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MIXING OF GASES WITHIN RESPIRATORY SYSTEM WITH A NEW TYPE NITROGEN METER[1]

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STUDY of the gas phase events occurring during a single respiratory cycle in the human subject usually is limited to an examination of gas expired from the lungs. In studying the mixing of gases in the effective, absorptive zones of the lungs, direct continuous alveolar gas samples would tell us far more about the fluid mechanics of pulmonary function than do expired samples after passing back from the alveoli through a long series of irregular passageways to the investigator's 'gas traps' outside. Undoubtedly, mixing and dilution occur during this trip. Let us grant the fact that even after about 50 years of research on the mechanics of gas transport into and out of animals, no exhaustive study has been made of gases in the alveoli. And let us grant also the obvious limitations of the expired gas analysis method of visualizing pulmonary gas dynamics. How can we best examine the gases issuing from the subject's respiratory system so that we may know, at least, what is happening each instant as they pass, say, the mouth?

First of all, we would like a continuous measure of the total volume of all gases leaving or entering the pulmonary tree. Secondly, we desire a continuous record of the concentration of the gases. These measurements ideally should give us accurate results during even very rapid movements of the gases, such as occur during hyperventilation and coughing. In the present study, both the total volume and the gas concentration were measured by continuous, physical methods which are rapid enough to give a reasonably true picture of the expired gas events occurring during rapid flow states (1, 2).

APPARATUS

The total volume of the inspired and expired gases was measured by having the subject breathe into and out of a large rigid reservoir, the volume of which was about 3000 l. (110 cubic feet). As the subject adds to or subtracts from the gas in the reservoir, the pressure rises or falls a small amount, about 10 mm. of water for an increment of 3 l. Recording these pressure changes gives a fairly linear record of the volume changes at ambient temperature and pressure. A rapid electrical condenser pressure gauge (3, 4) was used to measure the pressure increment and hence gave a record of the gas volumes breathed by the subject. For extremely accurate results, especially during very fast volume flow conditions, a temperature correction must be

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applied to the volumes measured in this way (an adiabatic process, not an isothermal process). (As is to be expected the time it takes the pressure change to be transmitted to the pressure gauge was demonstrated, over a 40-foot path in the B29 pressure cabin, to be set by the velocity of sound (5).)

In regard to recording the gas concentrations, an ideal system would give us the instantaneous fraction of each gas species as it entered or left the subject. In the present experiments, we were limited to one species, nitrogen, a relatively physiologically inert gas. The sampling was done at the subject's mouth with a new instrument, called a nitrogen meter, presented diagrammatically in figure 1 (6, 7). In figure 1 can be seen a one-inch diameter tube about $\frac{3}{4}$ inch in length, one end of which is fastened in the wall of the volume reservoir, the other end in the subject's mouth. In the wall of this short connecting tube, there is a small needle valve, labeled 'inlet orifice.' One side of this valve is immersed in the stream flowing between the subject and the reservoir, the other side is in a vacuum system. The valve is adjusted so that a small part, about $\frac{1}{2}$ cc/second, of the gas in the short connecting tube flows

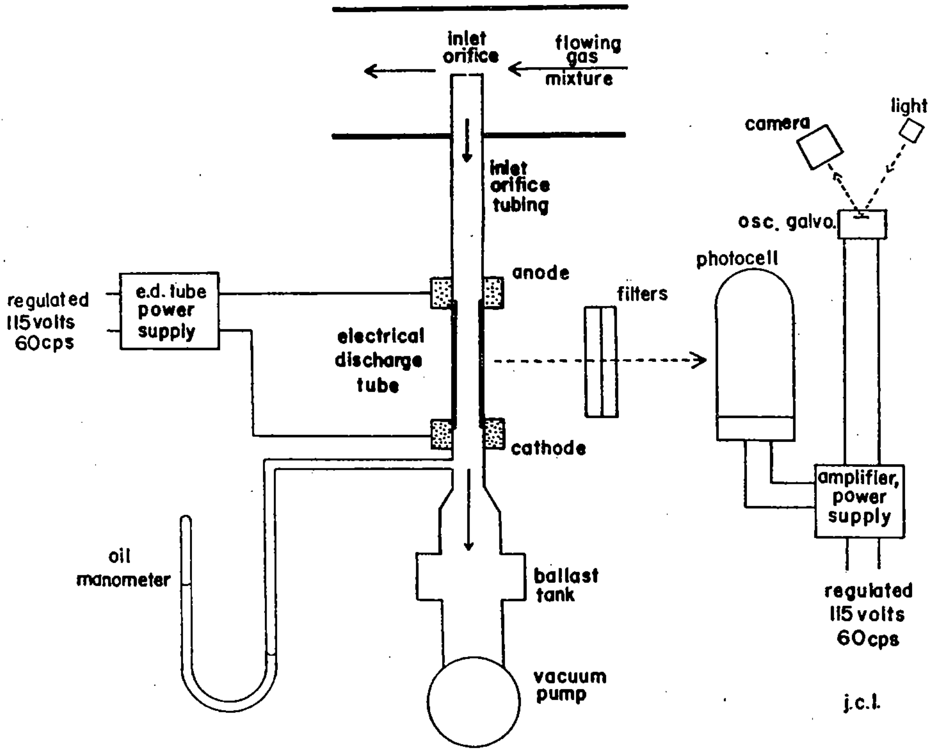

Fig. 1. DIAGRAM OF NITROGEN METER used in this study. The tube in wall of the volume recorder reservoir (text) is shown as containing the flowing gas mixture and the inlet orifice. The actual orifice does not have the flat end shown here: it is a short length ($\frac{1}{4}$ inch) of a No. 25 gauge hypodermic needle, which does not impede the flowing gas perceptibly. For details of this instrument, see text and references (6) and (7).

at a constant rate into the vacuum system. Once it is in the vacuum, the gas travels at about 100 feet/second through the electrical discharge tube, and then out through the vacuum pump. If we now apply a high electrical voltage to the hollow electrodes in the discharge tube, the flowing gas emits light in the way the familiar 'neon sign' does. The light passes through the walls of the pyrex tube between the anode and the cathode; the light characteristic of nitrogen gas is selected by the filters; and its intensity is recorded by the photoelectric system.

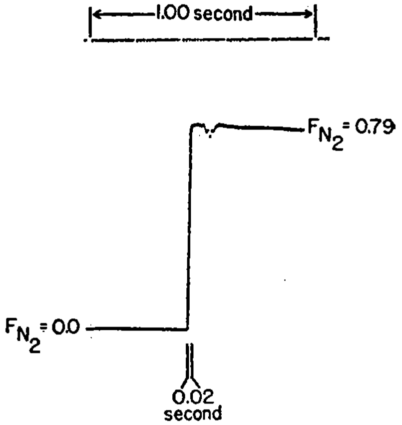

Fig. 2. RESPONSE OF THE NITROGEN RECORDER to a step change in composition. The inlet orifice valve of the N_2 meter was placed in a stream of oxygen, rapidly flowing into room air. After the record was started, the valve was rapidly jerked into room air out of the stream. The small downward deflection in final level can be shown to be due to eddies of mixed air and O_2 near the stream due to turbulence in the surrounding air. The response interval was measured on the record with a microscope. The step-response line has been retouched for clear reproduction. This response time is several times shorter than the observed changes shown in figures 3 and 4. The volume recorder responds in 0.02 seconds to step changes in volume, which is also several times shorter than the changes observed in this study.

Figure 2 shows that this nitrogen meter will record a composition change (from oxygen to air) taking place in two one-hundredths of a second.

RESULTS WITH NORMAL SUBJECTS

Figures 3 and 4 show results with air-breathing *1*) with previous air-breathing (fig. 3) and *2*) with previous O_2-breathing (fig. 4). If we have a subject breathe oxygen for 30 minutes to bring his expired nitrogen down to one per cent or less, and have him then breathe air from the volume recorder reservoir, the resulting record of volume and of nitrogen fraction is shown in figure 4. The dark line is the volume record, the lighter line is the nitrogen record. The time marker shows one-second intervals. On the volume record, expiration is an upward deflection and inspiration a downward one. On the record of figure 3 we see a small change in nitrogen fraction in the expired gas, due mainly to water vapor dilution of the inspired air, assuming an *RQ* (respiratory quotient) near 1.0. On the 2 records of figure 4, this same small drop F_{N_2} is visible at the beginning of expiration, and is followed by a rather sudden decrease in the F_{N_2} to a sloping 'plateau' at the end of a normal expiration. The lower record of figure 4 shows that this plateau continues to the end of a full expiration. This continuation of the plateau apparently implies fairly complete mixing of the previously inspired air with the nitrogen-poor gas in the lungs.

Figure 4 shows, at the top, a typical record of normal ventilation, starting with the subject's first expiration of low-nitrogen gas, and shows how the plateau of each succeeding expiration has increasing amounts of nitrogen. The lower record is a typical one of a 'vital capacity' maneuver, a full inspiration followed by a complete expiration. Here we see the expired gas phases defined by an F_{N_2} criterion: *1*) Water vapor

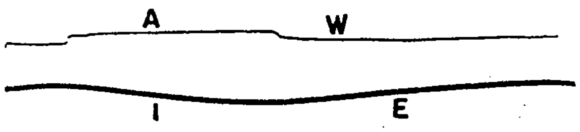

Fig. 3. Patterns of gas concentration and volume in Respiration I. The subject has been breathing only air, and breathes air during this record. The upper trace is N_2; the lower is volume record. *A* is 79 per cent N_2; *W* is 72.8 per cent N_2. *I* is inspiratory volumes; *E* is expiratory volumes. This record shows that, assuming a respiratory quotient of 1.0, the water vapor plateau continues throughout expiration when breathing air alone. For records showing water vapor plateau after breathing O_2 and going back to air, see figures 4 and 5. The above records were taken at a lower amplification on N_2 and volume, than were those of figure 4. From *I* to *E* is 2.0 seconds.

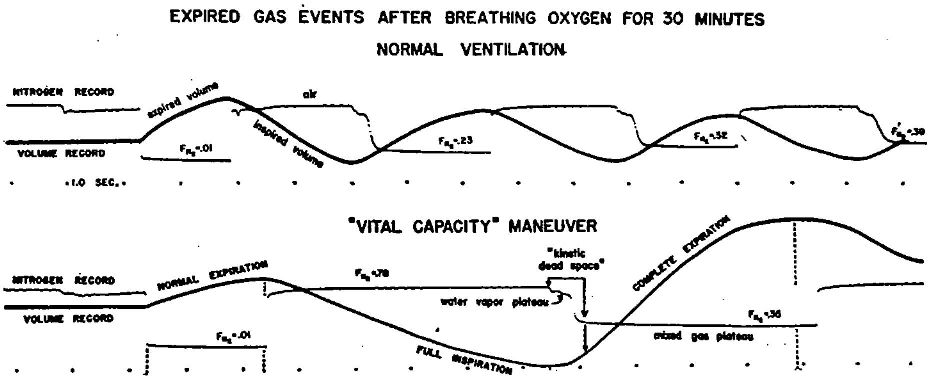

Fig. 4. Patterns of gas concentration and volume in Respiration II. Upper record is that of normal ventilation, lower one is of a vital capacity maneuver. Looking at the left-hand edge of each record, the upper, thin-line trace is the nitrogen; the next trace is the volume record; the lowest is the time marker, marking one-second intervals. Before the record starts, the subject has been breathing 99.4 per cent oxygen for 30 minutes. At the time the subject's mouth is placed on the apparatus tube (fig. 1) there is a small drop in the N_2 trace due to moistening of the air in the tube; as he makes his first expiration, there is a sudden large drop in (N_2) and a start of the rise of the volume trace: This expiration gives the control level (near zero N_2) of N_2 in the subject's expired gas. As the volume trace reverses to inspiration, the N_2 rises sharply to the air level, which is the inspired mixture. The beginning of the first expiration after this first air inspiration is the one dealt with in the text and in later figures. In this figure the form of the first part of this expiration in the N_2 trace can be clearly seen to be similar in 4 cases, 3 in normal ventilation, and one in a complete expiration. The volume record in the upper record is taken with twice the amplification of that of the lower record. Analysis of the lower record is presented in figure 5. The tidal volume in the upper record is about 850 ml. The mole fraction of nitrogen values (F_{N_2}) are those near the end of expiration. For the explanation of the terms used on the lower N_2 record, see text. The total lung volumes at the beginning of the normal expiration, the maximal inspiration, the maximal expiration, and at the end of the maximal expiration are 4355, 3470, 6020, and 1290 ml., respectively. For the method of determination of these values, see text and figure 5.

plateau, (about 70 to 125 ml. in 5 subjects); *2*) rapidly falling F_{N_2} phase, about 100 to 150 ml. to 90 per cent of the final F_{N_2} value; and *3*) the final sloping plateau.

In somewhat arbitrary fashion, that volume which comes out in expiration

The record from such an ideal respiratory system, determined in the same fashion as that of figure 5, would present a staircase appearance with sharp corners. At the beginning the line would drop instantly from 79 per cent nitrogen to 72.8 per cent, in crossing the dry to wet air front, as expiration starts. The line would level off at 72.8 per cent nitrogen and stay there to an expired volume equal to that of the conduction system; this is the first step in the staircase. As thoroughly mixed gas from the ideal mixer arrived, there would be a sudden drop in percentage N_2 to a level maintained throughout the rest of expiration; this is the second step.

The records of figures 4 and 5 show that we do not have an ideal respiratory system: the conduction system and the mixer give records with sloping steps, rounded corners and a sloping 'riser.' The water vapor plateau and the mixed gas plateau (fig. 4 and 5) both slope from the horizontal; the riser connecting the plateaus slopes from the ideal vertical. What are the factors which may cause these deviations in performance from that of our model? *1*) The non-uniform velocity gradients across a section of a conducting tube (parabolic gradient in Poiseuille flow, and the seventh root gradient of Prandtl in turbulent flow (8)) causing the central portion of the tube stream to outstrip those portions nearer the walls. *2*) Fore and back mixing due to acceleration and deceleration eddies (8) in slowing inspiration, reversing and speeding-up expiration. *3*) Non-uniform velocity gradients due to expansions, contractions and bends in the conducting tubes. *4*) Non-simultaneous emptying of all parts of the 'mixer' into the conduction system.

Probably all of these factors influence our records simultaneously. At the present time we cannot analyze their relative importance by means of records taken on expired gas issuing from the mouth. By analyses done deeper down in the respiratory tract, and by simultaneous analyses across various flow sections in the conduction and mixing systems, these factors can probably be evaluated.

To pin down the explanations of the various parts of these records, at the present time it can be said that the portions of gas visualized in figure 5 probably come from respective parts of the respiratory system as follows: water vapor plateau, mouth and pharynx; sloping riser, pharynx, trachea, bronchi and bronchioles; mixed gas plateau, primary lobules (alveoli, etc.). However, it is to be remembered that the boundaries between these volumes are diffuse, not sharp, and that the gas mixes between sequential parts.

The connection between the first part of *curve 1* and the 'dead-space' of Krogh and Lindhard (9), is the connection between the actual respiratory system and the ideal system discussed above. Krogh's formula assumes the ideal system, with a staircase record. We can make a geometrical construction on figure 5 which would give a staircase, and hence a value for Krogh's type of dead-space (the volume would be that of the vertical riser so constructed). But the problem is to find the criteria which guide one in placing the vertical riser. One could draw the riser through the halfway point on the actual curve, through the maximum slope point, or draw it so that equal areas are created between the riser, the upper and lower parts of the actual curve, the 72.8 per cent N_2 line and the mixed gas plateau extrapolated back to the zero volume line; replotting the data of *curve 1* (see below) on a 10× volume scale gives the following volumes for these 3 risers: 165, 173 and 170 ml., respectively.

Such constructions and their interpretation are purely arbitrary until a more realistic functional model of the respiratory system is determined by experiment.

In order to emphasize the connection between the kinetic factors discussed above and the curves obtained (*curve 1*, fig. 5), the volume between the beginning of the record and the point at which the percentage N_2 reaches 90 per cent of that of the mixed gas plateau (extrapolated to zero volume) is called the kinetic dead-space (290 ml. for *curve 1*, fig. 5). This is the gross volume in which fore and back mixing and unequal cross sectional velocities presumably would show their maximum effects. Non-simultaneous alveolar emptying and 'layering' probably become important near the end of this volume and for the rest of the curve.

The mixed gas plateau has a linear slope (*curve 1*, fig. 5), which may be useful in deriving a measure of the efficiency of lung mixing. In the subject (the author) used, the slope of this plateau is -1.75 per cent N_2/liter of expired gas. In the ideal model the slope would be zero per cent N_2/l. In an emphysematous subject the slope would presumably be very much greater than -1.75 per cent N_2/l. With the further experiments planned at the present time (10), the individual variations in normal subjects and the results on patients with lung disease will be determined.

If one defines the mixing efficiency as the slope of the final plateau the question arises as to whether or not the slope at the end of a resting, average expiration of say, 700 ml., is the same as that found during a maximal expiration of, say, 4.5 l. Taking the maximal expiration of *curve 1*, figure 6, terminating the data at 750 ml. as if it were a normal expiration, and plotting it on a volume scale 10 times the length of figure 6, gives a terminal slope of -4.6 per cent N_2/l. rather than the -1.75 per cent N_2/l. of the later 3 liters. Thus, though the curve slope does become constant, it decreases from a maximum value in the riser, and approaches its final value during the first liter of expiration. In *curve 1*, the measured slopes are as follows: -215 per cent N_2/l. (the maximum value) at 57 per cent N_2 and 170 ml., -4.6 per cent/l. at 41.5 per cent N_2 and 700 ml., and -1.75 per cent N_2/liter between 40.0 per cent and 33.5 per cent N_2 and between 1.00 l. and 4.73 l.

Further work is being done on the mechanisms causing these records and their relation to the classical work of Haldane, Krogh and others (11–13). Factors whose effects on these curves are to be evaluated are: total lung volume at the beginning of expiration, inspiratory and expiratory velocities, the composition pattern of the inspired gas volumes, and varying breath holding time before expiration. The analysis of the series of expirations following the first is also being done (13).

ALTERNATIVE PROCEDURES

Instead of having the subject breathe oxygen for 30 minutes, he can breathe air and then oxygen from the reservoir. The resulting records are 'upside down' compared to the ones presented, and lack a water vapor plateau; otherwise, results are obtainable with this less time-consuming procedure which are comparable with those presented.

Volumes can be measured with a flowmeter whose output is graphically or electronically integrated; however, apparatus dead-space must be allowed for (14).

CLINICAL APPLICATIONS

Since this analysis method takes only a few minutes to do and promises to give valuable data on lung mixing efficiency, it will probably be clinically useful. In impaired mixing conditions we would expect the mixed gas plateau to slope further from the horizontal, and the riser to slope more toward the horizontal than do the above records on a normal subject. It will be interesting to see the records on subjects with lung pathology in view of the above records on normal subjects.

Clinical studies using this technique have not yet been done. However, the exploratory work is being planned at the present time (13). Cases of immediate interest are those afflicted with asthma, emphysema, bronchial and pulmonary pneumonia, diffuse pulmonary tuberculosis, tuberculosis with cavity formation, well developed silicoses, and lung neoplasms. Cases of especial interest in the elucidation of the influence of the larynx in the gas mixing process are those with a tracheotomy, either with or without a patent larynx. The first records on these cases will probably show changes characteristic of each type of pathological pulmonary function, and may ultimately be an aid to diagnosis and to evaluation of the patient's progress.

SUMMARY

By means of rapid recorders for measuring nitrogen gas and expired and inspired volumes, the patterns of gas concentration and volume during single expirations are presented for normal human subjects. To emphasize the patterns due to mixing processes, the subject first effectively cleared his lungs of nitrogen by breathing oxygen and results were recorded when he started breathing air; during the short recording time (10 seconds) it can be shown that only about 5 ml. of nitrogen can be taken up by the blood from the lungs. In a maximal expiration, the records show three main phases: *1*) a sloping water-vapor plateau of between 70 and 125 ml., curving downward into *2*) a rapidly falling N_2 phase (riser) of 100 to 150 ml., which slowly curves into *3*) a sloping final plateau, starting at 1000 ml. and continuing to the end of the expiration. By determining the volume of nitrogen inspired and expired from these records, one can calculate the residual lung volume and hence the total lung volume at each instant. To emphasize the kinetic mechanisms responsible for phases *1*) and *2*), a factor called the kinetic dead-space is defined in terms of these 2 phases. The slope of the final plateau ($\%$ N_2/l. expired) is taken as a measure of mixing efficiency; it is shown that a normal, resting expiration does not reach the constant slope seen in a maximal expiration; in one case the slope of the curve varied from a maximum, in phase *2*), of -215 per cent N_2/l. at 170 ml. to -4.6 per cent N_2/l. at 700 ml. to -1.75 per cent N_2/l. between 1000 and 4730 ml., of total expired volume. Relations between these recorded patterns and the following factors are discussed: Krogh's dead-space, 'ideal' respiration and pathological processes impairing mixing efficiency. Alternative procedures, using these and other rapid recorders, are discussed.

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