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Pulmonary Microembolism in the Canine Model: Report of a Pilot Study

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Use of in-line final filters to prevent the infusion of foreign particulates has lowered the rates of postinfusion phlebitis in several controlled studies. The systemic effect of particulate infusion, however, has not been thoroughly studied. In this study, 12 mongrel dogs recovering from a right pneumonectomy were studied following infusion of various-sized particulates. Ten of the dogs were infused with either 10 or 40 million, 9 or 25 μm, latex particles. The remaining two dogs were control animals. Hemodynamic parameters were monitored in each animal. At death or 72 hours following particle injection, the left lung was examined grossly and histologically. Changes in hemodynamic parameters were not seen. Three of the dogs became clinically ill 48 hours following microsphere injection. All dogs injected with particles had multiple discrete punctate areas of hemorrhagic pulmonary infarction. The control dogs showed no sign of clinical illness or pulmonary injury. More sophisticated animal and human studies are required to fully determine the physiologic effect of injected particles. (Henry Ford Hosp Med J 1986;34:109-12)

Use of final in-line filters to prevent the infusion of foreign particulates (in the size range of 1 to 25 μm) present in intravenous (IV) solutions, drugs, and infusion sets continues to be controversial (1). The local effect of particulate infusion appears to be an increased rate of postinfusion phlebitis, as several well-controlled double-blind studies with large numbers of patients have documented (2-8) (Table). Falchuk et al (8) recently demonstrated that postinfusion phlebitis rates double at the end of 72 hours when filters are not used.

The effect of injected particulates on tissues away from the injection site and/or the systemic effects of these particulates have not been studied thoroughly, and most published reports consist of case reports of some specific adverse effect (9-12). Animal studies have been published that give some insight into the systemic distribution of injected particles (10,13-16).

Experimental work to date has focused on the distribution and clinical effects of infused particles in healthy dogs. However, the pulmonary reserve of the dog is quite good, and the lack of changes seen in clinical parameters may not accurately reflect the susceptibility of clinically ill patients to the infusion of large numbers of particles during a prolonged hospitalization. In an attempt to more closely mimic the clinical situation, we have evaluated the effect of particulate infusion in a "compromised" animal model with decreased pulmonary reserve during its recovery from surgery.

Materials and Methods

Twelve mongrel dogs weighing between 15 and 25 kg were selected for these acute experiments. These dogs underwent a left pneumonectomy two weeks before the planned embolism experiments. This was carried out to reduce the pulmonary vascular reserve of the animals so that any measurable effects could be magnified. Before initiation of the embolism protocol, each dog was noted to be healthy and its thoracotomy wound well healed.

Table
Summary of Studies of the Effect of In-line Filtration on the Incidence of Postinfusion Phlebitis

Author	Year	No.	Phlebitis, Filter	Phlebitis, No Filter
Ryan et al (2)	1973	100	2%	45%
DeLuca et al (3)	1975	146	12%	61%
Maddox et al (4)	1977	120	20%	60%
Evans et al (5)	1976	50	8%	56%
Rusho and Bair (6)	1979	150	6%	27%
Allcutt et al (7)	1983	194	9%	24%
Falchuk et al (8)	1985	541	25%	58%

For the embolization protocol, the dogs were anesthetized with thiopental sodium intubated and ventilated with a volume piston-type respirator. A Swan-Ganz triple lumen thermal dilution catheter was placed via a right internal jugular cutdown. Accurate placement was confirmed by wave pressure tracing, which showed a wedge position in the right pulmonary artery. The right femoral artery was cannulated for pressure monitoring of systemic pressure via a Walthem strain gauge transducer connected to a Gilsen recorder. The right femoral vein also was cannulated to allow a site for supplemental anesthesia as needed and for venous sampling.

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The animals were allowed to stabilize before obtaining baseline arterial blood pressure, pulse, arterial blood gases, pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure, and cardiac output via thermal dilution technique. Following microsphere embolization, these measurements were repeated at 15, 30, 45, and 60 minute intervals following embolization.

Two control animals received only saline infusions. Ten experimental animals were infused with nonreactive, nondegradable microspheres manufactured by the Minnesota Mining and Manufacturing Company. Dogs #3, 4, and 5 received 1×10^7 of the 9 μm microspheres infused over five minutes via the right atrial port of the Swan-Ganz catheter; dogs #6 and 7 received 4×10^7 of the 9 μm microspheres. Dogs #8 through 12 received 25 μm microspheres over five minutes via the right atrial port of the Swan-Ganz catheter, with dogs #8, 9, and 10 receiving 1×10^7 and dogs #11 and 12 receiving 4×10^7 of the microspheres.

Following completion of the one hour study period, the catheters were removed and the groin wounds sutured. The dogs were allowed to recover with anticipation of repeating the measurements 72 hours postinfusion. However, dog #11 (who received 4×10^7 25 μm particles) died in less than 24 hours, and dog #6 (who received 4×10^7 9 μm particles) died at 48 hours.

Shortly after the deaths of dogs #6 and 11, and 72 hours following the recording period for the surviving animals (dogs #1 through 5, 7 through 10, and 12), autopsies were performed and the right lungs examined for gross evidence of injury.

Results

Data obtained from the 12 experimental animals were recorded for each group (control, 9 μm/microspheres low dose, 9 μm/microspheres high dose, 25 μm/microspheres low dose, and 25 μm/microspheres high dose).

The mean arterial pressure did not vary significantly between groups during the one hour study period. There were no consistent changes in arterial blood gases (PO_2, PCO_2, pH) during the one hour study period.

The two animals who received 25 μm particles (dogs #8 and 11) had an early rise in mean pulmonary artery pressure (PAP) which returned toward baseline within one hour. Dogs #3 and 4 who received 9 μm particles had an early fall in PAP which also returned toward baseline by one hour. However, there were no significant differences between the study groups.

The right atrial pressure changes were small; however, an early rise in pressure was seen in the 25 μm infused animals (dogs #8 and 11), while the 9 μm infused animals (dogs #3 and 4) had an early fall in pressure. In both groups, these pressures returned toward normal by one hour. Again, there appeared to be no significant differences between the groups. No changes occurred in the pulmonary wedge pressure during the one hour study period. There were also no consistent changes in the cardiac output during the one hour study period.

The pulmonary artery resistance changes were small, but of interest. An early rise in resistance was seen in the 25 μm particle infused animals (dogs #8 and 11) compared to the fall in resistance seen in the 9 μm infused animals (dogs #3 and 4). However, when the groups were compared, no significant differences were apparent. The changes seen in the total pulmonary resistance were similar to those noted with pulmonary artery resistance. Also, no consistent changes were seen in total systemic resistance during the one hour study period.

Autopsy

Deaths—Dog #11 (4×10^7 25 μm particles) died 24 hours postembolization. The lung had multiple areas of patchy mottling consistent with hemorrhagic infarction, which was quite severe. Dog #6 (4×10^7 9 μm particles) died 48 hours postembolization. The lung had multiple punctate areas consistent with hemorrhagic infarction.

Survivors—For the control dogs (dogs #1 and 2), no gross pulmonary pathology was noted. Dogs #8, 9, 10, and 12 (25 μm particles) were killed at 72 hours. The lungs were quite heavy and appeared beefy with punctate hemorrhages. (Dog #8 appeared ill at 72 hours sample time.) A photomicrograph from dog #12 demonstrates the microspheres lodged in a pulmonary arteriole with inflammatory response at 72 hours (see Figure). Dogs #3, 4, 5, and 7 (9 μm particles) were killed at 72 hours. The lungs were beefy with multiple small punctate hemorrhages.

Discussion

In a series of investigations focusing on the consequences of particulate contamination of parenteral fluids and drugs, we have demonstrated that a) substantial numbers of particulates are present in routinely administered fluids and drugs (1), b) these particulates appear to react specifically with vascular endothelium (17), c) the particulates significantly influence the incidence of infusion phlebitis (2-8), and d) the particulates can be prevented from entering the patient by using a 0.22 or 0.45 μm in-line filter (3,18). Use of filters to eliminate particulate administration to the patient receiving IV solutions and drugs is associated with a significant decrease in the incidence of infusion phlebitis, which results in decreased cost and discomfort with IV therapy (18,19).

Although filtration was found to decrease the incidence of infusion phlebitis, it was also associated with a decrease in WBC count and sedimentation rate when compared to patients receiving unfiltered fluids (3,18). The reduction in WBC count appears to be a pure filtration phenomenon which is not associated with the development of infusion phlebitis (15). In a series of animal studies designed to investigate the systemic impact of particulate infusion manifested as an increased white count, sedimentation rate, and fever in humans, we have determined that a) inert particulates cause leucocytosis when infused in the venous system of dogs (10,13); b) the distribution of infused particulates varies with particle size (14); c) particulates smaller than 7 μm are phagocytized by white cells and retained within the liver and spleen (14); d) small microspheres (3 μm) tend to agglomerate when administered intravascularly, presumably due to protein adherence and a large surface-to-mass ratio (14); and e) particulates in the size range studied, from 3 to 25 μm, are initially retained in the lungs and slowly redistribute from the lungs to other organs (14).

The infusion of even very small particulates (3 μm) was associated with an immediate rise in WBCs (25% to 40% increase within 2 hours) (13), and approximately 20% of 3 μm micro-

sphere particulates are retained in the lung during the first hours following infusion (14). These findings have led to a series of investigations studying the effect of microsphere particulate embolization on the canine lung. The initial studies focused on the immediate postinfusion period (up to four hours postinfusion) in an intact animal with no significant changes in either hemodynamics or histology being found. The lack of observable response was attributed to the enormous pulmonary reserve in the dog (10,13,14).

This second series of experiments was undertaken to investigate the impact of microsphere particulate embolization in animals with depletion of pulmonary reserve by surgical excision of one lung. In these animals, as well, no acute hemodynamic changes were observed even with doses of 40×10^7 25 μm microspheres. These animals, however, did exhibit marked clinical deterioration over the next 24 to 72 hours with death occurring in 33% of the studied animals within 48 hours. The surviving animals were killed at 72 hours and subsequently found to have multiple punctate hemorrhagic pulmonary infarcts interpreted as being secondary to the microsphere emboli.

Similar findings have been made in both animal and human studies of macroparticulate infusions associated with multiple blood transfusions (20-28). Studies focusing on the first 24 hours following transfusion have had equivocal results (21,22,26,27). Studies following either the experimental animals or patients up to 48 to 72 hours after transfusion have found histologic and clinical changes (decreased PO_2 and increased dead space) consistent with a microembolic pulmonary injury (20-26). Curiously, 20, 40, and 170 μm blood filters have not been consistently effective in preventing the transfusion-associated pulmonary injury (20,22,23,29,30). This failure has been attributed to damage caused by particles small enough to pass through the large pore-sized filters (20,30). It has also been observed that blood filters begin to generate an increased number of microparticulates after the passage of several units of blood, thereby adding to the embolic load received by the patient (20,30).

We feel that the available evidence supports the need for small pore-sized filtration as a means of reducing both the incidence of infusion phlebitis and the potential for pulmonary injury secondary to particulate embolism. The role of microparticulates as the etiologic agent in pulmonary injury needs to be verified. The nature and the time course of the microembolic lesion needs to be further defined in the experimental animal with follow-up studies to confirm these findings in humans.

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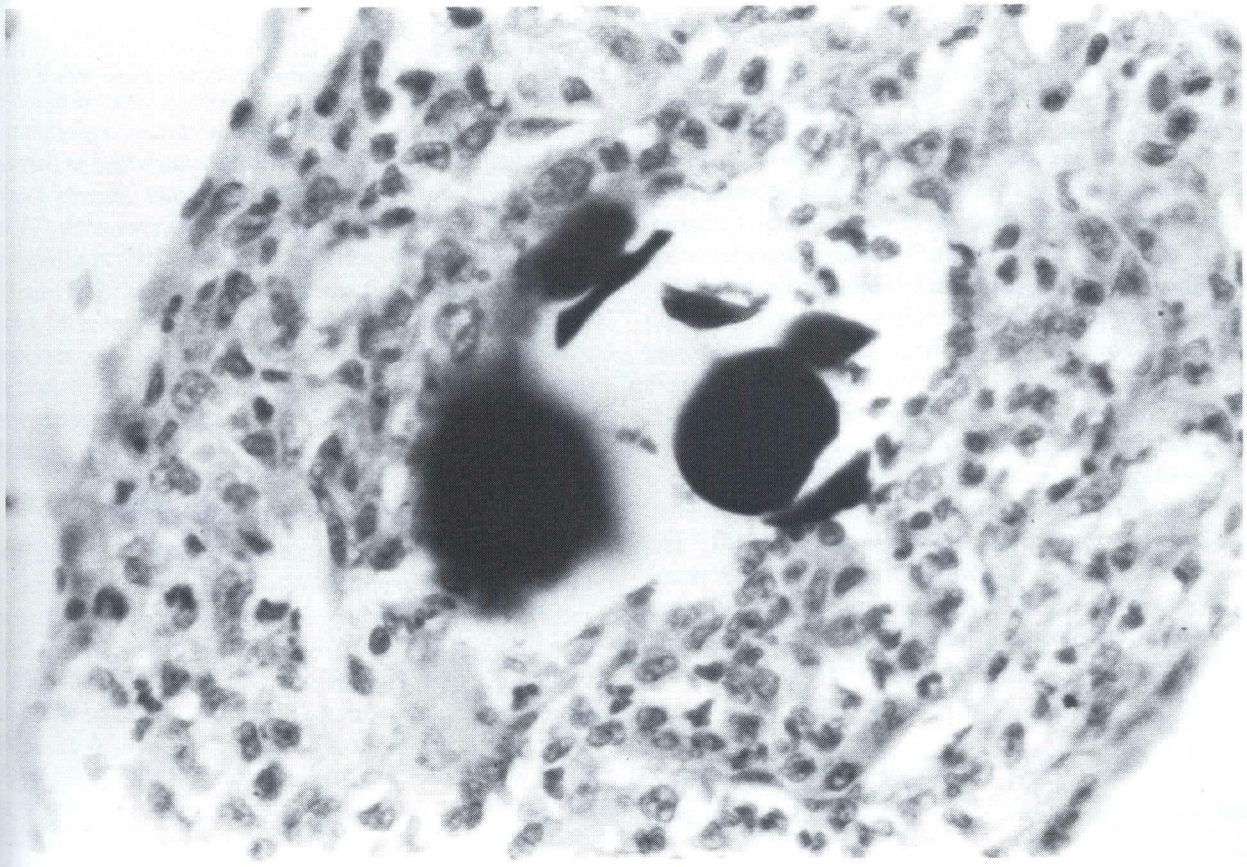

Figure—Photomicrograph demonstrating microspheres lodged in pulmonary arteriole with inflammatory response seen at 72 hrs.

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