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Improved Arterial Blood Oxygenation Following Intravenous Infusion of Cold Supersaturated Dissolved Oxygen Solution

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ABSTRACT

BACKGROUND: One of the primary goals of critical care medicine is to support adequate gas exchange without iatrogenic sequelae. An emerging method of delivering supplemental oxygen is intravenously rather than via the traditional inhalation route. The objective of this study was to evaluate the gas-exchange effects of infusing cold intravenous (IV) fluids containing very high partial pressures of dissolved oxygen (>760 mm Hg) in a porcine model.

METHODS: Juvenile swines were anesthetized and mechanically ventilated. Each animal received an infusion of cold (13 °C) Ringer's lactate solution (30 mL/kg/hour), which had been supersaturated with dissolved oxygen gas (39.7 mg/L dissolved oxygen, 992 mm Hg, 30.5 mL/L). Arterial blood gases and physiologic measurements were repeated at 15-minute intervals during a 60-minute IV infusion of the supersaturated dissolved oxygen solution. Each animal served as its own control.

RESULTS: Five swines (12.9 ± 0.9 kg) were studied. Following the 60-minute infusion, there were significant increases in PaO_2 and SaO_2 ($P < 0.05$) and a significant decrease in $PaCO_2$ ($P < 0.05$), with a corresponding normalization in arterial blood pH. Additionally, there was a significant decrease in core body temperature ($P < 0.05$) when compared to the baseline preinfusion state.

CONCLUSIONS: A cold, supersaturated dissolved oxygen solution may be intravenously administered to improve arterial blood oxygenation and ventilation parameters and induce a mild therapeutic hypothermia in a porcine model.

KEYWORDS: supersaturated dissolved oxygen, intravascular gas exchange, hyperoxygenated solutions, hypoxemia, mechanical ventilation, gas exchange

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Background

For more than two centuries, researchers have evaluated methods to augment gas exchange via the intravenous (IV) route and improve oxygenation during treatment of severe cardiopulmonary disease.[1–5] One such method attempted has been the IV injection of gaseous oxygen.[6,7] However, subsequent research into the direct IV injection of gaseous oxygen found the technique to be extremely hazardous and frequently fatal due to the formation of large gaseous emboli.[8,9]

Over the past three decades, an alternate method has been described, which utilizes hyperbaric oxygen physically dissolved in fluid.[10] Research from *in vitro* hyperbaric medicine studies has shown strong correlations between predicted

and actual pO_2 levels in both saline and blood, when specific gas partial pressures and liquid are mixed, or tonometered, inside a hyperbaric chamber and subsequently withdrawn outside the hyperbaric chamber for blood gas analysis.[11] *In vivo* animal studies utilizing infused dissolved oxygen in IV fluids have demonstrated physiologic benefits of improved blood oxygenation in rabbits,[12–14] decreased pulmonary hypertension in calves,[15] and reduced intrapulmonary shunt during single-lung ventilation in pigs.[16]

Another method studied to augment gas exchange is to decrease the metabolic demand for oxygen by infusion of cold IV fluids with induction of mild therapeutic hypothermia (32–34 °C). Studies of mild therapeutic hypothermia have demonstrated beneficial effects, such as reduced neurologic injury, limitation of primary and secondary brain injury, reduction of oxygen free-radical formation, decreased destructive enzymatic reactions, and reduced tissue oxygen consumption.[17,18] However, studies of induced mild hypothermia utilizing cold IV liquids have not evaluated the gas-exchange augmentation possibilities when utilizing supersaturated dissolved oxygen solutions as the induction agent.

We hypothesized that the IV infusion of cold, supersaturated dissolved oxygen solution will increase blood oxygenation, specifically the oxyhemoglobin saturation level and the partial pressure of oxygen dissolved in arterial blood (PaO_2) and induce mild hypothermia when compared to baseline (control) blood gases in an animal model. The objective of this study was to evaluate the efficacy of gas-exchange augmentation by infusing cold, supersaturated dissolved oxygen gas in IV fluid using a novel gas mixing (tonometry) system to produce a mild therapeutic hypothermia in a stable, mechanically ventilated, porcine animal model.

Methods

The surgical procedures and animal care in this investigation were in compliance with the guidelines established by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee.

Five juvenile swines were premedicated with ketamine (22 mg/kg) and acepromazine (1.1 mg/kg). Propofol (10 mg/kg) was administered to facilitate intubation and mechanical ventilation (AVEA, CareFusion Inc., Yorba Linda, CA). Each animal was orally intubated and received the following ventilator settings: volume-controlled ventilation with tidal volume 8 mL/kg, I:E ratio 1:2, and respiratory rate adjusted to a $PaCO_2$ of 40–50 mm Hg. PEEP was set at 5 cm H_2O, and FiO_2 remained at 0.21 throughout the study.

Anesthesia was maintained with a Propofol continuous infusion (5–10 mg/kg/hour) and intramuscular boluses of ketamine (10 mg/kg). Instrumentation included placement of a femoral arterial line and a large bore IV catheter. Ringer's lactate IV fluid was provided at 5 mL/kg/hour. A 60-second lung recruitment maneuver was performed using 10 cm H_2O for each animal after intubation. Baseline arterial blood gas and cardiovascular measurements were obtained following a 20-minute stabilization period.

The tonometry system (Fig. 1) consisted of a disposable burette containing the sterile IV fluid and a series of separate coils immersed within the fluid, which continuously circulated refrigerated ice water throughout the IV fluid, without direct contact between the infused and refrigerant liquids. The burette system was connected to a gas blender and flowmeter for precise control of the partial pressure of oxygen dissolved in the liquid. The tonometry system mixed known partial pressures of gaseous oxygen within the infused liquid prior to and during IV infusion. Following mixing of the infusate, the cold, supersaturated oxygen infusion was infused via an IV pump and fluid filter.

The infusate consisted of IV Ringer's lactate, which was supersaturated with 100% oxygen gas bubbling through the hyperbaric tonometer at a flow rate of 3 L/minute for a preliminary preparation period of 20 minutes, and gas was continuously bubbled through the IV liquid within the burette throughout the infusion period.

The temperature of the supersaturated IV fluid was initially decreased to 13 °C prior to gas solvation in the fluid. The temperature of the infused liquid was maintained during infusion via insulated IV fluid tubing. Insulation consisted of neoprene tubing cut lengthwise and secured by adhesive strips. During continuous infusion, the fluid was administered at a dose of 30 mL/kg/hour. Arterial blood gas measurements and oxygen supersaturation of the IV fluid was confirmed by a blood gas analyzer (GEM Premier 3000, Instrumentation Laboratories, Bedford, MA). However, since the upper limit of the blood gas analyzer PO_2 measurement is 760 mm Hg and the dissolved oxygen infusate exceeded that limit, the dissolved oxygen tension of the infusate was confirmed via a second device (Hanna Instruments HI 98186 Dissolved Oxygen Meter, Ann Arbor, MI). The dissolved oxygen content of the infusate measured at 13 °C was 39.7 mg/L, which equates to a dissolved oxygen gas tension of approximately 992 mm Hg or 30.5 mL O_2/L. The temperature of the IV fluid was decreased further (7 °C) to increase the liquid solubility for dissolved oxygen. The supersaturated IV fluid was administered for 60 minutes, with cardiopulmonary measurements and arterial blood gases measured at baseline prior to the infusion and at 15-minute intervals throughout the infusion period.

All blood gas samples were measured at a temperature of 37 °C. All arterial blood gas samples were withdrawn from the femoral arterial line following removal of flush solution in the arterial line. Blood gas assay samples of 2 mL were collected in disposable, preheparinized, plastic syringes containing dried lithium heparin crystals. Samples were inspected to ensure the absence of air bubbles within the blood sample, sealed with a rubber cap, and mixed with the dried heparin within the syringes by rolling the syringe between the hands for a minimum of 10 seconds. All blood gas samples were immediately analyzed following collection of the assays using the GEM Premier 3000 blood gas analyzer.

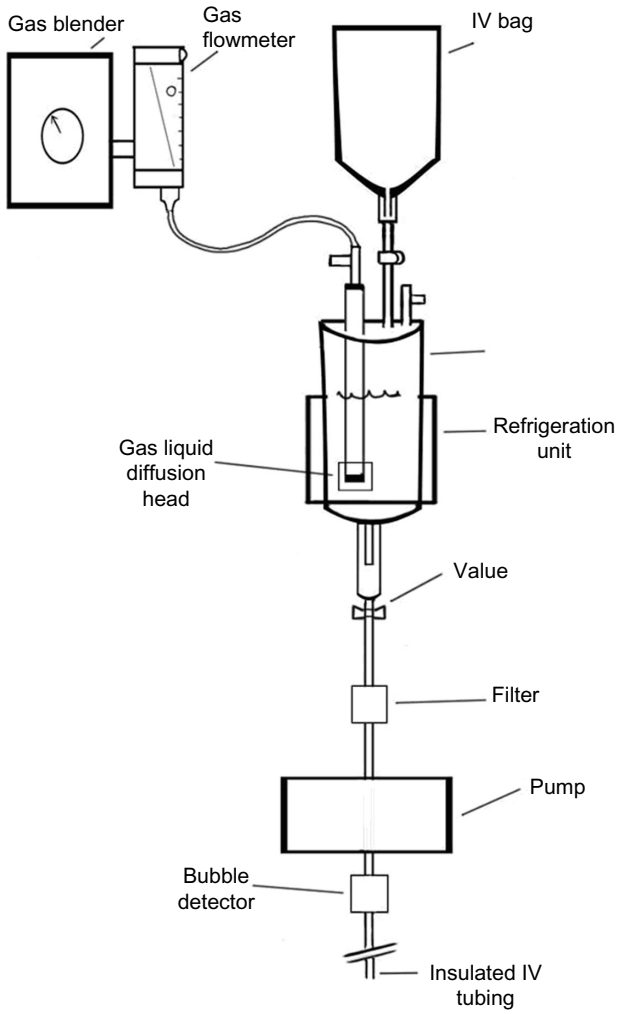

Figure 1. Schematic of IV infusion of cold, supersaturated dissolved oxygen solution delivery system.

Statistical analyses were performed with statistics software (Excel, Microsoft Office Excel, 2013). Data are reported in Table 1 as mean ± standard deviation. Figures 2, 3, and 4 report mean ± standard error. Descriptive statistics were calculated for blood gases and physiologic measurements taken at baseline (preinfusion) and at 15-, 30-, 45-, and 60-minute intervals. A total of five blood gas samples were analyzed at each of the above intervals. Differences between pairs of groups were determined using a *t*-test, and comparison between the mean at preinfusion with the mean at the 60-minute interval was evaluated for each blood gas and physiologic measurement shown in Table 1. Differences were considered significant when P was <0.05.

Results

All animals yielded data sets consisting of baseline (preinfusion) vital signs, blood gas parameters, and blood measures of hematocrit and serum lactate. These measures were compared with parameters measured at 15-minute intervals during the 60-minute infusion period of supersaturated dissolved oxygen solution. The results are summarized in Table 1. Following the 60-minute infusion, containing a dissolved PO_2 of approximately 992 mm Hg, there were significant differences in core body temperature, $PaCO_2$, PaO_2, and SaO_2 when compared to preinfusion baseline measurements for these parameters ($P < 0.05$).

Relative to the preinfusion baseline PaO_2 of 78 ± 8 mm Hg, the postinfusion PaO_2 increased to 94 ± 10 mm Hg after 60 minutes of supersaturated dissolved oxygen infusion ($P = 0.012$). After 1 hour, the infusion resulted in a 20% increase in PaO_2 from preinfusion baseline. Compared to the preinfusion baseline SaO_2 of 95% ± 2%, the postinfusion SaO_2 increased to 97% ± 1% after 60 minutes of supersaturated dissolved oxygen infusion ($P = 0.033$).

Relative to the preinfusion baseline $PaCO_2$ of 52 ± 5 mm Hg, the postinfusion $PaCO_2$ decreased to 46 ± 2 mm Hg ($P = 0.034$). After 1 hour, the infusion resulted in a 12% reduction in $PaCO_2$. Corresponding to the decreased $PaCO_2$, the preinfusion arterial pH of 7.36 ± 0.03 increased to a pH of 7.40 ± 0.5 after 60 minutes of infusion ($P = 0.10$, not significant). Notably, the changes in mean $PaCO_2$ and corresponding change in mean arterial pH occurred with no changes in mechanical ventilator settings.

The preinfusion core temperature of 37.7 ± 0.7 °C decreased to a postinfusion core temperature of 36.2 ± 0.8 °C ($P = 0.006$). Relative to preinfusion baseline levels, there was no difference in serum lactate levels and hematocrit levels. As shown in Table 1 and Figures 1–3, the changes in gas exchange occurred gradually over the course of 1 hour during the infusion period.

Discussion

This study demonstrated that a simple, disposable, bedside tonometry system may increase arterial blood oxygenation with a simultaneous decrease in carbon dioxide levels, while simultaneously inducing a mild therapeutic hypothermia. Previous studies have demonstrated positive clinical benefits of using iced IV fluids to induce mild therapeutic hypothermia as a resuscitation technique.[19–22] Furthermore, the benefits of utilizing mild therapeutic hypothermia in the treatment of the adult respiratory distress syndrome and sepsis have been extensively reviewed by Villar and Espinosa.[23] More recently, the long-term beneficial outcomes from hypothermia in reducing death and long-term disability in neonatal hypoxic-encephalopathy have been described.[24]

Several other studies in humans have demonstrated improved blood oxygen transport, increased ventricular wall motion, increased ejection fraction, and reduced myocardial infarct size following the intracoronary infusion of fluid containing high dissolved oxygen tensions (sometimes called aqueous oxygen), in the treatment of acute myocardial infarction.[25,26] The present study combined the techniques of infusing fluid with high dissolved oxygen tensions with induction of therapeutic hypothermia by chilling the supersaturated infusate at ambient barometric pressure.

Table 1. Cardiopulmonary measurements and arterial blood gases following intravenous infusion of supersaturated dissolved oxygen solution. Mean ± SD, (n = 5 pigs).

PARAMETER	PRE-INFUSION	15 MIN	30 MIN	45 MIN	60 MIN
	Baseline				
Heart Rate (Beats/min)	162 (31)	152 (23)	151 (23)	144 (21)	146 (25)
Core Temperature (C)**	37.7 (0.7)	36.9 (0.6)	36.6 (0.6)	36.3 (0.6)	36.2 (0.8)
Arterial pH	7.36 (.03)	7.37 (.05)	7.37 (.05)	7.38 (.04)	7.40 (0.5)
Arterial $PaCO_2$ (mm Hg)**	52 (5)	50 (3)	48 (3)	49 (3)	46 (2)
Arterial PaO_2 (mm Hg)**	78 (8)	85 (10)	88 (10)	89 (11)	94 (10)
SaO2 (%)**	95 (2)	96 (2)	96 (2)	96 (1)	97 (1)
Lactate (mmol/L)	1.42 (0.7)	1.8 (0.9)	1.8 (0.8)	1.6 (0.8)	1.5 (0.8)
Hematocrit (%)	24.2 (3.5)	22.8 (3.1)	22 (2.9)	21.8 (2.5)	21.2 (2.2)

Note: ** = Significance: $P < 0.05$.
Abbreviation: NS, Not significant.

There are several differences between this study and previous studies, which have evaluated intravascular methods to improve oxygenation. First, this study significantly differs from the early work, where gaseous oxygen was directly injected into the veins, since the present study utilized a preliminary process of gas solvation to physically dissolve gaseous oxygen in liquid prior to IV infusion. A second difference between this study and the studies of induced hypothermia using iced IV fluids is that we used a novel tonometry system to control the temperature and the partial pressure of dissolved oxygen in the infusate during both preparation and infusion. In the prior study by Kim and Chung,[12] warm (37 °C) IV liquid with lower levels of dissolved oxygen (approximately 500 mm Hg) achieved improvement in blood oxygenation; however, the researchers experienced difficulty regulating consistent dissolved oxygen tensions and did not utilize hyperbaric dissolved oxygen levels. The study by Kim and Chung[12] concluded that some augmentation of oxygenation is possible; however, the technical difficulties of providing consistent, precise partial pressures of dissolved oxygen were solved by our system.

Also, this study differed from the work related to aqueous oxygen studies, since those studies utilized a hyperbaric system to generate gas and saline mixing conditions, extracorporeally mixed blood with the infusion, and utilized a special catheter to reperfuse coronary arteries (post-angioplasty) with blood mixed with fluid at temperatures of 37 °C. In contrast, this study utilized a simple, disposable, bedside tonometry system, which dissolved hyperbaric (>760 mm Hg) tensions of dissolved oxygen in fluid at ambient barometric pressure.

Hyperbaric gas tensions in fluid were achievable due to the increased solubility of IV fluid for gaseous oxygen at decreased fluid temperatures, hydrostatic pressure of the IV solution, and the ability of water to form a weak dipole–dipole bond with oxygen molecules. Supersaturation of gas in liquid has been described as an application of "SuperHenry's law" where the equilibrium gas solubility results in extreme liquid supersaturation.[27] Supersaturation of liquid with dissolved oxygen gas at cold temperatures creates a stable solution, unless the supersaturated solution is adversely affected by sonication or agitation.

Because this study combined therapeutic hypothermia with the infusion of hyperbaric tensions of dissolved oxygen gas, significant improvements in arterial blood oxygenation were achieved as well as significant changes in $PaCO_2$ and temperature. An improvement of 20% increased dissolved arterial PaO_2 combined with a 12% decreased $PaCO_2$ may be clinically significant, especially in conditions where conventional ventilation and oxygenation techniques have failed or permissive hypoxemia is necessary.[28]

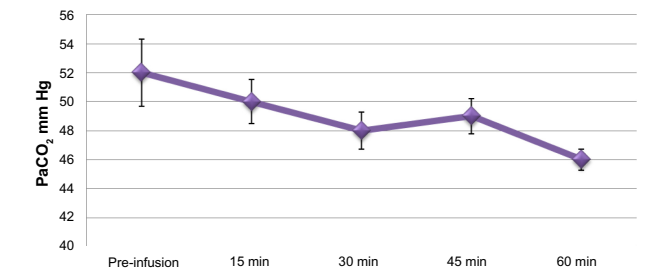

Figure 2. Change in $PaCO_2$ (mm Hg) during IV infusion of cold, supersaturated dissolved oxygen solution; mean (n = 5) ± standard error.

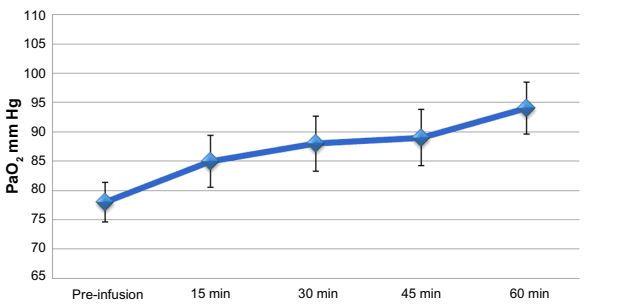

Figure 3. Change in PaO_2 (mm Hg) during IV infusion of cold, supersaturated dissolved oxygen solution; (n = 5) ± standard error.

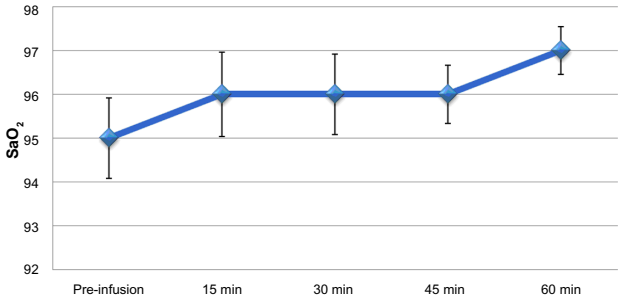

Figure 4. Change in SaO_2 during IV infusion of cold, supersaturated dissolved oxygen solution; (n = 5) ± standard error.

The beneficial changes in $PaCO_2$ and pH following 60 minutes of the cold infusion most likely resulted from several complex intravascular gas-exchange mechanisms. First, the supersaturated dissolved oxygen fluid was cold, which affected both the metabolic rate and the affinity between hemoglobin and oxygen. Tissue metabolic rate decreases in response to a localized cold environment by decreasing oxygen consumption and CO_2 production. Second, the decrease in $PaCO_2$ was thought to occur primarily due to Gay-Lussac's law, which states that the temperature and pressure of gases are directly related. Further, the decreased fluid temperature increased the plasma solubility for CO_2. Another process that affected the $PaCO_2$ following the infusion of cold supersaturated dissolved oxygen solution resulted from the Haldane effect, where increased dissolved oxygen caused dissociation between hemoglobin and carbon dioxide. Additionally, the Haldane effect is thought to be accelerated due to the decreased intravascular infusion temperature, which beneficially affects the bonding affinity between hemoglobin and oxygen.

Recently, rapid improvement in blood oxygenation was reported via the infusion of lipid-encapsulated oxygen-gas microspheres (LOMs).[14] Following infusion of the LOMs, the authors reported short-term decreases in hypoxemia in rabbits, following 15 minutes of tracheal occlusion. The authors also reported several limitations of lipidic oxygen-containing microspheres such as increased viscosity of the lipid infusate, a requirement for continuous infusion of lipidic oxygen–infused microspheres, short-term treatment of hypoxemia, unknown long-term risks of LOMs on blood and tissue, unknown metabolic fate of LOMs, and unknown free-radical injury. Also, the lipid oxygen microspheres had no effect on carbon dioxide removal or metabolic rate.[14] In contrast, this study demonstrated improvement in arterial blood gas oxygenation and reduced carbon dioxide with subsequent pH balance, utilizing hospital-acquired gaseous oxygen and Ringer's lactate solution used with an inexpensive, disposable, bedside tonometry system.

Since dissolved oxygen is normally responsible for a much smaller percentage of blood oxygen transport compared to hemoglobin, dissolved oxygen has frequently been dismissed as an insignificant process for improving blood oxygenation.[29] However, hyperbaric medicine studies have demonstrated that sufficient levels of dissolved oxygen tensions in plasma alone may support life without hemoglobin.[30] Further, Kylstra has demonstrated that a modified hyperbaric tonometer may be utilized to dissolve sufficient tensions of oxygen in saline to support life via fluid breathing in rats and dogs.[31] More recently, hyperoxygenated solutions produced from ultraviolet light and decomposition of ozone resulted in high tensions of dissolved oxygen in IV liquid and are reported to have widespread use in China to treat and prevent hypoxia.[32] However, the researchers report inconsistent dissolved oxygen tensions due to mixing of air within the fluid infusion container. In contrast, the hyperbaric tonometer system utilized in this study was constructed from inexpensive plastic materials and was designed for rapid assembly and ease-of-use at the bedside or in an ambulance for emergency field response. Most importantly, this tonometry system maintained consistent dissolved oxygen tensions and temperatures of the infusate, by refrigeration of the infusate and insulation of the IV tubing.

The limitations of this study include a small sample size and a study design that utilized each animal as its own control. Also, the animals were healthy, and thus, the study did not evaluate blood gas changes during disease states. Lastly, hemodynamic monitoring consisted of invasive blood pressure monitoring and Electrocardiogram. More invasive hemodynamic monitoring is necessary to determine physiologic effects of dissolved oxygen solution on cardiac function and the pulmonary vasculature.

Additional *in vivo* studies are needed to more thoroughly evaluate the hemodynamics of supersaturated dissolved oxygen infusion, determine the degree to which ventilator support may be decreased when the dissolved oxygen solution is administered, and determine gas-exchange efficacy during disease states such as induced hypoxia and acute lung injury. Further, to ensure safety, additional studies are needed to ensure the absence of gaseous emboli following the change in temperature, which occurs during infusion. This study evaluated gas exchange during slow infusion and did not evaluate the potential for gas emboli formation following the injection of a bolus of supersaturated liquid.

Conclusions

This study has shown that a cold, supersaturated dissolved oxygen solution may be intravenously administered to improve arterial blood oxygenation and ventilation parameters while inducing mild therapeutic hypothermia in a porcine model.

Author Contributions

Conceived and designed the experiments: DG, MG, JR, IC. Analyzed the data: DG, MG, JR, IC. Wrote the first draft of the manuscript: DG, MG. Contributed to the writing of the manuscript: DG, MG, JR, IC. Agree with manuscript results and conclusions: DG, MG, JR, IC. Jointly developed

the structure and arguments for the paper: DG, MG, JR, IC. Made critical revisions and approved final version: DG, MG, JR, IC. All authors reviewed and approved of the final manuscript.

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