If we look at an x-ray film of the chest, it is not immediately obvious that there are regional differences of structure and function within the lung. Indeed, until some 15 or so years ago, very little was known about these differences. However, there is now very good evidence of striking regional differences in bloodflow, ventilation, gas exchange, pleural pressure, alveolar size, and mechanical stresses within the upright human lung. Many of these regional differences have important implications in the way pathologic processes occur in the lung, and I propose to review them one by one.

Let’s start with the distribution of bloodflow in the lung. Suppose that a normal subject is seated in front of a series of radiation counters and that radioactive xenon dissolved in physiologic saline solution is injected into a peripheral vein (Fig 1). When the radioactive gas reaches the pulmonary capillaries, it is evolved into the alveolar gas, and it remains there for a short period of time during breath-holding. The counting rate from various regions of the lung can then be measured; and since the radioactive xenon has arrived by means of the pulmonary bloodflow, this enables us to calculate the bloodflow per unit volume at different levels in the lung. Figure 1 shows typical results from an upright normal subject. Note that the bloodflow per unit volume is very high near the bottom of the lung and decreases steadily up the lung, reaching very low values at the apex.

It is easy to show that this normal distribution of bloodflow is very much affected by change of posture and exercise. For example, when a normal subject lies supine, the apical bloodflow increases, and the basal bloodflow does not change much. Therefore, the differences between the apex and the base of the lung are largely abolished, although under these conditions, the bloodflow in the most anterior part of the lung, which is uppermost, is less than the bloodflow in the dependent posterior region of the lung. On exercise in the upright position, both the apical and the basal bloodflow increase, so that the differences down the lung become less.

In order to elucidate the factors responsible for this uneven distribution of the bloodflow in the lung,
It is useful to study an isolated lung preparation, because only here is it possible to change one pressure at a time and see what this does to the distribution of the blood flow. Figure 2 shows the distribution of the blood flow in one of these preparations in an animal with normal vascular pressures (that is, normal pulmonary arterial, venous, and alveolar pressures). It can be seen that the blood flow per unit volume decreased from the bottom toward the top of the lung, again reaching very low values at the extreme apex. Note that this distribution is very similar to that found in the normal upright human lung (Fig. 1).

Now we can ask the question: what happens if we change the various pressures one by one? Figure 3 shows the effect of reducing the pulmonary arterial pressure by turning down the pump controlling flow into the lung. You can see that the blood flow per unit volume decreased, as in Figure 2, but now reached zero some two-thirds of the way up the lung. In other words, near the apex of the lung, there was a region that was completely unperfused. This occurred in spite of the fact that most of the lung was receiving a substantial amount of blood.

What is the reason for the lack of perfusion at the top of the lung? If it is possible to obtain some information about this by rapidly freezing the lung by flooding it with very cold liquid gas and then looking at the tissue with a microscope. Figure 4A shows the normal appearance of well-perfused lung. The engorged capillaries in the alveolar walls are well seen, and individual red blood cells can be identified. By contrast, Figure 4B shows a section from the apex of a lung in which the pulmonary arterial pressure was abnormally low. Note that the appearance is strikingly different. Although the thin alveolar walls can be identified, there is hardly a red blood cell to be seen, and the capillaries appear to be completely closed. Apparently the reason for this is simply that, under these conditions, the pulmonary capillary pressure falls below alveolar pressure, and the very thin-walled delicate blood vessels collapse.

Figure 5 shows what happens if we increase the pulmonary venous pressure. You can see that the

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The result was to introduce an inflection into the distribution of blood flow. In other words, there is now a somewhat more uniform distribution of the flow of blood in the lowest region of the lung. It should be added that in many preparations the slope of the distribution of the flow of blood near the bottom of the lung was steeper than in this example.

It is possible to use these and other data to build up a simple three-zone model of the lung (Fig 6). The three zones are determined by the relative magnitudes of the pulmonary arterial, venous, and alveolar pressures. First, near the apex of the upright lung, there may be a region (zone 1) where there is no blood flow. As we saw in Figure 3, this occurs when the pulmonary arterial pressure is reduced. Why should this occur in the uppermost region of the lung? The reason is the hydrostatic pressure gradient within the pulmonary blood vessels. If we consider the pulmonary arterial tree as a continuous column of blood, we find that as we go down the arterial system, the pressure increases by approximately 1 cm H2O per centimeter of distance; and, likewise, the pressure decreases as we go up toward the apex of the lung. As a result, we may reach a point where the arterial pressure falls below the alveolar pressure. Under these conditions, capillary pressure is less than alveolar pressure, and apparently these delicate vessels collapse when the pressure outside them exceeds the pressure inside them (Fig 4B).

It should be emphasized that this unperfused region of lung is not seen under normal physiologic conditions. Indeed, it would be very odd if we walked around with the tops of our lungs unperfused! But a zone 1 can be seen under abnormal conditions, and we can predict what these will be. Examples are when the pulmonary arterial pressure is reduced (as, for example, in hemorrhagic shock) or when the alveolar pressure is increased (as in mechanical ventilation with positive pressure). Naturally, an unperfused region is particularly likely to occur if both conditions are combined, as, for example, in a patient who comes into the operating room with a depleted circulating blood volume and who receives mechanical ventilation with positive pressure. Indeed, an increased physiologic dead space (that is, ventilation of underperfused lung) is well known to occur under these conditions. It should be emphasized that this is a gravitational effect, with the result that the unperfused region always occurs at the top of the lung. This would be the anterior region in a supine patient.

As we go down the lung (Fig 6), we come to zone 2, which is a region where the pulmonary arterial pressure has now increased sufficiently that it exceeds alveolar pressure, and, consequently, there is flow. This is an interesting region from the point of view of the physiologist, because it can be shown that under these conditions when arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure, the blood flow is independent of venous pressure. Naturally, this is an unusual situation, because we normally think of blood flow as being determined by the arteriovenous pressure differences; but it can be clearly shown in experimental preparations that under these conditions (when alveolar pressure exceeds venous pressure), the venous pressure becomes immaterial. This is sometimes referred to as the Starling resistor effect or the waterfall effect. The reason for the phenomenon is not fully understood but probably has to do with the fact that a point of collapse develops at the downstream end of the pulmonary capillary, and, therefore, the downstream pressure that is determining flow is not venous pressure but alveolar pressure.
The same kind of behavior can be obtained on the laboratory bench using a collapsible rubber tube as a model for the capillaries. In any event, the difference in pressure that is responsible for flow is arterial minus alveolar pressure. Arterial pressure increases down the lung; however, alveolar pressure is constant throughout the lung, since the alveoli are air sacs connected by air tubes. Therefore, the difference in pressure that is responsible for flow (that is, arterial minus alveolar pressure) increases as we go down the lung, and this explains the increase in bloodflow down zone 2.

Finally, we get to the bottom of the lung (Fig 6), where now venous pressure exceeds alveolar pressure, the collapsible vessels are held open, and bloodflow is determined in the ordinary way by the arteriovenous pressure difference. Why does bloodflow increase down this zone? Chiefly, it increases because of distention of the pulmonary capillaries; and, indeed, direct measurements of the mean width of capillaries in this region show that this width increases down the lung.

This simple three-zone model satisfactorily accounts for most of the changes in the distribution of the flow of blood which occur with alterations of posture, exercise, and various forms of cardiac and pulmonary disease that alter the vascular pressures. Other factors, such as lung volume, play a role under some conditions, but there is not time to pursue these.

Now let us leave the bloodflow and turn to the distribution of ventilation. This can be measured with equipment similar to that used for determining the distribution of the bloodflow (Fig 7); however, instead of the radioactive xenon being injected into a vein, it is inhaled either as a single breath or in a series of breaths. From the regional counting rates, it is then possible to derive the ventilation per unit of lung volume. Note that ventilation decreases up the lung. This is the same direction as the change in bloodflow (Fig 1), but the magnitude of change is less for ventilation.

What is responsible for this uneven distribution of ventilation in the lung? Again, it transpires that gravity is the culprit, however, in this instance, it is not the weight of the column of blood in the lung but the weight of the lung itself. Figure 8 shows a simple scheme that accounts for this uneven distribution in a reasonably satisfactory way, although it must be an oversimplification.

It is well known that the pressure in the intrapleural space around the lung is negative (that is, less than atmospheric pressure). What is not so well known is that the intrapleural pressure is not constant throughout the intrapleural space but in fact is greater at the bottom of the lung than it is at the top. Figure 8 shows typical values. The reason for these regional differences in pressure is not fully understood, but they are probably caused by the weight of the lung. Whenever anything is supported (for example, a book on a table), the pressure under the book has to exceed the pressure above it. Otherwise, there is nothing to counteract the downward-acting forces of the weight of the book. In the same way, the lung is supported to a large extent by the rib cage and diaphragm; and, therefore, the pressures around the bottom of the lung are greater (in this instance, less negative) than the pressures around the top.

Now what does this uneven distribution of intrapleural pressure do to the way the lung ventilates? Figure 8 shows a pressure-volume curve of lung. In other words, this is the kind of curve obtained if you take a lobe of lung and gradually inflate it by reducing the pressure around it. Note that the pressure-volume curve is nonlinear. In other words, the lung tends to get stiffer at high lung volumes. The two lines shown on Figure 8 are just to remind us that
the lung does not take quite the same path during inflation as it does during deflation, but this is relatively unimportant in the present context.

First look at the base of the lung, which has an expanding pressure on it of 2.5 cm H2O. Recall that the pressure in the alveolar spaces is atmospheric at the end of inspiration or the end of expiration (there is no flow); and, therefore, this pressure of 2.5 cm H2O is responsible for expanding this part of the lung. Thus, if we locate this pressure on the pressure-volume curve, we see that the resting volume of the lung is relatively small; and, furthermore, for a small decrease in intrapleural pressure, the change in volume of the lung is relatively large. Now, what we mean by "regional ventilation" is the change in volume per unit resting volume, so with both the change in volume being large and the resting volume being small, clearly the base of the lung is well ventilated.

Contrast this with the apex of the lung. The apex of the lung has a much larger pressure expanding it, and, therefore, it is located higher on the pressure-volume curve (-10 cm H2O). The apex thus has a larger resting volume; however, the change in volume for a given fall in intrapleural pressure is smaller because the pressure-volume curve is not so steep, and, therefore, the change in volume per unit resting volume (or the regional ventilation) is less at the apex than it is at the base.

Incidentally, notice a paradox here. The base of the lung has a smaller expanding pressure on it, but it actually ventilates better than the apex of the lung. One way of looking at this is to argue that the poorly expanded lung at the base is much more easily expanded than the relatively overexpanded apex of the lung.

Now let's turn from the distribution of ventilation to the relations between ventilation and bloodflow and how these affect gas exchange. It is well known that the gas exchange in any region of the lung depends on the ratio of ventilation to the bloodflow. Naturally, ventilation is important; so is bloodflow, but the key factor is the ventilation-perfusion ratio. Therefore, since ventilation and bloodflow tend to be mismatched as we go up the normal upright lung, this inevitably means that there must be regional changes in gas concentration.

Figure 9 summarizes the changes in ventilation and bloodflow that occur from bottom to top of the normal upright lung. Ventilation decreases up the lung, but the change is relatively small. Bloodflow, on the other hand, decreases much more rapidly. Therefore, the ratio of ventilation to perfusion is relatively low at the bottom of the lung but as high as 3 at the apex. Recall that the normal value is between 0.8 and 1.0.

Figure 10 shows a model in which the lung has been divided into nine imaginary horizontal slices, and the regional gas exchange has been calculated in each. Note first that the volume of the uppermost slice is rather less than that at the bottom because of the shape of the lung. Ventilation increases down the lung (0.24 to 0.82 L/min), but the increase in bloodflow (from 0.07 to 1.29 L/min) is greater. Therefore, the ventilation-perfusion ratio is higher at the apex than the base. As a result, there are substantial differences in oxygen partial pressure (PO2) down the lung, the values at the apex and...
base being 132 and 89 mm Hg, respectively. The carbon dioxide tension (P\textsubscript{CO\textsubscript{2}}) increases by approximately 14 mm Hg from top to bottom. The oxygen and carbon dioxide contents of end-capillary blood at the different levels reflect the differences in partial pressures. Note the high pH at the apex (7.51), compared with the lower value at the base (7.39). The amounts of oxygen and carbon dioxide taken up by the uppermost slice are remarkably small. In other words, the apex of the lung is behaving as a reservoir for gas exchange under resting conditions; however, on exercise, when the distribution of blood-flow becomes more uniform, the apex makes a substantially greater contribution to overall gas exchange. It should be emphasized that the numbers shown on Figure 10 are only approximations, and there will be variations between different subjects.

There are a number of clinical implications of these regional differences in the gas exchange. For example, it was suggested many years ago that the predilection of adult pulmonary tuberculosis for the apex of the lung is related to the low blood-flow and consequently high P\textsubscript{O\textsubscript{2}} there. Many pieces of evidence support this, and I will not marshall them here. However, Figure 11 shows the results of a colorful experiment carried out by Rothlin and Undritz. These workers showed that in the bat, which spends a good deal of its time upside down, pulmonary tuberculosis tends to develop at the bases of the lung! I have to add that this conclusion was based on very few experiments.

Figure 10 shows that the pH of the end-capillary blood is much higher at the apex of the lung than the base because of the differences in P\textsubscript{CO\textsubscript{2}} between the two regions. It is likely that these differences in pH have several implications for regional function. Figure 12 shows a Gough section sent to me by A. A. Liebow, M.D., some three or four years ago. The lung was from a young woman with severe leukemia and bone destruction who developed the unusual condition of metastatic calcification in the lung. Notice that the calcification is localized to the apex of the lung. The same appearance was seen in the other lung. It seems likely that the higher pH at the apex may well be a factor in this condition. It is also possible that the behavior of the pulmonary macrophages and other cellular functions of the lung may be influenced by the substantial regional differences in pH and P\textsubscript{O\textsubscript{2}}.

Now let's leave the subject of gas exchange and look at the regional differences in alveolar size. Figure 8 implies that the apical alveoli of the upright lung are larger than the basal alveoli because of distortion of the lung by its weight. From time to time when this claim is made, a pathologist retorts that he has been looking at lungs for many years and

Figure 11. Localization of pulmonary tuberculosis at bases of lung in bat, which spends much of its time upside down (from Rothlin and Undritz).
has never seen any consistent difference in alveolar size between the upper and lower lobes! But that is not the point. The contention here is not that there are intrinsic differences of structure between the upper and lower regions of the lung, but that when the lung is within the chest, the lung distorts because of its weight; and as a result, we see a relative compression of the lower regions and a relative expansion of the upper regions.

It follows that the only way to demonstrate regional differences of alveolar size is to fix the lung within the chest. Glazier et al.18 did this several years ago by surrounding anesthetized dogs with solid carbon dioxide and freezing the lungs solid. Pieces were then removed from different levels, and Figure 13 shows examples of the results obtained. These animals were frozen in the head-up position because we are basically more interested in man than in the dog. Figure 13A (top) shows alveoli from the apex of the upright lung, and Figure 13B (bottom) shows tissue from the base. The apical alveoli certainly seem larger.

In order to obtain reliable data on this, we measured alveolar size using morphometric techniques pioneered by Weibel.19 Figure 14 shows that when the average volume of the alveoli on an arbitrary scale was plotted against the distance down the lung, very striking differences in alveolar size were seen.18 In fact, the apical alveoli were almost four times larger by volume than the basal alveoli. Although these measurements are from dogs, there is every reason to believe that the same kind of pattern exists in the upright human lung.

As we pondered the data shown in Figure 14, we became intrigued by the striking changes in alveolar size that apparently occurred over the uppermost region of the lung. Notice that over half of the total change in alveolar volume occurs over the top 4 cm or so of the lung. This set us wondering about the mechanical forces operating at the apex of the upright lung. If you ask an engineer where a structure such as a bridge is likely to fail, the first question he will probably ask you is where is it stressed most. It is curious that although we often see patients with pulmonary disease in whom there has been structural breakdown of lung tissue (for example, emphysema), physicians and physiologists have rarely asked the question, “Where is the lung stressed most?”

Figure 13. Regional differences in alveolar size in dog lungs fixed in situ by freezing. A (top), Alveoli from apex of upright (head-up) animal. B (bottom), Tissue from base (from Glazier et al.18).

Figure 14. Regional differences in alveolar size in dog lungs frozen in upright (head-up) position (from Glazier et al.18).
Now this turns out to be a very difficult question to answer. No one has come up with a way of measuring stress in intact lung tissue without seriously interfering with its function. Therefore, we set about doing a theoretic analysis of the distribution of stress in the lung. The work was done in cooperation with Mr. Frank Matthews of the Department of Aeronautics at the University of London Imperial College, where there happened to be a group of investigators who had pioneered finite element techniques for analyzing the distribution of stresses. This kind of technique is used extensively, for example, in the aircraft industry, for calculating the distribution of stresses in the wings of aircraft.

The details of the analysis need not concern us, but the results are of interest. Figure 15 shows a plot of vertical and horizontal stresses against distance down the lung. Note that the stresses in the vertical direction (solid line) are greatest at the apex, and this is also the case for the stresses in the lateral direction (broken curve). Probably this is because, as the lung is distorted downward because of its weight, it is stretched laterally due to the increasing cross-sectional area of the thoracic cage. The main conclusion from these results is that indeed the mechanical forces operating on the alveolar walls are highest at the apex of the upright lung.

It seems likely that there are several diseases in which this distribution of stress may play a role in localization. One of these is centrilobular emphysema. Recall that there are two common forms of...
pulmonary emphysema. One is centrilobular (or centriacinar), and the other is panlobular (or panacinar). Figure 16 shows a typical example of the predominantly apical distribution of centrilobular emphysema. Note the obvious concentration of the disease at the extreme apex and the gradual lessening of intensity toward the base of the lung.

Several studies have confirmed the predominantly apical preference of this disease; for example, Figure 17 shows the distribution found by Thurlbeck when he looked at the localization of centrilobular emphysema in a series of autopsies at the Massachusetts General Hospital. Note the striking similarity between the distribution shown in Figure 17 and the distribution of mechanical stresses in Figure 15. The only disparity is the relatively high incidence of emphysema in the apex of the lower lobe; however, even this may be consistent with the stress hypothesis. It may be that the peculiar shape of this lobe, with its rather pointed apex, causes a relative stress concentration in this region.

These notions can be incorporated into a hypothesis for the development of this disease. The essential lesion of centrilobular emphysema is dilatation and destruction in the region of the respiratory bronchioles. This is well seen in the histologic section shown in Figure 18, where the central area of destruction is surrounded by relatively normal alveoli at the periphery of the acinus.

Why should the respiratory bronchioles show the most severe damage? A likely reason is that these small airways are particularly vulnerable to the effects of air pollution. When an aerosol is inhaled, the particles move down to the region of the terminal and respiratory bronchioles by bulk flow. However, the particles cannot travel to the peripheral alveoli because this movement chiefly takes place by diffusion in the gaseous phase. The aerosol particles are so heavy, compared with gas molecules, that their rates of diffusion are very low, and the particles therefore do not move to the alveoli. As a consequence, a considerable amount of deposition takes place in the vicinity of the respiratory bronchioles.

The hypothesis would then be as follows: pollutants in the air that we breathe tend to deposit in the region of the respiratory bronchioles, and presumably this process is more or less generalized throughout the lung. Some of the pollutants cause inflammation of the bronchial wall, which weakens the tissue; however, the structural failure occurs first where the lung is stressed most, that is, at the apex. As the disease progresses, the lesions are seen in regions where the stresses are not quite so high, but the general pattern of localization conforms to the distribution of mechanical stresses. It might be added that centrilobular emphysema is an extremely common disease. In fact, the majority of postmortem lungs from middle-aged patients show a small amount of centrilobular emphysema, and this is often confined to the extreme apex.

Other types of emphysema exist, and these have different forms of distribution within the lung. Presumably, this reflects different etiologies of the different types of the disease. For example, the emphysema of $\alpha_1$-antitrypsin deficiency is often predominantly basal in its distribution. A possible hypothesis here is that because of the higher bloodflow to the base of the upright lung, many leukocytes are sequestrated in that region. Some of these white blood cells break down, liberating their proteases. In the absence of $\alpha_1$-antitrypsin, these proteases tend to destroy the pulmonary tissue, and this destruction occurs predominantly in the lower zones because of the greater flow of blood there. Again, it should be emphasized that this is only a hypothesis.

![Figure 18. Histologic appearance of centrilobular emphysema. Note destruction in region of respiratory bronchioles but sparing of peripheral alveoli (from Heppleston and Leopold).](image-url)
I'd like to conclude by briefly discussing some very recent data. We have been examining the various ways in which gravity affects the distribution of the bloodstream, ventilation, gas exchange, pleural pressure, alveolar size, and mechanical stresses. It would be of considerable interest to know how the lung behaves in the absence of gravity, that is, when weightless. Such a measurement is clearly very difficult to perform, but in about 1981, the National Aeronautics and Space Administration (NASA) will be launching Spacelab, and we have been preparing for some years now to measure pulmonary function in this exotic laboratory. A battery of single-breath tests has been prepared, and this was recently exhaustively tested during a simulated Spacelab experiment at the Johnson Space Center in Houston.

The year 1981 is a long way off, and recently, Dr. David Michels, who is in charge of this experiment in our laboratory, took the mass spectrometer and other equipment to the NASA Ames Research Center in Mountain View, Calif, and mounted the experiment in the passenger compartment of a NASA Learjet. It is possible to fly this relatively high-performance aircraft in a parabolic profile and so obtain up to 25 seconds of weightlessness. In this way, we were able to obtain the first measurements of the effects of weightlessness on the distribution of ventilation in the lung.

We used the familiar single-breath nitrogen washout, in which the subject takes a breath of 100 percent oxygen vital capacity and then exhales slowly to residual volume (RV). A bolus of argon was also introduced at RV, and the concentrations of nitrogen and argon were plotted against the expired volume. Figure 19 shows the results of performing the test under normal conditions (1 g) while the aircraft was flying straight and level. Note the cardiogenic oscillations of nitrogen and argon on the alveolar plateau and the abrupt terminal rise in the concentrations of both gases toward the end of the

**Figure 19.** Single-breath nitrogen washout performed under normal conditions (1 g). Bolus of argon was added at beginning of test inspiration. Note cardiogenic oscillations and terminal rise in levels of both argon and nitrogen.

**Figure 20.** Same test as Figure 19, but test inspiration was taken with subject weightless, while expiration was done under conditions of 2 g. Virtually no cardiogenic oscillations or terminal rises in levels of argon or nitrogen are seen. This indicates that normal topographic distribution of ventilation was abolished by weightlessness.

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expiration.

There is not time to go into the mechanism of this well-known pattern in detail; however, both the cardiogenic oscillations and the terminal rises are believed to reflect the topographic inequality of ventilation caused by the effect of gravity on the lung. We were therefore very interested to see what happened when the test was performed under conditions of weightlessness.

Figure 20 shows the results when the test inspiration was made at zero g, but the test expiration was carried out at 2 g. This sequence is one of the most informative, because the presence of acceleration during expiration ensures that the lung empties sequentially and thus reveals any topographic inequality in the distribution of inspired gas. Note the striking reduction of cardiogenic oscillations on the alveolar plateau and the absence of any abrupt terminal rise toward the end of the tested expiration. The conclusion that we reached from a number of experiments like these is that virtually all of the topographic inequality of ventilation in the normal lung can be ascribed to gravity.

Let’s summarize the regional differences which we have been discussing (Fig 21). The distribution of bloodflow is normally very uneven, with the apex only barely perfused under resting conditions. The distribution of ventilation is also uneven, but the difference between apex and base is not as marked as for that of the flow of blood. As a result, there is mismatching of ventilation and perfusion at different levels, and this is responsible for regional differences in gas exchange; for example, the apex of the lung has a relatively high PO$_2$ but low PCO$_2$. The low PCO$_2$ is responsible for a high pH in the end-capillary blood. It seems likely that these regional differences in gas exchange may affect the growth of organisms and possibly the efficiency of the defense mechanisms of the lung.

The apex of the lung is relatively overexpanded, while the base is relatively compressed. This distortion is probably caused by the weight of the lung itself and is associated with a more negative intrapleural pressure at the apex than the base. Finally, the apex of the lung is a highly stressed region, which is therefore particularly vulnerable to mechanical failure. Centrilobular emphysema is a disease in which this distribution of stress may play a factor in the localization. I am sure that we do not fully understand all of the implications of these regional differences of structure and function in terms of the development of pulmonary disease, and this seems to be a fruitful area for further study.

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REFERENCES
8 Permutt S, Bromberger-Barnea B, Bane HN: Alveolar pressure, pulmonary venous pressure and the vascular...