Eur Respir J
1989, 2, 893–904

REVIEW

# Anatomy and physiology of collateral respiratory pathways

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**ABSTRACT: When complete obstruction of an airway occurs, ventilation and gas exchange distal to the obstruction can be preserved if "collateral ventilation" exists. Three collateral pathways have been described: the interalveolar, the bronchioloalveolar and the interbronchiolar communications. The various techniques used to measure collateral flow, resistance, compliance and time constant are described, with particular attention to those trying to separate the resistances of intrasegmental and collateral pathways. The relative importance of collateral ventilation in humans and animals is shown; factors affecting this ventilation are described: type of flow, lung volume, surface tension, alveolar $CO_2$, pulmonary circulation and oedema, cholinergic and adrenergic receptors, histamine, interdependence. Parenchymal diseases disturb collateral flow; on the other hand, collateral channels can provide alternative pathways in various human pathologies.**
*Eur Respir J., 1989, 2, 893–904*

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Keywords: Alveoli; collateral ventilation; pores of Kohn.

Received: July 29, 1988; accepted after revision June 1, 1989.

## History and location of collateral respiratory pathways

### *Interalveolar communications*

The interalveolar communications were first described in the lung almost 100 years ago by KOHN [1], but disagreement persisted for years amongst pathologists as to whether they exist normally or develop during disease, senescence, after tobacco smoking, or are only artefacts formed during fixation of the lung.

The potential significance of these channels was largely ignored until 1931 when VAN ALLEN and co-workers [2] were puzzled by the observation that complete obstruction of an airway was not always followed by alveolar collapse of the upstream lung. In a series of ingenious experiments, they demonstrated that ventilation and gas exchange distal to a bronchial obstruction could be well preserved. They adopted the term "collateral respiration" to describe the ventilation that bypassed the obstructed airway [2].

In 1936, MACKLIN [3] stimulated by the physiological studies of Van Allen's group, re–evaluated the old opinion that pores were produced during fixation of the lung and showed that the interalveolar communications could actually be found in dogs, cats, rabbits, guinea-pigs and rats: the size of these communications ranged between 3 and 13 μm in diameter [3]. The dog is the most studied species: MARTIN [4] reported that there are approximately eight interalveolar communications per alveolus in dogs. However, whilst reviewing the results of Martin, MACKLEM [5] estimated that the counts had been made "per alveolar wall" rather than "per alveolus". If so, each alveolus in the dog lung might contain about 50 pores. Many theories have speculated about the origin of these pores: their scarcity at birth and large quantity during old age lead to the conclusion that they appear during life. Since the mechanical stretch of the alveolar wall during ventilation widens any intercellular hole, the vacated positions of the macrophages migrating from the wall to the lumen of the alveoli could be maintained empty and open and pores be created [4]. Any condition of macrophage activation could then increase the number of pores, *e.g.* tobacco-smoking, air-pollution, infections.

The role of the interalveolar pores in collateral ventilation has not yet been defined. We know from the studies of VAN ALLEN *et al.* [2] that, when airways are obstructed, pathways for ventilation are provided by the communications between obstructed and non-obstructed portions of the lung; however, whether these pathways are the same as the alveolar pores seen in fixed sections of the lung is not known [6].

From the beginning, classic studies have assumed that the collateral ventilation in the mammalian lung occurs by way of the alveolar pores of Kohn [7]. Further studies have supported that belief: MENKES *et al.* [8] inactivated surfactant of dog lungs with kerosene and found that, with the increase of surface tension, the resistance of the collateral pathways (Rcoll) decreased whether comparisons were made at equivalent pressures or volumes. They reasoned that the alveolar pores have two radii of curvature, one parallel to the alveolar wall and the other at right angles to the wall: any increase in surface

tension around the latter radius of curvature should open the pore. Thus, they concluded that alveolar pores provide the major pathways for collateral ventilation [8]. It is nevertheless disturbing that the increase of surface tension and the subsequent decrease of collateral resistance were simultaneous to an increase of the effective compliance of the segment where they performed their measurements. The opposite could have been expected! Despite the fact that they tried to explain discordance by mechanisms such as a heterogeneous distribution of kerosene between the segment and the surrounding lung, or the suppression of the contribution of surfactant to interdependence between adjacent units within the lung, it is likely that changes occurred in segment volume that could be responsible for changes in collateral resistance: this could make their conclusion a little questionable.

In a subsequent study, FLENLEY *et al.* [9] measured the gas tensions in air samples aspirated distally to a bronchial obstruction during controlled ventilation in dogs. As the bronchus was occluded, air had to be supplied by the surrounding lung through collateral pathways. They found that these "collateral air" samples had oxygen tension ($Po_2$) values between alveolar and arterial and carbon dioxide tension ($Pco_2$) values close to those in arterial blood. Thus, they showed that collaterally ventilated lung units are contaminated with alveolar gas of the surrounding segments and concluded, like Menkes, that alveolar communications could provide the major route for collateral ventilation without excluding a possible pathway through small airways. It is nevertheless disturbing that further studies have shown that the size of the pores of Kohn at physiological transpulmonary pressure (0.5–1.5 kPa) (5–15 $cmH_2O$) is very small (1.2–2.2 μm) [10] and that most are closed by surfactant [11].

MARTIN [12], using Laplace's law where $P=2\lambda/r$ (P is the opening pressure, λ is the surface tension, r is the radius) and a value λ of 0.47 $N \cdot m^{-1}$ (47 $dynes \cdot cm^{-1}$) [13], calculates the theoretical opening pressure for a collapsed alveolar pore: 19.2 kPa (192 $cmH_2O$). Since such pressure differences do not occur in normal lung, larger pathways must exist for collateral ventilation. Later, MENKES and TRAYSTMAN [6] found that resistances through both collateral channels and small airways decrease as lung volume increases, perhaps with the collateral resistance (Rcoll) decreasing slightly less. Thus they suggested that the route for airflow either through peripheral airways or through collateral channels tends to remain the same at different lung volumes and that collateral channels behave like "small airways". We must conclude that, if the pores of Kohn supply interalveolar communications, physiological studies suggest that larger collateral pathways do exist.

### *Bronchioloalveolar and bronchiolobronchiolar pathways*

In 1955, LAMBERT [14] discovered that there were accessory bronchioloalveolar communications extending from respiratory bronchioles to alveolar ducts and sacs subtended by the bronchiole. Their size ranged from "practically closed" to 30 μm in diameter. Later, MARTIN [12] was able to pass polystyrene spheres up to 120 μm in diameter from one segment of the canine lung to another, through the collateral channels. He reasoned that, unless Lambert's canals are remarkably compliant, there must be additional larger collateral airways. He showed that respiratory bronchioles connecting terminal bronchioles from adjacent lung segments do exist in dogs [12]. Similar bronchiolobronchiolar communications were also recently demonstrated in human lungs [15].

Physiological studies suggest that these pathways provide the major route for collateral ventilation. TRAYSTMAN and co-workers [16] have shown that the distension of pulmonary vessels surrounding collateral pathways has trivial effects on Rcoll measured at functional residual capacity (FRC). Since it seems unlikely that alveolar pores could escape the effects of capillary distension, they concluded that bronchioles provide the major route for collateral ventilation at FRC [16]. Similar conclusions can be inferred from a study by SASAKI *et al.* [17]: using excised dog lungs, these authors measured the collateral resistance between separate groups of alveoli by measuring pressure and flow in capsules glued onto the multipunctured pleural surface in front of every alveolar zone. When the main airway opening was closed, collateral ventilation appeared to occur mainly through the regular airway system. When the segmental bronchi were occluded, collateral flow appeared to occur within the segment through its airway system, and through the intersegmental collateral channels to other segments. When the airway was obstructed down to the bronchiolar level with silicone rubber, the collateral resistance became extremely high. It can, thus, be concluded that collateral resistance at the alveolar level is considerably higher than collateral resistance through the airway system [17]. Three collateral pathways have, therefore, been described: the interalveolar, the bronchioloalveolar and the interbronchiolar communications (fig.1). Their respective importance is unknown.

## Measurement of collateral ventilation and resistances

### *Former studies*

These gave measurements of the various parameters of collateral ventilation in excised animal and human lungs. In their classic study, WOOLCOCK and MACKLEM [18] rapidly injected a small quantity of air into a lung segment through one lumen of a double-lumen catheter wedged in a bronchus: the pressure recorded from the other lumen increased abruptly whilst the subtended air spaces became distended and fell rapidly back to the original value as air escaped through the collateral channels. That situation is analogous to an electrical circuit where a step charge on a capacitor (the segment) discharges passively through a resistor (the collateral pathways) to the ground (the surrounding lung): the fall of voltage is exponential and its time constant is defined as the time at which the voltage is 36.8% of its original value. If the lung is analogous, the time constant for

collateral ventilation (T) can be similarly measured during the fall of pressure and is the product of the resistance (R) of the collateral channels and the compliance (C) of the subtended segment ($T=R \times C$).

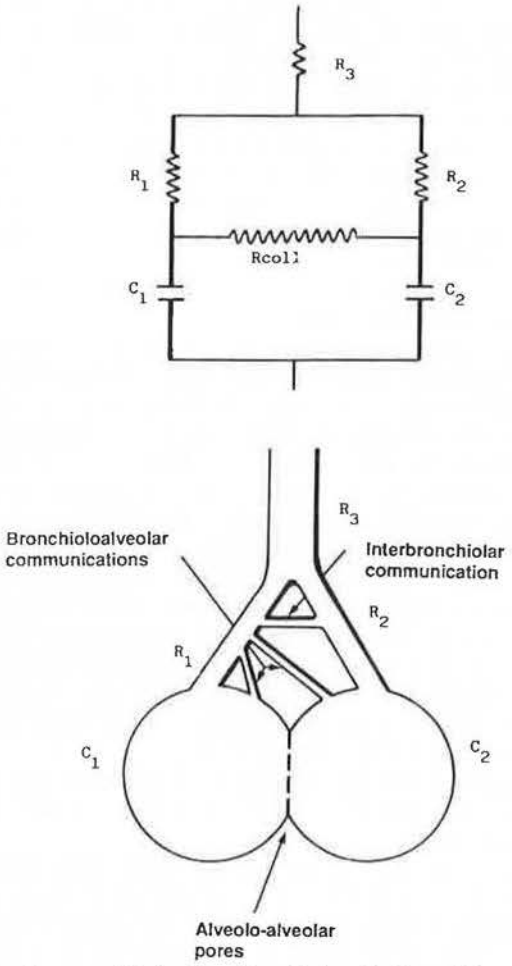


Fig. 1. – Lung model of collateral ventilation: $R_1$, $R_2$ and $R_3$ are the bronchial resistances and Rcoll is the collateral resistance. $C_1$ and $C_2$ are the compliances of both pulmonary units. The various pathways for bronchial and collateral ventilations are summarized.

If both the volume injected and the peak distending pressure are measured, the effective compliance of the subtended segment can be calculated. The resistance to collateral flow can consequently be computed, R=T/C [18]. This technique is mainly useful if collateral resistance is relatively high. If collateral resistance is low, the infused volume leaks from the segment very rapidly, and therefore the estimation of effective segment compliance from the peak change in pressure and the injected volume is inaccurate.

WOOLCOCK and MACKLEM [18] showed that the emptying of rapidly inflated air spaces through collateral channels is not a single exponential process whether the resistance of collateral channels is alinear or the volume subtended is comprised of two or more compartments in parallel, each with its own time constant for emptying. They chose to analyse their data as if the volume subtended was comprised of two or three compartments with differing mechanical properties, although they acknowledged that it would be incorrect to conclude that this is actually the case. They, therefore, developed a second technique with the purpose of measuring a mean time constant for collateral ventilation of a segment: a lung lobe is held at a given volume and oscillated by applying a sinusoidally varying pressure to the bronchial cannula at various frequencies by means of a loudspeaker powered by a sinewave generator, while the pressure is measured inside an isolated segment of the lobe through the wedged catheter.

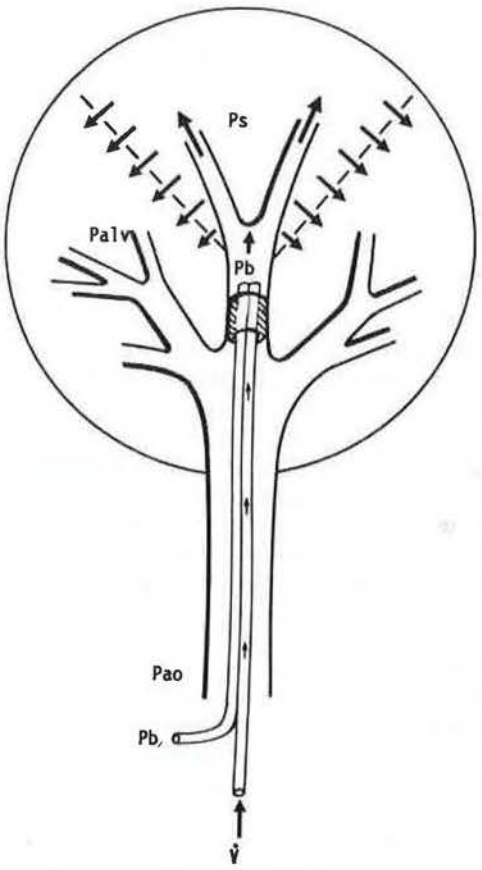


Fig. 2. – Hilpert's technique for measuring collateral ventilation with a catheter wedged in a lung segment. $\dot{V}$ is the gas flow blown through the segment. Pb is the pressure in the airway immediately distal to the tip of the catheter. Ps is the pressure in the segmental alveoli. Palv is the pressure in the alveoli of the surrounding lung. Pao is the pressure at the mouth. $(Pb - Ps)/\dot{V}$ = resistance of intrasegmental small airways. $(Ps - Palv)/\dot{V}$ = Rcoll

The volume of the lobe is plotted against the pressure inside the segment on a storage oscilloscope: a loop is obtained. To a close approximation, volume is in phase with the difference between alveolar and pleural pressure, whereas the pressure difference between the obstructed segment and the pleural surface is assumed to be in phase with the volume change in obstructed alveoli. The phase angle by which pressure lags behind volume is determined by the time constant for collateral ventilation: phase angle=$\tan^{-1}$ ($2\pi$ frequency) $\times$RC, where RC is the time constant. The assumption that the pressure difference and the volume difference are in phase could

lead to an overestimation of the time constant for collateral ventilation and of the collateral flow resistance. On the other hand, the technique used to measure the effective compliance of the segment (peak pressure) can underestimate the effective compliance, overestimate the degree of interdependence and overestimate collateral flow resistance [18].

*Presently published studies*

Most of these use the so-called Hilpert's technique for investigating collateral ventilation *in vivo* in animals and humans [6]. A flow of gas ($\dot{V}$) is blown into an isolated segment through a catheter wedged in a bronchus, and the pressure drop between the pressures in the segment (Pb) and the surrounding lung (Palv) is measured (fig. 2): the collateral resistance can be computed; Rcoll=(Pb-Palv)/$\dot{V}$.

*Separate measurements*

Since the resistance measured by this technique is the sum of the resistance of intrasegmental airways and that of collateral pathways, some techniques have been attempted to measure these two resistances separately. Using isolated dog lungs, ROBINSON and MUKHTAR [19] inserted, from the pleural side, firstly a subpleural catheter into the wedged segment and secondly a subpleural catheter into the surrounding lung. They used the pressure drop from the wedged catheter to the segment subpleural catheter to calculate the airway resistance in the segment, and the pressure drop between the two subpleural catheters to calculate the collateral resistance. They concluded that in isolated dog lungs there is a significant airway resistance within the segment. This method was attempted during vagal stimulation in open-chest, living dogs but discontinued because of the haemorrhage following the puncture of the living lung [20].

The second method, by SMITH *et al.* [21], partitions the total resistance by use of a "curve stripping" technique, where the difference between the initial pressure and the extrapolated pressure at zero time is used to calculate airway resistance in the wedged segment: a double-lumen catheter is wedged into a peripheral bronchus under the direct vision of a fibreoptic bronchoscope and pushed during lung inflation to assure perfect wedging (fig. 2). The response characteristics of the catheter and pressure recording system have to be analysed by the method described by OLSON and ROBINSON [20] to establish the lower limit of the time constant values that can be detected and the 90% response time of the system.

One lumen of the catheter provides a channel for the constant infusion of gas ($\dot{V}$) while the second lumen allows the measurement of pressure distal to the tip of the catheter (Pb). Flow is administered into the wedged segment of the lung until a steady-state of end-expiratory Pb is reached. The mean flow of gas is in the range 0.2–8 $ml \cdot s^{-1}$ in recent studies [22–24]. These values must be far below those able to give a drying effect with consequent constriction [25]. When the steady-state of end-expiratory Pb is reached, the ventilation is stopped and measurements of Pb and $\dot{V}$ are made in apnoea at FRC. The flow is then suddenly discontinued (fig. 3): Pb decays as the obstructed segment empties into the surrounding lung through the collateral channels. In most measurements, stopping the flow is followed initially by an obvious fast drop in Pb, followed by an exponential decline in Pb (fig. 3). This difference in the speed of Pb decline also occurs in most other measurements where it is not immediately obvious by inspection but can be perceived by calculation of data [21]. The initial drop in Pb is attributed to resistance in the intrasegmental airways, whereas the subsequent gradual decline is attributed to deflation of the distended obstructed segment through collateral channels [21].

When plotted as a percentage of pressure change on semilogarithmic paper, the subsequent gradual decline in Pb approximates to a single exponential: thus, the rate at which the pressure decreases can be conveniently described by the time it takes to achieve 63% 1/e of the total decrease [6]. In order to allow calculations of small airways resistance (Rsaw) and of the mechanics of collateral ventilation, measurements of Pb are made every 0.2 s for 1 s after stopping the flow. The pressure in the obstructed segment of lung (Ps) prior to the cessation of flow is then calculated from an extrapolation through zero time of a least-square linear regression of the logarithm of the 0.2 s measurements of Pb (fig. 3). Pb - Ps at zero time is assumed to represent the pressure drop in the airways during constant flow [21, 26]. It must be emphasized that the measure of Rsaw with this technique sometimes gives values so low that Rsaw cannot be estimated [27].

The following calculations are made from the data obtained: resistance to collateral ventilation, Rcoll = Ps/$\dot{V}$; airway resistance of the obstructed segment, Rsaw = (Pb - Ps)/$\dot{V}$. If the decay of the curves can be described as single exponential functions of time in a first approximation [22], this supports the analysis for Tcoll (time constant) and Cs (effective compliance of the segment) as described: the mechanical properties of the isolated segment are then characterized by treating it as a capacitive element discharging through a resistance. The time constant is measured as the time necessary for pressure to decay to 37% of its initial value. Since the time constant is determined by the product Rcoll × Cs [28], the compliance of the obstructed segment Cs = Tcoll/Rcoll [18]. Strictly speaking, Tcoll defines a system having constant Rcoll and Cs within the range of measurements [6]. Cs is the "effective" compliance of the segment, that is to say the change in volume of the segment divided by the change in the pressure difference between the alveoli of the segment and the pleural surface; it is not necessarily the "true" compliance of the segment [18]. If either Rcoll or Cs increases during a pathological process, the segment will take a longer time to empty and Tcoll will be extended. There is a wide range of Tcoll values with this technique (0.4–4 s in dogs) [21, 22, 29]. This range depends on the lung volume, and on the volume of the

obstructed segment. Of course, these factors are also the cause of the large range observed for Rcoll and Cs. Another potential factor of variability is the place where the catheter has been wedged: wide variations in these three parameters are observed according to the lobe where the catheter is situated, with the longest time constant in the right middle lobe [30–32].

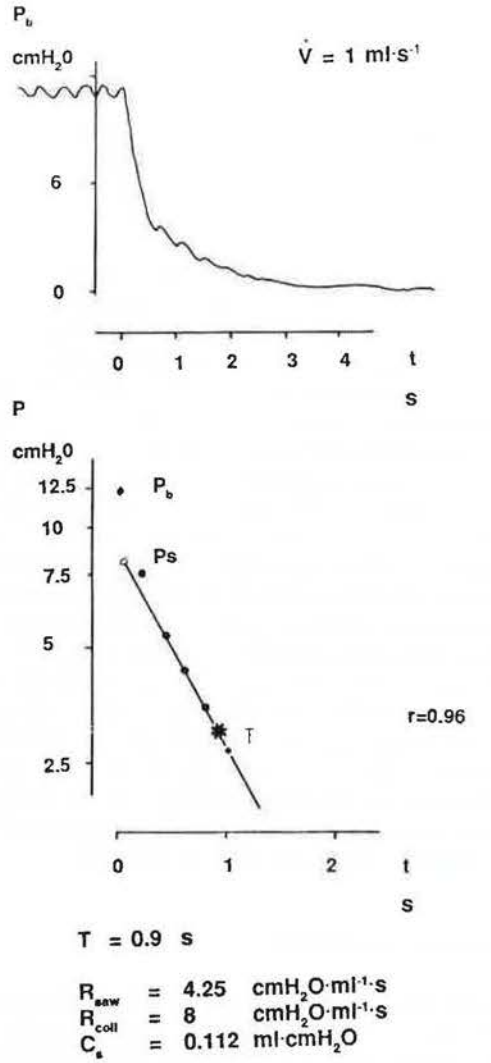


Fig. 3. – Measurement of the decay of Pb (pressure at the tip of the catheter). The top panel shows Pb on the ordinate and time on the abcissa. $\dot{V}$ was the airflow during steady-state. The middle panel shows the values of Pb (●) at 0.2 s intervals after the cessation of airfow: the pressure in the obstructed segment of the lung prior to cessation of flow Ps (○) is calculated as described in the text. Pb - Ps at zero time is assumed to be the pressure drop in the airways during constant flow. r is the regression coefficient of the decrease in pressure (in logarithmic values), as a function of the time t. T is the time constant of the collateral ventilation. Rsaw is the computed resistance of intrasegmental small airways, Rcoll is the collateral resistance of the segment and Cs is the effective compliance of the segment.

With the catheter in different bronchi with the same diameter in the same lobe, a wide range of variations is still observed, depending on other factors such as the volume of the wedged segment, the volume of the surrounding segments and their relationships to pleura.

*Calculation of time constant*

The calculation of the time constant with the former technique assumes the pressure decay to be exponential: it must be emphasized that it is only an approximation and, moreover, restricted to the first part of the pressure decay [6, 22]. When obstruction is induced in the periphery of the lung, significant deviation from a single exponential behaviour occurs: upon examination of the pressure decay curves in dogs, it is obvious that they can deviate greatly from a single exponential behaviour after cholinergic stimulation [20] or hypocapnia (fig. 4) [29]. When seeking the possible causes of double exponential behaviour, one must consider the anatomical arrangement of the segment within the lung: there are several generations of airway between the wedged catheter tip and collaterals, in as much as collaterals are thought to begin at the level of respiratory bronchioles. Because the segment always inflates up to the wedged catheter tip, it might be expected to behave functionally as two compartments, one within the other. The first compartment might represent airways distal to the catheter tip, yet proximal to the collaterals, and the second compartment the collaterals and lung parenchyma [20]. Therefore, Olson and Robinson [20] did not feel able to report a time constant as defined above during airway constriction and calculated instead the time for 90% decay of pressure ($T_{90}$). Since residual positive pressure can be observed at the end of Pb decays during constriction in animals and humans [29, 33], $T_{90}$ cannot always be measured and is difficult to use.

## Importance of collateral ventilation in normals

*Humans*

What is the relative importance of collateral ventilation in proportion to bronchial ventilation in humans in physiological conditions?

If Rcoll is 306 kPa·$l^{-1}$·s (3,060 $cmH_2O$·$l^{-1}$·s) as reported by Terry *et al.* [33] for the middle lobe of supine humans at FRC for an obstructed segment that occupies 5 percent of the lung, then 20 parallel collateral pathways serving the whole lung should have a combined resistance of 15 kPa·$l^{-1}$·s (150 $cmH_2O$·$l^{-1}$·s) which is at least 100 times as great as that for flows through airways [6]. Lower values of Rcoll (4–90 kPa·$l^{-1}$·s (40–900 $cmH_2O$·$l^{-1}$·s) have been found for the lower lobe of upright humans by Bartels [6], but Rcoll of the whole lung always remains much higher than airway resistance. As a consequence, collateral ventilation does not play a significant role in healthy humans, but can become important when airways are obstructed by disease.

*Animals*

Rcoll varies according to the species, depending on the degree of lobulation of the lung. For instance, Rcoll is significantly lower in dogs (0.1–0.33 kPa·$ml^{-1}$·s 1–3

$cmH_2O \cdot ml^{-1} \cdot s$) than in humans (0.3–1 $kPa \cdot ml^{-1} \cdot s$ (3–10 $cmH_2O \cdot ml^{-1} \cdot s$) and horses (0.6–1.2 $kPa \cdot ml^{-1} \cdot s$) (6–12 $cmH_2O \cdot ml^{-1} \cdot s$), and is very high in pigs [18, 33–36]. Since collateral ventilation helps keep interregional oxygen tensions homogeneous, then in its absence (cattle and pigs), local ventilation-perfusion balance must rely on arterial constriction: the additional work causes arterial walls to be more muscular even at low altitude. This characteristic of cattle and swine lungs appears to be a prerequisite for the development of pulmonary hypertension at high altitude. In contrast, species with large collateral ventilation have thin-walled pulmonary arteries and therefore should not sustain pulmonary vasoconstriction at high altitude [37]. The collateral ventilation could then explain why some species with huge collateral ventilation (dogs and sheep) are protected against high altitude pulmonary hypertension while those with poor collateral ventilation (cows and pigs) are not [37, 38]. The species without collateral ventilation may have a greater potential for experiencing regional hypoxia and would have to rely on pulmonary vasoconstriction to maintain ventilation-perfusion balance [38].

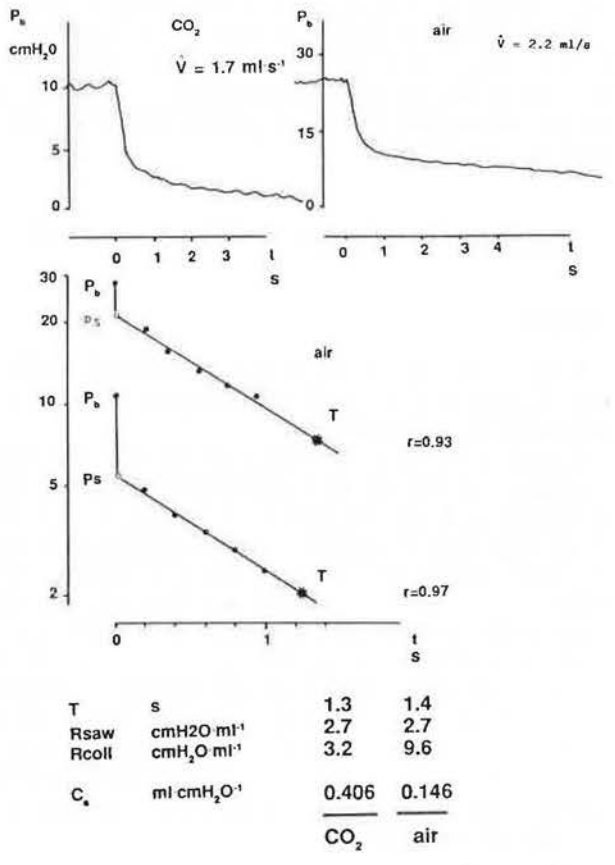


Fig. 4. – Measurements of decay of $P_b$ during both 5% $CO_2$ and air flow (top panel). $\dot{V}$ is the flow of 5% $CO_2$ or air during the steady-state, t is time (s); the middle panel shows the decrease of Pb values on a logarithmic scale, at 0.2 s intervals after air (upper line) and $CO_2$ (lower line) flows. Ps is the pressure in the segment prior to cessation of flow. Other parameters are described in fig. 3. Such an increase of Cs after 5% $CO_2$ infusion is ususual and probably not relevant.

*Age*

Within the same species, Rcoll is high after birth, decreases during maturation [33] and increases with ageing [39].

## Factors affecting collateral ventilation

*Collateral ventilation is a flow*

Despite the fact that diffusion across collateral channels can occur [40], HILPERT [41] has presented evidence that makes diffusion unlikely to be an important mechanism of collateral gas exchange. The collateral ventilation is related to a laminar flow of gas [42], which is controlled by the collateral resistance (Rcoll) to allow the exchange of gas between an obstructed segment and the lung [43]. Since the bronchioloalveolar channels have a muscular wall of their own [14], a regional control of this airflow seems to be possible. When the driving pressure and subsequently the flow are increased into the isolated segment of the lung, resistance to collateral flow decreases in intact dog lungs [26] but increases in excised dog lungs [35]. The discrepency between the findings in excised *versus* intact lungs has not been resolved, although it has been suggested that flow through the segment could become turbulent at the high flow rates used in excised lungs resulting in an increased resistance. This question has been studied by OLSON *et al.* [42], who showed that at Reynolds numbers less than 100 in the airway serving the segment, flow for a collaterally ventilating lung segment remains laminar; their results also showed that the variation in resistance could have resulted from recruitment of airways or variation of the radius of intrasegmental airways: the resistance of structures changes when lung volume changes [42].

*Influence of lung volume*

An increase of the total lung volume decreases Rcoll [6, 18]. Rcoll probably decreases more than the resistance of distal small airways (Rsaw) and the total airway resistance (Raw) while lung volume increases, but Rcoll always remains higher than Raw and Rsaw because its starting value is far more important [26, 44]. Inversely, the ratio Rcoll/Raw increases when the total lung volume decreases [45].

Increasing the size of the subtended segment decreases the Rcoll by enlarging the interface area and the number of collateral pathways connecting the segment with the remainder of the lung [32]. As could be expected, the further the total lung volume decreases, the more important is the influence of the volume subtended segment on Rcoll [46]: at large lobar volumes, airways (including collateral pathways) within the segment are maximally dilated and the stiffness of the parenchyma prevents any significant distortion when intrasegmental pressure is altered; inversely, at low lung volumes (FRC level), these

pathways are affected by changes in transmural pressure due to the increased airway and parenchymal compliance [47].

*Influence of surface tension*

The previously mentioned study of MENKES *et al.* [8] showed that an increase of surface tension can decrease Rcoll. Rcoll is then related to the surfactant layer, which could close the alveolar pores by decreasing the surface tension around the radius of curvature at right angles to the alveolar wall. Another possibility could be the complete closure of the pores by surfactant: TAKARO *et al.* [11] have shown that up to 84% of interalveolar apertures can be closed by the surfactant layer. The results of Menkes *et al.* could then be explained by the fact that the disappearance of surfactant could open supplementary pathways for collateral ventilation.

Local changes in the surfactant layer may also affect the degree of interdependence between an isolated segment of the lung and the surrounding lobe. This could be a major factor in altering collateral flow and resistance.

*Influence of alveolar gases*

Blowing air into an isolated segment causes a local hypocapnia that increases the local Rcoll [16, 22]. Hypoxia has the same effect but seems to be active only through a reflex vasoconstriction which decreases the local release of $CO_2$ [22]. The local increase of collateral resistance induced by hypocapnia can be decreased by locally blowing 5% $CO_2$ in air (fig. 4) [16]. This effect could determine the distribution of intraregional ventilation [6]; it varies from one part of the lung to another according to the local ventilation/perfusion ratio [48].

Thus, the hypocapnic response of collateral channels could provide a mechanism for homeostatically redistributing ventilation to areas of the lung that are hypoventilated [21].

The constrictive effect of hypocapnia seems to be diminished during concomitant vagal stimulation or methacholine aerosol [21, 29, 49], probably because, when smooth muscle contraction occurs during any form of cholinergic stimulation, there is little place for a further contraction induced, for instance, by hypocapnia.

*Influence of pulmonary circulation and oedema*

*Pulmonary circulation.* Since collateral pathways are surrounded by vessels, pulmonary circulation could be expected to influence Rcoll. TRAYSTMAN and co-workers [16] have shown that a decrease of the pulmonary vascular flow increases Rcoll. That increase was inhibited by blowing $CO_2$ locally, and could thus be attributed to the local hypocapnia caused by hypoperfusion [16].

Similarly, OLSON and ROBINSON [20] did not find any change in Rcoll during very short cardiac arrest. On the other hand, an increase of vascular hydrostatic pressure does not influence the collateral ventilation [10, 16, 50]. If pulmonary venous pressure increases, Rcoll does not change at high transpulmonary $P_L$ but decreases at low $P_L$: this is probably due to an erectile effect of the veins at low lung volume [51].

*Pulmonary oedema.* On the contrary, oedema increases the collateral resistance as a consequence of alveolar flooding [6, 52, 53]. During the production of pulmonary oedema, the collection of fluid first appears in extra-alveolar interstitial spaces and later in alveoli [54]. The progressive accumulation of liquid in these interstitial spaces from the bottom to the top of the lung modifies the regional distribution of inspired gas [55, 56] whereas no gas trapping or change in the shape of the P-V curve is yet observed [57]; this absence of closure of air spaces has been attributed to the persistence of collateral ventilation at the extra-alveolar early stage of oedema [57]. On the contrary, air trapping and a shift of the P-V curve occurred when alveolar flooding was obvious [58].

*Influence of cholinergic and adrenergic systems*

The stimulation and/or inhibition of cholino- and adrenoceptors should influence the diameter of collateral pathways if they contain smooth muscle in their walls.

*Cholinoceptors.* The effects of vagotomy on Rcoll have been studied by several authors with various results: from no change [20, 59] to slight decrease [27]. The same variability in the results from the literature can be seen with atropine injection: from no effect [60] to decreases of Rcoll of 5% [61], 32% [32] and 44% [48]. The recent studies of BATRA *et al.* [48] showed that the effects of atropine on Rcoll were different according to the place where the bronchial catheter had been wedged in the lung: atropine has a more powerful dilating effect on collateral pathways of the non-dependent lung. Since the ventilation/perfusion ratio is higher in the non-dependent lung, the light local hypocapnia could favour a stronger basal collateral tone at that level and inversely increase the effect of atropine on that basal tone [48]. A small decrease of Tcoll is observed after atropine, and is related to the decrease of Rcoll as the compliance of the segment Cs does not change [32]. Electrical vagal stimulation induces a very slight increase of Rsaw and Rcoll and no change of Tcoll [18, 20, 29].

This poor effect seems to corroborate the results of previous workers showing a decrease of vagal activity towards the periphery of the lung in dogs [62, 63]. The direct local stimulation of cholinoceptors with methacholine increases the resistance to collateral flow in dogs, whether the drug is injected within the segment [21] or added by aerosol throughout the lung surrounding the segment [24]. This effect is immediately inhibited by isoprenaline or atropine injections [24].

Thus, differences exist between the effects obtained during vagal stimulation and methacholine injection in dogs: these two cholinergic stimulations do not have an equivalent action on the cholinoceptors of the collateral

structures [29]; a similar difference has also been shown in lung parenchymal strips in sheep [64]. The possible causes of the differences obtained during vagal stimulation and methacholine injection can be anatomical or physiological: while cholinoceptors may be present in collateral structures and respond to methacholine administration, constriction of collateral pathways will only occur in response to vagal stimulation if the cholinoceptors are innervated [29]. Alternatively, it is possible that there are inhibitory systems which block the effect of vagal stimulation in the periphery of the lung.

*Adrenoceptors.* Sympathetic drugs have a dilating effect on collateral pathways either in the control condition [65] or during cholinergic constriction [24].

### *Histamine*

Histamine increases the resistance (Rcoll) to collateral flow, so that collateral ventilation can cease [6]. It appears to stimulate the smooth muscles directly as neither vagotomy nor hypocapnia influence the response to histamine challenge [27].

The blood flow through both pulmonary and bronchial circulations affects the time course of recovery from histamine-induced constriction in the lung periphery, by affecting the wash-out of histamine and the delivery of histaminase or circulating bronchodilating substances in the blood [66, 67]. On the other hand, the metabolism of muscarinic agents (acetylcholine and methacholine) by specific and nonspecific cholinesterases represents a perfusion-independent mechanism of recovery of the lung periphery [67]. The airways reactivity to histamine in the lung periphery seems to be more important among male mongrel dogs than among females: these variations could be due to hormonal factors [68].

### *Interdependence*

Before concluding this summary on factors influencing collateral ventilation, we must emphasize the importance of interdependence of pulmonary units on the collateral ventilation between them.

If an airway is obstructed, the pressure in the obstructed lung will deviate from the pressure in the adjacent lung, producing a gradient of driving pressure for collateral flow. This gradient of driving pressure, between the isolated segment of the lung and the surrounding lung tissue, and the collateral resistance will together determine the magnitude of collateral ventilation. This gradient of driving pressure depends on the magnitude of interdependence between the two sections of the lung. The interdependence between adjacent portions of the lung may be considerable, so that movements of one portion of the lung are affected by the surrounding lung [69, 70]: interdependence thus tends to promote homogeneous or synchronous ventilation throughout the lung [6]. The magnitude of interdependence is dependent on the geometry of the isolated segment, *i.e.*, the amount of pleural surface and the amount of parenchymal interface. The chest wall increases the effects of interdependence between adjacent portions of the lung [70, 71]. Any increase in lung volume decreases the magnitude of interdependence, but any increase in the volume of the obstructed segment relative to the surrounding lung volume increases the effects of the interdependence [72]. If any tissue distortion occurs with volume change or disease, the effect of interdependence decreases [73]. Interdependence between adjacent portions of the lung favours collateral ventilation provided that the collateral pathways are open.

## Influence of smoke and pollution on collateral ventilation

### *Cigarette smoke*

Cigarette smoke induces an acute increase of collateral resistance in dogs [74]: this response is inhibited by chlorpheniramine and must, therefore, be attributed to a histaminic stimulation. If the constriction is induced by methacholine, it cannot be inhibited by chlorpheniramine. Thus, cigarette smoke does not seem to constrict the collateral pathways through a vagal reflex [75]. The more toxic effect of cigarette smoke on the male population could thus be partially explained by the susceptibility of its histaminic receptors [68].

### *Ozone*

The inhalation of ozone increases collateral resistance immediately but the resistance increases still further after 30 min [60]. The immediate response is inhibited by vagotomy or atropine, and is due to a vagal reflex [61]. The late response is not inhibited by vagal blockade but by chlorpheniramine, and must be attributed to a histaminic stimulation [60]. Moreover, the reactivity of the collateral channels to histamine is increased by ozone inhalation [76]. This constrictive effect of ozone on Rcoll is not related to a decrease in the local pulmonary perfusion [77].

## Influence of parenchymal diseases on collateral ventilation

### *Emphysema*

Diseases of the lung parenchyma can directly affect the resistance of the collateral channels. Despite an increase in the resistance of the intrasegmental small airways, emphysema decreases the collateral resistance [33]. Cutillo *et al.* [78] computed a theoretical model by modifying the classical model of Otis *et al.* [28] and taking into consideration the influence of collateral pathways on pulmonary ventilation (fig. 1). The analysis showed

that the effects of collateral ventilation are negligible when Rcoll largely exceeds airway resistance (as in normal lungs) but become important when marked time constant inequalities with regionally high airway resistance occur with relatively low collateral resistance (as in emphysema). The increase of FRC due to the loss of elastic recoil can also increase the size of the collateral channels in emphysema [45]. Accordingly, collateral ventilation seems to play a more important role in the gas distribution of emphysematous lungs than normal ones [78].

*Fibrosis*

On the other hand, collateral resistance increases in fibrotic segments because lung volume decreases, and because the collateral pathways are involved directly in the fibrotic process [79]. As a consequence, the pulmonary interdependence is unable to decrease the Rcoll of the fibrotic regions during lung inflation because the collateral pathways are directly obstructed.

*Atelectasis*

Similarly, the poor collateral ventilation of the human middle lobe explains why atelectasis of the middle lobe occurs after airways obstruction or infection (middle lobe syndrome) [15, 30]. This poor collateral ventilation is probably due to the greater ratio of pleural surface to nonpleural surface in the right middle lobe, where the segments with a high ratio of pleural surface area to volume should be more prone to atelectasis after airway obstruction [31].

## Implications of collateral ventilation in human pathology

As previously discussed, the relative importance of collateral ventilation in healthy humans is weak. This does not imply that collateral channels do not provide definite alternative pathways for ventilation in disease. Clinical evidence of effective collateral ventilation is seen in young persons when obliterative bronchiolitis develops or when a foreign body or adenoma obstructs a segmental bronchus and no atelectasis occurs. However, the pleural sheet prevents collateral ventilation between lobes when a complete obstruction occurs in a lobar bronchus. The increase of collateral resistance with ageing or with restrictive conditions (obesity, kyphoscoliosis) is one of the mechanisms by which these patients are more prone to develop atelectasis. As previously discussed, frequent atelectasis of the middle lobe after obstruction or infection is due to its particular anatomical properties.

In the idiopathic respiratory distress syndrome of the newborn, disappearance of the surfactant should theoretically open new pathways for collateral ventilation; the alveolar pores are poorly developed in newborns and the lack of surfactant tends to induce alveolar atelectasis.

Local hypercapnia is a regulating mechanism that homeostatically redistributes ventilation from more ventilated to less ventilated units of the lung by dilating collateral pathways; concomitant hypoxia decreases local hypercapnia by inducing arteriolar spasm and, as a consequence, lessens the compensating effect of hypercapnia. Oxygen therapy in obstructive disease could then be useful by dilating pulmonary vessels and opening collateral pathways.

Insufficiency of the left heart induces complex consequences on collateral pathways: a decrease of the blood flow in pulmonary arteries could induce a reduction of local $CO_2$ release and an increase of Rcoll in some parts of the lung, while the increase in pulmonary venous pressure would maintain collateral ventilation in other zones by its erectile effect.

Cardiogenic and noncardiogenic pulmonary oedema close collateral ventilation: one part of the beneficial effects of positive end expiratory pressure (PEEP) on blood oxygen tension is probably due to the opening of collateral pathways by increasing end-expiratory volume.

Patients with emphysema frequently have a lower resistance through collateral channels than through airways; this discrepancy accounts for the preserved oxygenation and increased physiological dead-space in the obstructed patients with emphysema. TERRY *et al.* [33] and MACKLEM [36] suggested that the ventilation through collateral channels could be the mechanism by which improved blood oxygen tensions are observed among emphysematous "pink puffer" patients rather than among bronchitic "blue bloaters" [80]. On the other hand, the closure of collateral pathways prevents similar ventilatory compensation in fibrotic patients.

The acute constrictive effect of cigarette smoke and ozone on collateral pathways is only one of the mechanisms by which they can induce and aggravate obstructive disease: that confirms the importance of preventive action.

Whether collateral ventilation plays a part in reducing the hypoxaemia seen in the asthmatic attacks when airways are closed or obstructed by muscular constriction and mucus is not known. Stimulation of histaminic [27] and cholinergic [21, 24] receptors in the peripheral lung of dogs constricts the collateral channels; the bronchodilators (like sympathomimetics or anticholinergics) could, therefore, be active not only on bronchi, but also on the opening of collateral pathways, when bronchi remain closed by mucus or inflammation [24]. It should be pointed out that bronchodilators could only affect collateral pathways when given by intravenous route; indeed, if airways are obstructed, inhaled bronchodilators cannot reach the collateral pathways. These experimental results in animals have not been confirmed in human asthmatics.

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*Anatomie et physiologie des voies collatérales respiratoires. L. Delaunois.*
RÉSUMÉ: La ventilation et les échanges gazeux peuvent être préservés en amont d'une obstruction bronchique à condition qu'existe une ventilation collatérale. Trois voies ont été décrites pour celle-ci: les communications interalvéolaires, bronchioloalvéolaires et interbronchiolaires. Nous décrivons les différentes techniques utilisées pour mesurer le flux collatéral, sa résistance, la compliance du segment ventilé par voie collatérale, et la constante de temps, en attirant l'attention sur les

techniques qui tentent de séparer les résistances intrasegmentaires de celles des voies collatérales proprement dites. Nous discutons de l'importance relative de la ventilation collatérale chez l'humain et différentes espèces animales, ainsi que des facteurs qui l'influencent: le flux, le volume pulmonaire, la tension de surface, les gaz et enfin les récepteurs cholinergiques, adrénergiques et histaminiques. La fumée de cigarette et l'ozone ont un effet délétère. Les maladies du parenchyme altèrent les voies collatérales, cependant que celles-ci peuvent servir de voies respiratoires de suppléance dans diverses pathologies humaines.

*Eur Respir J., 1989, 2, 893–904*