How Does HeO_2 Increase Maximum Expiratory Flow in Human Lungs?

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ABSTRACT We used the retrograde catheter technique to investigate the effect of HeO_2 on resistance to maximum expiratory flow ($\dot{V}_{max}$) in airways subsegments between alveoli and the equal pressure point (EPP), and between EPP and the flow-limiting segment (FLS). FLS were found at the same airway site in sublobar bronchi (i.d., 0.54±0.13 cm) on both air and HeO_2 in the six human excised lungs studied. Static elastic recoil pressure (5±1 cm H_2O) and the lateral pressure at FLS (critical transmural airway pressure −6±3 cm H_2O) were not different on the two gases. $\Delta\dot{V}_{max}$ averaged 37±8.9% and was similar to the value found in healthy subjects of similar age (66±10 yr). EPP were located on HeO_2 in peripheral airways (i.d., 0.33±0.03 cm), and EPP on air were located more downstream. Resistance between EPP and FLS was highly density dependent. Resistance between alveoli and EPP behaved as if it were density independent, due in part to Poiseuille flow in the peripheral airways and in part to the consequent narrowing of peripheral airways on HeO_2. This density-independent behavior in peripheral airways reduced $\Delta\dot{V}_{max}$ on HeO_2 from its predicted maximal amount of 62%. Assuming that FLS is the "choke point" these findings are consistent with wave-speed theory of flow limitation modified to include functionally density-independent pressure losses in peripheral airways. These results and conclusions are similar to those found in living dogs. They question previous interpretation of $\Delta\dot{V}_{max}$ as an index of peripheral airway obstruction, and demonstrate the utility of the wave-speed theory in explaining complicated mechanisms of expiratory flow limitation.

INTRODUCTION

Because a helium-oxygen (HeO_2) gas mixture has a lower gas density than air, the normal response to breathing this mixture is an increase in maximum expiratory flow ($\dot{V}_{max}$) (1, 2). The magnitude of this increase ($\Delta\dot{V}_{max}$) is often less in persons with obstructive airway disease and the decrease in response is presumed to be dependent upon the site of air-flow obstruction. Those persons who have little or no response to breathing HeO_2 are thought to have increased airflow resistance in the peripheral airways where the flow regime is laminar and unresponsive to gas density. Those who are responsive to HeO_2 breathing are said to have obstruction centrally when the flow regimes are responsive to the effect of gas density.

Yet, even in normals, the response to breathing HeO_2 is variable and $\Delta\dot{V}_{max}$ may vary from 20 to 80% (1, 2). This nonuniform response to HeO_2 may indicate that the density dependence of resistance to airflow must also show wide variability, and the resistance to different flow regimes may contribute to this varied response. To determine the cause of this wide variation, we previously examined and described the mechanisms of $\Delta\dot{V}_{max}$ in dogs (3). The latter study was designed within the framework of our understanding the mechanism of flow limitation, which included the equal pressure point (EPP) theory of Mead et al. (4), and the Starling resistor concept of Pride et al. (5). The pertinent concepts of these approaches have been recently reviewed (3). In the previous canine experiment, to partition the airway segment relevant to flow limitation, we placed retrograde catheters at the EPP on HeO_2 and just upstream from intrathoracic loci where flow became limited (i.e., the flow-limiting segment [FLS] of Pride et al.). Accordingly, we measured the pressure drop and flow resistance along the two airway segments during breathing of air and HeO_2 at maximum expiration. We therefore determined the airway site that allowed $\dot{V}_{max}$ to increase. The resistance to airflow upstream from the HeO_2 EPP was independent of the gas used to ventilate the lung and the pressure drop was explained by viscous losses (Pfr). Resistance between the HeO_2 EPP and FLS was highly density dependent and the pressure loss was due to convective acceleration (Pca). Moreover, the magnitude of $\Delta\dot{V}_{max}$ on HeO_2 could be explained by the rela-

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tive proportion of the total pressure drop (Ptot) from the alveolus to the FLS that was dependent on gas density. We further analyzed our results in terms of the wave-speed theory (6), and by modifying equations derived from this theory, we were able to predict $\Delta\dot{V}_{max}$ from the ratio of Pfr/Ptot.

To determine whether the above mechanisms and concepts were pertinent to the response to breathing HeO_2 in the human lung as well, we performed a similar experiment in excised human lungs.

GLOSSARY OF SYMBOLS

A*	Critical cross-sectional area of the choke point
EPP	Equal pressure point
FLS	Flow-limiting segment
lps	Liters per second
P*	Pressure head at the choke point
Pbr − Ppl	Lateral bronchial pressure minus pleural surface pressure (transmural airway pressure)
Pc	Transmural airway pressure at the central catheter position
Pca	Pressure loss due to convective acceleration
Pel	Elastic recoil pressure of the lung
Pfr	Pressure losses due to friction
Pp	Transmural airway pressure at the peripheral catheter
Ptot	Total pressure drop
Rc	Airway resistance upstream from the central catheter
Rc-p	Airway resistance between the two catheters
Rp	Airway resistance upstream from the peripheral catheter
Rus	Upstream resistance
VEPP	Volume at the HeO_2 EPP
$\dot{V}$max	Maximum expiratory flow
$\Delta\dot{V}$max	Increase in $\dot{V}$max on HeO_2

METHODS

The six human lungs (three right, three left) in this experiment were studied within 6 h of postmortem examination and were normal upon gross inspection. The vessels at the hilum of the lung were tied and the lung placed in a volume displacement plethysmograph, where it was ventilated through a mainstem bronchus. A single retrograde catheter was placed in the lower lobe to measure lateral bronchial pressure (Pbr) according to the technique of Macklem and Mead (7), and an identical catheter was placed within the plethysmograph to record pleural surface pressure (Ppl). The experiment protocol and the apparatus for measuring lung flow, volume, and transmural airway pressure (Pbr − Ppl) at two different catheter sites (HeO_2 EPP and FLS) were described in detail elsewhere (3). A brief description is given here to indicate minor differences.

With the retrograde catheter in a peripheral airway (HeO_2), quasistatic and forced expiratory (Pbr − Ppl)-lung volume and lung flow-volume curves were recorded on a dual beam oscilloscope during successive deflations from total lung capacity to minimal gas volume. After two sets of curves were obtained on either air or an 80:20 mixture on HeO_2, they were repeated three times on the other gas and then twice more on the first gas. Then the catheter was moved mouthward to the site of flow limitation at the volume of EPP on HeO_2 (VEPP) detected and described (3). As in the canine studies, this central catheter position was 0.25–0.75 cm upstream from the FLS where Pbr − Ppl decreased abruptly and varied with reservoir pressure. Once this central catheter position was so identified, the sequence of measurements were repeated as described above for the peripheral catheter position. By superimposing the photographic records of all curves on each gas, composite flow-volume, static pressure (Pel)-volume, and dynamic (Pbr − Ppl)-lung volume curves for the peripheral (Pp) and central (P_c) catheter position were obtained. These were analyzed at VEPP for $\dot{V}_{max}$, Pel, Pc, and Pp. Resistance to the total airway segment (Rc = [Pel − Pc]/$\dot{V}_{max}$, peripheral airway segment (Rp = [Pel − Pp]/$\dot{V}_{max}$), and intervening segment (Rc-p = (Pc − Pp)/$\dot{V}_{max}$) were calculated as described (3). Statistical comparison between air and HeO_2 measurements were performed using the Wilcoxon matched pair test. The adequate frequency response of the apparatus and the small error in lateral pressure measurement was described (3).

At the end of each experiment, the lung was placed in liquid formalin at a transpulmonary pressure of 20 cm H_2O for 4–5 d. Then the position of each catheter was determined in the fixed lung in terms of distance from the carina, the upper lobe bronchus, airway diameter, and airway generation. Trachea was considered generation 1, whereas lobar bronchi to the left lower lobe and right lower lobe were generations 4 and 5, respectively. In two of the exiced lungs (5 and 6), morphometrics were performed. This included grading the extent of any emphysema present, and measurements of mean internal bronchiolar diameter and the ratio of internal bronchiolar diameter to the external adventitial arterial diameter. Moreover, to determine if there was any artifact produced by using only one lung, one additional experiment was performed where measurements were made with both lungs intact and the retrograde catheter placed in its usual position in the lower lobe. After all measurements were made, the left lung was removed and the procedure repeated as in the other six experiments.

RESULTS

Table I shows the characteristics of the excised lungs used in this study. All were male with an average age of 66 yr. In general, death was due to arteriosclerotic heart disease and autopsy weights of four of our lungs were slightly high when compared to the normal values of this institution. Because of the nature of the autopsy series, a more detailed pulmonary history could not be obtained. However, although some lung weights were slightly heavy, Fig. 1 shows that their individual values of $\dot{V}_{max}$ on air were not different from $\dot{V}_{max}$ predicted from a normal population of similar age (8). Moreover, their values of $\Delta\dot{V}_{max}$ on HeO_2 were similar to those found by Dosman et al. (2) for normal elderly subjects, and the mean value of their upstream resistance (see below) was similar to that calculated by Mead et al. (4). Additionally, in the two lungs in which morphometrics were performed, bronchiolar measurements were normal in both cases, and the extent of emphy-

TABLE I
Clinical Summary of Excised Lungs

Lung	Age	Sex	Lung wt*	Cause of death
	yr		*g*	
1	60	M	380 (R)	Arteriosclerotic heart disease
2	84	M	770 (L)	Acute myocardial infarct
3	70	M	910 (R)	Acute myocardial infarct
4	59	M	410 (L)	Arrythmia
5	60	M	720 (R)	Arteriosclerotic heart disease
6	63	M	480 (L)	Bleeding ulcer
	66±10		nl R (360–570)	
			nl L (325–480)	

Abbreviations used in this table: M, male; L, left lung; R, right lung; nl, normal.

sema was judged mild and focal.[1] However, artificially ventilating the mainstem bronchus may have produced physiological changes in the parameters tested, and its possible consequences are outlined in the discussion below.

Fig. 2 shows the composite flow volume and pressure volume curves at the two retrograde catheter positions for each experiment. There were no systemic changes observed in the curves on one gas measured before and after the second gas, or changes in the flow volume curve after the catheter was moved from its peripheral to downstream position. Flow was ~37% higher on HeO_2 over the upper range of the vital capacity. There was no difference observed between the quasi-static pressure volume curves on air or HeO_2, so a single curve is displayed (Fig. 2, dotted line). At most lung volumes, the dynamic pressure at the peripheral catheter was less on HeO_2 (solid line) than on air (broken line) indicating that the flow-related pressure drop between alveoli and the peripheral catheter was greater on HeO_2. This was not true in the downstream catheter where at some lung volumes dynamic Pbr − Ppl was greater on air and at other volumes it was greater on HeO_2.

The mean lung volume at VEPP was 56±8.2% vital capacity. Table II presents the analysis of the curves at VEPP, indicated by the arrow in Fig. 2. At that lung volume, $\dot{V}_{max}$ increased in all experiments and mean $\dot{V}_{max}$ increased from 2.1±1.1 to 2.8±1.5 liters per second (lps). This 37% mean increase in $\dot{V}_{max}$ was not associated with a change in Pel, which averaged 5.4±1.3 cm H_2O on air and 5.1±1.4 cm H_2O on HeO_2. The pressure measured at the downstream position tended to be lower on HeO_2 than on air but was not significantly different. The mean values were −5.3±3.9 cm H_2O on air and −6.4±2.5 cm H_2O on HeO_2. These values approximate critical transmural airway pressure on the two gases. Pel − Pc averaged 10.7±3.2 cm H_2O on air and 11.5±2.8 cm H_2O on HeO_2. However, because of increased flow, Rc decreased on HeO_2 in all experiments from 6.6±4.08 to 5.09±2.63 cm H_2O/lps. This 30% decrease in Rc corresponded to the 37% mean increase in $\Delta\dot{V}_{max}$ on HeO_2.

The retrograde catheter in the peripheral position partitioned the resistance between alveoli and FLS. At VEPP on HeO_2, Pbr − Ppl was greater on air than on HeO_2. Pp was about zero on HeO_2 (0.1±0.4 cm H_2O).[2] Mean Pp on air (1.6±1.3 cm H_2O) was significantly greater than that on HeO_2 ($P < 0.05$). Therefore, the pressure drop between alveoli and the peripheral catheter was smaller on air (3.8 cm H_2O) than on HeO_2 (5.0 cm H_2O). Moreover, since Pp on air was higher than

[1] Emphysema was focal and grade 20 or less in both lungs. Internal bronchial diameter for excised lungs 5 and 6 was 0.88 mm and 0.82 mm, respectively, and external adventitial arterial Diam was 0.86 and 0.70, respectively.

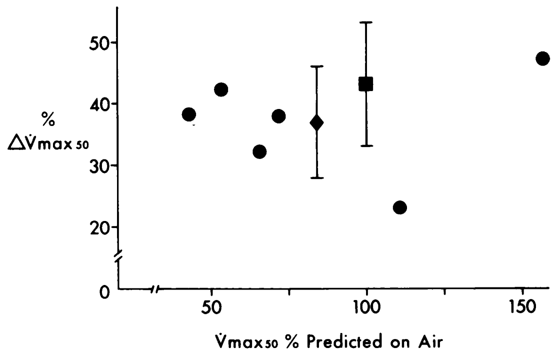

FIGURE 1 Percent predicted $\dot{V}_{max}$ on air for the six excised lungs (closed circles) at 50% vital capacity is plotted on the abscissa against their response to breathing the HeO_2 mixture on the ordinate. Mean (±SD) of the present study shown by closed triangle and the closed square represents the mean value (±SD) found by Dosman et al (2).

[2] Pp on HeO_2 was slightly greater than zero because lung 6 was examined at a slightly higher lung volume than VEPP, where the peripheral catheter plugged.

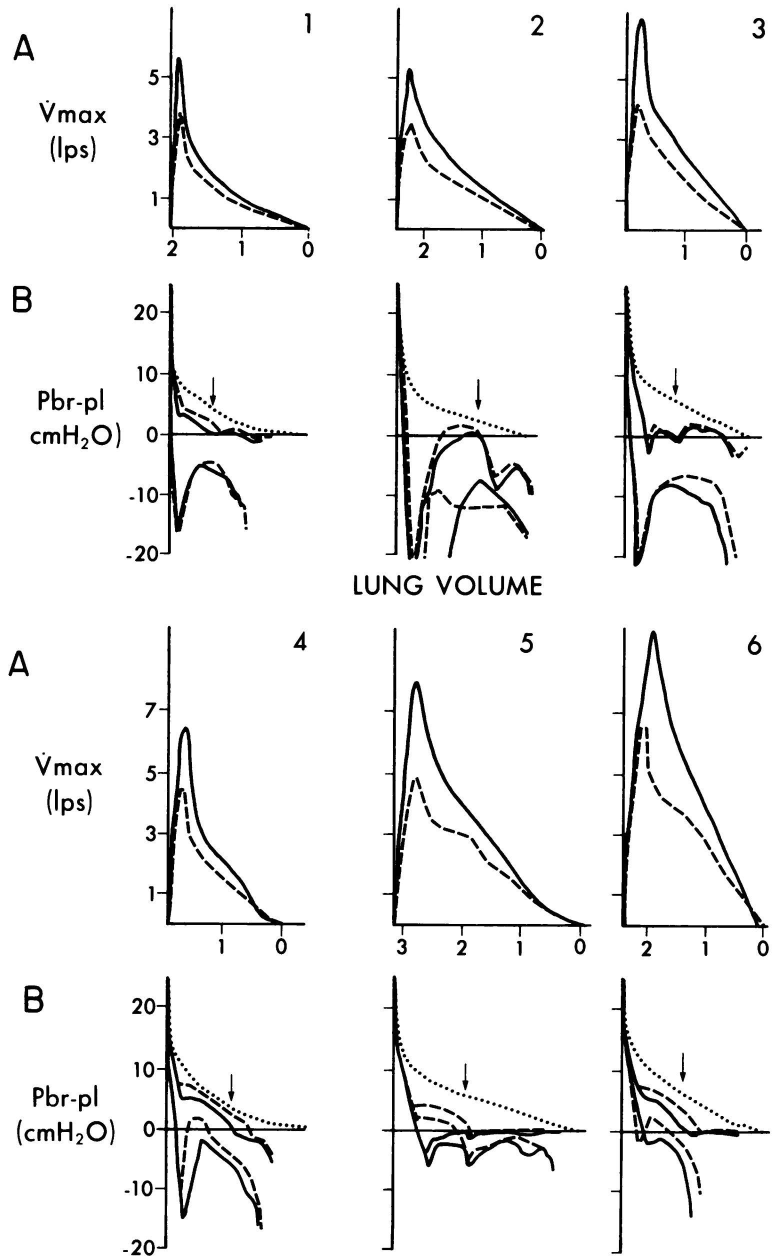

FIGURE 2 Flow-volume (A) and pressure-volume (B) curves in each of the six experiments on air (broken lines) and HeO_2 (solid lines). The static (Pbr – Ppl)-lung volume curves were not different between gases (dotted lines). The dynamic (Pbr – Ppl)-lung volume curves at the peripheral and downstream catheter position are represented by the upper and lower curves, respectively. Arrow indicates VEPP.

on HeO_2, the peripheral catheter location did not represent the position of the air EPP. An additional 1.6 cm H_2O pressure drop would be necessary before Pbr – Ppl was zero during air breathing. Accordingly, the EPP on air were located downstream from the peripheral catheter where the lateral intraluminal pressure decreased by an average of 1.6 cm H_2O. Resistance between alveoli and the peripheral catheter was greater on air in two experiments and greater on HeO_2 in four. Mean Rp was 2.04±0.91 on air and 2.02± 0.61 cm H_2O/lps on HeO_2 and these values were not different on the two gases indicating that resistance in this airway segment was independent of the ventilating gas.

TABLE II

*Effect of HeO_2 on Pressure-$\dot{V}_{max}$ Relationships in Airway Subsegments. Analysis of VEPP on HeO_2**

	$\dot{V}_{max}$	Pel	Pc	Pp	Rc	Rp	Rc-p
Air	2.1±1.1	5.4±1.3	−5.3±3.9	1.6±1.3	6.61±4.08	2.04±0.91	4.57±3.66
HeO_2	2.8±1.5	5.1±1.4	−6.4±2.5	0.1±0.4	5.09±2.63	2.02±0.61	3.07±2.07
$P <$	0.03	NS	NS	0.05	0.03	NS	0.05

* Mean±SD v_L at VEPP was 56±8.2% vital capacity. All values are mean±SD.

The pressure drop between the catheters (Pc − Pp) averaged 6.9±3.5 on air and 6.5±2.7 cm H_2O on HeO_2. Resistance between the catheters was greater on air in all experiments and the increase from 3.07±2.07 to 4.57±3.66 cm H_2O/lps was 49% indicating greater density dependence between the catheters than in the whole Rc segment.

The average position of the HeO_2 EPP was in a peripheral bronchus (generation 11±1.3) having an airway Diam of 0.33±0.03 cm, and situated 14.6±2 cm from the carina. This corresponded to order 23 in model 2 in reference 9. Using the values in the latter reference, this catheter subtended 2.8±9% of the total flow. The location of the HeO_2 FLS was in a sublobar bronchus between the seventh and eighth generation having an airway Diam of 0.54 cm and 10.4±2.7 cm from the carina. The FLS were usually positioned at the junction of posterior and lateral basal segments or just slightly upstream and approximately correspond to order 25 in the same reference. At this location, the catheter subtended a larger percentage of the total flow which averaged 10.4±3%. In the one experiment where two lungs were used and the entire intact trachea connected to the gas source, the FLS was also located peripherally and did not change when one lung was excised.

DISCUSSION

As in the previous study, this experiment was designed within the conceptual framework of the two prevailing theories of flow limitation (4, 5). Therefore, selecting a mid-vital capacity lung volume, we prospectively placed our intraluminal catheters to lie in mid-vital capacity on HeO_2 at the equal pressure point (4, 10, 11) and just upstream from the FLS (5, 12). In this way, we determined in which airway segment the low density gas was acting to lower flow resistance and so increase $\dot{V}_{max}$. The FLS represents a site in the airway where a large pressure drop is dissipated. Upstream from this location the geometry of the airway is fixed, whereas just downstream from this point events are determined by changes in reservoir pressure. Because slightly downstream from our central catheter (<1 cm) intrabronchial pressure became very negative ($\leqslant -50$ cm H_2O) and varied with reservoir pressure, we conclude that flow became limited in the airway segment just downstream from our central catheter. We will interpret our measurements partitioning the pressure drops and resistances upstream from the site of flow limitation to describe the mechanisms setting $\dot{V}_{max}$ on each gas. We will try to integrate our results with the intuitive approaches of Mead et al. (4) and Pride et al. (5) as well as the mathematical approach described by the wave-speed theory (6, 13). Furthermore, we will use equations derived from the previous canine study (3) and apply them to the data found in the excised human lungs.

Mechanisms of $\Delta\dot{V}_{max}$. In each of the six lungs, the position of the FLS was consistently located in an intraparenchymal airway 2–3 cm upstream from the takeoff of the superior segment of the lower lobe where intrabronchial pressure averaged about −6 cm H_2O (Table II). Therefore, for the similar driving pressures on the two gases, $\Delta\dot{V}_{max}$ increased by 37% on HeO_2 due to a reduction in flow resistance between alveolus and FLS. Whereas the increase in $\dot{V}_{max}$ was the result of a decrease in flow resistance between alveoli and FLS, HeO_2 had no effect on the resistance between alveoli and the peripheral catheter position (Table II). This was because both $\dot{V}_{max}$ and the peripheral pressure drop were larger on HeO_2. Accordingly, the resistance between alveoli and HeO_2 EPP was independent of the gas used to ventilate the lung. Furthermore, since the transmural pressure at the peripheral catheter was higher on air than on HeO_2 (Fig. 2), the EPP on air must have been positioned further downstream from the peripheral catheter a distance long enough to account for the additional 1.6 cm H_2O pressure drop. We conclude therefore that one effect of ventilating excised human lungs with HeO_2 was to shorten the airway segment upstream from the EPP by moving EPP peripherally.

In the airway segment between the HeO_2 EPP and the FLS, Rc-p was 50% greater on air than on HeO_2, and the influence of the ventilating gas on the resistance to airflow took place entirely within this segment. Accordingly, in these lungs, the total airway resistance to the FLS was composed of Rp between alveoli and HeO_2 EPP, which was independent of the ventilating gas and Rc-p between the two catheters, which was lower on HeO_2 than on air.

Although Rp behaved as if it were density independent, this was not necessarily due to a laminar flow regime in this airway segment. Because (Table II) Pp on air was 1.6 cm H_2O and less on HeO_2 (0.1 cm H_2O), there may have been a change in the dimensions of the airway geometry when the lung was ventilated on the two gases. Consequently, the diameter of the airway would be expected to be larger on air than on HeO_2. We found a similar result in the canine study (3) and argued that since the airways were subjected to different transmural pressure on the two gases, the airway would be narrower on HeO_2 (14) (Fig. 3B), therefore increasing the resistance to airflow and consequently increasing the pressure cost. Because resistance would be equal on the two gases, it would suggest a laminar flow regime when in reality, the flow regime could be turbulent with different airway geometries. The initial mechanism for the differences in airway geometry would be the direct result of a true laminar flow regime in a peripheral airway site near the alveolus.

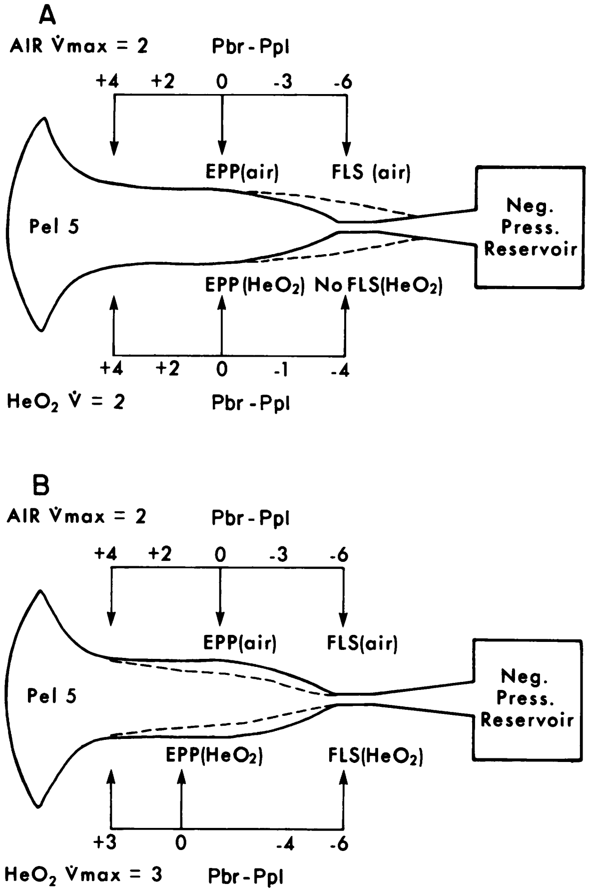

FIGURE 3 Schematic model comparing airway events during $\dot{V}_{max}$ on air (2 lps) with those on HeO_2. (A) When HeO_2 flow is also 2 lps, transmural airway pressure (Pbr − Ppl) and airway area decrease more on air (solid lines) than HeO_2 (broken lines) because pressure losses are density dependent. Flow limits at Pbr − Ppl = −6 cm H_2O on air, fixing EPP air, but does not limit at increased Pbr−Ppl (−4 cm H_2O) on HeO_2. (B) Further lowering of reservoir pressure increases HeO_2 flow until it becomes limited at 3 lps at the same airway site and Pbr − Ppl as FLS air. EPP HeO_2 are fixed further upstream, and Pbr − Ppl and airway geometry are reduced on HeO_2 (broken lines).

The results of the partitioned resistances were similar to those noted in most of the dogs (group 1) that we studied (3) and suggest a similar model as to how breathing HeO_2 increased $\dot{V}_{max}$. Fig. 3 depicts a schematic diagram of the lung at mid-vital capacity which was subjected to progressively decreasing reservoir pressure during breathing air until flow limitation occurred. The transmural airway pressure from alveoli to airway opening are depicted at the onset of flow limitation on air ($\dot{V}_{max}$ = 2 lps). At similar flows on HeO_2, e.g., 2 lps which was not $\dot{V}_{max}$, the EPP would be identically located or even further downstream on HeO_2. The latter may occur because at similar flows there would be no narrowing of the airway on HeO_2, and resistance between alveoli and EPP may be less than on air. Between EPP and FLS resistance along the airway segment on HeO_2 would also be less than on air. Therefore, the transmural pressure on HeO_2 would be larger and the cross-sectional area of the airway would be greater than on air. Accordingly, expiratory flow limitation would not occur.

When the reservoir was lowered further to increase flow on HeO_2, as shown in Fig. 3B, transmural pressure decreased at each airway site because the flow resistive pressure drop increased. When flow reached 3 lps, Pbr − Ppl fell to the critical value of −6 at the site of the air FLS, converting the airway to a Starling resistor. As was the case with air, the EPP on HeO_2 were fixed at the point where Pbr−Ppl was zero. Because resistance upstream to this point appeared to behave as if it were independent of the ventilating gas and because $\dot{V}_{max}$ on HeO_2 was greater than that on air, the resistive pressure drop to this point was greater on HeO_2 than air. Therefore, the HeO_2 EPP were further upstream.

According to the EPP theory (4), the pressure drop from the alveoli to EPP is equal to Pel, and the ratio of this pressure drop to $\dot{V}_{max}$ is defined as upstream resistance (Rus). For a given Pel, a reduction in $\dot{V}_{max}$ would imply an increase in Rus. Therefore, although Rus decreased during breathing of HeO_2, this occurred because of a geometry change which was unrelated to peripheral airway function. We therefore conclude that Rus is a very indirect indicator of peripheral airway resistance.

In summary, ventilating the lung with HeO_2 decreased resistance from alveoli to FLS by 30% and was associated with a $\Delta\dot{V}_{max}$ of 37%. Whereas resistance from EPP to FLS was highly density dependent, resistance from alveoli to HeO_2 EPP behaved as if it were density independent in part because of a narrower airway on HeO_2. Accordingly, ventilating the lung with HeO_2 resulted in systematically narrower airways between alveoli and FLS, compared to air. Inspite of this, flow actually increased and the resistance between alveoli and FLS was less on HeO_2 than on air. Thus density dependence of resistance outweighed the geometric changes. This density dependence of resistance must have occurred throughout all segments of the upstream airways where there was any significant geometric difference in order to allow for the increase in flow through the segment. Our data indicate that density dependence was greatest between the catheters where resistance decreased by 50%.

Although the above explanation and analysis appear to describe the mechanism of $\Delta\dot{V}_{max}$ on HeO_2 at VEPP, different mechanisms may be responsible at other lung volumes. In some of the lungs shown in Fig. 2, it can be seen that at high lung volumes, both Rc and Rc − p appear to be density independent. Accordingly, this would invoke explanations of $\Delta\dot{V}_{max}$ on HeO_2 other than that previously described. Similar seemingly density independent observations of both partitioned segments have been shown to occur in group II dogs (3). This finding has been associated with different locations of the FLS on the two gases. Since our catheter was not placed at the FLS at these high lung volumes, it is not clear whether similar conclusions hold true for human lungs.

Effect of peripheral pressure drop on $\Delta\dot{V}_{max}$. Our results show that mean $\Delta\dot{V}_{max}$ increased by 37%. If resistance to airflow were completely inertial, $\Delta\dot{V}_{max}$ would vary as density $^{-0.5}$, and $\Delta\dot{V}_{max}$ would have increased by 62% (1, 2, 6, 15–17). Such an inertial pressure loss due to Pca was probably the majority of the pressure drop (6.5 cm H_2O, Table II) between HeO_2 EPP and FLS. The finding that the resistance in the peripheral segment behaved as if it were density independent may explain why $\Delta\dot{V}_{max}$ was less than maximal. Since the Pfr was due to resistance that behaved as if it were density independent, an appreciable portion of the Ptot between airspaces and FLS varied with $\dot{V}_{max}$ independent of the ventilating gas. Consequently, the intuitive reason why flow on HeO_2 increased by only 37% was that measured Pfr reduced the density-dependent component of Ptot that was responsible for $\Delta\dot{V}_{max}$. In effect, the density-independent peripheral flow regime and the consequent airway geometry change induced on HeO_2 reduced the influence of gas density on $\dot{V}_{max}$. Since Pfr on HeO_2 accounted for 0.45 Ptot, $\Delta\dot{V}_{max}$ lies about half way between the maximal value of 62% predicted for the frictionless extreme (Pfr/Ptot = 0) and the minimal value of zero predicted for the completely viscous extreme (Pfr/Ptot = 1).

A more rigorous explanation of how Pfr/Ptot would reduce $\dot{V}_{max}$ can be derived from the wave-speed theory of flow limitation (3, 6, 13). According to the theory, $\dot{V}_{max}$ occurs when at a point in the airway, the choke point, linear velocity equals the speed of propagation of the pressure pulse waves. We previously used equations derived from the wave-speed theory to describe how increasing amounts of Pfr affected $\Delta\dot{V}_{max}$ on HeO_2 (3). In the present experiment, where the FLS was located at the same airway site on both gases, similar equations can be used. Additionally, from these equations, the ratio of the area at the choke point as well as the ratio of the pressure drop to the choke point could be determined on the two gases.

Fig. 4 shows the graphic solutions of these equations for these three relationships (3, appendix). In Fig. 4A $\Delta\dot{V}_{max}$ is plotted on the ordinate against increasing values of Pfr/Ptot. When Pfr/Ptot is zero, $\Delta\dot{V}_{max}$ is maximal at 62%. With increasing values of Pfr/Ptot $\Delta\dot{V}_{max}$ decreases in a curvilinear manner. As illustrated in the Fig. 4 when mean (±SD) Pfr/Ptot (0.45±0.15) found in the present experiment is plotted against mean (±SD) $\Delta\dot{V}_{max}$ (37%), the point fall was close to the relationship predicted by the wave-speed theory. In effect, func-

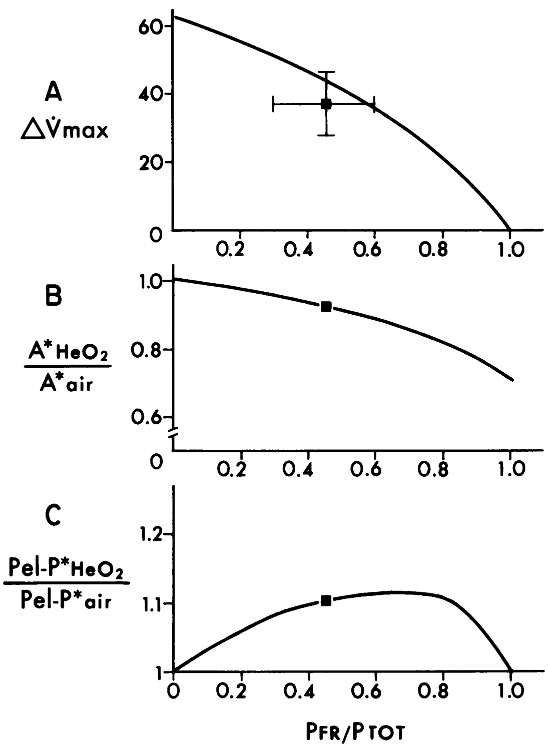

FIGURE 4 Effects of viscous resistance on predictions of HeO_2 effects of wave-speed theory of flow limitation. Abscissa: ratio of functionally density-independent Pfr on HeO_2 to Ptot between alveoli and choke point. Ordinates: (A) $\Delta\dot{V}_{max}$ decreases in a curvilinear manner from 0.62 at Pfr/Ptot = 0 to 0 at Pfr/Ptot = 1.0. Note that mean (■) (±SD) values are just below the predicted relationship. (B) The ratio of A^*HeO_2/A^*air decreases as Pfr/Ptot increases, explaining why $\Delta\dot{V}_{max}$ decreases. (C) The ratio Pel − P^*HeO_2/Pel − P^*air increases initially as Pfr/Ptot increases and then declines as Pfr/Ptot approaches one.

tionally density-independent losses caused wave-speed theory to predict a lower than maximal $\Delta\dot{V}_{max}$.

What is the mechanism responsible for this effect? Dawson and Elliott (6) point out that such viscous losses reduce the local distending pressure head at the choke point (P*) below the static recoil value. This reduced head implies a reduced critical cross-sectional area of the choke point (A*) resulting in reduced critical flow. Because the viscous losses were greater on HeO_2, P* was reduced by a greater amount than on air so that A* was reduced more on HeO_2 than air.

These latter two relationships are illustrated in the second and third panels of Fig. 4. In the second panel, the ratio A* HeO_2/A* air is plotted against Pfr/Ptot. When Pfr/Ptot is zero, A* HeO_2/A* air is one and $\Delta\dot{V}_{max}$ is 62%. With a value of Pfr/Ptot found in the present experiment A* HeO_2/A* air would be about 10% less on HeO_2 than on air. The third panel shows that the ratio of the pressure drops Pel-critical transmural airway pressure for HeO_2/Pel-critical transmural airway pressure for air would also change at different values of Pfr/Ptot. When $\Delta\dot{V}_{max}$ is 62%, Pfr/Ptot would be zero and the ratio of the pressure drop would be one. As Pfr/Ptot increased, this ratio would become greater and at a Pfr/Ptot = 0.45 the pressure drop on HeO_2 would be ~10% greater than on air. This prediction would be consistent with the slightly increased pressure drop on HeO_2 found in the present study, although our methodology was not sensitive enough to detect this change systematically. Note that with increasing values of Pfr/Ptot, $\Delta\dot{V}_{max}$ decreases, yet the ratio again approaches one. The physiologic mechanism that would allow the ratio of the pressure drops to decrease while the ratio of the areas increased is unclear to us at the present time.

In summary, we were able to predict $\Delta\dot{V}_{max}$ on HeO_2 from equations derived from the wave-speed theory. The lower $\Delta\dot{V}_{max}$ than predicted for the frictionless state (62%) occurred because functionally density-independent losses on HeO_2 exceeded those on air, reducing the P* and A* on HeO_2. Greater Pfr occurred on HeO_2 because $\dot{V}_{max}$ was greater, and viscous resistance behaved as if it was independent of gas density.

Comparison of the present study to previous studies. Macklem and Wilson (18) measured intrabronchial pressure in man and showed that EPP develop in the trachea, move upstream as lung flow increases, and become fixed at the level of segmental bronchi when $\dot{V}_{max}$ is attained. Over the middle half of vital capacity, it is estimated that EPP remained fixed in this airway location, while below 25% vital capacity, it was thought that EPP move further upstream. Our results show that EPP were located more peripherally than found in the above study. There are many reasons for this discrepancy considering the varying techniques and methods used in each experiment including the fact that this study measured the EPP on HeO_2. However, the most important reason may be related to the different age group used in the two studies. The mean age in Macklem's study was 32 yr whereas in our study, the mean age was 66 yr. Previous work (4) has shown that age is accompanied by a decrease in elastic recoil of lungs resulting in decreased static recoil pressure at a given lung volume. This would tend to decrease the driving pressure and move EPP peripherally.

In contrast to the canine lung in which FLS was in the trachea (3), FLS in the aged human excised lung is located in a sublobar bronchus. We wondered whether our studies of one lung changed $\Delta\dot{V}_{max}$ by eliminating a length of trachea and reducing the airway compliance as described by Jones et al. (19). To the extent that the tube in the mainstem bronchus prevented flow limitation in that airway at reduced $\dot{V}_{max}$, flow increased until transmural pressures of upstream intraparenchymal airways reached their critical transmural airway pressure. This sequence predicts that study of both lungs expiring through a common trachea segment is associated with lower $\dot{V}_{max}$ on each gas and a more downstream locus of FLS. Note that even if this occurred, $\Delta\dot{V}_{max}$ will again be determined by Pfr/Ptot. Although we cannot predict the effect of a changed FLS locus on either Pfr or Ptot, we know from our canine studies (3) that tracheal FLS are associated with $\Delta\dot{V}_{max}$ quite similar to that observed in aged human lungs. Furthermore, the one pair of human lungs studied with tracheal cannulation demonstrated the same sublobar locus of FLS as when it was studied with cannulation of the mainstem bronchus. Finally, our findings of intraparenchymal FLS supports the prediction of Melissinos et al. (20), that flow limitation shifts into intraparenchymal airways as lung volume decreases during forced expiration. We conclude that the determinant of $\Delta\dot{V}_{max}$ in the aged human lung as in the canine lung is the ratio of the apparent viscous pressure drop to the Ptot between air spaces and the choke point.

Defining this mechanism does not simplify our understanding of $\Delta\dot{V}_{max}$ as a test of early and peripheral airways obstruction. Despas et al. (1) reasoned that because HeO_2 is a less dense gas than air, it could be used to determine the site of airway obstruction in asthma. They therefore assumed that in those asthmatics when $\Delta\dot{V}_{max}$ increases <20%, airway obstruction was present peripherally in the small airway (<2 mm) where the flow regime was unresponsive to gas density and considered laminar. On the other hand, those who had a >20% increase were considered to have obstruction more centrally where turbulent and convective flow regimes would be responsive to the lower density of HeO_2. More recently, Dosman et al. (2) used similar concepts to study airway function in smokers. A decrease in $\Delta\dot{V}_{max}$ was found in smokers whose airway function was otherwise normal on air, and this finding was considered to represent early evidence of small airway obstruction. Therefore, the response to breathing HeO_2 was thought a useful clinical test to detect persons with early and presumably peripheral airway obstruction.

Our study introduces some complexities to the interpretations given by the latter studies because from our findings, an abnormal response to breathing HeO_2 is not necessarily indicative of either airway or parenchymal disease. Consider, for example, how in the normal population different magnitudes of central airway caliber and therefore A* will alter $\Delta\dot{V}_{max}$ on HeO_2 independently of any additional factors. In the instance in which A* is large and Ptot the same, since Pca is inversely related to A*, $\dot{V}_{max}$ will also be large, and Pfr ($\dot{V}_{max} \times$ Rfr) will tend to represent a large proportion of the Ptot from air spaces to the choke point. This will result in an increase in Pfr/Ptot and will reduce $\Delta\dot{V}_{max}$ on HeO_2 even in a lung free of airway obstruction. Accordingly, normal subjects with large central airways and so large $\dot{V}_{max}$ will have low $\Delta\dot{V}_{max}$, and vice versa. Indeed, using similar analysis and assumptions, such a result has been found by Castile et al. (21). Moreover, extending the influence of central airway size on $\Delta\dot{V}_{max}$ to persons with peripheral airways disease complicates the interpretation of breathing HeO_2 even further. In a given lung, peripheral airways obstruction tends to reduce $\dot{V}_{max}$ by reducing P* and A* at the choke point. If choke point loci do not change with peripheral airways obstruction, Ptot will not change and Pfr/Ptot will increase because Pca is more flow dependent than Pfr. Accordingly, $\dot{V}_{max}$ and $\Delta\dot{V}_{max}$ decrease with peripheral airways obstruction, but which variable falls outside the range classified as normal first depends on the caliber of the central airways. As peripheral airways obstruct, the subject having small central airways and large $\Delta\dot{V}_{max}$ will be considered to have a clinically low $\dot{V}_{max}$ before his $\Delta\dot{V}_{max}$ noticeably decreases. On the other hand, the subject with a large trachea and therefore small $\Delta\dot{V}_{max}$ will develop appreciably low $\Delta\dot{V}_{max}$ before $\dot{V}_{max}$ is reduced beyond the normal range. Consequently, the ability of HeO_2 breathing to discriminate between normal and obstructed peripheral airways is affected by large variation in normal $\dot{V}_{max}$ attributable to normal variations in central airways caliber (22). This confounds the interpretation of $\Delta\dot{V}_{max}$ on HeO_2 as an indicator of peripheral airways obstruction, and detracts from the use of HeO_2 as a valuable clinical tool.

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