

- cholinesterase. Determination of dibucaine numbers, *Canad. J. Biochem.* 35: 339, 1957.
- Harris, H., and Whittaker, M.: Differential inhibition of human serum cholinesterase with fluoride: Recognition of two new phenotypes, *Nature* 191: 496, 1961.
 - Liddell, J., Lehman, H., and Sieh, E.: A silent pseudocholinesterase gene, *Nature* 195: 561, 1962.
 - Foldes, F. F., McNall, P. G., and Birch, J. H.: The neuromuscular activity of succinylcholine iodide in anesthetized man, *Brit. Med. J.* 1: 967, 1954.
 - Kalow, W.: The distribution, destruction, and elimination of muscle relaxants, *ANESTHESIOLOGY* 20: 505, 1959.
 - Robertson, G. S.: Serum cholinesterase deficiency I: disease and inheritance, *Brit. J. Anaesth.* 38: 355, 1966.
 - Simpson, N. E., and Kalow, W.: The "silent" gene from serum cholinesterase, *Amer. J. Hum. Genet.* 16: 180, 1964.
 - Goedde, H. W., Fuss, W., Gehrig, D., and Baitsch, H.: Studies on formal genetics of the pseudocholinesterase polymorphism: An atypical segregation in a family, *Biochem. Pharmacol.* 13: 603, 1964.
 - Golz, H. M.: Controlled human exposures to malathion aerosols, *Arch. Industr. Health* 19: 516, 1959.
 - Wulfsohn, N. L., Smith, J. C., and Foldes, F. F.: Acute phospholine intoxication after intracutaneous injection, *Clin. Pharmacol. Ther.* 7: 44, 1966.
 - Pantuck, E. J.: Ecothiopate iodide eye drops and prolonged response to suxamethonium, *Brit. J. Anaesth.* 38: 406, 1966.

Pulmonary Surfactant: Determinations from Lung Extracts of Patients Receiving Diethyl Ether or Halothane

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Beecher¹ first suggested that the decreased lung volume observed in postoperative patients were the result of diffuse partial alveolar hypoventilation. Subsequently Bendixen *et al.*² proposed that progressive atelectasis might occur in patients with controlled ventilation under general anesthesia unless periodic hyper-ventilation was practiced. The possible contribution of inhalation anesthetics to depletion, deactivation or destruction of the surface active alveolar material to aggravate a state of progressive atelectasis has not been studied

in the clinical setting. In a series of patients undergoing thoracic surgical procedures in this clinic, the surface tension of lung extracts prepared from specimens was normal, suggesting that the anesthetic and technique of administration did not adversely affect pulmonary surfactant.³ The present investigation was undertaken to substantiate this impression.

PROCEDURE

Ten patients with pulmonary disease necessitating operation were selected for this study. Operation was done for removal of tuberculous residua, neoplasm or diagnosis of neoplasm (table 1). Eight were men, 2 women, whose ages varied from 19 to 50 years. They were in good health except for the pulmonary disease.

Each patient received meperidine 75 mg. and scopolamine 0.2 mg. one hour prior to induction of anesthesia.

Thiopentothal and succinylcholine were administered intravenously for tracheal intubation. Ventilation was controlled manually and anesthesia supplemented by a mixture of 70

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Supported by Department of the Army Medical Research Grant No. 62156011 3A025601A 26 01 105. Work originated in the Anesthesia and Thoracic Surgery Services, Department of Surgery, Valley Forge General Hospital, Phoenixville, Pennsylvania.

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TABLE 1. Indications for Surgery, Operation Performed and Complications Among Study Patients

Case	General Diagnosis	Operation	Complication
59-A-1	Carcinoma	Exploration	None
61-A-2	Tuberculosis	Segmental Res.	None
62-A-3	Tuberculosis	Subseg. Res.	None
63-A-4	Tuberculosis	Lobectomy	Air Leak
64-A-5	Tuberculosis	Segmental Res.	None
67-A-6	Tuberculosis	Segmental Res.	Atelectasis
69-A-7	Tuberculosis	Segmental Res.	Air Leak
70-A-8	Tuberculosis	Segmental Res.	Atelectasis
72-A-9	Susp. Carcinoma	Lobectomy	Air Leak
73-A-10	Carcinoma	Bilobectomy	None

per cent nitrous oxide and 30 per cent oxygen. The thoracic incision was made and the initial lung specimen was removed by wedge excision. When this was accomplished succinylcholine was discontinued and either diethyl ether (5 patients) or halothane (5 patients) was added to the breathing mixture. The maximum concentration of diethyl ether delivered was 10 to 13 per cent. The maximum concentration of diethyl ether delivered was 10 to 13 per cent. The maximum concentration of halothane was calculated to be 2.3 per cent. Both agents were vaporized in an Ohio Vernitrol vaporizer. Upon completion of the operation, resection or exploration, a second lung specimen was removed. Termination of the operation was not thereby unduly prolonged. Postoperative complications of minor nature were observed in 5 patients (table 1).

The first lung biopsy specimen was taken from a disease-free portion of the anatomic unit to be excised or from a remote area of lung to remain. The second specimen was removed from a readily accessible location of the lung remaining after excision. On each occasion the lung was momentarily held in an inflated attitude by compressing the bag of the anesthesia apparatus prior to application of excluding forceps to minimize the amount of blood trapped in the excised lung specimen.

Patients were selected for this study who had anatomically limited pulmonary disease from whom two specimens of normal lung could be anticipated. The validity of the assumption that normal lung could be distinguished by gross examination for this purpose was tested by preparation of histologic sec-

tions from those specimens generous enough to provide excess tissue. Microscopic examination of 10 specimens available for study confirmed the gross impression that normal lung had been removed (table 2).

METHOD

The method of preparing lung extracts for measurement of surface tension from surgical lung biopsy specimens was developed in this laboratory.⁴ This technique requires a specimen of lung weighing 1 to 3 g. The fresh lung was weighed on an analytical balance and excess tissue was trimmed away and prepared for histologic study. The tissue was suspended in 0.9 per cent sodium chloride solution as follows: 50 ml. for 3.0 g., 40 ml. for 2.5 g., 35 ml. for 2.0 g., 30 ml. for 1.5 g. and 25 ml. for 1.0 g. of lung. This solution was saturated with carbon dioxide by bubbling with a 100 per cent concentration. Re-inflation of the partially collapsed lung biopsy specimen was achieved in 10 to 25 minutes.⁵ This was done to expose a larger area of the alveolar surface to the mechanical extraction process. The inflated tissue was finely minced and stirred as a suspension in the sodium chloride solution. After 10 minutes of agitation the particulate matter was removed by filtration through coarse gauze. The extract was placed in the trough of a modified Wilhelmy balance and the surface film permitted to mature for 30 minutes before cycling the instrument.

Measurements were made with a Wilson self-cycling, direct writing surface tension balance.* A platinum strip partially submerged in the extract was suspended so that the downward force exerted was proportional to the surface tension of the extract. The surface film was confined in the trough by a continuously moving barrier which alternately compressed and expanded the film. The cycle from maximum surface area through compression to 20 per cent of that area and return to full area expansion required 10 minutes. The instrument recorded a surface tension-surface area loop with each completed cycle. Operation of the balance was continued until the same minimal surface tension was recorded

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for at least 2 cycles. The surface characteristics of these lung extracts are described as follows: (1) Minimal surface tension, dynes per centimeter at maximal film compression, (2) maximal surface tension, dynes per centimeter at maximal film expansion, and (3) stability index (\bar{S}) the change in tension/average tension, calculated as $2(\max. S.T. - \min. S.T.) / (\max. S.T. + \min. S.T.)$.

RESULTS

The results of surface tension measurements of lung extracts are presented in table 2. The total time of exposure to the inhalation anesthetic varied in response to the clinical requirement. By using sequential biopsies as

† S.T. = surface tension.

paired experiments the influence of events prior to exposure to the anesthetic was minimized. Five patients exposed to diethyl ether experienced a time lapse of 50 to 160 minutes between biopsies. Similarly, an exposure of 110 to 225 minutes was experienced by the 5 patients receiving halothane. Although individual surface tension differences were observed between specimens no consistent trend was detected for either group of patients. Statistical analysis of the difference between paired determinations by the "signed-ranks" test of Wilcoxon showed no significant changes.

DISCUSSION

Critique of the Methods. There is now convincing experimental evidence that alveoli of

TABLE 2. Time of Anesthetic Exposure and Surface Tension Measurements of Human Lung Extracts

Case	Anesthetic Agent	Time of Exposure (min.)	Lung Specimen	Histologic Finding	Surface Tension (dynes/cm.)		
					Max.	Min.	\bar{S}
59-A-1	Ether	80	A	Normal	46	6	1.54
			B		36	7	1.35
61-A-2	Ether	75	A	Normal	39	1	1.90
			B		47	12	1.18
62-A-3	Ether	50	A	Normal	44	13	1.09
			B		43	9	1.30
63-A-4	Ether	120	A	Normal	47	18	0.89
			B		43	17	0.87
67-A-6	Ether	160	A	Normal	36	6	1.42
			B		46	5	1.61
64-A-5	Halothane	190	A	Normal	49	5	1.63
			B		38	2	1.80
69-A-7	Halothane	150	A	Normal	30	1	1.86
			B		36	3	1.68
70-A-8	Halothane	110	A	Normal	28	1	1.86
			B		30	2	1.74
72-A-9	Halothane	195	A	Normal	42	6	1.42
			B		38	11	1.10
73-A-10	Halothane	225	A	Normal	35	3	1.68
			B		32	5	1.46

Specimen A—Control, before administration of test agent.
Specimen B—Study, after administration of test agent.

adult mammalian lungs are lined with a surface-active phospholipid material (surfactant) that insures their stability. In this study evaluation of surfactant function before and after exposure of the alveoli to diethyl ether or halothane was based on measurable surface tension properties of lung extracts. The ability of a given extract to reach a low surface tension (lower than 20 dynes/cm.) on compression of its surface area, a large tension-area hysteresis, and a high stability index (\bar{S} above 0.85) indicate the presence of surfactant in the surface film of extract. This is taken to mean that normal surface tension properties existed at the moment of excision of the lung specimen. Sequential paired determinations before and after exposure to the anesthetic were made for direct comparison. This was done to avoid reliance on pooled data from other experiments to express an anticipated normal range of surface tension measurements.

The method of preparing lung extracts for surface tension measurements is quite critical. Mechanical removal of the phospholipid surface-active material from the alveolar surfaces is determined by the area exposed. The importance of inflating the alveoli prior to mincing the lung was emphasized by Levine and Johnson.⁶ Soon after excision of a peripheral portion of lung the specimen loses its inflated attitude. This is rapidly restored using carbon dioxide as described by Anderson and Lapuerto.⁵ Application of this method of lung inflation did not affect the measurement of surface tension of canine lung extracts in this laboratory.

The correlation between the histologic status of the alveoli and surface-active lung extracts is good whereas bronchial diseases frequently influence pulmonary ventilatory abilities without affecting the alveoli or pulmonary surfactant. Although a few pulmonary diseases may be associated with abnormal surfactant they have not yet been defined. For these reasons reliance was placed on the surgeon's ability to recognize normal lung and select appropriate sites for biopsy. This judgment was confirmed by microscopic examination of 10 specimens all of which were normal.

Several methods of measuring surface ten-

sion are available. The simplest method which combines the measurement of surface tension with a capability for changing the surface area has been incorporated in the instrument used in these experiments. A detailed description of the modified Wilhelmy balance (Wilson surface tension balance) used in this investigation was presented by Avery and Said.⁷

Theoretical Relations Between Inhalation Anesthetics and Pulmonary Surfactant. Clements, Brown and Johnson⁸ initially ascribed the peculiar physical behavior of the lung to the changing surface tension of the alveolar lining film. Subsequently, it has been implied that impaired production, excessive depletion, deactivation or destruction of a phospholipid lecithin protein complex could produce atelectasis. Although atelectasis frequently complicates the postoperative recovery of patients undergoing major surgery with inhalation anesthesia, atelectasis has not yet been demonstrated to have any direct relation to surfactant depletion, deactivation or destruction. However, since properly administered inhalation anesthetics must reach and pass through the alveolar surfaces they could conceivably adversely influence the surface-active material. This would be a plausible explanation for abnormal volume-pressure studies, nitrogen wash-out and blood gas values observed in postoperative patients.⁹

In this study the lung extractable surface-active material was not affected by administration of diethyl ether or halothane. Therefore, the pathogenesis of postoperative, post-anesthetic atelectasis does not seem to be related to alveolar instability resulting from loss of pulmonary surfactant initiated by exposure to these anesthetics.

SUMMARY

Lung extracts prepared from sequential lung biopsies secured from patients undergoing thoracotomy were studied for the effect of diethyl ether or halothane on surface activity of the alveolar lining substance. Five patients were in each group. Lung biopsies were taken before and after administration of the anesthetic and extracts prepared. Maximal and minimal surface tension measurements

and calculated stability indices from each paired experiment demonstrated that administration of these inhalation anesthetics had no appreciable effect on pulmonary surfactant under the conditions of this investigation.

REFERENCES

1. Beecher, H. K.: Effect of laparotomy on lung volume. Demonstration of a new type of pulmonary collapse, *J. Clin. Invest.* 12: 651, 1933.
2. Bendixen, H. H., Hedley-Whyte, J., and Laver, M. B.: Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: A concept of atelectasis, *New Eng. J. Med.* 269: 991, 1963.
3. Thomas, P. A.: Observations from the respiratory history of 30 patients with normal pulmonary surfactant, *J. Thorac. Cardio. Surg.* 52: 11, 1966.
4. Thomas, P. A.: A technique for surface tension determination of extracts from lung biopsy specimens, *J. Surg. Res.* 6: 142, 1966.
5. Anderson, W. H., and Lapuerta, L.: A new technique for distension and fixation of lung biopsy specimens, *Medical Abstracts, Annual Meeting of the National Tuberculosis Association, 1965*, p. 52.
6. Levine, B. E., and Johnson, R. P.: Surface activity of saline extract: from inflated and degassed normal lungs, *J. Appl. Physiol.* 19: 333, 1964.
7. Avery, M. E., and Said, S.: Surface phenomena in lungs in health and disease, *Medicine* 44: 503, 1966.
8. Clements, J. A., Brown, E. S., and Johnson, R. P.: Pulmonary surface tension and the mucus lining of the lungs: some theoretical considerations, *J. Appl. Physiol.* 12: 262, 1958.
9. Okinaka, A. J.: Closure of pulmonary air spaces following abdominal surgery, *Surg. Gynec. Obstet.* 121: 1282, 1965.

Central Venous Pressures via Peripheral Veins

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Central venous pressure monitoring to assess myocardial function and right heart filling pressure relationships can be a valuable aid in the treatment of shock or other conditions which significantly alter the cardiac function-filling pressure relationship.^{1,2} Venous pressure measurements can be accomplished in a variety of ways. The subclavian vein has frequently been used. However, published reports are sparse and the complications significant.³⁻⁵ The external jugular vein and peripheral veins have been employed with variable success.^{6,7} Such variability and lack of a generally acceptable approach prompted this study to develop a safe technic for peripheral placement of a catheter.

The following disadvantages were considered: (1) air embolism, (2) obstruction to catheter advancement, (3) perforation of a central vein, and (4) phlebitis and local tissue reaction. It was reasoned that these risks

might be minimized by a technique in which the catheter is initially connected to a conventional intravenous set and the solution allowed to flow during its insertion through a needle, so that the rate of fluid flow could serve to monitor the advancement of the catheter tip.

METHODS

A catheter unit** which included a 21-inch long radiopaque plastic catheter (15 gauge) housed in a longitudinally slit plastic tube was used. A 19-inch extension tube attached to the catheter allowed its direct connection to an intravenous solution bottle. The catheter was inserted through a 14 gauge needle introduced into an appropriate arm vein, basilic, median cubital or cephalic, in order of preference, after the infusion system was allowed to fill the extension tubing and catheter. Infusion was begun after tourniquet release. With fluid running rapidly the catheter was ad-

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** Catheter units were supplied by Sorenson Research Corporation, Salt Lake City, Utah.