Correlation of Mechanical Properties of Lungs and Surface Tension; Deficiency vs. Inactivation of Surfactant*

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A specific pulmonary surfactant becoming highly active on reduction of the surface area during expiration, is responsible for the well known hysteresis of pressure-volume curves, and for the normal stability of lung expansion. Thus, a normal lung specimen may require a pressure of more than 20 cm. of water to initiate expansion, and higher pressures for full aeration; yet on deflation to 5 cm. it contains well over half the air previously introduced and retains some air even upon return to atmospheric pressure. When this surfactant activity is decreased, most of the inspired air leaves the lung upon gradual deflation at pressures much higher than 5 cm., and little or no air remains at atmospheric pressure. This occurs in spontaneous disease and as a side effect of treatment in man, and may be produced in experimental animals.

The exact nature of the active substance (or group of substances) present in the alveolar lining layer is not known and it is therefore impossible at this time to determine its presence or concentration. Only activity can be assessed by three methods: (1) deflation characteristics of artificially inflated, intact lung specimens, (2) surface tension determination of extracts, washings, etc. on a balance with a variable area, and (3) the stability of air bubbles squeezed from lungs. The latter method was instrumental in the discovery of the specific pulmonary surfactant, but has not been widely used; it will not be discussed further. Results of the first two methods agree sufficiently well to confirm the postulate that they measure closely related properties.

Examination of Surface Properties

If an intact lung or lobe is available, deflation characteristics may be studied by means of a static pressure-volume curve. This method directly assesses the mechanical properties of lungs, but it determines resistance and elasticity of tissue along with surface forces. It does not allow one to separate the properties of portions within one lung that may vary in surface activity. With small lungs the procedure is quite simple, but with large volumes it is cumbersome. The role of tissue forces alone may be assessed by expansion with liquids when interfacial tension is absent or low. The limitations of that method, and choice of liquid to be used were discussed elsewhere. It is usually assumed that the specific surfactant in question does not control the opening pressure to a predominant extent, but rather affects deflation and with it the stability of expansion. An index has been devised, based on the proportion of maximal air content which is retained on deflation to 10 and 5 cm. Since inflation and deflation are not controlled by the same mechanisms, the extent of hysteresis (the pressure difference between inflation and deflation curve) is not a useful index of surfactant activity, or of stability of expansion. In lungs with uniform properties, it is easy to distinguish good and poor stability by means of an index: values obtained for these two groups are separated by an intermediate range in which very few observed values fall.

Examination of fluid containing the pulmonary surfactant on a surface balance with a variable area, determines changes in tension with compression of the surface area, as would happen during expiration.

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Either the lowest value of surface tension at maximal compression has been evaluated, or an index based on the highest and lowest points of the loop. This index correlates well with the one obtained from pressure-volume curves of the same lungs, suggesting that the same agent controls both parameters studied.

Examination of a lung extract on the surface balance is the method of choice when only pieces of lung are available, or when several portions of one lung are to be compared with one another. While the principle of the surface balance with a variable area is simple, the equipment is not easy to handle. The technique of obtaining the sample has recently been subjected to critical evaluation. It had been customary to mince rather than grind tissue, in an effort to reduce contamination by blood and tissue components. Now it appears that this method does not provide adequate contact of the extracting fluid with alveolar surfaces when the sample is completely collapsed; some previous studies showing poor activity of extracts of atelectatic lungs may therefore have to be confirmed with adequate technique.

The pulmonary surfactant is fairly stable in an intact lung specimen. A lung will yield consistent deflation curves for several days if refrigerated (above freezing) between examinations. Most workers would not take it for granted that an extract prepared by mincing or grinding the tissue would be equally stable, but this has not been studied in detail. Frozen extracts lose activity in about two months.

**Occurrence and Significance of Poor Stability**

The only spontaneous disease in which a diffuse, severe defect of stability (measured either by deflation curves or on the balance) occurs, is the respiratory distress syndrome of newborn infants, characterized pathologically by atelectasis and hyaline membranes. Similar defects have been found under conditions produced in man by treatment, or in animals experimentally, by prolonged pulmonary bypass, ligation of the pulmonary artery, atelectasis due to pneumothorax, or experimental pulmonary edema. It has been suggested that inhibition of pulmonary circulation is the common factor in the pathogenesis of some or all of these conditions.

Poor stability of expansion results in failure to establish or maintain a functional residual capacity. Thus the lungs, or portions of lungs collapse extensively at expiration and the work of inflating them anew at each inspiration is abnormally great. If efforts to re-expand these lungs are not entirely successful, atelectasis will recur and eventually persist. (This may become a vicious circle if atelectasis should, in turn, promote poor stability.) In newborn premature infants who are particularly prone to the respiratory syndrome, there is the added complication of atelectasis of prematurity: the bronchi and respiratory bronchioles are aerated with relative ease, whereas much higher pressure is required to open the terminal air spaces. With added poor stability, these infants may be limited to respiration by means of their respiratory bronchioles. However, it should be noted that the respiratory distress syndrome does not occur in premature infants only. If occasionally a mature infant is affected, this special form of atelectasis is absent.

**DEFICIENCY VS. INACTIVATION OF THE SURFACTANT**

Several experimental procedures are known to inactivate the pulmonary surfactant, as demonstrated by either of the methods just mentioned. The detergent Tween 20 has this property, as do certain lipid fractions from lung tissue. It is further known that lungs with inactive saline extracts may yield active material by different methods of extraction, owing presumably to removal of inhibitors. The question then arises whether in spontaneous or experimental deficiency of surfactant activity (which is all that can be detected) the active principle was either not produced, or chemically altered, or present but otherwise inactivated. Morphologic studies have suggested failure of production: absence or
reduction of the laminated bodies of alveolar lining cells which are thought to produce the surfactant,\textsuperscript{10,11} and absence of a fluorescent surface layer supposedly representing the surfactant\textsuperscript{12} have been reported to correlate with poor activity of lung extract on the balance. On the other hand, lung specimens with poor stability show on heating to 48°C a reversible increase of stability, suggesting that an inactivated surfactant had been present.\textsuperscript{13} Similar conclusions have been drawn from the above mentioned fractionation experiments.\textsuperscript{14,15}

The process resulting in the peculiar, area-dependent pulmonary surface activity is probably a very complex one, involving not only one or several key substances, but also accessory substances or conditions which, in certain constellation, determine activity or inactivation.

Much more work needs to be done before it can be decided whether or when in a given abnormal state the surfactant was not produced or, in contrast, was reversibly or irreversibly inactivated. This is a problem of great medical significance: if in a given condition the surfactant were absent, one should attempt to introduce it therapeutically; if on the other hand, the surfactant were present but prevented from being active, knowledge of the factors influencing activity may be most important for rational therapy.

**Resumen**

1. Un agente superfactante específico que alcanza gran actividad al reducirse el área de superficie durante la respiración condiciona normalmente la estabilidad del re-expansión pulmonar. La naturaleza exacta de esta sustancia es desconocida y por lo tanto solamente su actividad y no su presencia o concentración es susceptible de determinación mediante los tres siguientes métodos: (1) características de desinflación del tejido pulmonar intacto e inflado artificialmente. (2) determinación de la tensión superficial de extractos o productos del lavado en una balanza de área variable o (3) estabilidad de las burbujas gaseosas exprimidas del pulmón. Los resultados de estos métodos son comparables y la selección del procedimiento se basa en consideraciones de orden técnico.

2. La única enfermedad espontánea humana en la que se observa un déficit difuso de la estabilidad ocurre en el síndrome de dificultad respiratoria en el recién nacido.

Estados similares han sido observados en el hombre como resultado de procedimientos terapéuticos y en animales en condiciones experimentales, como por ejemplo derivación prolongada de la circulación pulmonar, ligadura de la arteria pulmonar, atelectasia por neumotórax o edema pulmonar experimental.
3. No se conoce si en los estados espontáneos o experimentales de deficiencia de actividad surfactante el principio activo deja de producirse, esta alterado químicamente o presente pero inactivado. Esta distinción es de importancia práctica ya que si falta puede ser miniminado terapéuticamente y si esta presente pero inactivado y conocimiento de los factores que determinan la actividad sería de la mayor importancia para instituir una terapéutica racional.

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REFERENCES


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