value of $P_{1}CO_2$ is obtained from a collection of expired gas

$$\frac{V_D}{V_T} = \frac{(P_aCO_2 - P_{1}CO_2)}{P_aCO_2}$$

This is spoken of as the $V_D/V_T$ or wasted fraction of each tidal breath. Multiplying this fraction by the tidal volume or minute ventilation gives the volume of physiological dead space or wasted ventilation. Dead space has the effect of diluting the CO2 content of expired air below the alveolar level. Since the body needs to expire a certain volume of CO2 per minute the effect of a low $P_{1}CO_2$ requires more total ventilation to maintain homeostasis.

In carrying out a measurement of physiological dead space, it must be remembered that the volume of air in mouthpiece, connections, and valve (mechanical dead space) will also contribute CO2-free air to the expired collection.


Further Reading


**Collateral**

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Abstract

When an airway in the lung becomes obstructed, there exists the possibility for that obstructed region to get limited ventilation through pathways that are commonly called collateral channels. Ventilation that results from such pathways is called collateral ventilation. Collateral ventilation may have functional roles in both normal and pathologic situations. Several different channels have been suggested as the site of such ventilation, with the alveolar pores of Kohn being most commonly cited. However, when considering the anatomy and physiology of such potential pathways, it is highly unlikely that these alveolar pores could provide sufficiently low resistance to account for the measured magnitude of collateral flow. Rather, the interbronchial channels of Martin, which exist at the level of the terminal bronchiole, are far more likely to be the primary site of collateral ventilation. These collateral channels exist in nearly all mammalian species. In humans, the collateral channels have been shown to be altered in lung pathology, particularly in both emphysema and asthma. Measurement of the collateral resistance may provide the only means of directly measuring the dimensions of most peripheral airways in the lung in living subjects.

Introduction

The term collateral ventilation refers to ventilation of a region of lung through ‘collateral’ airways. In vernacular usage, the word collateral has several relevant definitions, including ‘accompanying, but secondary or subordinate’ and ‘corresponding in rank or function’. Nearly all reviews of collateral ventilation have emphasized this secondary nature, ignoring the corresponding nature of the collateral airways. This has led to a common notion that not only are the specific collateral airways responsible for collateral ventilation in some way different from the normal airways but also they take no part in normal ventilation. This is not the case. Collateral airways are in fact normal airways that are normally ventilated with each breath. However, the secondary nature of ventilation through these collateral airways can arise if and when a larger airway becomes obstructed. In this case, collateral ventilation to the obstructed region can now occur via increased flow through a limited number of normal airways.

To provide a functional definition of collateral ventilation, one first must consider an anatomical region of lung parenchyma served by a given bronchus. Within this region ventilation normally occurs through that bronchus via the standard airway branching pattern from larger to smaller airways. Collateral ventilation to this given region then refers to any ventilation that arrives from a neighboring airway branching structure. Collateral ventilation can thus be defined at any level of airway branching. In pathologic conditions in which airway obstruction may occur at any airway size, collateral ventilation may thereby serve partially to bypass the obstruction. However, in the common practical measurement of collateral ventilation with a clinical bronchoscope or wedged catheter, the collateral communications are those that occur between distinct segmental bronchi.
Pathways for Collateral Flow

There are three possible pathways for collateral ventilation: channels of Lambert, pores of Kohn, and channels of Martin. However, of these possible channels, the channels of Martin comprise the major functional pathway for collateral ventilation. The location and potential contribution of each of these are discussed separately.

Channels of Lambert

In 1955, Lambert first described accessory bronchiolo-alveolar communications in normal human and cat lungs. These channels consisted of epithelialized tubular communications through the bronchiolar wall to adjacent alveoli. The size of the channels varied from being practically closed to up to 30 μm in diameter. A later study suggested a potential role of these channels in the pathogenesis of pneumoconiosis, where it was observed that the Lambert channels and adjacent alveoli contained a high concentration of macrophages. The channels could be found associated with nearly every parabronchiolar accumulation. These channels of Lambert may be involved in the pathogenesis of pneumoconiosis, but there is little evidence showing how these channels relate to functional measurements of collateral flow. Although it is clear that these channels exist in many species, there is considerable doubt whether these channels can provide collateral ventilation when obstruction occurs at the level of segmental bronchi. Channels of Lambert never arise from segmental bronchi or allow communication between parenchymal regions served by different segmental bronchi. Thus, although the channels of Lambert might provide accessory collateral ventilation to adjacent alveoli, were obstruction to occur at a level smaller than terminal bronchioles (i.e., at the level where collateral ventilation is measured in experimental situations), the channels of Lambert would not otherwise be expected to play any significant role.

Alveolar Pores (Pores of Kohn)

The functional description of alveolar pores dates back to the middle of the nineteenth century, and this early work is reviewed elsewhere. However, when one closely examines the anatomical and physiologic literature regarding these pores, it becomes fairly clear that alveolar pores are unlikely to be normal pathways of collateral ventilation. The key anatomical evidence is related to the size of the pores. The diameters reported by various investigators range typically from 2 to 30 μm, and there simply are not enough of these tiny high-resistance pathways to allow much flow. In addition, the pores are almost certainly blocked by fluid in a living animal. The method of fixation plays a significant role in the size and appearance of the alveolar pores observed histologically. Since the alveolar wall is almost completely vascularized in the healthy lung, it is crucial to study lungs that have been fixed with the capillaries filled. When one views casts of the capillary network, it can be appreciated that normal pores, to the extent they are patent, could hardly be much larger than half a capillary diameter. In addition, these small intercapillary spaces in the alveolar wall are partially filled with structural fibers. The importance of fixing the lungs with the vessels filled cannot be overemphasized, but this is rarely done.

In considering how much pressure it would take to open an alveolar pore that was filled with fluid, theoretical calculations show that it would require approximately 200 cmH2O. Such a high pressure would never occur in normal lungs. Thus, when either airway obstruction occurs in vivo or when collateral resistance is measured, the pressure differential that might be expected across a pore is generally less than 30 cmH2O. It is clear that in the normal lung the alveolar pores are not patent. The relative unimportance of pores of Kohn to functional collateral ventilation is demonstrated by the fact that pig does have alveolar pores of Kohn, despite there being a complete absence of measurable collateral ventilation. Further evidence of such pores being nonfunctional was supplied by studies in which pulmonary vasculature pressure was decreased. If one considered alveolar pores to be the collateral connections, then one would predict that decreases in capillary dimensions would tend to enlarge the pores in the intercapillary spaces, thereby decreasing the resistance. However, experimental results show just the opposite (i.e., collateral resistance increases).

Channels of Martin

In 1966, Martin reported a painstaking histologic study of the interlobular septum in a dog lobe in which he first marked the collateral pathways by aerosolizing India ink and blowing this through a wedged catheter and the collateral pathways. Following fixation, 1600 serial sections (10 μm thick) were cut through the intersegmental plane, and he traced the track left by aerosolized India ink to outline the collateral airways. Martin showed connections at the level of the respiratory bronchiole and alveolar duct. This connection, at a level near the alveolar duct, was emphasized by Macklem in his 1971 review, in which he also noted that Martin seemed to have misinterpreted the histologic sections shown in his paper. However, subsequent schematic
drawings by most other investigators have led to the general impression that channels of Martin are simply short segments of bronchi connecting other bronchi. This impression is wrong.

Quantitative analysis suggests that the channels of Martin by themselves have sufficiently low resistance to account for the observed degree of collateral ventilation. However, since Martin's work was carried out in canine lungs, it is reasonable to ask if the communications described by him appear in other species, especially humans. Unfortunately, because of the difficulty of these anatomical studies, there is only limited evidence from other species. Nevertheless, such communications between different bronchi through the alveolar duct have been demonstrated by several investigators in human lungs. Boyden studied a wax reconstruction of the lung from a 6-year-old child and described the same kind of communication found by Martin. In addition, several casting studies with infusion of separate colors into adjacent segmental bronchi always showed one color passing into another, and the communicating airway was almost always at the level of a terminal respiratory bronchiole.

In summary, the pathways described by Martin have sufficiently low resistance to account quantitatively for the degree of collateral ventilation measured as described in the next section. To the extent that some large alveolar pores might be patent at the segmental borders or that channels of Lambert might originate from larger bronchi, the quantitative contribution of such auxiliary communications to collateral ventilation is likely to be very small. One can therefore conclude that the primary pathways for collateral ventilation are normal airways that connect at the level of the terminal and respiratory bronchioles.

**Measurement of Resistance through Collateral Pathways**

A simple method of measuring the resistance through collateral pathways was first described in 1970. This method consists of first wedging a small double lumen catheter or bronchoscope into an intralobar bronchus. A flow of gas is then passed through one lumen and the other lumen is used to measure pressure (Figure 1). At end expiration, the pressure in the trachea is atmospheric, and one can then divide the measured pressure by the known flow to calculate a resistance. Although many investigators have called this collateral resistance ($R_{coll}$), it is clear from Figure 1 and the preceding discussion that the resistance includes the entire airway sequence from the end of the wedged catheter down through the alveolar duct/respiratory bronchiole connections and back up the airways of the adjoining segment out to the trachea. Because most of the resistance to this flow occurs in the very smallest peripheral airways, the notation $R_p$ is preferred for this resistance. Indeed, based on theoretical calculations, it can be shown that in the normal lung more than 90% of the resistance of this pathway would be in the respiratory bronchioles and alveolar ducts. Although this may not be true under all pathologic conditions, a simple calculation of resistance through single airways indicates that there would have to be extreme constriction for airways with baseline diameters larger than 0.5 mm to offer any substantial resistance.

However, precisely where in the airways the resistance occurs in this technique, is not always certain since it will depend on the exact airway dimensions and the number of airways in parallel. It is worth noting that to the extent that $R_p$ does measure the dimensions of the most terminal bronchioles, respiratory bronchioles, and alveolar ducts, these airways (in what is sometimes called 'the silent zone') cannot
be assessed by any other pulmonary function tests. Since all conventional measures of airway resistance in the whole lung can only reflect airways in which there is a pressure drop resulting from bulk flow, these measurements are completely insensitive to changes in these very peripheral airways. However, when $R_p$ is measured, only a relatively few number of these peripheral airways are ventilated. This has the effect of increasing the rate of bulk gas flow much above normal, to the point at which there is now a measurable pressure drop. Again, it is important to emphasize that these ‘collateral’ airways are not different from normal airways. Without airway obstruction, they are normally ventilated with inspiratory and expiratory flows. They also show a similar sensitivity to pharmacologic challenges as normal small airways. Their uniqueness only arises from the fact that they can be supplied by two distinct larger bronchi. When measured with a wedged catheter, the flow may be transiently increased to obtain a resistive pressure drop, but this does not render these airways any less normal. There is also general agreement that increasing lung volume results in a substantial decrease in collateral resistance. This is a result of the increased outward acting forces of interdependence exerted on the airways of the surrounding lung and obstructed segment by the increased segment volume. Therefore, since the collateral airways behave exactly like normal bronchi with regard to the effect of lung inflation, this experimental approach thus provides a unique and probably the only means to assess the dimensional changes of very peripheral airways in vivo.

**Species Variation**

Collateral ventilation has been measured in several species, including man, dog, horse, cat, rabbit, and ferret. The pig lacks any pathways for collateral flow that can be experimentally measured. Comparing the relative magnitude of collateral ventilation in the different species is difficult because it requires some form of normalization to compare for different size lungs. The collateral ventilation will clearly depend on how much of a lobe is wedged in addition to the extent of collateral airways. Considering the extremes, if the wedge occurs in a lobar bronchus of a completely independent lobe, the collateral ventilation through the wedge must be zero. At the other end, if one were to wedge at the level of a single alveolar duct, the collateral ventilation must also be zero. Thus, at intermediate levels, wedges progressing from the lobar bronchus down to an alveolar duct, the collateral ventilation must first increase and then decrease. The shape of such a plot of collateral ventilation versus distance along the airway tree has not been well defined theoretically or experimentally. In one of the two studies that did address this important issue experimentally, the investigators found that moving the wedged catheter by an average of 2 cm had no effect on collateral resistance in sheep lungs. In contrast, in the other study, the investigators found that in dog lungs, advancing the wedged bronchoscope tip into the lobe a short distance resulted in a doubling of the collateral resistance. The reason for this discrepancy is unclear. Whether it relates to anatomical differences in the species studied or methodological or technical differences has not been determined.

It has been speculated that the extent of collateral ventilation in different species is related to the degree of hypoxic pulmonary vasoconstriction. The teleological rationale presented for this speculation is that if an animal can compensate for airway obstruction with collateral ventilation, then a strong hypoxic pulmonary response is not required. At least for two animals with extreme variations of hypoxic vasoconstriction, the pig and the dog, this hypothesis would seem to hold. The dog constricts poorly to hypoxia and has low collateral resistance, whereas the pig has one of the strongest hypoxic vasoconstrictor with no collateral ventilation. However, this conjecture breaks down when one considers that the ferret also has a strong hypoxic vasocostrictr response, but the collateral resistance is quite low.

**Changes in $R_p$ with Age and Pathology**

Collateral ventilation has been shown to increase with age in post-mortem and living human lungs. Reasons for this increase are unclear, but $R_p$ is also known to increase with age in dogs, despite an increase in the size and number of alveolar pores. With such an increase in pore size, the only plausible interpretation is that the most peripheral airways likely narrow with age. However, not all species show this effect. For example, in sheep there is a significant decrease in the resistance to collateral flow with maturation. Reasons for these discrepant results regarding the effects of age on collateral ventilation are unclear, and thus this remains an unresolved controversy.

There is limited information regarding changes in collateral resistance in lung disease. Several investigators have shown a substantially lower resistance to collateral flow in emphysematous lungs compared to normal lungs. A decrease in resistance to collateral flow might be expected in emphysema since with the destruction of alveolar walls there would not only be a progressive enlargement of the alveolar ducts but
also creation of new pathways through the missing walls. This concept has been supported by imaging results showing relatively large interlobar collateral pathways. The importance of collateral pathways also has impact on several new potential treatments for emphysema. One treatment actually involves the creation of new collateral channels (with physical implants) to allow emphysematous regions to empty more efficiently. Another method to empty emphysematous regions, which involves one-way valves placed in the airways, seems to be significantly improved by the presence of existing collateral channels. With regard to asthma, if collateral ventilation were to be beneficial in this disease with narrowed airways, such patients should have a lower resistance. However, direct measurements show just the opposite: asthmatic subjects have nearly an order of magnitude higher resistance to collateral flow than normal subjects. This striking separation between asthmatic and normal subjects suggests that the very small airways that comprise the $R_p$ may reflect early pathologic changes in lung structure. This was further emphasized by the fact that the asthmatic subjects all had normal lung function as assessed with spirometry. It is thus possible that measurement of $R_p$ might prove to be a sensitive method for the early detection of obstructive lung disease. Consistent with this conjecture are results showing that the airways responsible for $R_p$ also contract more vigorously when stimulated with very dry air.

See also: Ventilation: Overview; Control. Ventilation, Mechanical: Negative Pressure Ventilation; Noninvasive Ventilation; Positive Pressure Ventilation; Ventilator-Associated Pneumonia.

Further Reading


