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Research Article

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Lung Volumes in Diffuse Obstructive Pulmonary Syndromes

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ABSTRACT Lung volumes in irreversible diffuse obstructive pulmonary syndromes (DOPS_I) have been studied by using an analog of the lung that simulates an 18-breath nitrogen washout. The functional residual capacity (FRC), the dead space volume (V_D), the distribution of ventilation, as well as the pattern of lung emptying have been measured in normal subjects and those with obstructive syndromes. The V_D increased progressively with severity of the obstructive syndrome, as did FRC. For all subjects, both normal and obstructed, the ratio of V_D /FRC remained relatively fixed with the regression line of V_D upon FRC showing a minimal value for V_D of 67 cm³. V_D increased by an average value of 33 cm³ per liter of lung volume above this value. The increase in FRC resulted from the increased volume of the poorly ventilated compartment for the most part. X-ray evidence of emphysema was poorly correlated with the changes in V_D or FRC. A significant increase in anatomical V_D in DOPS_I makes up an appreciable portion of the total V_D (physiological).

INTRODUCTION

Anatomical dead space (V_D)¹ is often difficult to assess. First measured from casts made of the tracheobronchial tree (1), a value of 144 ml, excluding the intralobar bronchi, was found to be present in collapsed lung. Since that time, expired volume and gas concentrations of O₂ (2), CO₂ (3), hydrogen (4), nitrogen (5, 6), and several other inert gases have been used

to measure V_D in vivo. Bartels, Severinghaus, Forster, Briscoe, and Bates (2) showed that by the single breath method and graphic analysis there was no measurable difference in the V_D for O₂, N₂, and CO₂. Helium had a somewhat smaller V_D in two subjects. The techniques employed to analyze for V_D using these gases have included graphic analysis of single breath tracings (5) and the nitrogen clearance curve (7).

The functional residual capacity (FRC) of the lung has been measured by dilution techniques with several inert gases in open and closed circuits (8-10). Dilution equations or graphic analysis into compartmental volumes of the washout or washin curve have given similar values. These techniques have been criticized as failing to reveal the trapped volume in those areas of lung with no, or poor, communication with the airways. Prolonged washouts of nitrogen, however, have shown lung volumes similar to those measured by helium (11).

We have recently reported the ability to measure the FRC from the washout curve of nitrogen (breathing oxygen) through 18 breaths (12). Reported here is the use of this short washout to provide sufficient data from which one can measure V_D , FRC and the dispersion of ventilation-to-volume ratios. This technique has been used in irreversible diffuse obstructive pulmonary syndromes (DOPS_I), where V_D has been most difficult to assess and FRC poorly estimated.

METHODS

45 volunteers, divided into two groups, were studied in the seated position. The 26 normal subjects, as reported elsewhere (12), had no chest symptoms, a normal chest X ray, and spirometry. Six males and six females of this group were less than, and eight males and six females were more than 40 yr of age. The 19 patients of the second group had a diffuse obstructive pulmonary syndrome (DOPS). This group ranged in age from 41 to 76 yr and had no volume restriction evident on spirometry. Three measures were used to categorize the severity of DOPS_I: maximal voluntary ventilation (MVV), peak expiratory

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¹Abbreviations used in this paper (see also Table I): ADR, alveolar dilution ratio; DOPS, diffuse obstructive pulmonary syndrome; DOPS_I, irreversible diffuse obstructive pulmonary syndrome; FRC, functional residual capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; V_D , dead space volume; V_D physiol, physiologic dead space.

TABLE I
Equations

- 1a $F_{ik+1} = a_{i1}F_1 + a_{ii}F_{ik} + \sum_{j \neq i} a_{ij}F_{jk}$
- 1b $F_{ik+1} = a_{ii}F_{ik}$
when $F_1 = 0$, $a_{ij} = 0$, $j \neq i$
- 1c $F_{ik} = (a_{ii})^k F_0$
- 2 $F_{ik} = F_0 \sum_l b_{li}(\omega_l)^k = \sum_l b_{li}(F_0(\omega_l)^k)$
- 3 $F_{Emk} = \sum d_{ml}F_0(\omega_l)^k$
- 4 Quantity of tracer gas expired during interval m from compartment l on k^{th} breath
 $= V_{Em}d_{ml}F_0(\omega_l)^k$.
- 5 Total quantity of tracer gas expired during interval m from compartment l for all breaths
 $= V_{Em}d_{ml} \sum_k (\omega_l)^k F_0 = V_{Em}d_{ml} \frac{\omega_l F_0}{(1 - \omega_l)}$.
- 6 Total tracer gas expired
 $= \sum_m \sum_l V_{Em}d_{ml} \frac{\omega_l F_0}{(1 - \omega_l)}$.
- 7 $F_{smk} = \sum_{l=0,1,2,3} \beta_{ml}(\omega_l)^k$.

F_{ik} , fraction of tracer gas in i^{th} unit on k^{th} breath of washout; a_{ij} , fraction of gas in i^{th} unit which comes from inspired gas on each breath; F_1 , fraction of tracer gas in inspired gas (normally zero during washout); F_0 , initial fraction of tracer gas in all units; F_{Emk} , fraction of tracer gas in m^{th} interval of expiration on k^{th} breath; b_{li} , fraction of tracer gas in unit i which is from l^{th} compartment; d_{ml} , fraction of tracer gas in m^{th} interval of expiration which is from the l^{th} compartment; V_{Em} , volume of gas expired in interval m of expiration; ω , $\omega = V_0/(V_0 + \Delta V) = \text{ADR}$ where V_0 is the compartmental volume before the breath and ΔV the volume of fresh air inhaled; F_{smk} , fraction of tracer gas in m^{th} interval of expiration during breath k of simulated washout; β_{ml} , fraction of gas in m^{th} interval of simulated washout from compartment l .

flow (PEF), and a damped measure of expiratory flow (13). The latter is normally above 260 liter/min in males and above 210 liter/min in females (13). By using the best measure of flow, the DOPS were divided into three groups, i.e., severe (<40% predicted MVV and PEF, mean $\text{FEV}_1/\text{VC} = 0.38$); moderate (40–69% predicted MVV and PEF, mean $\text{FEV}_1/\text{VC} = 0.53$); and mild (70–85% predicted MVV and PEF, mean $\text{FEV}_1/\text{VC} = 0.63$). The obstructive syndrome in these patients was irreversible (DOPS_r), i.e., in no instance did the flow rates become normal with treatment. Current X rays of the chest (PA and lateral) were reviewed for signs of emphysema.

The subject breathed oxygen in an open circuit system through 18 breaths with continuous monitoring of flow, volume, and nitrogen concentration (FN_2) at the mouth. The method of data analysis which has been reported elsewhere (12) is amplified here.

Theory. Consider an individual terminal unit during washout of an inert tracer gas. The time-course of the mean gas concentration is described in Fig. 1. At end expiration the tracer concentration is considered uniform within an individual (i^{th} unit) and is denoted by F_{i1} , F_{i2} , ... F_{ik} for the first, second, ... k^{th} breath (14, 15). It follows that the gas in a particular terminal unit at the end

of the $k+1^{\text{th}}$ breath must consist of: (a) fresh gas (usually containing no tracer gas) inspired during the $k+1^{\text{th}}$ breath, (b) gas which remained in the unit or was expired into the dead space and re-inspired, and (c) gas which was in other units at the end of the k^{th} breath (Table I, Eq. 1a). When the contribution from other regions is small, the equation simplifies so that the ratio of concentrations

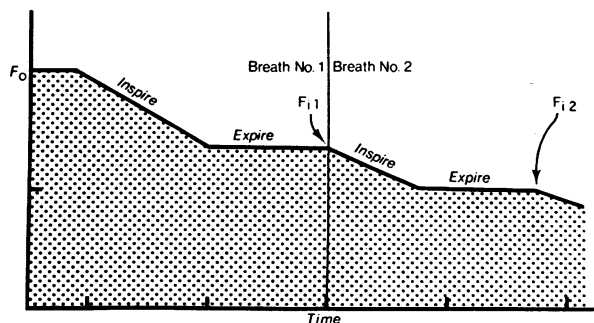


FIGURE 1 A plot of the time-course of tracer concentration in the i^{th} unit during washout.

TABLE II
Volumes (Mean $\pm$ SD) of Lung Compartments for Young and Old Normal Subjects and those with DOPS_I.
V_D Increases Significantly with the Airway Obstruction as Does the FRC

Subjects	Poorly ventilated		Moderately ventilated		Well ventilated		V _D	ΣV ₀ (FRC)
	ΔV	V ₀	ΔV	V ₀	ΔV	V ₀		
	<i>liters</i>		<i>liters</i>		<i>liters</i>		<i>liters</i>	
DOPS _I								
Severe	0.126 ±0.04	4.16 ±0.97	0.118 ±0.06	0.74 ±0.72	0.08 ±0.02	0.18 ±0.21	0.272 ±0.07	5.35 ±1.08
Moderate	0.122 ±0.03	3.53 ±1.41	0.098 ±0.05	0.55 ±0.49	0.073 ±0.022	0.054 ±0.04	0.211 ±0.04	4.34 ±0.04
Mild	0.133 ±0.05	2.23 ±0.60	0.154 ±0.03	0.62 ±0.24	0.106 ±0.055	0.04 ±0.04	0.168 ±0.02	3.05 ±0.83
Normal								
>40 Yr	0.164 ±0.07	1.53 ±0.67	0.187 ±0.09	0.64 ±0.41	0.155 ±0.072	0.141 ±0.12	0.156 ±0.016	2.45 ±0.63
<40 Yr	0.141 ±0.06	1.29 ±0.49	0.202 ±0.05	0.82 ±0.43	0.162 ±0.06	0.100 ±0.1	0.129 ±0.016	2.36 ±0.57

on successive breaths has a fixed value (Eq. 1b and c). This value is the alveolar dilution ratio (ADR) of Fowler (16). This simple model may be reasonably close to the truth.

Even when these conditions are not met the concentration of gas in every unit consists of a mixture of gases

with ADRs characteristic of the system. A general statement of the solution of the difference equation (1a) is Eq. 2 (17).

The lung appears to consist of a number of compartments (equal to or less than the number of terminal units) each with a specific ADR. Dead space is a special compartment whose ADR is zero.

Each terminal unit contains a mixture of gases from the compartments. The contribution of the l^{th} compartment to the i^{th} unit is the b_{il} of Eq. 2. The concentration of gas from compartment l on the k^{th} breath is $F_0(\omega_l)^k$. During expiration, gas leaving the mouth between any two expired volumes (for example between 300 and 400 cm³ of expirate) is made up of volumes contributed by each unit. These volumes do not change from breath to breath, hence compartmental contributions also do not vary from breath to breath. If we assume that we have the ability to analyze the gas expired during any interval m into its compartmental components we have Eq. 3, where d_{ml} is the fraction of gas expired during interval m coming from compartment l . To measure the quantity of tracer gas expired from compartment l on the k^{th} breath during interval m would require knowledge of the volume expired during the interval (V_{Em}), the fraction of gas from the compartment (d_{ml}) and the concentration ($F_0(\omega_l)^k$) of gas in compartment l (Eq. 4). The total amount of tracer gas summed over all breaths coming from compartment l during interval m is expressed in Eq. 5. The total tracer gas expired during a washout is the sum of the gas from all compartments during all intervals and all breaths (Eq. 6). Knowing this quantity and the initial tracer concentration we can calculate the lung volume. Similarly, it follows that the volume expired from the dead space during any interval m is simply the total volume (V_{Em}) expired during this interval less the amount ($\Sigma V_{Em} d_{ml}$) expired from all the other compartments.

A plot of the summed volume of all compartments with ADRs less than that indicated by ω on the horizontal axis

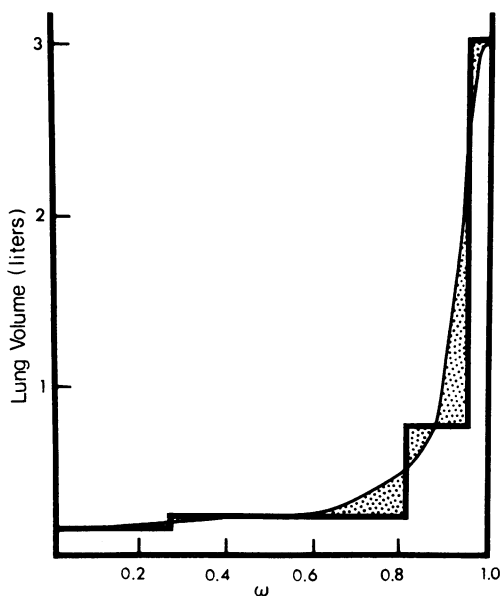


FIGURE 2 A plot of lung volume versus ADR (ω) in which the continuous line represents the summed volumes of all compartments in a hypothetical lung with ADR equal to or less than the corresponding value of ω on the horizontal axis. The steps describe this lung in macro-compartments.

is shown by the continuous line in Fig. 2. A similar plot for expired volume is shown by the continuous line in Fig. 3.

Data analysis. Since we cannot obtain sufficient data to completely describe these curves we make a reasonable attempt to simulate the many compartments by four macrocompartments (shown as steps in Figs. 2 and 3), each with its characteristic ADR. The position of the step on the horizontal axis determines ω , while the height of the step represents the volume within that compartment (Fig. 2) or the tidal volume from the compartment (Fig. 3). The step data shown here correspond to the mean values for the macrocompartments in mild DOPSI (Table II). One of the ADRs is set at zero and the compartment associated with this ADR is dead space. A distribution of ω , such as that described by the smoothed curve, could also be simulated with these four compartments. Our simulated response of the system for any interval m on the k^{th} breath is shown in Eq. 7. β is to the macrocompartment what dm_i was to the compartment. Our electronic simulator has potentiometers which can be set to give any four desired values of β_{mi} and any four desired values of ω_i . The simulator then gives the predicted values of F_{ime} for 18 values of k ($k=1,2,\dots,18$). These simulated values are compared directly with the data obtained from a specified interval in each of the 18 breaths of the washout. The sum of the absolute values of these 18 differences is displayed.

A routine search over the range of values for β_{mi} and ω_i is then performed and the values corresponding to a minimum for the summed difference is selected. In practice, we first simulate the end-tidal nitrogen concentrations through 18 breaths of a nitrogen washout using four ω 's and four β 's. The nitrogen concentrations appearing at

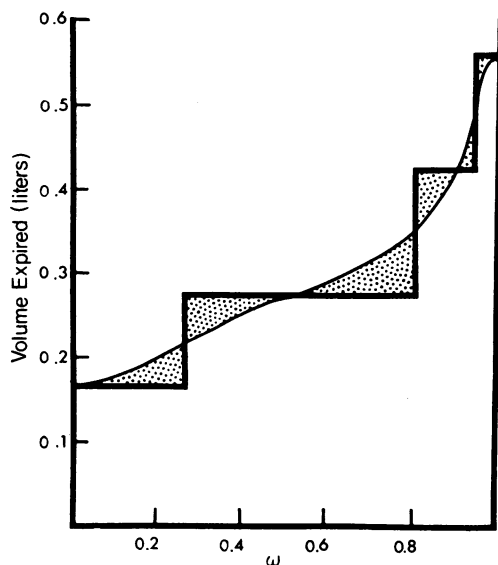


FIGURE 3 A plot of volume expired versus alveolar dilution ratio (ω) in which the continuous line represents the summed volumes expired from all compartments with ADR equal to or less than the corresponding value of ω on the horizontal axis. By using the mean data of patients with mild DOPS the steps describe this lung in macrocompartments.

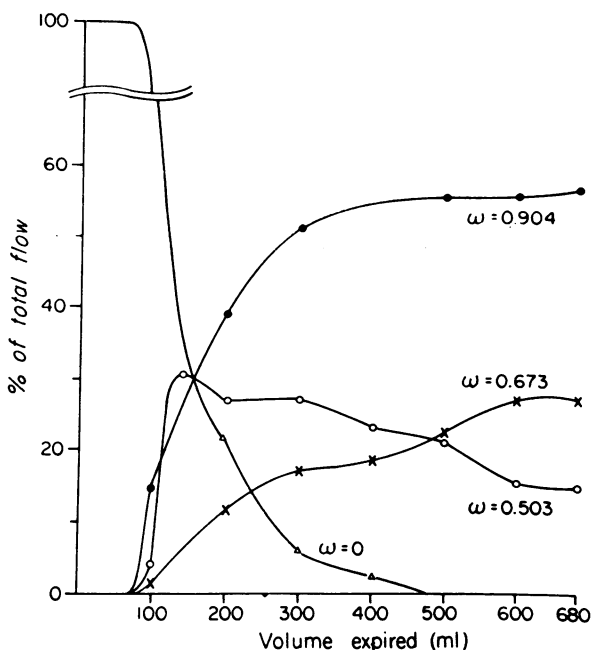


FIGURE 4 The pattern of emptying dead space and three macrocompartments in normal man.

specific volumes in the 18 expirations are then fitted by varying β 's and using the same ω 's. One of these ω 's equals zero. Fig. 4 is an example of a lung washout analyzed into four macro compartments having four β 's that vary throughout expiration.

RESULTS

Dead space volume (V_D) increased progressively with the severity of DOPSI and the increase in FRC (Table II). The mean value of V_D varied from 129 ml in normal young individuals to 272 ml in those with severe DOPSI. Differences in the mean V_D between groupings were all significant except in the adjacent category, i.e., mild DOPS was not different from the elderly normal or moderately severe DOPS, but was significantly greater than that found in normal young subjects and less than that found in severe DOPSI. In some, V_D was not completely delivered within one tidal volume. A correction for unexpelled V_D in those with moderate and severe DOPS may be made by extrapolation, but would change the value here by less than 10 ml. The V_D was not significantly different from that obtained by Fowler's (5) single breath method in normal subjects (paired sample analysis).

The FRC increased progressively with the severity of airway obstruction (Table II). FRC averaged 2.35 liters in those less than 40 yr, 2.45 liters in those beyond 40 and normal, and increased to a mean of 5.35 liters in those with severe airway obstruction. FRC in DOPSI, except for the milder abnormalities of airway

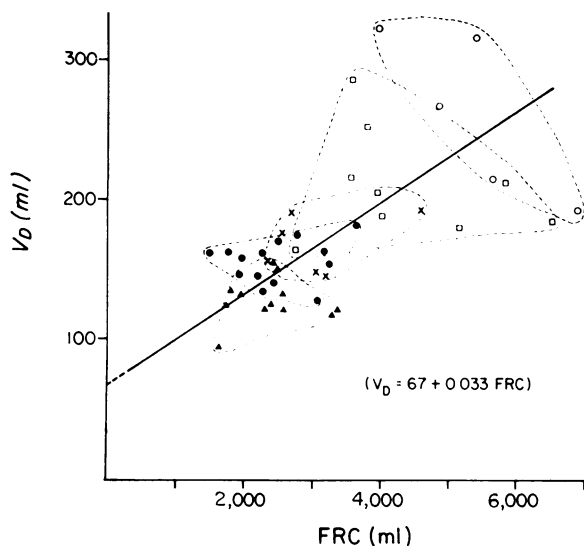


FIGURE 5 The relationship between V_D and FRC in normal subjects ($\blacktriangle$ —normal <40 yr; $\bullet$ —normal >40 yr) and increasing degrees of airway obstruction ($\times$ —mild DOPS; $\square$ —moderate DOPS; $\circ$ —severe DOPS).

obstruction, was significantly greater than that found in normals, both young and old. The FRC was similar to that measured simultaneously by the Darling technique (9) in normal subjects (paired sample analysis). In five subjects with severe DOPS_I the mean difference in FRC was 0.080 liters with the range of values obtained on the analog within ± 0.2 liters of the FRC measured by an extended nitrogen washout.

For all normal and obstructed subjects the ratio of V_D /FRC remained relatively fixed (Fig. 5). The regression of V_D upon FRC ($r = 0.56$) showed a minimal value for V_D of 67 cm³. V_D increased by a value of 33 cm³ per liter of lung volume above this value.

The volume of the poorly ventilated compartment in DOPS_I was significantly larger than that found in

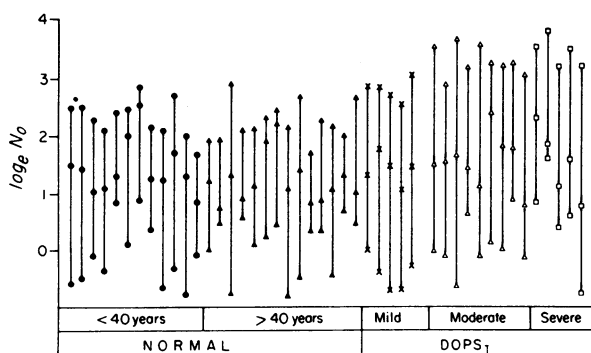


FIGURE 6 The dispersion of alveolar dilution ratio (ω) expressed as the $\log_e N_0$ ($\log_e N_0 = -\log_e (-\log_e \omega)$). An increased dispersion of ω occurs with DOPS as well as an absolute increase in the poorly ventilated compartment.

normals (Table II). The large difference in FRC was principally a change in the size of this compartment. There was no significant difference in the volume of the moderately and well ventilated compartments between normals and those with DOPS.

X-ray evidence of emphysema (hyperinflation and vascular signs) correlated poorly with changes in V_D or FRC. Several subjects with severe DOPS had no evidence of emphysema by X ray but had a large V_D and FRC.

The ω of the poorly ventilated compartment in DOPS_I was significantly greater than that found in normals (Fig. 6). In this figure N_0 is the number of breaths required for the concentration in that compartment to fall to $1/e$ of its initial value. The expression $\log_e N_0$ has the advantage of giving equal scale distances for equal ratios of N_0 (18). When compared with normal subjects there was an increased dispersion of ω in patients with DOPS ($P < 0.005$).

DISCUSSION

Measures of anatomical V_D estimate the volume of inspired gas in the conducting airways as opposed to the gas in the alveolar volume (19). Single breath tests (5) have difficulty in such assessment if no plateau in gas concentration occurs in the last phase of expiration. The method used here does not require a plateau and will measure V_D in DOPS_I where such estimates have been most unreliable. Values obtained by this method agree well with single breath tests in normal subjects and with normal values reported in the literature. The few emphysematous subjects in whom V_D has been measured by using the single breath test have had lower values than those reported here (6). Other methods of estimating anatomical V_D in clinical emphysema have employed a rebreathing method and an analysis of the nitrogen washout using a single chambered model (7, 8). In both instances these have given larger values for anatomical V_D than we show.

The data reported here show the anatomical V_D to increase with the severity of DOPS_I (Table II) as the resting lung volume enlarges. V_D increased by 33 cm³ per liter FRC with a minimal value of 67 cm³ (Fig. 5). An increase in physiologic dead space (V_D physiol) is expected with progression of the DOPS and the appearance of areas having high ventilation-perfusion ratios (alveolar dead space). Unexpectedly, an appreciable part of the change in V_D physiol is due to a change in the size of the anatomical dead space. The anatomical V_D/V_T ratio averaged 0.45 in the severe DOPS reported here. Fowler (6) has reported the V_D/V_T ratio as being similar in normal patients and those with emphysema. The severity of airway obstruction in his subjects is unknown. Read and Lee

(20) measured the V_D physiologically in patients with obstructive syndromes and found a mean V_D/V_T ratio of 0.53 without reference to the severity of DOPS. It is evident from the studies reported here that as airway obstruction progresses, more hyperventilation is necessary to maintain a normal P_{CO_2} with this added anatomical and physiological V_D . Our estimation of the degree of mismatch between ventilation and blood flow in DOPS_I may need revision.

The minimal V_D of 67 cm³ that would be present in collapsed lung is approximately the volume of the extrathoracic airways (Fig. 5). Nunn, Campbell, and Peckett (21) reported that 72 ± 32 ml (mean $\pm$ SD) of the total dead space was outside the thorax. This suggests that the airways which increase in volume with DOPS_I are within the thorax.

Hogg, Nepszky, Macklem, and Thurlbeck (22) have shown centrilobular spaces to be limited in their distensibility, i.e., they have a high initial volume with a smaller increase in volume than does normal parenchyma for equal distending pressures. They suggest that the V_D/V_T ratio should decrease with greater tidal volume, with the centrilobular spaces forming part of the anatomical V_D . In our patients with obstructive syndromes, the V_D/V_T ratio increased with the severity of the airway obstruction (Table II). The V_D/V_T ranged from 0.24 in a normal older subject to 0.52 in a patient with severe DOPS. When we searched through these patients for X-ray signs of emphysema, there was no constant relationship to the V_D/V_T or the V_D/V_0 ratio, i.e., X-ray signs of emphysema (hyperinflation and vascular changes) were little related to the dead space volume. Since minimal anatomical changes of emphysema may be present and not recognized by these X-ray signs, the lack of correlation may not entirely rule out the increased V_D as being a measure of the volume of the centrilobular spaces. On the other hand, an increase in V_D may occur as part of the greater distensibility of small airways.

Martin and Proctor (23) showed in the dog that isolated small bronchi (<2 mm in diameter) increased their volume by 5% per cm H₂O while medium-sized bronchi (5 mm) increased volume by 3.9% per cm H₂O and trachea by 2.2% per cm H₂O. More recent work has shown airway diameters to be independent of transpulmonary pressure although diameter and length of bronchi increased with lung volume (24). These authors found similar diameter changes in all bronchi throughout the lung and suggest that the presence of lung parenchyma altered the forces distending the airways. The question of airway distensibility is not settled, however, as a recent report using a similar technique has shown peripheral airways to be more distensible than central airways with parenchyma present

(25). Whether there is greater distensibility of peripheral airways or not, most of the airway volume is in the periphery where the effect of an increase in diameter and length is magnified. One model of the lung (26) shows that 70% of the airway volume down to and including the first order of respiratory bronchioles is in airways less than 2 mm in diameter.

Klingele and Staub (27) have shown that the diameter of the terminal bronchi in normal cat lung correlates well with the cube root of the volume change of the lobe. These authors affirm their belief that bronchiolar structural framework is integrated into alveolar wall, so that bronchiolar size might be expected to be a function of lung volume. In the group of patients reported here, the volume of dead space correlated moderately well with the increased volume of the poorly ventilated compartment (Table II) ($r = 0.55$) which in turn was responsible for most of the lung volume change. In fact, the correlation of V_D with the total lung volume was little different than that with this most poorly ventilated compartment, suggesting the increase in V_D is in the airways to this compartment.

The increase in V_D with increasing FRC (Fig. 5) in those with DOPS_I might be expected from the alteration in tissue properties reported in this condition (28). The maximum extensibility of alveolar wall is diminished in those with irreversible obstructive syndromes and the evidence suggests this is due to an increase in the resting length of the tissue with little change in the "mechanical stop." Since volume is proportional to the third power of the linear dimension, the greater resting length maintained without force results in large resting lung volumes. Since these increased volumes are associated with changes in airway volume, the changes in resting tissue length found in alveolar wall may be present in the tissues of the small and contiguous airways as well.

Such a change in the tissue properties is also represented in the dispersion of ventilation-to-volume ratios shown in these subjects with DOPS_I (Fig. 6). The poorly ventilated compartment which is significantly less well ventilated than in normal subjects is responsible for the increase in the total lung volume with increasing severity of the airway obstruction. The change in volume of such a compartment is compatible with the permanent deformation of alveolar tissue, i.e., the increase in resting length.

The lung model described here cannot define whether the compartments are ventilated in series or parallel. Compartmental volumes can be determined and the model does several things well, i.e., it measures dead space where this has been difficult heretofore, it measures FRC and the sequence of emptying. V_D , although

a series unit, treated here as a parallel compartment, starts emptying before any other compartment and is almost completely emptied within a normal expiration. Whether the other compartments in this model are in series or parallel must await further studies.

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