Respiratory Carbon Dioxide Response Curve Computer

It gives more complete alveolar ventilation-P_{CO_2} response curves than could formerly be obtained.

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The time and effort required to analyze and plot data for alveolar ventilation-alveolar P_{CO_2} response curves has constituted a serious limitation to their ready use. The advent of rapid automatic carbon dioxide gas analyzers and the pneumotachograph has made the accumulation of the basic data needed for such a plot fairly simple. However, the reduction of continuous automatic records of both carbon dioxide concentration and volume of expired air to the response curve has been tedious and time consuming. Moreover, because of the labor involved it could be done at only a few specified points for each curve despite the fact that the basic data were such as to permit a continuous plot. To overcome these limitations, a respiratory computer which carries out the calculations continuously and automatically has been built.

The basic method employed depends on rebreathing endogenous carbon dioxide and has been previously described (*1*). It represents a modification of the method described by Eckenhoff, Helrich, and Hege (*2*). The subject is fitted with a nose clip and a rubber metabolism mouthpiece which connects to a one-way flutter valve. There are two three-way valves in the circuit so that with both valves closed and a measured amount of oxygen in the system, the subject rebreathes in a closed-circle system (Fig. 1). As the endogenous CO_2 accumulates in the system, the alveolar P_{CO_2} steadily increases, and with it alveolar ventilation. It is these two steadily increasing values which are finally plotted against one another. The rate of increase of alveolar P_{CO_2} is about 3 mm-Hg P_{CO_2} per minute, and this rate of increase is maintained for about 8 minutes.

In order to compute alveolar ventilation (V_A), the tidal volume (TV), physiologic dead space (DS), and frequency (f) must be known. The rate of air flow during respiration is measured. This is integrated to give tidal volume. This tidal volume is corrected to standard conditions ($BTPS$). Physiologic dead space, calculated according to the cylindrical formula of Gray (*3*), is subtracted out to give an alveolar volume. The alveolar tidal volumes for a given time interval are added together to give an alveolar ventilation in liters per minute.

$$V_A = \sum_{t=0}^{t=1} \left[\left(\int f \, dt \right) \times \frac{BP}{760} \times \frac{310}{760 - VP} - \left(\frac{DS_0}{8TV} + DS_0 \right) \right]$$

The calculations involved in obtaining an alveolar P_{CO_2} are as follows: Inhaled and exhaled air are continuously sampled, and the carbon dioxide content is measured. The highest concentration of CO_2 in each exhalation is recorded and taken as an index of the alveolar P_{CO_2}.

The method for accumulating data and carrying out the calculations is indicated in Fig. 1. The carbon dioxide content in the exhaled air sampled at the lips by a microcatheter technique is analyzed in an infrared Liston-Becker CO_2 gas analyzer (*4*). The amplified output of the CO_2 infrared pickup unit is then fed into an instrument linearizer (*5*) which is set up so that the output voltage is linearly proportional to the CO_2 concentration in the infrared pickup unit. The voltage from the instrument linearizer representing the instantaneous CO_2 concentration in the exhaled air is fed to the analog computer (*6*), where the voltage representing the highest CO_2 concentration in each breath is detected, held, and fed onto the x-axis of an x-y plotter (*7*).

The flow of exhaled air is detected by measuring the pressure drop across a fine-mesh screen (*8*). The output from the strain-gauge manometer is amplified in a carrier-type amplifier (*9*) and fed into the analog computer. In the computer the flow for each exhalation is integrated to obtain the tidal volume. The computer then corrects this volume of air to a volume at standard pressure, and a thermistor feeds into the computer from the rebreathing system so that a correction to body temperature saturated with water vapor can be carried out. In the computer the operations are carried out for determining the physiologic dead space and subtracting it from the tidal volume so that a running average can be taken and expressed as alveolar ventilation. The voltage output from the analog computer representing alveolar ventilation in liters per minute is then fed onto the y-axis of an x-y plotter.

Carbon Dioxide Measurement

Carbon dioxide concentration in the exhaled air is sampled by a microcatheter technique from the level of the lips. A 4-cm polyethylene catheter introduced through a low-resistance, one-way respiratory valve (Warren E. Collins–J-2 valve) has its tip terminating at the level of the lips. A continuous sample of air is drawn through the microcatheter cell at a constant rate of 500 ml per minute and then returned to the circle system. With this flow of gas through the CO_2 gas analyzer and the delay of the analyzer, the over-all response time is approximately 1/5 second. The CO_2 gas analyzer is calibrated before and after each run by introducing from separate cylinders appropriate concentrations of carbon dioxide in oxygen. The contents of each cylinder mixture are assayed by the micro-Scholander

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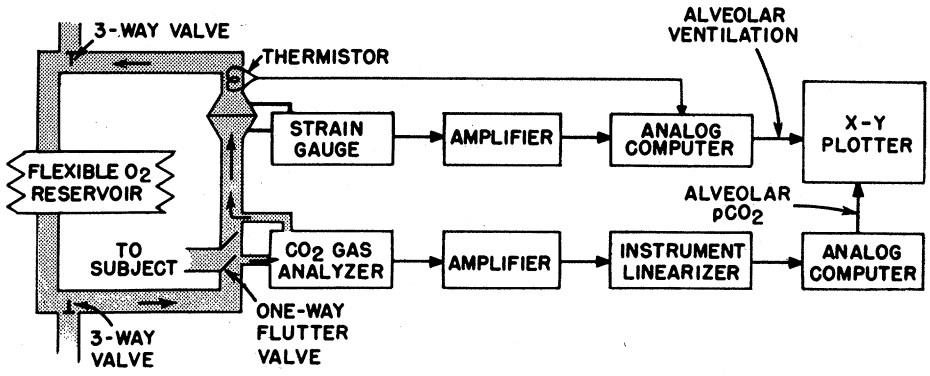

Fig. 1. Rebreathing circuits, sensing elements, amplifiers, computers and *x-y* plotter.

technique. The P_{co_2} measurements are accurate to within 0.5 mm-Hg.

The calibration curve for voltage output of the CO_2 analyzer versus percentage of carbon dioxide in the microcatheter cell is not a linear function. Therefore, in order to correct the output of the CO_2 analyzer so that the voltage is linearly proportional to the percentage of carbon dioxide drawn through the microcatheter cell, an instrument linearizer is used. This instrument is designed so that a variable correction voltage is automatically and continuously added to or subtracted from the input voltage to give a voltage output that is linearly proportional to the carbon dioxide concentration in the microcatheter cell.

P_{co_2} Calculation

The end expiratory P_{co_2} is taken as an index of alveolar P_{co_2} (*10*). The end expiratory P_{co_2}, which is the highest P_{co_2} obtained during exhalation, is detected by means of a peak-voltage follower (stage 1, Fig. 2; Fig. 3). The output of the peak-voltage follower representing the peak voltage obtained during exhalation is held on a 0.2-μf capacitor (Fig. 3) which represents a sequential charge transfer or "delay line." The capacitor is connected to terminal 15 of a four-pole, double-throw relay (6HY4C) so that, as exhalation ends, the peak voltage stored during that exhalation is presented to the voltage-follower stage (stage 2, Fig. 2; Fig. 3). The voltage-follower stage then holds this peak voltage throughout inspiration and the following exhalation. At the end of this exhalation it resets to the peak voltage of the exhalation. Working in tandem with this set of relay contacts is the 50,000-ohm resistor attached to terminal 14 of the relay. The circuit connected to relay contact 14 serves to discharge the 0.05 μf capacitor during inhalation so that it is ready to follow the peak voltage of the next exhalation. The output of stage 2, the voltage follower, then feeds the *x*-axis of an *x-y* plotter. In this way a voltage is constantly applied to the *x*-axis, which represents the peak P_{co_2} attained on the previous breath.

The response times of the electrical components along the CO_2 axis are quite adequate for physiologic work. The CO_2 analyzer reaches 90 percent of full scale in 0.1 second. Since expiration seldom lasts less than 1 second, and since the concentration of CO_2 rises very fast at first and then slowly toward the end of expiration, this response time is more than adequate; moreover, the deeper the respiration the more accurate the CO_2 analysis. The instrument linearizer requires approximately 0.1 msec to reach 99 percent of full-scale deflection. Because of the delay line, the actual recording of each CO_2 concentration is one breath behind all the time. Hence the major delay in recording CO_2 concentration depends on the frequency of respiration.

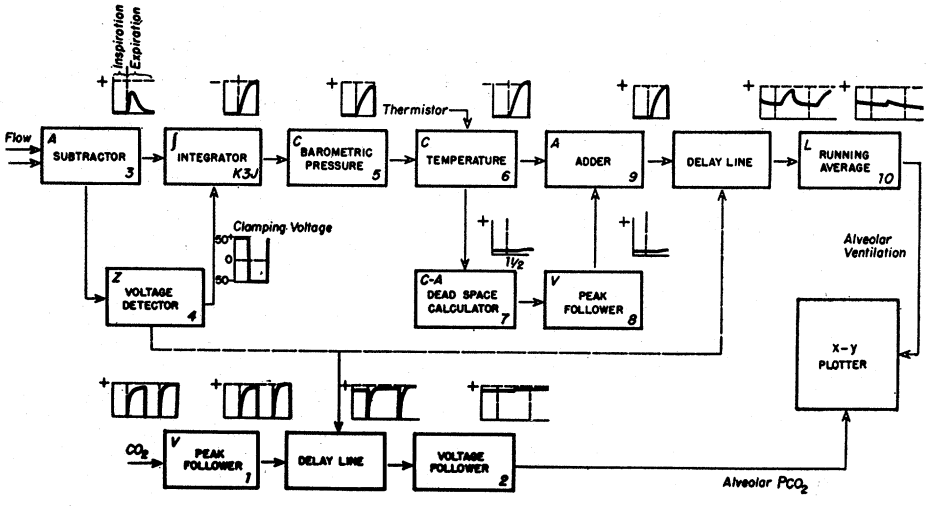

Fig. 2. Analog computers for calculation of alveolar ventilation and alveolar P_{co_2}. Waveforms (output and polarity) of each stage are shown. Stage numbers correspond to numbered stages in Fig. 3.

Measuring Flow

The flow in the rebreathing system is measured by determining the differential pressure across a fine-mesh screen. Since condensation of moisture on this screen would increase the resistance to air flow and thus would interfere with flow measurements, the flow meter is wrapped with heating tapes so that condensation does not take place. The flow meter is linear over the range of flows encountered during rebreathing. The differential strain-gauge manometer is connected into a carrier-type amplifier. The output of this amplifier is a push-pull or double-ended signal which must be converted to a single-ended signal in the analog computer for further processing.

Alveolar Ventilation Calculation

The first stage of the analog computer (stage 3, Fig. 2; Fig. 3) is a subtractor stage. This stage converts the push-pull or positive and negative signal from the carrier amplifier into a single-ended signal which is then fed through the rest of the computer. This single-ended signal is fed simultaneously to two stages, a voltage detector (stage 4, Fig. 2; Fig. 3) and an integrator (K3J, Fig. 2; Fig. 3). The voltage detector stage is designed to control

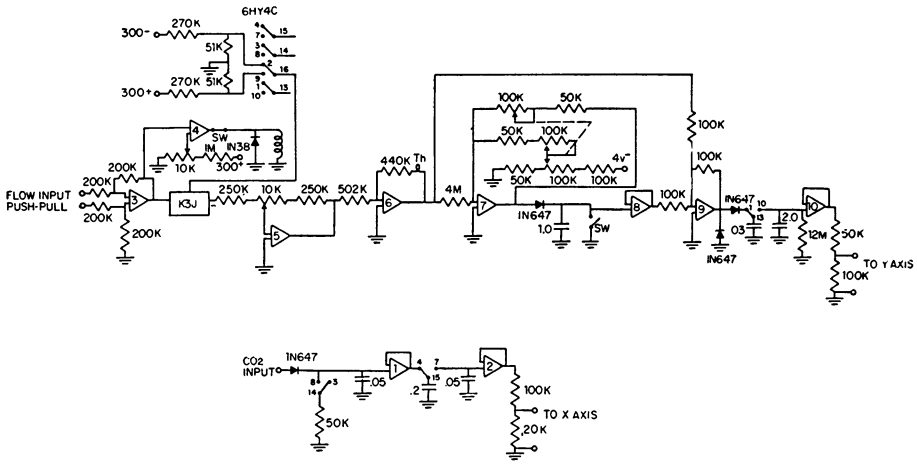

Fig. 3. Analog computers for calculating alveolar P_{CO_2} and alveolar ventilation. Each stage (numbers in triangles) represents an operational amplifier type K2W (George A. Philbrick Researches, Inc.). All relay contacts are shown in the deenergized (exhalation) position.

a relay (6HY4C) (Fig. 3). As soon as the input voltage becomes positive, the relay is deenergized (beginning of exhalation), and when the signal becomes zero (end of exhalation) the relay is energized. This relay controls the two sequential charge-transfer or delay lines, one delay line in the CO_2 section (terminals 14 and 15, Fig. 3) and one delay line in the running average section (terminal 13, Fig. 3), and in addition generates a ± 50-volt clamping voltage (terminal 16, Fig. 3) to the K3J integrator.

The second output of the subtractor stage representing flow is integrated by the K3J integrator. The integration time interval is controlled by the ± 50-volt clamping voltage generated by the relay (terminal 16, Fig. 4). Thus, as soon as the voltage output from the subtractor becomes positive—that is, as soon as expiration starts—integration begins. Integration of flow in the K3J continues until the output of the subtractor stage returns to zero—that is, until expiration ends. The output of the K3J integrator represents tidal volume under nonstandard conditions.

The correction to standard barometric pressure is a simple coefficient function. It involves setting the gain of this stage (stage 4, Fig. 2; Fig. 3) so that the output of the K3J integrator is multiplied by barometric pressure divided by 760 mm-Hg. This stage is initially calibrated so that this setting is a convenient front panel dial adjustment. The output of the fifth stage, then, represents tidal volume corrected for barometric pressure.

In stage 6, (Figs. 2 and 3) the correction to a volume of gas at body temperature saturated with water vapor is carried out. A thermistor located immediately after the flow meter is part of a resistance network which determines the gain of stage 6 so that it automatically varies in such a manner that the output will represent a gas volume corrected to body temperature saturated with water vapor. In the resistance network shown for stage 6 in Fig. 3, the values are calculated on the basis of a calibration of our particular thermistor. The output of stage 6, then representing a tidal volume at standard conditions, is then fed simultaneously to an adder stage, stage 9, as well as to a dead-space calculator stage, stage 7.

In the dead-space calculator stage, stage 7, the physiologic dead space is calculated according to the cylindrical formula of Gray (*3*):

$$DS = \frac{DS_0}{8TV} + DS_0$$

The value for DS_0, the theoretical dead space at zero ventilation, is calculated for each individual from the Bohr equation (*11*). This value is introduced by presetting the triple ganged 100,000-ohm potentiometer which is located to the extreme right on the front panel of the computer (Fig. 4). The first term DS_0 alone is introduced by the voltage divider network and 4-volt bias cell, while the second term is generated by the other two resistance networks in combination with the 4-megohm input resistance and the output from stage 6. The output of the dead-space calculator is then held on a peak follower, stage 8.

The correction term for dead space is the peak voltage generated by stage 7. This peak voltage is obtained in stage 8 and stored there for subtraction from the corrected tidal volume in stage 9. This peak follower circuit does not reset to zero after each breath, since during rebreathing the tidal volume increases progressively and the physiologic dead space increases progressively. Before a new run is begun, the peak follower must be manually reset to the DS_0 value. This is accomplished by short-circuiting the 1 μf capacitor

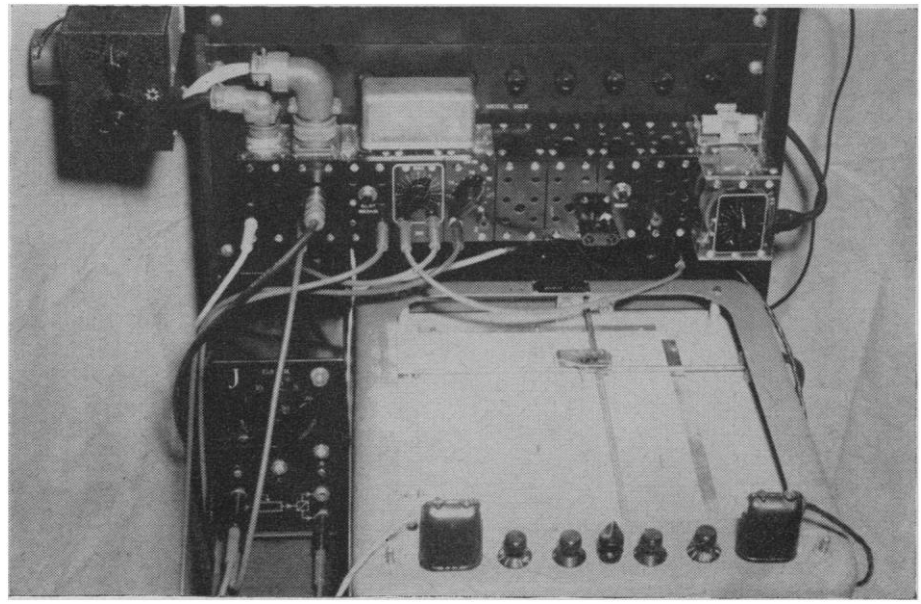

Fig. 4. Analog computer and *x-y* plotter. Calibrator is shown on the extreme upper left. The K3J integrator (George A. Philbrick Researches, Inc.) is to the left of the *x-y* plotter.

to ground through a reset switch (SW) located on the front panel of the computer.

In stage 9 the physiologic dead space is subtracted from the tidal volume. This is done with an adder circuit rather than a subtractor circuit, since the output of the dead-space calculator is inverted from its input voltage and we have two signals of opposite polarity. The peak output of the adder stage, stage 9, is a voltage which represents an alveolar volume.

The capacitor connected to terminal 13 of the relay serves to record the peak voltage output of stage 9. The capacitor and accompanying relay switch and diodes constitute the delay line of Fig. 2. At the end of each expiration, this capacitor is discharged into the running-average circuit, stage 10 (Figs. 2 and 3).

Alveolar ventilation is the sum of all alveolar volumes occurring during 1 minute. Thus, it is the sum of all charges accumulating on the delay line capacitor in 1 minute. This summing operation is carried out by transferring each charge to the 2.0-μf capacitor of stage 10. The rate of transfer is governed by the rhythm of breathing. Thus, frequency (f) is taken into consideration at this point. The time interval over which the sums are taken is determined by the decay time of the 12-megohm resistor and the 2-μf capacitor of stage 10. The output of this running-average circuit is then introduced onto the y axis of the x-y plotter.

The limiting factor in the response time of the ventilation axis is the final averaging circuit and the frequency of respiration. All electrical components except the averaging circuit perform at speeds far in excess of those needed for accurate measurement at maximum rates and depths of ventilation. The time constant of the final averaging circuit is such that with a respiratory rate of 20 per minute 50 percent of full-scale response is obtained in 17 seconds. At faster rates of respiration full-scale response is obtained sooner. During a response curve run ventilation builds up gradually and hence the recording lag is never as great as would be implied by a half-time of 17 seconds. Moreover, the response curve is not determined as an absolute value in itself but for comparison with other curves run under similar conditions—here the lag due to the averaging circuit is insignificant. In actual practice plots of alveolar ventilation-alveolar CO_2 curves obtained from continuous, direct, separate recordings of ventilation and CO_2 concentration are the same as those obtained by the computer from the same experimental data.

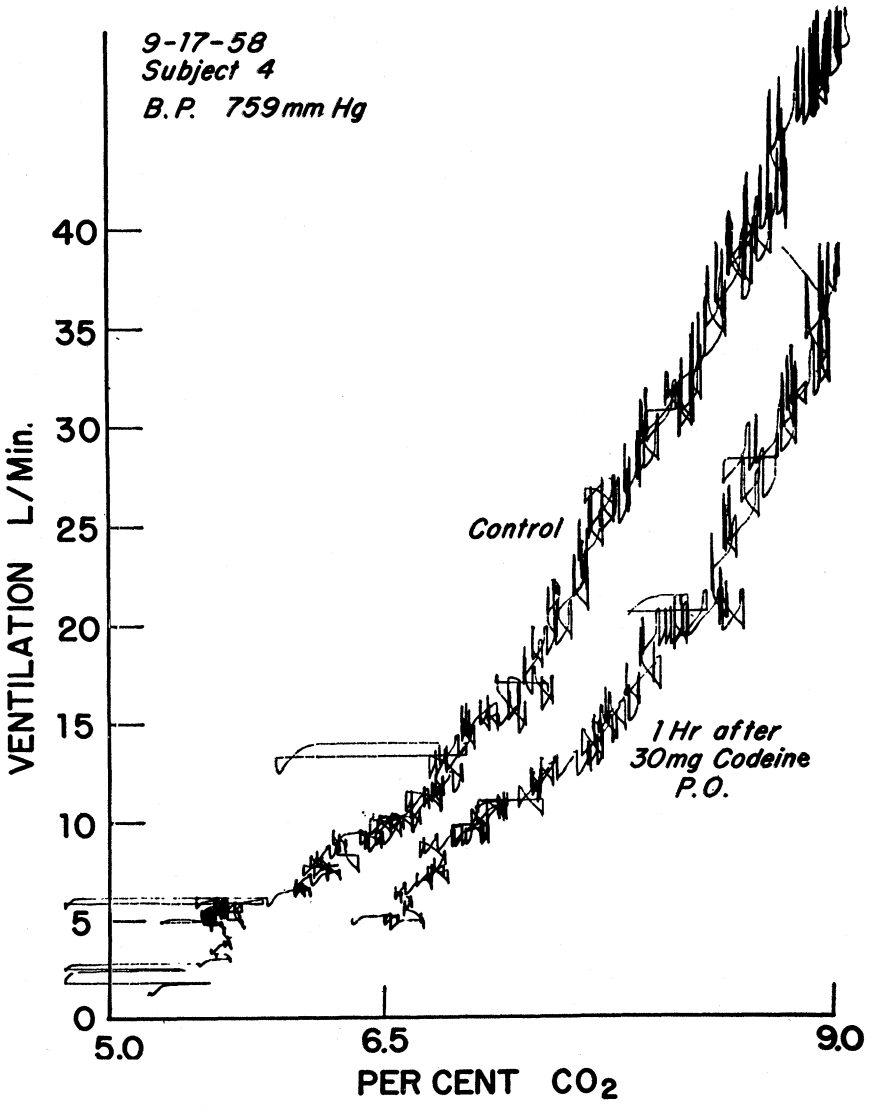

Fig. 5. Plot of alveolar ventilation versus alveolar CO_2; 4.98, 6.50, and 9.08 percent CO_2 were used for routine calibration of the x-axis.

x-y Plotter

The x-y plotter is a servo-driven potentiometer balance-type recorder. There are two separate amplifiers, one for each axis, so that information on the x-axis energizes the x-mandrel, while information fed on the y-axis energizes the y-mandrel. A pen is suspended between these mandrels, and it continuously plots out a function of x versus y. The particular type x-y plotter used in this application takes standard 8½ by 11 inch graph paper and has separate gain and zero controls for each axis. A typical record of plots obtained before and after administration of a drug is shown in Fig. 5.

Calibrating the System

In order to calibrate the infrared CO_2 gas analyzer, known concentrations of carbon dioxide in oxygen (4 and 9 percent) are introduced into the microcatheter sampling cell. The instrument linearizer is then checked by introducing mixtures of 5, 6.5, and 9 percent CO_2 in oxygen, and the output is adjusted for linearity. Simultaneously with the calibration of the instrument linearizer, the x-axis on the x-y plotter is calibrated so that the left-hand margin of the graph paper is represented by 5 percent CO_2 and the right hand margin by 9 percent CO_2,

and the intermediate gas concentration falls in the appropriate position.

Calibration of the y-axis of the x-y plotter is a bit more complicated. The strain-gauge manometer and amplifier are calibrated daily by introducing a gas flow of 50 liters per minute of O_2 from a precision-calibrated rotameter (*12*). Bias controls for stages 3 through 10 are adjusted for zero output with zero input. The zero bias of the y-axis of the x-y recorder is adjusted so that the pen is at the bottom of the graph paper. By means of an appropriate timing device, a standard voltage is introduced at the delay line following stage 9, and the relay is actuated every 3 seconds. The gain of the y-axis of the x-y plotter is then adjusted to 80 percent of full-scale deflection. A standard voltage representing a known volume of gas (approximately 2.3 liters) is then applied to the integrator by means of the same timing mechanism, and the reading on the y-axis of the recorder is checked. This reading corresponds to an alveolar ventilation of 40 liters per minute.

Discussion

The alveolar ventilation-alveolar P_{CO_2} response curve is one of the most sensitive and precise ways of assessing the effects of drugs upon respiration. Since we desired to study the effects of a number of drugs on respiration, it was more efficient to build a computer to carry out the operations automatically rather than to continue doing them by hand. Furthermore, a continuous plot gives a more complete picture of the final result and produces it while the data are being collected. Control response curves are very reproducible in the same subject within 1 mm-Hg P_{CO_2}. If the subject becomes at all drowsy during a run, it is immediately apparent as respiratory depression (a shift to the right), and the subject can be reminded to stay awake.

The effects of drugs on respiration are assessed by running two control response curves and then administering the medication. At 1, 2, and 3 hours after medication, repeat response curves are determined. In the work to date with narcotic-type analgesics, the effect of drug has been primarily to displace the response curve toward higher values of P_{CO_2} but the after-drug curve has been essentially parallel to the control response curve at P_{CO_2} values above 55 mm-Hg. An effect of narcotics on the slope of the response curve has been reported by other workers, but this is probably attributable to a failure to achieve sufficiently high values of P_{CO_2}. The respiratory depression produced after oral administration of 30 milligrams of codeine is readily apparent with the method we have described. The respiratory computer and other electronic equipment described here serve as further illustrations of how analog computers may readily be used to solve computational problems in the biological sciences. The whole system has been assembled from standard parts. The analog computer part of the system consists of a commercial 10-stage operational amplifier, and the computing operations are carried out by a series of home-made operational plug-in units made from modular assembly units. Two aspects of the computing operations are worthy of further comment and might be applicable to a number of other biological problems. These are the delay lines and the dead-space computer.

The delay line in the calculation of alveolar P_{CO_2} makes it possible to read out a constant CO_2 value while the preceding peak-follower stage is resetting, so that it may follow the peak CO_2 value of the next breath. At the end of this breath the CO_2 value being read out is reset to that of the breath just completed. The CO_2 value read out follows variations in alveolar P_{CO_2} up and down from breath to breath. For rapid following it is important that the capacitor on the input of stage 2, Fig. 3 (0.05 μf) be smaller than the one on relay terminal 15 (0.2 μf).

The delay line in the alveolar ventilation computation, although somewhat similar in construction to the P_{CO_2} delay line, performs a different function. At the end of expiration the charge accumulated on the 0.03 μf capacitor connected to relay contact 13 represents a volume of alveolar air. The injection of this charge at the end of expiration into the running-average stage permits the read-out of alveolar ventilation in liters per minute. Frequency of breathing as well as depth is taken into consideration in this circuit, since the end of expiration determines when the charge representing alveolar air will be injected into the averaging circuit. Thus, the four-pole, double-throw relay controls integration and coordinates the presentation of data to the x-y recorder.

The dead-space calculator is a novel circuit for carrying out the operation of multiplying a function by a coefficient and adding a constant to this product. This is done with only one operational stage. The key to the solution of this problem is a precision triple-ganged potentiometer.

Summary

The respiratory computer described here makes it possible to obtain more accurate and precise alveolar ventilation-P_{CO_2} response curves than formerly and with fewer man-hours of labor. It is hoped that the ease of obtaining these response curves will lead to their more frequent use in evaluating respiratory phenomena. Clinical applications in evaluating the effects of changes in compliance and airway resistance on respiration are readily apparent. This technique is being used to study the degree of respiratory depression caused by narcotics and anesthetics and to study the effects of stimulating drugs. Respiratory stimulation and depression in a variety of disease states are also being pursued (*13*).

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13. This article is based on a paper presented before the American Society for Pharmacology and Experimental Therapeutics in April 1959 [*Federation Proc.* **18**, 367 (1959)]. We are indebted to Robert Crane of Crane and Egert Corp., New York, for his advice and encouragement.