Pulmonary Vascular Effects of Fat Emulsion Infusion in Unanesthetized Sheep

PREVENTION BY INDOMETHACIN

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ABSTRACT Pulmonary diffusing capacity and arterial blood P_{O_2} decrease in humans when 10% fat emulsion is infused. To study its effects on the pulmonary circulation and lung fluid balance, we infused 0.25 g/kg × h of a 10% fat emulsion (Intralipid, Cutter Laboratories, Inc., Berkeley, Calif.) into an awake sheep lung lymph preparation. The emulsion caused a sustained increase in pulmonary artery pressure to approximately twice base line with little change in left atrial pressure. Pa_{O_2} decreased an average 13 torr and lung lymph flow increased two- to threefold. Lymph/plasma total protein concentration fell as lymph flow increased; the magnitude of the lymph/plasma protein decrease was similar to that reported previously when lung vascular pressures were mechanically elevated. Heparin infusion (loading dose = 4,000 U, maintenance dose = 2,000 U/h) cleared the serum of triglycerides but did not alter the response to fat emulsion. Indomethacin infusion (loading dose = 5 mg/kg, maintenance dose = 3 mg/kg × h) blocked the rise in pulmonary artery pressure, the increase in lung lymph flow, and the fall in Pa_{O_2}. Neither extravascular lung water nor [^{14}C]urea lung vascular permeability surface area products were altered by fat emulsion infusion. We conclude that fat emulsion infusion in sheep increases lung microvascular filtration by increasing vascular pressures, but has no effect on vascular permeability. Since the effects are blocked by indomethacin, they may be prostaglandin mediated.

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INTRODUCTION

There are several reports that intravenous infusion of a fat emulsion, 10% Intralipid (Cutter Laboratories), in humans is benign and beneficial (1–4). However, in the few patients where pulmonary function has been studied, carbon monoxide diffusing capacity and arterial P_{O_2} decreased during infusion of recommended doses (5). To measure effects in the lung circulation, we infused 10% fat emulsion intravenously into chronically instrumented unanesthetized sheep. The infusion caused pulmonary hypertension, hypoxemia, and increased lung lymph flow. Lymph responses were like those we have reported when lung vascular pressures were mechanically elevated (6). The response was unaltered by heparin but blocked by indomethacin. We conclude that intravenous fat emulsion in sheep causes pulmonary vasoconstriction and increased transvascular fluid filtration. The effects may be mediated by prostaglandins.

METHODS

Description of sheep preparation

We used an unanesthetized chronic sheep lung lymph preparation as described (6–9). Each sheep had two thoracotomies and neck dissections with cannulation of the pulmonary artery, left atrium, an external jugular vein, a carotid artery and the efferent duct from the caudal mediastinal lymph node. We ligated the tail of this node to eliminate nonpulmonary lymph. Lymph collected this way is largely from the lungs (8, 9). Also, lymph protein concentration appears to reflect protein concentration in the lung perimicrovascular space (10, 11). Under steady-state conditions, we assume that lymph flow is proportional to the net volume of fluid filtered from lung exchanging vessels.

Before we made experiments, sheep recovered from surgery for at least 3–4 days and had a stable, blood-free lymph flow.

Experimental protocols

General. Sheep stood unanesthetized in a cage with free access to food and water. We estimated the level of the left atrium with the animal standing and fixed miniature strain gauges (Micron Instruments, Inc., Los Angeles, Calif.) to the cage wall at this level. We recorded mean pressures in the pulmonary artery, left atrium, and thoracic aorta continuously using an electronic recorder (Hewlett-Packard Co., Palo Alto, Calif.) and measured lung lymph flow every 15 min by recording the volume drained into a tube fixed to the animal's side. We measured the total protein concentration in lymph samples pooled every 30 min and in a sample of peripheral blood plasma drawn every 60 min. A stable base-line period of at least 60 min preceeded any experimental intervention. During this time, we sampled arterial blood for measuring P_{O_2}, P_{CO_2}, and pH.

Fat emulsion alone. The fat emulsion used was 10% Intralipid, prepared for intravenous use in humans. In 1 liter, there are 100 g of soybean oil as the major source of calories and 12 g of egg yolk phospholipids that emulsifies the soybean oil. 25 g glycerol and the necessary quantity of distilled water are also added, making the osmolarity of the emulsion 280 mosmol/liter. The estimated particle size is 0.5 μm. Free fatty acids are derived from both soybean oil and the phospholipids; the main fatty acids are shown in Table I (12).

We infused 10% fat emulsion through the vena caval catheter nine times in six sheep at a maximum rate of 0.25 g/kg × h (the highest rate recommended for children [13]). With a constant-rate infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.), we started infusions at 0.025 g/kg × h, increased the rate to 0.1 g/kg × h and then to the final rate, maintaining the infusion at 0.25 g/kg × h until vascular pressures and lymph flow were stable for 60 min. Toward the end of this steady-state condition, we repeated arterial blood gas and pH measurements.

Heparin and fat emulsion. Seven times in five sheep, after a base-line period, we gave 4,000 U aqueous heparin (heparin sodium injection, U. S. Pharmacopeia; Abbott Diagnostics, Diagnostic Instruments, Dept., North Chicago, Ill.) intravenously and then continuously infused 2,000 U/h. 30 min after beginning heparin, we infused the fat emulsion exactly the same way as when the fat emulsion was given alone. Lee-White clotting times (14) stayed more than three times the base-line value throughout the experiments.

Indomethacin alone. Once in each of seven sheep, we infused 5 mg/kg indomethacin i.v. over 30 min and then 3 mg/kg per h for 3 h. Just before each experiment, we made a fresh solution by mixing indomethacin powder (Merck Sharp, & Dohme, Rahway, N. J.) with sodium carbonate powder (anhydrous, Matheson, Coleman, and Bell, East Rutherford, N. J.) in a ratio of 3.1:1 in normal saline.[1] The 5 mg/kg solution was in 50 ml saline and 3 mg/kg × h solution was in 300–350 ml. When vascular pressures and lymph flow were stable for 45–60 min, we repeated arterial blood gas and pH measurements and stopped the infusion.

Indomethacin and fat emulsion. We gave indomethacin and the fat emulsion together in six experiments. In four experiments, we gave indomethacin first and in two, we gave the fat emulsion first. Each experiment was preceeded by a stable base-line period. The fat emulsion and indomethacin were infused according to the protocols described above. When indomethacin was given first, we started the fat emulsion infusion when we started the 3 mg/kg × h indomethacin infusion. When the fat emulsion was given first, we waited until the sheep was in a steady state at the higher rate of infusion (0.25 g/kg × h) and then started the indomethacin infusion. In both sets of experiments, we continued observations until pressures and lymph flow were stable during the double infusion, measured arterial blood gases and pH and stopped the experiment.

TABLE I
Partial Fatty Acid Composition of 10% Intralipid

Fatty acids	100 g soybean oil	12 g egg yolk phospholipids
	%	%
Oleic	26.4	32.0
Linoleic	54.3	11.3
Linolenic	7.8	0.3
Arachic	0.1	0.1
Arachidonic	—	0.2

Other methods

Protein analysis. We measured total protein concentrations in lymph and blood plasma with an automated system (AutoAnalyzer, Technicon Instruments Corp., Tarrytown, N. Y.) by a modified biuret method (15); duplicate determinations differed by <5%.

To correct for possible effects of lipemia, we ran a blank for each serum sample and subtracted the g/dl protein equivalent of the blank from the serum value. The "blank solution" was made by dissolving 9 g sodium potassium tartrate and diluting to 1 liter with a solution of 5 g potassium iodide and 8 g sodium hydroxide, dissolved in distilled water up to 1 liter. Duplicate determinations of samples with a triglyceride level up to 400 mg/dl varied at most by 6%.

Indicator dilution studies. We did single-pass indicator studies to measure cardiac output, extravascular lung water, and microvascular permeability during the steady-state base-line period and again during the steady-state experimental period. We did studies this way eight times in sheep with fat emulsion alone, six times in sheep with heparin and fat emulsion, and five times in sheep with indomethacin and fat emulsion.

We have described the indicator methods before (7, 8, 16, 17). A bolus of [^{51}Cr]erythrocytes, ^{125}I-albumin, [^{3}H]-water, and [^{14}C]urea was injected through the right atrial catheter and samples collected from the aortic catheter. From the radioactivity measured in arterial samples and in the injected mixture, we calculated cardiac output and extravascular lung water volume (7, 8, 16, 17). The [^{14}C]urea permeability surface area product was calculated by two methods: (*a*) the widely accepted integral extraction calculation (18); and (*b*) using a Krogh convolution circulatory model (19). The mathematical techniques are described in detail in prior publications (20, 21).

Blood gas measurements. We measured P_{O_2}, P_{CO_2}, and pH in samples of arterial blood collected anaerobically during steady-state base line and experimental periods with a blood gas analyzer (model 127, Instrumentation Laboratories, Inc., Lexington, Mass.).

Statistics. We tested significance of differences between steady-state base line and experimental measurements made

[1] Modification of recipe from personal communication with Dr. H. J. Robinson, Vice President for Scientific Affairs, Merck Sharp & Dohme.

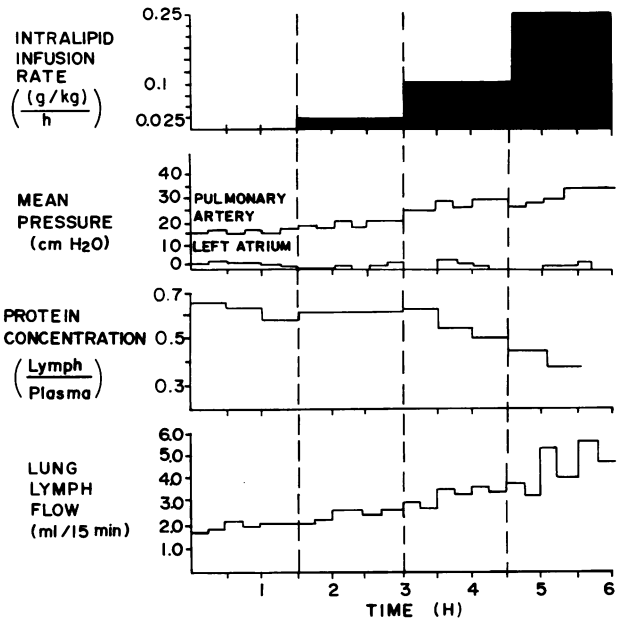

FIGURE 1 Response of lung vascular pressures, lymph flow and protein concentration to 10% fat emulsion infusion in a sheep.

in the same animals in the same experiments using a paired t test and between measurements made in different animals with a t test for independent groups (20). We considered a P value <0.05 significant.

Lipid analysis. We measured triglyceride and free fatty acid content of the plasma and lung lymph in each of the three experimental groups where fat emulsion was infused. Plasma and lymph triglyceride concentrations were measured with a semiautomated system (AutoAnalyzer, Technicon Instruments Corp.) using a fluorometric reaction based on the work of Kessler and Lederer (23). Free fatty acid content was determined by a modification of the extraction technique of Dole and Meinerty (24).

RESULTS

Hemodynamic and lymph responses. Fig. 1 illustrates the response of a sheep to the infusion of 10% fat emulsion. Pulmonary artery pressure increased with each increase in infusion rate and was sustained in each case. Left atrial pressure changed minimally. There was also a dose-dependent increase in lung lymph flow. The lymph/plasma protein concentration ratio decreased as lymph flow increased. Pulmonary vascular pressures and lymph flow promptly decreased toward base line when the fat emulsion was stopped and were stable at base-line levels 2–4 h later.

Table II contains summaries of responses to fat emulsion when given alone and after heparin. In both cases, the emulsion caused similar degrees of pulmonary hypertension and increased lymph flow with decreased lymph protein concentration. Arterial P_{O_2} fell significantly in both cases with no change in P_{CO_2} or pH.

TABLE II

Summary of Steady-State Hemodynamic, Lung Lymph, and Arterial Blood Gas Data during 10% Fat Emulsion Infusion Alone, with Heparin, and with Indomethacin

	No.	Body weight	Condition	Mean pressure (cm H_2O)		Lymph flow	Protein concentration (g/dl)		Arterial blood		pH	Hematocrit
				Pulmonary artery	Left atrium		Lymph	Plasma	P_{O_2}	P_{CO_2}		
		kg				*ml/15 min*			*mm Hg*	*mm Hg*		*%*
Mean±SEM	9	36 ±2	Base line	19 ±1	−0.5 ±1	1.4 ±0.2	3.8 ±0.2	6.0 ±0.3	80 ±3	30 ±1	7.53 ±0.04	28 ±2
			Intralipid	35* ±1	−2 ±1	3.2* ±0.6	3.2* ±0.2	6.7* ±0.2	67* ±2	32 ±2	7.56 ±0.03	30 ±3
Mean±SEM	7	33 ±2	Base line	19 ±1	0 ±1	2.0 ±0.4	3.5 ±0.3	5.7 ±0.3	82 ±3	32 ±2	7.51 ±0.03	29 ±4
			Heparin/ Intralipid	34* ±2	−4 ±2	5.2* ±1.3	2.7* ±0.4	5.9* ±0.3	71* ±5	36 ±1	7.51 ±0.03	33 ±4
Mean±SEM	6	35 ±3	Base line	16 ±2	1 ±1	3.2 ±0.2	3.2 ±0.2	5.5 ±0.4	86 ±2	32 ±3	7.50 ±0.02	26 ±3
			Indomethacin plus Intralipid	18 ±2	1 ±1	2.9 ±0.2	2.9 ±0.2	5.3 ±0.6	82 ±2	36 ±3	7.49 ±0.01	26 ±3

* Significantly different from base line ($P < 0.05$).

When lung vascular pressures are increased mechanically in sheep lymph preparations, lymph/plasma protein concentration ratios decrease as a linear function of increasing lymph flow (6). Fig. 2 shows the relationship between lymph/plasma protein ratio and lymph flow during the steady-state response to fat emulsion infusion alone and with heparin: the regression line and confidence limits for the previously reported increased pressure studies are also shown. Fat emulsion values are very similar to those for mechanically increased pressure; heparin did not alter the fat emulsion response.

Control infusions of indomethacin alone caused pulmonary artery pressure and lymph flow to increase slightly during the loading dose but the changes were transient and pulmonary artery pressure and lymph flow were stable at base-line levels during the maintenance dose infusion. Fig. 3 shows the response to fat emulsion in a sheep pretreated with indomethacin superimposed on the response to fat emulsion alone in the same sheep on another day. Indomethacin blocked the increase in pulmonary artery pressure and lung lymph flow. Table II summarizes the steady-state responses to fat emulsion with indomethacin: none of the measured variables were affected.

We measured triglycerides and free fatty acids in plasma and lymph for some experiments in each category. Representative results are listed in Table III. With fat emulsion alone, triglyceride and free fatty acid levels rose in the plasma but not in the lymph. With heparin pretreatment, the plasma triglyceride level remained low as expected and the free fatty acid level rose; but lymph levels were unaffected. After indomethacin pretreatment, the changes in the plasma and lymph were similar to those with fat emulsion alone.

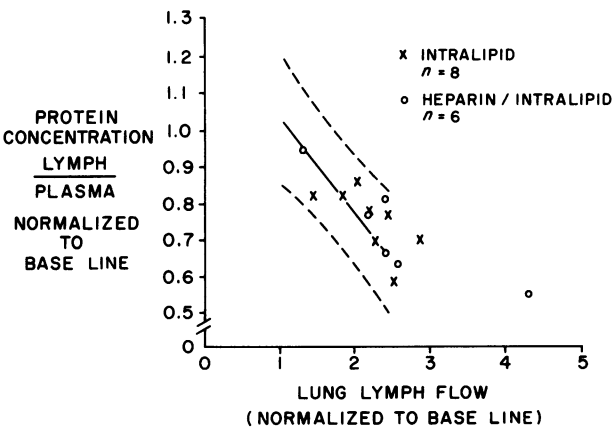

FIGURE 2 Steady-state lymph/plasma protein concentration as a function of lung lymph flow during Intralipid infusion alone and after heparinization in sheep. Both axes are normalized to base line. The regression line and 95% confidence limits (broken lines) are for reported studies where lung vascular pressures were increased mechanically (6).

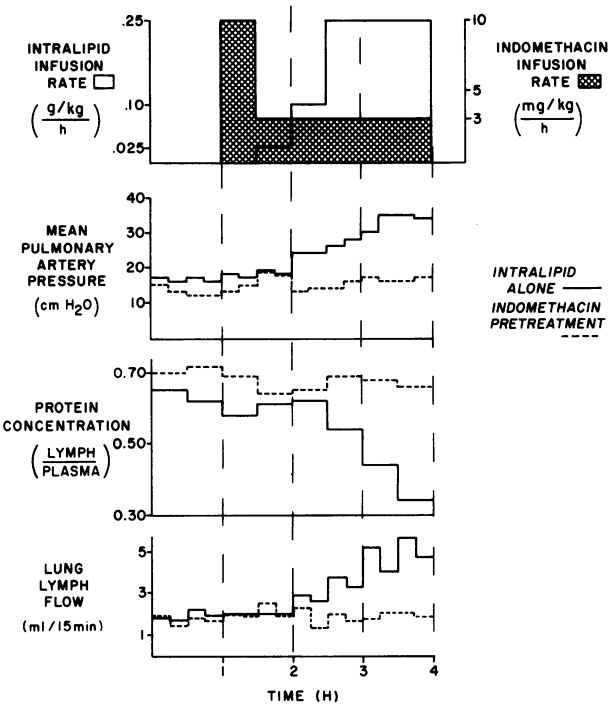

FIGURE 3 Responses of lung vascular pressures, lymph flow, and protein concentration to fat emulsion infusion in a sheep with and without indomethacin pretreatment.

Indicator dilution studies. Indicator dilution studies before and during fat emulsion infusion under all three protocols are summarized in Table IV. Percentage recoveries (mean±SE) of ^{125}I-albumin, [^{3}H]-water, and [^{14}C]urea, relative to [^{51}Cr]erythrocytes, were respectively 100±1, 97±1, and 95±1. Neither cardiac output nor extravascular lung water changed significantly in any of the groups. Pulmonary vascular resistance nearly doubled during fat emulsion infusion and heparin did not affect this response. Indomethacin pretreatment prevented the rise in pulmonary vascular resistance. Lung vascular permeability surface area product for [^{14}C]urea was calculated by both methods and was unchanged from base line in all experimental groups.

DISCUSSION

In these studies intravenous fat emulsion infusion in unanesthetized sheep caused a dose-dependent, reversible increase in pulmonary artery pressure, a decrease in arterial oxygen tension, and an increase in transvascular fluid filtration reflected in increased lung lymph flow. The increased filtration appeared to be solely a result of increased pressure in exchanging vessels because lymph protein concentration de-

TABLE III

Triglyceride and Free Fatty Acid Measurements in Plasma and Lymph in Three Experiments

Condition	Sheep number	Sample source	Base line		Experimental	
			Tri-glyceride	Free fatty acid	Tri-glyceride	Free fatty acid
			mgm/dl	*μmol/ml*	*mgm/dl*	*μmol/ml*
Intralipid	VS49e5	Plasma	46	0.636	350	1.290
		Lymph	26	0.350	23	0.258
Heparin/ Intralipid	VS48e7	Plasma	52	0.268	74	1.310
		Lymph	40	0.196	40	0.282
Indomethacin/ Intralipid	VS48e8	Plasma	24	0.360	256	1.440
		Lymph	17	0.230	32	0.360

creased with increasing lymph flow in the same way as our previously reported studies where lung microvascular pressure was increased by inflating a balloon in the left atrium (6). This strongly suggests that at least some of the increase in pulmonary vascular resistance was in post-capillary vessels. Indicator dilution measurements of [^{14}C]urea permeability surface area products also showed no increase in microvascular permeability. The fat emulsion effect was apparently limited to the lung circulation because there was no change in cardiac output or arterial pressure.

If the pulmonary hypertension and hypoxemia caused by fat emulsion were due to increased blood viscosity (25) or to a diffusion defect caused by hyperlipemia (26), then heparin-induced lipolysis should prevent those changes (5, 26). In the studies where we gave heparin in doses sufficient to clear the serum of triglycerides, sheep responded to fat emulsion the same way as when no heparin was given. The effects of fat emulsion on the lung circulation in these experiments cannot be attributed to hyperlipemia per se.

Indomethacin, a potent inhibitor of prostaglandin synthesis both prevented and reversed the pulmonary vascular effects of fat emulsion infusion. In previous studies we have shown that the classical prostaglandins E_2 and $F_{2\alpha}$ are not very potent pulmonary

TABLE IV

Summary of Indicator Dilution Studies

	Average body weight±SEM	Condition			
		Base line	Intralipid	Heparin/ Intralipid	Indomethacin/ Intralipid
	kg				
Cardiac output, *ml/s* (mean±SEM)	35±4 (n = 10)	71±6 (n = 20)	73±5 (n = 8)	67±4 (n = 7)	62±6 (n = 5)
Extravascular lung water, *ml* (mean±SEM)	35±4 (n = 10)	187±15 (n = 20)	164±16 (n = 8)	166±12 (n = 7)	217±8 (n = 5)
Pulmonary vascular resistance, *cm* H_2O/ml × s (mean±SEM)	34±3 (n = 10)	0.296±0.037 (n = 19)	0.484*±0.056 (n = 8)	0.583*±0.059 (n = 6)	0.354±0.033 (n = 5)
[^{14}C]Urea permeability surface area product, *ml/s* (mean±SEM)					
Integral extraction	35±4 (n = 10)	15.9±1.6 (n = 20)	12.8±1.7 (n = 8)	16.0±2.0 (n = 7)	15.2±2.5 (n = 5)
Krogh convolution	35±4 (n = 10)	9.2±1.2 (n = 19)	8.3±1.4 (n = 7)	8.5±1.6 (n = 7)	8.1±1.8 (n = 5)

* Base-line values were averaged for brevity, but statistics were done on paired base line and experimental studies. All three experiments were not done in every sheep.

‡ Significantly different from paired base line ($P < 0.05$).

vasoconstrictors in sheep, but that the labile endoperoxide intermediate prostaglandin H_2 and its stable 9-methylene cyclic ether analog are very potent and specific vasoconstrictors in the lung circulation (27). Others have reported similar findings in other preparations (28). The effects of lipid emulsion infusion are remarkably similar to the effects of prostaglandin H_2 infusion. Both agents caused a dose-related increase in pulmonary artery pressure without affecting cardiac output or systemic pressures. Both agents caused lung lymph flow to increase and lymph protein concentration to fall. In both cases, the relationship between lymph/plasma protein concentration ratio and lymph flow was like that seen with mechanically increased pulmonary vascular pressures (6). Based on our data, the most plausible explanation for the fat emulsion effect is that it is mediated through the prostaglandin system and that the cyclic endoperoxides are the mediators.

How does fat emulsion infusion increase prostaglandin synthesis? Wicks and coworkers (29) doubled the mean pressure in the lobar artery of an isolated perfused dog lung by injecting a 100 μg/kg bolus of arachidonic acid into the perfusate. From the composition of the fat emulsion we used, we calculate that our sheep received 60 μg/kg × h arachidonic acid at the highest fat emulsion infusion rate. This effect could be due to the arachidonic acid. Also, a number of experimental manipulations including inflation (30), pulmonary embolism (31) and endotoxin injection (32) cause the lung to increase prostaglandin release. It is possible that perfusion of the lung with blood containing high fat concentrations causes increased prostaglandin synthesis independent of substrate concentration. If so, this cannot be triglyceride dependent because the response was not blocked by heparin which clears the serum of triglycerides.

In these studies, infusion of indomethacin alone caused no prolonged effects on lung vascular pressures or lymph flow. This is different from the effects of salicylate which is also an inhibitor of prostaglandin synthesis. In the same sheep preparation used in this study, we showed that salicylates increase pulmonary vascular permeability and cause pulmonary edema (33). The indomethacin results may mean that the salicylate effect is not due to inhibition of prostaglandin synthesis, but rather to some other salicylate action or that, in vivo, aspirin is a more effective inhibitor of prostaglandin synthesis.

We conclude that, in unanesthetized sheep, intravenous infusion of a fat emulsion in doses recommended for use in humans causes pulmonary hypertension, increased lung microvascular pressure, and arterial hypoxemia. Because these effects are not changed by heparin-induced lipolysis but are both prevented and reversed by indomethacin, they are probably mediated by the prostaglandin system. Based on earlier studies (27) we believe the prostaglandin cyclic endoperoxides are the most likely mediators. We do not know yet whether the results reported here are relevant to fat embolism or endogenous hyperlipemic states.

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