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RELATIONSHIPS BETWEEN TIDAL VOLUME AND PHRENIC NERVE ACTIVITY DURING HYPERCAPNIA AND HYPOXIA

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Abstract. The purpose of this study was to determine if the contribution of a muscle to an increase in V_T remained the same regardless of the chemical stimulus used to provoke the increase. In seven anaesthetized cats one phrenic nerve was transected and placed on platinum electrodes. The activity was rectified and integrated. After a control period the cat was given either an 8% CO_2 in air or an 8–10% O_2 mixture to breathe for 30–45 breaths until a relatively constant V_T appeared. Phrenic nerve activity/time (*PE*) was correlated with tidal volume (V_T) for each breath. The linear correlation coefficient (*r*) for the hypercapnic response was 0.958; for the hypoxic response it was 0.858. The slope of the hypercapnic response (PE, V_T) was 0.0619 while that for hypoxia was 0.0379. The rate of phrenic nerve activity was significantly more responsible for the generation of an increase in V_T than was the duration of the phrenic burst. And the relative contribution of each was significantly different for the two different stimuli. These results suggest that when equal V_T is demanded in response to hypercapnia or hypoxia, the diaphragm is less active in generating the increase in V_T during hypercapnia. Or if the diaphragm contracts equally in generating equal V_T's, more neural energy per unit time is required if the stimulus is hypoxia.

INTRODUCTION

Bouverot and Fitzgerald (1969) and other investigators have shown that hypoxia increases FRC. They have also demonstrated that hyperoxia decreases FRC. These investigators and others have shown that hypercapnia does not increase FRC. From these results the question arose — "Do the muscles of respiration simply double their contribution when twice as much ventilation is called for, or is there a redistribution of

their participation in the response which depends on the chemical stimulus?" This paper presents evidence suggesting that hypoxia and hypercapnia generate an equal increase in tidal volume (V_T) through different muscular mechanisms.

METHODS

Seven cats anaesthetized with sodium pentobarbitone or Ketalar had their left phrenic nerve totally or partially transected and placed on recording electrodes. For each breath we recorded the magnitude of integrated phrenic nerve activity, the duration of the phrenic burst (d) and from these the rate of phrenic nerve activity (PE) during the burst was calculated. We also recorded the tidal volume (V_T), duration, and expired minute volume ($\dot{V}_E$) of the breath. The data were recorded on-line and computed in PDP 12 computer (Digital Equipment Corporation).

The animal after a brief control period was given either an 8–10% CO_2 or an 8–10% O_2 mixture to breathe. After 30–45 breaths when the V_T seemed relatively constant, the run was stopped. Several total regression coefficients and correlation coefficients for the run were computed.

RESULTS

Initial observations

1. The results of a sample experiment can be seen in Fig. 1. Although V_T values during the initial stages of the two runs (lower points) are the same, the PE values are different. There were, however, other runs in which the initial PE values for each run overlapped, and still other runs in which the initial PE values for the hypercapnic run were to the right of those for the hypoxic run. In all cases, however, the slopes for the hypercapnic runs were greater than those for the hypoxic runs.

2. When we pooled the data (Fig. 2), we found that the mean total regression coefficient of V_T on *rate* of phrenic nerve activity for hypercapnia was about 1.63 that for hypoxia. These two regression coefficients are statistically different at the 0.02 level.

3. We observed a high correlation between phrenic nerve activity and the total counts from a diaphragmatic EMG ($r = 0.9798$), indicating that phrenic nerve activity was a good index of diaphragmatic activity. In three experiments we correlated diaphragmatic counts with V_T. The r value was 0.675. However, the correlation coefficient for rate

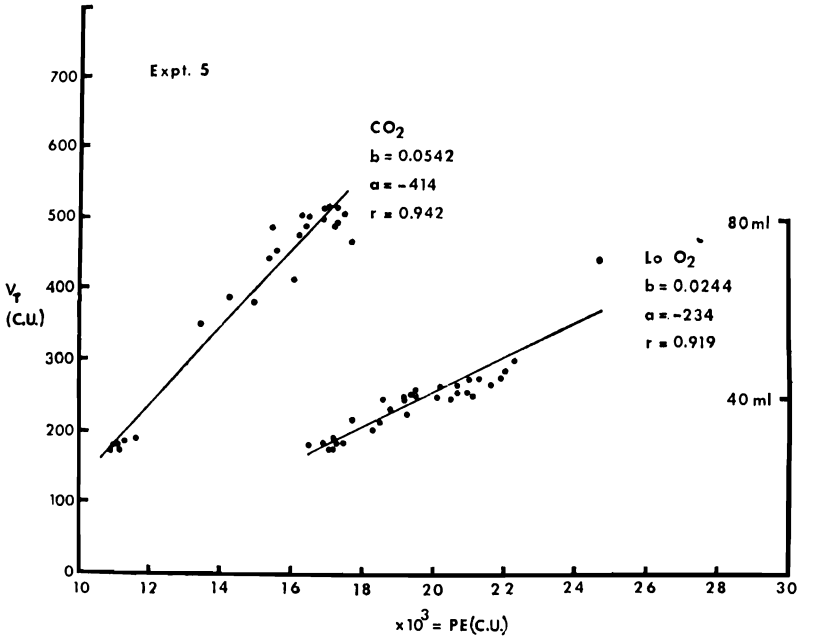

Fig. 1. Sample experiment. Ordinates: left is V_T in computer units (C. U.); right is V_T in milliliters. Abscissa: rate of phrenic nerve activity (PE) in arbitrary computer units. Each dot represents the V_T and PE of a single breath. The regression line is calculated by the method of least squares, has a slope (*b*) and an intercept (*a*); *r* is the correlation coefficient. Here the slope of PE *vs.* V_T during 10% CO_2 breathing is more than twice that during the breathing of a 10% oxygen mixture.

of diaphragmatic counts (number of EMG counts/duration of inspiration) with V_T was 0.916.

4. We also observed a much poorer correlation between phrenic nerve activity and V_T ($r = 0.573$) than between the *rate* of phrenic nerve activity and V_T ($r = 0.908$). This was puzzling for it seemed that V_T should depend not just on the *rate* of activity in the burst but on the duration of the burst as well. This prompted us to question how significant were the rate and the duration of the phrenic burst, taken separately, on the increase in V_T.

Calculations of partial regression coefficients

1. To answer the above question we calculated the partial regression coefficients, b_1 and b_2, for the following equation: $V_T = b_1\text{PE} + b_2 d$. The partial regression coefficient for the *rate of* phrenic nerve activity at constant duration, b_1, was found to be highly significant as one might expect ($p < 0.001$) in all 26 runs, 13 for CO_2 and 13 at low O_2.

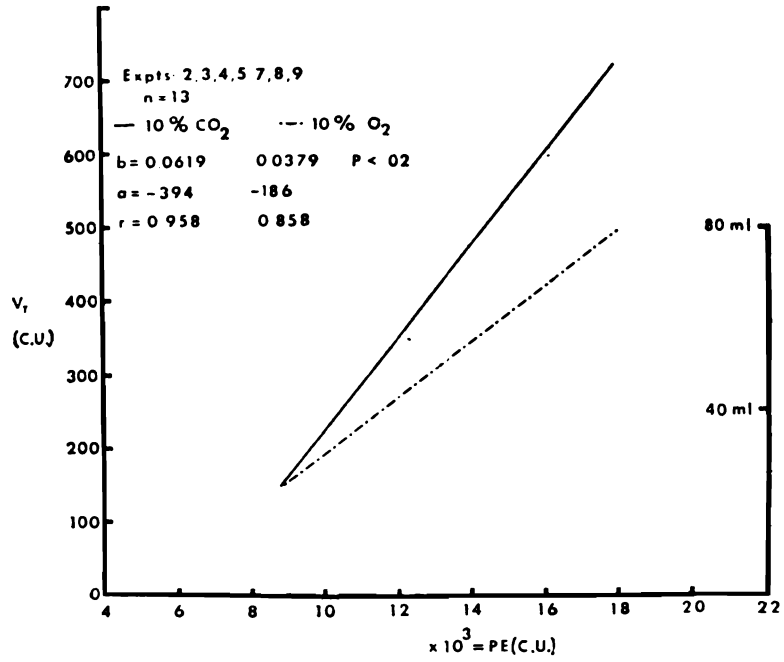

Fig. 2. Mean regression lines for seven experiments, thirteen paired runs of hypercapnia and hypoxia. Ordinates and abscissae same as in Fig. 1. Values for *b*, *a*, *r* are mean values for thirteen runs in seven animals.

2. We found that b_1 for hypercapnia was greater than b_1 for hypoxia in 13/13 pairs. This calculation, then, confirmed our original composite graph were *b*, the total regression coefficient, for hypercapnia was greater than that for hypoxia. In that analysis, the duration (*d*) had not been held constant (Fig. 1).

3. We found that b_2, the partial regression coefficient of V_T against duration at constant rate was significant in only 13/26 runs. And in only 6/13 pairs did the b_2 for hypercapnia differ significantly from that for hypoxia.

Calculations of the effectiveness of each of these two variables on the increase in V_T

1. The increase in V_T due to an increase in rate of phrenic nerve activity (PE) was obtained by multiplying b_1 by the standard deviation of the PE [$\Delta V_{T(PE)} = b_1(SD_{PE})$]. The standard deviation was used simply as a more accurate index of the ΔPE than the range of PE values. The increase in V_T due to an increase in the duration of the phrenic nerve burst was similarly calculated [$\Delta V_{T(d)} = b_2(SD_d)$]. Adding the partial in-

crease in V_T due to each of the two variables together we get the total increase in V_T. And from this we can calculate the amount due to each variable.

$$\Delta V_{T\,(Total)} = \Delta V_{T(PE)} + \Delta V_{T\,(d)}$$

$$\frac{\Delta V_{T\,(PE)}}{\Delta V_{T\,(Total)}} = \% \Delta V_{T\,(PE)}$$

2. We found that in 13 hypercapnic runs the mean per cent increase in V_T to the increase in PE was 98.8 and only 1.2% of the ΔV_T was due to a change in the duration of the burst. Whereas the respective figures for the hypoxic runs were 81.1 and 19.9%. 81.1 differed significantly from 98.8 as did 19.9 from 1.2.

DISCUSSION

Referring to Fig. 2, one can see that for a given tidal volume a greater rate of phrenic nerve activity is needed if the stimulus is low oxygen than if the stimulus is carbon dioxide. Two possible explanation of this observation are the following: First one might speculate that hypoxia decreases the contractility of the red and intermediate muscle fibres (many mitochondria) so that diaphragmatic contraction is more dependent on the less oxygen-dependent white fibres. In skeletal muscles (gastrocnemius, soleus) white fibres are larger than either red or intermediate fibres. And it has been suggested for gastrocnemius muscle (Henneman 1968) that the presence of large, rapidly conducting fibres in the nerve to this muscle is presumably correlated with the presence of large, pale muscle fibres found in this muscle (as opposed to the soleus). Further, the larger a motoneuron is the greater is the amount of excitatory input required to discharge it. If these same relationships hold for the cat diaphragm, then during hypoxia when the non-white muscle fibres would be "relatively poisoned", the white fibres would take a relatively larger role. And a greater *rate* of phrenic nerve activity would be required by the following mechanism. Activity coming from the centres would first stimulate the phrenic motoneurons to the red and intermediate fibres. But this phrenic nerve traffic would be ineffective in generating a tidal volume because these non-white muscle fibres are "poisoned" by the hypoxia. Activity from the centres would have to increase sufficiently to stimulate the phrenic motoneurons going to the white fibres. These fibres would then contract to generate the tidal volume. Hence there would have to be more phrenic nerve activity per

unit time during hypoxia where white fibres are involved than during hypercapnia where intermediate and red fibres can develop the needed tidal volume.

A second possibility is if FRC increases in the cat with hypoxia as it does in the dog, rabbit and man, then the amount of work done by the diaphragm also increases as shown in Fig. 3. Breathing at higher

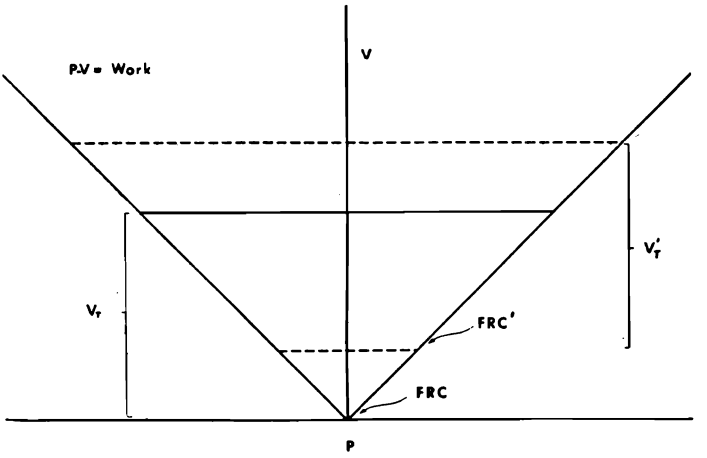

Fig. 3. P-V work diagram. FRC, V_T are values during the breathing of room air. FRC′, V'_T are values during hypoxic breathing. The area of the triangle (P-V = work) during room-air breathing is less than the area of the trapezoid during hypoxic breathing.

lung volumes requires more work. This would require greater neural output. It is possible, too, that with the increase in FRC the diaphragm has become more "flattened". Geometrically this is a less efficient configuration. It might also be a less efficient position for the diaphragm on its length-tension curve. The requirement of more work for the same tidal volume at higher lung volumes, and a possibly less efficient type of contraction are two reasons why greater neural output would be required during hypoxia than during hypercapnia (where no increase in FRC has been observed).

With regard to the different influences that the rate and the duration of a phrenic burst have in generating a change in V_T during hypercapnia and hypoxia, I am afraid any explanation would have to await the results of hypoxia on the pontine and medullary structures we have been hearing about, as well as its effect upon the spinal integrating network. We all know that hypoxia depresses centrally, but what does this mean? I suspect that Dr. Cohen (this Symposium) might have the

best tool for studying this in that it would be interesting to see what effect hypoxia would have on his high frequency oscillations in the medullary and phrenic neurons.

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