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RESPIRATORY EXPERIMENTS ON MAN

YANDELL HENDERSON, Ph.D.
NEW HAVEN, CONN.

The recent remarkable advances in the physiology of respiration have been largely based on observations made on man.[1] This fact, coupled with their simplicity and ease of performance, fits these experiments to fill a widely felt pedagogic need. In the training of medical students heretofore, experiments on animals under more or less unnatural conditions have predominated. On man, who is properly the chief interest of the future physician, relatively little has been attempted. Indeed, it is not the least of the contributions which recent advances in the field of respiration have made that they have shown that, given the ingenuity to devise proper experiments, man himself, the normal healthy subject as well as the patient exhibiting functional disturbances, becomes a more profitable *Versuchstier* than dog, rabbit or frog.

The development of the art of conceiving experiments suitable for performance on man, and a more general recognition of the fact that such experiments are possible, free from danger and peculiarly instructive, would go far toward effecting the long-needed but heretofore difficult cooperation of physiology and internal medicine. Respiration is a field peculiarly suited to such cooperation. It is already evident that the vogue in internal medicine, which the introduction of the sphygmomanometer and the methods for determining arhythmia have given to circulatory problems during the past few years, will be exceeded during the period now beginning by interest in the application of physiologic methods to the clinical problems of respiration. Clinicians are beginning to realize that the alveolar carbon dioxid is a normal constant at least equal in clinical importance to arterial pressure. In fact, the variations of the former are probably of greater significance in disease than are those of the latter function. The method for determining the alveolar carbon dioxid is almost as easy and as readily applicable to clinical conditions as is the measurement of arterial pressure.

Up to the present time, however, respiratory experiments on man have been introduced into physiologic laboratory courses in very few medical schools, and into even fewer laboratory manuals. To meet this lack the experiments described below will, it is hoped, be found useful. They are susceptible of almost unlimited modification and extension. They are drawn from the work of many investigators. Their present interpretation as applied to the normal control of respiration is mainly due to Haldane and his collaborators. On the abnormal side I have particularly attempted to emphasize their significance for respiratory failure under anesthesia and for a form of shock. Recent observations by a number of investigators both in laboratory and clinic suggest that the greatest value of the theory of respiration which they support will probably be found in the new point of view which it affords for attack on the difficult problems of acidosis. In cardiorenal and in diabetic cases, as well as in normal persons at great altitudes, the alveolar carbon dioxid is an index of the degree of acidosis.

I. FORCED BREATHING

1. *Forced Breathing and Apnea Vera.*—The subject, seated or lying down, breathes as deeply as possible about eighteen times a minute. Attention should be fixed on drawing deep inspirations. After from twenty to forty seconds the effort is discontinued, and the subject allows his respiration to act involuntarily. In typical cases, for a period varying from ten to thirty seconds thereafter, the subject either stops breathing altogether or breathes in a very shallow and ineffective manner. The carbon dioxid content of the blood having been decreased (acapnia), the respiratory center ceases to act until it reaccumulates up to the normal stimulating amount or "threshold value." In a large class of students one finds marked individual differences in the results of this experiment, some giving a perfect apnea, others merely a shallow or irregular respiration. Numbness and tingling in the hands and feet usually occur also. The principal difficulty is to keep the subject from breathing too fast and making such vigorous exertions, particularly in expiration, that the increase in carbon dioxid production is considerable and the increased elimination (the whole object of the experiment) only slight. Under these conditions of course no apnea occurs.

2. *Prolonged Forced Breathing Followed by Cheyne-Stokes Respiration.*—If the forced breathing is continued for two or three minutes or longer, and apnea vera then allowed to occur, many subjects toward the end of the period of apnea experience an oxygen want. The lips turn slightly blue. This oxygen lack may initiate Cheyne-Stokes breathing lasting sometimes for several minutes. Prolonged forced breathing induces "light-headedness," polyuria, shivering, muscular weakness and other functional disturbances.

3. *Forced Breathing without Excessive Elimination of Carbon Dioxid.*—A large paper bag (obtained from a grocery store) is held over the nose and mouth while the subject does forced breathing. The peculiar and disagreeable sensations of acapnia do not occur, as excessive loss of carbon dioxid is prevented by the

1. For a review of the entire literature see C. Gordon Douglas: Ergebn. d. Physiol., 1914, xiv, 338.

rebreathing. The voluntary effort is found to be much less than in the previous experiments. If the bag has been so closely applied to the face that the same air has been breathed again and again, the subject subsequently experiences no apnea, and may even be unable to stop breathing if he tries. This experiment shows that the apnea in 1 and 2 was due to alteration in the blood gases (mainly decrease of carbon dioxid), and not to a nervous reflex set up by the distention and collapse of the lungs during the forced breathing. It was not apnea vagi.

For this and similar experiments the only recording apparatus necessary consists of a pneumograph fastened around the body and connected by means of a small rubber tube with a tambour writing on a smoked drum. An easily constructed form of pneumograph consists of a coil of spring wire from 16 to 20 cm. long, 2 cm. in diameter, covered with thin-walled rubber tubing, and fastened around the body with a small chain. For teaching purposes it is best to require students to get graphic records of everything possible. The record fixes their attention and they learn incidentally.

II. EXPERIMENTS ON HOLDING THE BREATH AS LONG AS POSSIBLE

1. The subject holds his breath after a moderate inspiration until the breaking-point is reached. This usually occurs after about forty seconds.

2. The breath is held after a very deep inspiration. Fifty seconds or a minute may elapse before the breaking-point is reached.

3. The subject performs forced breathing for a couple of minutes. The breath can then be held for two or three minutes.

4. The subject draws two or three deep breaths of oxygen from a bag. In some subjects the breath can then be held no longer than merely with air. In others it may be held a few seconds more.

5. The subject performs forced breathing for as long a time as in 3. He then draws two or three deep breaths of oxygen, and holds his breath with the lungs full of oxygen. It can be held much longer than in 3. The record (Vernon) for this experiment (after six minutes of forced breathing and with the lungs full of oxygen) is eight minutes and thirteen seconds.

These five parallel experiments show that the imperative demand to breathe (in 1 and 2) is chiefly due to accumulation of carbon dioxid and not to any great extent to lack of oxygen (compare 4); but that in a prolonged period of apnea vera and voluntary apnea a lack of oxygen occurs and reinforces the stimulus of carbon dioxid.

III. EXPERIMENTS ON REBREATHING

1. *The Immediate Effects of Total Rebreathing (Due Chiefly to Excess Carbon Dioxid).*—The nostrils are compressed with a nose-clip and the subject breathes from and into a rubber bag containing 20 to 40 liters of air. The amplitude of respiration is soon augmented. and in the course of a few minutes the subject is panting heavily forty times a minute. He usually develops a typical carbon dioxid headache, but this wears off in fifteen or twenty minutes after the experiment is ended.

2. *The Effects of Insufficient Oxygen without Excess of Carbon Dioxid.*—The bag is refilled with fresh air and the experiment performed again, but with this difference that a vessel of 1 or 2 liters capacity filled with soda-lime or broken sticks of sodium hydrate is placed between the bag and the subject's mouth so that he breathes through it into and from the bag. The carbon dioxid exhaled by the subject is thus absorbed, and he gradually consumes the oxygen in the bag. As a rule there is no noticeable deepening or quickening of the breathing, and the subject will first become cyanosed and then unconscious without appreciable augmentation of breathing. This experiment should *always be carefully supervised,* as it is not free from danger. If continued for more than ten minutes it is usually followed by a severe frontal headache, developing slowly for several hours thereafter, together with other ill effects, and lasting from twenty-four to forty-eight hours.

3. *Cheyne-Stokes Breathing from Partial and Intermittent Lack of Oxygen.*—In place of the bag a tube or pipe from 3 to 5 cm. in diameter and from 80 to 150 cm. in length is attached to the soda-lime tin. After breathing through this device for a few minutes marked Cheyne-Stokes breathing usually results. The carbon dioxid exhaled by the subject is absorbed by the soda-lime close to his mouth, and the long dead space of the tube beyond produces a deprivation of oxygen. This deprivation induces a few deeper breaths. The subject thus gets more fresh air from the tube; the lack of oxygen is temporarily relieved; and apnea results because of the loss of carbon dioxid during the preceding deep breaths. Thus alternating periods of apnea and hyperpnea develop.

The vessel to hold soda-lime or sodium hydrate is conveniently made of a large tin can with a well-fitting top made air-tight with tire tape or plasticine. Into the top and bottom short pieces of metal tubing 2 cm. in diameter are soldered. Inside each end of the can is placed a slightly concave disk of wire gauze. Soda-lime must be granular and quite moist to act well. That on the market is much too dry and must be moistened. Soda-lime is easily made of slaked lime and sodium hydroxid solution mixed in an iron pot.

IV. EFFECTS OF CARBON DIOXID AND OXYGEN, RESPECTIVELY

1. *Carbon Dioxid as a Respiratory Stimulant.*—The bag is filled with fresh air to which from 2 to 4 per cent. of carbon dioxid gas has been added. Breathing this mixture induces immediately a considerable increase in the volume of breathing.

2. *Oxygen under Normal Conditions Neither a Stimulant Nor a Depressant.*—The bag is filled with pure oxygen gas, which the subject breathes through soda-lime. Neither increase nor decrease in the rate or volume of breathing is induced. This experiment is very conveniently performed with the so-called Hill's bag. in which oxygen is generated by the addition of water to sodium peroxid, for when the bag is merely shaken the sodium hydrate solution which remains absorbs the carbon dioxid. If a spirometer is used (as in VI) it is easily shown that the consumption is no greater from pure oxygen than from air.

V. REFLEX INHIBITION OF THE RESPIRATORY CENTER BY DISTENTION OF THE LUNGS

A spirometer is loaded so that the air within it is under a pressure of 8 to 10 cm. water gauge. This is connected either to a large T-tube or a large three-way tap. The spirometer is filled with fresh air, the connecting tube clamped, and the nose compressed.

During a preliminary period the subject breathes through the tap or T-tube to the outside air. At the end of an expiration the outside air is suddenly shut off and the connection to the spirometer opened. Under the stimulus of pulmonary distention the breathing becomes markedly slower and deeper. After eight or ten seconds the connection to the spirometer is shut off and that to the outside opened. Normal breathing almost immediately returns.

This experiment was first performed by Miss Johanne Christiansen working with Dr. J. S. Haldane. The inhibitory influence on respiration which it shows occurs to some extent under the so-called positive and negative pressure conditions for spontaneous breathing after the opening of the thorax, and also under intratracheal insufflation. It is one of the principal advantages of insufflation that it thus tends to prevent the development of acapnia by inhibiting spontaneous breathing, the jet of air supplying ample oxygen, but not washing out carbon dioxid to an equal extent.

VI. THE OXYGEN CONSUMPTION DURING REST AND WORK

The subject breathes from and again into a spirometer, exactly counterbalanced so as to move as easily as possible, through soda-lime or sodium hydroxid. As the oxygen is consumed, the spirometer sinks and this is easily recorded on a smoked drum. The spirometer is raised at intervals by running oxygen into it from a tank or generator of this gas. The consumption of oxygen by the subject is recorded first at rest, and then during exercise with the arms or legs. The student should then graduate the spirometer and the graphic records so as to determine the oxygen consumption in cubic centimeters per minute, by pouring measured volumes of water into a bottle from which the air is thus displaced into the spirometer. During rest the consumption may be less than 300 c.c. per minute, and during exercise on a stationary bicycle more than 3,000 c.c. per minute.

VII. ARTIFICIAL RESPIRATION

Both the Schäfer[2] and Sylvester methods of artificial respiration are tested by placing a clip on the subject's nose and a tube in his mouth. The tube is attached to a well counterpoised gasometer arranged to record on a smoked drum. Before each test the gasometer is filled with fresh air. A more accurate arrangement is to use a mouthpiece with inspiratory and expiratory valves connected with a large gas-meter. The experiments are repeated after the subject has performed forced breathing. Artificial respiration, when applied to a subject in apnea vera, affords far less tidal movement of air than when the subject is not apneic.

(In an experiment of this sort with Dr. J. S. Haldane in which I was the subject and the tidal volume was determined with a gas-meter, the effects of the Schäfer method after forced breathing were so markedly intermittent as to form a sort of artificial Cheyne-Stokes breathing. Such observations indicate that even when natural breathing has ceased, as after drowning, the condition of the respiratory center and of muscle tonus largely determines the efficiency of manual methods of artificial respiration.)

VIII. DETERMINATION OF THE ALVEOLAR CARBON DIOXID[3]

For this the apparatus consists essentially of a gas buret (a bulb and narrow tube) holding from 10 to 20 c.c., graduated in 0.01 c.c., and with a three-way stopcock, one tube of which is connected with a bulb containing 10 per cent. potassium hydroxid solution. A rubber tube 100 to 150 cm. long and 2 cm. in diameter has a small hole punched near one end. This hole is slipped over the inlet tube of the gas buret, which is then filled with mercury or (for student purposes) with acidulated water.

1. While at rest and breathing naturally, the subject at the end of a normal inspiration makes a sudden and very deep expiration into the tube, and then holds his tongue against the end of the tube until the buret has been filled with the air from the depths of the lungs which is caught within the tube. This is termed the "inspiratory sample," as it gives the percentage of carbon dioxid in the alveolar air at the height of inspiration. It is sufficient for most purposes, although for very accurate work it is averaged with an "expiratory sample" obtained from a sudden deep expiration into the tube at the end of a normal expiration. The alveolar air of normal men contains 5.3 to 5.7 per cent. carbon dioxid.

2. The subject takes a few minutes of vigorous exercise (running up and down a flight of stairs five or six times) and then makes another determination.

3. He then performs forced breathing and makes a determination of the carbon dioxid content of the air of the lungs during the period of apnea and again (4) at the instant when spontaneous breathing returns.

(The instruments — the so-called portable Haldane apparatus — for such determinations are made by Siebe, Gorman & Co., 187 Westminster Bridge Road, London. They analyze for carbon dioxid, oxygen and combustible gases. I have recently suggested to Siebe, Gorman & Co. that they supply a smaller Haldane apparatus to analyze only for carbon dioxid and to be called "The Small Haldane Apparatus for Clinical Purposes." They are also sole makers of the Douglas bag, Hill bag, and other useful respiratory apparatus. Bohr gas meters [1 and 10 liters per revolution] are also very useful. They are made by the Dansk Maaler Fabrik, Copenhagen.)

IX. METABOLISM EXPERIMENTS DURING REST AND EXERCISE WITH THE DOUGLAS BAG

This apparatus consists of a nose-clip, mouthpiece, inspiratory and expiratory valves, a large three-way tap and a rubber bag carried on the back. During a measured period of time (from one to five minutes) the entire volume of the expired air is caught in the bag. The volume of this air is later measured and its oxygen and carbon dioxid content determined by analysis. The oxygen consumption, and carbon dioxid elimination per minute, and the respiratory quotient are thus determinable in man under normal conditions and forms of exercise.

X. THE DEAD SPACE OF THE RESPIRATORY TRACT

The large rubber tube is placed over the Haldane analyzer (as in VIII), the other end of the tube being connected either with a rubber bag (capable of contain-

2. The illustrated chart describing this method drawn up by the Commission on Resuscitation from Electric Shock may be obtained from the National Electric Light Association, 29 West Thirty-Ninth Street, New York City.

3. For the analytical methods in convenient and compact form see "Methods of Air Analysis," by J. S. Haldane, C. Griffin and Company London, 1912.

ing 3 or 4 liters) or with a small graduated spirometer. After a normal inspiration the subject suddenly makes the deepest possible expiration through the tube into the bag or spirometer. The alveolar air is thus obtained and determined as in Experiment VIII. A sample of the air in the bag or spirometer is also analyzed, and the total volume of the expiration measured. From these data, and the dead space of the apparatus, the volume of the dead space of the respiratory tract (assumed to have been filled with air containing no carbon dioxid) is easily calculated. This method which I devised has not previously been published. It is now being used in experiments to determine the influence of close, fresh and chill air on the dilatation and contraction of the bronchi.

THE CARDIAC EFFECTS OF IMMODERATE COLLEGE ATHLETICS *

LEOPOLD SHUMACKER, M.D.

AND

WILLIAM S. MIDDLETON, M.D.

MADISON, WIS.

The frequency of cardiac lesions among the men participating in competitive sports at the University of Wisconsin has emphasized the urgency for a study of this subject from a clinical point of view. From this aspect it may be divided into three parts: first, the immediate effects of severe muscular strain on the heart; second, the effects of training and a series of severe athletic contests on the heart, and, third, the ultimate effects on the subsequent life of an individual of alterations brought about in the heart through athletic contests in early life.

Recent medical literature has been rich in the study of the immediate effects on the heart of severe prolonged muscular exertion.[1] From the physiologic point of view the results of the various investigations in this field coincide sufficiently to make it possible to draw the following rather definite conclusions:

1. Muscular exercise sufficient to cause an increase in cardiac activity causes a rise in the systolic and diastolic arterial blood-pressure, as well as in the venous blood-pressure.

2. As a rule, the rise in the systolic pressure is greater than in the diastolic, thereby giving an increase in pulse-pressure. Lowsley interprets this as meaning augmentation as well as acceleration of cardiac action.

3. The rise in the systolic pressure increases after the exercise is begun and increases to a maximum, after which it may decline, to increase again to the maximum, if renewed effort is made. It remains above normal, however, until the muscular effort ceases, after which it usually declines to and frequently below normal.[2] The rise of the diastolic pressure reaches its maximum at about the same time as the systolic or a little later.[3] It fluctuates little after the maximum is reached, and returns to normal more slowly than the systolic and invariably shows a fall to subnormal after exercise (Lowsley).

4. The pulse-pressure curve generally follows the contour of the systolic curve, because of the fact that the systolic pressure fluctuates more than the diastolic (Lowsley).

5. The venous pressure usually rises to a maximum, which is maintained throughout the period of exercise. If, however, the exercise be not severe and deep breathing come on, it may drop to normal during the exertion. As a rule, it drops fairly rapidly to normal after exercise, but in some individuals remains high for a considerable period (Hooker).

6. In exercises requiring severe strain with the chest rigid and the glottis closed, the blood-pressure is increased more than the heart-rate, and the venous pressure is especially high.

7. The pulse-rate rises rapidly at first, but usually does not reach its maximum as soon as the blood-pressure does.[4] After the maximum rate has been reached, there is not much variation until the muscular effort ceases, when there is a fall to normal, or, rarely, to subnormal (Lowsley). The fall of the pulse-rate after exercise is, however, much less rapid than the fall of the blood-pressure. After prolonged rapid muscular exercise, the pulse-rate may persist above normal for a long period of time. There may be a secondary rise "which is probably a reflex effort due to the low blood-pressure of the subnormal stage" (Lowsley).

8. Since, after prolonged exertion, the systolic pressure falls more rapidly than the diastolic, there results a low pulse-pressure (Lowsley). At the time of this low pulse-pressure, albumin is frequently found in the urine. An albuminuria due to low blood-pressure has been described by Erlanger and Hooker.

9. "Rapid exercises, vigorous, fatiguing and exhausting, are followed by a fall of pressure below normal, which lasts longer than after moderate exercise, even if the former is continued for a very short period and the latter for quite a long period of time" (Lowsley).

10. "Long-distance running races and similar forms of exhaustive exercise give rise to a serious strain on the heart, as is indicated by the long period of subnormal blood-pressure" (Lowsley).

11. In hypertrophied hearts in which there is a systolic murmur not due to valvular lesions, the murmur may temporarily disappear after a severe athletic contest. On the other hand, murmurs of this character may appear in the heart, where none were heard before the contest. Barach has called attention to cases of this nature.

12. After prolonged severe contests arhythmia may appear in the cardiac action. It is possible that this may be due to a mechanical injury to the conducting apparatus; that is, fibrillary tears in the myocardium.

Concerning the morphologic effects of prolonged muscular exercise on the heart, there is less agreement than concerning the immediate physiologic effects.

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* From the Department of Clinical Medicine, University of Wisconsin.

* Owing to limitations of space, this article has been abbreviated in The Journal. The complete article appears in the authors' reprints, a copy of which will be sent by the authors or by The Journal on receipt of a stamped addressed envelope.

1. Von Frey, 1890; Kaufmann, 1892; Christ, 1894; Lewy and Zuntz and Schubray, 1896; Staehelin, 1900; Bowen, 1903; De la Camp, 1904; Gordon, Norris, 1907; Dietlen and Morwitz, Hornung, Krone, Moritz, Schott, 1908; Barach, 1910; Hooker, Lowsley, 1911; Grober, Albu and Katz and Leyhoff, 1913.

2. The extent of increase of systolic pressure depends on the exercise, the individual and his condition. In young men sprinting on a stationary bicycle, Lowsley found the time for reaching the maximum systolic pressure to vary from five to twenty-five minutes and the increase to vary from 10 to 65 mm. Hg. It was greatest when the man was fresh. The average rise in sixteen men was 32.7 mm. Hg.

3. In Lowsley's work, cited above, the rise in the diastolic pressure varied from zero to 40 mm. with an average in seventeen individuals of 22.9 mm. Hg.

4. In Lowsley's experiment the average time for reaching the maximum pulse-rate was 35.4 minutes. The average increase of pulse-rate in nine experiments was 51 per minute.