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NSPIRATORY FLOW RATE AND VENTILATION DISTRIBUTION N NORMAL SUBJECTS AND IN PAT ENTS WITH SIMPLE CHRONIC BRONCHITIS

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SUMMARY

1. Seated subjects stopped ventilation briefly at end expiration while a 5 ml bolus of ^{133}Xe was injected close to the mouth. They then inspired air at different flow rates and the distribution of radioactivity in the lungs was measured with a scanning technique during a period of breath-holding at maximal inspiration.

2. In five normal subjects the dependent zones received a greater fraction of the ^{133}Xe bolus than the apex during slow inspirations, but apical distribution exceeded basal for fast inspirations. The volume history of the lungs before the bolus injection had no effect on the slow/fast difference in four out of five subjects.

3. In five patients with clinical bronchitis but normal forced expired volume, dependent zone ventilation was much reduced on a slow inspiration compared with normals, but at fast flow rates the distribution was normal.

4. Insofar as the bolus in the fast inspiration was distributed according to regional airway conductances, these results suggest that in normal subjects differences in airway resistance exist between the upper and lower zones of the upright lung. An early abnormality in bronchitis appears to be a reduction of compliance in the dependent zones, as judged from the decrease in basal ventilation on a slow inspiration.

Key words: Regional lung function, distribution of ventilation, lung compliance, airways resistance, volume history.

In chronic bronchitis the main functional abnormalities appear to arise from disease of the small airways (Macklem, Thurlbeck & Fraser, 1971). For example, at necropsy the lungs in these cases show large increases in flow resistance of airways less than 2 mm in diameter, whereas the resistance of bronchi greater than 2 mm is nearly normal (Hogg, Macklem & Thurlbeck, 1968). Since airways of less than 2 mm internal diameter contribute only about 20% of the flow resistance of the tracheo-bronchial tree in intact dog (Macklem & Mead, 1967)

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and excised normal human lungs (Hogg *et al.*, 1968) an increase in peripheral airways resistance in life would be difficult to detect from measurements of total airways resistance or even 1 s forced expired volumes (FEV_1). Nevertheless, patients with simple chronic bronchitis, as defined by the Medical Research Council (1965), with normal or near-normal lung volumes, FEV_1 and airways resistance often have frequency dependence of compliance (Woolcock, Vincent & Macklem, 1969), a disturbed distribution of ventilation (Anthonisen, Bass, Oriol, Place & Bates, 1968), and abnormalities of gas-exchange at rest and on exercise (Levine, Housley, Macleod & Macklem, 1971). In the presence of a normal static elastic-recoil curve for the lungs, these disturbances of function can be explained on the basis of uneven ventilation due to peripheral airways disease.

In five normal subjects and in five patients with persistent expectoration but no impairment of lung function, we have measured the regional distribution of inspired gas with radioactive gases. Since inspiratory flow rate affects the regional distribution of gas in normal subjects (Robertson, Anthonisen & Ross, 1969), we have compared regional ventilation at slow (<0·3 l/s) and fast (>3·0 l/s) inspiratory flow rates. We shall show that marked differences in regional ventilation occur between normal subjects and those with simple chronic bronchitis at low inspiratory flow rates which are not present at high flow rates.

In addition, our results provide information about normal differences in airways resistance and time constants between the upper and lower regions of the upright lung.

METHODS

The normal subjects consisted of four men and one woman (A.T.) without cough or sputum and with no history of respiratory disease. Subjects D.M. and D.L. were light smokers (five cigarettes/day); the others were non-smokers. They were familiar with the respiratory manoeuvres. The patients with simple chronic bronchitis were from a group of men not attending hospital, who were taking part in a study into the effects of different types of cigarettes on respiratory symptoms. They volunteered to take part after the nature of this investigation was explained to them. Admission to the study was limited to men aged 25–55 years who smoked at least ten cigarettes a day, and who had chronic cough and sputum, on the basis of Medical Research Council (1965) criteria. In addition, the subjects with bronchitis had a monthly assessment of their cough frequency, measurement of morning sputum volume, FEV_1 and vital capacity (VC). None of this group complained of dyspnoea at rest or undue breathlessness on exercise. Chest X-rays were normal. All had smoked 25–45 cigarettes/day for 13–36 years. M.T. admitted to an attack of 'pleurisy' when aged 25 years, and N.Mc. to 'infective bronchitis' when aged 24 years. There were no other reports of respiratory illnesses. None had symptoms of asthma.

Physical characteristics, lung volumes (calculated at BTPS) and airways resistance are set out in Table 1. Lung volumes and airways resistance (at functional residual capacity) (FRC) were measured in a constant volume body-plethysmograph. Values for the normal subjects were normal or above predicted normal (Cotes, 1968).

Lung volumes for the subjects with bronchitis were normal. The values for FEV_1/VC ratio were lower than in the normal group, possibly because those with bronchitis were older. FEV_1, on the other hand, was normal. Airways resistance was below 2·0 cm $H_2O\,s^{-1}\,l^{-1}$ in all cases.

TABLE 1. Physical characteristics, lung volumes and airways resistance. Abbreviations: TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; FEV_1, forced expired volume in 1 s; VC, vital capacity; Raw, airways resistance.

	Age (years)	Ht. (cm)	Wt. (kg)	TLC (% predicted)	FRC (% TLC)	RV (% TLC)	FEV_1 (% predicted)	FEV_1/VC (%)	Raw (cmH_2O $s^{-1}l^{-1}$)
Subjects									
M	37	188	89	102	52	22			
D.L.	28	185	78	102	48	23	98	73	0·85
A.T.	29	183	72	105	52	20	133	84	0·87
D.O.	28	170	70	145	52	32	123	80	0·52
D.E.	21	189	75	97	53	25	92	77	
Mean	29	183	77	110	51	24	111	79	
Bronchitis patients									
M.T.	42	178	89	97	47	15	105	70	0·94
J.A.	46	172	62	114	63	31	94	65	0·7
N.Mc.	37	172	79	101	46	24	92	70	1·1
A.S.	54	164	70	101	56	31	100	71	0·9
D.C.	31	174	78	115	58	25	86	60	1·9
Mean	42	172	78	106	54	25	95	67	1·18

Procedure

The distribution of ventilation was measured using boluses of ^{133}Xe as described by Dollfuss, Milic-Emili & Bates (1967), and a lung-scanning technique (Hughes, Glazier, Maloney & West, 1968). All subjects were seated upright. They were connected to a spirometer containing air and after three or four tidal breaths to achieve a constant end-expiratory level, they were instructed to pause at end-expiration (FRC); about 2·5 mCi of ^{133}Xe in 5 ml of air was rapidly injected into tubing close to the mouth, and subjects inhaled as slowly or fast as possible. After inspiration of the bolus of labelled gas, subjects continued to inspire from the spirometer until full inspiration was achieved. They held their breath at full inspiration for 14–20 s while the lungs were scanned with two pairs of scintillation detectors. Inspirations of labelled gas at fast and slow rates were also made with different volume histories, i.e. immediately preceded either by a maximum inspiration to total lung capacity (TLC) followed by slow expiration to FRC—'deflation volume history', or by a maximum expiration to residual volume followed by a slow inspiration to FRC—'inflation volume history'. In these manoeuvres we guided subjects back to their end-expiratory value (FRC) from the spirometer tracing. Normal subjects made a single fast and a slow inspiration each preceded by either a tidal breathing or a deflation or an inflation volume history. Subjects with bronchitis made two (occasionally three) slow and fast inspirations keeping the same volume history—a tidal breathing history for M.T. and D.C., and a 'deflation volume history' for the others. Finally, all subjects rebreathed ^{133}Xe gas (about 1 mCi/l) from a spirometer for about 70 s for normal subjects and 140 s for subjects with bronchitis, and the lungs were scanned while the breath was held at TLC.

By relating regional count rates after inspiration to those after equilibration, regional ^{133}Xe concentrations can be obtained as described by Ball, Stewart, Newsham & Bates (1962).

To assist comparisons between groups of subjects, the values for both lungs were normali so that 100% represented the concentration expected had the inspired ^{133}Xe been distribu uniformly throughout the lungs. Normalizing in this way is valid if most of the lung is inclu in the counting field, as it was with our scanning technique. Expressed in this way regic Xe concentrations represent regional ventilation distribution 'per alveolus' (Sutherla Katsura & Milic-Emili, 1968).

Scanning speeds varied from 1·5 to 1·63 cm/s in normal subjects, and from 1·72 to 2·2 (m 1·9) cm/s for those with bronchitis. For each cm of distance travelled the radioactive co and the time were accumulated by a scaler-timer chain and fed sequentially to a data lo with a punch tape output. Because of the faster scanning speed in those with bronchitis ab 15% less counts were accumulated over each lung region for the same ^{133}Xe bolus ra activity. Comparisons between subjects were made from the bottom of the lung, which defined as the lowest level in the equilibration lung scan where the count rate equalled or greater than 20% of the maximum count rate. At mid-lung level, on average 600–800 co were accumulated over each lung for each 2 cm distance. An electrical output from the sp

TABLE 2. Inspiratory capacity (IC) and inspiratory flow rate ($\dot{V}$) for slow and fast inspirations

Normal subjects	IC (litres, ATPS)						$\dot{V}$ (litres/s, ATPS)					
	Slow			Fast			Slow			Fast		
	Tidal*	De-flation	In-flation	Tidal	De-flation	In-flation	Tidal	De-flation	In-flation	Tidal	De-flation	fl
D.M.	3·3	3·5	3·4	3·4	3·7	3·45	0·27	0·26	0·22	2·5	3·0	3
D.L.	2·85	3·2	3·1	2·85	3·2	3·2	0·19	0·12	0·1	3·55	4·2	3
A.T.	3·2	3·2	3·2	2·9	2·6	3·1	0·07	0·19	0·17	3·3	2·65	2
D.O.	3·6	3·9	3·9	3·3	3·7	3·5	0·34	0·38	0·23	2·8	5·4	4
D.E.	3·3	3·25	3·2	3·3	3·25	3·2	0·2	0·22	0·17	5·0	4·4	3
Mean	3·25	3·21	3·36	3·15	3·29	3·29	0·21	0·23	0·18	3·43	3·93	3

Bronchitis patients	IC (litres, ATPS)					$\dot{V}$ (litres/s, ATPS)				
	Slow			Fast		Slow			Fast	
	No. 1	No. 2	No. 3	No. 1	No. 2	No. 1	No. 2	No. 3	No. 1	No. 2
M.T.	3·35	3·35		3·0	2·9	0·35	0·21		—	4·3
J.A.	2·3	2·5		2·65	2·5	0·34	0·3		1·85	1·55
N.Mc.	4·1	3·9	3·8	3·45	3·9	0·58	0·27	0·18	2·9	4·2
A.S.	2·5	2·2		2·3	2·15	0·07	0·25		1·65	1·75
D.C.	2·65	3·05		2·0	2·56	0·1	0·1		2·88	3·31
Mean	2·98	3·00		2·68	2·80	0·29	0·23		2·32	3·02

* Tidal breathing, deflation or inflation volume history.

meter was fed into an u.v. recorder from which inspiratory capacity and inspiratory flow rates were calculated. The flow rate was calculated from the slope of the volume–time plot 0·1–0·2 litres after the onset of inspiration. For fast inspirations the chart speed was 50 mm/s. Although the initial part of a fast inspiration cannot be measured very accurately in this way, we wish to emphasize the ten-fold difference (see Table 2) between the fast and slow flow rates rather than the absolute values.

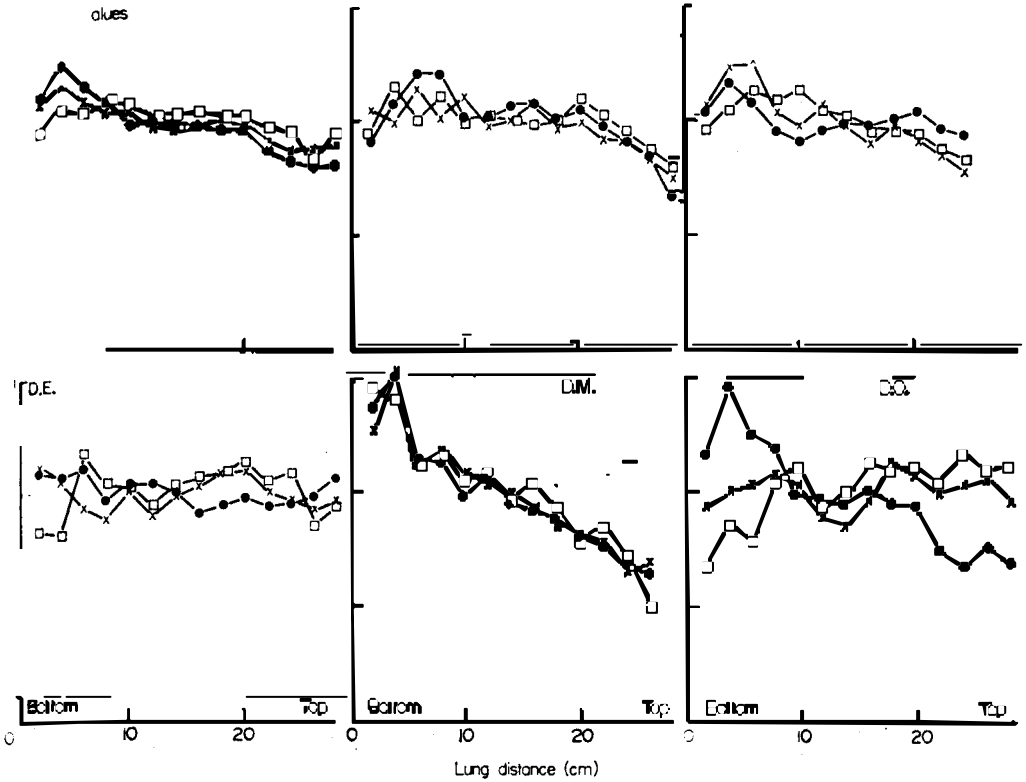

FIG. 1. Regional distribution of ventilation after the slow inspiration (from FRC) of a bolus of ^{133}Xe for five normal subjects. Regional ventilation is expressed as % of the ventilation 'per alveolus' predicted if the bolus had been distributed uniformly to all alveoli. The volume history immediately preceding the inspiration was varied from tidal breathing to a prior lung deflation or inflation (see text). Mean values for the right and left lung in each individual are given, as well as mean values for the group. Note that the bottom of the lungs receives more ventilation than the top. Varying volume history has no effect on the distribution. ●, Tidal breathing; ×, deflation history; □, inflation history.

The radiation dosage to the lungs from the whole procedure was about 200 millirads, and to the rest of the body less than 20 millirads.

RESULTS

Table 2 gives the inspiratory capacity (IC) and flow rates ($\dot{V}$) for the slow and fast inspirations. For the normal subjects, IC and $\dot{V}$ were about the same for the three different volume histories.

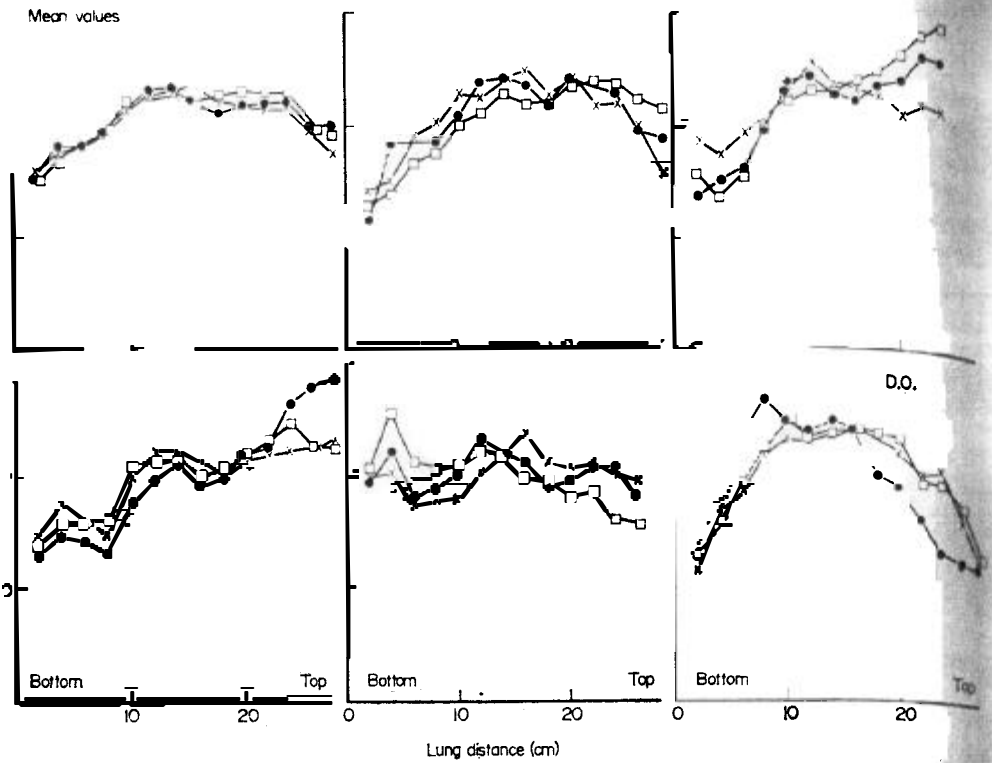

FIG. 2. Regional distribution of ventilation for five normal subjects plotted against lung distance as in Fig. 1, after a fast inspiration from FRC of ^{133}Xe. Note that, in contrast to Fig. 1, the bottom of the lung receives less ventilation than the top. The symbols are as in Fig. 1.

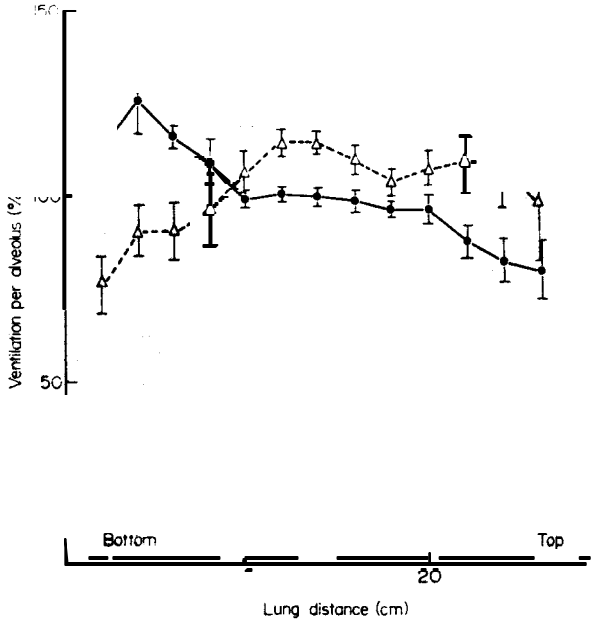

FIG. 3. Regional distribution of ventilation for normal subjects after fast (△) and slow (●) inspirations of ^{133}Xe boluses from FRC. Mean values with 1 SEM. The preceding volume history was tidal breathing.

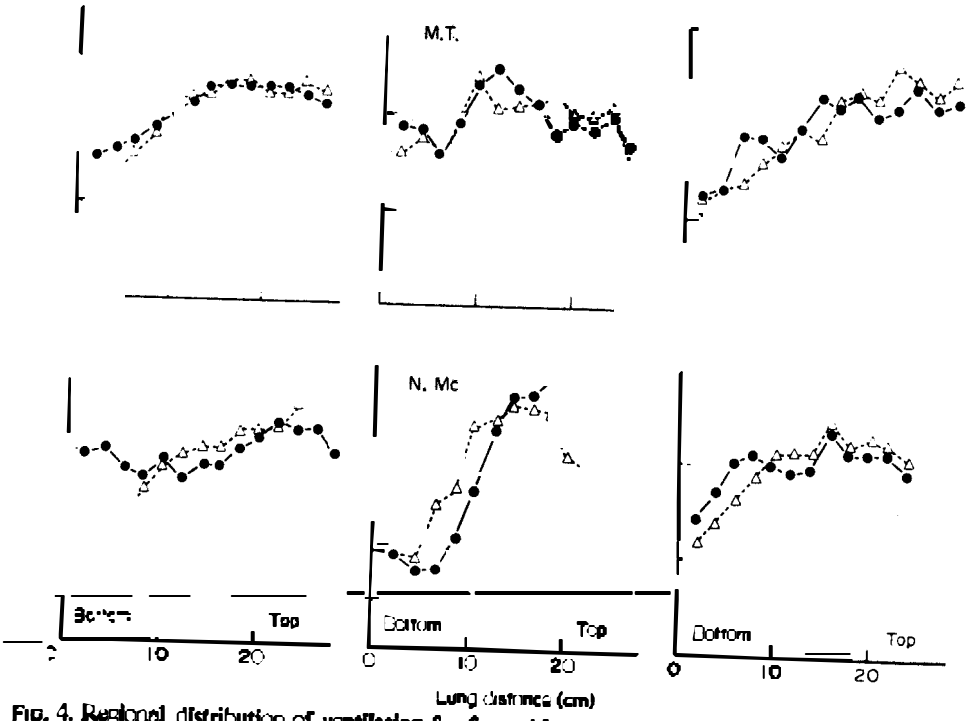

FIG. 4. Regional distribution of ventilation for five subjects with bronchitis following slow (●) and fast (△) inspirations of ^{133}Xe from FRC, plotted as in Fig. 1. Mean values for the right and left lungs in each individual and for the group are shown. The same volume history was used for each individual (see text).

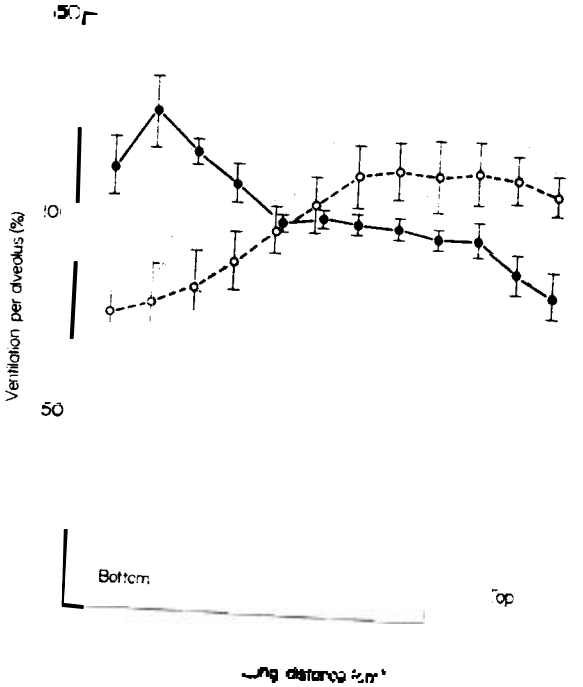

FIG. 5. Regional distribution of ventilation following a slow inspiration of the ^{133}Xe bolus in five normal subjects (●) and in five subjects with bronchitis (○). Mean values for each group with 1 SEM.

The relatively constant IC suggests that all inspirations started from the same value of FR
The patients with chronic bronchitis had lower flow rates for the fast inspirations compar
with the normal subjects, but there was little difference in $\dot{V}$ for the slow inspirations.

Fig. 1 shows the ventilation distribution for the slow inspiration in the normal subjec
All except subject D.E. showed significantly greater ventilation to the bottom of the lu
although the gradient of apex to basal ventilation varied from subject to subject. The me
values show an apex/base ventilation ratio of about 0·66 which is in close agreement with
values for regional ventilation found by others (Sutherland *et al.*, 1968) at low flow ra
($<0·5$ litre/s). Except for subject D.O., alterations in the previous volume history of the lu
had no effect on the distribution of inspiration starting from FRC; this finding is also in agr
ment with the results of Sutherland *et al.* (1968).

Fig. 2 shows the distribution of ventilation for fast inspirations (3·4–3·9 l/s). All subje
showed a shift in ventilation distribution to the apices; apex/base ventilation ratios w
greater than one in all subjects except D.M. Again, there was no significant effect from alter
the volume history. In Fig. 3 the mean results for the slow and fast inspirations (tidal breath
volume history) are plotted and show a significant decrease in basal ventilation at fast insp
tory flow rates.

The results for the subjects with bronchitis are shown in Fig. 4. The most striking findin
the reduction in ventilation to the lung bases for both the slow and the fast inspirations. For
group as a whole, the mean values for ventilation distribution on the fast inspiration do
differ significantly from those seen in normal subjects, but quite marked differences betw
the two groups occur in the distribution of the slow inspiration as shown in Fig. 5.

DISCUSSION

Determinants of regional distribution of inspired gas

Fowler (1949) pointed out that the ventilation of lung regions may be uneven in s
(volume change) or in time (filling pattern). Otis, McKerrow, Bartlett, Mead, McIlroy, Se
stone & Radford (1956) analysed the distribution of ventilation on the assumption tha
lungs consisted of parallel pathways, each with its own flow-resistive (R) and volume-el
or compliance (C) properties. Using an electrical analogue they concluded that the distribu
of gas between two units would not alter with changes of breathing frequency if their
constants (the product of R and C) were equal. In other words, although the units might
had a different ventilation per unit volume, their proportional volume changes in time
space would have remained unchanged and in phase. Units with different time-const
however, change their relative ventilation in time and space as breathing frequency a
This leads to differences in intra-pulmonary gas distribution at different frequencies, a
alterations in the overall dynamic compliance and airways resistance of lungs.

Radioactive gases can be used to distinguish lung regions with different time cons
by measuring separately the regional airways resistance and regional lung compliance. U
quasi-static conditions (inspiratory flow rates of 0·1 l/s) airways resistances will have
little effect on the distribution of inspired gas which will be determined by regional compli
In theory, extremely high resistances (relative to compliances) might affect the distrib
at low flow rates, but in fact the overall airways resistance in our subjects was normal. S

authors (Robertson *et al.*, 1969; Macklem, 1971) have pointed out that the distribution of the first part of a very fast inspiration will be determined mostly by regional resistance, a conclusion which follows from the lung model and equations given by Otis *et al.* (1956). Nevertheless, regional compliances must have some influence (probably small) on the distribution of a fast inspiration but the extent of their contribution remains to be determined. Because the distribution of ventilation is expressed per alveolus (or per unit volume), we can thus derive a distribution of specific compliance and specific resistance.

Distribution of airways resistance

Insofar as the distribution of a bolus of gas inhaled at the onset of a fast inspiration reflects the distribution of airways resistances, our results suggest that the resistance of the dependent zones at mid-lung volumes in normal subjects exceeds that of the upper zones. Thus the apex/base ratio of ventilation distribution for fast inspirations is proportional to the ratio of airway conductances; in our experiments this ratio was about 1·4. Robertson *et al.* (1969), also using radioactive Xe, found a uniform distribution of gas at 40% VC at inspiratory flow rates of 4 l/s; they argued that the distribution of airways resistance in the upright position was uniform. Their results received some support from the studies of Wood, Ruff, Bryan & Milic-Emili (1969) who found that even when gases of increased density were rapidly inhaled (SF_6 at 2 atmospheres ambient pressure) the distribution of ventilation still remained uniform. Indeed, we too would have come to this conclusion had we not included in our scan the bottom 8 cm of the lung (Figs. 2 and 3).

There are reasons for believing that bronchial calibre, and hence airway conductance, might be less in the dependent zones at resting lung volumes. At FRC the lower zones are only expanded to some 30–40% of their regional total lung capacity, compared with 55–60% for the upper zones (Milic-Emili, Henderson, Dolovich, Trop & Kaneko, 1966); differences in regional pleural surface pressure at end-expiratory lung volume appropriate for these volumes have been measured (Daly & Bondurant, 1963). Simply on the basis of the relationship between airways resistance and lung volume (Briscoe & Dubois, 1958) or transpulmonary pressure (Butler, Caro, Alcala & Dubois, 1960), the conductance of the upper zones should exceed that for the lower zones by about 1·5 times, which is close to the value we have obtained experimentally. Further, in excised dog lungs the change of calibre of intrapulmonary bronchi appears to be almost linearly related to changes in the cube root of lung volume (Hughes, Hoppin & Mead, 1972); the relationship of both to changes in transpulmonary pressure is therefore similar. Nevertheless, other factors must play a part because the ventilation per alveolus on the fast inspiration does not continue to increase from base to apex as expected, but remains relatively constant over the upper two-thirds of the lung. Although there may be variations in smooth muscle tone at different levels in the lung, we would have expected the influence of bronchomotor tone to have been considerably less for the measurements made following a maximal inspiration, i.e. 'deflation volume history' (Vincent, Knudson, Leith, Macklem & Mead, 1970; Nadel & Tierney, 1961), but no difference in ventilation distribution was found (Fig. 2). However, if most of the airways resistance below the bifurcation of the trachea was in the main and lobar bronchi the distribution of gas would have a lobar, rather than a zonal distribution, with fast inspirations. But in dogs, Macklem, Woolcock, Hogg, Nadel & Wilson (1969) found that less than 10% of the airways resistance from main bronchus to alveolus was located in the main and lobar bronchi. In addition, fluid dynamic considerations, outside

the scope of this report, may play some part in determining the flow pathways taken by th bolus as it passes through the larynx and meets the birfurcations of the main and lobar bronchi

Although we favour the explanation that the major determinant of the distribution of th rapidly inhaled boluses is the distribution of bronchial calibre within the lung, it is clear tha the issue is not yet settled and that bronchographic measurements in man of bronchial calibr at different levels in the upright lung at FRC would be very useful. In anaesthetized dogs a FRC in the vertical position the diameter of the apical bronchi from tantalum bronchogram as a percentage of their maximum diameter, is considerably greater than that of airways in th lower lobe; these differences disappear in the supine position (A. G. Wilson, H. Jones & J. M. B. Hughes, unpublished work). Nevertheless, additional support for our conclusion comes from predictions of ventilation distribution developed by Pedley, Sudlow & Milic Emili (1972). They allowed regional airways resistance and lung compliance to vary wit regional lung volume, and resistance to vary with flow rate, all in a non-linear manner. The predicted that when boluses of gas were inhaled from FRC a greater proportion of the bolu would be distributed to the upper zone as flow rate increased; at flow rates of about 2 l/ a reversal of the distribution for a slow breath occurred with the upper zone receiving a large fraction than the lower.

Distribution of time constants in the normal lung

For slow inspirations from FRC the distribution of inspired gas depends principally o differences in regional compliance. Milic-Emili *et al.* (1966) have shown how this arises fro systematic differences in regional expansion at FRC, and the non-linear elastic properties c lung tissue. Insofar as the distribution of the slow inspiration is proportional to lung com pliance and the distribution of the fast inspiration is inversely proportional to intra-pulmonar airways resistances, the ratio of the slow to fast ventilation distribution for any lung zone wi be proportional to the time constant ($C \times R$) for that region. This ratio is plotted for the norm subjects in Fig. 6. The ratios indicate relative differences and are not absolute values. Tim constants in the dependent zones exceed those in the upper zones by a factor of 1·8.

Because the bolus has to traverse a common dead-space and because infinitely fast and slo inspirations cannot in fact be achieved, the slow/fast ratios probably underestimate differenc in regional time constants by as much as 50–100%. How is it then that time constants diffe ences within the upright lung of two or three times do not give rise to frequency dependen of compliance? [It is generally accepted that normal subjects do not show frequency depen ence of compliance (Otis *et al.*, 1956) but the reader is referred to a recent review (Macklem 1971) for more detailed discussion.] A possible explanation is suggested by Macklem & Mea (1967) who point out that the phase-angle between any two units whose time constants diff is influenced by the absolute values of the time constants. Lower airways resistance (fro alveolus to trachea) in man appears to be very low (Vincent *et al.*, 1970) about 0·5 cm $H_2O\,s^{-1}\,l^{-1}$ consequently intrapulmonary time-constants will be short, about 0·1 s. It follows from th equations given by Otis *et al.* (1956) that a three- or four-fold difference in such short tim constants would give rise to little or no change of dynamic compliance at frequencies of up t 100 breaths/min. According to Macklem (1971, pp. 385–395) other factors which might co tribute to frequency independence of overall compliance in the presence of intrapulmonar time-constant discrepancies are (1) interdependence between units and (2) collateral pathway The relative importance of these mechanisms is not known.

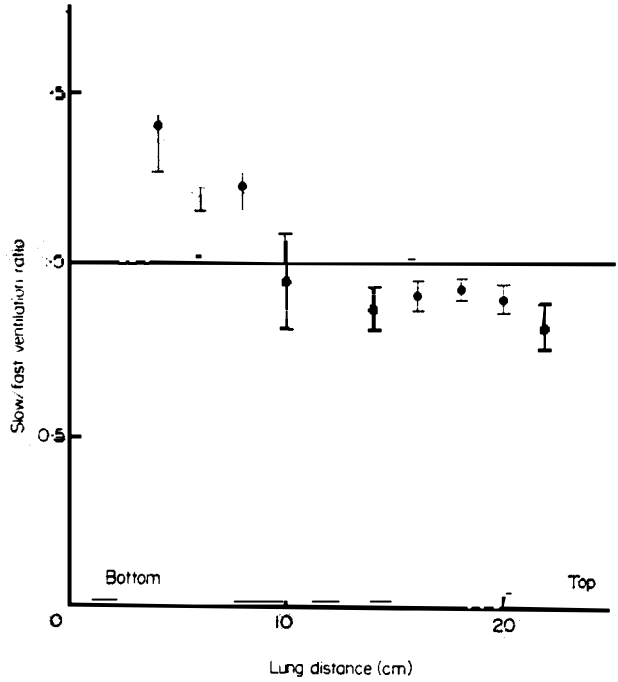

FIG. 6. Ratio of ventilation distribution for the slow inspiration to that for the fast inspiration for the five normal subjects. Volume history of tidal breathing. Mean values of the results in each subject with 2 SEM.

Distribution of ventilation in subjects with bronchitis

The subjects with early bronchitis showed a normal distribution of ventilation for fast inspirations but a much reduced basal ventilation compared with normal subjects for slow inspirations. In other words, they appeared to have a normal distribution of airways resistance but a reduction in the compliance of the dependent zones. It is possible that compliance was abnormally high in the middle and upper regions of the lung. Although we did not measure the static elastic properties of the lungs in these patients we think this an unlikely supposition. Abnormally high compliance indicates emphysema, and none of our patients had lung function tests or X-ray changes to suggest this. Altered lower-zone compliance could result from an abnormal distribution of regional volume at FRC, but more recent studies which we have carried out in these subjects have shown that they have a normal distribution of regional volume at resting lung volume.

Pathological studies in patients with airways obstruction and chronic cough and mucus production have shown mucus plugging, narrowing and inflammation of small bronchi and bronchioles (Macklem *et al.*, 1971). Peribronchiolar fibrosis was also common. Because normally the resistance of airways less than 2 mm in diameter makes up only a small fraction of the lower airways resistance (Macklem & Mead, 1967; Macklem *et al.*, 1969) these lesions would not necessarily affect the distribution of intrapulmonary airways resistance very much. Nevertheless small airways obstruction leading to closure might well reduce the compliance of such regions by reducing the number of units taking part in local expansion.

In these subjects the distribution of ventilation for the fast and slow inspirations was similar; consequently the slow/fast ventilation ratio was uniform throughout the lung. It cannot be concluded, however, that their intrapulmonary time-constants were equal. In each counting zone there are up to 10^6 alveoli and many thousand airways which in disease are likely to be heterogeneous in function. Inhomogeneity of ventilation within, as well as between counting regions, has been shown in patients with chronic bronchitis (Anthonisen *et al.*, 1968). Therefore a wide spectrum of time-constants probably exists within each zone because frequency dependence of compliance is commonly found in these patients (Woolcock *et al.*, 1969).

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