"IN VIVO" MEASUREMENT OF TOTAL GAS PRESSURE IN MAMMALIAN TISSUE

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ABSTRACT

An in vivo method for the quantitative estimation of total gas pressure in mammalian tissue has been established. This method utilizes a rigid-walled capsule specially constructed to be permeable to oxygen, carbon dioxide and nitrogen (O_2,CO_2, and N_2), but negligibly permeable to water vapor. The results obtained at equilibrium, after subcutaneous implantation of this capsule, demonstrate directly that the total gas pressure in the adjacent tissue, which is represented by the intracapsular total gas pressure, is about 40 to 50 mm Hg less than the concomitant atmospheric pressure. The difference between these gas pressures is a result of the metabolic gas exchange and may, therefore, be used to detect quantitative changes in tissue gas metabolism. Work is in progress on miniaturization and modification of the capsule device so that it may be used at intravascular as well as tissue sites in a broad variety of physiological states.

The metabolizing tissues of mammals combust carbon (food stuff) in oxygen with the consequent production of carbon dioxide. Under "steady state" conditions, the metabolic amounts of O_2 used and CO_2 produced in any particular tissue manifest a fair degree of constancy, thus establishing fairly constant partial pressures of these gases in the tissue. Any sudden metabolic increase in such tissue produces an increased O_2 utilization and CO_2 production whereby the partial pressure of oxygen (P_{O_2}) decreases and that of carbon dioxide (P_{CO_2}) increases. Because of the marked difference in slope of the O_2 versus the CO_2 dissociation curves of the blood, the decrease in tissue P_{O_2} will be much larger than the increase in tissue P_{CO_2}. Therefore, the total gas pressure in the tissue (P_T) should also decrease, since the partial pressure of the metabolically inert nitrogen (N_2) remains essentially constant. Thus, in any tissue, a change in P_T reflects metabolic changes affecting the P_{O_2} and P_{CO_2} which, as yet, cannot be measured readily. It is for this reason that the availability of direct P_T measurements would be extremely useful for the detection of these metabolic effects in any tissue.

One of the earliest measurements of total gas pressure in mammalian tissue was obtained in 1908 by August Krogh[1]. Using an acute preparation and an "in vivo" volumetric method, Krogh ascertained that the total gas pressure in the arterial blood of the anesthetized rabbit was less than that of the atmosphere. Aksnes and Rahn[2] in 1956 repeated and extended Krogh's measurements of total gas pressure. Using an "in vitro" method, these investigators were able to obtain estimates of mixed-venous as well as arterial total gas pressures in the anesthetized dog. The measurements were obtained using blood samples withdrawn during "steady state" conditions. They found the mixed-venous total gas pressure to be 54 mm Hg less than the concomitant atmospheric pressure (average of 12 data). This technique as that of Krogh, does not permit the chronic measurement of the total gas pressure in the blood or other tissue of the unanesthetized animal.

The subcutaneous injection of a gas bubble consisting of O_2, CO_2 and N_2 is followed by the gradual absorption of those gases by the surrounding tissue and blood.[3] The absorption of an injected mixture of these gases can be divided arbitrarily into two phases. In the first phase, each gas can diffuse into or out of the bubble towards the site of its lowest partial pressure. This trans-interface flux continues until the intra-bubble concentrations of the three gases become equal to those of the adjacent tissue interface. This interface is composed of tissue cells, tissue liquid and the capillary blood which flows through the area. When constant gas-composition in the bubble is attained, the second phase of absorption commences. All the gases now diffuse out of the bubble at an overall rate depending on the physical properties of the slowest diffusing gas. Since the loose, overlying skin does not significantly compress the bubble, the total gas pressure in the bubble is essentially equal to that of the atmosphere and remains so during the complete absorption process. Since it has been empirically established that the bubble gases are absorbed, it follows that the total gas pressure in the tissue-liquid interface must be less than that within the gas bubble and that this pressure difference (the absorption gradient) is the diffusion driving-force for the absorption process. This gradient must also remain essentially constant during the whole process of absorption.

The nature of this gradient may be visualized in Figure 1, which presents typical CO_2 and O_2 blood-gas dissociation curves for dogs of the surrounding geographical region. It has been assumed that these curves and the arterio-venous O_2 and CO_2 differences shown in Figure 1 represent the essential conditions for the gas exchange between the capillary blood and the tissue-liquid interface of the subcutaneous bubble. The addition of 4 volumes % CO_2 by the tissue cells to the traversing capillary blood results in an increase of 6 mm Hg in the total gas pressure of the blood. Concomitantly, the unloading of 5 volumes % O_2 into the tissue cells by the blood results in a decrease of 47 mm Hg in the total gas pressure of the blood. The net effect of these two processes is a 41 mm Hg decrease in the total gas pressure of the blood. An additional decrement may occur as the combined result of the alveolar-capillary-blood barrier and the dilution effect of intra-pulmonic arterio-venous shunts. In "normal," unanesthetized, air-breathing dogs, this additional decrement could approximate 10 mm Hg. Since these were the conditions under which the data in this study were obtained, one would predict that the total decrement or equilibruim absorption gradient should approximate 40 to 50 mm Hg. The subtraction of this gradient from the concomitant barometric pressure should yield a quantitative estimate of the total gas pressure of the tissue-liquid interface.

METHODS

The equilibrium absorption gradient may be measured by using a specially-constructed, constant volume, rigid-walled bubble which is permeable to O_2, CO_2, and N_2 but with relatively negligible permeability to water vapor. The total gas pressure in such a subcutaneously implanted bubble will come into equilibrium with the total gas pressure of the tissue-liquid interface; the absorption gradient manifesting itself at equilibrium as a constant, negative, hydrostatic pressure within the bubble.

The construction detail of the rigid-bubble capsule is shown in Figure 2. The volume chamber and two membrane-retention rings are made of acrylic plastic. The volume chamber communicates freely with the lumen of the externalizing mylar-plastic tube and metal stopper-housing. A rigid, wire mesh screen is flush-mounted on each side of the volume chamber. A 5-mil thick, siliconated rubber membrane is placed on each noncollapsible wire screen and locked in, water-tight, by the plastic retention rings. The CO_2 diffusibility constant of a one mil thick portion of this membrane as measured at 25 degrees centigrade is 0.56 ml/min/cm^2 surface area at a gradient of one atmosphere (Dow Corning). This diffusibility is listed as being 3053 times that of water vapor. The permeability of the mylar tubing to O_2, CO_2, N_2 and water vapor is virtually zero. The internal gas volumes of the three capsules used in this study were 1.0, 0.75, and 0.70 ml respectively. Figure 3 shows the general appearance of an assembled capsule.

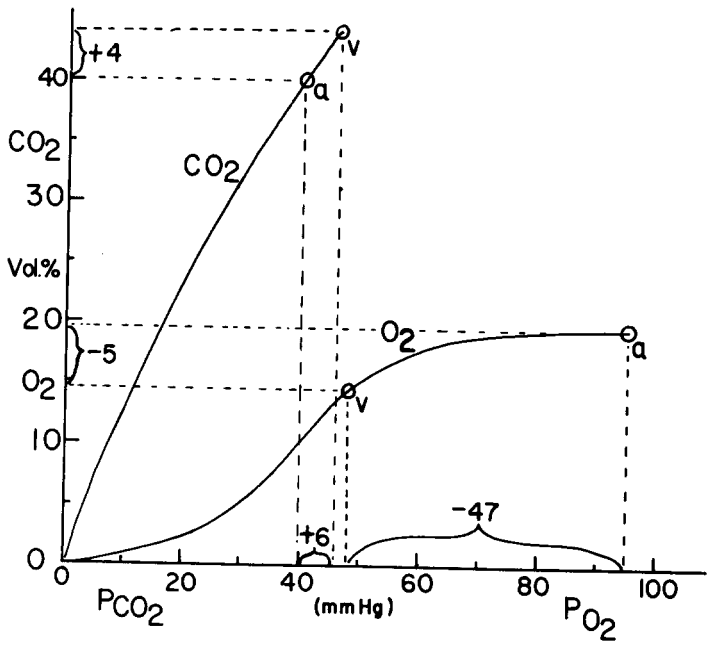

FIGURE 1. Typical O_2 and CO_2 blood-gas dissociation curves for dogs of the local geographical area.

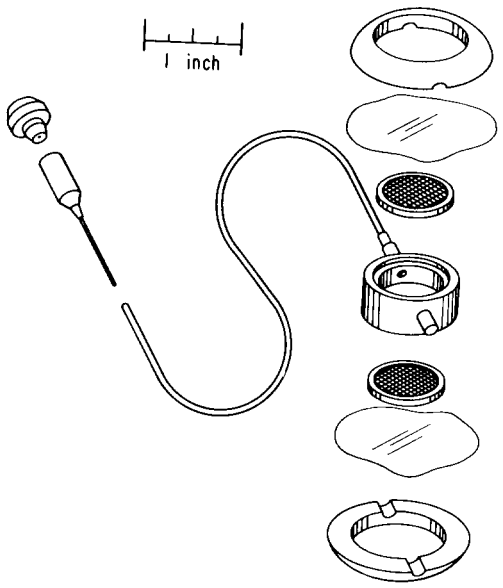

FIGURE 2. Construction detail of the rigid-bubble capsule.

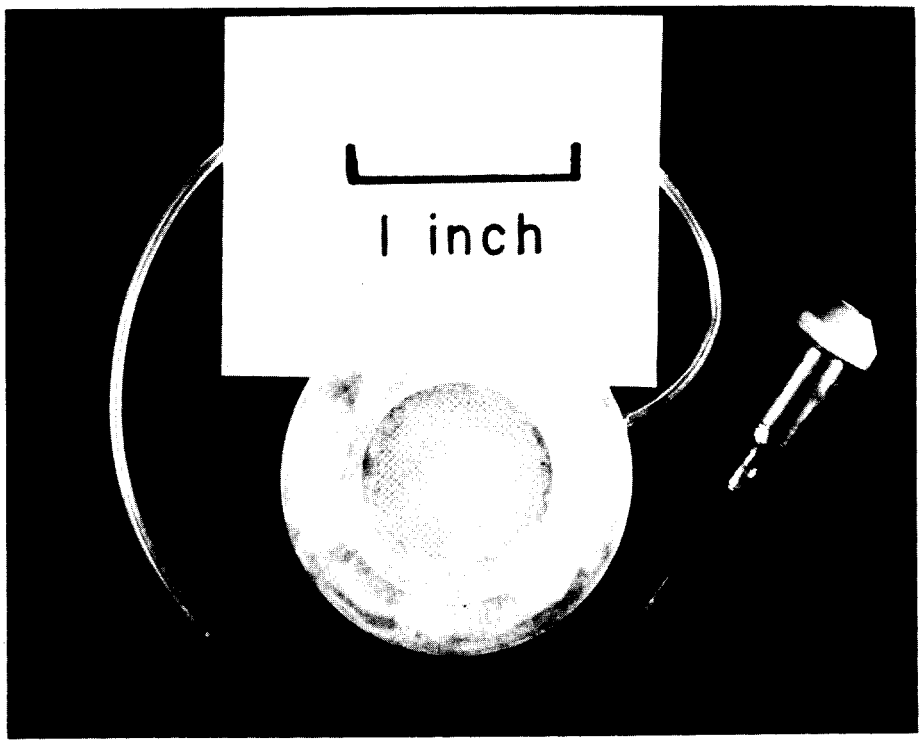

FIGURE 3. General appearance of an assembled rigid-bubble capsule.

This type of capsule was surgically implanted subcutaneously in each of three dogs under Nembutal anesthesia. The subcutaneous position of the capsule in each dog is shown in Figure 4. Following one week allowed for surgical healing, the metal housing was inserted into the external orifice of the mylar tube and occluded with a rubber stopper. Measurements of the intracapsular negative-pressure were obtained for pressure-buildup durations of 1 to 6 days. The intracapsular pressure was reduced to zero (atmospheric pressure) at the start of each pressure-buildup period. The dogs were unanesthetized during all the measurement and pressure-buildup periods. A small-bore water manometer was used as the pressure measuring device. It was connected to the intracapsular volume via a hypodermic-needle forced into the self-sealing rubber stopper.

RESULTS

The change in the intracapsular negative-pressure with respect to time is shown in Figure 5. The mean pressures for the 2nd, 3rd, and 4th days are not significantly different at the 5% level of probability. Therefore, all the pressure determinations representing pressure-buildup periods of 2 or more days duration were considered representative of the equilibrium state. It is this pressure which represents the absorption gradient. The subtraction of this value from the concomitant barometric pressure yields a quantitative estimate of the total gas pressure of the tissue-liquid interface.

The summarized equilibrium data are shown in Table 1. The means and standard errors are shown for the absorption gradient ($\triangle P$), the concomitant barometric pressure (P_B) and the calculated "tissue" total gas pressure (P_T). The three mean values for P_T are not significantly different at the 5% level of probability. Each mean P_T is, however, significantly different from its related mean P_B in all three cases. Two of the three mean values of $\triangle P$ are significantly less than the corresponding concomitant value of 54 mm Hg obtained by

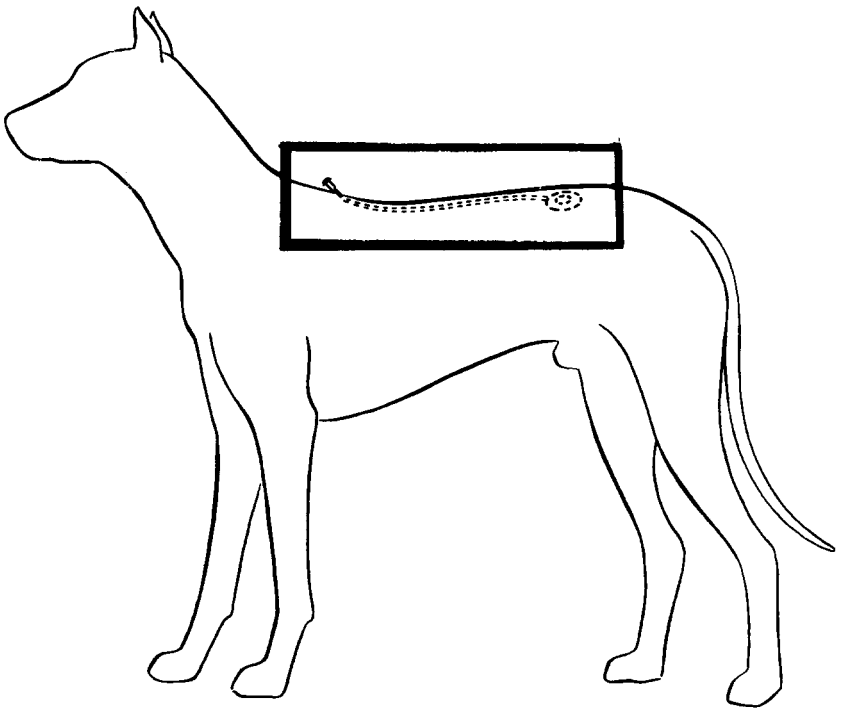

FIGURE 4. Subcutaneous location of the capsule system in the dog.

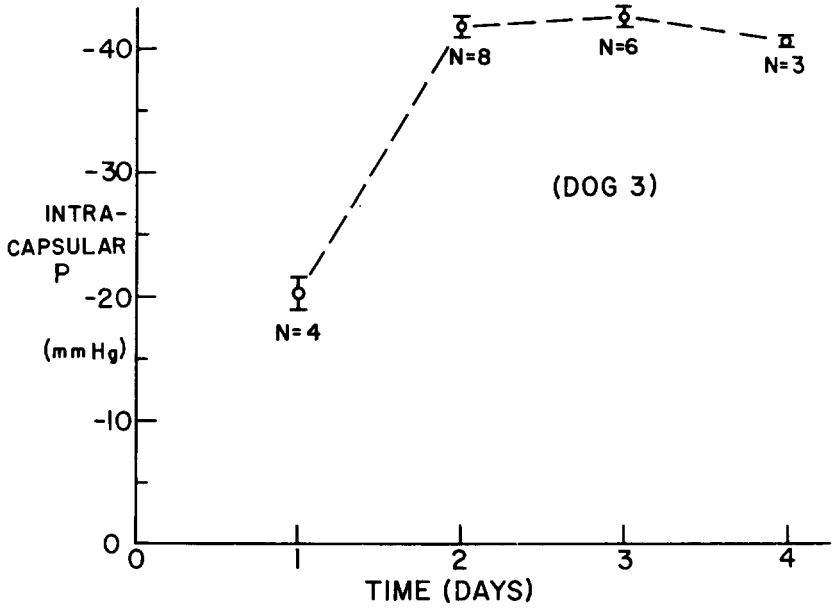

FIGURE 5. A graphical plot of the negative intracapsular pressure versus time indicating the minimum amount of time necessary to attain the equilibrium value of the absorption pressure-gradient.

TABLE I

DOG NO.	△P mm Hg	P_B mm Hg	"TISSUE"P_T mm Hg	(P_B—"TISSUE"P_T)
1	48 ±3.3 N-4	731 ±0.9 N-4	683 ±3.5 N-4	P = <0.1%
2	43.9 ±0.9 N-13	729.3 ±1.3 N-13	685.4 ±2.0 N-13	P = <0.1%
3	41.6 ±0.6 N-17	729.5 ±0.9 N-17	687.9 ±1.2 N-17	P = <0.1%

Aksnes and Rahn for mixed-venous blood. The difference may be real and possibly accounted for by the presence of a considerably larger alveolar-arterial O_2 gradient in the anesthetized versus unanesthetized dog.

DISCUSSION

The experimentally obtained mean △P values (Table 1) lie within the range of values predicted for this parameter. Although the mean P_T values (Table 1) for the three dogs do not differ significantly at the chosen statistical probability level, the biological possibility does exist that these small mean differences are, in fact, real and are related to minor variations in tissue metabolism at the capsule site. A continuous measurement of P_T might resolve this possibility.

The potential uses of the capsule device described in this study are manifold. A few examples of these projected uses are as follows:

1. According to the work of Van Liew [3], the equilibrium concentrations of any combination of O_2, CO_2 and N_2 injected into a subcutaneous gas bubble closely resemble the concentrations of the same gases in the venous blood of the tissue surrounding the bubble. Since the pulmonary artery is the site of mixed-venous blood from the whole organism, the total gas pressure measured at this site by means of a miniaturized version of the capsule device should represent an approximation of the mean total gas pressure of the whole organism in conjunction with its existing state of metabolism.

2. Since the total gas pressure in any tissue is related to its concomitant metabolic gas exchange, the presence of a miniaturized capsule device in skeletal muscle could allow the assessment of metabolic gas exchange during rest versus various degrees of muscular work.

The measurement of mean metabolic changes occurring in the whole organism (e.g., at a mixed-venous blood site) or of individual metabolic changes at some specific site (e.g., skeletal muscle) in a broad variety of physiological states should be of extreme value.

SUMMARY

An in vivo method for the quantitative estimation of total gas pressure in mammalian tissue has been established. This method utilizes a rigid-walled capsule specially constructed to be permeable to oxygen, carbon dioxide and nitrogen (O_2, CO_2, and N_2), but negligibly permeable to water vapor. The results obtained at equilibrium, after subcutaneous implantation of this capsule, demonstrate directly that the total gas pressure in the adjacent tissue, which is represented by the intra-capsular total gas pressure, is about 40 to 50 mm Hg less than the concomitant atmospheric pressure. The difference beween these gas pressures is a result of the metabolic gas exchange and may, therefore, be used to detect quantitative changes in tissue gas metabolism. Work is in progress on miniaturization and modification of the capsule

device so that it may be used at intravascular as well as tissue sites in a broad variety of physiological states.

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