Ventilatory drive and ventilatory response during rebreathing

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Maranetra, N. and Pain, M. C. F. (1974). *Thorax*, **29**, 578–581. **Ventilatory drive and ventilatory response during rebreathing.** The increase in inspiratory airway pressure generated against a transiently occluded airway during rebreathing is proposed as a simple index of ventilatory drive ($\Delta P/\Delta P_{CO_2}$). A study of this index in 12 normal subjects and 50 patients with chronic airways obstruction demonstrated no significant difference between normals and patients in $\Delta P/\Delta P_{CO_2}$ despite an overall reduction in the ventilatory response to carbon dioxide ($\Delta\dot{V}E/\Delta P_{CO_2}$) in the patients. A significant association was demonstrated between the ventilatory response to carbon dioxide, $\Delta P/\Delta P_{CO_2}$ and the degree of airways obstruction. Patients with a low $\Delta P/\Delta P_{CO_2}$ showed greater hypoxaemia, hypercapnia, and polycythaemia than patients with a higher $\Delta P/\Delta P_{CO_2}$ for the same degree of airways obstruction.

The increase in minute ventilation that occurs during rebreathing has been expressed as the ventilatory response to carbon dioxide ($\Delta\dot{V}E/\Delta P_{CO_2}$) and used as an index of respiratory centre sensitivity. This implies that the output from the stimulated 'respiratory centre' is faithfully reflected by the output from the ventilatory apparatus. While this may be reasonable in subjects with normal mechanical loading of the respiratory muscles, it is probably erroneous in patients with abnormal ventilatory mechanics, and this has prompted a search for a more appropriate means of assessing the output from the respiratory centre during carbon dioxide stimulation. Thus increases in transpulmonary pressure (O'Donnell and Hood, 1971) and diaphragmatic electrical activity (Lourenco and Miranda, 1968) have been studied to define the rate of increase in respiratory muscle work in response to rebreathing. These techniques are not simple and not very comfortable for the subject so that data from repeated measurements become difficult to obtain.

We have attempted to measure the increase in airway pressure generated during inspiration against a momentarily closed airway during rebreathing in normal subjects and patients with chronic airflow obstruction and used this index as an expression of ventilatory drive.

SUBJECTS AND METHODS

Two groups were studied. Twelve normals, whose ages ranged from 18 to 36 years, were medical and technical staff of the hospital.

The 50 patients, 42 men and 8 women, had been referred to the laboratory for assessment of airways obstruction. Their ages ranged from 41 to 73 years. Their pulmonary functional status is shown in Table I. Measurements of forced expired volume in one second ($FEV_{1.0}$), fractional carbon monoxide uptake, and arterial blood and expired gases were performed using standard techniques.

TABLE I
CLINICAL AND FUNCTIONAL STATUS OF 50 PATIENTS WITH AIRWAYS OBSTRUCTION

Study	Mean	SD
$FEV_{1.0}$ (% predicted)	37	14
Fractional CO uptake (%)	31	6
Bronchodilator responsiveness (%)	23	12
Pa_{O_2} (mmHg)	70	14
Pa_{CO_2} (mmHg)	43	10
Haematocrit (%)	49	7
RVH ECG score[1]	2·5	2
Right heart failure	20/50	

[1]RVH ECG score refers to the sum of abnormalities noted on the basis of: P pulmonale=1; right QRS axis deviation=1; clockwise rotation=1; dominant R wave in V4R or V1=2; ST-T depression in V1–3=2.

The rebreathing circuit is shown in Fig. 1 and is basically that used by Read (1967). At the end of normal expiration the patient is connected to a 7 litre bag containing about 7% carbon dioxide in oxygen. Ventilation during a 4-minute rebreathing period is recorded with a water-filled spirometer and kymograph, and the carbon dioxide tension is continuously monitored using an infrared
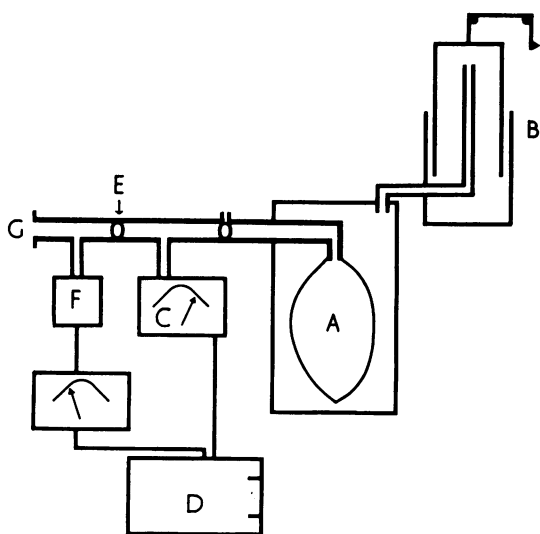
FIG. 1. *The rebreathing circuit. A, rebreathing bag; B, spirometer and kymograph; C, CO_2 analyser; D, recorder; E, manually operated interrupter tap; F, pressure transducer; G, mouthpiece.*

rapid CO_2 Analyser (Godart Capnograph). At 30 second intervals during rebreathing a tap is turned by hand at the beginning of inspiration and the subject attempts to inspire against an occluded airway. The period of occlusion begins within 200 msec of the start of inspiration and the period of occlusion is about 600 msec. The inspiratory pressure so generated is monitored using a pressure transducer (1280 c Hewlett-Packard) and amplifier (Sanborn 350–1100 c), and displayed with the Capnograph signal on a two-channel Sanborn recorder (Fig. 2). The

FIG. 2. *Example of changes in ventilation and airway pressure measured during rebreathing in a normal subject.*

slope of the line of best fit between $\dot{V}E$ and PCO_2 ($\Delta\dot{V}E/\Delta PCO_2$) is expressed as the ventilatory response (litre min^{-1} mmHg^{-1}) and similarly that between the inspiratory airway pressure against the occluded airway and PCO_2 ($\Delta P/\Delta PCO_2$) is termed the ventilatory drive (cm H_2O mmHg^{-1}).

RESULTS

NORMAL SUBJECTS The ventilatory response ranged from 0·7 to 4·7 litre min^{-1} mmHg^{-1} (mean 1·9; SD$\pm$1·0), and the ventilatory drive was 0·2 to 2·4 cm H_2O mmHg^{-1} (mean 0·95; SD$\pm$0·5). There was a significant correlation between the two (r=0·6; P<0·001).

PATIENTS The ventilatory response was 0·1 to 2·7 litre min^{-1} mmHg^{-1} (mean 0·73; SD$\pm$0·5) and the ventilatory drive was 0·1 to 2·5 cm H_2O mmHg^{-1} (mean 0·88; SD$\pm$0·7). Again the correlation between drive and response was significant (r=0·71; P<0·001). The results are summarized in Table II.

TABLE II
$\Delta P/\Delta PCO_2$ AND $\Delta\dot{V}E/\Delta PCO_2$ VALUES (MEAN$\pm$SD) IN 12 NORMALS AND 50 PATIENTS

	Normal	Obstructed	
$\Delta P/\Delta PCO_2$	0·95$\pm$0·5	0·88$\pm$0·74	NS
$\Delta\dot{V}E/\Delta PCO_2$	1·9 $\pm$1·0	0·73$\pm$0·55	t=5·4 P<0·001

DISCUSSION

The increase in ventilation that normally occurs during rebreathing is associated with increases in inspiratory work (Milic-Emili and Tyler, 1963). Transpulmonary pressure differences between inspiration and expiration will increase, resulting in a certain increase in tidal volume (depending on the static compliance and flow resistive properties of the lungs), and the pressure generated during attempted inspiration against a transiently occluded airway would seem intuitively to represent some function of the drive to the ventilatory apparatus. There are a number of factors which might mitigate against the ready acceptance of $\Delta P/\Delta PCO_2$ measured by this technique as a simple index of ventilatory drive. Thus, ventilation increases due to an increase in rate without change in tidal volume would result in a lower $\Delta P/\Delta PCO_2$ in subjects without frequency dependence of compliance. The use of the absolute increase in airway pressure over the rebreathing period overlooks the difference in volume expansion produced in lungs with differences in static pressure-volume curves, and the exact onset and duration of each interruption and attempted inspiration may well
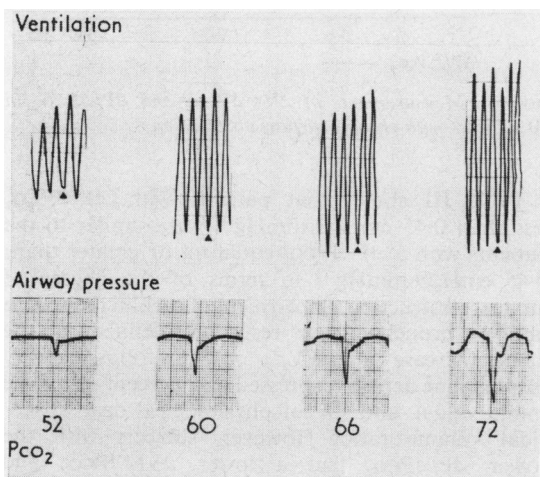
determine the extent of the pressure generated. While these factors require further examination in patients in whom more detailed information concerning pulmonary mechanical properties is available, the following points can be made.

The pattern of ventilation increase in both normals and subjects with airflow obstruction is invariably one of an increase in both rate and tidal volume. In a few patients we made simultaneous measurements of transpulmonary pressure increases and interrupted airway pressure increases during rebreathing and these measurements showed a highly significant linear correlation ($r = 0.87$, $n = 10$) with a slope of 0.73 (unpublished observations).

Manual tap operation may induce differences in the time of onset of interruption and differences in the duration of interruption. Studies on sudden airways occlusion in cats (Whitelaw and Milic-Emili, 1973) would suggest that reflex inhibition of inspiratory effort is absent with occlusion occurring within the first 250 msec of inspiration, and that duration of occlusion is of minor importance. We were able, with practice, to achieve interruption within an average of 150 ml of the start of inspiration and this is equivalent to an average onset of interruption of 150 msec from the start of inspiration. Studies designed to demonstrate the influence of interruption at different volumes above functional residual capacity showed that there was little change in the generated pressure ($\pm 20\%$) provided the interruption occurred within 200 ml of the start of inspiration. Because of concern about possible cortical inhibition influencing the pressure generated during attempted inspiration against the occluded tap, the rate of change in pressure was also calculated. It was found that this index $[(dp/dt)/\Delta Pco_2]$ appeared to have no advantage over $\Delta P/\Delta Pco_2$ and the two were highly significantly related.

Obviously considerable technical improvement would be achieved by making the interruption procedure an electronically activated one by which means the onset and duration of interruption can be precisely controlled.

As expected, the wide normal range of $\Delta\dot{V}E/\Delta Pco_2$ found by other workers (Read, 1967; Rebuck and Read, 1971) was again demonstrated in this study and was significantly associated with a range of $\Delta P/\Delta Pco_2$. Although our normals are a younger group than the patients, and direct comparison is not strictly possible, the mechanical load imposed by airways obstruction reduces the output ($\Delta\dot{V}E/\Delta Pco_2$) by an average of 60%, and the individual ventilatory response is associated with the drive ($\Delta P/\Delta Pco_2$) and the extent of airways obstruction according to the following equation:

$$\Delta\dot{V}E/\Delta Pco_2 = 0.5\ \Delta P/\Delta Pco_2 + 0.01\ FEV_{1.0}\%N - 0.09$$
$$n = 50 \quad R = 0.76$$

where $FEV_{1.0}\%N$ is the one second forced expiratory volume expressed as a percentage of predicted normal.

The value for $\Delta P/\Delta Pco_2$ among the subjects with airways obstruction was not significantly different from that of the normals despite a difference in $\Delta\dot{V}E/\Delta Pco_2$, suggesting that the development of airways obstruction does not necessarily lead to a reduction of drive. This agrees with the findings of O'Donnell and Hood (1971), who showed similar preservation of Δtranspulmonary pressure/ΔPco_2 relationships with very low $\Delta\dot{V}E/\Delta Pco_2$ in patients with hypercapnic airways obstruction.

Figure 3 illustrates that while the overall correlation between drive and response was significant, some individual patients had a higher than normal drive whereas others had a lower than normal drive for the same ventilatory response.
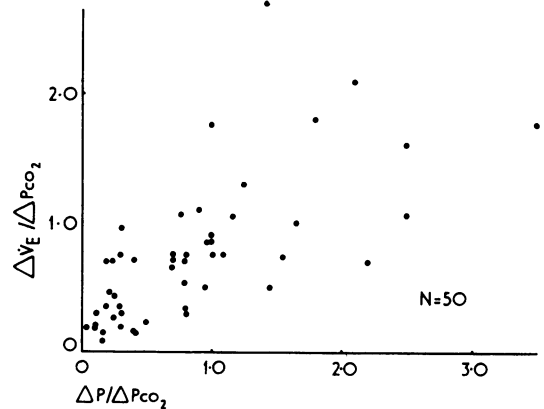

FIG. 3. *Measurements of $\Delta\dot{V}E/\Delta Pco_2$ and $\Delta P/\Delta Pco_2$ in 50 subjects with chronic airflow obstruction.*

Table III shows that patients with $\Delta P/\Delta Pco_2$ less than 0.45 cmH$_2$O mmHg^{-1} were similar to the patients with a $\Delta P/\Delta Pco_2$ equal to, or greater than, 0.45 cmH$_2$O mmHg^{-1} in terms of the degree of airways obstruction, impairment of carbon monoxide uptake, bronchodilator response (defined as the acute increase in $FEV_{1.0}$ or VC following 1% isoprenaline aerosol expressed as a percentage of the initial value), and size of physiological dead space/tidal volume ratio. However, subjects with the lower $\Delta P/\Delta Pco_2$ had a lower $\Delta\dot{V}E/\Delta Pco_2$ and arterial oxygen tension and higher arterial carbon dioxide tension, haematocrit, and incidence of

TABLE III
RELATIONSHIP BETWEEN 'VENTILATORY DRIVE' AND CLINICAL FEATURES

	$\Delta P/\Delta P_{CO_2} < 0\cdot45$ (N = 19)		$\Delta P/\Delta P_{CO_2} =$ $0\cdot45$—$1\cdot45$ (N = 22)		
	Mean	SD	Mean	SD	
$FEV_{1\cdot0}\%$ predicted	32	12	37	12	NS
$F_{CO}\%$	29	6	31	4	NS
V_D/V_T	0·4	0·1	0·4	0·07	NS
Bronchodilator responsiveness (%)	19	12	25	12	NS
Right heart failure	10/19		8/22		NS
$\Delta\dot{V}_E/\Delta P_{CO_2}$	0·3	0·2	0·8	0·5	P < 0·001
P_{aO_2}	62	12	72	14	P = 0·025
P_{aCO_2}	51	9	40	6	P < 0·001
Haematocrit	52	9	46	5	P = 0·01
RVH ECG score	3·4	2	1·8	2	P = 0·025

electrocardiographic abnormalities suggesting cor pulmonale.

The prognostic significance of a low $\Delta P/\Delta P_{CO_2}$ in a normal subject who develops airways obstruction in terms of his clinical presentation, susceptibility to agents producing respiratory depression, and the development of polycythaemia and cor pulmonale is of some interest but present data do not yet allow any definite conclusions to be drawn.

We believe that this index, which is easily measured with no patient discomfort, is an expression of ventilatory drive as distinct from ventilatory response and as such is more relevant to the assessment of ventilatory control in patients with airways obstruction.

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