Hyperventilation and Abdominal Reflex Inhibition in the Rat

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IN the interest of achieving muscle relaxation without deep general anesthesia or excessive amounts of neuromuscular blocking agents, several authors [1, 2, 3] have described a decreased requirement for anesthetic or curariform drugs during hyperventilation in clinical anesthesia. The relation between hyperventilaton and relaxation of the abdominal muscles has been attributed to multiple factors which are altered by ventilation and which in their turn alter muscle tone. Among these are hypocapnia, hypotension secondary to excessive postive pressure ventilation, control of respiration with elimination of abdominal respiratory movements and Hering-Breuer reflexes.

This investigation was undertaken first, to demonstrate any effect of hyperventilation upon abdominal muscle tone in a controllable experimental preparation; and second, to see if this effect could be demonstrated in the absence of hypocapnia or hypotension.

Method

The contraction of the rectus abdominis muscle of the rat in response to electrical stimulation of the tail was used as a test of abdominal reflex excitability. Respiration was mechanically controlled and reflex responsiveness compared during variations in depth of passive pulmonary inflation.

Sixteen rats weighing 400–500 g. were given pentobarbital 24 mg., intraperitoneally, to induce surgical anesthesia of about two hours duration. Additional 6 mg. supplements were injected as needed. The trachea was cannulated with polyethylene 240 tubing through a tracheotomy, a tight seal produced by circumtracheal ligature. Respiration was controlled with a ventilator at 48 breaths/minute. The ventilator provided fixed inspiratory and expiratory times (one-third and two-thirds of the respiratory cycle, respectively) and a variable inspiratory flow rate. To produce hyperventilation inspiratory flow rate was doubled or tripled. Endotracheal pressure was recorded as a marker for the onset of hyperventilation, increasing proportionately to the increase in flow rate. The inspired gas during control periods was 100 per cent O_2. During hyperventilation either 100 per cent O_2 was used or, to prevent "blow off" of endogenous CO_2, 2.7 per cent CO_2 in 97.3 per cent O_2.* Dead space during controlled respiration was less than 0.4 ml.

The abdomen was opened through a transverse subcostal incision and the recording arm of a strain gauge clamped to the severed rectus abdominis as shown in figure 1. Diaphragmatic movements of the viscera were prevented from bumping the rectus by a sleigh interposed between the viscera and the rectus. The strain gauge did not measure pure contraction of the rectus abdominis but was also influenced by contraction of the entire abdominal musculature.

A Teca model CD4P low voltage generator provided an electrical stimulus every five seconds. The stimulus was delivered to the tail (through needle electrodes) rather than the abdomen to avoid direct stimulation of muscle.

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* The effectiveness of 2.7 per cent exogenous CO_2 in preventing hypocapnia during hyperventilation was evaluated by thoractomy and direct catheterization of the left ventricle with serial determinations of Pa_{CO_2} (Instrumentation Laboratories P_{CO_2} electrode). Of five pairs of determinations in three rats (before and one minute after hyperventilation with 2.7 per cent CO_2) Pa_{CO_2} rose in three and fell in two. The maximal change was 4.7 mm. of mercury.)

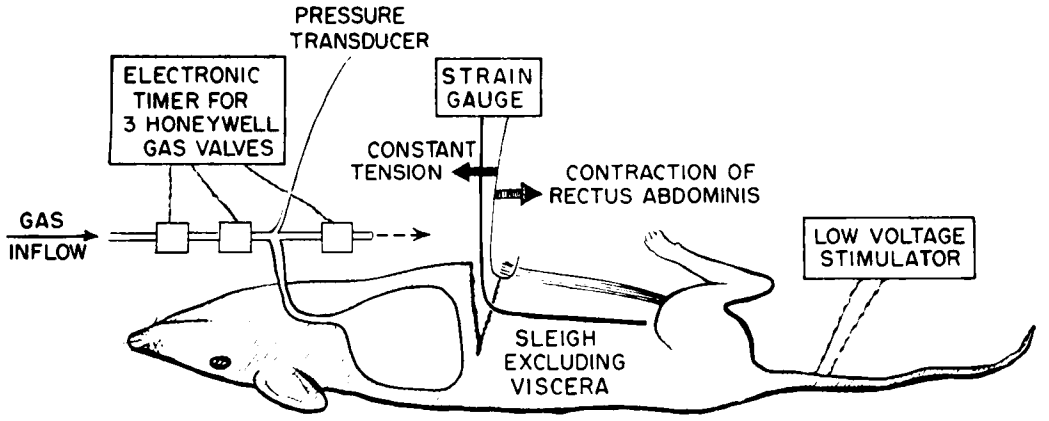

FIG. 1. Diagram of experimental apparatus.

Each stimulus consisted of a train of 2,000/second pulses at 2½–8 milliamperes and 5–8 volts. Contractions of the abdominal musculature were measured with a Statham 387 transducer, and tracheal pressure or blood pressure with a Statham 1091 transducer. A Sanborn Polyviso was used for recording.

Results

The Reflex Response. A prominent feature of the abdominal reflexes was their ease of fatigue. Continuous stretch of the muscle by retractors, or uninterrupted electrical stimulation of the abdomen, feet, or tail all resulted in an initially strong muscle contraction which soon relaxed despite continued stimulation.

Using an interrupted stimulus the first several stimuli induced a central excitatory state with an apparent lightening of anesthesia as shown by the rapidly increasing strength of abdominal contractions with each successive stimulus, and an increase in spontaneous leg and trunk movements. This central excitatory state then gradually declined until a fairly steady level of reflex response was obtained.

The reflex response could be decreased by deepening anesthesia, but, without changing the depth of anesthesia, reflex excitability could be altered by factors such as movement of the endotracheal tube or expiratory obstruction. In addition, certain animals showed a pronounced spontaneous waxing and waning of the excitability of this reflex without any apparent explanation. A prominent example of this waxing and waning is shown in figure 2.

The Effect of Hyperventilation. Hyperventilation produced an inhibition of reflex responsiveness in fifteen of the sixteen animals tested, although the magnitude of the inhibition varied considerably from test to test, even in the same animal. Figure 3 shows little or no response to double the inspiratory flow rate, and a marked response to triple the inspiratory flow rate.

To ascertain the role which hypotension might play in reflex inhibition, femoral arterial catheterization and blood pressure manometry were accomplished in five animals. With the onset of hyperventilation there was usually a transient fall of 5–20 mm. of mercury in mean blood pressure which quickly returned to its previous value despite continued hyperventilation. Abdominal reflex inhibition, however, persisted for the duration of hyperventilation, usually extending into the subsequent control period.

To test the importance of CO_2 elimination in reflex inhibition, exogenous CO_2 was added during the period of hyperventilation (2.7 per cent CO_2 in 97.3 per cent O_2). Maximal inhibitory effects could still be obtained.

(To test the effects of hypercapnia, 4 per cent CO_2 in 96 per cent O_2 was substiuted for 100 per cent O_2 at the same inspiratory flow rate. The effect of 4 per cent CO_2 on abdominal reflex excitability in this preparation was minimal and inconsistant. Respiration could be easily controlled using 4 per cent CO_2 in 96 per cent O_2 save in very light anesthesia.)

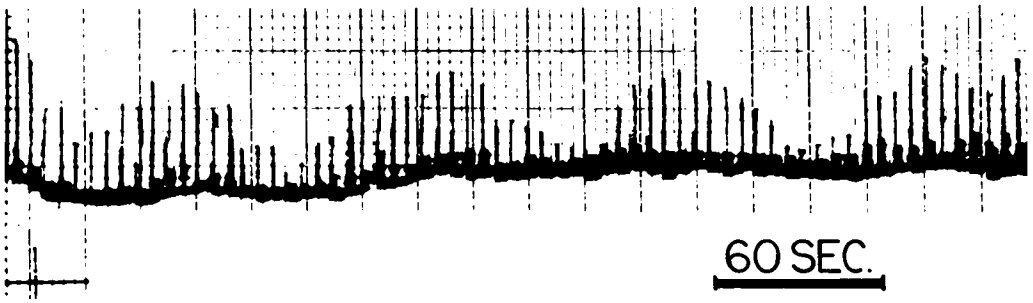

FIG. 2. Spontaneous waxing and waning of abdominal reflex excitability at a fixed tension. Since attenuation was frequently changed to provide optimal stylus deflection for each experiment it is not possible to indicate deflection in terms of a fixed unit.

Discussion

Electromyographic studies by Fink [3, 4] showed a small resting tone to be present in the abdominal muscles even during anesthesia. This resting tone is least during inspiration and greatest during expiration but is not equivalent to the "tight" abdomen of surgery, which is a reflex response to nociceptive stimulation.

The reflex arcs upon which such nociceptive responses depend have been studied by Downman and associates in the cat,[5, 6, 7] and Kugelberg and Hagbarth, in man.[8] Both groups of investigators found the abdominal reflexes to depend upon polysynaptic spinal chains whose activities were subject to modification by higher neural centers. Downman [7] found a discrete area in the cat's brainstem which exerted an inhibitory influence upon the abdominal reflexes through fibers descending in the dorsolateral columns of the spinal cord.

In the absence of generalized myoneural block or of deep general anesthesia, abdominal relaxation during operation must depend upon the state of function within these polysynaptic spinal reflexes and their higher inhibitory or facilitory centers. Function in these polysynaptic chains depends upon many factors other than depth of anesthesia or strength of surgical or experimental stimulation. One such factor evident in these rat experiments was a spontaneous waxing and waning of excitability. Spontaneous waxing and waning of reflex excitability has been noted in many studies, but its significance during actual sur-

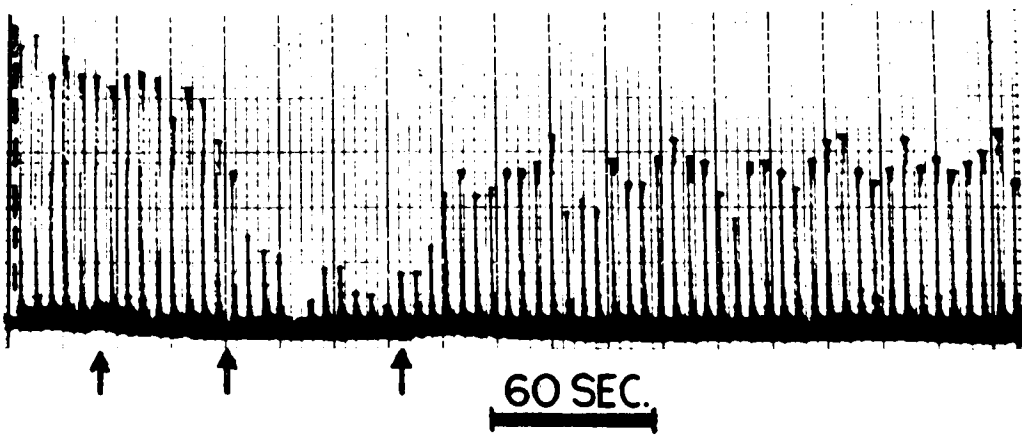

FIG. 3. Abdominal reflex inhibition attending hyperventilation. The inspiratory flow rate was doubled at the first arrow with little or no reflex effect, and then tripled at the second arrow causing a definite reflex inhibition. The third arrow marks return of the inspiratory flow rate to control values. Note some persistence of effect past the period of hyperventilation.

gical anesthesia and its physiological mechanism are obscure.

Another factor modifying function within these polysynaptic chains was hyperventilation, which produced a definite inhibition of abdominal reflexes. Blood pressure manometry indicated that hypotension secondary to the effects of positive pressure breathing was not a significant factor in this inhibition.

Excessive elimination of endogenous CO_2 during hyperventilation has been postulated to be responsible for the effects of hyperventilation. Hypocapnia might alter neurophysiological processes either directly by the action of an abnormally low P_{CO_2} on neuronal function,[9] or indirectly by causing vasoconstriction and relative neuronal anoxia.[10] In addition, hypocapnia might significantly alter the strength of muscle contraction; [11] neuromuscular transmission or action of drugs at the myoneural junction; [12] and the binding or redistribution of anesthetic agents.[13]

In these experiments it is not possible to say what effect hypocapnia alone had upon the abdominal reflexes. Hypocapnia, however, was not the primary cause of the decrease in abdominal reflex excitability. Maximal reflex inhibition could be produced by hyperventilation even when exogenous CO_2 (2.7 per cent) was added during the period of hyperventilation.

Part of the inhibitory effect of hyperventilation may be due to movement of the thoracic cage and changes in form of the abdomen with diaphragmatic descent so that the abdominal muscles are repositioned. In reflex studies upon extremities, large effects have been observed from small changes in position and baseline stretch. Possibly, similar factors were at work here.

Stimulation of vagal pulmonary stretch receptors resulting in medullary inhibition of abdominal reflexes is another possible explanation. The Hering-Breuer reflex, as originally described, consisted of inhibition of inspiratory and facilitation of expiratory activity in response to expansion of the lungs.[14] As originally described, this reflex is inappropriate to explain abdominal reflex inhibition during hyperventilation because abdominal muscle activity, in contrast to diaphragmatic activity, is greater during expiration than during inspiration. This difficulty was partially resolved by later investigations which showed that stimulation of the vagus could augment either expiratory or inspiratory activity depending on the species and the form of stimulation.[14]

The field of influence of vagal pulmonary afferents is probably not strictly confined to the respiratory center. Anatomically the caudal medial medulla oblongata contains not only the respiratory center of Pitts, *et al.*[15] but also the spinal inhibitory area of Magoun and Rhines [16] and the area which Downman [7] found to inhibit abdominal reflexes. Neither anatomically nor physiologically can these "centers" be wholly separated and the inhibition of abdominal reflex excitability with hyperventilation may be one expression of this overlap.

Summary

The excitability of abdominal reflexes in the rat was investigated during varying degrees of passive pulmonary inflation with 100 per cent O_2 or with low concentrations of CO_2 in oxygen. Hyperventilation was found to produce inhibition of abdominal muscle reflexes not referable to hypocapnia or hypotension. Possible mechanisms involved in the inhibition of abdominal reflexes during hyperventilation were discussed.

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The views and opinions expressed herein do not necessarily represent those of the Surgeon General, The Department of The Army or the Department of Defense.

References

1. Gray, T. C., and Rees, G. J.: Role of apnoea in anesthesia for major surgery, Brit. Med. J. 2: 891, 1952.
2. Dundee, J. W.: Influence of controlled respiration on dosage of thiopentone and D-tubocurarine chloride required for abdominal surgery, Brit. Med. J. 2: 893, 1952.
3. Fink, R. B.: A method of monitoring muscular relaxation by the integrated abdominal electromyogram, ANESTHESIOLOGY 21:178, 1960.
4. Fink, R. B.: Electromyography in general anesthesia, Brit. J. Anaesth. 33: 555, 1961.
5. Downman, C. B. B.: Skeletal muscle reflexes of splanchnic and intercostal nerve origin in

acute spinal and decerebrate cats, J. Neurophysiol. **18**: 217, 1955.
6. Downman, C. B. B.: The distribution of splanchnic afferents in the spinal cord of cat, J. Physiol. **137**: 66, 1957.
7. Downman, C. B. B., and Hussain, A.: Spinal tracts and supraspinal centres influencing visceromotor and allied reflexes in cats, J. Physiol. **141**: 489, 1958.
8. Kugelberg, E., and Hagbarth, K. E.: Spinal mechanism of abdominal and erector spinae skin reflexes, Brain **81**: 290, 1958.
9. Bonvallet, M., and Dell, P.: Reflections on mechanism of the action of hyperventilation upon the EEG, Electroenceph. Clin. Neurophysiol. **8**: 170, 1956.
10. Sugioka, K., and Davis, D. A.: Hyperventilation with oxygen—a possible cause of cerebral hypoxia, ANESTHESIOLOGY **21**: 135, 1960.
11. Finerty, J. C., and Gesell, R.: The effect of pH on humoral stimulation of striated muscle and its application on the chemical control of breathing, Amer. J. Physiol. **145**: 1, 1945.
12. Kalow, W.: Influence of *p*H on ionization and biological activity of d-tubocurarine, J. Pharmacol. Exp. Ther. **110**: 433, 1954.
13. Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. A.: The fate of thiopental in man and a method for its estimation in biological material, J. Pharmacol. Exp. Ther. **98**: 85, 1950.
14. Oberholzer, R. J. H., and Tofani, W. O.: The neural control of respiration, *In:* Handbook of Physiology, Section I: Neurophysiology. Baltimore, Waverly Press, 1960, vol. 2, pp. 1120–1122.
15. Pitts, R. F., Magoun, H. W., and Ranson, S. W.: Localization of the medullary respiratory centers in the cat, Amer. J. Physiol. **126**: 673, 1939.
16. Magoun, H. W., and Rhines, R.: Inhibitory mechanism in bulbar reticular formation, J. Neurophysiol. **9**: 165, 1946.

SYMPATHETIC BETA BLOCKERS Female guinea pigs were anesthetized with urethane and given an intravenous infusion of ouabain. Electrocardiograms were recorded and doses noted that were required to lengthen the PR interval, to produce unequal intervals between beats, to induce extrasystoles, to cause a purely ventricular rhythm, to induce ventricular fibrillation, and to stop the heart. These experiments were repeated after the intravenous use of a sympathetic beta blocker (nethalide). The results showed that ventricular fibrillation could be prevented and cured by use of the beta blocker, and evidence was uncovered to suggest that the cause of slowing of heart rate by cardiac glycosides might be due to a block of sympathetic activity on the heart. (*Williams, E. M. V.: Prevention of Arrhythmias due to Cardiac Glycosides by Block of Sympathetic Receptors, Lancet 1: 420 (Feb. 23) 1963.*)

NOREPINEPHRINE Influence of *l*-norepinephrine upon hepatic blood flow has been investigated in dogs. These studies were performed in normovolemic and hypovolemic dogs. Hypovolemia, induced by hemorrhage, always resulted in a marked depression of hepatic flow which could be reversed by reinfusion of blood. In both normovolemic and hypovolemic animals, infusions of norepinephrine increased hepatic flow. However, the most concentrated solutions always decreased hepatic flow regardless of normovolemia or hypovolemia. Excessive amounts of norepinephrine should be avoided in the treatment of hypotension. (*Teramoto, S., and Shumacker, H. B.: Influence of l-Norepinephrine upon Hepatic Blood Flow, Surg. Gynec. Obst. 116: 443 (Apr.) 1963.*)