The Effects of Wetting and Antifoaming Agents on Pulmonary Surfactant

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The effects of a wetting agent (Alevaire®), and an antifoaming agent (ethyl alcohol) on normal canine pulmonary surfactant were studied *in vitro* and *in vivo*. Surface tension–surface area characteristics of the surfactant changed progressively when these agents were added *in vitro* until, finally, the curves drawn were indistinguishable from those of the wetting and antifoaming agents alone. While both agents altered the compressibility of surfactant, the Alevaire exerted its effect at minimum surface area while changes due to alcohol were first seen at maximum surface area. Since compressibility was altered before minimum values for surface tension changed, the surfactant activity index was not reliable for evaluating normal compressibility.

Pulmonary surfactant extracted from the lungs of nine of ten dogs that breathed ultrasonic aerosols generated from Alevaire had normal surface tension properties. Surfactant extracted from the lungs of animals that breathed alcohol aerosol was normal in eight of ten dogs. We conclude that, while wetting and antifoaming agents in high concentrations change the normal surface tension–surface area relationships of surfactant *in vitro*, continuous breathing of aerosols of these agents for eight hours does not change the surface tension characteristics of the alveolar-lining layer.

IT HAS BEEN POSTULATED that if wetting agents were spread over the normal lining material of the lung, the surface tension which resulted at the air–liquid interface would be entirely that of the wetting agent. This would prevent the interfacial film from appreciably changing surface tension characteristics as the surface area was compressed, resulting in unstable alveoli and atelectasis at normal transpulmonary pressures.[1] Recently, ultrasonic nebulizers that produce large volumes of small-particle aerosols have been introduced for clinical use. The possibility that with continuous administration sufficient wetting agent could be deposited in the periphery of the lung to alter the normal surface tension properties of pulmonary surfactant must be considered. A similar situation might be possible when antifoaming agents are delivered in small-particle form for extended periods, *e.g.*, during treatment of acute pulmonary edema with ethyl alcohol aerosol.

Studies were conducted *in vitro* and *in vivo* to determine whether aerosols generated from a wetting agent (Alevaire §), or an antifoaming agent (ethyl alcohol) altered the surface tension characteristics of pulmonary surfactant.

Methods

IN VITRO STUDIES

In vitro studies were performed on a modified Wilhelmy balance.[2] The substances to be analyzed were added to a teflon-lined tray which contained 150 ml saline solution (0.9 per cent). Surface tension of the surface film was measured as a vertical force exerted on a platinum strip immersed through the surface at a 0° angle. The strip was suspended from a strain gauge and the displacement was transmitted via a Sanborn model 311-A transducer to a Mosely XY recorder, model 2D-2A. The surface area of the film was alternately compressed and expanded at a frequency of

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§ A sterile aqueous solution containing tyloxapol 0.125 per cent, sodium bicarbonate 2 per cent, glycerin 5 per cent, and distilled water.

one cycle every 90 seconds. The maximum surface tension was reached on expansion of the film to 100 cm² and the minimum surface tension on compression to an area of 20 cm². The surface area–surface tension loop was recorded on the recorder.

For each determination of surface tension (ST) a surfactant activity index (SAI) was calculated according to the equation suggested by Clements and co-workers [3]:

$$SAI = 2\frac{(ST\ maximum - ST\ minimum)}{(ST\ maximum + ST\ minimum)}$$

The range of possible values for SAI is from 0 to 2. Lung extracts with normal surfactant activity have an SAI greater than 1.25 and lung extracts with loss of surface activity have a low SAI. SAI thus serves as an index of surface compressibility, with high values indicating that alveolar lining layers are capable of maintaining a stable surface tension–surface area relationship which promotes alveolar stability.

Wetting Agent, Alevaire

The balance was calibrated by measuring the surface tension activity of normal saline solution (0.9 per cent) before each experimental run. The surface tension characteristics of Alevaire were then measured as from 1 to 30 ml were added to 150 ml of saline solution in the trough.

The effect of wetting agent on normal pulmonary surfactant was determined in the following manner. Pulmonary surfactant was extracted from the lungs of a normal dog by the foam fractionation method.[4] The foam was air-dried, after which 10 mg of surfactant (dry foam) were added to 150 ml of normal saline in the trough. The surface tension characteristics of this material were determined as outlined above. After readings were recorded, increasing increments of Alevaire (from 1 to 30 ml total dose) were added to the trough. Measurements of surface tension activity were made after each addition of wetting agent. To check whether adding Alevaire physically disturbed the surfactant film, thus altering the results, the experiment was repeated by introducing the surfactant after the wetting agent had been added to the saline solution. The results were comparable with both methods.

Antifoaming Agent (Ethyl Alcohol)

The surface tension characteristics of absolute ethyl alcohol (1 to 100 ml in 150 ml saline solution) were tested in the trough as described above. Surface tension activity of 10 mg of normal surfactant was then determined and the effect on surfactant of adding from 1 to 100 ml of absolute ethyl alcohol (in 5–10 ml increments) measured.

Table 1. Results of Adding Alevaire to a Subphase of 150 ml Normal Saline Solution (0.9 per cent) in Each of Two Troughs*

Alevaire in Trough (ml)	10 mg Surfactant Added			No Surfactant Added		
	Surface Tension (dynes/cm)		SAI	Surface Tension (dynes/cm)		SAI
	Min.	Max.		Min.	Max.	
0	8	48	1.43	—	—	—
1	5	58	1.68	27	56	0.70
5	4	58	1.74	22	53	0.83
10	4	56	1.73	27	57	0.71
20	9	56	1.45	27	56	0.70
25	25	55	0.75	28	56	0.67
30	22	55	0.86	29	56	0.64

* The surface of one trough contained 10 mg of normal surfactant; the other trough had no surfactant. Minimum surface tension (ST) was reached on compression of the surface film to 20 cm² and maximum on expansion to 100 cm². The calculated surfactant activity index (SAI) is also listed.

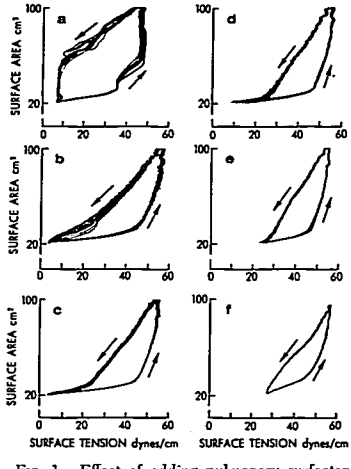

FIG. 1. Effect of adding pulmonary surfactant and/or Alevaire on surface tension–surface area loops recorded when the surface area of a trough containing 150 ml of saline solution (0.9 per cent) was alternately compressed to 20 cm^2 and expanded to 100 cm^2. 1*A*, 10 mg surfactant only; 1*B*, 10 mg surfactant plus 5 ml Alevaire; 1*C*, 10 mg surfactant plus 10 ml Alevaire; 1*D*, 10 mg surfactant plus 20 ml Alevaire; 1*E*, 10 mg surfactant plus 25 ml Alevaire; 1*F*, 25 ml Alevaire only.

IN VIVO STUDIES

Twenty healthy adult greyhound dogs were anesthetized with sodium pentobarbital (Nembutal®), 25 mg/kg, injected intravenously, and placed in the supine position. Additional 50-mg increments of pentobarbital were administered as needed during the experiment to prevent spontaneous movement. Respiration and lid reflex remained active throughout. A cutdown was performed and a polyethylene catheter (I.D. 0.066″) threaded through the left femoral artery into the abdominal aorta. A modified Carlens endotracheal catheter was passed via a tracheostomy to isolate the two mainstem bronchi. Correct placement of the catheter was determined by auscultation during alternate inflation of each lung.

Baseline studies of all animals included determination of arterial *p*H, P_{O_2} and P_{CO_2} using direct-reading electrodes in the IL 113-S1 apparatus. The electrodes were kept at 37 C and recalibrated immediately before each analysis. Samples were withdrawn anaerobically from the aortic catheter into siliconized, heparinized syringes and analyzed within two to three minutes.

One limb of the Carlens catheter was connected via a T piece to a DeVilbiss model 880 ultrasonic nebulizer[*] containing half-normal saline solution (0.45 per cent). The opposite lung was connected in similar fashion to another ultrasonic nebulizer containing Alevaire (ten dogs), absolute ethyl alcohol (five dogs) or 25 per cent ethyl alcohol (five dogs). The nebulizers were set to deliver the equivalent of 6 ml of liquid in aerosol form per minute. The actual output of each nebulizer was checked hourly, and they were tuned as necessary. An open-ended reservoir of approximately 300 ml was added to the distal end of the T to prevent dilution of the aerosol with room air. Rebreathing was prevented by the flow of 35 l/min of fresh, aerosol-ladened air through the system. The animals breathed these aerosols continuously for eight hours.

At two, four, six and eight hours after the beginning of aerosol breathing, arterial blood was drawn for analysis of blood gases. In addition, alcohol concentrations in the blood of animals that breathed alcohol aerosol were determined prior to the experiment and after two, four, six, and eight hours.[5] The pre-experimental values were subtracted from subsequent values to minimize the effects of other reducing substances on the blood alcohol level.

At the completion of the eight-hour experiment, necropsies were performed. (Surviving animals were sacrificed.) The placement of the endotracheal catheter was confirmed and the right and left mainstem bronchi were clamped individually. The lungs and trachea were removed intact and surfactant was obtained from the right and left lungs individually by the foam fractionation method. The foam was air-dried. The surface tension characteristics of 10 mg of dry foam were then determined.

To determine whether the aerosol reached the periphery of the lung, a Carlens tube was

[*] Courtesy of the DeVilbiss Company.

passed in another dog which breathed aerosol generated from a 2:1 mixture of Alevaire and sodium fluorescein 5 per cent into the left limb of the tube for 35 minutes while the right limb was open to air. The dog was sacrificed with an overdose of sodium thiopental (Pentothal®) and the lungs inspected under ultraviolet light for evidence of fluorescence.

Results

Wetting Agent

In vitro: No difference was found in surface tension activity whether 1 or 30 ml of Alevaire were added to the 150 ml saline solution. The average minimum surface tension was 27 dynes/cm and the average maximum 56 dynes/cm (table 1). Addition of 1 ml Alevaire to normal pulmonary surfactant did not alter the surface tension–surface area loop. When increasing amounts were added to normal surfactant, however, there was a progressive decrease in the surface compressibility of the film, with a narrowing hysteresis loop (fig. 1). In spite of the change in hysteresis, normal values for minimum surface tension and surfactant activity index were obtained until 25 ml Alevaire had been added (table 1). When 25 ml or more had been added to the surfactant film the narrowed portion of the loop disappeared and the surface tension readings obtained on compression of the film to 20 cm^2 were similar to those seen with Alevaire alone (fig. 1).

In vivo: All ten dogs that breathed aerosol generated from Alevaire into one lung and aerosol generated from half-normal saline solution (0.45 per cent) into the other lung survived the eight-hour experiment. A significant decrease in arterial oxygen tension was seen when the animals breathed aerosol ($P < 0.001$) (fig. 2). There was also a slight decrease in Pa_{CO_2} with a corresponding increase in *p*H.

At necropsy the most dependent portions of both lungs were heavy and discolored reddish-purple in all dogs. There was no visible difference between lungs that received Alevaire aerosol and those exposed to saline solution. The remaining areas of the lungs were normal in appearance. When the lungs were

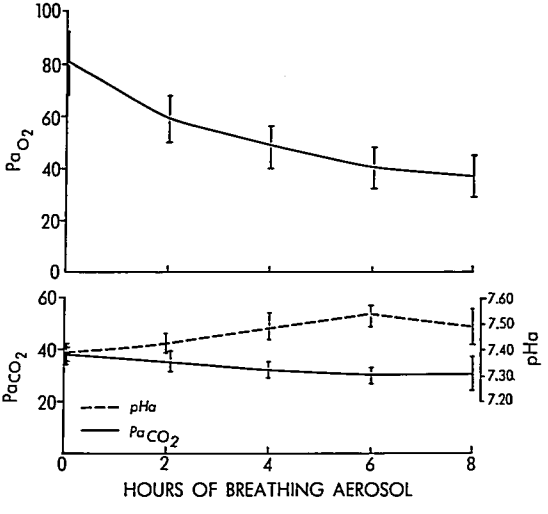

FIG. 2. Arterial blood gas and *p*H determinations from dogs that breathed aerosol generated from Alevaire into one lung while breathing aerosol generated from half-normal saline solution (0.45 per cent) into the other lung. Each point represents the mean mean value of ten dogs. The standard deviation is also indicated.

TABLE 2. Surface Tensions and Surfactant Activity Indexes (SAI) of 10-mg Samples of Surfactant*

Dog	Alevaire Lung			Saline (0.45 per cent) Lung		
	Surface Tension (dynes/cm)		SAI	Surface Tension (dynes/cm)		SAI
	Min.	Max.		Min.	Max.	
367	10	62	1.44	9	61	1.49
368	19	68	1.13	9	59	1.47
369	11	70	1.46	15	68	1.28
371	9	63	1.50	10	56	1.39
385	7	64	1.61	4	49	1.70
386	7	64	1.61	8	67	1.57
387	9	62	1.49	1	48	1.92
388	13	69	1.37	9	71	1.55
389	8	55	1.49	6	56	1.61
415	4	49	1.70	6	60	1.64
MEAN	9.7	62.6	1.48	7.7	59.5	1.56
S.D.	4.1	6.4	0.16	3.8	7.7	0.18

* Extracted by the foam fractionation method after dogs breathed Alevaire aerosol into one lung and saline (0.45 per cent) aerosol into the other for eight hours. Minimum surface tension was reached on compression of the surface film to 20 cm²; maximum on expansion to 100 cm².

foamed to extract surfactant, all areas including the dependent portions could be inflated easily.

The surface tension readings and SAI of pulmonary surfactant extracted from all the lungs exposed to saline aerosol were normal (table 2). Surfactant extracted from lungs exposed to Alevaire gave normal results in all but one animal, number 368. The surface tension–surface area loop showed normal hysteresis in all cases. The narrowed hysteresis loop observed in the *in vitro* studies was not seen (fig. 3A, B).

ANTIFOAMING AGENT (ETHYL ALCOHOL)

In vitro: Ethyl alcohol decreased the surface tension of normal saline solution in the trough proportional to the amount of alcohol added. Surface tensions of the saline–alcohol mixtures were unaffected by changes in surface area (table 3).

When 1 ml alcohol was added to a trough containing a surface film of 10 mg of normal surfactant, the shape of the surface tension–surface area loop and the absolute readings and SAI were normal. As increasing amounts

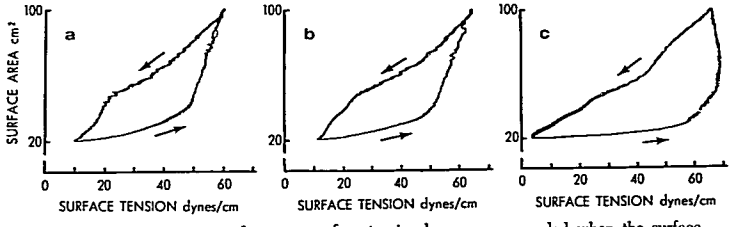

FIG. 3. Representative surface area–surface tension loops were recorded when the surface area of a trough containing 150 ml of normal saline solution (0.9 per cent) and 10 mg of surfactant was alternately compressed to 20 cm² and expanded to 100 cm². 3A, surfactant from a lung exposed to saline aerosol; 3B, surfactant from a lung exposed to Alevaire aerosol; 3C, surfactant from a lung exposed to alcohol aerosol.

of alcohol were added, however, there was a diminution of the width of the hysteresis loop (fig. 4). When at least 10 ml alcohol had been added there was a marked loss of surface compressibility at the onset of compression; there was also a decrease in the maximum surface tension reached when the surface film was expanded. With 20 ml alcohol, surface tension remained at a maximum when the film was compressed until the surface area had been compressed from 100 cm^2 to approximately 50 cm^2. On further compression to 20 cm^2 the film displayed a hysteresis loop and normal values for minimum surface tension were obtained. In spite of the lowered maximum surface tension readings and the altered compressibility shown on the surface tension–surface area loop, normal SAI's could be calculated (table 3). When at least 75 ml absolute alcohol were added, hysteresis disappeared and a straight line at 28 dynes/cm was drawn regardless of surface area.

In vivo: Three of the five dogs that breathed aerosol generated from absolute ethyl alcohol died before the eight-hour experiment was completed. High blood alcohol levels appeared to be a significant contributing factor (table 4). One dog which breathed aerosol generated from 25 per cent ethyl alcohol died after six hours, but the blood alcohol level was considerably lower.

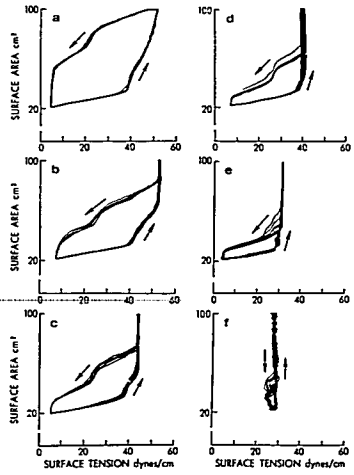

FIG. 4. Effect of adding pulmonary surfactant and/or absolute ethyl alcohol on surface tension–surface area loops recorded when the surface area of a trough containing 150 ml saline solution (0.9 per cent) was alternately compressed to 20 cm^2 and expanded to 100 cm^2. *4A*, 10 mg surfactant only; *4B*, 10 mg surfactant plus 5 ml alcohol; *4C*, 10 mg surfactant plus 10 ml alcohol; *4D*, 10 mg surfactant plus 20 ml alcohol; *4E*, 10 mg surfactant plus 50 ml alcohol; *4F*, 10 mg surfactant plus 100 ml alcohol.

TABLE 3. Results of Adding Absolute Ethyl Alcohol to a Subphase of 150 ml Normal Saline Solution (0.9 per cent) in Each of Two Troughs*

Alcohol in Trough (ml)	10 Mg Surfactant Added			No Surfactant Added
	Surface Tension (dynes/cm)		SAI	Surface Tension (dynes/cm)
	Min.	Max.		
0	4	52	1.71	66
1	5	60	1.69	63
5	7	53	1.53	57
10	6	45	1.53	44
20	7	42	1.43	42
30	5	38	1.53	39
50	4	32	1.56	26
75	16	27	0.51	—
100	26	28	0.07	26

* The surface of one trough contained 10 mg of normal surfactant; the other had no surfactant. Minimum surface tension (ST) was reached on compression of the surface film to 20 cm^2; maximum on expansion to 100 cm^2. The calculated surfactant activity index (SAI) is also listed. Since surface tension did not change with surface area in the second trough, SAI is zero for this group.

No significant changes were seen in pH_a or Pa_{CO_2} in either of the alcohol groups during the experiment. The scattergraph of Pa_{O_2} values (fig. 6) demonstrates a gradual decrease in Pa_{O_2} with time. Mean Pa_{O_2} values after two, four, six, and eight hours of aerosol inhalation were significantly lower than after breathing room air ($P < 0.05$). Although mean Pa_{O_2} was slightly higher in these dogs than in those that breathed Alevaire, the difference was not significant ($P > 0.15$).

At necropsy the lungs of both survivors and animals that died appeared similar to those of

the Alevaire group, except that the changes were not as prominent in lungs exposed to alcohol aerosol as in lungs exposed to saline solution or Alevaire. All lungs inflated easily during foaming.

The surface tension properties of surfactant extracted from the lungs of these animals and the corresponding surfactant activity index are listed in table 4. The surface tension readings, SAI and surface area–surface tension loops were normal in all dogs that breathed aerosol generated from absolute ethyl alcohol (fig. 3C). Two dogs that breathed aerosol generated from 25 per cent ethyl alcohol had abnormal surface tension readings and SAI in both lungs. The SAI of the lung exposed to alcohol aerosol was lower than that of the lung receiving saline aerosol in both animals, however. Blood alcohol levels in these dogs were not higher than those of animals who survived and had surfactant with normal surface tension characteristics (table 4).

Fluorescein: At necropsy the cuff on the left limb of the Carlens endotracheal catheter was found to occlude partially the left upper lobe bronchus. Brilliant fluorescence was seen at the surface of the lung exposed to aerosol generated from the Alevaire–fluorescein mixture. The superior portion of the left upper lobe and the right lung did not show gross fluorescence, however (fig. 5A). Representative cross sections from the right and left lower lobes are shown in figure 5B. While the intensity of fluorescence was greatest in the airway of the left lower lobe, it could be seen throughout the periphery, demonstrating that the aerosol reached the most peripheral parts of the lung (fig. 5C).

Discussion

Our results prove that both wetting agents and antifoaming agents can change the surface tension–surface area loops recorded on compression and expansion of normal pulmonary surfactant. This phenomenon is concentration-dependent, however, and small quantities of either of the two substances can be present without altering surface tension.

Although both substances alter the characteristics of the surface tension–surface area loop of surfactant *in vitro*, the patterns are quite different with the two compounds. Increasing the concentration of wetting agent causes a progressive decrease in the width of the hysteresis loop, most evident at minimum surface area. The changes in surface compressibility of the film suggest that the characteristics of the surfactant are altered, in spite of the fact that normal values for surface tension and surfactant activity index are re-

TABLE 4. Surface Tension Values and Blood Alcohol Levels*

	Dog	Surface Tension Data				Blood Alcohol Levels (mg/ml)			
		Alcohol		Saline					
		(dynes/cm) Min./Max.	SAI	(dynes/cm) Min./Max.	SAI	2 Hours	4 Hours	6 Hours	8 Hours
25 Per Cent Ethyl Alcohol	362	8/48	1.43	10/58	1.41	0.13	0.10	0.15	0.19
	363	26/57	0.75	15/60	1.20	0.10	0.07	0.05	Exp.
	364	9/61	1.49	10/54	1.38	0.23	0.53	0.89	1.45
	365	25/60	0.82	18/68	1.16	0.41	0.65	0.74	0.94
	366	8/57	1.51	13/63	1.32	0.41	0.60	0.92	1.08
Absolute Ethyl Alcohol	404	4/52	1.71	1/44	1.91	0.33	2.87	3.25	3.61
	405	4/50	1.70	4/40	1.64	3.45	4.64	5.74	Exp.
	409	1/50	1.92	1/46	1.91	7.82	Exp.	—	—
	410	5/53	1.65	3/45	1.75	3.48	7.97	Exp.	—
	414	7/66	1.63	7/65	1.61	2.70	3.02	3.41	4.57

* Surface tension data are reported separately for each lung in animals that breathed either 25 per cent ethyl alcohol aerosol or absolute ethyl alcohol aerosol into one lung while breathing half normal saline (0.45 per cent) aerosol into the other. Blood alcohol levels are reported during breathing of alcohol aerosol.

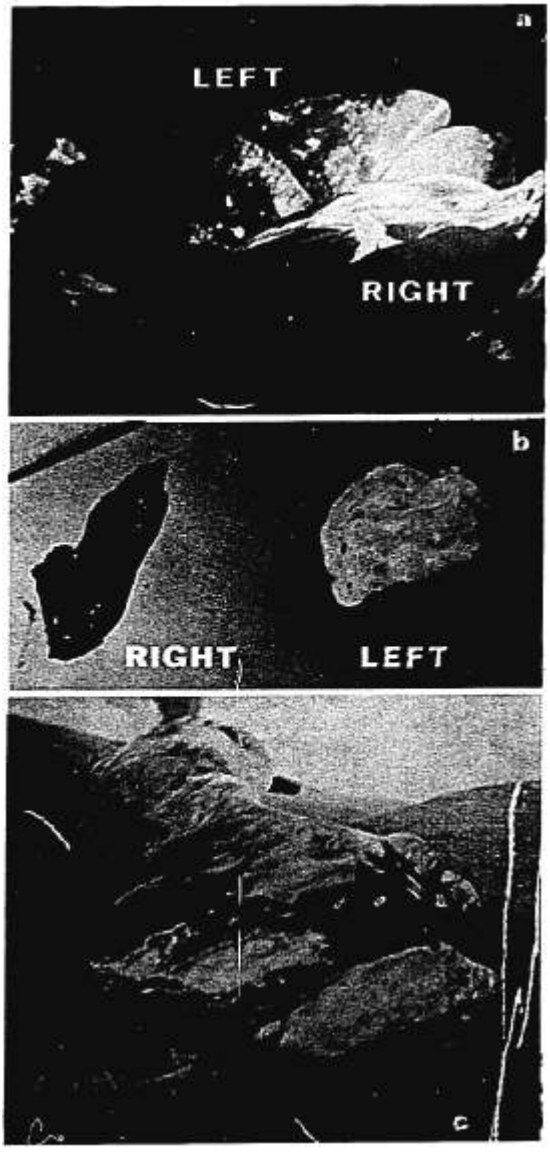

FIG. 5. Lungs from a dog after breathing Alevaire–fluorescein mixture into the left lung and room air into the right lung for 35 minutes. *5A*, fluorescence on the surface of the left lung but no fluorescence of the right lung. *5B*, representative cross sections from the right and left lower lobes. *5C*, fluorescence on cut section of the left lower lobe.

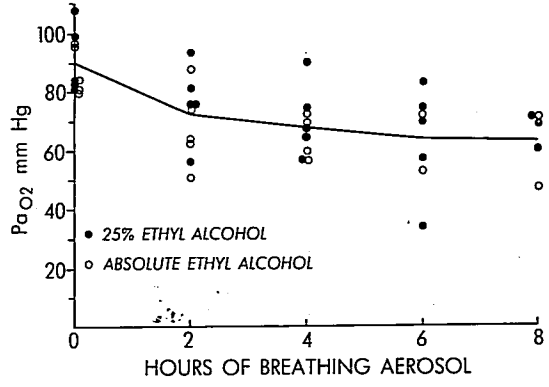

FIG. 6. Arterial oxygen tension was analyzed while dogs breathed aerosol generated from 25 per cent ethyl alcohol or absolute ethyl alcohol into one lung while breathing aerosol generated from half-normal saline solution (0.45 per cent) into the other lung. The value for each dog is listed separately. For better visualization of trends, the two alcohol groups are combined for plotting of the mean value.

corded. Higher concentrations of wetting agent, rather than lowering the surface tension, elevate the minimum surface tension obtainable to coincide with that of the Alevaire. As the concentration of alcohol added to surfactant is increased it decreases maximum surface tension obtained on expansion of the film and interferes with the normal hysteresis loop on compression. When the subphase contains at least 25 per cent alcohol the surfactant film no longer has the ability to change surface tension on changing surface area. If the alveoli were completely lined with either of these two compounds, they would not be as stable as when normal pulmonary surfactant is present at the air–liquid interface.

The alteration in the compressibility of the surface film, as demonstrated by the hysteresis loop, was striking when sufficient quantities of these two substances were added to normal pulmonary surfactant. A normal surfactant activity index was still calculated, however, since surface compressibility was altered independent of changes in minimum surface tension. This suggests that using SAI as the sole criterion for evaluating compressibility will not always indicate alteration in the characteristics of the surface film, because the shape of the surface tension–surface area loop must also be considered in assessing the compressibility of the film.

All animals that breathed aerosol showed decreases in Pa_{O_2}. This has been shown to occur when aerosols generated from half-normal (0.45 per cent) or normal saline solution (0.9 per cent) were inhaled.[6] We compared the Pa_{O_2} values of both the Alevaire and alcohol groups after six hours of aerosol-breathing in this study with results of the previous study. All aerosol groups had lower Pa_{O_2} values than anesthetized animals spontaneously breathing room air ($P < 0.05$).[6] However, no significant differences between the mean values of any of the groups that breathed aerosol were found ($P > 0.15$). The fall in Pa_{O_2} during aerosol-breathing has been shown to be secondary to intrapulmonary shunting or perfusion of nonventilated (possibly fluid-filled) alveoli.[6]

In both studies the dependent portions of the lungs looked similar and suggested fluid accumulation. The lungs exposed to alcohol aerosol did not appear as involved as those exposed to Alevaire or saline solution. The alcohol aerosol, being less dense, may have been absorbed from the alveoli more rapidly than the heavier saline or Alevaire particles.

Pulmonary surfactant extracted from the lungs of all but one of the dogs that breathed Alevaire aerosol had normal surface tension properties. Apparently, a greater concentration of this material is required than is supplied during an eight-hour exposure to con-

tinuous breathing of ultrasonic aerosol to alter or inhibit pulmonary surfactant *in vivo*. This was suggested in an earlier study in which dogs breathed Alevaire aerosol through an intact upper airway.[7] In the present study the aerosol was delivered directly into the trachea, eliminating precipitation in the pharynx or upper airway. It is doubtful that during clinical use a higher concentration of Alevaire could be delivered to the lung with existing equipment. Another possibility is that the aerosols did not reach the alveoli. The fact that fluorescence was seen in the periphery of the lung exposed to the Alevaire–fluorescein mixture but not in the contralateral lung suggests, however, that the aerosol did reach the alveoli. The possibility that sufficient wetting agent can be spread over the normal lining material of the lung to alter the interfacial tension and promote atelectasis, therefore, does not seem to be of clinical importance.

Pulmonary surfactant extracted from the lungs of eight of the ten dogs that breathed aerosol generated from alcohol had normal surface tension characteristics. This suggests that, although alcohol does change the surface tension–surface area properties of normal surfactant when added in sufficient quantities *in vitro*, the amount deposited during breathing of the aerosol is insufficient to cause similar changes at the air–liquid interfaces of the lung. Possible explanations for the abnormal readings in two dogs are: they had abnormal pulmonary surfactant prior to the experiment; or, since both lungs were affected, sufficient alcohol was absorbed and excreted through the contralateral lung to alter the pulmonary surfactant on that side as well. While the animals appeared healthy, we can only assume their lungs were normal prior to the experiment. It is unlikely that alcohol excreted from the contralateral lung altered pulmonary surfactant, since the blood levels reached in these two dogs were among the lowest in the series.

In conclusion, small quantities of wetting agent (Alevaire) and antifoaming agent (ethyl alcohol) do not alter the surface tension–surface area relationship of normal pulmonary surfactant *in vitro*. When increasing increments of these agents are added, however, there is a progressive change in the surface tension–surface area characteristics of the surfactant, until finally the surface tension–surface area relationship is indistinguishable from that of the wetting agent or antifoaming agent alone. During the transition stage the compressibility characteristics of the surface film are altered before the minimum surface tension reached on compression changes. Thus, the surfactant activity index is not a reliable tool for evaluating normal compressibility. When ultrasonic aerosols generated from these agents are breathed continuously for eight hours, changes in the surface tension–surface area characteristics of surfactant are rare, probably because concentrations of agent necessary to produce these changes are not achieved at the air–liquid interface. The concern that these agents will alter surface tension at the air–liquid interface and result in unstable alveoli and atelectasis when used for a reasonable period of time does not appear justified. A more likely hazard with continued use is the accumulation of fluid in dependent areas of the lung, resulting in intrapulmonary shunting and hypoxia.

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References

1. Finley, T. N.: Pulmonary surface activity and the problems of atelectasis, wetting, foaming and detergents in the lung, Anesth. Analg. 42: 35, 1963.
2. Clements, J. A.: Surface tension of lung extracts, Proc. Soc. Exp. Biol. Med. 95: 170, 1957.
3. Clements, J. A., Hustead, R. F., Johnson, R. P., and Gribetz, I.: Pulmonary surface tension and alveolar stability, J. Appl. Physiol. 16: 444, 1961.
4. Giammona, S. T.: Effects of furniture polish on pulmonary surfactant, Amer. J. Dis. Child. 113: 658, 1967.
5. Aull, J. C., and McCord, W. M.: A simple apparatus and procedure for the determination of blood alcohol, Amer. J. Clin. Path. 42: 315, 1964.
6. Modell, J. H., Moya, F., Ruiz, B. C., Showers, A. V., and Newby, E. J.: Blood gas and electrolyte determinations during exposure to ultrasonic nebulized aerosols, Brit. J. Anaesth. 40: 20, 1968.
7. Modell, J. H., Giammona, S. T., and Alvarez, L. A.: Effect of nebulized suspensions on pulmonary surfactant, Dis. Chest. 50: 627, 1966.