The following is the abstract of the article discussed in the subsequent letters:

Sun, Xing-Guo, James E. Hansen, William W. Stringer, Hua Ting, and Karlman Wasserman Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. J Appl Physiol 90: 1798–1810, 2001.—To calculate cardiac output by the indirect Fick principle, CO₂ concentrations (C\text{CO}_2) of mixed venous (C\text{V}_\text{CO}_2) and arterial blood are commonly estimated from P\text{CO}_2, based on the assumption that the CO₂ pressure-concentration relationship (P\text{CO}_2-C\text{CO}_2) is influenced more by changes in Hb concentration and blood oxyhemoglobin saturation than by changes in pH. The purpose of the study was to measure and assess the relative importance of these variables, both in arterial and mixed venous blood, during rest and increasing levels of exercise to maximum (Max) in five healthy men. Although the mean mixed venous P\text{CO}_2 rose from 47 Torr at rest to 59 Torr at the lactic acidosis threshold (LAT) and further to 78 Torr at Max, the C\text{V}_\text{CO}_2 rose from 22.8 mM at rest to 25.5 mM at LAT but then fell to 23.9 mM at Max. Meanwhile, the mixed venous pH fell from 7.36 at rest to 7.30 at LAT and to 7.13 at Max. Thus, as work rate increases above the LAT, changes in pH, reflecting changes in buffer base, account for the major changes in the P\text{CO}_2-C\text{CO}_2 relationship, causing C\text{V}_\text{CO}_2 to decrease, despite increasing mixed venous P\text{CO}_2. Furthermore, whereas the increase in the arteriovenous C\text{CO}_2 difference of 2.2 mM below LAT is mainly due to the increase in C\text{V}_\text{CO}_2, the further increase in the arteriovenous C\text{CO}_2 difference of 4.6 mM above LAT is due to a striking fall in arterial C\text{CO}_2 from 21.4 to 15.2 mM. We conclude that changes in buffer base and pH dominate the P\text{CO}_2-C\text{CO}_2 relationship during exercise, with changes in Hb and blood oxyhemoglobin saturation exerting much less influence.

Carbon Dioxide Pressure-Concentration Relationship in Arterial and Mixed Venous Blood

To the Editor: In this era of molecular biology and genetics, it is a real pleasure for those of us who began our careers in pulmonary physiology in an earlier era to read such a lucid expounding of exercise physiology. I got out my old manuscripts and the original Fortran computer program, as well as a more recent version, using the same equations but now written in C, to see how well the results calculated by my program agreed with the results of the present study. Unfortunately, the present study did not provide enough data on individual subjects or indeed at all levels of exercise (specifically CO₂ production) to calculate cardiac output individually, and the only level for which there was enough information was at maximum exercise.

To use my program, I needed to know the P\text{V}_\text{CO}_2 in fully oxygenated blood, since that is the way the program was designed to operate based on the oxygenated rebreathing method of measuring P\text{V}_\text{CO}_2. Therefore, I took the value of mixed venous whole blood CO₂ content at maximum exercise (23.88 mM) and applied the correction factors of Visser (3) for hemoglobin, actual mixed venous pH, and an O₂ saturation of 100% to derive a theoretical value for oxygenated plasma CO₂ content. I then used the Henderson-Hasselbalch equation to calculate oxygenated P\text{V}_\text{CO}_2, which was 85.9 Torr (compared with actual P\text{V}_\text{CO}_2 in hypoxic blood of 78.1 Torr) and calculated the arterial base deficit (−9.5 mM) using the Siggard-Andersen nomogram. I inserted the value for oxygenated P\text{V}_\text{CO}_2, measured arterial P\text{CO}_2 (37.9 Torr), arterial O₂ saturation, calculated base deficit, and CO₂ output (4.84 l/min) into my program; the value it calculated for cardiac output was 27.9 l/min. This should be compared with the average value found by the present authors (see RESULTS in Ref. 2) of 25.4 l/min. The difference is quite small, especially when allowance is made for the assumptions inherent in estimating the oxygenated P\text{V}_\text{CO}_2 from the whole blood CO₂ content.

My program uses the Visser correction factors for arterial blood desaturation and another correction factor that I derived for the effect of base excess or deficit and hemoglobin on the slope of the logarithmic CO₂ dissociation curve (1). This curve is used to determine the venous-to-arterial CO₂ content difference from the oxygenated venous-to-arterial CO₂ pressure difference.

In summary, the equations and computer program that I described some 31 years ago, which include corrections for acid-base status, appear to perform quite well in comparison with the direct Fick study of Sun et al. (2), even at high work levels and with marked acid-base changes. If the authors of that study would care to send me data for all their subjects at all work levels, I would be happy to calculate all the individual values with my program so that a full comparison could be made.
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To the Editor: The recent paper in the Journal of Applied Physiology by Sun and colleagues (6) on CO2 pressure-concentration relationships in arterial and venous blood during exercise points to the problem of using the traditional approach to acid-base homeostasis by solely considering PCO2, pH, and bicarbonate in any fluid compartment, including blood. The primary observation by Sun and colleagues is that, during exercise above the lactate threshold, the relationship between PCO2 and total CO2 or bicarbonate in arterial or venous blood does not follow the standard relationship defined by the CO2 association curve of blood. The observations are important and demonstrate that the relationships among “acid-base variables” depend not only on PCO2 but also on changes in a number of other entities in the blood. The concept of the relationship between dependent and independent variables in acid-base homeostasis was first put forth by Stewart in 1981 (4, 5) and subsequently has been found to be a useful method of evaluating acid-base status in blood and other body fluids, including cerebrospinal fluid (1, 2).

The gist of Stewart’s formulation is that acid-base homeostasis should be viewed as an interaction between “dependent” and “independent” variables. An independent variable is one that can only be changed from outside the system, whereas a dependent variable cannot be changed directly from outside the system unless one of the independent variables is also altered. In this concept, PCO2 is an independent variable; however, bicarbonate and hydrogen ion concentrations are dependent variables and their values will change only when one or more of the independent variables are changed. The other independent variables are weak acids, strong ions that are completely dissociated (including Na+, K+, Ca2+, Mg2+, and PO43–), and lactate (when the latter is added, as occurs during severe exercise). The bicarbonate concentration at any given point depends on PCO2, on the concentration and dissociation constant of weak acids and bases, and on the difference between the dissociated cations and anions, the so-called strong ion difference. Addition of lactic acid, which then dissociates into the lactate ion and the hydrogen ion, would bring about changes in bicarbonate and hydrogen ion concentrations independent of change in PCO2. Thus the relationship between PCO2 and whole blood CO2 content and bicarbonate will not be, as expected, based on the CO2 dissociation curve of blood. The Stewart approach to acid-base analysis allows for better understanding of mechanisms underlying changes in acid-base homeostasis, and the data presented by Sun and colleagues further confirm that Stewart’s hypothesis is relevant in exhaustive exercise (3) as well as a host of other acid-base disorders.

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REPLY

To the Editor: We thank Dr. Godfrey for his comments and congratulate him for his physiological insights published over three decades ago (1) regarding the modification of relationship between blood PCO2 tension and CO2 concentration by lactic acidosis and other acid-base disturbances. As pointed out by Godfrey and confirmed by our data (3), mixed venous CO2 concentration cannot be calculated from estimated or known mixed venous PCO2 (PVCO2) values without knowledge of the concurrent pH or base deficit.

Dr. Godfrey intelligently used the maximal exercise mean values of our subjects (the actual mixed venous pH, PCO2, hemoglobin, oxyhemoglobin saturation, and CO2 production). Visser’s formula for estimation of oxygenated PVCO2 (as is used with CO2 rebreathing methods for calculating cardiac output), and his published formulas and computer program. He thereby calculated the mixed venous-arterial CO2 concentration differences at peak exercise. His calculated peak cardiac output value, derived from the various assumptions built into his program, differed from the actual value, calculated from our measurements, by only ~10%. However, as Godfrey points out in his letter, there are assumptions inherent in estimating whole blood CO2 content from oxygenated PVCO2, primarily due to the influence of pH. This inability to predict the actual pH of mixed venous blood in normal subjects.
and patients, whether oxygenated or not, even at rest, strikingly decreases the accuracy and utility of estimating cardiac output by CO₂ rebreathing techniques (3).

Fortunately, without addition of special maneuvers and with the use of values obtained during routine noninvasive gas-exchange cardiopulmonary exercise testing, cardiac output can be estimated at the lactate threshold and at maximum exercise with reasonable accuracy in normal subjects and in most patients (2).

In their letter, Drs. Kazemi and Systrom conclude that there are problems using the traditional relationships between PCO₂, pH, and bicarbonate in blood to calculate blood CO₂ concentrations above the lactate threshold due to changes in a number of other entities (ions) in blood (and other fluid compartments). On the contrary, our data clearly show that 1) the Henderson-Hasselbalch equation is valid in both arterial and mixed venous blood (3, 4), 2) the Fick principle of estimating cardiac output is valid using either O₂ or CO₂ concentrations of arterial and mixed-venous blood (4), 3) the change in blood CO₂ concentration during exercise is attributable to the displacement of HCO₃⁻, a volatile anion, by lactate, a fixed anion (5), and 4) estimating mixed venous CO₂ concentration by measuring PᵥCO₂ without knowledge of mixed venous pH leads to gross errors above the lactate threshold (3).

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