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How to Ventilate Lungs as Small as 12.5% of Normal: The New Technique of Intratracheal Pulmonary Ventilation

ECKHARD E. MÜLLER,[1] THEODOR KOLOBOW, SRINIVAS MANDAVA, MICHAEL JONES, GIOVANNI VITALE, MICHELE APRIGLIANO, AND KOJI YAMADA

Section on Pulmonary and Cardiac Assist Devices, Laboratory of Cell Biology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892

ABSTRACT. We wished to determine in a laboratory animal model how much residual lung was needed to sustain total gas exchange. In a series of young, healthy lambs weighing approximately 10 kg that were sedated and paralyzed, we progressively excluded from gas exchange all the left lung (a total of 43%), plus the right lower and cardiac lobes (81%), plus the right middle lobe (87.5%). In some studies, the respective lobes were surgically removed; in others, the bronchi and the pulmonary arteries to the respective lobes were ligated. We provided pulmonary ventilation using the pressure control mode (Servo 900 C) at a tidal volume of 20 mL/kg multiplied by the fraction of the remaining lungs, a respiratory rate up to 120/min, a peak inspiratory pressure of 12–15 cm H_2O, and a positive end-expiratory pressure of 3 cm H_2O. Those lambs with at least both the right upper lobe (RUL) and right middle lobe remaining (19% of total lungs) were weaned to room air on mechanical ventilation within 48 h. Ventilating RUL (12.5% of remaining lung) with the same ventilator required a substantially higher tidal volume and peak inspiratory pressure to result in adequate alveolar ventilation but led to respiratory failure and death within 8 h. We then applied a newly developed system of intratracheal pulmonary ventilation to ventilate the RUL (12.5% of remaining lung) alone. A continuous flow of humidified mixture of air and oxygen was directly passed into the trachea at the level of the carina through a diffuser at a tidal volume of 2.5 mL/kg. A single valve controlled expiration and respiratory rate. Lambs with only RUL remaining were weaned to room air within 2 h, at a respiratory rate of 60–120/min and peak inspiratory pressure of 14–9 cm H_2O, inspiration to expiration ratio of 1:1, and positive end-expiratory pressure of 3 cm H_2O. Initial mean pulmonary artery pressure progressively decreased from 40 ± 5 to 25 ± 7 mm Hg within 6 h after surgery. (*Pediatr Res* 34: 606–610, 1993)

Abbreviations

CMV, controlled mechanical ventilation
FiO_2, inspired oxygen concentration
I:E ratio, inspiration to expiration ratio
ITPV, intratracheal pulmonary ventilation
MV, mechanical ventilation
PEEP, positive end-expiratory pressure
PIP, peak inspiratory pressure
RR, respiratory rate
RUL, right upper lobe
VT, tidal volume
PaO_2, arterial O_2 tension
$PaCO_2$, arterial CO_2 tension

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Correspondence: Theodor Kolobow, M.D., National Institutes of Health, NHLBI, LCB, Building 10, Room 5 D 17, 9000 Rockville Pike, Bethesda, MD 20892.
[1] Current address: Department of Anesthesiology and Intensive Care Therapy, Philipps-University Hospital, Baldingerstrasse 1, D-W-3550 Marburg/Lahn, Germany.

There are no reliable experimental data that show how much lung tissue can be surgically removed while still sustaining total blood gas exchange. In experiments in dogs, it was shown that survival in awake animals was not possible when greater than 75% of the total lung parenchyma was surgically resected, with death resulting from pulmonary edema (1). Those studies had also shown a lack of adaptation, even if resection was undertaken in two steps after an interval of 6 wk.

In a laboratory animal model using anesthetized, paralyzed, healthy lambs, we explored what minimal fraction of normal lung was needed to sustain normal gas exchange. We also explored whether pulmonary deterioration was primarily related to the fraction of the lungs remaining or to other factors, such as the method of MV.

In the studies reported here, using healthy young lambs, we excluded from gas exchange progressively more lobes of the lungs, and we then attempted to sustain pulmonary ventilation using the remaining lobes of the lungs. With 12.5% of lungs remaining, the use of conventional MV resulted in progressive CO_2 retention and hypoxia, whereas aggressive management led to respiratory failure and death. Under identical circumstances, the application of the newly developed technique of ITPV permitted weaning to room air ventilation within a few hours at normal peak airway pressures.

MATERIALS AND METHODS

These studies were conducted in anesthetized, paralyzed young sheep. Proper animal care was taken according to the *NIH Guide for the Care and Use of Laboratory Animals*. The protocol of this study was approved by the NIH Animal Care and Use Committee. The studies were divided into two parts.

Group 1: resection studies ($n = 4$). Through left and/or right thoracotomy and using sterile surgical techniques, we removed progressively more lung, in the following order: *1*) the left lung (estimated remaining lung: 57% of normal) ($n = 1$); *2*) left lung plus RUL (estimated remaining lung: 44.5% of normal) ($n = 1$); and *3*) left lung plus right lower and accessory lobes (estimated remaining lung: 19% of normal) ($n = 2$) (Fig. 1).

We used standard surgical techniques of thoracotomy and pneumonectomy, and resection of lung segments where appro-

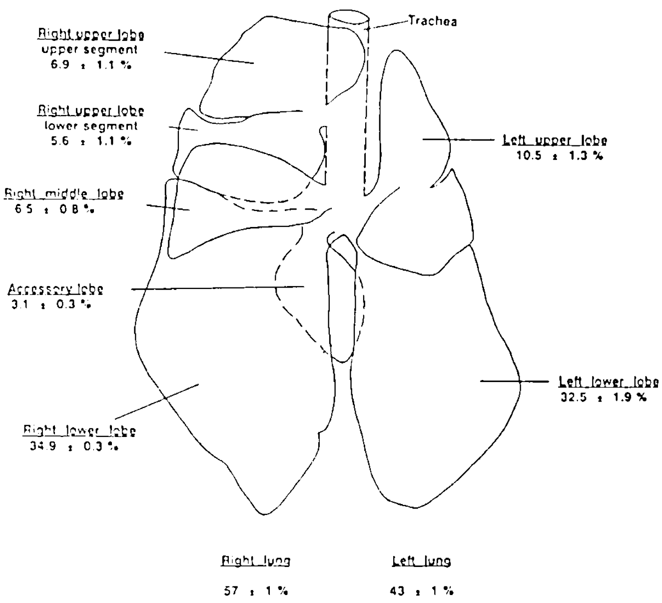

Fig. 1. The lobes of the lung of the sheep (in percent; total lung = 100%) (n = 21).

priate. We took particular care to avoid damage to the remaining lung. During closure of the chest, a chest drain was inserted but left open and not connected to suction.

Group 2: ligation studies (n = 6). This approach was designed to provide the least possible impairment to lung function from surgical intervention in areas adjacent to the RUL. In studies similar to those reported in group 1 lambs, we had found that surgical resection for the removal of all but the RUL resulted in some impairment in lymphatic and arterial flow and in impairment in venous drainage. This invariably compromised the lower segment of the RUL with severe edema, atelectasis, and hemorrhage, which we wished to avoid.

Through a right-sided thoracotomy, we first ligated the respective pulmonary arteries and bronchi to all but the RUL, leaving those so-ligated lobes *in situ*. After this, through a left-sided thoracotomy, we ligated the pulmonary artery to the left lung. The ductus arteriosus was routinely ligated. Finally, we ligated the trachea below the RUL bronchus, thereby totally isolating the left lung, the bronchi to all but the RUL having been previously ligated. The estimated fraction of lungs participating in gas exchange was thus reduced to 12.5%. Chest drains were inserted as in group 1 and managed in a similar manner.

Anesthesia and general management. Anesthesia was induced with 5 mg of diazepam and 20–30 mg/kg thiopental sodium i.v. After endotracheal intubation, the animals underwent general anesthesia. All sheep received continuous i.v. infusion of 0.9% NaCl, alternating with 5% dextrose in water, at a rate of 8.3 mL/kg/h, adjusted as needed. Sodium bicarbonate was administered, as needed, to maintain base excess at greater than −3 mmol/L. The sheep were placed on a water blanket to control body temperature. The right carotid artery was cannulated for blood pressure monitoring and arterial blood sampling. A 5 F Swan Ganz thermodilution catheter was introduced percutaneously through the right external jugular vein and was advanced into the pulmonary artery. A tracheostomy was performed approximately 5 cm above the sternum and a tracheostomy tube (6 mm inner diameter) was inserted. All sheep were then turned prone, and the body temperature was cooled to 34°C for the duration of the surgical procedure (as described above), after which the temperature was returned to 38°C for the remainder of the study. Ceftriaxone sodium was given in a dose of 0.5 g/12 h i.v.

Monitoring. The hemodynamic variables, gas exchange, and body temperature were measured and recorded before, during, and after all surgical procedures on an hourly basis and more frequently when needed. Arterial, pulmonary artery, central venous, and airway pressure at the level of the tracheostomy tube were continuously measured on transducers (Statham P 23 D, Gould Inc.) and recorded on an ink recorder (Type 200, model 2222, Gould Inc., Oxnard, CA). Arterial blood samples were analyzed on a gas analyzer (ABL 300, Radiometer, Copenhagen, Denmark).

Blood temperature was monitored via the thermodilution catheter using a cardiac output computer (9520 A, American Edwards Laboratories, Irvine, CA) and was adjusted through changes in water blanket temperatures (Blanketrol, Cincinnati Sub-Zero Products, Cincinnati, OH).

Ventilator management. We used two modes of pulmonary ventilation: conventional MV and ITPV.

Conventional MV. Before, during, and after surgery, the lambs in group 1 were ventilated with a Servo ventilator 900 C (Siemens Medical Systems, Iselin, NJ) in the pressure control mode. The VT was adjusted to keep PIP between 12 and 18 cm H_2O. The VT was kept at 10 mL/kg with the whole lung intact. During the resection and ligation studies in group I and II sheep, the VT was increased to 20 mL/kg of body weight multiplied by the proportion of the lung remaining and participating in gas exchange. We adjusted RR up to 120/min and used a PEEP of 3 cm H_2O and an I:E ratio of 1:1. We used a Concha-therm-III humidifier (Respiratory Care Inc., Arlington Heights, IL) for gas heating and humidification. We took special care to avoid water condensation by insulating gas tubing with multiple layers of plastic film.

ITPV. This method was developed to greatly reduce dead space ventilation, and was to be applied to group II lambs. We introduced through the endotracheal tube a small catheter with multiple perforations at its distal tip (diffuser), the diffuser resting at the level of the carina (Fig. 2). The gas flow through this catheter was continuous during both inspiration and expiration and was set at 5 mL/kg/respiratory cycle. In a 10-kg lamb, at an I:E ratio of 1:1, this gave an inspiratory VT of 2.5 mL/kg for RUL alone (equal to 20 mL/kg, times fraction of lungs remaining, as under conventional MV).

With the tracheal dead space greatly reduced or eliminated, we used an RR up to 120/min for enhanced alveolar ventilation. High RR later allowed us to reduce VT to as low as 1.2 mL/kg and to maintain low PIP (3–4 cm H_2O above PEEP) while still effecting adequate alveolar ventilation with normal Pa_{CO_2} values (6.6–6.0 kPa/35–45 mm Hg).

We used this technique in combination with a Servo ventilator 900 C with the air/oxygen supply to the ventilator disconnected. Using the pressure control mode, the inspiratory pressure above PEEP was set at zero. The expiratory valve of the Servo ventilator provided the desired PEEP (3 cm H_2O), I:E ratio (1:1), and expiratory frequency (RR). With those settings, the inspiratory valve of the Servo ventilator remained closed. In essence, the Servo ventilator was used solely to control the expiratory valve to make the system operable. FiO_2 was adjusted as needed to keep $Pa_{O_2} \geq 6.7$ kPa (50 mm Hg).

Definition of endpoint. Successful weaning was based on the ability to tolerate room air ventilation at normal body temperatures, with $Pa_{O_2} \geq 6.7$ kPa (50 mm Hg), FiO_2 0.21, Pa_{CO_2} 4.6–6

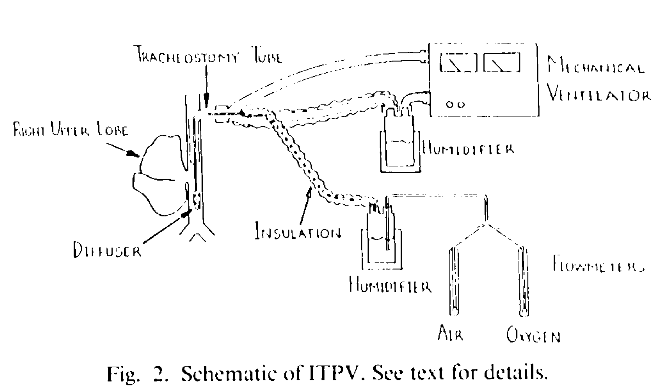

Fig. 2. Schematic of ITPV. See text for details.

kPa (35–45 mm Hg), a PIP less than 20 cm H_2O, and normal or near normal hemodynamic variables.

Crossover studies. To provide for meaningful comparison between CMV and ITPV, we performed crossover studies using three group 2 lambs. Those lambs (with 12.5% of lungs remaining) had initially been managed with ITPV and had been weaned to room air. We switched quickly from ITPV to CMV at the same PIP and range of RR and monitored over the ensuing minutes changes in gas exchange and hemodynamics. After that, ITPV was resumed in the usual fashion.

Two additional group 2 lambs were initially managed on ITPV until weaned to room air. Those lambs were then switched to CMV at VT and RR sufficient to maintain adequate alveolar ventilation. We closely monitored hemodynamics and gas exchange until death.

Presentation of results. At the time of death, the general appearance of the lung was noted. The lobes were excised and weighed. The weight of the lobes was expressed in grams and in percent of normal. In randomly selected samples, the bloodless lung wet/dry-weight ratio was measured. This ratio was compared with data obtained from healthy lambs used in studies not related to these experiments. Other samples were placed in buffered formaldehyde; sections were taken and stained with hematoxylin and eosin. Where appropriate, data are presented as mean ± SD.

RESULTS

The baseline data define a homogeneous population of healthy sheep with a body weight of 10.67 ± 3.04 kg. With 57, 44, and 19% remaining lungs managed on conventional MV, all sheep in group 1 were weaned to room air [$Pa_{O_2} \geq 6.7$ kPa (50 mm Hg), normal Pa_{CO_2}] within 3–46 h after end of surgery.

All four group 2 sheep with 12.5% of lungs remaining were weaned to room air on ITPV within 2 h from the end of surgery. There was no difficulty controlling Pa_{CO_2}, pH, or Pa_{O_2} with PIP between 9 and 17 cm H_2O (2 h after surgery: 12 ± 1.6 cm H_2O). The mean pulmonary artery pressure immediately after ligation of trachea and respective pulmonary arteries was 40 ± 5 mm Hg, with further decrease in pulmonary artery pressure to a mean of 25 ± 7 mm Hg by the end of 6 h (Fig. 3).

One sheep died with progressive hemodynamic instability 8 h after surgery (Table 1). At autopsy, the lungs of all sheep except the one sheep referred to (no. 2, Table 1) grossly appeared normal. Histologic sections of the lungs showed normally aerated tissue, with a normal appearance of the terminal bronchioli and alveolar structures. In some areas, the cellularity of the alveolar septa was increased, with some interstitial edema. There was no hemorrhage, atelectasis, overdistension of airway structures, or necrosis of the alveolar septa.

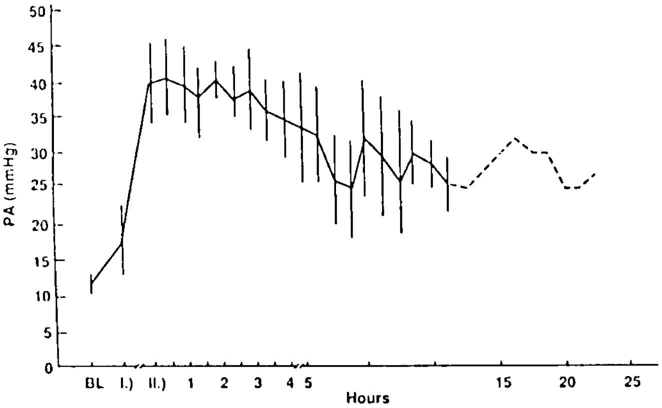

Fig. 3. Mean pulmonary artery pressure (mean ± SD). Group 2 sheep, sheep 1–6. *I.)*, Pulmonary artery ligation to all but the RUL. *II.)*, Pulmonary artery to left lung ligated, followed by cross clamping the trachea below RUL-bronchus. *BL*, Baseline. See text for details.

Crossover studies with RUL. After weaning to room air on ITPV and quickly switching from ITPV to conventional MV, Pa_{CO_2} could no longer be controlled, and the sheep developed severe respiratory acidosis and hemodynamic instability within 40 min of starting conventional MV (sheep no. 1, 3, 4, Table 1). Return to ITPV at the same settings as before was followed by recovery in blood gases within 2–4 min (Fig. 4).

In the second crossover group, arterial blood gases in both lambs remained at Pa_{O_2}/FiO_2 ratios > 350 and at normal Pa_{CO_2} values for the first 12 h (not shown). After that, there was a progressive respiratory acidosis and hypoxia, with death by the end of 18–25 h. At autopsy, the lungs were hemorrhagic and atelectatic, with a liver-like consistency. The histologic sections showed hemorrhage, atelectasis, and massively overdistended peripheral airways and alveolar structures, with necrosis of the alveolar septa, regions of alveoli containing polymorphonuclear leukocytes, and formation of hyaline membranes—all changes indistinguishable from hyaline membrane disease. There was interstitial edema with engorged alveolar septa and hypercellularity of the interstitial tissue, very similar to the observations reported earlier by Carlson *et al.* (1). The bloodless wet/dry weight ratio was 8.532 ± 0.277 (normal: 4.599 ± 0.259).

DISCUSSION

This study was designed to explore the minimal fraction of total lung needed to sustain adequate pulmonary ventilation. The group 1 animal model was a reasonable first approach to address the issue. We surgically removed progressively more lobes of the lungs. By sustaining a VT of 2 times normal, and choosing an appropriately higher RR, we succeeded in weaning lambs to room air ventilation with right middle lobe and RUL remaining (19% lung volume) using conventional MV. We used a VT not over 2 times "normal" times fraction of remaining lung and an RR sufficient to keep PIP within the preselected range. Still, the time for weaning to room air was at times rather prolonged. Animals in both groups 1 and 2 were provided with a tracheostomy, which in itself lowers the dead space. Such reduction is likely to have been beneficial with conventional means of MV but was expected to have no bearing on the efficiency with ITPV.

In group 2 animals, we had removed all but the RUL, or 12.5% of total lung. The initial mean pulmonary artery pressure was elevated but gradually declined. It was surprising to learn that the RUL vasculature was able to accommodate total cardiac output, without cardiac decompensation. We limited VT to 2.5 mL/kg, and used RR up to 120/min, the limit set on the Siemens Servo ventilator. An RR in excess of 120/min would likely have been feasible, since alveolar ventilation improved with rise in RR, limited only by the maximal RR of the ventilator. With the RUL alone remaining, adequate ventilation could not be established in group 2 lambs using a conventional mechanical ventilator of the type now often used clinically. The key advantage of ITPV lies in its greatly reduced dead space ventilation, as fresh air/oxygen enters the lungs at the level of the carina. Successful use of the new technique, however, must be predicated on special attention for optimal heating and humidification.

The superiority of ITPV over conventional MV was shown in crossover studies to MV in group 2 sheep previously weaned to room air on ITPV. Gas exchange deteriorated acutely at identical respirator frequency and pressure, only to recover on return to ITPV. When ventilation was limited to conventional MV so as to result in adequate alveolar ventilation, the initial good arterial blood gases declined some hours later and lambs died after 18–25 h with severe hypercapnia and hypoxia.

Our studies gave us the opportunity to explore how much healthy lung was needed to provide for adequate pulmonary gas exchange. Our studies implicate conventional MV at high PIP in the evolution of acute lung injury and respiratory failure in this animal model. Under identical conditions, we were also able

Table 1. *Tracheal ligation model with RUL (remaining lung = 12.5% of normal)*

Sheep no.	Body weight (kg)	Weaned to room air: Yes	Weaned to room air: No	Last Pa_{O_2} on room air (mm Hg)*	Time to death (h)	Cause of death†	Weight of RUL: g	Weight of RUL: % of normal	Wet/dry ratio	Gross findings
1	14.1	×		79.3	5	1	61.7	350	6.126:1	Lung pink, soft, well aerated, normal appearance
2	12.1	×		89.9	8.5	2, 3	64.6	427	8.41:1	Lung 5% aerated, 95% atelectatic, 100% recruitable, foam, firm, heavy appearance, no hemorrhage
3	10.4	×		100.4	22	1	23.7	182	4.68:1	Lung pink, soft, well aerated, no signs of barotrauma, normal appearance
4	8.9	×		95.9	14	1	26.5	238	4.80:1	Normal appearance of the lung, no signs of barotrauma/injury

* 1 mm Hg = 0.1333 kPa.

† 1, Electively killed; 2, respiratory acidosis/metabolic decompensation; 3, hemodynamic instability.

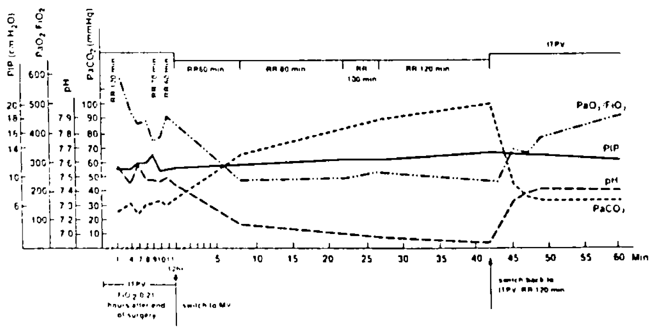

Fig. 4. Crossover studies with the RUL. Changes in Pa_{O_2}/FiO_2, Pa_{CO_2}, pH, and PIP after switching from ITPV to MV and back to ITPV, all at the same PIP (VT constant at 2.24 mL/kg = 2 times expected normal for RUL).

to explore the significant benefits of a new mode of ventilation (ITPV) and to assess its safety and efficiency.

In our current studies, all blood flow was directed through the healthy, albeit small, lungs. Such would almost certainly not be the case in the majority of clinical cases when healthy regions of the lungs are interspersed with diseased regions of the lungs. In studies yet to be reported, we have shown that ITPV, at normal PIP, can be successfully applied to the ventilation of lungs with induced diffuse acute disease processes, and even more readily so when only 10% of lungs are intentionally kept disease free. By keeping the PIP under 20 cm H_2O, using low PEEP, and avoiding aggressive recruitment at high airway pressures, pulmonary blood flow in a matter of hours is directed to the remaining low resistance, high compliance lung units as reflected in a decrease in venous admixture and dead space ventilation.

These studies may be relevant to the clinical area. It is now widely appreciated that the disease process in acute respiratory failure in newborns, children, and adults is not homogeneous. Areas of consolidation are interspersed with what appears to be normal lung tissue; the amount of normal lung tissue may be reduced to only 10–20% (2–14). In the clinical setting, the ventilator is attuned to ventilating the lung as a whole. Such an approach is based on practical considerations because it is neither possible nor practical to provide MV to individual lobes, let alone subunits of the lobes of the lungs. The bulk of MV is directed to the most compliant parts of the lungs, thus also to the healthiest parts. This scenario implies that the truly healthy or healthiest parts of the lungs will be ventilated at nearly the same high pressures used to ventilate the most diseased parts of the lungs, invariably resulting in great distension or overdistension of the previously healthy airway structures and likely in ventilator-induced lung injury. Injury to such lungs can be avoided by optimal ventilation of these remaining healthy parts. Due to the anatomical dead space, conventional MV at low VT (and thus at a low PIP) is often not effective at any RR. With ITPV, normal alveolar ventilation seems possible and practical.

Although quite different in underlying cause, the severely hypoplastic lungs in congenital diaphragmatic hernia present possibilities and limitations (15–25). Compared with conventional MV, ITPV may greatly improve alveolar ventilation, result in lower VT, lower PIP, and lower minute ventilation, and provide the margin where all modes of MV, including neonatal extracorporeal membrane oxygenation, have failed (26).

Our studies show that adequate pulmonary ventilation can be attained in lungs reduced in size to as low as 12.5% of normal using the newly described method of ITPV. The key advantage of ITPV lies in a greatly reduced anatomical dead space ventilation, permitting the use of an RR of up to 120/min at normal PIP.

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