Reports

Oxygen Consumption of Tissues in the Human Lung

Abstract. A method for estimating the metabolic rate of the human pulmonary tissues is described. Six patients with far advanced pulmonary tuberculosis showed an average rate of 12 percent of the total oxygen consumption. A method for measuring the right ventricular output with an inert gas is also outlined, and the use of this approach to minimize errors in the estimation of the tissue metabolic rate is described.

Little is known about the metabolism of human pulmonary tissues. The only study cited in the recently published "Handbook of respiration" is that of Krebs (*1*) who found that lung tissue from a human embryo consumed 3.7 mm^3 of oxygen per hour per milligram of dry weight. While this figure can be used to calculate the oxygen consumption of the lungs within the body, the accuracy of the calculation is uncertain. No alternative is available, however, since direct measurements have not, to our knowledge, been made in living man.

The pulmonary tissues have access to several sources of oxygen, including the air in the alveoli, the blood in the pulmonary vessels, and the blood draining from the bronchial circulation into the pulmonary veins and arteries. Whether the tissues utilize all of these sources is uncertain. The consensus is that the alveolar walls derive oxygen chiefly from the alveolar air, while the bronchi, the smaller air passages, and major portions of the visceral pleura utilize oxygen carried by the bronchial flow. A fourth source, the bronchial-hemiazygos blood-flow, supplies oxygen to the main stem bronchi and their first two subdivisions. The oxygen consumed by these structures, which lie partially within the mediastinum, is not included in the analysis that is presented below.

Figure 1 depicts the exchanges of oxygen which theoretically can take place within the lungs. Inspection of the drawing provides a basis for summing the rates at which oxygen enters and leaves the intravascular volume delineated by vertical hatching.

$$\dot{Q}_R C_{\bar{v}O_2} + \dot{Q}_B C_{B_{O_2}} + \dot{V}_{O_2} - \dot{V}_{T_A} - \dot{V}_{T_C} - (\dot{Q}_R + \dot{Q}_B)\, C_{a_{O_2}} = 0 \quad (1)$$

where $\dot{Q}_R$ = volumetric flow from the right ventricle; $\dot{Q}_B$ = volumetric flow from the bronchial arteries draining into the pulmonary vessels; $C_{a_{O_2}}$ = concentration of oxygen in the arterial blood; $C_{\bar{v}O_2}$ = concentration of oxygen in the mixed venous blood; $C_{B_{O_2}}$ = concentration of oxygen in the bronchial blood draining into the pulmonary vessels; $\dot{V}_{O_2}$ = oxygen uptake measured at the mouth; $\dot{V}_{T_A}$ = oxygen supplied to the pulmonary tissues by the alveolar air; and $\dot{V}_{T_C}$ = oxygen supplied to the pulmonary tissues by the pulmonary blood flow.

It should be emphasized that $\dot{V}_{T_A}$ and $\dot{V}_{T_C}$ represent potential, not proven, exchanges of oxygen. They are included in the equation for the sake of generality.

In a similar way, an equation can be written to describe the oxygen exchange in the intravascular volume defined by oblique hatching. Thus

$$\dot{Q}_B C_{a_{O_2}} = \dot{V}_{T_B} + \dot{Q}_B C_{B_{O_2}} \quad (2)$$

where $\dot{V}_{T_B}$ = oxygen supplied to the pulmonary tissues by the bronchial blood flow.

Adding Eqs. 1 and 2 yields the following expression:

$$\dot{V}_{T_A} + \dot{V}_{T_B} + \dot{V}_{T_C} = \dot{V}_{O_2} - \dot{Q}_R\,(C_{a_{O_2}} - C_{\bar{v}O_2})$$

The three terms of the left-hand member represent the oxygen extracted, respectively, from the alveolar air, the bronchial flow, and the pulmonary flow. Hence, the sum of these terms ($\dot{V}_{T_{O_2}}$) is an estimate of the metabolic rate of the pulmonary tissues.

$$\dot{V}_{T_{O_2}} = \dot{V}_{O_2} - \dot{Q}_R\,(C_{a_{O_2}} - C_{\bar{v}O_2}) \quad (3)$$

The equation indicates that the calculation of $\dot{V}_{T_{O_2}}$ entails measuring the flow from the right ventricle ($\dot{Q}_R$), the oxygen uptake at the mouth ($\dot{V}_{O_2}$), and the concentrations of oxygen in the arterial ($C_{a_{O_2}}$) and mixed venous ($C_{\bar{v}O_2}$) blood. $\dot{Q}_R$ can be measured from a dye-dilution curve inscribed through a cardiac catheter with its tip in the pulmonary artery (*2*), $\dot{V}_{O_2}$ can be obtained by using a Scholander microanalyzer, and $C_{a_{O_2}}$ and $C_{\bar{v}O_2}$ can be determined by Van Slyke's method.

In an earlier study we compared the outputs measured by the Fick and dye-dilution methods in patients with either heart disease, bronchiectasis, or minimal tuberculous infections (*3*). Our results, like those of others, showed that the two measurements agreed well in the majority of patients, and that the difference between the two had a random distribution. These observations suggested that the oxygen consumed by the pulmonary tissues lay within the errors of the measuring techniques. But a series of patients with advanced pulmonary tuberculosis presented a unique pattern in that the Fick output almost always exceeded the dye output by a small amount. One possible explanation was that the presence of tuberculosis interfered with the methods of measurement, causing either an underestimation of flow by the dye principle or an overestimation of flow by the conventional Fick. However, there was no reason to believe that the results could be attributed to such artifacts of measurement. Thus, we favored the alternative explanation that a small part of the oxygen accounted for in the Fick calculation was, in reality, metabolized by the lungs.

This reasoning led to the present study in which the metabolic rate of the pulmonary tissues was calculated

---

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* **125**, 16 (1957)].

in six patients with severe pulmonary tuberculosis. Three estimates were obtained in four of the patients and two estimates in two. Of these 16 values two were negative. The remaining 14 indicated that the pulmonary tissues consumed an average of 12 percent of the total oxygen consumption of the body. The range extended from 0 to 20 percent.

While the average rate of 12 percent seems a high figure, two lines of evidence provide support for its validity. The first is that inflammation enhances metabolic activity, and the second is that patients with advanced tuberculosis sometimes display a high metabolic rate. On the basis of these observations, it seems reasonable to think that part of the extra oxygen consumed by such patients is metabolized by the inflamed tissues in the chest. That the metabolic rate of normal lungs is lower can be inferred from experiments performed in animals. Dawes and his colleagues (*4*) calculated the oxygen consumption of the lungs of the fetal lamb by multiplying the pulmonary blood flow by the arteriovenous oxygen difference. This calculation revealed that the lungs accounted for 8 percent of the total oxygen consumed. Carlyle (*5*) obtained a similar figure by placing fetal lung in the Warburg apparatus; when he studied the tissues of the adult sheep in the same manner, however, he found that the lung utilized only 1 to 4 percent of the total oxygen consumption.

The present approach has several limitations. One is that the technique ignores the role of anaerobic metabolism, and, while the importance of this role has not been established, the possibility that it has significance exists. A second limitation may be present if Thebesian veins carry venous blood into the left atrium or ventricle. In this situation the oxygen which the myocardium has extracted from the blood will be included in the calculated oxygen consumption of the lungs. Whereas the Thebesian veins represent only a potential source of error (*6*), larger systemic-pulmonary channels, such as those known to connect the chest wall and lungs through pleural adhesions or those thought to join the portal and pulmonary vessels in Laennec's cirrhosis, could introduce an error of considerable magnitude. This error would, however, be associated with a discrepancy between the outputs of the right and left ventricles (*3*), and since in this series comparisons of these outputs revealed an insignificant difference, any error from this source was probably small.

A third difficulty may be introduced by the dye curve used to measure the output of the right ventricle. A previous study demonstrated that curves drawn simultaneously either from the pulmonary and brachial arteries or from the two brachial arteries gave outputs which showed a satisfactory average agreement, yet occasionally differed by more than 10 percent (*3*). A final deficiency is one which is encountered in any calculation based on the relation between the oxygen consumption measured at the mouth and the rate at which oxygen enters the pulmonary capillaries. Extraneous factors, such as changes in the mean volume of the lungs during the period of measurement, can artificially influence this relationship.

As previously mentioned, the method cannot be used to study patients free of severe infection because such patients do not show a systematic difference between the Fick and dye-dilution outputs. While this is probably attributable to the fact that the oxygen consumption of the normal lung lies within the errors of the methods, it may also be due to the circumstance that the dye and Fick measurements are customarily made in sequence, rather than simultaneously. In an attempt to minimize the effects of these factors, we are investigating the feasibility of measuring $\dot{Q}_R$ by infusing into the right atrium a solution containing an inert gas dissolved in saline. The principle of the method may be demonstrated by writing an equation similar to Eq. 1 written for oxygen. Thus

$$\dot{Q}_R C_{\bar{v}_K} + \dot{Q}_B C_{B_K} - \dot{V}_{E_K} - \dot{V}_{T_{A_K}} - \dot{V}_{T_{C_K}} - (\dot{Q}_R + \dot{Q}_B)\, C_{a_K} = 0 \quad (4)$$

where $\dot{V}_{E_K}$ = rate of elimination of the gas in the expired air, and the other symbols correspond to those defined for oxygen. Rearranging, we have

$$\dot{Q}_R\,(C_{\bar{v}_K} - C_{a_K}) - \dot{V}_{E_K} + [\dot{Q}_B\,(C_{B_K} - C_{a_K}) - \dot{V}_{T_{A_K}} - \dot{V}_{T_{C_K}}] = 0 \quad (5)$$

In the steady state, the tissues are saturated and, because the gas is inert, $\dot{V}_{T_{C_K}}$ and $\dot{V}_{T_{A_K}}$ are zero. Further, $C_{a_K} = C_{B_K}$ so that the term $\dot{Q}_B(C_{B_K} - C_{a_K})$ becomes zero also. Hence

$$\dot{Q}_R = \frac{\dot{V}_{E_K}}{C\bar{v}_K - C_{a_K}} \quad (6)$$

and, substituting Eq. 6 in Eq. 3 gives

$$\dot{V}_{T_{O_2}} = \dot{V}_{O_2} - \dot{V}_{E_K}\left[\frac{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}{C\bar{v}_K - C_{a_K}}\right] \quad (7)$$

In a similar manner, one can show that the carbon dioxide ($\dot{V}_{T_{CO_2}}$) pro-

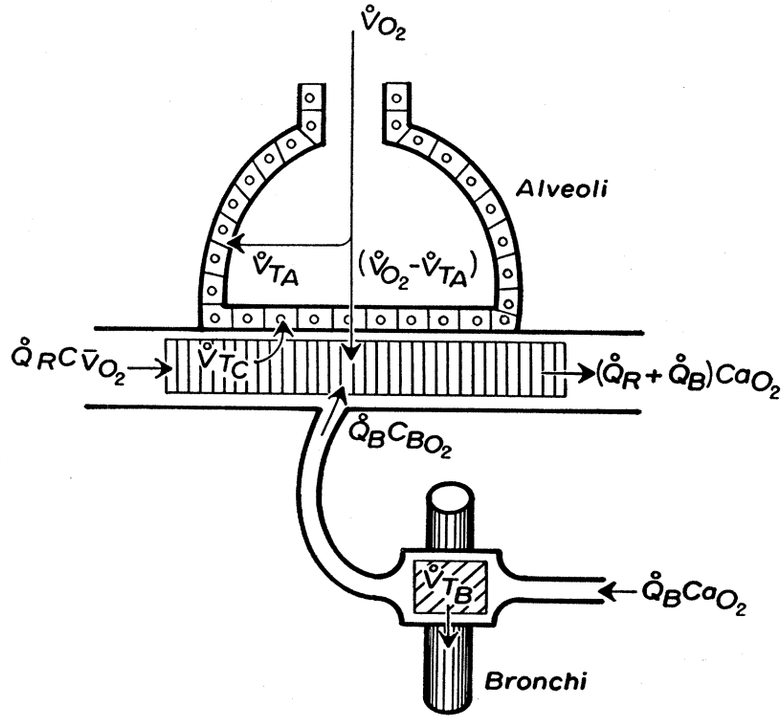

Fig. 1. Theoretical exchanges of oxygen within the lungs. For explanation of symbols, see text.

duced by the pulmonary tissues can be calculated from

$$\dot{V}_{T_{CO_2}} = \dot{V}_{CO_2} - \dot{V}_{E_K}\left[\frac{C_{\bar{v}CO_2} - C_{aCO_2}}{C_{\bar{v}_K} - C_{a_K}}\right] \quad (8)$$

where the symbols correspond to those defined for oxygen. And, finally, the respiratory quotient (R_T) of the tissues can be calculated by dividing Eq. 7 into Eq. 8.

$$R_T = \frac{\dot{V}_{CO_2}(C_{\bar{v}_K} - C_{a_K}) - \dot{V}_{E_K}(C_{\bar{v}CO_2} - C_{aCO_2})}{\dot{V}_{O_2}(C_{\bar{v}_K} - C_{a_K}) - \dot{V}_{E_K}(C_{aO_2} - C_{\bar{v}O_2})}$$

In essence, this approach consists of simultaneously applying the Fick principle with two different gases. One of these, oxygen, is metabolized, while the other, an inert gas, is not.

The success of this approach hinges on the degree to which a steady-state can be approximated, particularly in regard to the equilibration of the gas with the tissues. If equilibrium cannot be achieved, $\dot{Q}_R$ can still be estimated by substituting the rate of infusion for $\dot{V}_{E_K}$ in the last four equations, and by using the gas concentration in arterial blood as an estimate of that in the blood draining from the tissues into the right side of the heart. Results from this method with the inert gas Kr^{85} have been more reproducible than those obtained with dye. But whether the errors will be sufficiently minimized to assure the applicability of the technique to patients free of pulmonary infections is not yet known.

If the utility of the approach can be established, the method might provide information on several disputed points. For example, the role of metabolism in the genesis of pulmonary diseases might be studied, the effect of therapy on the metabolism of pulmonary lesions might be investigated, and the participation of the pulmonary tissues in diseases of metabolism, such as hyperthyroidism, might be explored (*7*).

H. W. FRITTS, JR.
D. W. RICHARDS
A. COURNAND

Department of Medicine, Columbia University, College of Physicians and Surgeons, and *the Cardio-Pulmonary Laboratory, First Medical and Chest Services, Bellevue Hospital, New York*

References and Notes

1. H. A. Krebs, in *Handbuch der Biochemie des Menschen und der Tiere,* Oppenheimer, Ed. (Fischer, Jena, 1933) [cited in "Handbook of respiration," *Wright Air Development Center Tech. Rept. 58-352* (August 1958), p. 291].
2. H. W. Fritts, Jr., P. Harris, C. A. Chidsey III, R. H. Clauss, A. Cournand, J. *Appl. Physiol.* **11**, 362 (1957).
3. ———, *Circulation,* in press.
4. G. S. Dawes, J. C. Mott, J. G. Widdicombe, *J. Physiol. London* **126**, 38 (1954); G. V. R. Born, G. S. Dawes, J. C. Mott, J. G. Widdicombe, *Cold Spring Harbor Symposia Quant. Biol.* **19**, 102 (1954).
5. A. Carlyle, *J. Physiol. London* **107**, 355 (1948).
6. D. E. Gregg, *Physiol. Revs.* **26**, 28 (1946).
7. This investigation was supported by a research grant, H-2001 (C), from the National Heart Institute, U.S. Public Health Service, Bethesda, Md.

12 December 1960

Uptake of Tritium-Labeled Norepinephrine in Brain and Other Tissues of Cat in vitro

Abstract. Slices of cat cerebral cortex, heart, and spleen that have been incubated in media containing approximately 5 to 25 mμg of *dl*-norepinephrine-7H^3 per milliliter contain levels of isotopic amine greater than those in the medium. The effects of norepinephrine concentration, reserpine, and ouabain on the uptake suggest that the amine enters cells both by diffusion and by a concentrating mechanism that is saturated at low levels of norepinephrine. The drugs inhibit the latter.

Hughes and Brodie (*1*) have presented evidence that active transport of 5-hydroxytryptamine is an important factor in maintaining the high concentrations of this amine in blood platelets. The present studies were undertaken to determine whether a similar mechanism contributes to the relatively high levels of catecholamines maintained in parts of the brain and in sympathetically innervated organs (*2*).

Tissue slices were incubated in Krebs bicarbonate medium containing 5 mμg of *dl*-norepinephrine-7H^3 per milliliter. The concentration of isotope in cat cerebral cortex (Fig. 1) rose to several times that in the medium. Uptake curves for slices of hypothalamus, cerebellum, heart, and spleen were very similar to those in Fig. 1. Liver and muscle, however, did not accumulate concentrations of norepinephrine significantly greater than that in the medium. Approximately 75 percent of the radioactivity in cortex and heart after 1 hour of incubation was accounted for as unchanged norepinephrine by column chromatography of the contents of pooled slices (*3*). Chromatographic analysis of the incubation media indicated that 70 percent of the metabolites produced by cortical slices were 3,4-dihydroxy or 3-methoxy-4-hydroxymandelic acid. In the heart media the O-methyl ether of norepinephrine accounted for 60 percent of the metabolites.

In order to determine the effect of norepinephrine concentration on the rate of uptake, tissue levels of labeled norepinephrine were measured after 20 minutes of incubation, during which time the uptake is approximately linear. The ratio of tissue concentration of isotope to concentration in the medium was maximal in cortex and heart at levels between 5 and 25 mμg/ml. At higher levels the tissue concentration approached that of the medium. These data, which resemble those obtained with epinephrine (*4*), suggest that catecholamines, like 5-hydroxytryptamine in platelets (*1*), enter nervous tissue in two ways. At low levels of norepinephrine most of the inward flux would occur by a concentrating mechanism involving a carrier, presumably enzymatic. The data of Table 1 would be consistent with the saturation of such a carrier at norepinephrine levels of about 25 mμg/ml above which the rate of entry by this mechanism could not be further increased.

The second component of the inward flux would be a simple diffusion by which the internal concentration of the amine should gradually approach the external one. The rate of this process, however, should not be subject to an upper limit since diffusion rates vary linearly with concentration. Thus the limited quantity entering in a given time by the concentrating mechanism should become a negligible fraction of the much larger amounts forced through the diffusion barrier by very high external concentrations, and the ratios of Table 1 would be expected to approach unity.

Uptake of norepinephrine by the concentrating mechanism could represent either chemical binding to tissue components or active transport by an energy-requiring pump of low capacity. That it may be the latter is suggested by the marked inhibition of the inward flux by ouabain (Fig. 1), since cardiac

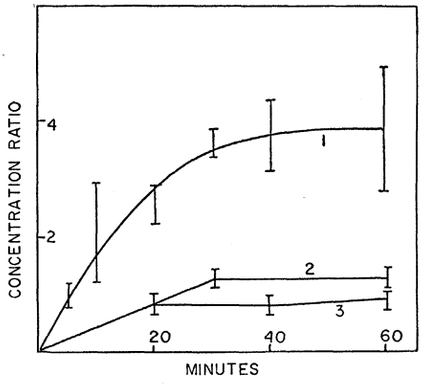

Fig. 1. Ratio of concentration of radioactivity in cat cerebral cortex slices to that in a Krebs bicarbonate medium containing 5 μg of *dl*-norepinephrine-7H^3 per milliliter. Curve 1, control. Curve 2, 24 hours after reserpine (3 mg/kg) was injected intraperitoneally. Curve 3, slices from normal cats incubated in media containing $10^{-5}M$ ouabain. Vertical bars represent standard deviation of values obtained with tissues from eight cats.