The primary role of the heart is to provide energy for the circulatory transport of oxygen \( (O_2) \) to cells at rates commensurate with their metabolic activity. At rest, even a "sick" heart may be capable of transporting \( O_2 \) adequately. But during exercise, the increase in \( O_2 \) required by muscle cells demands that their blood flow be increased. The supply of \( O_2 \) needed to meet the \( O_2 \) requirement for muscle mitochondrial high-energy phosphate generation during exercise is a critical function of the circulation. Thus, the adequacy of cardiovascular function can be estimated, noninvasively, from the pattern of \( O_2 \) uptake in response to an exercise stimulus. While arterial \( O_2 \) tension (\( P_{aO_2} \)) is dependent on pulmonary function (except for intracardiac right-to-left shunt), the mass transfer of \( O_2 \) (\( V_{O_2} \)) between the cells and lungs depends on pulmonary blood flow (i.e., cardiac output) and \( O_2 \) concentration difference between the pulmonary arterial and pulmonary venous blood, \( C(a-v)O_2 \) (Fick principle). Thus, \( V_{O_2} \) in the first 15 seconds of exercise can be used to describe the initial increase in pulmonary blood flow and stroke volume, while the subsequent rise in \( V_{O_2} \) results from the further increase in pulmonary blood flow and widening of \( C(a-v)O_2 \). Abnormal patterns of increase in \( V_{O_2} \) in response to work rate increase are used to detect circulatory disturbances. Also, the rate of \( CO_2 \) output (\( V_{CO_2} \)) has been valuable in the assessment of cardiovascular function when related to \( V_{O_2} \). Inadequate \( O_2 \) availability results in anaerobic metabolism, causing increased muscle lactic acid production. At the pH of cell water, most of the hydrogen ions produced with lactate are buffered by bicarbonate. The \( CO_2 \) generated by the buffering reaction (22 ml for each milliequivalent) causes a net increase in \( V_{CO_2} \) relative to \( V_{O_2} \) at the work rate at which buffering begins. This provides a useful estimate of the anaerobic threshold. Thus, study of the dynamic coupling of external to cellular respiration during a work rate stimulus provides valuable, direct, and noninvasive information about cardiovascular mechanisms in health and disease. (Circulation 1988;78:1060–1071)

It was my privilege to give the Dickinson W. Richards lecture at the 1987 American Heart Association National Meeting. Nobel Prize laureate in physiology, Dickinson W. Richards, with his longtime colleague and Nobel Prize co laureate, Andre Cournand, perhaps more than any other investigators in recent times worked with the hypothesis that the lungs, heart, and pulmonary and systemic circulations form a single system for the exchange of respiratory gases between the environment and the cells of the organism. They recognized that the functions of the heart, peripheral and pulmonary circulations, and the lungs were coupled subsystems of a gas transport system\(^1\) without which life could not exist (Figure 1). Thus, like the lungs, the primary function of the cardiovascular system is gas exchange. Death of the organism occurs with circulatory insufficiency because of inadequate gas exchange between the blood and the tissue cells. While in a healthy state, the gas exchange functions of the heart, peripheral and pulmonary circulations, and the lungs are efficiently coupled, disease states are associated with inefficient coupling at the defect site, ultimately causing a disproportionate increase in ventilation relative to metabolism.

Potential Information From Gas Exchange Analyses

Because of advances in technology that allow continuous measurement of \( O_2 \) uptake and \( CO_2 \) output and computer techniques to reduce data
used dynamic gas exchange responses to specific work rate perturbations to address the central question in cardiovascular medicine—is the cardiovascular system limiting work performance, and if so, which component?

As described by the Fick formulation to calculate cardiac output, oxygen uptake by the lungs is equal to the product of pulmonary blood flow and the pulmonary artery minus pulmonary vein $\dot{V}O_2$ difference, which, in the absence of a right-to-left shunt, equals cardiac output times the arterial–mixed venous oxygen difference ($\dot{V}O_2 = CO \times (a - v)O_2$), where CO is cardiac output. Certainly cardiac output is dependent on cardiac function. $(a - v)O_2$ depends on blood flow as related to the metabolic rate, a cardiovascular function. Thus, mass transfer of oxygen into the pulmonary circulation ($\dot{V}CO_2$) is also a cardiovascular function, but it could be transiently affected by changes in ventilation because of the sigmoid shape of the oxyhemoglobin dissociation curve. Mass transfer of $CO_2$ from the pulmonary circulation ($\dot{V}CO_2$) is also a cardiovascular function, but it could be transiently affected by changes in ventilation because of the relative steepness of the $CO_2$ dissociation curve at physiological values of arterial PCO$_2$. In a steady state such as could be achieved at a moderate work rate intensity for the subject, $\dot{V}O_2$ would be the same for a given work rate for both normal subjects and patients with heart disease. But as the rate of change of $\dot{V}O_2$ in response to exercise depends on the rate of change of cardiovascular function, we have focused on the pattern of rise in $\dot{V}O_2$ rather than on steady-state requirements.

Lung diseases affect the arterial blood gas tensions, but they do not affect $O_2$ uptake dynamics unless these diseases are accompanied by a significant cardiovascular defect (e.g., disease of the pulmonary circulation).

Evidence for Lack of Effect of Ventilation on $\dot{V}O_2$

To demonstrate, experimentally, that $\dot{V}O_2$ in response to exercise is uninfluenced by changes in exercise ventilation, Casaburi et al.9 studied the $\dot{V}O_2$ and $\dot{V}CO_2$ kinetic responses to electrically induced exercise in anesthetized ventilated dogs during controlled exponential changes in ventilation. Regardless of the exponential rate with which the animal’s ventilation was increased by the investigators, the $\dot{V}O_2$ kinetics were unchanged (Figure 2). This is contrasted by the $\dot{V}CO_2$ kinetics (Figure 2). The time constants for $\dot{V}O_2$ and $\dot{V}CO_2$ for all rates of change in ventilation in response to exercise are shown in Figure 3. Changing the time constant of ventilation over a 10-fold range did not change the $\dot{V}O_2$ kinetics.

Further demonstration that $\dot{V}O_2$ increase in response to exercise is uncoupled from the ventilatory response is found in the study by Weissman et al.9 illustrated in Figure 4. In this study, tidal volume and breathing frequency were constrained to the subject’s resting level when starting exercise. Despite no change in ventilation at the start of exercise, $\dot{V}O_2$
increased in a similar pattern to that for unrestrained ventilation. The increase began immediately, primarily because pulmonary blood flow increased, bringing larger amounts of desaturated blood to the alveolar capillaries. After a circulatory delay, \( \dot{V}_O_2 \) increases not only because of increasing pulmonary blood flow but also consequent to progressively increasing \( C(a-V)O_2 \). Because the mass transfer of \( O_2 \) into the pulmonary circulation will not be affected by the falling alveolar \( P_O_2 \) until it has fallen by approximately 30 mm Hg, \( \dot{V}_O_2 \) should increase virtually normally to the subject's "breaking point" when he or she could no longer constrain his or her breathing. In contrast, while \( \dot{V}CO_2 \) initially increased like \( \dot{V}_O_2 \), the subsequent rise in \( \dot{V}CO_2 \) was less rapid because some of the \( CO_2 \) remained in the arterialized blood as alveolar \( PCO_2 \) increased (because of the relatively steep \( CO_2 \) dissociation curve). Consequently, the gas exchange ratio (\( VCO_2:VO_2 \)) decreased progressively during each subsequent breath (Figure 4).

Because of the shape of the oxyhemoglobin dissociation curve, changes in ventilatory pattern and degree of ventilation relative to metabolism do not significantly affect \( VO_2 \) dynamics. Only when the arterial blood is considerably desaturated and \( PACO_2 \) is changed can changes in ventilation affect \( VO_2 \). Thus, the Fick principle, applied to breath-by-breath analyses of \( VO_2 \), can be used to assess cardiovascular function in response to the acute cardiovascular demands of exercise.

**Evidence That Change in Pulmonary Blood Flow Affects \( VO_2 \) Kinetics**

Jones et al.\(^{10}\) demonstrated that increases in heart rate (average increase from 48 to 82 beats/min) in patients with heart block transiently increased \( VO_2 \). Similarly, abruptly decreasing the heart rate transiently decreased \( VO_2 \).

Casaburi et al.\(^{11}\) further demonstrated that the circulatory response to exercise in patients with congenital heart block affects the \( VO_2 \) response. When heart rate was 50 beats/min at rest and failed to increase at the start of exercise, the initial increase in \( VO_2 \) was relatively small in contrast to the increase in \( VO_2 \) when heart rate was abruptly increased from 50 to 100 beats/min at the start of exercise (Figure 5). Similarly, decreasing heart rate at the cessation of exercise resulted in a greater decrement in \( VO_2 \) than if heart rate did not abruptly decrease.\(^{11}\) The steady-state \( VO_2 \) was the same under both paced and nonpaced conditions. Thus,
varying the initial heart rate response only transiently affected the $\dot{V}O_2$ response, as one might expect if pulmonary blood flow were changed acutely by the change in heart rate.

**Phases of the Gas Exchange Responses to Exercise and Their Relation to Cardiovascular Function**

At rest, gas exchange at the lungs is equal to gas exchange at the cells (Figure 2). At the start of moderate intensity exercise, the immediate increase in pulmonary blood flow resulting from increased cardiac inotropy, increased venous return, and increased heart rate causes an abrupt increase in $\dot{V}O_2$ and $\dot{V}CO_2$ (Figure 6, middle panel). Because this phase of mass transfer of O$_2$ and CO$_2$ is due primarily to increase in pulmonary blood flow (phase I), it is referred to as cardiodynamic gas exchange. During this phase, the gas exchange ratio does not change. When gas exchange from the exercising muscles starts to arrive at the lungs (phase II), $\dot{V}CO_2$ rise lags the increase in $\dot{V}O_2$ (Figure 6, middle panel) because CO$_2$ is more soluble in tissues and venous blood than O$_2$ (gas exchange ratio decreases). Thus, $\dot{V}O_2$ during phase II reflects more closely the rate of rise in muscle respiration and has an exponential pattern with a time constant of approximately 30 seconds. A steady state is reestablished within 3 minutes for $\dot{V}O_2$ and 4 minutes for $\dot{V}CO_2$, and gas exchange at the lungs is again equal to cellular gas exchange (phase III).

In normal subjects, the time constant for phase II $\dot{V}O_2$ becomes prolonged for heavy work, while for very light work, it might be extremely short. In contrast, in cardiac patients performing what would be light exercise for normal subjects, phase II $\dot{V}O_2$ kinetics can be quite prolonged and $\dot{V}O_2$ may not reach a steady state by 6 minutes.

**Effect of Posture on Gas Exchange Kinetics**

Stroke volume is known to increase in response to exercise performed in the upright posture but to remain relatively unchanged when performed in the supine position. Weiler-Ravell et al. studied normal subjects when performing the same cycle ergometer exercise in the two positions to determine if...
differences in gas exchange could be detected during phase I. In the upright position, VO₂ abruptly increased at the start of exercise as anticipated by an abrupt stroke volume and heart rate increase (Figure 7). In contrast, VO₂ changed little when starting to cycle in the supine position. That the small increase in VO₂ in the supine position during phase I was primarily attributable to the failure for stroke volume to increase is evident from the concept of O₂-pulse (VO₂/heart rate): VO₂/heart rate = stroke volume × C(a – v)O₂. Because the C(a – v)O₂ would not increase significantly until muscle blood flow reached the lungs, most of the increase in O₂-pulse during the first 15 seconds of exercise must be attributable to the increase in stroke volume. In this study (Figure 7), O₂-pulse increased by 100% (accounting for a possible doubling of stroke volume) at the start of exercise in the upright position, but it changed little in the supine position.

Gas Exchange in Patients With Cyanotic Congenital Heart Disease

Sietsema et al.15 studied patients with cyanotic congenital heart disease to demonstrate the importance of the increase in pulmonary blood flow on oxygen uptake during phase I. Because these patients can perform only very low grades of exercise (i.e., approximately double the resting metabolic rate), the O₂ uptake noise:signal ratio is relatively high. To reduce random breath-by-breath noise and enhance physiologically important information, four to six repetitions of the work rate performed by each subject were averaged. The rationale for using patients with this syndrome is that much of the increase in venous return will pass through the right-to-left shunt rather than enter the pulmonary circulation at the start of exercise. As might be predicted, the increase in VO₂ was found to be substantially diminished compared with normal during phase I (Figure 8). Figure 9 shows the phase I values of the individual subjects compared with a matched group of normal subjects. Three of the nine patients had no increase in VO₂ during phase I, a phenomenon not observed in normal subjects during upright exercise. The mean phase I increase for the patient group was only about one fifth of that of the normal group.

To determine if the size of phase I had physiological significance, Dr. Sietsema and her coworkers15 gave 13 of her patients with cyanotic congenital heart disease questionnaires inquiring into their activity capabilities. The patients were then ranked both with respect to functional activity level and with respect to the size of phase I VO₂. As can be seen in Figure 10, the most limited patients had the smallest phase I responses.

Because VO₂ must reach the same steady-state level for the same work rate in both normal subjects and patients, it is evident that the small phase I observed in the patient group will be complemented by a large phase II. This is in fact the case (Figure 8). Thus, the phase II kinetics can be used as an alternate analysis of impaired increase in pulmonary blood flow caused by disease.

Anaerobic Threshold by V-Slope

It would not be appropriate to discuss cardiovascular assessment by gas exchange without mentioning the anaerobic threshold. The latter has important physiological significance,18 and its measurement has great potential value in diagnosis.2–6,19 The anaerobic threshold can be used to noninvasively assess the metabolic rate at which lactic acidosis occurs.2,6,20 To estimate the anaerobic threshold, we find it advantageous to use an incremental exercise testing protocol in which the work rate is progressively increased over very short intervals of time, such as continuously increasing work rate in a ramp pattern21 or at 1-minute intervals,6 so that the subject reaches his or her maximum work rate in 8–15 minutes (Figure 11). VCO₂ increases as a function of VO₂ in response to aerobic metabolism depending on the muscle substrate. But when anaerobic glycolysis complements aerobic metabolism, such as occurs with heavy exercise, lactic acid accumulates. The latter is over 99% dissociated at cell pH and must be buffered. Bicarbonate is the primary buffer of lactic acid resulting in the formation of carbonic acid, which dissociates to CO₂ and H₂O. Because 22 ml CO₂ is produced for each milliequivalent of lactic acid, which is buffered by HCO₃⁻, CO₂ production increases over that expected from aerobic metabolism in proportion to the rate of increase in lactic acid:

\[
\text{La}^- + \text{H}^+ + \text{HCO}_3^- + \text{K}^+ \rightarrow \text{K}^+\text{La}^- + \text{H}_2\text{O} + \text{CO}_2
\]

The normal response of VCO₂ to increasing VO₂ (work rate) is shown in Figure 12.18 VCO₂ increases linearly with VO₂ with a slope that is slightly less than 1 until the mid-work rate region when the
slope increases to values more than 1. That the anaerobic threshold has been surpassed is shown by the inflection point because the only mechanism to account for this slope steepening is excess CO₂ production secondary to HCO₃⁻ buffering of lactic acid. The steeper the slope, the greater is the rate of bicarbonate buffering of lactic acid. The latter becomes strikingly steep in many patients with cardiovascular disease (Figure 13).

**Vo₂–Work Rate Relation**

After a rest period in which Vo₂ and VCo₂ are measured, our standard incremental exercise protocol allows the subject to cycle on an unloaded cycle ergometer for 3 minutes to establish familiarity with cycling and to warm up. In patients who are considerably impaired, this may be the only work rate performed, and the analysis will have to be done as described above for patients with cyanotic congenital heart disease. For subjects who are less impaired and can be studied during a progressively increasing work rate protocol on a cycle ergometer, Vo₂ will normally increase linearly with a slope of $10.3 \pm 0.8$ ($\pm SD$) ml/min/W until the subject's maximum work rate is reached.²² Because Vo₂ is equal to cardiac output times arterial-mixed venous O₂ difference, Vo₂ often fails to track the increase in work rate in patients with diseases limiting muscle blood flow increase, such as myocardial ischemia or arrhythmias developing during exercise, or in patients with valvular heart disease, cardiomyopathy, congenital heart disease, peripheral vascular disease, or pulmonary vascular disease. Thus, the increase in Vo₂ relative to the increase in work rate may be reduced at a level of work well below the subject's predicted Vo₂ maximum.²²
The study shown in Figure 13 is from that of a 54-year-old man, known to have a vasculitis, who developed considerable dyspnea with exertion. His \( \text{VO}_2 \) did not increase appropriately as work rate was increased (Figure 13A). The evidence for the patient developing a significant lactic acidosis at a low work rate was a low anaerobic threshold and a very steep increase in \( \text{VCO}_2 \) relative to \( \text{VO}_2 \) (Figure 13B). There is little difficulty in defining the work rate above which a lactic acidosis occurs in this patient. The low stroke volume is evident from the low \( \text{O}_2 \)-pulse and its failure to increase appropriately as work rate is increased (Figure 13C). The low, unchanging \( \text{O}_2 \)-pulse implies that \( (a - v)\text{O}_2 \) has reached a maximum value at a low work rate.

**Constraint to \( \text{VO}_2 \) Increase Determines Heart Rate Response**

Finally, I would like to return to the constant work rate protocol to address the interesting physiological interplay between the heart rate response to exercise and the adequacy with which oxygen is supplied to the exercising muscles (Figure 14). The data presented in Figure 14 are taken from the report of Sietsema et al.\(^\text{15}\) As illustrated earlier, phase I \( \text{VO}_2 \) is low in cyanotic congenital heart disease compared with normal, and, at very low

**FIGURE 7.** Gas exchange responses to upright and supine cycle ergometer exercise in a normal subject. See text for detailed description. (From Weiler-Ravell et al.\(^\text{17}\))

**FIGURE 8.** Oxygen uptake in patients with cyanotic congenital heart disease and a matched group of normal subjects. Phase I is the increase in gas exchange resulting from the increase in pulmonary blood flow as described in Figure 6. See text for details. (Data from Sietsema et al.\(^\text{15}\))
work rates, most of the $V_O_2$ increase occurs during phase II. This is in marked contrast to that found for normal subjects who may, for this low work rate exercise, approximate their steady-state $V_O_2$ during phase I. The $O_2$-pulse data are also in marked contrast between the two groups. Phase I increase in $O_2$-pulse is very small in the patient group and large in the normal group. During phase II, $O_2$-pulse rises in both groups because the increase in blood flow goes predominantly through the exercising muscle capillary bed in which the oxygen extraction is high compared with other tissues of the body. Thus, there is a small further increase in $O_2$-pulse during phase II in the normal subject. But the patients have little increase in stroke volume as shown by the small phase I $O_2$-pulse increase. Therefore, to meet the $O_2$ requirement, they depend primarily on widening of the arterial–mixed venous oxygen difference, and the phase II increase dominates the total $O_2$-pulse response in contrast with normal.

Note that the average increase in heart rate during phase I is about the same in both groups (approximately 15 beats/min). However, because of the large phase I increase in oxygen uptake and small further increase in $C(a-v)O_2$ in normal subjects, the oxygen supply to the muscles may be in excess of the steady-state oxygen requirement. Thus, a cardiac output downward correction may be necessary for low work rates in fit subjects during phase II to avoid an unnecessary oversupply of $O_2$. This correction is achieved by a downward readjustment of heart rate.

In contrast, cardiac output and, therefore, heart rate must continue to increase during phase II in patients in whom phase I increase in cardiac output supplied little of the steady-state oxygen requirement. Thus, heart rate must adjust upward in these patients, in contrast to the downward adjustment in normal subjects. The striking difference in the heart rate responses observed in the patients with diseases of the heart and pulmonary circulation in contrast to normal subjects are predictable from the physiological mechanisms operating to deliver the increased $O_2$ required for exercise. These findings suggest that heart rate adjustment during phase II is
based on the concept that the primary function of the cardiovascular system is gas exchange, particularly O₂ transport, between the lungs and the cells. Thus, cardiovascular function can be assessed by the adequacy of the circulatory supply of O₂ in meeting the cellular O₂ requirement under conditions of physical stress. Using less-refined techniques than those available today, Auchincloss et al. showed oxygen uptake kinetics to be slowed in response to exercise in patients with peripheral vascular disease and to improve with revascularization of the ischemic limbs. Taking advantage of new measuring devices and computers to measure O₂ uptake kinetics, we now obtain noninvasive information about cardiovascular function, an approach that was not practical previously. One limitation in this approach is the noise in the data at low work rates because of breathing irregularity. But this is resolved by performing many repetitions, which, when time averaged, reduces random noise and enhances the physiological response.

Abnormally small increases in O₂ use occur in many patients who have electrocardiographic changes suggestive of myocardial ischemia but who do not have pain. This would reflect failure of O₂ to be delivered to the periphery at the increased rate dictated by increasing work rate, a finding that might be expected to occur if myocardial ischemia decreased ventricular contraction. With an impaired cardiovascular response to exercise, oxygen uptake kinetics are likely to be abnormal, although additional information during exercise (e.g., the electrocardiogram, heart rate, blood pressure, and gas...
exchange efficiency) is needed to reveal the site of the defect. I have described the following four gas exchange methods of assessing adequacy of oxygen delivery: 1) the rate of rise of oxygen uptake as related to work rate increase (ml/min/W) during a progressively increasing work rate test; 2) the anaerobic threshold as defined by the V-slope method during a progressively increasing work rate test; 3) the slope of the buffering component of the $V_{\text{CO}_2}$: $V_{\text{O}_2}$ relation during a progressively increasing work rate test; and 4) the magnitude of phase I relative to phase II oxygen uptake kinetics during a constant work rate test. Which of these methods is most sensitive for assessing cardiovascular performance and least influenced by breathing noise is still unknown. Sensitivity might vary with the type of defect (e.g., cardiac, pulmonary vascular, or peripheral vascular) and severity.

**Potential Difficulties in the Interpretation of Adequacy of Tissue Oxygenation During Exercise in Patients With Lung or Combined Lung and Heart Disease**

While the dynamics of gas exchange are affected by disorders of the gas transfer functions illustrated in Figure 1, the increase in $V_{\text{O}_2}$ needed to perform a given work rate in normal subjects and patients with heart and/or lung diseases is the same in the steady state. Also, when assessing cardiovascular function by gas exchange in response to a given work rate, two additional points need to be appreciated: 1) despite the presence of lung disease, there should be no significant error in measuring the mass transfer of oxygen into the body either dynamically (changes in lung $O_2$ stores are relatively small) or in the steady state (as illustrated in Figures 2 and 3) and 2) a steady state in $V_{\text{O}_2}$ (no systematic change in $V_{\text{O}_2}$ with duration of work) cannot be assumed but must be measured. Because of the obviously essential role that the circulation plays in the coupling of pulmonary to cellular gas exchange, the rate of $V_{\text{O}_2}$ increase to steady state, accurately measured, is an important aspect of cardiovascular function. But a significant amount of pulmonary vascular disease accompanying primary lung disease can impair the increase in pulmonary blood flow in response to exercise so that a patient will be cardiovascularly limited although secondary to lung disease. Typical gas exchange abnormalities of pulmonary vascular disease (i.e., ventilation-perfusion mismatching causing an increased physiological dead space: tidal volume ratio, increased arterial–end tidal PCO$_2$ difference, and increased alveolar–arterial O$_2$ difference) distinguish primary heart and peripheral vascular diseases from pulmonary vascular disease. Both cardiac and pulmonary vascular diseases are associated with low output states and tachycardia relative to the oxygen uptake.

In the past, it was thought that the anaerobic threshold could not be determined in patients with lung disease by gas exchange methods. The reason given for this was that patients with obstructive

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**Figure 14.** Oxygen uptake, heart rate, and $O_2$ pulse in response to unloaded cycling exercise in patients with cyanotic congenital heart disease and a matched group of normal subjects. Hypothesized mechanism for the opposite changes in heart rate observed in the patient and normal groups is discussed in the text. $Q_c$, pulmonary capillary blood flow. (Data from Sietsema et al.)
lung disease fail to hyperventilate as part of the ventilatory compensation for metabolic acidosis. While the latter is true, the newly described V-slope method for determining the anaerobic threshold does not rely on the ventilatory compensation for metabolic acidosis as do earlier methods. It depends only on the physical-chemical process of buffering of lactic acid. The amount of CO₂ released relative to oxygen consumed in a progressive exercise test of the type we commonly perform is so great that buffering is readily discerned without hyperventilation. Thus, the V-slope method can be used to detect the anaerobic threshold in patients with severe obstructive lung disease. We find that this new method is far easier to use and more reliable than methods that we and others have previously described and believe that it should be used as the gas exchange method to detect the lactate (anaerobic) threshold.

But when exercise protocols used for testing involve slow increases in work rate, gas exchange reflection of the onset of lactic acidosis might be difficult to detect because the rate of lactic acid accumulation and HCO₃⁻ buffering of the acid is too slow. It should be noted that the increase in CO₂ from HCO₃⁻ buffering of lactic acid is generated only when lactate concentration is increasing. Insensitivity might also be caused by too infrequent gas exchange sampling. Thus, while there are no limitations in the concept of the essential role of the cardiovascular system in gas transport, limitations may be imposed on the sensitivity of gas exchange techniques to detect cardiovascular abnormality by the exercise protocol used to study the patient.

In summary, I attempted to demonstrate that VO₂ increase in response to exercise is a cardiovascular function and that measurements of gas exchange dynamics can be used noninvasively to reveal essential information about cardiovascular function. The application and perfection of these techniques have barely started. But because the information obtained is highly relevant to the questions that cardiologists ask when assessing the cardiovascular function of patients and because these measurements can be used for sequential assessment of cardiovascular function without significant morbidity and at low expense, I think that dynamic gas exchange measurements can play a very important role in diagnostic and therapeutic cardiology.

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