Pulmonary Physiology, Pathology, and Ventilation-Perfusion Studies

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Much of our present understanding of regional lung function derives from experiments using radioactive tracers. Today studies of regional pulmonary blood flow and regional ventilation are readily available in most nuclear medicine laboratories.

This review serves to emphasize the relationships between lung structure, function, and pathophysiology and to relate these to the procedures that are currently performed in nuclear medicine.

AIRWAYS AND ALVEOLI

The airways divide about 16 times, in an irregular dictotomous fashion, before the terminal bronchioles are reached. Beyond this level, the respiratory bronchioles divide two to seven times to reach alveolar ducts, alveolar sacs, and alveoli. Although the walls of the bronchi contain cartilaginous plaques, much of their support, and all that of the bronchioles, comes from the meshwork of surrounding alveoli extending through the lobules, segments, and lobes to the pleural surface. Smooth muscle and connective tissue encircle the bronchial tree from the larynx to the alveolar ducts. It is important to realize that the cross-sectional area of the bronchial tree increases very rapidly beyond the terminal bronchioles, and that airflow rates, pressure differences, and airway resistance are very low here during normal breathing (*1–3*).

The alveoli are packed together like the cells of a honeycomb. They are surrounded by a three-dimensional network of collagen and elastic fibers, which is continuous with that of the airways and blood vessels and extends to the visceral pleura. The structural arrangement ensures considerable stability, because changes in one alveolus—for instance, shrinkage—will be mitigated by opposite changes in surrounding alveoli (*4*).

The communications between alveoli (pores of Kohn) become more numerous in older subjects, and allow collateral ventilation to take place. The canals of Lambert, which extend from respiratory bronchioles to neighboring alveolar ducts and sacs, may serve a similar function (*5*).

The mucosa of the bronchial tree is lined by a ciliated columnar epithelium as far as the terminal bronchioles. A few goblet cells are found in the larger airways. Bronchial glands lie beneath the mucosa. Clara cells are found protruding through the cilia in increasing numbers as the terminal airways are approached. The alveoli are lined by Alveolar Type I cells, with Alveolar Type II cells, or granular pneumocytes, occupying the corners, while the alveolar macrophages creep about the surface of the alveoli, removing inhaled debris. A thin film of surfactant, produced by the Alveolar Type II cells, spreads as far as the entrance of the terminal bronchioles. It may well be continued up the peripheral airways, perhaps produced by Clara cells, to mingle with the mucous blanket that starts at the terminal bronchioles and moves continuously towards the larynx at an ever-increasing velocity (*6*).

BLOOD VESSELS AND LYMPHATICS

The pulmonary arterial branches follow the divisions of the bronchial tree. The pulmonary arterioles that accompany the terminal bronchioles are about 100 μ in diameter, while the precapillary vessels are about 35 μ in diameter and number 250–300 million, each vessel serving one alveolus. Anastomoses between the pulmonary capillaries and bronchial capillaries may be found along the respiratory bronchioles. Each alveolus is surrounded by about 1,000 capillaries in a richly interlacing pattern (*3*). The

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capillaries are 7–10 μ in diameter with endothelium that seems to have quite tight junctions. The pulmonary veins drain blood from the alveolar capillaries, as well as the peripheral parts of the airways and the pleura. They lead towards the hilum separately from the bronchial tree at the periphery of lobules, to empty into the left atrium.

The bronchial arteries usually arise from the aorta, and accompany the airways, nourishing them as well as the pulmonary arteries and veins. Small bronchial veins drain into the right atrium. Anastomoses with pulmonary capillaries exist as indicated above, and most of the venous return from the bronchial circulation is through the pulmonary veins.

The pleura is richly supplied with lymphatic vessels. Within the lung parenchyma, lymph vessels start in the interstitial spaces and gather around bronchovascular bundles. Their endothelium has large fenestrations, and they are equipped with valves, directing lymph flow towards the hilar lymph nodes. Lymphatics are not found around alveoli.

MECHANICS OF BREATHING

During normal tidal breathing, the volume of air in the lungs at the end of each expiration—called functional residual capacity—is determined by the balance between the elastic recoil forces of the lung and the elastic recoil forces of the chest wall. The recoil forces in the lung are due in part to the structural arrangement of the alveoli, with the collagen and elastic fibers intertwined within their walls, and in part to the surface tension generated by surfactant. The surface tension increases as the lungs get larger, and so do the forces developed by the structural arrangement of alveoli and connective tissue. Thus, as the lungs expand, greater pressures are required to draw in more air, and likewise a greater force is available to expel air.

Compliance of the lungs depends not only on their structural integrity but also on the degree of expansion. For instance, as total lung capacity is approached, the lungs become less compliant (that is, they are stiffer) than they are at functional residual capacity. The intrapleural pressure is typically less than atmospheric (about 5 cm H_2O less at functional residual capacity), because the recoil forces in the lung tend to collapse the lung, pulling inwards against the parietal pleura. The weight of the lung within the thorax causes this pressure (negative with respect to the atmosphere) to be unevenly distributed from top to bottom of the lung. Intrapleural pressure is most negative (about -10 cm H_2O) at the top of the lung, where the weight of the lung has very little influence, and least negative (about -2.5 cm H_2O) at the bottom, where the effect of the weight is greatest. This means that in healthy lungs the alveoli at the top of the lung are more expanded than those at the bottom, and hence less compliant. Thus during normal tidal breathing more air will enter the lower part of the lung because this region is more compliant and expands more for a given change in pressure than the upper part (*7–10*).

This effect of gravity, or acceleration, is seen in any position. The more dependent parts of the lung exchange more air for a given change in pleural pressure than the less dependent parts. However, the support of the lungs within the chest, the shape of the thorax, variations in local pleural pressure over ribs or interspaces, and the use of intercostal muscles or the diaphragm may all influence the distribution of a breath within the lungs and so modify the effect of gravity or posture.

Any disease process that alters lung compliance on a regional basis will alter the local compliance. For instance, inflammatory, edematous or fibrotic disease processes are all associated with decreased compliance, largely because the inflammatory exudate, edema fluid, or collagen tissue infiltrate the lung parenchyma or fill the alveoli and require a greater force to overcome them than healthy lung tissue. Such regions will shrink in volume, and also receive less air than surrounding normal lung during each breath. Destruction of lung parenchyma by emphysema is associated with an increase in static compliance because the structural basis for elastic recoil and surfactant are lost.

The compliance of the chest wall can also be altered by conditions such as obesity and kyphoscoliosis, in which it is reduced, or muscular paralysis, in which it is increased.

The airways offer resistance to airflow—resistance being an expression of the ratio of the driving pressure to the airflow rate. It has been shown that about half of the total airway resistance lies above the larynx. Within the bronchial tree, however, most airway resistance lies in the larger airways. Only 10–20% is accounted for by the vast majority of small airways (arbitrarily referred to as those less than 2 mm in diameter) (*11*). In the larger airways, air flow is turbulent and the pressures required to generate flow are influenced by the square of the velocity of the gas and by its density. In the smaller airways where air flow is thought to be laminar, Poiseuille's Law holds good: resistance to flow is directly proportional to the length of the tube and inversely to the fourth power of the radius. In such small airways, gas density plays no part in resistance to airflow. Gas viscosity influences both turbulent and laminar flow, but its effect on turbulent flow is very small.

During inspiration the airways expand and airway resistance diminishes. During expiration they narrow and, towards residual volume, airway resistance increases several-fold. As air-flow rates increase, flow becomes more turbulent and airway resistance increases (*12*).

Expiration during a tidal breath is a passive process, the energy coming from the elastic recoil forces within the lungs. During a forced expiration, pleural pressure is increased. The driving force in the alveoli is the sum of both pleural pressure and elastic recoil pressure. However, the pleural pressure is transmitted to the airways and will compress them at that point along the airways where pleural pressure just exceeds the pressure within the airway. This so-called "dynamic compression of the airways" limits the maximum air-flow rates that can be generated during a forced expiration. The force causing the air to leave the lungs, once dynamic compression occurs, is elastic recoil. Because elastic recoil gets less as lung volume diminishes, so air-flow rates lessen as lung volume diminishes.

Airway resistance is increased in any condition associated with narrowing of the airways, such as bronchospasm, edema of the bronchial walls, excess mucus, or tumors, strictures, or foreign bodies. In addition, any process that weakens the support of the airways within the lung and allows them to become distorted, such as emphysema, will be associated with increased airway resistance. A further mechanism for reduced air-flow rates in emphysema is the loss of elastic recoil, the main driving force for expiration.

The amount of air entering any given region of the lung will be related to both local compliance and local airway resistance. The product of these two—called the time constant—gives an indication of the time required for proper expansion of the lungs; this will be shorter in lungs with low compliance and longer in those with high compliance, or high airway resistance, or both. This also applies on a regional basis, so that some parts of a lung may require more time than others to fill or empty properly. If the time for a breath is shorter than this, ventilation becomes more uneven and the lungs begin to behave as if they were stiffer. Such lungs show frequency dependence of dynamic compliance: that is, as the respiratory rate increases, dynamic compliance decreases (*13*).

BLOOD FLOW

The lungs are remarkable because the full cardiac output passes through them at such a low driving pressure—the mean pulmonary artery pressure being 11 mm Hg. Pulmonary vascular resistance (the ratio of pressure to flow) is much less than that in the systemic circulation. Even in states of high cardiac output—such as during exertion—the pulmonary arterial pressure rises very little; vascular resistance actually decreases.

Gravity, acceleration, and posture play important parts in the distribution of blood flow within the lungs. As with ventilation, the support of the lungs within the chest, and the shape of the thorax, may modify the effect.

The low pulmonary arterial pressure is barely sufficient to raise blood to the apices of the lungs in the upright position, so that very little blood flows there. In this region of the lungs, alveolar pressure exceeds pulmonary arterial pressure and the capillaries are virtually closed. Once pulmonary arterial pressure exceeds alveolar pressure, blood flow increases and the flow rate then depends on the difference between these two pressures. Pulmonary venous pressure exceeds alveolar pressure farther down in the lung, and at this point the driving force for blood flow is the difference between pulmonary arterial pressure and pulmonary venous pressure. Both increase together relative to alveolar pressure so that capillaries are more dilated, offering less resistance, and flow increases further (*14*). At the bases of the lungs, interstitial pressure is thought to compress the extra-alveolar vessels, reducing blood flow. The vertical gradient of blood flow is least at residual volume and greatest at total lung capacity. In addition, vascular resistance increases at the extremes of the lung volume. As residual volume is approached the extra-alveolar vessels are compressed, while towards total lung capacity the capillaries are stretched thin. Although the intraluminal pressures are different, the lung parenchyma offers support to the blood vessels just as it does to the airways (*10,15–17*).

VENTILATION-PERFUSION RATIOS

In the upright position, breathing at functional residual capacity, ventilation per unit volume increases one and a half to twofold between the upper zones and the lower zones, while blood flow increases three- to fivefold (*18*).

The different gradients in ventilation and blood flow down the normal upright lung mean that the ratio in which ventilation and blood flow mix is not uniform. In fact the ratio changes from about 2 or 3 in the apices to about 0.6 in the bases. It has been calculated that at the apices the PO_2 and PCO_2 are 132 and 28 mm Hg, respectively, while at the bases the figures are 89 and 42 mm Hg. In spite of this, the overall performance of the lungs leads to a fall of only 4 mm Hg in the PO_2 between alveolar PO_2 and arterial PO_2, the PA-aO_2 gradient, is a convenient measure of how closely ventilation and per-

fusion are matched. The worse the match, the greater the difference, indicating the presence of disease.

Determination of the ratio of physiologic dead space to tidal volume, (V_D/V_T) calculated from the modified Bohr equation

$$\left[V_{D_{phys}}/V_T = \frac{PaCO_2 - P_ECO_2}{PaCO_2}\right],$$

provides a useful indication of the inefficiency of ventilation by showing what proportion of each breath is wasted. Likewise, determination of the amount of physiologic shunting by using the shunt equation

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{C\acute{c}O_2 - CaO_2}{C\acute{c}O_2 - CvO_2},$$

(where $\dot{Q}s$ is shunt flow, $\dot{Q}t$ is cardiac output, and CaO_2, CvO_2, and $C\acute{c}O_2$ are the oxygen contents of arterial, mixed venous and end pulmonary capillary blood, respectively) gives a useful indication of wasted blood flow.

Calculation of the alveolar-arterial oxygen-tension difference and measurement of physiologic dead space and shunt provide an indication of the extent of the failure to match ventilation and blood flow, as well as providing a symbolic way of representing this in terms of additional dead space or a right-to-left shunt. When studies of regional ventilation and blood flow are combined to provide "functional" or "parametric" images of the ventilation-perfusion ratios, it is sometimes possible to visualize where in the lung the major problem is situated. Such functional images do not represent the real ventilation-perfusion ratios. This is partly because it is most unusual to measure alveolar ventilation and cardiac output during these studies, but more importantly because the inequalities of ventilation and blood flow are average values of the many lung units in the cores of tissue being viewed by the detector. The degree of ventilation-perfusion inequality detected by external counting considerably underestimates the degree of inequality actually present in the lung.

TECHNIQUES TO STUDY REGIONAL VENTILATION

Studies of regional ventilation should permit an assessment of the effects of alterations in local compliance and airway resistance, as well as of lung volume (*18*).

Radioactive xenon is most widely used, but its solubility in blood and tissue is a disadvantage when measurements of regional ventilation are to be made from washout curves. Nitrogen-13, which is considerably less soluble, serves as a standard for such measurements (*20*), while krypton-81m offers a new approach to this problem (*21*).

Two rather different methods of studying regional ventilation are in vogue. In the quasi-static method, radioactive xenon is inhaled to total lung capacity and its distribution measured during breath holding. The gas is then rebreathed, through a closed circuit with a CO_2 absorber, until equilibrium is reached, at which time its distribution is again measured during a breath held at total lung capacity (*9,22*).

After normalization, the regional distribution of activity of the single breath is divided by the regional distribution of activity at equilibrium (which represents lung volume) to give regional ventilation per unit lung volume.

In the dynamic methods, measurements of regional count rates are made continuously during a washin of radioxenon to equilibrium and then during the washout while breathing air (*23,24*). Methods of "quantitating" these studies fall into two groups:

1. Most commonly the time during the washout, for the count rate to fall to 50% of the equilibrium count rate, is used as an expression of ventilation; the longer the time the worse the ventilation. Modifications of this idea include the time to 50% or 90% of the equilibrium value during the washin, or measurements of the turnover time from the washout phase, which require knowledge of functional residual capacity and minute ventilation (*7*).

2. Less commonly, rate constants are derived from the regional washout curves. These may be obtained by curve stripping, or by arbitrarily fitting a straight line to a semilog plot of the first 50 or 60% of the washout curve, or by using the height/area approach, which measures the mean rate constant.

The quasistatic and dynamic methods are often combined in a single study, starting with a single breath, proceeding to equilibrium during a rebreathing phase, and finishing with the washout study.

In studies in which the distribution of a single breath to total lung capacity is compared with that of lung volume (at total lung capacity), the results indicate how much air entered a part of the lung in proportion to the local lung volume. For slow breaths the distribution will depend more on local compliance than airway resistance, while for a rapid breath airway resistance will dominate the distribution (*19*). Since no exchange of air is determined, the results, strictly speaking, should not be referred to as ventilation. For instance in patients with obstructive airway disease, air may enter a region but may *not* be exchanged with any there before being expired (*25*). If single-breath studies are to be used clinically, the rate of inspiration should be controlled.

Measurements based on washin and washout studies relate more closely to ventilation or the exchange

of air. How much air is actually exchanged in a breath depends on how large the breath is (i.e., on tidal volume), and also on how large the physiologic space is. The greater the V_D/V_T ratio, the smaller the proportion of the tidal breath that is actually exchanged. In measurements made over time, several breaths will take place, so that the frequency of ventilation will also influence the rate at which equilibrium is approached, and likewise the rate of clearance.

Measuring the half-times of clearance—i.e., the time to 50% of the equilibrium activity—is a convenient and much-used way of expressing regional ventilation. It must be distinguished from $T_{1/2}$. The $T_{1/2}$ is derived from the clearance curve and is inversely proportional to the rate constant (λ),

$$\lambda = \frac{0.693}{T_{1/2}},$$

and is usually determined from semilog plots of the washout data.

Measurement of the mean rate constants from washout curves gives an indication of the efficiency of gas exchange, that is, what proportion of local lung volume is actually being used for exchange. For such calculations, the solubility of radioxenon in blood and tissue must be considered, and the chest-wall and pulmonary-vascular contributions to the count rate should be allowed for, in order to obtain more realistic figures for regional ventilation (*20,25*).

Comparisons of the clearance of radioxenon and of the less soluble nitrogen-13, measured from the washout following equilibrium, have shown that the activity in the chest wall accounts for about 25% of the difference in clearance rates, while the xenon in the pulmonary vasculature accounts for the remaining 75% of the difference (*26*).

The inhalation of boluses of radioxenon at different lung volumes permits determination of the regional distribution of lung volumes and the regional distribution of different parts of a single inspiration. Similarly, radioxenon has been used to measure closing volume, but this can be done as accurately, and with no radiation to the patient, using either the single-breath nitrogen test (the resident-gas technique) or boluses of other, nonradioactive tracer gases, such as argon or helium (*27,28*).

Increases in closing volume merely reflect disease processes affecting the small airways in a nonspecific, though quite sensitive, fashion. Closing capacity (closing volume plus residual volume) increases with age and overlaps functional residual capacity in the seventh decade. It has also been shown to be increased in apparently healthy (but often symptomatic) cigarette smokers, in obesity, and in patients with early obstructive airways disease, pneumoconiosis, ischemic heart disease, or cirrhosis of the liver (*27,29*). In childhood, closing volume has been shown to overlap functional residual capacity at the age of 6; it then decreases to unmeasurable levels by the end of the second decade (*30*).

Krypton-81m, with a half-life of only 13 sec, provides a unique way of studying regional ventilation. Theoretical considerations suggest that during tidal breathing, an equilibrium is reached when the count rate is proportional to ventilation per unit lung volume. The relationship, moreover, is almost linear (*21*). Excellent agreement has been found in comparisons between measurements of regional ventilation using xenon-127 or nitrogen-13 and krypton-81m. Furthermore, rapid changes in regional ventilation may be studied, because equilibrium is reached within a minute or so of the change.

TECHNIQUES TO STUDY REGIONAL PULMONARY BLOOD FLOW

Regional blood flow was first studied using $C^{15}O_2$. This gas is very soluble, and after inhalation is rapidly removed from the lungs by blood flow, the rate of clearance being proportional to blood flow (*31*). The less soluble gas radioxenon, or the even less soluble gas radionitrogen, may also be used, but the principle governing their use is different. These gases are dissolved in saline and given intravenously. As they reach the alveoli they come out of solution and enter the alveolar air. During breath holding their distribution is proportional to blood flow. Krypton-81m may be given by continuous i.v. infusion. The physical decay of this radionuclide is so rapid that its distribution is proportional to blood flow, which enables rapid changes of pulmonary blood flow to be visualized almost instantaneously (*21*).

Today studies of pulmonary blood flow usually involve the i.v. injection of labeled particles of albumin—either microspheres or macroaggregates. For a reliable indication of relative blood flow, there must be enough particles (more than 15,000 is adequate; 60,000–150,000 plenty) and they must be properly mixed with the blood stream to ensure that they are accurately tracing blood flow. Mixing takes place as the particles traverse both chambers of the right heart before entering the pulmonary circulation (*32–37*).

In infancy and childhood, the number and size of the pulmonary vessels are important considerations in determining the number of particles to inject. Too few will cause irregularities in the apparent distribution, and too many can compromise the available vascular bed.

Because these particles are trapped in the termi-

nal pulmonary arterioles and capillaries, their distribution reflects pulmonary arterial blood flow to these regions (*34*).

When the relatively insoluble gases radioxenon and radionitrogen are used, they give an indication of capillary blood flow to air-containing alveoli, particularly those in the more proximal parts of the primary lobules. Areas with pneumonic consolidation, infarction, or atelectasis will appear to have no blood flow using these gases.

BASIC MECHANISMS UNDERLYING DISTURBANCES IN REGIONAL LUNG FUNCTION

The distribution of pulmonary arterial blood flow is altered by changes in cardiac output, and also by changes in resistance in the pulmonary arteries or veins. An increase in cardiac output, such as occurs in exertion, causes a more uniform distribution of blood flow, with loss of the normal gradient. Increases in resistance in the pulmonary vasculature may be brought about by changes in the vessels themselves, by changes in the lung parenchyma, or by elevations of left-atrial pressure.

It should be remembered that alveolar hypoxia is a powerful vasoconstrictor of the pulmonary arterioles. Local pulmonary arteriolar constriction takes place in response to a diminished concentration, or pressure, of oxygen in the airway, but not in the blood (*38,39*).

A number of disease processes directly affect the pulmonary arterial tree, the commonest problem here being pulmonary embolism (*37,40,41*). Pulmonary emboli, fat emboli, amniotic-fluid emboli, air emboli, and others may all produce defects in blood flow by partial or complete obstruction of pulmonary vessels. Pulmonary stenosis, pulmonary arteriovenous fistulae, pulmonary vasculitis, and the loss of pulmonary capillary bed in emphysema or interstitial fibrosis may all alter the distribution of pulmonary arterial blood flow.

Compression of the pulmonary vessels by tumor or enlarged lymph nodes at the hilum, or tumor invasion of the pulmonary veins (which is usually accompanied by thrombosis) and, much less commonly, invasion of the pulmonary arteries may also cause changes in blood flow (*42*).

Increases in left-atrial pressure in mitral stenosis or left-ventricular failure cause a redistribution of blood flow from the bases towards the apices. For the same elevation of left-atrial pressure, the redistribution of flow is more marked in mitral stenosis than it is in left-ventricular failure (*43,44*).

The underlying disease process can be localized to the pulmonary vasculature with considerable confidence, but not complete certainty, when it is found that ventilation of the affected region is preserved, or clearly less impaired than blood flow (*41,45*).

Another group of mechanisms relates to reductions in blood flow secondary to alterations in ventilation. The diseases collectively known as chronic obstructive airway disease are the chief offenders (*46–49*).

Local hypoxia is thought to play the major role here. It is brought about by uneven ventilation, which is due to local changes in airway resistance and compliance. As mentioned earlier, airway resistance may be increased by mucous plugs, bronchoconstriction, bronchial-wall thickening, or grossly distorted airways. Compliance will increase in emphysema, but diminish in other parenchymal processes. When the diminution of blood flow is due to hypoxia, it can be altered favorably by administration of oxygen or bronchodilators. In some of these diseases, particularly emphysema, there is also loss of capillary bed, leading to a further diminution in blood flow.

Local bronchial obstruction by foreign bodies, tumors, or mucous plugs may also cause diminished ventilation, with local hypoxia and a reflex local diminution in blood flow. The local reflex vasoconstriction that accompanies local hypoxia is somewhat variable and rarely reduces blood flow to the same extent as the reduction in ventilation. Such regions have low ventilation-perfusion ratios, and hence the blood leaving them is hypoxic. Atelectasis and pneumonic consolidation are extreme examples, with no ventilation and greatly reduced blood flow. What blood flow there is acts as a right-to-left shunt, causing hypoxemia.

The last mechanism is compression of the lungs by pleural effusions or large hearts. The apparent defect in blood flow and ventilation corresponds to the volume of lung occupied by the fluid or the heart.

It simplifies thinking about pulmonary diseases to divide them into those in which the predominant effect is a diminution in static compliance and those in which there is an increase in airway resistance. In both categories the process may be local or general. For instance, compliance is diffusely reduced in conditions such as diffuse fibrosing alveolitis or pulmonary edema, but locally reduced in pneumonia or atelectasis. Airway resistance is diffusely, but irregularly, increased in asthma, chronic bronchitis, and emphysema, but locally increased in obstruction due to a foreign body or large endobronchial tumor.

In the restrictive lung diseases, measurement of regional ventilation and blood flow are generally of little clinical value. They are considerably more useful in obstructive airway disease, partly because early disease is quite readily recognized but more especially for their help in the differential diagnosis of

suspected pulmonary embolism. Here the impact of ventilation studies has largely been to show which patients had obstructive airway disease to account for their abnormal perfusion scans, thereby improving both the sensitivity and specificity of the technique (*41*).

Locally delayed clearance from the lungs means locally impaired exchange of air, and this could be due to local small-airways disease or a more proximal partial or complete obstruction—complete at the segmental level because exchange can take place between segments through the pores of Kohn. Widespread irregularly delayed clearance may be due to generalized obstructive airway disease, but a similar appearance is seen in hypoventilation due to drug overdose, or neurologic disorders such as myasthenia gravis or peripheral neuropathies, or many other causes of alveolar hypoventilation, including the Pickwickian syndrome.

Increased clearance implies hyperventilation, and is likely to be seen in diseases in which compliance is decreased, such as diffuse interstitial fibrosis, early heart failure, and other causes of pulmonary edema.

Images obtained at equilibrium indicate the distribution of lung volume. In moderate to severe obstructive airway disease, however, it is unusual to reach equilibrium in 3–4 min (a time that is often used for the washin, since longer times increase the radiation burden), so that many so-called "equilibrium images" do *not* show the distribution of lung volume. The uneven patterns seen in these situations accurately reflect the worst-ventilated parts of the lung. Defects at the end of a washin will also be seen with pneumonic consolidation, infarction, atelectasis, and pleural effusion.

Whether single-breath or washout techniques are used, these tests measure aspects of lung function that are different from regular pulmonary function tests such as Forced Vital Capacity, Forced Expiratory Volume in one second, and airflow rates. The Forced Vital Capacity is after all a forced maneuver, an attempt to study the patient's maximum performance at this time, while a washin-washout study is done during resting tidal breathing and reflects the usual exchange of air in the alveoli.

In children with cystic fibrosis, the whole-lung clearance of radioxenon has been shown to be correlated with Forced Expiratory Volume at 1 sec and Peak Flow Rates (*50*). In adults with obstructive airway disease, the whole-lung clearance has been correlated with Forced Expiratory Volume at 1 sec and Maximum Mid-flow Rate, less well with ratios of Forced Expiratory Volume-$_1$-to-Forced Vital Capacity, and with $PaCO_2$ but not PaO_2. The correlation coefficients are 0.7 or less and, although statistically significant, serve as useful reminders that these tests are looking at different aspects of lung function (*25*).

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