Resistance of central and peripheral airways measured by a retrograde catheter

PETER T. MACKLEM AND JERE MEAD
Department of Physiology, Harvard School of Public Health, Boston, Massachusetts

MACKLEM, PETER T., AND JERE MEAD. Resistance of central and peripheral airways measured by a retrograde catheter. J. Appl. Physiol. 22(3): 395-401. 1967. Pressure in airways 1.5-2.5 mm internal diameter was measured in open-chested living dogs and in excised lungs from different species with a “retrograde” catheter extending from the lumen through the bronchial wall, parenchyma, and pleura to the manometer. The pressure was used to partition pulmonary flow resistance (RL) into a peripheral resistance (Rp) between the catheter and alveoli and a central resistance (Rc) between the catheter and the trachea. Rp was too small to detect above 80% VC but increased at lower volumes to 15% of RL at 10% VC. RL increased considerably at low volumes due primarily to an increase in Rc. RL increased at high lung volumes as well, usually due entirely to an increase in Rc. The low value of Rp favors equality of gas distribution, but constriction of peripheral airways might affect gas distribution and exchange with little change in Rc. Because lung tissue resistance is included in Rp, it must be a negligible component of Rc in the dogs studied.

Errors and Assumptions

The retrograde catheter offers an advantage over conventional methods of bronchial pressure measurement only if distortions in pressure caused by its presence are less than those caused by other techniques. Unquestionably, the catheter traumatizes and distorts the lung tissue through which it passes and intrapulmonary hemorrhage in that portion of the lung is not infrequently seen at post mortem. Furthermore, the passage of air in and out of that portion of lung is impeded, although we observed that it did fill and empty slowly, presumably through collateral channels. This portion is small because the bell of the catheter was situated 1 cm or less from the pleural surface. Trauma in this area is presumably unimportant in causing an artefact in pressure measurement because the airways to it are blocked by the retrograde catheter and are completely cut off from the rest of the lung. This area is presumably unimportant in causing an artefact in pressure measurement because the airways to it are blocked by the retrograde catheter and are completely cut off from the rest of the lung. As illustrated in Fig. 1, the catheter does not measure pressure in airways leading to the traumatized areas, it measures pressure in a neighboring part of the lung (the wedge of tissue outlined by the interrupted line). The important consideration then is whether or not there is trauma or distortion where the catheter measures pressure. Certainly there is a possi-

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*McLaughlin Traveling Fellow. Present address: Joint-Cardiorespiratory Service, Royal Victoria Hospital, Montreal 2, Canada.
bility that the presence of the catheter could in some way partially or totally immobilize lung tissue for unknown distances in all directions. If this occurred the flow of air past the catheter tip would be less than normal, or conceivably might stop altogether. This consideration allows the establishment of limits for the distortions in flow. At one extreme there would be no distortion in flow and the pressure measured by the catheter would be accurate. At the other extreme, flow past the catheter would stop altogether. In this instance the bronchus into which the catheter opens would act as an extension of the catheter and measure pressure at the nearest branch towards the hilum through which flow is occurring. This will lead to an overestimate of the pressure difference between the alveoli and the catheter tip. If in one extreme, flow is normal, whereas in the other, flow is stopped, then flow must be less than normal in all conditions which lie in between these extremes. Similarly, if when flow is normal, the pressure measurement is accurate, whereas when flow is stopped, the pressure difference along airways peripheral to the point of measurement is overestimated, then this pressure difference must be overestimated in all conditions lying between the extremes.

Because the catheter acts as an obstruction in the peripheral airways by blocking the bronchus in which it is lodged, it causes an error in pressure measurement on this account. This will lead to an overestimate of the pressure difference between the alveoli and the point of measurement to the extent that the intervening resistance is increased by the catheter and an underestimate of the pressure between the catheter and the airway opening to the extent that the resulting flow is less than without the catheter.

Another error results when lateral pressures in a tube are used to measure pressure differences due to frictional resistance, if the linear velocities are different at the points of measurement (g). In our experiments we have related bronchial pressure where the velocity is finite to alveolar pressure where the velocity is negligible. During deflation the pressure difference measured between the alveoli and the retrograde catheter will then overestimate the frictional losses by an amount necessary to accelerate the gas.

Therefore, all three sources of error discussed to this point will overestimate the pressure drop along peripheral airways during deflation. The first two possibilities will overestimate the pressure difference on inflation as well. In general, as will be seen, the pressure differences between the alveoli and retrograde catheter were very small compared to the total driving pressure between the alveoli and the airway opening. This was particularly true above 40% VC where these pressure differences were frequently so small as to be difficult to measure, even during forced deflations with flow rates exceeding 8 liters/sec. At these flow rates, accelerative effects and distortions due to the presence of the catheter should maximally overestimate the pressure difference between the alveoli and the catheter. Therefore, relative to the total driving pressure, the overestimate of pressure along the peripheral airways must be virtually negligible.

In the normal lung all the alveoli fill and empty synchronously with each other (18). If the retrograde catheter changes the mechanical properties of adjacent lung to any significant degree, phase differences between this part and the rest of the lung would be expected. In fact, the presence or absence of such shifts is perhaps the best test of artifacts introduced by the catheter. We did not observe significant phase differences. Dynamic compliance, estimated from the pressure difference between the catheter and the pleural surface, and the tidal volume was independent of cycling frequency over wide ranges, and the same as dynamic compliance measured from transpulmonary pressure and tidal volume. If phase shifts had occurred, dynamic compliance measured by the retrograde catheter would have been frequency dependent and different from dynamic compliance measured by transpulmonary pressure.

Occasionally, damping of the catheter due to mucus plugging was observed. In this instance the pressure difference between the catheter and alveoli is underestimated when pressure changes are applied to the trachea. This is easily detectable as a rise in compliance with frequency (as measured by the retrograde catheter) and a reversal of the direction of the pressure-volume loop. Usually the catheter could be unplugged by flushing it with air. Records which gave evidence of persistent damping despite flushes were discarded.

Once the pressure can be satisfactorily measured it is possible to partition pulmonary flow resistance (RL) into two components—one between the retrograde catheter and the alveoli, the peripheral resistance (Rp), and one between the retrograde catheter and the trachea, the central resistance (Rc). This assumes that the pressure in a single bronchus is representative of all other bronchi in the lung of a similar size. In the normal lung, with compliance independent of frequency (3, 14, 18), this situation presumably pertains and this is supported by the uniformity of results we obtained when pressures were measured in same-sized airways in different lungs.

In the calculation of Rp and Rc the presence of the catheter might have introduced an additional source of error if it had any effect on total flow but, in fact, this effect was negligible.
METHODS

The results to be reported were obtained mainly in eight living young mongrel dogs anesthetized with Nembutal, with their tracheas cannulated and their chests opened widely by a sternal splitting operation. In addition, similar experiments were performed on two living cats as well as on excised lungs from the dog, monkey, and man.

The technique by which resistances were measured is shown in Fig. 2. The lungs or the animal were enclosed in a plethysmograph from which lung volume was obtained. Flow was measured with a Fleisch pneumotachograph and a Sanborn 270 transducer. Suitable pressure taps were available for measurement of pleural and tracheal pressures (Ppl and Ptr, respectively) in addition to bronchial pressure measured by the retrograde catheter. The pressure probes were attached to Sanborn 267B transducers and gave a 90% response to a square wave of pressure in 0.01 sec or less. The dynamic response of the plethysmograph and pneumotachograph was adequate to approximately 15 cycles/sec. The most rapid cycling frequency used in the experiments was 10 cycles/sec. All parameters were recorded on a Sanborn Poly-Viso and pressure flow curves were monitored on a Tektronix 564 storage oscilloscope. Data could be obtained from the oscilloscope directly by storing the image and tracing the curves with an oscillocracer (R. A. Waters, Inc.).

The lungs were oscillated rapidly by a loudspeaker powered by a variable-frequency sine-wave generator. The loudspeaker was in an enclosed chamber. Lung volume was controlled by pressurizing the chamber with air. The air leaked through the speaker cone and inflated the lung to any desired level. The resistances were measured as a function of vital capacity (defined arbitrarily as the volume of air expelled when PTV was changed from 30 to 0 cm H2O).

The living preparations were ventilated on a Harvard pump attached by a three-way tap to the tubing between the pneumotachograph and plethysmograph. Just prior to each resistance measurement the pump was turned out to atmosphere and the animal connected to the loudspeaker. Resistance could be obtained either by storing and tracing pressure-flow curves on the oscillo-

scope or by dividing the amplitude of pressure obtained from the Sanborn tracings by the amplitude of flow.

Rl was measured by relating flow to PTV while oscillating the lungs at their resonant frequency (4, 6, 13, 17). At this frequency the pressure required to overcome inertia cancels that required to overcome elastic recoil and only the flow-resistive component of transpulmonary pressure is measured.

Rp was obtained by measuring the pressure difference between Ppl and PTV, electrically subtracting from the former the pressure due to elastic recoil and relating this to flow at the trachea.

Re was obtained by measuring the difference between Pbr and Ptr and relating this to flow. At the frequencies used Pbr-Ptr had a fairly large inertial component so that there was a phase difference between pressure and flow resulting in a looped pattern on the oscilloscope. This loop was closed, i.e., the phase difference decreased to about 0—either graphically or electrically. The former technique consisted of varying the amplitude of the speaker-cone deflection and measuring the pressure and flows only at points of peak flow when accelerations were zero. This is illustrated in Fig. 3A. The latter method consisted of electrically subtracting from the pressures measured a signal proportional to acceleration. This was obtained by differentiating flow. Examples of the oscilloscope tracings are shown in Fig. 3B. The electrical method appeared to be more satisfactory.
Results obtained in one of the living dogs. Alternatively, Rp and Rc were obtained by measuring Ppl-Pbr and Pbr-Ptr during known constant flow rate deflations from TLC. No accelerations are present during this maneuver except at the very beginning and end so that Pbr-Ptr contains no inertial component. An example is shown in Fig. 3C. Ppl-Pbr, of course, still contains the elastic recoil pressure, but by plotting Ppl-Pbr against volume the deviation of this curve from the static pressure-volume curve gives the flow-resistive pressure drop along the peripheral airways. The results to be reported were obtained by measuring Rp and RL. Rc was estimated by subtraction of Rp from RL. RL was curvilinear and the value measured was the inverse of the slope of the pressure-flow curve as it passed through zero flow. Rp was measured either by the inverse of the slope of the peripheral airways or by measuring the deviation from the static pressure-volume curve of Pbr-Ppl and dividing by flow. No attempt was made to determine the relative flow sensitivity of Rp and Rc although it was our impression that the central airways were more sensitive (see Fig. 3, A and B).

RESULTS AND DISCUSSION

Figure 4 shows the partitioning of resistance in one of the living dogs. Rp is a negligible fraction of the total above 80% VC. Between 80 and 90% it is small but measurable, below 30% there is a distinct increase but it is not nearly as great as the increase in RL as volume diminishes. Furthermore, there is a slight increase in RL at high lung volumes but not in Rp.

Figure 5 shows mean values of RL and Rp and standard errors plotted as a function of lung volume in all eight dogs. At low lung volumes the catheter tended to become obstructed so that 10% VC data were available in only six dogs. The results are closely similar to the results shown in Fig. 4.

Figure 6 shows mean Rp ± se expressed as a percent of RL. Between 80 and 100% VC virtually all of the RL is central. From 80% to 10% VC the relationship between Rp and RL is approximately linear with a slope of -0.20 so that Rp becomes an increasingly greater fraction of RL as volume diminishes. Even so, mean Rp was only 15% of RL at 10% VC. Postmortem dissection of these lungs revealed the retrograde catheters (all of which had a 3-mm bell) to be situated in bronchi 1.5 to 2.5 mm in diameter in the relaxed state, generally in the 10th to 15th generation (estimated by counting the number of branches beyond the lobar bronchus which was termed generation 1). Essentially the same result was obtained in two living cats, two excised monkey lungs, and five excised dog lungs using catheters with 3-mm bells and measuring pressures in bronchi 1.5-2.5 mm internal diameter. In two normal human lungs obtained at autopsy a catheter with a 2-mm bell was required to measure pressure in bronchi where the flow resistance peripherally was comparable to the other species.

Two of the findings illustrated in Figs. 5 and 6 were particularly surprising to us: the increase in RL at high lung volumes, and the small contribution of the Rp to RL. The former result was observed in six of the eight dogs and in each instance the increase occurred in the central airways. There was an increase in Re at high lung volumes in excised cat, monkey, dog, and human lungs as well. Occasionally, in the excised lung, Rp increased as well. It should be remembered that our results were obtained in young dogs anesthetized with barbiturates. In preliminary studies in older dogs, anesthetized with chloralose-urethan, Rp increased at high lung volumes while Re diminished. To our knowledge an increase in RL at high lung volumes has not
been previously reported. At high lung volumes the upper airway presumably accounts for more than 50% of RL (6, 9), so that small increases in lower airway resistance might go undetected. It is unlikely that lengthening of the airway alone can account for the increase. The mean minimal RL occurred at 70% VC so that as volume increased 43% to TLC, mean RL increased from 1.17 to 1.47 cm H2O/liter per sec, or 26%. Airways might be expected to lengthen approximately as the cube root of lung volume, in which case a volume change of 43% would correspond to a change in length of only 13%. The observed increase was twice this value which suggests that narrowing of central airways may have occurred as well. This implies that the airways have different area pressure relationships at different lengths. Such differences have been described for the trachea and the main bronchi in man (10), although they were not present in smaller bronchi in dog lungs (8). Alternatively, the results would be explained if most of the lengthening occurred in bronchi contributing the most to Rc.

Although no attempt was made to compare in any detail the flow resistance of intact and excised dog lungs, there did not appear to be any systematic qualitative differences. If the results in the excised human lungs also are representative of conditions pertaining during life, the flow resistance peripherally in human lungs is much smaller than previously thought. Rohrer (90) estimated that 90% of lower airway resistance was in airways less than 1 mm internal diameter. His measurements were made in collapsed lungs, however, and he apparently underestimated the total number of airways smaller than 4 mm internal diameter (21, p. 124). Weibel (21, p. 195), on the other hand, made careful measurements of airway diameters in human lungs inflated to about 75% TLC and found that the mean diameter of the smallest bronchioles was 0.5 mm (compared to Rohrer's measurements of 0.2 mm). Although there are no data available on how these airways change their diameter with lung volume, Weibel's measurements at least suggest that Rp should be considerably smaller than Rohrer's estimates. In fact, Green (7) and Gomez (personal communication) have used Weibel's measurements to estimate the flow resistance of each generation of the human airway. Green's calculations were based on the measurements made at 75% TLC, and indicate that the resistance of airways between the alveoli and 12th generation should be 10% of the total airway resistance. Gomez corrected all dimensions to a lung volume corresponding to FRC. His estimates are also in close agreement with our measurements. Both investigators assumed a regular dichotomous branching pattern of the tracheobronchial tree. In reality the tracheobronchial tree is irregularly dichotomous and the size of an airway gives little indication of its generation. In the human lung an airway of 2 mm internal diameter may be situated any where between the 4th and 14th generation (21, p. 125). In our experiments the airway in which pressure was measured is obviously determined by its size, not by its generation. Considering this, and that most of our data were obtained in dogs, the agreement between our results and that of Green and Gomez is remarkable.

Because the measurements of Rp in our experiments also include the measurements of lung tissue flow resistance it follows that tissue resistance is negligible. It has been variously estimated at between 40-57% of RL, but no method has previously measured it directly. The measurements of Marshall and DuBois (11) and Ferris, Mead, and Opie (6) are probably the most accurate but include any nonflow-resistive pressure-volume hysteresis that may be present. This might conceivably account for the discrepancy between their results and ours.

Our data show that the central airways account for most of the absolute increase in RL at low lung volumes and therefore most of the decrease in conductance. Martin and Proctor (18) have shown that the smaller the airway the larger its compliance. On this basis, the greatest caliber change and therefore the largest percent decrease in conductance should occur in the smallest airways. Figure 7 shows mean values for total, peripheral, and central conductance, plotted over the lower half of the vital capacity. As predicted, Gp decreases about 80% between 50 and 10% VC, whereas Gc decreases in an approximately linear manner about
ically as it implies that the time constants (the product of resistance and compliance) of the various and multitudinous parallel pathways within the lung must be equal. There is an alternative explanation. The phase angle between any two units whose time constants differ depends upon the magnitude of the difference, the absolute values of the time constants, and the frequency (see equation 6B in ref. 10). Thus, at a frequency of 30 cycles/min, two units with a fivefold variation in time constants will be out of phase by about 40° if their respective time constants are 0.1 and 0.5 sec, whereas they will be only about 2° out of phase if their respective time constants are 0.01 and 0.05 sec. In applying this to the lung one sees that if most of the resistance were in a common path (trachea and upper airway) then the resistances and the time constants of the units in parallel would be very small. There could well be considerable variation in the time constants of these units which would affect neither compliance nor distribution until frequencies exceeded physiological limits. In fact, the common path accounts for about 45% of \( R_t \) (6, 9). Most of the rest is in the central airways which comprise relatively few parallel pathways. Assuming \( R_p \) to be 10% of \( R_t \) and the time constant for the lungs as a whole to be 0.2 sec, the time constants of the various peripheral units in parallel will average out to a time constant of 0.02 sec. This permits considerable variation of the time constants which make up the periphery of the lung with virtually no fall in compliance with frequency. At lower lung volumes when \( R_p \) is considerably larger, compliance is more frequency dependent (15). Although variations in time constants in the periphery are thus compatible with frequency independence of compliance there still needs to be a remarkable uniformity of the time constants of units subtended by the central airways. Our data shed no light on how this uniformity is achieved. Considering the rather rigorous requirements for compliance to be unaffected by frequency, it is not surprising that in some otherwise normal individuals compliance falls when frequencies exceed about 50/min (1, 3).

The relationship between the time constants of the peripheral units and dynamic compliance (\( C_{dyn} \)) is clarified by Fig. 8A. In this graph, \( C_{dyn} \) is plotted as a function of frequency in a two compartment lung model. In the model the time constants \( T_1 \) and \( T_2 \) of each compartment are different. Curves have been plotted for different values of \( T_1 \) and \( T_2 \) giving the graphical solution of equation 13 in the article by Otis et al (18). In plotting these curves the compliances of the two compartments are assumed to be equal and the variation in \( T_1 \) and \( T_2 \) are entirely due to inequalities of resistance. \( C_{dyn} \) is expressed as the fraction of its value at a frequency, \( f \), where the two compartments will be nearly in phase. The phase angle between any two units whose time constants differ depends upon the magnitude of the difference, the absolute values of the time constants, and the frequency (see equation 6B in ref. 10). Thus, at a frequency of 30 cycles/min, two units with a fivefold variation in time constants will be out of phase by about 40° if their respective time constants are 0.1 and 0.5 sec, whereas they will be only about 2° out of phase if their respective time constants are 0.01 and 0.05 sec. In applying this to the lung one sees that if most of the resistance were in a common path (trachea and upper airway) then the resistances and the time constants of the units in parallel would be very small. There could well be considerable variation in the time constants of these units which would affect neither compliance nor distribution until frequencies exceeded physiological limits. In fact, the common path accounts for about 45% of \( R_t \) (6, 9). Most of the rest is in the central airways which comprise relatively few parallel pathways. Assuming \( R_p \) to be 10% of \( R_t \) and the time constant for the lungs as a whole to be 0.2 sec, the time constants of the various peripheral units in parallel will average out to a time constant of 0.02 sec. This permits considerable variation of the time constants which make up the periphery of the lung with virtually no fall in compliance with frequency. At lower lung volumes when \( R_p \) is considerably larger, compliance is more frequency dependent (15). Although variations in time constants in the periphery are thus compatible with frequency independence of compliance there still needs to be a remarkable uniformity of the time constants of units subtended by the central airways. Our data shed no light on how this uniformity is achieved. Considering the rather rigorous requirements for compliance to be unaffected by frequency, it is not surprising that in some otherwise normal individuals compliance falls when frequencies exceed about 50/min (1, 3).

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possible in a purely viscoelastic system. That is, one compartment will be emptying during half the time that the other compartment is filling. If this situation ever occurs in life it is obvious that gas distribution and exchange will be markedly abnormal. Not so obvious is the fact that airway resistance might only be slightly affected. This point is shown in Fig. 8B, which is the graphical solution to equation 14 in the article by Otis et al. (18) in which resistance is plotted as function of frequency. A two-compartment model similar to that used for Fig. 8A was used to calculate this figure. The time constants $T_1$ and $T_2$ of each compartment are different, the variations being entirely due to variations in resistance. A common resistance of 0.9 cm H$_2$O/LPS is shared by both compartments. At higher breathing frequencies the measured resistance with a fourfold variation in the time constants ($T_1$ and $T_2$ = 0.04) is actually higher than it is when the variation is 1,000 fold ($T_1$ and $T_2$ = 0.01 and 10.0). It is only at rather low frequencies that the thousandfold variation is readily detectable. In the extreme situation, not shown on this graph, where one-half of the peripheral airways closed in a randomly distributed manner throughout the lung, the peripheral resistance would be doubled, but this would only cause a 10% increase in RL if Rp is only 10% of RL.

Whether or not the foregoing speculations apply to the living lung is unknown. However, evidence is accumulating that it is possible to selectively constrict the peripheral airways. Nadel, Colbath, and Oben (16) have shown that peripheral airways may become greatly constricted with only a small rise in RL. Our results explain why RL is an insensitive means of detecting such gross changes in $R_p$. Although the abnormalities in gas exchange that might result from profound peripheral constriction are unknown, Raine and Bishop (19) have shown that reflex bronchoconstriction in normal subjects following dust inhalation caused considerable abnormalities in A-a differences for O$_2$. It is conceivable, then, that constriction of the peripheral airways might cause an increase in the A-a difference for O$_2$ with only a minimal effect on RL (although in this situation compliance should be frequency dependent). Because Raine and Bishop did not measure lung mechanics, it is unknown whether the gas exchange abnormalities are out of keeping with the changes in resistance and compliance that are known consequences of dust inhalation (5).

By contrast, RL, which is relatively insensitive to changes in Rp, should be very sensitive to changes in $R_p$. Nonuniform constriction of central airways could lead to a marked increase in RL and work of breathing, a much grosser anatomical misdistribution of gas, as well as a fall in compliance with frequency.

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REFERENCES