Respiratory measurements of cardiac output: from elegant idea to useful test

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Laszlo, Gabriel. Respiratory measurements of cardiac output: from elegant idea to useful test. J Appl Physiol 96: 428–437, 2004; 10.1152/japplphysiol.01074.2001.—The measurement of cardiac output was first proposed by Fick, who published his equation in 1870. Fick’s calculation called for the measurement of the contents of oxygen or CO₂ in pulmonary arterial and systemic arterial blood. These values could not be determined directly in human subjects until the acceptance of cardiac catheterization as a clinical procedure in 1940. In the meanwhile, several attempts were made to perfect respiratory methods for the indirect determination of blood-gas contents by respiratory techniques that yielded estimates of the mixed venous and pulmonary capillary gas pressures. The immediate uptake of nonresident gases can be used in a similar way to calculate cardiac output, with the added advantage that they are absent from the mixed venous blood. The fact that these procedures are safe and relatively noninvasive makes them attractive to physiologists, pharmacologists, and sports scientists as well as to clinicians concerned with the physiopathology of the heart and lung. This paper outlines the development of these techniques, with a discussion of some of the ways in which they stimulated research into the transport of gases in the body through the alveolar membrane. CO₂; acetylene; foreign gas; rebreathing

Knowledge of the factors that limit oxygen delivery to the tissues is essential to an understanding of the limits of human endurance and our ability to adapt to adverse circumstances and to disease. For over 100 years, physiologists have applied much ingenuity and intelligence to the conceptual and technical difficulties associated with the safe measurement of cardiac output in human subjects. In this article, I have tried to outline the intellectual and practical hurdles they had to overcome and to show how these efforts have resulted in our present understanding of respiratory gas exchange.

Fick set out his equation for the measurement of cardiac output in steady states in 1870 (27). It states that the volume output of the heart (Q) can be calculated if the uptake of oxygen (VO₂) is measured and the amount of oxygen in each volume of arterial blood (CAO₂) and mixed venous blood (CVO₂) is known

\[ Q = \frac{V_{O_2}}{C_{O_2}} - C_{V_{O_2}} \]  

This is also valid for CO₂. The principle was applied in 1886 by Grehant and Quinquaud (30) to measure cardiac output in dogs and again by Zuntz and Hagemann in the horse in 1898 (88). It was not until 1929 that Werner Forssmann described how he inserted a catheter into his own heart and walked round the X-ray department to demonstrate its position (28). He planned to inject medicines by this route. This technique was used in a clinical setting 11 years later by Courmand and Richards, who measured the chamber pressures and cardiac output of a New York policeman before and after blood transfusion; from that time it was possible to employ the Fick principle directly in human volunteers and patients. Forssmann, Courmand, and Richards won the Nobel Prize for Medicine in 1950.

Direct sampling from the human pulmonary artery could not be contemplated at the end of the 19th century, and a number of indirect approaches to the measurement of mixed venous gas pressures were developed, employing respiratory techniques. These allowed physiologists in the early part of the 20th century to assess the contribution of the circulation to human adaptation with at least an approximate idea of the quantities involved. The purpose of this article is to recall how the respiratory measurement of cardiac output developed, was engulfed by the emergence of cardiac catheterization and dye dilution techniques, and reemerged with the development of rapid gas analyzers. We shall see that almost all the limitations of these techniques were recognized from the outset.

In the "indirect Fick" procedure, mixed venous gas pressures are estimated and blood-gas contents are derived from knowledge of the chemical combination of the gas with blood at various partial pressures (association-dissociation relationship, usually known as dissociation curve). The uptake or output of the gas is measured, and from this information a version of the Fick equation is used to calculate cardiac output. If arteriolar gas is sampled, the estimate reflects total cardiac output. When pulmonary end-capillary pressure is estimated from expired gas experiment samples, the result is known as the effective pulmonary blood flow, that is, the blood flow to the well-ventilated part of the lung. This is virtually the same as total blood flow when the lungs are normal and a good approximation of it in those diseases in which inspired gas is rapidly distributed to the whole of the alveolar volume. The flow of blood that is not ventilated in the pulmonary capillaries or that is shunted through the heart is not measured.

Two approaches are presently in use: 1) the employment of CO₂ as a test gas and 2) a number of moderately soluble foreign gases; these are absent from the pulmonary venous blood. Nitrous oxide, Freon-22 (now banned), and acetylene have all been used; in the last 5 years, acetylene has supplanted the others in the physiological and clinical literature. Rapid
THE INDIRECT FICK MEASUREMENT EMPLOYING CARBON DIOXIDE

In mild to moderate submaximal exercise, venoarterial pressure differences are relatively wide so small errors of measurement of $P_{CO_2}$ have relatively little effect. Indirect determinations of cardiac output can be achieved with 90% confidence to within $\pm 10\%$ of reference values (85). The measurement depends on the accurate determination of the arterial $P_{CO_2}$. Arterial blood sampling can cause discomfort so transcutaneous and capillary sampling are sometimes used as a less reliable substitute; these are necessary in studying patients in whom there is all but the mildest mismatching of ventilation and perfusion.Physiologists studying subjects with normal lungs have generally used continuous end-tidal sampling with appropriate corrections for the pattern of breathing (70).

Appropriate dissociation curves are needed to convert arteriovenous pressure differences to content differences. Much of the basic work was done by employing mathematical expressions of standard dissociation curves based on analyses in a fairly small number of analyses. These have to be corrected for pH, which alters during exercise because of lactate produced by anaerobic metabolism, for hemoglobin concentration, and, in the case of $CO_2$, for blood oxygen content (21, 29, 79). These corrections have to be applicable to the blood at the time of the gas analysis and are not linear. The degree of lactic acidosis and therefore of pH change varies with age and fitness and in different disease states; therefore, it is difficult in practice to compare groups without accurate estimates of blood pH.

**Rebreathing estimates of oxygenated mixed venous $P_{CO_2}$**

Mixed venous $P_{CO_2}$ is most elegantly determined by the equilibrium method (2, 13, 36). The subject breathes in and out of a bag, slightly greater in volume than the tidal volume, which is primed with a gas containing $CO_2$ at a partial pressure that is slightly higher than the anticipated mixed venous value and sufficient oxygen to maintain normal arterial oxygen saturations throughout the procedure. This results in a plateau of $P_{CO_2}$, which can be recognized visually from the output of a rapid $CO_2$ analyzer. This represents oxygenated mixed venous $P_{CO_2}$, that is, the $P_{CO_2}$ of the mixed venous blood when it has been fully saturated with oxygen in the lung, but has the same $CO_2$ content as the true mixed venous blood that entered the lung. It is higher than true mixed venous because of the Christiansen-Douglas-Haldane effect. This estimate can be used to derive cardiac output, provided that the dissociation curve of fully oxygenated blood is used to derive the venoarterial content difference. This approach assumes that no retained $CO_2$ has recirculated from the tissues and that $CO_2$ equilibrates across the alveolar membrane. Valid results can be obtained by using the same approach with oxygen, but the hypoxia that develops is hazardous in exercise and at rest in subjects with cardiovascular disease (20).

**Alveolar and end-capillary gaseous equilibrium in the lung.**

The idea of estimating blood-gas pressures from alveolar gas measurements arose in the 19th century, but it was not then known whether the pulmonary blood reached equilibrium with the pulmonary capillary blood or whether the lung secreted oxygen as suggested by Ludwig in 1865 (39). Haldane and Priestley wrote (39)

> It was at a time when physiological research was very active in Germany; and friendly, or sometimes anything but friendly, shots were often exchanged between the leading laboratories.

The Leipzig idea was accordingly put to the test by Pflüger and his pupils at Bonn. . . .

This led to three papers. Strassburg (78) described the use of Pflüger’s aerotonometer as an instrument to measure the mixed venous gas pressures of the dog. This was a glass chamber primed with different gases of known concentration into which the blood of the animal was introduced. Blood-gas pressures were deduced from the change of gas concentration in the instrument. Next, Wolfberg (86) used an ingenious technique devised by Pflüger to obtain samples of air in the lungs by introducing a cuffed bronchial catheter into the airway of dogs. Inflation of the cuff effectively isolated the portion of the lung distal to it. Analysis of the gas in the isolated segment should have given the same gas pressures as that in the mixed venous blood if pulmonary gas exchange took place by a process of simple diffusion under these circumstances, whereas differences might be taken to indicate that the lung secreted gases against a diffusion gradient. Wolfberg’s measurements of $P_{CO_2}$ and $P_O_2$ were essentially the same as those obtained by Strassburg in mixed venous blood. Subsequently, Nussbaum (63) measured blood and gas pressures simultaneously in the same animal; the results agreed well, and it was accepted that gas exchange took place by simple diffusion alone.

The secretion theory for oxygen was revived by Bohr (7), and the ensuing argument continued for over 30 years. Bohr and Haldane with his colleagues supported the secretion theory, especially at altitude (37, 38, 39). Unfortunately, they used fallacious methods of measuring blood $P_O_2$. The Kroghs (52) showed that the diffusing capacity of the lung was sufficient to allow equilibrium to be achieved by passive diffusion even under hypoxic conditions and in exercise. They (51, 53) and Joseph Barcroft et al. (4) made reliable measurements and showed that arterial $P_O_2$ never exceeded alveolar $P_O_2$, even under conditions of acclimatization to altitude. This was soon accepted by physiologists (64, 65). The bubble aerotonometer developed by Krogh was used in various forms for over 40 years until blood gas electrodes were developed (69).

During all these vigorous debates, Krogh and Haldane were extremely polite to each other over the equilibration of $CO_2$. The identity of alveolar and arterial $CO_2$ pressures were “in the most complete harmony with the recent work of Haldane and his co-workers on the regulating influence of the $CO_2$ tension on respiration, which postulates that the arterial $CO_2$ tension must follow exactly every change in the alveolar percentage of $CO_2$...” Krogh did, however, observe that $CO_2$ exchange was impaired in animals breathing gas mixtures enriched with $CO_2$ (51).

**Cardiac output by the indirect $CO_2$ method in human subjects.** Clinical physiologists soon began to take an interest in the techniques that were made available as a result of the experiments of Pflüger and Bohr. In 1898, Zuntz and Hagemann (88) cannulated the arterial system and the right ventricle in horses and measured the oxygen and $CO_2$ content of the mixed venous blood. From simultaneous determination of metabolic rate, they were able to calculate pulmonary blood.
flow by Fick’s formula. They obtained consistent results with oxygen but immediately encountered the difficulty experienced by subsequent workers over the next 100 years when making the same calculations with CO\(_2\). The results were inconsistent, and, worse, the ratio of CO\(_2\) output to oxygen consumption was different when calculated from the arteriovenous content difference and from the respiratory measurements, an observation that has been made repeatedly (80). In another monumental study, Loewy and von Schrotter (60) estimated the cardiac output of human volunteers and patients by the first application of the method now known as the indirect Fick procedure. They modified the lung catheter of Pflüger and passed this into a lower lobe bronchus under fluoroscopic control in conscious subjects. The air in the occluded segment was taken to be in equilibrium with mixed venous blood, arterial P\(_{O_2}\) was calculated by Bohr’s formula, and the arteriovenous content difference was derived from dissociation curves, taking into account the oxygen capacity of the patient’s blood. Presumably in the clinical studies, the arterial estimates were incorrect because of pathological increases in dead space. However, they showed that the general principles about the circulation and mixed venous gas pressures in exercise that had been demonstrated in the horse also applied to humans. Loewy and von Schrotter observed that calculations using CO\(_2\) would lead to difficulties because of the wide variation in the position of the CO\(_2\) dissociation curve found in the blood of different individuals. They were also aware of the difficulty with CO\(_2\) (60), so they based their calculations on oxygen. Incidentally, they went to considerable lengths to justify their use of the bronchial cannula by giving reasons why they thought Bohr was wrong about the secretory function of the lung. Their patients appeared to be reasonably comfortable, especially the one with the patent tracheostomy (Fig. 1). Their average mixed venous P\(_{CO_2}\) was reported to be 42.5 Torr and mixed venous P\(_{O_2}\) 37.5 Torr, “embarrassing precision for a pilot study” (20).

The idea of using the whole lung as a tonometer and rebreathing for short periods of time to obtain an estimate of mixed venous gas pressure was first tried by Plesch in 1909 in a study of the circulation (66). He estimated mixed venous oxygen pressure by rebreathing after breathing nitrogen to render the alveoli hypoxic. This was not adopted for clinical studies because of the risk of hypoxia. Rebreathing CO\(_2\) in the presence of oxygen is quite safe, so the indirect CO\(_2\) Fick method was kept in use by various workers, notably Christiansen et al. (15). They and Wardlaw (84) examined the accumulation of CO\(_2\) during prolonged expiration, which may be considered to be breath holding at low lung volumes. Grollman’s account of this (32) reads:

They evolved the following procedure for determining the cardiac output which served as a basis for many subsequent methods: After a deep expiration, a maximal inspiration of CO\(_2\) in air was taken, the breath was held for about five seconds, about a liter was expired through a tube, and an alveolar sample was taken. After an interval the expiration was continued and a second and sometimes a third sample was taken. The CO\(_2\) tension in the venous blood was inferred from its relative concentrations in these various samples. If it agreed in the successive samples, it was assumed that the gas truly represented the mixed venous blood. If it did not, the composition of the gas mixture was altered until the desired constancy of the alveolar samples were obtained. To avoid change in the CO\(_2\) tension of the mixed venous blood due to variation in the oxygen content of the blood, the above method of “straddling” was also applied to the oxygen content which was maintained constant in the successive samples.

It was quickly recognized that rebreathing generated the problem of poor mixing in the early part of the procedure. In techniques involving alveolar sampling after breath holding, the difficulty lay in washing out the dead space. Grollman again:

Burwell and Robinson, [9–11] cognizant of the necessity of having perfect mixture in the lung-bag system and of possible changes in the mixed venous blood, described a procedure aimed at satisfying these demands. Their method consisted of first washing out the subject’s lungs by two respirations from a spirometer containing nitrogen and then equilibrating by rebreathing suitable mixtures of CO\(_2\), oxygen, and nitrogen. This entire procedure required eighteen to twenty seconds and was
Fig. 2. Alveolar gas sampler designed and used by Grollman for the “triple extrapolation” method of measuring mixed venous PCO\textsubscript{2}. Grollman found the mixed venous plateau for CO\textsubscript{2} elusive when using the lung as an aerotonometer. He therefore adapted the method of Redfield et al. (68) to obtain an estimate by extrapolation. After a period of rest breathing through tube C and valve B, the subject inspired deeply from bag D, exhaled, inhaled again, held the breath for a second, and exhaled to mid-capacity through tube E and valve J into bag K. The first alveolar sample was taken through port G. After 5 to 10 s the remainder of the alveolar gas was exhaled and sampled through port H. Six determinations were made. (Reproduced in Ref. 32 with permission from the American Physiological Society.)

repeated seven to eleven times with three-minute intervals. Analysis showed that with proper mixtures in the spirometer and in the bag, a constant CO\textsubscript{2} mixture was attained after the third rebreathing and a constant oxygen mixture after the eighth. After the rebreathing, the subject’s blood was equilibrated in a tonometer with the gas from the rebreathing bag and its oxygen and CO\textsubscript{2} contents determined. The arterial blood was similarly analyzed. The differences of the gas tensions thus obtained plus the value for the respiratory metabolism gave the necessary data for calculating the cardiac output from both the oxygen and CO\textsubscript{2} values. The results of determinations on normal individuals in the resting basal condition as obtained by Burwell and Robinson gave a cardiac index of 1.9 to 2.0 in nine individuals, and 3.5 and 3.7, respectively in two others. Their method thus gave accurate results in nine of the eleven cases studied. The cardiac output of one individual studied at five different times over a period of a year varied from 3.70 to 3.96 liters. . . . [9, 11] Subsequent workers, however, did not utilize this method, being tempted by the easier procedures involving no blood gas analyses. [From Ref. 32, p. 21]

Grollman himself performed a number of background experiments in his quest for a bloodless measurement (31, 33, 61). He showed that an insoluble gas (hydrogen) equilibrated during rebreathing of a 2.5-liter bag in about six breaths (Humphry Davy showed this for six deep inspirations of pure hydrogen in 1800; the equilibration time is reduced if the bag is only slightly larger than the tidal volume to be used; Ref. 18). Grollman described an experiment in which a single subject held his breath for varying lengths of time after two deep breaths of 6% CO\textsubscript{2} in oxygen. A plateau of 45.2–45.6 Torr was achieved between 15 and 20 s, after which PCO\textsubscript{2} rose. When validating his acetylene method, Grollman used a more complicated procedure called the triple extrapolation method for oxygen and CO\textsubscript{2} described by Redfield et al. (68) (Figs. 2 and 3). This was cumbersome but allowed the operator to recognize and reject seriously erroneous readings. There was reasonable agreement between the CO\textsubscript{2} method and Grollman’s acetylene technique, and Grollman dealt skillfully with the problem often faced by investigators wishing to introduce a new method: the new technique was clearly more reproducible and probably more reliable than the reference method. In the 1920s, common sense was often applied to clinical science; only experimental results that made sense to the investigator were accepted (Fig. 3 and legend).

Grollman and his contemporaries realized that in resting subjects very small errors in the estimation of alveolar and rebreathing gas pressures would result in gross errors in the determination of cardiac output because of the small venoarterial pressure difference. The CO\textsubscript{2} method is very sensitive to small changes in ventilation, unlike oxygen consumption. Furthermore, Hamilton and his colleagues questioned its validity physiologically. He showed that the gas phase often did not achieve equilibrium. Moreover, he calculated that the amount of CO\textsubscript{2} that could be accounted for by gas exchange was inadequate and suggested that there must be sequestrated blood and plasma in the lungs (40, 41). The discrepancies were probably due to the use of a bag that was too large so that it was impossible to achieve gas mixing before recirculation and to the CO\textsubscript{2} combining power of lung tissue.

"Rebreathing mixed venous PCO\textsubscript{2}, 1960–2001. Despite all this and the development of alternative methods of estimating cardiac output, physiologists interested in gas exchange have remained attracted to the indirect CO\textsubscript{2} Fick method. The development of rapid physical gas analyzers in 1950 made it possible to observe the process of equilibration, and rapidly repeated attempts at obtaining rebreathing equilibria in the alveolar gas were usually successful. The wide venoarterial
Pco₂ difference in exercise makes it possible to obtain reasonably consistent results for cardiac output. By 1960, there was a considerable volume of information about normal values for cardiac output in exercise by using direct Fick and dye dilution methods. The time was ripe for the reintroduction of easy, safe, noninvasive techniques of estimating oxygenated mixed venous Pco₂ in the clinical setting and for the study of cardiac function; the CO₂ rebreathing method seemed suited to the purpose (17, 19, 36).

One such method was developed by Ashton and McHardy in 1963 (2). The subject rebreathed mixtures of CO₂ in oxygen until a plateau was achieved. Ashton and McHardy described the various types of patterns during rebreathing of CO₂-rich mixtures. They noted that periods of constant alveolar Pco₂ ending with a rise of Pco₂, which was presumed to be due to recirculation, occurred at various levels of Pco₂ depending on the initial concentration of CO₂ in the rebreathing bag. They assumed that recirculation occurred in 6–8 s and that plateaus lasting longer than this were at Pco₂ values higher than oxygenated mixed venous. Venoarterial CO₂ content differences calculated from these estimates accorded well with values in the literature obtained by other methods.

To validate the results, Campbell, Jones, and colleagues tackled the question of the rebreathing estimate of mixed venous Pco₂ in a series of studies. Indicator dilution experiments were performed to obtain independent estimates of cardiac output and to check the assumed values of recirculation time (76). Even at the highest work loads, recirculated dye did not appear until 8 s after injection; usually the time was 10 s. The immediate conclusion was that the method of Ashton and McHardy was based on a false transient equilibration and that true equilibrium with oxygenated mixed venous blood was represented by the alveolar plateaus that lasted from the fifth to the tenth second of rebreathing. When these values were used to calculate cardiac output, the results were consistently lower than those obtained by dye dilution; the latter agreed well with those in the literature for normal subjects under the same conditions using the dissociation curves available to them. Jones et al. (47) therefore measured Pco₂ in the downstream arterial blood leaving the lungs during the rebreathing “plateau.” Pco₂ appeared to fall after leaving the lungs by up to 10 Torr (1.5 kPa) depending on the actual level of mixed venous Pco₂. When cardiac output was calculated from arterial Pco₂ and oxygenated mixed venous Pco₂ corrected downward by an empirically determined factor, good agreement was obtained with dye dilution methods (Fig. 4) (12, 47, 48).

Possible failure of alveolar and arterial Pco₂ equilibration during rebreathing. Positive differences between alveolar Pco₂ and that in blood leaving the lungs and analyzed later were also found during a number of other experiments around 1967 in which CO₂ exchange was abolished (16, 56). At about this time, Gurtner et al. (35) rebreathed one lung in a series of closed-chest anesthetized dogs and demonstrated very large positive alveolar-to-pulmonary arterial Pco₂ differences, which could be as high as 30 Torr (4 kPa) and were dependent on metabolic rate. Similar but smaller gradients were found in other closed-chest preparations (62, 87). Gurtner caused a stir among physiologists by postulating that a negative charge on the alveolar membrane could sustain a gradient of this magnitude and that this might occur elsewhere, such as in the placenta. This was questioned on electrophysiological grounds (23), but more importantly the phenomenon was shown not to occur in the well-perfused excised isolated lung (55, 73) and in isolated lung lobes in open-chest experiments in dogs (57). Gurtner’s findings may have been the result of very low blood flow to the anoxic lung in his closed-chest preparation.

Various suggestions have been put forward to explain how Pco₂ might appear to fall in the circulation during rebreathing experiments after it has left the pulmonary capillaries.

1) Errors in the assumptions regarding the time taken for the blood to reach the artery, the amount of exchange across the endocardium, and the true alveolar temperature might influence the results.

2) Red blood cells and lung tissue, but not plasma, contain carbonic anhydrase, leading to inadequate equilibration during transients of CO₂ and bicarbonate exchange as the blood passes though the lungs. Jones and Heigenhauser (49) suggested that when blood is oxygenated but is prevented from leaving the pulmonary capillaries, the relationship of Pco₂ and CO₂ content is disturbed because of the differences in the red blood cells and plasma and the slowness of chloride-bicarbonate exchange between the red blood cells and the plasma. Campbell (12) suggested that the mixed venous and the arterial blood may not be as stable as is assumed, especially in exercise, which raises the question of the appropriate CO₂ dissociation
slope to use when the arterial and mixed venous blood are estimated at different times. Wasserman and colleagues (79) have, however, presented evidence suggesting that there is no in vivo CO2 disequilibrium except in the presence of carbonic anhydrase inhibitors. This issue has not been resolved, nor has the logical basis for the rebreathing determination of mixed venous Pco2.

To explore the issue of the in vivo CO2 dissociation slope, Winsborough et al. (85) measured cardiac output and the CO2 capacity of the lung tissue in exercise from the rate of rise of Pco2 toward a plateau value during a two-stage procedure employing the calculations of Dubois et al. (22). Allowing for errors in the assumption of the CO2 dissociation slope, the CO2 capacity of the lung was greater than would be expected from simultaneous N2O experiments. There is a suggestion in the literature that the transit time for CO2 may be longer than for other gases (26, 71, 75). In exercise, there may be a large pool of blood in the lungs with a high alveolar ventilation-to-perfusion ratio, which can act as a sump for CO2 either in series or in parallel with the stream of flowing pulmonary blood. Such a sump might hypothetically absorb CO2 from a primed lung bag rebreathing system and release it slowly to produce a false plateau at a higher Pco2 value than the oxygenated mixed venous level.

Practical measurements of oxygenated mixed venous Pco2. The simplest methods involve curve-fitting techniques that enable the plateau to be derived from the rate of rise of Pco2 in the lung bag system during the rebreathing of a CO2 mixture below mixed venous to an end point at around 20 s. Heigenhauser, Jones, and colleagues (1) explored several versions of this technique and showed that an exponential curve fitted to end-tidal Pco2 measurements starting with 4–5% CO2 and ending at 20 s predicted the equilibrium value corrected for the downstream alveolar-arterial difference.

Exponential estimates are most easily used in exercise in subjects with a normal distribution of pulmonary ventilation and perfusion. The equilibrium method described in Fig. 4 is more accurate at rest and in patients with abnormal lungs. It is somewhat difficult to learn and more uncomfortable for the subject; some patients cannot master it. It is still being used to validate curve-fitting techniques that change with each generation of computer software packages (83). In general, the CO2 method is not difficult to learn and requires only a rapid infrared analyzer, a bag, and a valve.

Two experiments devised by Farhi and colleagues (25, 50) deserve mentioning here because they were elegant and influential, although not applicable to patients. The first consisted of measuring PO2 and Pco2 continuously during a long slow expiration. The respiratory exchange ratio (R) was measured continuously throughout the breath, and from this it was possible to derive putative values for alveolar gas that corresponded to the point at which R was 0.82 or equal to the resting value, 0.3 (the true mixed Pco2), and infinity (when CO2 output is zero, at a point corresponding to oxygenated mixed venous Pco2). The CO2 capacity of the lung was ignored. In the second, the rate of rise of end-tidal Pco2 was plotted as it rose by rebreathing toward the previous alveolar value over 10–45 s. Despite complex assumptions, the mean results were similar to the reference method (acetylene).

FOREIGN GAS MEASUREMENTS

Foreign gas uptake measurements have the advantage that the mixed venous concentration of the test substance is zero before recirculation. Gases that do not combine with hemoglobin equilibrate rapidly in the alveoli with blood and plasma, so the alveolar component of the expire represents the mean end-capillary blood. The main limitation imposed by all these methods is the difficulty of defining the time between the alveolar-capillary contact and the sample. In the remainder of this review, I shall describe the evolution of the method as it is performed today, remembering that alveolar gas sampling can only reflect events in the well-ventilated portion of the lung.

Krogh and Lindhard (54) made the first estimates using foreign gases in Copenhagen, and their paper demonstrates a remarkable amalgam of intuition, intellectual rigor, technological ingenuity, and scientific integrity. They noticed that at the onset of exercise oxygen consumption rose very rapidly and deduced from this that since there did not appear to be the slightest reason to believe that any (hypothetical) consumption of oxygen in the lungs themselves should suddenly become more intense, we were forced to the conclusion that the flow of blood through the lungs must be almost instantly increase in about the same proportion as the absorption of O2. . . . This result did not in the least agree with our expectations while it supported definitely the views of Zuntz and Hagemann, Plesch, Bornstein and others as to the blood flow during work. . . . For this purpose we intended to apply the ingenious principle introduced in 1910 by Bornstein [8]. Briefly stated Bornstein principle amounts to this: To produce a definite tension difference between the blood and the alveolar air with regard to a certain neutral gas (e.g., nitrogen) and to measure the quantity of the gas liberated or absorbed during a certain time. On the assumption that the blood leaving the lungs is in tension equilibrium with the alveolar air, the quantity of blood which must have passed during the time can be calculated from these data.

Bornstein used nitrogen, but after trying it Krogh and Lindhard decided that it would be more accurate to use a more soluble gas and switched to nitrous oxide.

Their method and calculation was simple. Either a full breath or two or three normal breaths were taken of 10–25% N2O and 20–25% oxygen (balance nitrogen) from a wedge spirometer (the famous Krogh spirometer that was described in detail in this paper). Two alveolar samples were delivered, at 5 and 15 s, to avoid recirculation. Cardiac output was calculated by measuring the volume of N2O absorbed, knowing the residual volume and the solubility coefficient of nitrous oxide in blood. Interestingly, although Christiansen, Douglas, and Haldane were aware of the presence of the gas storage capacity of lung tissue and of the blood sequestered within the lung, Krogh and Lindhard overlooked this. Other problems recognized by Krogh and Lindhard and their intrepid contemporaries included the need for a normal vital capacity, imperfect gas mixing, and the tendency for N2O to explode while being analyzed.

The next foreign gas to be investigated was ethyl iodide. This was supposed, erroneously, to be destroyed completely in the tissues, thus abolishing the problem of recirculation. It was introduced by Henderson and Haggard (43) and promoted enthusiastically by Starr and Gamble (77). The discovery that it was highly soluble in rubber tubing finished its career after...
some waste of effort, but many useful principles were established over this period.

The next major protagonist was Grollman of the Department of Physiology at Johns Hopkins Medical School, Baltimore. He summarized his extensive work and that of his predecessors in a book published in 1932 that became a standard text (32). Grollman adopted the foreign gas method for its simplicity and developed the method with the use of two different doses of ethylene and also nitrous oxide. He switched to acetylene, which is more useful than ethylene: the latter is soluble in lipids, and therefore its solubility coefficient in blood is variable.

Grollman’s technique and calculation were simple (32). An alveolar sample was taken after rebreathing from a 2.4-liter bag six times in 15 s and again 12 s later. Grollman extended the possibility of an important degree of recirculation by showing that the calculated value of cardiac output did not fall if the test was prolonged. The volume of acetylene in the bag on the two occasions was calculated from the concentrations of ethylene and nitrogen in the two samples. The uptake was considered to be a linear function of time so that the mean alveolar pressure of acetylene was the average of the two readings. The volume of blood passing through the lung during the rebreathing experiments was derived from the mean alveolar gas concentration and the uptake of the gas, knowing its solubility. The uptake of oxygen from the bag divided by the volume of flowing blood yielded the arteriovenous content difference. In this calculation, the volume of the bag and the exact time of rebreathing do not have to be measured because they cancel out. Cardiac output was determined from this, and the oxygen consumption was measured separately in the steady state. Grollman confirmed the subject’s solubility readings in each case. These painstaking experiments yielded cardiac outputs in five subjects averaging 4.1, 4.1, and 4.0 l/min when using low and high ethylene concentrations and N₂O, respectively. Duplicates agreed to within 10% in the same individual and analyses to within 1%. When Grollman changed to acetylene, repeatability was improved to 2% in the same individual.

Grollman was well aware of the now-familiar assumptions on which his method was based: 1) accurate alveolar sampling; 2) homogeneous mixture of the lung-bag system; 3) completion of the experiment before recirculation: constancy of the mixed venous oxygen content; 4) no important degree of absorption of the test gas by the tissues of the lungs and upper and lower airway; and 5) physicochemical equilibrium between the alveolar gas and the blood. This last assumption was tested in two dogs by employing acetylene (33). Interestingly, Baumann and Grollman (6) then compared the acetylene method with the direct Fick method in human subjects by using mixed venous blood obtained by right heart puncture. They regarded this as safer in the human than Forssmann’s technique of catheterization of the great veins. The two methods correlated very strongly in patients with cardiac outputs up to 11 l/min. Their paper was published in German and was summarized in the book. Grollman knew that his subjects had to be in a resting state to achieve reproducible results. Because of this, the patients were assured that the procedure was safe and were not warned about the cardiac puncture.

In the 1920s, peer review took place in the pages of journals, a practice that internet publishing looks likely to revive. Hamilton et al. (42) published a rather personal critique of Grollman’s acetylene work. It contained an experiment in which they ventilated one of a dog’s lungs with oxygen and the other with pure acetylene. Acetylene appeared in the contralateral lung in 8 s, confirming their view that recirculation occurred quite quickly. They thought that Grollman’s results were too low, especially in view of the known increase in cardiac output during forced ventilation. They attributed the consistent results to the small effect on recirculation in the presence of a low output and long circulation time in Grollman’s trained subjects and on the fortuitous canceling out of the effect of recirculation of oxygen and acetylene. In a footnote in his book, then in press, Grollman retorted, “The criticisms of Hamilton, Spradlin and Saam are based on such flagrant misinterpretations, misquotations and misunderstandings of previous work that they merit no serious criticism.” He also thought that the need for arterial puncture made the dye method unlikely to be accepted as a clinical tool. (32). With hindsight, this exchange of rather unfriendly shots ended in a draw.

Grollman’s method reflected changes of cardiac output under various conditions but yielded absolute values that were too low, and it was supplanted by the dye method, to be resuscitated later. Grollman carried out these studies at the start of a long and distinguished career. During his lifetime, he was recognized as an expert in renal physiology and hypertension, but he died in 1980, just after the revival of interest in acetylene as a tool for measuring the circulation (34).

**Foreign gas methods, 1950–2001.** The acetylene and nitrous oxide methods were further refined by Cander and Forster (14). They modified the calculation to allow for the logarithmic decline of the foreign gas concentration with time. They determined the solubility of the gases in lung tissue and showed that allowance should be made for it because it added ~10–20% to the calculated cardiac output, according to the solubility of the test gas (Fig. 5). Their experiments were cumbersome; subjects held their breath for varying lengths of

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Fig. 5. Uptake of nitrous oxide and acetylene during breath holding after inspiration from a bag containing ~10% of the tracer gas in a hyperoxic mixture. After dilution with the residual gas to an initial concentration defined as 1.0, the acetylene concentration declines logarithmically with time until recirculation occurs at ~10 s. Backward extrapolation of the lines through time zero shows that some tracer gas combined with lung tissue and the static blood volume before there was time for the circulation to reduce the concentration of the gas any further. (From Ref. 14.)
time; the alveolar gas concentration was shown to decay exponentially for 15–25 s, followed by recirculation.

Pulmonary blood flow was calculated by a differential equation from the rate of decline of the alveolar gas concentration expressed as a fraction of the “initial” concentration of gas, calculated from the volume inspired and the residual volume. This was the concentration of foreign gas within the lungs after the test inspiration but before any gas had been removed from the alveoli, pulmonary blood, and lung tissue.

Rapid gas analysis made it possible to employ this approach during rebreathing. By 1977 the acetylene rebreathing method had been evaluated fully and compared with dye dilution by Triebwasser et al. (82). By using the lung tissue correction and with attention to details such as rate of breathing and bag and tidal volumes, it was robust and accurate in healthy subjects at rest and in exercise. Since then, open-circuit methods, which are even easier for the subject, have been developed and validated (5, 46).

The accurate determination of lung tissue volume and of the “initial” concentration of acetylene was tackled by Sackner and colleagues (70, 72). The technique involved inspiring traces of carbon monoxide as well as acetylene and an insoluble gas. They reasoned that the rate of carbon monoxide uptake was determined entirely by the contact between the alveolar gas and red blood cells, so that “zero time” could be calculated by backward extrapolation of the semilogarithmic decline of carbon monoxide. However, small variations of lung tissue volume have relatively little effect on the calculation of pulmonary blood flow. Studies in which the acetylene method has been validated against invasive methods have employed the start of the first breath (45, 82). Some studies used a standard value of tissue volume based on body weight for the measurement of cardiac output (70). In theory, this approach would lead to an underestimate of cardiac output when tissue volume is actually elevated above normal.

A single-breath, slow-expiration method has been validated for normal resting subjects and is widely available commercially (SensorMedics). It is difficult to use in heavy exercise and only measures the effective part of the total pulmonary blood flow in the presence of a large physiological shunt, as well as ignoring tissue volume. In practice, the error may be <10% at rest in patients with mild disease (24).

For sports physiologists, acetylene rebreathing remains the most useful method of estimating cardiac output during maximal exercise in athletes because it requires only a reasonably constant blood flow over a few seconds (46). CO₂ rebreathing remains popular because it requires relatively inexpensive equipment.

CURRENT PRACTICE

Cardiac output measurements continue to interest physiologists who study human endurance. Clinical pharmacologists are interested in the effects of treatment on cardiac output. In clinical exercise testing, the measurement of cardiac output is mainly used to measure the stroke volume in patients who show an unexpectedly high heart rate during exercise. A low stroke volume implies impaired cardiac function. If cardiac function is normal and the output is high, the tachycardia is presumed to be due to impairment of the control of the peripheral circulation.

In a sample of 60 papers concerned with indirect Fick measurements published between 1985 and 2001 in five journals (Journal of Applied Physiology, American Review of Respiratory Disease (now AJRCCM), Chest, Clinical Science, and Thorax), CO₂ represented about half, whereas the foreign gases nitrous oxide and Freon-22 (useful but banned) were totally replaced by acetylene by 1995. Of 53 that could be classified, six were clinical, two were concerned with clinical trials, 12 were methods papers, and in a further nine some form of indirect Fick was the reference method; 20 were concerned with physiology. Thirty-three (60%) of these papers dealt with healthy subjects, 10 with respiratory disorders, 7 with circulatory or mixed disorders, and 3 could not be classified. By confining the search to acetylene and CO₂ Fick, it was possible to scan the whole of the Medline library. Between 1985 and 2001, acetylene appeared 55 times and CO₂ 78 times, increasingly in journals dealing with sports physiology. The majority of these, as in the sample, deal with refinements of the technique, including open-circuit gas uptake to avoid rebreathing and subtle curve-fitting methods. From time to time, useful clinical information appears, for example, limitations of stroke volume after pneumonectomy, the lack of any benefit on stroke output of dual-chamber pacing in certain situations, and the different effects of calcium antagonists and beta-blockers on blood flow in exercising hypertensive subjects (44, 58, 81).

Recently, astronauts have been taught to use rebreathing methods in space. Validated modifications of the nitrous oxide (3) and CO₂ (25) methods were used to study the effect of microgravity on the circulation (59, 67, 74). In all of these situations, the repeatability and simplicity of the indirect Fick procedure was valuable, as was the fact that cardiac output is expressed as an absolute value.

In conclusion, the estimation of pulmonary blood flow by the indirect Fick method has provided reference values for a number of populations and led to some useful clinical information. The research needed over 150 years to tackle the theoretical and practical problems posed by these measurements has resulted in many fascinating physiological insights.

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REFERENCES


