomoses between the external and internal

jugular veins may be responsible. The jugular venous system is linked via the thoracic wall to an extended venous plexus around the spinal cord. This may be one of many pathways between the SVC and IVC. In total, more than 20 direct venovenous anastomoses have been described in human beings.¹⁷

Antegrade cerebral blood flow was measured in this experiment at baseline and at 20°C, and the results were consistent with recent studies^{18*} that used the time-honored gold standard technique of employing radioactive microspheres, as well as the newer method involving fluorescent microspheres. As in previous studies, cerebral blood flow fell significantly during cooling, reflecting the expected reduction in oxygen consumption that is the basis for the use of hypothermia for cerebral protection and indicating that autoregulation continues to match flow to metabolic needs at these levels of hypothermia. Previous studies suggest that a decrease in metabolic rate to about 25% of baseline would be anticipated at 20°C; thus, an adequate flow to meet metabolic needs would be assured by the antegrade flow in this study and perhaps even by a flow somewhat below this level, given the possibility of increased oxygen extraction and other forms of compensation for marginally reduced cerebral blood flow. However, the flow actually demonstrated by the trapped microspheres in the brain was extremely low—only 0.1% of antegrade flow at 20°C. It seems unlikely that such a small fraction of optimal capillary flow to the brain provides any metabolic benefit whatsoever. We were not surprised by the fact that the oxygen saturation of blood returning into the isolated aortic arch decreased throughout the interval of RCP, despite the very low flow to the capillaries of the brain. Oxygen extraction occurs not only in the brain, but also in other capillary beds of the upper part of the body: the lower the flow, the higher the rate of oxygen extraction. With the low flow demonstrated during RCP to the entire upper part of the body, high extraction would therefore be anticipated.

With regard to the two different techniques for retrograde perfusion, we were surprised that RCP-O did not show more pronounced superiority of flow through brain capillaries than conventional RCP. In a recent study, RCP with IVC occlusion was more effective in washing out particulate emboli from the brain than conventional RCP.¹² In addition, previous work had shown that RCP-O had a higher rate of return of blood to the isolated aortic arch and reduced oxygen extraction, all suggesting more effective perfusion with RCP-O (with IVC occlusion) than with conventional RCP (without IVC occlusion).^{12,19} In the current study, we again

observed a higher amount of blood returning to the aortic arch with RCP-O than with RCP. When we looked specifically at cerebral blood flow, however, only minimally more brain capillary flow was achieved with RCP-O than with conventional RCP ($0.04 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ in the RCP-O group vs $0.02 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ in the RCP group; $P = .09$). This study confirms the earlier observation that a large amount of sequestered fluid accumulates during even a short interval of RCP with IVC occlusion. It reinforces the idea that this method enhances the risk of cerebral edema, as had been speculated previously in several studies in which a higher rate of histopathologic abnormalities was observed with RCP-O than with RCP.¹²

We observed no upward drift in deep brain temperature in either group during retrograde perfusion. This finding is probably one of the most important observations to emerge from this study. The cooler the brain remains, the smaller its energy requirement and therefore the smaller the oxygen debt incurred during arrest of antegrade circulation. The apparent superiority of RCP over HCA in a number of clinical and laboratory studies may be explained by the sustained intracranial cooling during HCA that is afforded by RCP, in contrast to the gradual upward drift of brain temperature that often occurs with prolonged simple HCA.^{13,20} However, because RCP has some potential for harm—probably related to its propensity for inducing cerebral edema—it may be better to maintain brain hypothermia during HCA by alternate strategies: more thorough and prolonged cooling before initiation of arrest, confirmation of metabolic suppression by monitoring of jugular venous saturation, and packing the head in ice.

A study by Pagano and colleagues,²¹ using a technetium-labeled perfusion agent and a portable gamma camera to take pictures during RCP, was interpreted as showing blood flow to the brain during RCP. However, such pictures cannot distinguish between real cerebral capillary flow and flow through nonbrain capillaries or venovenous and venoarterial anastomoses, and the good clinical outcome reported was observed with relatively short HCA durations. When examined closely, most studies that purport to demonstrate the clinical benefits of RCP involve its use for intervals that fall well within the limits for safe use of HCA alone and show improved results compared with historical controls.^{11,22,23}

In summary, the paucity of microspheres trapped within the brain indicates that neither RCP nor RCP-O provides sufficient cerebral capillary perfusion to confer any meaningful metabolic benefit. Previous studies have shown that only RCP-O is effective in removing particulate emboli from the cerebral circulation, but this technique of retrograde perfusion is associated with a high risk of cerebral edema and mild histopathologic injury^{12,24} and, although slightly more effective than conventional RCP, still fails to

*Ehrlich MP, McCullough JN, Juvonen T, Zhang N, Weisz DJ, Bodian CA, et al. Effect of hypothermia on cerebral blood flow and metabolism in the pig. Unpublished data.

achieve significant cerebral capillary perfusion. In the absence of any convincing evidence of the efficacy of retrograde perfusion in providing metabolic benefit or in reducing embolic damage, we think that its routine use to improve outcome during prolonged HCA should seriously be reexamined.

In reviewing our own clinical results, we were unable to demonstrate any benefit from using RCP in patients undergoing ascending aorta/aortic arch surgery, when patients undergoing similar operations using HCA alone or using antegrade cerebral perfusion for equivalent intervals were compared with patients who had operations using RCP.²⁵ Some of our results even suggested that RCP might be associated with a worse outcome, but our patients were not randomized and included a population with a relatively high risk of stroke. As a consequence of these clinical and experimental studies, we no longer use RCP.

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