Effect of Uneven Pulmonary Distribution of Blood and Gas on Induction with Inhalation Anesthetics

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Uneven ventilation-perfusion or shunting of blood from the right to left side of the heart causes a reduced proportion of the cardiac output to be exposed to alveolar anesthetic gas. This poses a barrier to the passage of anesthetic from alveoli to arterial blood and as such reduces the rate at which induction takes place. The delay of induction for various degrees of shunting may be quantitatively described through the use of electrical analogues. For very soluble agents (ether, methoxyflurane) the delay is minimal but for relatively insoluble agents (nitrous oxide, cyclopropane) the delay may be considerable. The delay is greater at higher lung volumes, as in the emphysematous patient, and in airway obstruction with gas trapped distal to the obstruction.

FROM his previous experience, the practicing anesthetist develops more or less fixed patterns in the administration of anesthesia. Usually these are based on the responses of normal patients. Such routines may be inadequate or hazardous if applied to the abnormal patient. Pertinent alterations must be made in the management of the emphysematous patient, the patient with atelectasis or pneumonitis, and the patient with a congenital heart defect causing a right-to-left shunt. All patients with these disorders have, in effect, a shunting of blood from right to left through or around the pulmonary bed.

The presence of such a shunt or uneven ventilation and perfusion imposes a significant barrier to uptake of an inhalation anesthetic. Since a portion of blood does not come in contact with inspired gas, a gradient or tension difference exists between mean alveolar gas and arterial blood, the magnitude of the gradient being directly related to the size of the shunt.

Although the gradient exists for all anesthetics, the changes in end-tidal and arterial tension vary with the solubility of the anesthetic. For example, imagine a pair of lungs which are ventilated only on one side but equally perfused in both. Alveolar ventilation is normal in volume although not in distribution: that is, ventilation of the one side is sufficient (essentially twice normal ventilation) to maintain mean arterial carbon dioxide tensions at normal levels. If a relatively insoluble gas (ethylene, nitrous oxide or cyclopropane) is now introduced into this pair of lungs, alveolar anesthetic tension on the ventilated side rises rapidly while that on the unventilated side does not begin to rise until recirculating venous blood brings anesthetic to the lung. Rise in alveolar tension in the absence of uneven ventilation-perfusion normally is rapid with an insoluble gas. Thus the rise in alveolar tension in the ventilated side of our example cannot appreciably exceed the rise in the normal state even though ventilation to that lung is twice normal. Since the arterial tension is the proportional average of the tensions in the blood issuing from each lung, and since the tension in the blood from one lung is only slightly higher than normal while that from the other is far below normal, the arterial tension must be significantly lower.

With this same pair of lungs which are ventilated on one side only but perfused equally on both, consider what occurs when a very soluble gas (ether, methoxyflurane) is inspired. The extraction of a very soluble gas from alveoli is nearly complete during induction. If ventilation to one lung equals the normal total ventilation (*i.e.*, twice the normal ventilation to the single lung), the amount of anesthetic taken up by that half of the cardiac output

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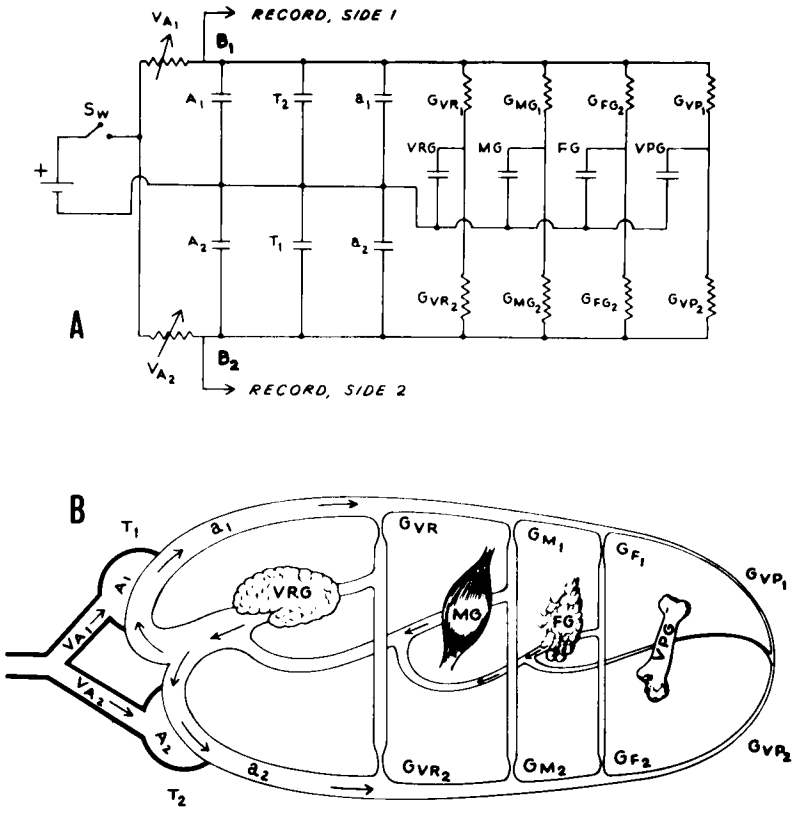

FIG. 1. *A*. The electrical analogue. See tables 1 and 2 for actual values. See Appendix for definitions and explanation. *B*. The biological equivalent of the analogue. The main arterial trunk appears to be divided equally as in the electrical model, illustrating the method by which the analogue treats blood from each lung separately, mixing them as they enter each tissue. This scheme permits the effect of mixed venous blood to be realistically simulated by the analogue which has no recirculation.

will almost equal the normal total, resulting in a high concentration in the blood coming from that lung. Thus despite the low tension in blood issuing from the unventilated lung, mean (*i.e.*, mixed) arterial tension is only slightly lower than when the same ventilation is normally distributed. The mean anesthetic tension in end-tidal gas is considerably more than normal since only the hyperventilated lung contributes to the end-tidal sample.

By altering the electrical analogues currently used to predict anesthetic uptake, we have made quantitative predictions of the effect of uneven distribution of ventilation and perfusion on alveolar and arterial anesthetic tensions.

Method

The analogue used is diagrammed in figure 1A. It is similar to those proposed by Severinghaus,[1] Mapleson,[2, 7] and MacKrell [3] except that the ventilatory and circulatory components are divided into two separate circuits which meet at the common tissue level. This allows ventilation and/or circulation to one lung to be altered independently of the other. Blood and gas are distributed uniformly throughout the individual lungs. An equivalent biological description is given in figure 1B. Details of this model are presented in the appendix of this paper.

Results and Discussion

The result of altering the normal distribution of ventilation-perfusion between the two lungs is illustrated in figures 2, 3, and 4 for cyclopropane, halothane, and ether, respectively. The effect of minor or even moderate changes is small. Even when 75 per cent of ventilation

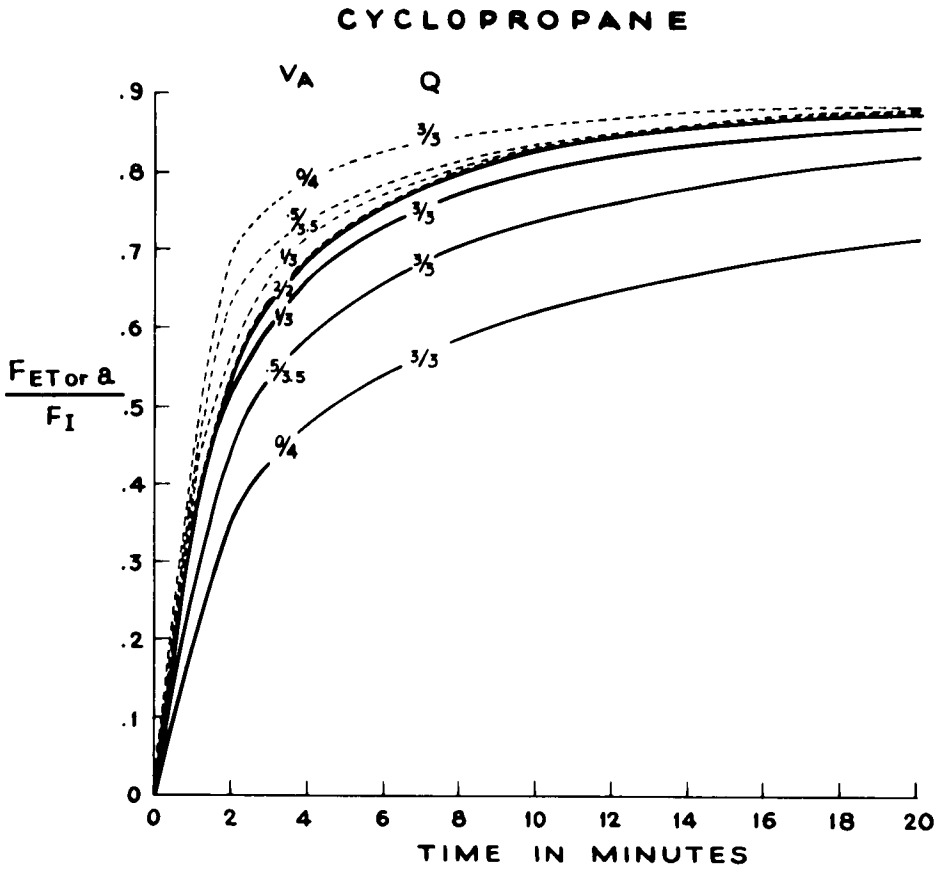

FIG. 2. The effect of uneven ventilation-perfusion on the approach of end-tidal (dashed graphs) and arterial (continuous graphs) cyclopropane tensions to inspired tension. Perfusion to each lung is noted and is constant and equally divided for all curves. Ventilation is altered as noted. The center curve where the dashed and continuous lines overlap represents the normal approach of alveolar (equals arterial in this case) to inspired tension.

is directed to a lung receiving 50 per cent of the cardiac output, there is little deviation of mean arterial or end-tidal tensions from their normal course. Beyond this point the deviations become much greater until a limit is reached when all ventilation is directed to one lung. As predicted, deviation of the arterial curve from normal is greatest with the relatively insoluble gas cyclopropane and is least with the soluble gas ether. Halothane is intermediate.

Since the course of an anesthetic induction is directly related to rise in arterial tension, abnormal distribution of ventilation necessitates significant changes in the inspired concentration of cyclopropane. On the other hand for the same time course for induction, minimal changes are required in inspired concentration of ether. In the case where one lung receives all the ventilation, the inspired cyclopropane concentration required to reach a given arterial level in five minutes must be increased by a factor of 0.45. That is, if 20 per cent inspired cyclopropane is normally given, 29 per cent is required in the abnormal state to achieve the same arterial level at five minutes. If an even more rapid induction is desired, the factor increases further. At two minutes, it equals 0.48; and at one minute, it equals about 1.0. With the soluble agent ether, the factors at one, two, and five minutes are 0.05, 0.05, and 0.04, respectively—small changes. Perhaps this is one of the reasons ether is a "safe" anesthetic; the course of anes-

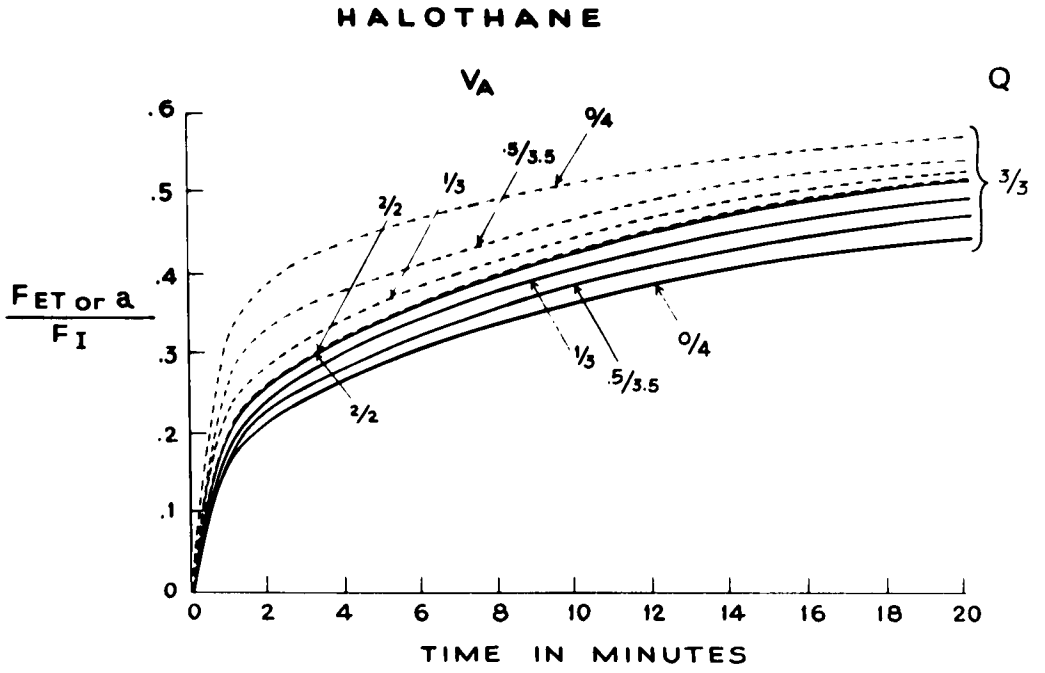

FIG. 3. The effect of uneven ventilation-perfusion on the approach of end-tidal (dashed graphs) and of arterial (continuous graphs) halothane tensions toward the tension inspired. Compare with figures 2 and 4.

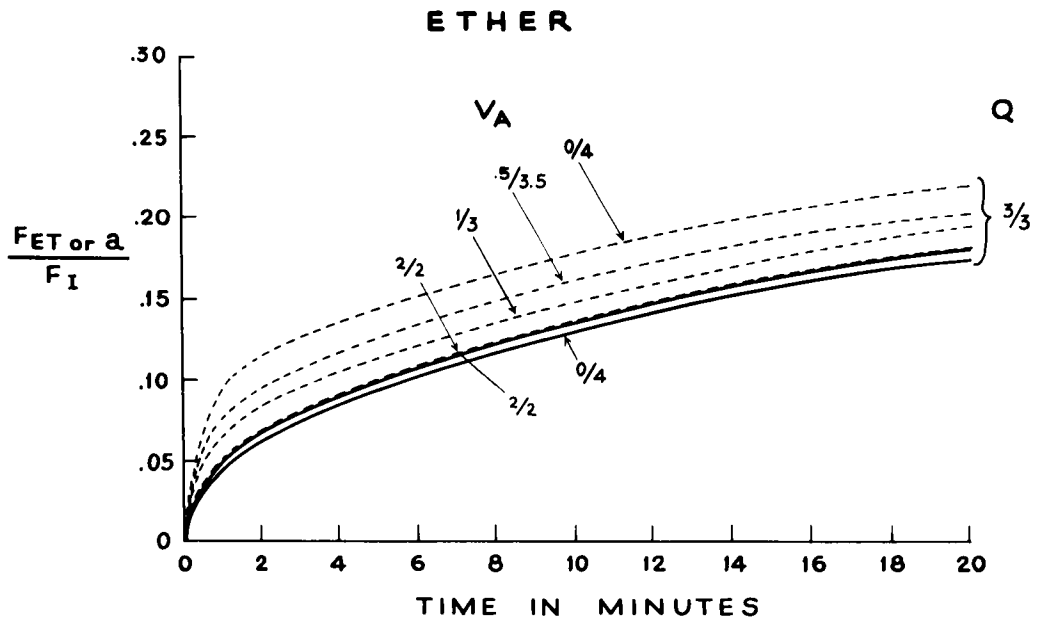

FIG. 4. The effect of uneven ventilation-perfusion on the approach of end-tidal (dashed graphs) and of arterial (continuous graphs) ether tensions toward the inspired tension. Only one arterial curve in which an abnormality exists (4/0 ventilation) is drawn since even with this extremely uneven ventilation-perfusion the deviation of arterial from the normal curve (overlapping dashed and continuous lines) is slight. Compare these curves with those in figures 2 and 3.

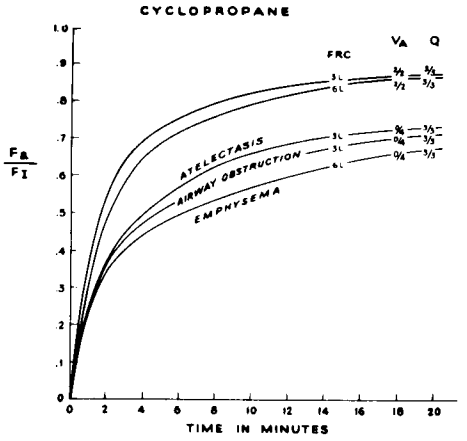

FIG. 5. The approach of arterial to inspired cyclopropane tension under a variety of circumstances. The uppermost graph illustrates the normal rise; *FRC* and ventilation-perfusion are normal. The second graph shows the effect of increasing the *FRC* to 6 L. in the presence of even ventilation-perfusion. Ventilation in the lower three curves is the same as that in the upper two ($V_A = 4$ *LPM*) but is all directed to one lung. Cardiac output is divided equally between both lungs. The curve entitled "atelectasis" is representative of a right-to-left shunt in that there is no air in the unventilated lung (*FRC* is zero) while the ventilated lung has an *FRC* of 3 L. The curve marked "airway obstruction" is based on an *FRC* of 3 L.; but of this, half (1.5 L.) is trapped in the unventilated lung. The lowest graph (emphysema) represents the effect of doubling the *FRC* in the presence of uneven ventilation.

thesia with this agent is unaffected by the above respiratory or circulatory abnormalities. A technique suitable for normal patients is equally suitable for patients with uneven distribution of ventilation or perfusion or both. This is not to say that induction with ether will be faster than cyclopropane even when administered routinely. The converse will probably still be true, but induction with cyclopropane will be much less rapid than usual.

This assumes, of course, that alveolar ventilation remains normal despite uneven distribution. Such is not the case with severe emphysema where carbon dioxide elimination is often impaired. In this case, the effect on the arterial anesthetic tension rise is difficult to assess because a diminished alveolar ventilation as defined for carbon dioxide may actually represent normal (or even increased) total ventilation of a reduced number of alveoli.[4]

It also should be noted that in man perfusion of unventilated lung may be reflexly reduced.[5] This would decrease the effect of uneven ventilation.

The time course of change of end-tidal anesthetic tension differs from the normal course particularly with ether, when only one lung is ventilated. The least deviation is found with cyclopropane while halothane is intermediate. Since, as noted, it was the less soluble agents whose arterial concentration was most affected, the relative gradient from end-tidal gas to arterial blood is essentially independent of agent solubility.

These effects are slightly increased at large lung volumes (fig. 5) in which large FRC and greater distribution simulate emphysema. The curves in figure 5 entitled "atelectasis" and "airway obstruction" differ from each other only because of the assumption of a volume of trapped gas in the latter; this gas takes anesthetic from venous blood and thus slows equilibration. The induction may be further slowed in the presence of shunting or uneven ventilation-perfusion if cardiac output is increased due to arterial oxygen desaturation. This results in a more rapid uptake and delivery of anesthetic to peripheral tissues, which retards the rise in the alveolar and mean arterial anesthetic tensions, particularly with soluble agents.[6]

Summary and Conclusion

An electrical analogue is presented which describes the effect of uneven ventilation-perfusion or right-to-left shunting on uptake and distribution of anesthetic agents. It is similar to those prepared by Severinghaus, by Mapleson, and by MacKrell except that the ventilatory and circulatory components are divided into two separate circuits which meet at the common-tissue level.

Uneven ventilation-perfusion or shunting of blood from the right-to-left side of the heart causes an anesthetic tension difference to appear between end-tidal gas and arterial blood during induction. This results in a delay of induction, particularly with the less soluble agents. This delay is greater at higher lung volumes, as in the emphysematous patient, and in airway obstruction with gas trapped distal to the obstruction.

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APPENDIX

V_{A_1} and V_{A_2} represent the alveolar ventilation to each lung. Electrically, these are represented by conductances (reciprocal of resistance) such that 1 liter per minute (LPM) flow equals 1 μ mho (1 megohm). An alveolar ventilation of 4 LPM is thus described by 4 μ mhos (0.25 megohm). Ventilation is directed to two lungs, the gaseous volumes of which are represented by capacitors A_1 and A_2. The capacities of these are chosen so that 1 liter (L) gaseous volume is represented by 1 μ fd. This arbitrary choice of conductance and capacity results in a time scale such that one analogue second is equivalent to one biological minute. The capacity of lung tissue and arterial blood for anesthetic agent is represented by the capacitor T_1, T_2 and a_1, a_2, respectively. The capacity of each to hold agent is obtained by multiplying tissue or blood volume by tissue/gas or blood/gas partition coefficient. The figure obtained is represented electrically in μ fd as with the lung gaseous volume. For example, the total volume of lung tissue is about 0.5 L. Dividing the lung into equal parts, the T_1 capacitor for halothane is thus $0.25 \times \lambda = 0.25 \times 2.3 = 0.575$ μ fd.

The rate at which anesthetic is carried to tissues is given by the conductances into tissue groups. Conductance is given in μ mhos and equals nu-

TABLE 1

	A_1	T_1	a_1	VGR or G_{VR_1}	MG or G_{M_1}	FG or G_{F_1}	VPG or G_{VP_1}
Volume (L)	1.5	0.25	0.5	6	33	14.5	12.5
Blood flow (LPM)	—	—	—	2.25	0.55	0.16	0.038
Cyclopropane Blood/gas or tissue/gas	—	0.47	0.47	0.64	0.433	6.91	0.47
C (μ farads)	1.5	0.118	0.235	3.78	14.3	100	5.8
G (μ mhos)	—	—	—	1.057	0.259	0.0752	0.0179
Halothane							
Blood/gas or tissue/gas	—	2.3	2.3	5.8	8.0	130	2.3
C (μ farads)	1.5	0.575	1.15	34.5	266	2000	28.8
G (μ mhos)	—	—	—	5.18	1.27	0.368	0.0875
Ether							
Blood/gas or tissue/gas	—	15	12.1	13.8	12.1	24.2	12.1
C (μ farads)	1.5	3.75	6.05	82.8	399	351	148
G (μ mhos)	—	—	—	27.2	6.7	1.94	0.45

A_1 is the gaseous volume of each lung or its equivalent capacity. T_1 is half the tissue volume of the lung and a_1 half the arterial blood volume. *VRG*, *MG*, *FG*, and *VPG* refer to vessel rich, muscle, fat, and vessel poor groups of tissue, respectively. The table gives the volumes, tissue/gas partition coefficients, and equivalent capacities of these tissues. G_{VR_1}, G_{M_1}, G_{F_1}, and G_{VP_1}, refers to half the blood flow to and to equivalent conductance for half flow for the above tissue groups.

TABLE 2

	F	G	V/P	F	G	V/P	F	G	V/P	F	G	V/P
V_{A_1}	2.0	2.0	0.67	3.0	3.0	1.0	3.5	3.5	1.167	4.0	4.0	1.333
V_{A_2}	2.0	2.0	0.67	1.0	1.0	0.33	0.5	0.5	0.167	0		0

F = ventilation in LPM; G = conductance in μ mhos; V/P = ventilation/perfusion ratio.

merically blood flow to the tissue group in LPM times the blood/gas partition coefficient. The capacity of each tissue group to take up agent is given in μ fd as the volume of tissue in liters times the tissue/gas partition coefficient. The particular tissue grouping was previously described. Briefly, *VRG* represents brain, liver, kidney, and heart; *MG* represents muscle and skin; *FG* represents fat; and *VPG* represents bone, cartilage, ligaments, and tendons.

Values for the various flows and capacities may be arbitrarily chosen provided the sums are physiologically reasonable. In this experiment, A_1 is set equal to A_2, $T_1 = T_2$, $a_1 = a_2$, $G_{VR_1} = G_{VR_2}$, $G_{M_1} = G_{M_2}$, $G_{F_1} = G_{F_2}$, and $G_{VP_1} = G_{VP_2}$. Circulation through the lungs is thus divided into two equal parts flowing through two lungs of equal size and tissue volume. Table 1 gives the appropriate values for three anesthetics: cyclopropane, halothane, and ether. Values for V_{A_1} and V_{A_2} are given in Table 2. Where $V_{A_1} = V_{A_2}$, the ventilation-perfusion ratio is identical for both lungs; that is, no abnormality exists. As V_{A_1} increases, V_{A_2} decreases so as to maintain total alveolar ventilation constant. Ventilation-perfusion becomes increasingly uneven until only one lung is being ventilated while both are perfused. Construction of the analogues proceeded as above for each of the three gases. Inspiration of gas at a constant tension was simulated by connecting the battery at A on figure 1A. The resultant rises in alveolar concentration as indicated by rises in voltage at point B_1 and B_2 were recorded separately from a high impedance (10^{13} ohms) voltmeter. Alveolar tension was considered identical to pulmonary venous blood tension. Since blood flow was equal through each lung, true arterial tension was the mean of alveolar tensions from each lung. On the other hand, mean end-tidal tensions were determined by multiplying alveolar tension by ventilatory minute volume for each lung, adding the resultant figures for the two lungs and then dividing by total ventilatory minute volume. Following these experiments, the model was altered so as to determine the effect of altering functional residual capacity (*FRC*). A_2 was increased to 4.5 μ fd, A_1 remaining 1.5 μ fd. This simulated the emphysematous patient having an increase in *FRC* with the underventilated or obstructed enlarged lung still being perfused. Following this, A_1 was increased to 3 μ fd, V_{A_1} maintained at 4 μ mhos and V_{A_2} and A_2 eliminated. This simulated the patient with atelectasis or with congenital heart disease and a right-to-left shunt.

MUCOVISCIDOSIS Adults with chronic lung disease up to the age of 45 have significantly higher levels of sweat sodium and chloride in response to thermal stimulation than do controls. Parents and siblings of children with mucoviscidosis also have elevated sweat chloride levels supporting the theory of a genetic basis for this disease. (*Karlish, A. J., and Tarnoky, A. L.: Mucoviscidosis and Chronic Lung Disease in Adults, Amer. Rev. Resp. Dis. 88: 810 (Dec.) 1963.*)