Evaluation of breath holding in hypercapnia as a simple clinical test of respiratory chemosensitivity

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Stanley, N. N., Cunningham, E. L., Altose, M. D., Kelsen, S. G., Levinson, R. S., and Cherniack, N. S. (1975). *Thorax*, **30**, 337–343. **Evaluation of breath holding in hypercapnia as a simple clinical test of respiratory chemosensitivity.** Breath holding was used as the basis of a simple test of respiratory chemosensitivity. Breath holding was begun at selected degrees of hypercapnia produced by CO_2 rebreathing. In 16 healthy control subjects there was a linear regression of the log of breath-holding time on the P_{CO_2} at the start of breath holding. Breath-holding time (BHT) and the slope of a log BHT/P_{CO_2} plot were closely correlated with the ventilatory response to CO_2. In five cases of the idiopathic hypoventilation syndrome, CO_2 retention and reduced ventilatory response to CO_2 were accompanied by prolonged breath-holding time and the regression of log BHT on P_{CO_2} was abnormally flat. However, in 17 patients with chronic airways obstruction, breath-holding time was never prolonged and the log BHT/P_{CO_2} relationship was normal, even though 13 had a diminished ventilatory response to CO_2 and four had chronic CO_2 retention. It is concluded that the BHT/P_{CO_2} relationship provides a useful index of respiratory chemosensitivity which is not influenced by airways obstruction. This may be helpful in the detection of impaired chemosensitivity as a cause of CO_2 retention even when the ventilation CO_2 response is reduced non-specifically by coexisting airways obstruction.

Chronic CO_2 retention is most frequently due to chronic airways obstruction which hinders the translation of respiratory motor activity into ventilation. Another important cause of chronic hypercapnia is impairment of respiratory chemosensitivity as in the idiopathic hypoventilation syndrome. The recognition of impaired chemosensitivity in cases of this syndrome is sometimes made difficult by the coexistence of chronic airways obstruction (McNicol and Pride, 1965; Rhoads and Brody, 1969). Respiratory chemosensitivity is usually measured by the increment in ventilation elicited by a change in the alveolar or arterial CO_2 tension produced by breathing a CO_2-enriched gas mixture. However, the ventilatory response to CO_2 is altered if ventilation is obstructed even when respiratory chemosensitivity is normal (Cherniack and Snidal, 1956). This has stimulated a search for other tests of respiratory

chemosensitivity which are not affected by mechanical factors (Brodovsky, Macdonell, and Cherniack, 1960; Milic-Emili and Tyler, 1963; Lourenço *et al.*, 1966).

Breath-holding time (BHT) has an inverse relationship with the alveolar CO_2 tension (P_{CO_2}) at the start of a breath hold (Hill and Flack, 1908; Godfrey and Campbell, 1969), which suggests that the BHT/P_{CO_2} relationship may provide an index of respiratory chemosensitivity. Moreover, observations by others in healthy subjects breathing through resistances have suggested that the BHT/P_{CO_2} relationship is insensitive to airway obstruction (Clark and Godfrey, 1969). The present study examines whether breath-holding time might provide a useful test of chemosensitivity in the presence of chronic airways obstruction.

METHODS

Measurements were made of breath-holding time at different P_{CO_2} levels and of the ventilatory

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response to CO_2 (ventilation CO_2 response) in 16 healthy control subjects. These data served two purposes: (*a*) they determined whether breath-holding time was correlated with the ventilation CO_2 response in subjects without airway obstruction, and (*b*) they were used to construct a normal range for the BHT/P_{CO_2} relationship. In addition, these measurements were obtained in 22 patients: 17 were obtained randomly from hospital in-patients and outpatients referred for evaluation of chronic airways obstruction to the pulmonary function laboratory. The five other patients were a specially selected group with persistent hyper-capnia due to the idiopathic hypoventilation syndrome; four of these also had mild airway obstruction, but severe depression of respiratory chemosensitivity had been established by demonstrating grossly diminished CO_2 responsiveness of the diaphragm electromyogram (Lourenço and Miranda, 1968).

APPARATUS   In all patients the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were obtained by standard techniques (Kory *et al.*, 1961) using a low-resistance spirometer (Warren E. Collins, Model P-1300). Residual volume (RV) and total lung capacity (TLC) were measured by the helium dilution method (Boren, Kory, and Syner, 1966). Arterial P_{O_2}, P_{CO_2}, and pH were measured by appropriate electrodes (Radiometer, E5046/E5036/PHM71), and the serum bicarbonate was calculated from the P_{CO_2} and pH values using the Siggaard-Andersen nomogram (1963).

Measurements of the ventilation CO_2 response in the patients and control subjects were made while they rebreathed through a heated pneumotachograph (Fleisch No. 2, Instrumentation Associates) from a rubber bag containing about 6 litres of 6–8% in oxygen. The initial CO_2 concentration in the bag was adjusted to be approximately equivalent to the subject's mixed venous P_{CO_2}, which was assumed to be 0·198 kPa (6 mmHg) more than the arterial P_{CO_2}. The pressure difference across the pneumotachograph was measured by a differential pressure transducer (Statham PM-5) to monitor airflow. Gas was continuously sampled at the mouth for the measurement of end-tidal CO_2 concentration by an infrared analyzer (Godart Capnograph). The signals of airflow and CO_2 concentration were displayed on a multi-channel recorder (Electronics for Medicine, DR-12); the airflow signal was also electronically integrated to provide a continuous record of tidal volume.

EXPERIMENTAL PROCEDURE   Two practice breath holds were made after room air breathing and then the subject began to rebreathe from the rubber bag. Within a few breaths the CO_2 concentration equilibrated within the bag and the subject's lungs, and after this the first test breath hold was made. Following this the subject rested for five minutes and a second test breath hold was performed after another period of rebreathing had raised the alveolar P_{CO_2} to at least 0·665 kPa (5 mmHg) more than the level at the start of the first test breath hold. In the control subjects the procedure was repeated several times so that several breath holds were made at different degrees of hypercapnia. All breath holds were made after full inspiration. Each breath hold was evaluated by measuring the end-tidal P_{CO_2} immediately before each breath hold and also the breath-holding time. The BHT/P_{CO_2} relationship was then assessed by plotting breath-holding time against initial P_{CO_2}. Ventilation was also recorded during a rebreathing period which was not interrupted by breath holding. The ventilation CO_2 response was assessed by plotting ventilation measured over five breath intervals against the P_{CO_2} at the mid-point of each interval.

RESULTS

CONTROL SUBJECTS

RELATIONSHIPS OF VENTILATION AND BREATH-HOLDING TIME WITH P_{CO_2} These are illustrated in Fig. 1 using the data obtained in a representative subject. Ventilation was plotted against P_{CO_2} during uninterrupted rebreathing (Fig. 1A) and breath-holding time against the initial P_{CO_2} of six breath holds made at different levels of hypercapnia (Fig. 1B). Ventilation increased linearly with alveolar P_{CO_2} during rebreathing, as previously described (Read and Leigh, 1967), and so the relationship between ventilation ($\dot{V}e$) and P_{CO_2} could be expressed by the well-known equation $\dot{V}e = S(P_{CO_2}\text{-}B)$ where S is the slope of the ventilation-P_{CO_2} line and B is its intercept with the P_{CO_2} axis. Since $\dot{V}e$ and P_{CO_2} were linearly related, the value of S was constant at all levels of P_{CO_2} and provided a satisfactory measure of the ventilatory response to CO_2. In contrast, breath-holding time had an inverse and curvilinear relationship with P_{CO_2} (Fig. 1B). Thus, while isolated measurements of breath-holding time could be related to the degree of the P_{CO_2} stimulus, the decrement of breath-holding time produced by a given increment of P_{CO_2} was not constant. The relationship was linear when breath-holding
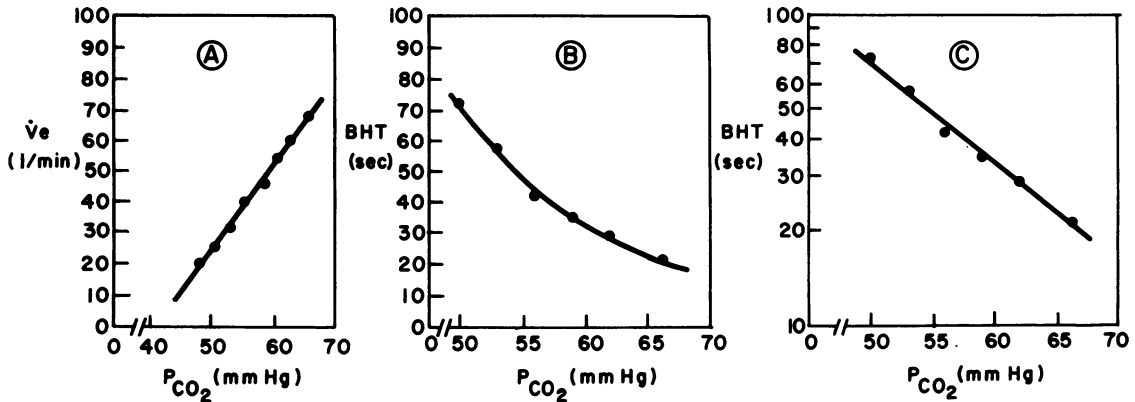
FIG. 1.   *Relationship between ventilation ($\dot{V}e$) and breath-holding time (BHT) and alveolar P_{CO_2} in a healthy subject: (A) ventilation and P_{CO_2} are linearly related; (B) the plot of BHT against the P_{CO_2} at the start of breath holding is curvilinear; (C) the BHT/P_{CO_2} relationship is linearized when drawn on semi-logarithmic paper.* Conversion: Traditional units to SI—P_{CO_2}: 1 $mmHg \approx 7.5$ kPa.

time was plotted on a logarithmic scale (Fig. 1C). The regression of breath-holding time on P_{CO}^2 could therefore be expressed in the form $BHT = a.10^{bP_{CO_2}}$ where b represents the slope of the BHT/P_{CO_2} line on semilogarithmic paper and a is the intercept at zero P_{CO_2}. The slope of the regression line may be more simply described by the increment in P_{CO_2} (ΔP_{CO_2}) required to halve the breath-holding time. This halving ΔP_{CO_2} is reciprocally related to the slope of the log BHT/P_{CO_2} line; it is independent of the P_{CO_2} range under consideration and its use is analogous to the description of the rate of an exponential decay curve by means of its half-time.

CORRELATION BETWEEN CO₂ RESPONSIVENESS OF VENTILATION AND BHT   The slopes of the ventilation CO_2 response lines (SVR) ranged from 11·25 to 46·5 1 min^{-1} kPa^{-1} (1·5 to 6·2 1 min^{-1} $torr^{-1}$) in the 16 control subjects. This fourfold variation in SVR provided further evidence of the considerable constitutional variability of respiratory chemosensitivity in healthy subjects (Schaefer, 1958; Lambertsen, 1960). Breath-holding time at any given level of hypercapnia was longer in subjects with low SVR values than in those with high values. The reciprocal relationship between breath-holding time and SVR is shown in Fig. 2; the breath holds were begun after rebreathing had raised the alveolar P_{CO_2} to 6·38–6·65 kPa (48–50 mmHg) and the inverse correlation of breath-holding time with SVR (r=0·89) was highly significant (P<0·001). It was also found that log BHT declined less steeply with rising P_{CO_2} in subjects with high SVR values than in those with low SVR values. Thus, as shown in
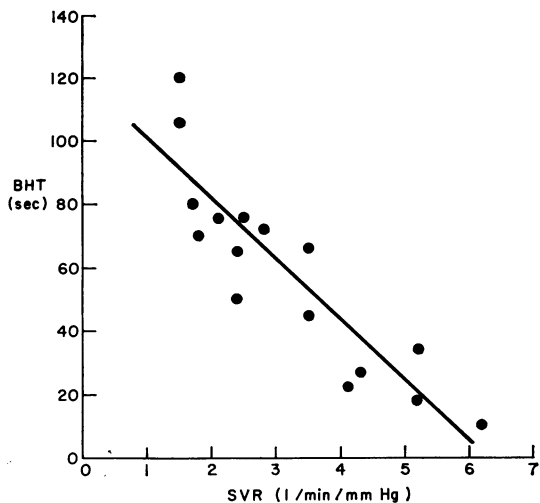

FIG. 2.   *Relationship between breath-holding time (BHT) and the ventilation CO_2 response (SVR) in 16 control subjects. The breath holds were begun after rebreathing had raised the alveolar P_{CO_2} to 6·4–6·7 kPa (48–50 mmHg). There was a close inverse correlation between BHT and SVR (r = −0·89, P <0·001).* Conversion: Traditional units to SI—SVR: 1 $l\,min^{-1}$ $torr^{-1} \approx 0.133$ $l\,min^{-1}$ kPa^{-1}.

Fig. 3, the ΔP_{CO_2} halving BHT was inversely correlated with the value of SVR (r=0·072, P<0·01).

PATIENTS WITH CHRONIC AIRWAYS OBSTRUCTION AND IDIOPATHIC HYPOVENTILATION SYNDROME
VENTILATORY DATA   The Table gives the mean values (±SE) of the static and dynamic lung volumes, blood gases, and slopes of the ventilation
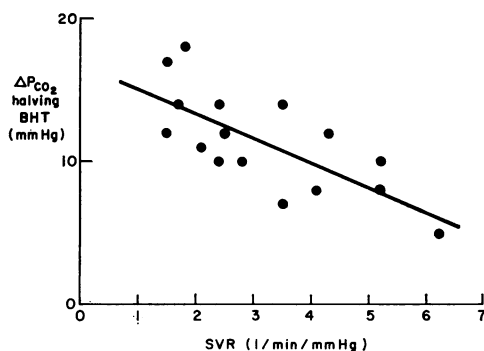
FIG. 3. *Relationship between the increment in* P_{CO_2} *(Δ P_{CO_2}) required to halve breath-holding time (BHT) and the ventilation CO_2 response (SVR) in 16 healthy subjects. The Δ P_{CO_2} halving BHT was inversely correlated with the SVR ($r = -0.72$, $P < 0.01$). Conversion: Traditional units to SI—SVR: $1 \, l \, min^{-1} \, torr^{-1} \approx 0.133 \, l \, min^{-1} \, kPa^{-1}$.*

CO_2 response in the patients. More detailed information can be obtained from the authors if required. The degree of airway obstruction was variable in the 17 randomly selected patients with chronic airways obstruction; their FEV_1 values ranged from 0·59 to 2·48 litres. Four were mildly hypercapnic (arterial P_{CO_2} 6·38–7·18 kPa (48–54 mmHg)) due to severe airway obstruction, since each had an FEV_1 of less than 0·9 litres which is commonly associated with CO_2 retention (Burrows, Strauss, and Niden, 1965). Five of the normocapnic patients had previously been hypercapnic, but this had occurred only transiently during an acute obstructive episode due to bronchopulmonary infection. The arterial P_{CO_2} was increased in all five cases of idiopathic hypoventilation syndrome and their FEV_1 values (1·8–3·1 litres) were much higher than in the hypercapnic patients with severe chronic airways obstruction.

Compared with the control subjects SVR was reduced ($<1·25$ $l \, min^{-1} \, kPa^{-1}$; $<1·5$ $l \, min^{-1} \, torr^{-1}$) in 13 out of the 17 patients with chronic airways

obstruction. The mean SVR in the patients with idiopathic hypoventilation syndrome (2·1 $l \, min^{-1} \, kPa^{-1}$; 0·28 $l \, min^{-1} \, torr^{-1}$) was less than in the patients with chronic airways obstruction (7·5 $l \, min^{-1} \, kPa^{-1}$; 1·0 $l \, min^{-1} \, torr^{-1}$), but the SVR values in the two patient groups overlapped and three of the patients with chronic airways obstruction had SVR values as low as in the cases of idiopathic hypoventilation syndrome. This demonstrated the non-specificity of the ventilation CO_2 response as a test of respiratory chemosensitivity in the presence of airway obstruction.

BHT/P_{CO_2} RELATIONSHIP Figure 4 shows the relationship of log BHT plotted against P_{CO_2} in breath holds made at various degrees of hypercapnia by the patients with chronic airways obstruction and idiopathic hypoventilation syndrome. The patients with chronic airways obstruction are divided into three groups; group A were normocapnic, group B were also normocapnic but had a previous record of hypercapnia, and group C were hypercapnic at the time of study. A normal range for the BHT/P_{CO_2} relationship was constructed from 78 breath holds made by the 16 healthy control subjects. Except in two patients with reduced breath-holding time the BHT/P_{CO_2} points in all subgroups of the patients with chronic airways obstruction lay within the normal range. Also there was a normal decline of breath-holding time in response to an increase in the P_{CO_2} at the start of breath holding. In contrast, the BHT/P_{CO_2} points in patients with the idiopathic hypoventilation syndrome were displaced above and to the right of the normal range, except in one breath hold begun in mild hypercapnia by patient 22. Also the slopes of the log BHT/P_{CO_2} lines linking the pairs of BHT/P_{CO_2} points were less steep than in the control subjects or in the cases of chronic airways obstruction. These findings suggested that breath-holding time in hypercapnia was prolonged and that its sensitivity to the P_{CO_2} stimulus was re-

TABLE
PULMONARY FUNCTION DATA IN THE PATIENTS

	Age (yr)	FEV_1 (l)	FVC (l)	RV (% predicted)	TLC (% predicted)	P_{O_2} (kPa)	P_{CO_2} (kPa)	pH (units)	Bicarbonate (m mol/l)	SVR ($l \, min^{-1} \, kPa^{-1}$)
Chronic airway obstruction (n = 17)										
Mean	58	1·22	2·80	170	105	9·2	5·7	7·39	25·0	7·5
SE	2·4	0·14	0·27	10	3·5	0·3	0·2	0·01	0·6	0·9
Idiopathic hypoventilation syndrome (n = 5)										
Mean	52	2·22	3·06	157	113	7·9	6·9	7·38	29·2	2·1
SE	3·0	0·23	0·19	21	6·4	0·3	0·3	0·02	1·3	0·7

$FEV_1 =$ forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; $P_{O_2} =$ arterial O_2 tension; $P_{CO_2} =$ arterial CO_2 tension; SVR = slope of the ventilation CO_2 response.
Conversion: SI to Traditional Units—P_{CO_2}, P_{O_2}: 1 kPa $\approx$ 7·5 torr;
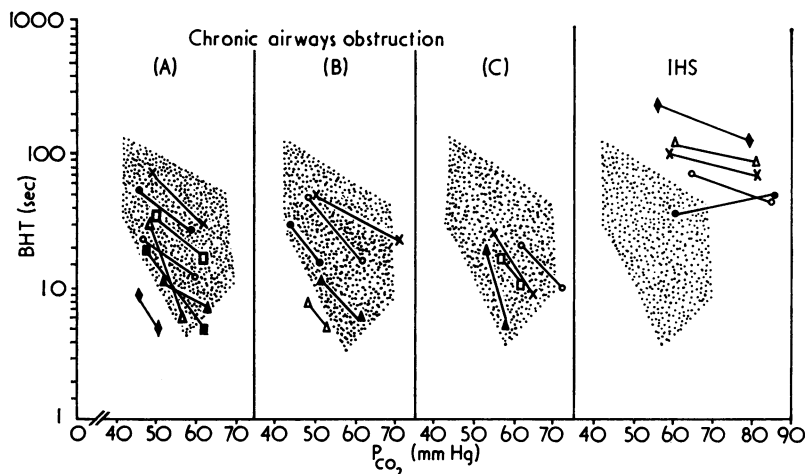—SVR: $1 \, l \, min^{-1} \, kPa^{-1} \approx 0.133 \, l \, min^{-1} \, torr^{-1}$.

FIG. 4. *Relationship between breath-holding time (BHT) and* P_{CO_2} *plotted on semi-logarithmic paper in 17 patients with chronic airways obstruction and five cases of the idiopathic hypoventilation syndrome (IHS). The symbols indicate pairs of breath holds made at different* P_{CO_2} *levels by individual patients, and the shaded areas indicate the normal range of the BHT/P_{CO_2} relationship. The patients with chronic airways obstruction are in three groups: A were normocapnic; B were also normocapnic but had a previous record of hypercapnia; and C were hypercapnic at the time of study. Note the normal BHT/P_{CO_2} relationship in the obstructed patients, but the prolonged breath-holding time and the flattening of the log BHT/P_{CO_2} slope in the cases of idiopathic hypoventilation syndrome.* Conversion: Traditional units to SI—P_{CO_2}: 1 *mmHg* $\approx$ 7·5 *kPa.*

duced in patients with a depression in the CO_2 responsiveness of the respiratory centres. Slightly increased levels of serum bicarbonate were an insufficient explanation for the altered BHT/P_{CO_2} relationship in the patients with the idiopathic hypoventilation syndrome since they were equally high in the hypercapnic obstructed patients with normal breath-holding time.

DISCUSSION

Respiratory drive of chemical origin is known to influence breath-holding time, since this is shortened when the breath is held during hypoxia (Engel *et al.*, 1946) or hypercapnia (Godfrey and Campbell, 1969). Reduction of breath-holding time has previously been used to detect the increased chemical drive caused by hypoxia at high altitude (Douglas *et al.*, 1913; Rahn *et al.*, 1953). The present study has examined whether breath-holding time can also be used to assess respiratory chemosensitivity even in the presence of airway obstruction. Breath-holding time in hypercapnia and the slope of a log BHT/P_{CO_2} plot were found to depend on respiratory chemosensitivity in healthy subjects, as judged by the ventilatory

response to CO_2. Unlike the ventilation CO_2 response, these measurements of the BHT/P_{CO_2} relationship were usually normal in patients with chronic airways obstruction, even when they had CO_2 retention. In patients with the idiopathic hypoventilation syndrome there was a prolongation of breath-holding time and a flattening of the log BHT/P_{CO_2} plot, as well as an alteration in the ventilatory response to CO_2. The findings suggest that the BHT/P_{CO_2} relationship in co-operative patients may allow a more satisfactory discrimination between depressed chemosensitivity and airway obstruction as causes of hypercapnia than the measurement of the ventilation CO_2 response alone.

Respiratory sensitivity to CO_2 is usually evaluated by the change in some index of respiratory drive, such as ventilation, produced by a known increment in the P_{CO_2} stimulus. Theoretically the slope of the log BHT/P_{CO_2} plot should therefore provide a better measure of chemosensitivity than isolated measurements of BHT at known P_{CO_2} levels. Thus, in physiological experiments using healthy subjects willing to make several breath holds, it is probably desirable to construct a log BHT/P_{CO_2} plot if chemosensitivity is to be as-

sessed. In practice, however, isolated measurements of breath-holding time in hypercapnia may provide useful clinical evidence of impaired chemosensitivity, since prolonged breath-holding time in hypercapnia was such a consistent feature in the cases of idiopathic hypoventilation syndrome. Also, while detection of impaired chemosensitivity using the breath-holding technique might sometimes be obscured by lack of volition, it is unlikely that a patient with normal chemosensitivity could deliberately prolong breath-holding time and thereby falsely suggest the diagnosis of idiopathic hypoventilation syndrome.

There are several advantages in evaluating the BHT/Pco$_2$ relationship by breath holding in the course of rebreathing an O$_2$-CO$_2$ gas mixture; some of these have been discussed previously by Godfrey and Campbell (1969). In brief, the preliminary breaths raise the Po$_2$ sufficiently to eliminate the complicating effects of hypoxic drive on breath-holding time and bring the Pco$_2$ into approximate equilibrium within the rebreathing bag, lungs, arterial blood, and brain tissue (Read and Leigh, 1967). Thus inspiration before breath holding does not dilute the alveolar Pco$_2$, and the end-tidal Pco$_2$ also closely represents the effective chemical stimulus at both the peripheral and central chemoreceptors—even in chronic airways obstruction when end-tidal and arterial Pco$_2$ may be widely different while breathing ambient air. Once this equilibrium is established the Pco$_2$ rises linearly with time: its effect on breath-holding time in the resting state can then be described equally well in terms of the initial as the breaking point Pco$_2$ since the difference between these Pco$_2$ values and breath-holding time itself become dependent variables. Finally, breath-holding time may be used most effectively as a test of chemosensitivity when the subject is hypercapnic. Besides the chemical stimulus to Pco$_2$, neural stimuli from the lungs (Guz *et al.*, 1966) and respiratory muscles (Campbell *et al.*, 1969) also contribute to the drive to terminate a breath hold. Thus breath-holding time will tend to be a more selective measure of a subject's sensitivity to the CO$_2$ stimulus if the breath is held at a high Pco$_2$.

The special merit of assessing respiratory chemosensitivity by the breath-holding technique in conjunction with the conventional ventilation CO$_2$ response is that airway obstruction does not alter the relationship of breath-holding time to Pco$_2$. This has previously been demonstrated using healthy subjects breathing through external resistances (Clark and Godfrey, 1969) and was confirmed by the normal BHT/Pco$_2$ relationship in

the presence of reduced SVR values in most of the patients with chronic airways obstruction in the present series. Mechanical obstruction to airflow has been regarded as the primary cause of CO$_2$ retention in chronic airways obstruction (Baldwin, Cournand, and Richards, 1949; Burrows, Strauss, and Niden, 1965). This was supported by the normal BHT/Pco$_2$ relationship in the four patients with hypercapnia in Figure 4. However, individual cases of chronic airways obstruction may be further predisposed to hypercapnia if they also have low levels of respiratory chemosensitivity due either to constitutional causes (Lambertsen, 1960) or to acquired factors such as occur in certain forms of metabolic alkalosis (Goldring *et al.*, 1968). Likewise, some degree of obstruction is frequently present in cases of the idiopathic hypoventilation syndrome (McNicol and Pride, 1965; Rhoads and Brody, 1969), which may accentuate their CO$_2$ retention, although this is primarily due to loss of chemosensitivity. When disorders of chemosensitivity and lung mechanics coexist in a patient with CO$_2$ retention it is desirable to identify the principal defect as a guide to therapy. Established techniques for assessing chemosensitivity in the presence of airway obstruction are technically difficult; they involve measuring the changes of inspiratory work rate (Brodovsky *et al.*, 1960; Milic-Emili and Tyler, 1963) or diaphragm electromyographic activity (Lourenço and Miranda, 1968) during CO$_2$ inhalation. It may therefore be gratifying to the clinician that supporting evidence for impaired chemosensitivity in the presence of obstructed breathing may be obtained by such a simple procedure as holding the breath.

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