

# Limiting factors for maximum oxygen uptake and determinants of endurance performance

DAVID R. BASSETT, JR. and EDWARD T. HOWLEY

*Department of Exercise Science and Sport Management, University of Tennessee, Knoxville, TN*

## ABSTRACT

BASSETT, D. R., JR. and E. T. HOWLEY. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med. Sci. Sports Exerc.*, Vol. 32, No. 1, pp. 70–84, 2000. In the exercising human, maximal oxygen uptake ( $\dot{V}O_{2max}$ ) is limited by the ability of the cardiorespiratory system to deliver oxygen to the exercising muscles. This is shown by three major lines of evidence: 1) when oxygen delivery is altered (by blood doping, hypoxia, or beta-blockade),  $\dot{V}O_{2max}$  changes accordingly; 2) the increase in  $\dot{V}O_{2max}$  with training results primarily from an increase in maximal cardiac output (not an increase in the a- $\bar{v}$  O<sub>2</sub> difference); and 3) when a small muscle mass is overperfused during exercise, it has an extremely high capacity for consuming oxygen. Thus, O<sub>2</sub> delivery, not skeletal muscle O<sub>2</sub> extraction, is viewed as the primary limiting factor for  $\dot{V}O_{2max}$  in exercising humans. Metabolic adaptations in skeletal muscle are, however, critical for improving submaximal endurance performance. Endurance training causes an increase in mitochondrial enzyme activities, which improves performance by enhancing fat oxidation and decreasing lactic acid accumulation at a given  $\dot{V}O_2$ .  $\dot{V}O_{2max}$  is an important variable that sets the upper limit for endurance performance (an athlete cannot operate above 100%  $\dot{V}O_{2max}$  for extended periods). Running economy and fractional utilization of  $\dot{V}O_{2max}$  also affect endurance performance. The speed at lactate threshold (LT) integrates all three of these variables and is the best physiological predictor of distance running performance. **Key Words:** CARDIORESPIRATORY, FITNESS, EXERCISE, OXYGEN TRANSPORT, MARATHON, RUNNING, RUNNING ECONOMY, LACTATE THRESHOLD

**M**aximum oxygen uptake ( $\dot{V}O_{2max}$ ) is defined as the highest rate at which oxygen can be taken up and utilized by the body during severe exercise. It is one of the main variables in the field of exercise physiology, and is frequently used to indicate the cardiorespiratory fitness of an individual. In the scientific literature, an increase in  $\dot{V}O_{2max}$  is the most common method of demonstrating a training effect. In addition,  $\dot{V}O_{2max}$  is frequently used in the development of an exercise prescription. Given these applications of  $\dot{V}O_{2max}$ , there has been great interest in identifying the physiological factors that limit  $\dot{V}O_{2max}$  and determining the role of this variable in endurance performance.

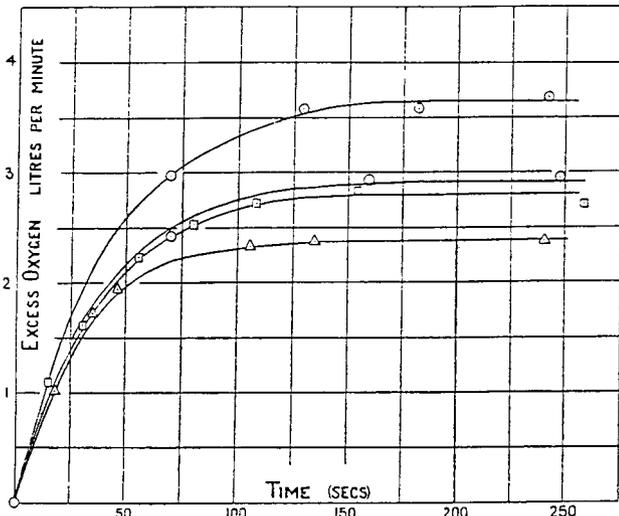
The current concept of  $\dot{V}O_{2max}$  began with the work of Hill et al. (41,42) in 1923–24. Their view of maximum oxygen uptake has been validated, accepted, and extended

by many world-renowned exercise physiologists (2,17,58,68,74,83). However, it has recently been argued that Hill's  $\dot{V}O_{2max}$  paradigm is an outdated concept, based upon critical flaws in logic (62). To consider these points of view, we weighed the arguments on both sides and concluded in 1997 (5) that the "classical" view of  $\dot{V}O_{2max}$  was correct. The present article is an attempt to clarify our views on  $\dot{V}O_{2max}$  and to present further evidence in support of Hill's theory.

Part I of this article reviews the history of the concept of  $\dot{V}O_{2max}$ . Part II describes the evidence for each of the four potentially limiting factors for  $\dot{V}O_{2max}$ . Part III discusses the role of  $\dot{V}O_{2max}$  and other factors in determining endurance performance.

## PART I: HISTORY OF MAXIMUM OXYGEN UPTAKE

The term "maximal oxygen uptake" was coined and defined by Hill et al. (41,42) and Herbst (39) in the 1920s (74). The  $\dot{V}O_{2max}$  paradigm of Hill and Lupton (42) postulates that:



**Figure 1**—The attainment of a “steady state” for oxygen uptake, at several constant running speeds. The horizontal axis depicts time from the start of each run; the vertical axis shows oxygen uptake ( $L \cdot \text{min}^{-1}$ ) in excess of standing. The speeds are 181, 203, 203, and 267  $\text{m} \cdot \text{min}^{-1}$  (from bottom to top). The three lower curves represent a genuine steady state, while in the top curve the oxygen requirement exceeds the measured oxygen consumption. From reference 42. Hill, A. V. and H. Lupton. Muscular exercise, lactic acid, and the supply and utilization of oxygen. *Q. J. Med.* 16:135–171, 1923. Used with permission of Oxford University Press.

1. there is an upper limit to oxygen uptake,
2. there are interindividual differences in  $\dot{V}O_{2\text{max}}$ ,
3. a high  $\dot{V}O_{2\text{max}}$  is a prerequisite for success in middle- and long-distance running,
4.  $\dot{V}O_{2\text{max}}$  is limited by ability of the cardiorespiratory system to transport  $O_2$  to the muscles.

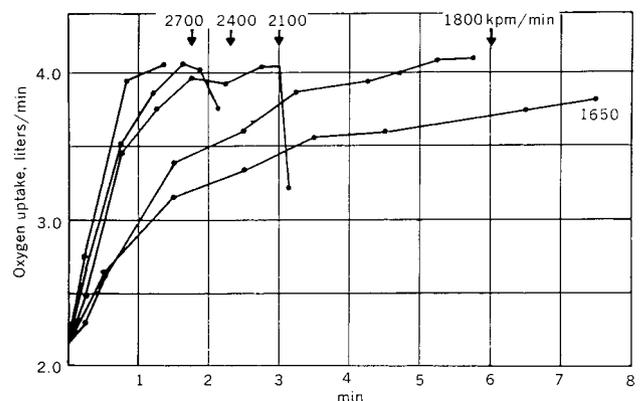
In 1923, Hill and Lupton (42) made careful measurements of oxygen consumption on a subject (A.V.H.) who ran around an 85-m grass track. The graph shown in Figure 1 was drawn primarily for the purpose of illustrating the change in  $\dot{V}O_2$  over time at three speeds (181, 203, and 267  $\text{m} \cdot \text{min}^{-1}$ ). In a study published the following year, Hill et al. (41) reported more  $\dot{V}O_2$  measurements on the same subject. After 2.5 min of running at 282  $\text{m} \cdot \text{min}^{-1}$ , his  $\dot{V}O_2$  reached a value of 4.080  $L \cdot \text{min}^{-1}$  (or 3.730  $L \cdot \text{min}^{-1}$  above that measured at standing rest). Since the  $\dot{V}O_2$  at speeds of 259, 267, 271, and 282  $\text{m} \cdot \text{min}^{-1}$  did not increase beyond that measured at 243  $\text{m} \cdot \text{min}^{-1}$ , this confirmed that at high speeds the  $\dot{V}O_2$  reaches a maximum beyond which no effort can drive it.

Today, it is universally accepted that there is a physiological upper limit to the body’s ability to consume oxygen. This is best illustrated in the classic graph of Åstrand and Saltin (4) shown in Figure 2. In a discontinuous test protocol, repeated attempts to drive the oxygen uptake to higher values by increasing the work rate are ineffective. The rate of climb in  $\dot{V}O_2$  increases with each successive attempt, but the “upper ceiling” reached in each case is about the same. The subject merely reaches  $\dot{V}O_{2\text{max}}$  sooner at high power outputs.  $\dot{V}O_2$  does not continue to increase indefinitely with increases in work rate (or running speed). This finding was predicted by Hill and Lupton ((42), p. 156), who stated that

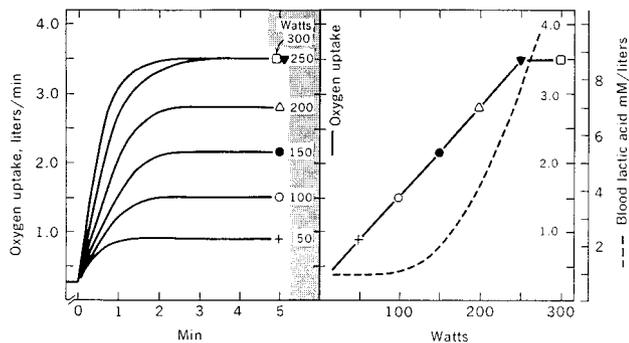
eventually, “. . . however much the speed [or work rate] be increased beyond this limit, no further increase in oxygen intake can occur”.

Not all subjects show a plateau in  $\dot{V}O_2$  at the end of a graded exercise test (GXT), when graphed against work intensity. It has repeatedly been shown that about 50% of subjects do not demonstrate a plateau when stressed to maximal effort (46). Failure to achieve a plateau does not mean that these subjects have failed to attain their “true”  $\dot{V}O_{2\text{max}}$  (26). In the first place, with a continuous GXT protocol a subject may fatigue just as  $\dot{V}O_{2\text{max}}$  is reached. Thus, the plateau may not be evident even though  $\dot{V}O_{2\text{max}}$  has been reached (69). Second, even with a discontinuous GXT protocol most researchers require that a subject complete 3–5 min at each stage (3,26,83). Thus, if a subject reaches  $\dot{V}O_{2\text{max}}$  in 2 min at a supramaximal intensity and then becomes too fatigued to continue, this data point would not be graphed. In this case, the  $\dot{V}O_2$  plateau will not be apparent in the final graph of work rate versus oxygen uptake, even though  $\dot{V}O_{2\text{max}}$  has been attained (Fig. 3). For these reasons, the plateau in  $\dot{V}O_2$  cannot be used as the sole criterion for achievement of  $\dot{V}O_{2\text{max}}$ . This is why it is recommended that secondary criteria be applied to verify a maximal effort. These include a respiratory exchange ratio  $>1.15$  (47) and blood lactic acid level  $>8\text{--}9$  mM (2), an approach that has been confirmed in our laboratory (26).

The  $\dot{V}O_2$  plateau represents a leveling off in cardiac output and a  $\bar{v}O_2$  difference that may be seen toward the end of a GXT. Since the  $\dot{V}O_2$  fails to keep pace with the increasing oxygen demand, there is an increased reliance on oxygen-independent pathways (i.e., anaerobic glycolysis). The significance of the  $\dot{V}O_2$  plateau has often been misinterpreted. In 1988, it was suggested that the absence of a  $\dot{V}O_2$  plateau in some persons meant that  $\dot{V}O_{2\text{max}}$  was not limited by the cardiovascular system (61). This led to the suggestion that “muscle factors” must be important in limiting  $\dot{V}O_{2\text{max}}$ . However, as we pointed out, the  $\dot{V}O_2$  plateau is not the principal evidence for a cardiovascular limitation



**Figure 2**—Time course of the increase in oxygen uptake during heavy exercise on a cycle ergometer. Arrows show the time when the subject stopped exercise because of fatigue. The power output (W) for each bout is also shown. Subject could continue exercising at a power output of 275 W for more than 8 min. From reference 3. Åstrand, P.-O. and K. Rodahl. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970. Used with permission.



**Figure 3—Oxygen uptake and blood lactate response to a discontinuous exercise test.** *Left side* shows the increase in oxygen uptake ( $L \cdot \text{min}^{-1}$ ) over time, with different intensities performed for 5 min each. *Right side* shows the oxygen uptake ( $L \cdot \text{min}^{-1}$ ) graphed against power output (W). Note that a power output of 250 W elicited this subject's  $\dot{V}O_{2\text{max}}$  and that 300 W did not further increase the oxygen uptake. This increase in power output was achieved through anaerobic processes. From reference 3. Åstrand, P.-O. and K. Rodahl. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970. Used with permission.

(5). More recently, it has been suggested that the  $\dot{V}O_2$  plateau signifies a leveling off in cardiac output, caused by progressive and irreversible myocardial ischemia (63). However, there is no evidence to support this view. In fact, a  $\dot{V}O_2$  plateau occurs in about half of all healthy adults performing maximal exertion (46), without accompanying signs or symptoms of myocardial ischemia. A more reasonable explanation is that maximal cardiac output is limited by the maximal rate of depolarization of the sino-atrial (SA) node and the structural limits of the ventricle.

Regarding the variability in  $\dot{V}O_{2\text{max}}$ , Hill and Lupton ((42), p. 158) stated, "A man may fail to be a good runner by reason of a low oxygen uptake, a low maximal oxygen debt, or a high oxygen requirement." This clearly shows that they recognized the presence of interindividual differences in  $\dot{V}O_{2\text{max}}$ . They did not believe in a universal  $\dot{V}O_{2\text{max}}$  of  $4.0 L \cdot \text{min}^{-1}$ , as has been suggested (63). Furthermore, they recognized the importance of a high  $\dot{V}O_{2\text{max}}$  for elite performers (42). They also stated that other physiological factors, such as running economy, would influence the race outcome (42). Subsequent researchers have verified these points (see discussion in Part III).

The fourth point in the  $\dot{V}O_{2\text{max}}$  paradigm has been the most controversial. Hill et al. (41) identified several determinants of  $\dot{V}O_{2\text{max}}$ . Based on the limited data available to them, they speculated that in exercising man,  $\dot{V}O_{2\text{max}}$  is limited by the rate at which  $O_2$  can be supplied by the cardiorespiratory system (heart, lungs, and blood). Over the next 75 years, many distinguished exercise physiologists studied this problem using a wide array of new experimental techniques. They have arrived at a consensus that supports the original  $\dot{V}O_{2\text{max}}$  paradigm of Hill et al. (41). The prevailing view is that in the exercising human  $\dot{V}O_{2\text{max}}$  is limited primarily by the rate of oxygen delivery, not the ability of the muscles to take up oxygen from the blood (see part II).

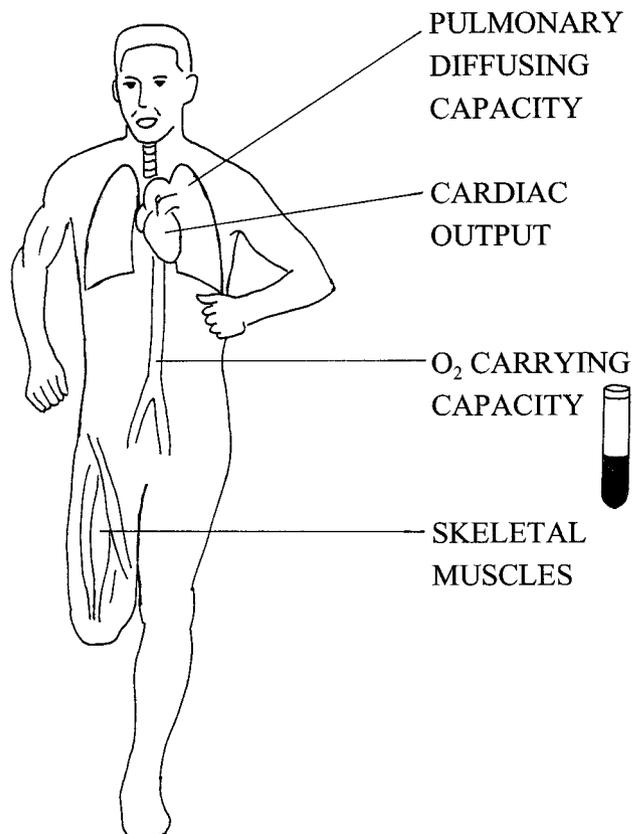
## PART II: LIMITING FACTORS FOR MAXIMUM OXYGEN UPTAKE

The pathway for  $O_2$  from the atmosphere to the mitochondria contains a series of steps, each of which could represent a potential impediment to  $O_2$  flux. Figure 4 shows the physiological factors that could limit  $\dot{V}O_{2\text{max}}$ : 1) the pulmonary diffusing capacity, 2) maximal cardiac output, 3) oxygen carrying capacity of the blood, and 4) skeletal muscle characteristics. The first three factors can be classified as "central" factors; the fourth is termed a "peripheral" factor. The evidence for each of these factors is discussed in the following sections.

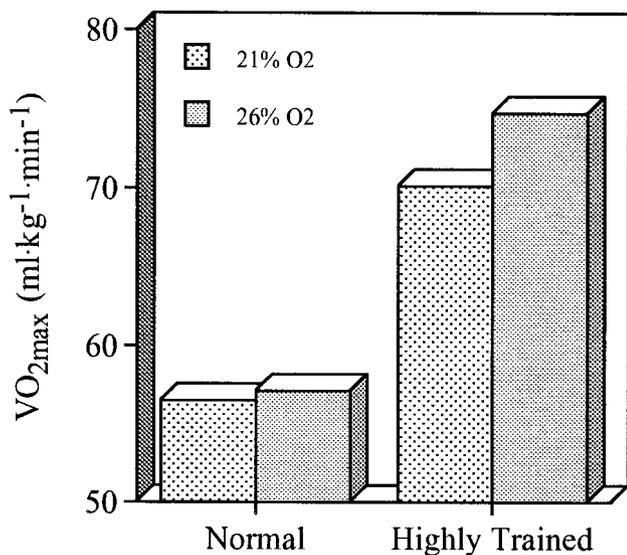
### The Pulmonary System

In the average individual exercising at sea level, the lungs perform their job of saturating the arterial blood with  $O_2$  extremely well. Even during maximal work, the arterial  $O_2$  saturation ( $\%S_aO_2$ ) remains around 95% (65). Hill et al. ((41) p. 161) predicted that a significant drop in arterial saturation ( $S_aO_2 < 75\%$ ) does not occur, based on the appearance of their subjects, "who have never, even in the severest exercise, shown any signs of cyanosis." However, they cautioned against assuming that a complete alveolar-arterial equilibrium is present because of the rapidity of the passage of the red blood cells within the pulmonary capillary at high work rates ((42) p. 155).

Modern researchers have verified that the pulmonary system may indeed limit  $\dot{V}O_{2\text{max}}$  under certain circumstances.



**Figure 4—Physiological factors that potentially limit maximum oxygen uptake ( $\dot{V}O_{2\text{max}}$ ) in the exercising human.**



**Figure 5**—Effects of hyperoxia on maximum oxygen uptake ( $\dot{V}O_{2max}$ ) in normal and highly trained individuals. The highly trained subjects had an increase in  $\dot{V}O_{2max}$  when breathing oxygen-enriched air, showing the presence of a pulmonary limitation in these subjects under normoxic conditions. From reference 65. Powers, S. K., J. Lawler, J. A. Dempsey, S. Dodd, and G. Landry. Effects of incomplete pulmonary gas exchange on  $\dot{V}O_{2max}$ . *J. Appl. Physiol.* 66:2491–2495, 1989. Used with permission.

Dempsey et al. (25) showed that elite athletes are more likely to undergo arterial O<sub>2</sub> desaturation during maximal work compared with normal individuals. Trained individuals have a much higher maximal cardiac output than untrained individuals (40 vs 25 L·min<sup>-1</sup>). This leads to a decreased transit time of the red blood cell in the pulmonary capillary. Consequently, there may not be enough time to saturate the blood with O<sub>2</sub> before it exits the pulmonary capillary.

This pulmonary limitation in highly trained athletes can be overcome with O<sub>2</sub>-enriched air. Powers et al. (65) had highly trained subjects and normal subjects perform two  $\dot{V}O_{2max}$  tests (Fig. 5). In one test the subjects breathed room air and in the other they breathed a 26% O<sub>2</sub> gas mixture. On hyperoxic gas, the highly trained group had an increase in  $\dot{V}O_{2max}$  from 70.1 to 74.7 mL·kg<sup>-1</sup>·min<sup>-1</sup> and an increase in arterial O<sub>2</sub> saturation (S<sub>a</sub>O<sub>2</sub>) from 90.6% to 95.9% during maximal work. None of these changes were observed in normal subjects ( $\dot{V}O_{2max}$  = 56.5 mL·kg<sup>-1</sup>·min<sup>-1</sup>).

Pulmonary limitations are evident in people exercising at moderately high altitudes (3,000–5,000 m) (22,31,53). Individuals with asthma and other types of chronic obstructive pulmonary disease (COPD) suffer from a similar problem (a reduction in arterial PO<sub>2</sub>). Under these conditions, exercise ability can be increased with supplemental O<sub>2</sub>, which increases the “driving force” for O<sub>2</sub> diffusion into the blood (23,67). The ability to increase exercise capacity in this manner shows the presence of a pulmonary limitation.

### Maximum Cardiac Output

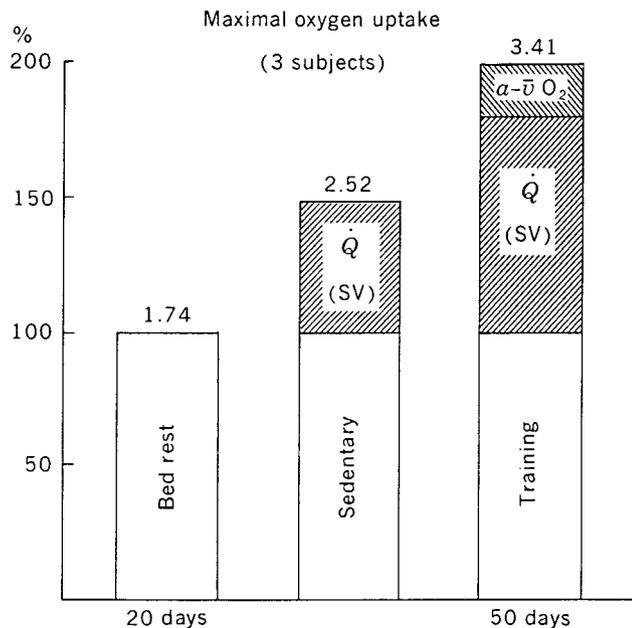
Hill et al. (41,42) proposed that maximal cardiac output was the primary factor explaining individual differences in

$\dot{V}O_{2max}$ . This was a major insight given the state of knowledge in 1923. Einthoven had only discovered electrocardiography a decade earlier. Hill used this new technique to measure maximal heart rates of around 180 beats·min<sup>-1</sup> ((41) p. 165). However, it was not until around 1930 that trained subjects were shown to have a lower heart rate at a fixed, submaximal work rate (11), providing evidence of increased stroke volumes. Other methods of showing enlarged hearts in endurance athletes (x-ray and ultrasound) did not become available until 1940–1950. Given the level of technology in 1923, it is incredible that Hill et al. (41,42) were able to deduce that endurance athletes have hearts with superior pumping capacities. How did they arrive at this remarkable conclusion? In 1915, Lindhard (55) had measured cardiac outputs of 20 L·min<sup>-1</sup> in average subjects during exercise and demonstrated the strong, linear relationship between cardiac output and  $\dot{V}O_2$ . Hill and Lupton ((42), p. 154) speculated that maximal cardiac output values of 30–40 L·min<sup>-1</sup> were possible in trained athletes. These speculations were based on knowledge of the Fick equation and assumed values for  $\dot{V}O_{2max}$ , arterial oxygen content, and mixed venous oxygen content.

Today, we know that the normal range of  $\dot{V}O_{2max}$  values (L·min<sup>-1</sup>) observed in sedentary and trained men and women of the same age is due principally to variation in maximal stroke volume, given that considerably less variation exists in maximal HR and systemic oxygen extraction. During maximum exercise, almost all of the available oxygen is extracted from blood perfusing the active muscles (76). The oxygen content of arterial blood is approximately 200 mL O<sub>2</sub>·L<sup>-1</sup>; in venous blood draining maximally working muscles it falls to about 20–30 mL O<sub>2</sub>·L<sup>-1</sup>. This shows that there is little oxygen left to be extracted out of the blood during heavy exercise. Hence, the dominant mechanism for the increase in  $\dot{V}O_{2max}$  with training must be an increase in blood flow (and O<sub>2</sub> delivery). It is estimated that 70–85% of the limitation in  $\dot{V}O_{2max}$  is linked to maximal cardiac output (10).

Longitudinal studies have shown that the training-induced increase in  $\dot{V}O_{2max}$  results primarily from an increase in maximal cardiac output rather than a widening of the systemic a- $\bar{v}$  O<sub>2</sub> difference (Fig. 6). Saltin et al. (71) examined  $\dot{V}O_{2max}$  in sedentary individuals after 20 d of bed rest and 50 d of training. The difference in  $\dot{V}O_{2max}$  between the deconditioned and trained states resulted mostly from a difference in cardiac output. In a similar study, Ekblom et al. (27) found that 16 wk of physical training increased  $\dot{V}O_{2max}$  from 3.15 to 3.68 L·min<sup>-1</sup>. This improvement in  $\dot{V}O_{2max}$  resulted from an 8.0% increase in cardiac output (from 22.4 to 24.2 L·min<sup>-1</sup>) and a 3.6% increase in a- $\bar{v}$  O<sub>2</sub> difference (from 138 to 143 mL·L<sup>-1</sup>).

One way to acutely decrease the cardiac output is with beta-blockade. Tesch (84) has written an authoritative review of 24 studies detailing the cardiovascular responses to beta blockade. Beta-blockers can decrease maximal heart rate (HR) by 25–30%. In these studies, maximal cardiac output decreases by 15–20%, while stroke volume increases slightly. Although the decreased cardiac output is partially



**Figure 6**—Summary of changes that occur in maximum oxygen uptake ( $\dot{V}O_{2max}$ ) following bed rest and physical training. The higher  $\dot{V}O_{2max}$  under sedentary conditions compared with that under bed rest results from an increased maximal cardiac output. The further increase after training results from an increase in cardiac output and, to a lesser extent, an increase in the  $a-\bar{v} O_2$  difference. From reference 3. Åstrand, P.-O. and K. Rodahl. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970. Used with permission. Data are from reference 71. Saltin, B., B. Blomquist, J. H. Mitchell, R. L. Johnson, K. Wildenthal, and C. B. Chapman. Response to submaximal and maximal exercise after bed rest and after training. *Circulation* 38(Suppl.7):1-78, 1968. Used with permission.

compensated for by an increase in  $a-\bar{v} O_2$  difference,  $\dot{V}O_{2max}$  declines by 5–15%. Tesch (84) concludes that the decline in  $\dot{V}O_{2max}$  seen with cardio-selective beta-blockade is caused by diminished blood flow and oxygen delivery.

### Oxygen Carrying Capacity

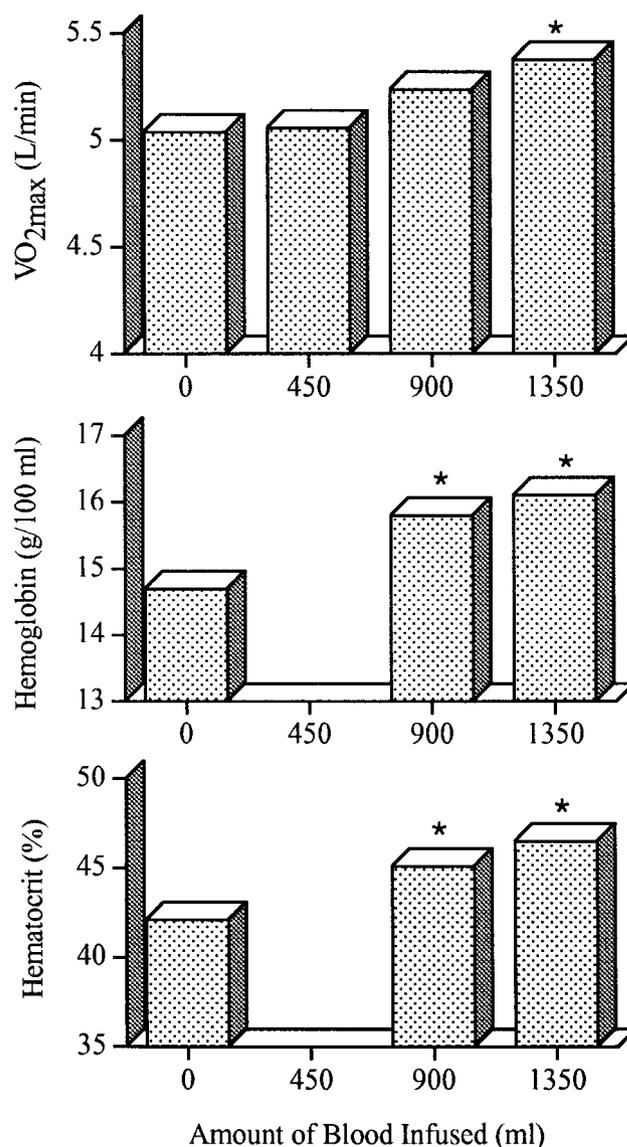
Another method of altering the  $O_2$  transport to working muscles is by changing the hemoglobin (Hb) content of the blood (28). Blood doping is the practice of artificially increasing a person's volume of total red blood cells through removal, storage, and subsequent reinfusion. Gledhill (35,36) completed comprehensive reviews of 15–20 studies that have examined the effects of blood doping. Reinfusion of 900–1,350 mL blood elevates the oxygen carrying capacity of the blood. This procedure has been shown to increase  $\dot{V}O_{2max}$  by 4–9% in well designed, double-blind studies (35,36) (Fig. 7). No improvement is seen in sham-treated individuals, infused with a small volume of saline (8). Once again, these studies provide evidence of a cause-and-effect link between  $O_2$  delivery and  $\dot{V}O_{2max}$ .

The evidence that  $\dot{V}O_{2max}$  is limited by the cardiac output, the oxygen carrying capacity, and in some cases the pulmonary system, is undeniable. This statement pertains to healthy subjects performing whole-body, dynamic exercise. Next we will consider whether skeletal muscle could also be a limiting factor for  $\dot{V}O_{2max}$ .

### Skeletal Muscle Limitations

**Peripheral diffusion gradients.** In a symposium on limiting factors for  $\dot{V}O_{2max}$ , Honig et al. (45) presented evidence for a peripheral  $O_2$  diffusion limitation in red canine muscle. According to their experiments and a mathematical model, the principal site of resistance to  $O_2$  diffusion occurs between the surface of the red blood cell and the sarcolemma. They report a large drop in  $PO_2$  over this short distance. Honig et al. (45) conclude that  $O_2$  delivery *per se* is not the limiting factor. They found that a low cell  $PO_2$  relative to blood  $PO_2$  is needed to maintain the driving force for diffusion and thus enhance  $O_2$  conductance.

The experimental model of Honig et al. (45) is quite different from that seen in an exercising human. They noted



**Figure 7**—Changes in hemoglobin, hematocrit (Hct), and maximum oxygen uptake ( $\dot{V}O_{2max}$ ) following autologous blood transfusions of either 1, 2, or 3 units of whole blood. An increase in the oxygen carrying capacity of the blood results in an increase in  $\dot{V}O_{2max}$ . From: Spriet, L. L., N. Gledhill, A. B. Froese, and D. L. Wilkes. Effect of graded erythrocythemia on cardiovascular and metabolic responses to exercise. *J. Appl. Physiol.* 61:1942-1948, 1986. Used with permission.

that simply increasing blood flow to isolated muscle is not sufficient to cause  $\dot{V}O_2$  to increase. The isolated muscle must also undergo contractions so that the mitochondria consume  $O_2$  (drawing down the intracellular  $PO_2$ ). Without a peripheral diffusion gradient, oxygen uptake will not increase. Their overall conclusion is that  $\dot{V}O_{2max}$  is a distributed property, dependent on the interaction of  $O_2$  transport and mitochondrial  $O_2$  uptake (45). We agree with this conclusion. However, this model cannot determine which of these two factors limits  $\dot{V}O_{2max}$  in the intact human performing maximal exertion.

**Mitochondrial enzyme levels.** Physiologists have done extensive work to examine whether mitochondrial enzyme levels are a limiting factor for  $\dot{V}O_{2max}$ . Within the muscle fibers, the mitochondria are the sites where  $O_2$  is consumed in the final step of the electron transport chain. In theory, doubling the number of mitochondria should double the number of sites for  $O_2$  uptake in muscle. However, human studies show that there is only a modest increase  $\dot{V}O_{2max}$  in (20–40%) despite a 2.2-fold increase in mitochondrial enzymes (72). This is consistent with the view that  $\dot{V}O_{2max}$ , measured during whole-body dynamic exercise, is limited by oxygen delivery (not muscle mitochondria).

Shephard (76) has asked, “If we reject the view that there is a significant limitation of oxygen transport at the tissue level, what alternative explanation can be offered to the teleologists to account for the doubling of tissue enzyme activity during endurance training?” In their landmark 1984 review paper, Holloszy and Coyle (44) propose an answer to this question. They argue that as a consequence of the increase in mitochondria, exercise at the same work rate elicits smaller disturbances in homeostasis in the trained muscles. Two metabolic effects of an increase in mitochondrial enzymes are that 1) muscles adapted to endurance exercise will oxidize fat at a higher rate (thus sparing muscle glycogen and blood glucose) and 2) there is decreased lactate production during exercise. These muscle adaptations are important in explaining the improvement in endurance performance that occurs with training. (This will be discussed further in Part III.)

The main effect of increasing mitochondrial enzymes is to improve endurance performance rather than to increase  $\dot{V}O_{2max}$ . Holloszy and Coyle (43,44) note that even in individuals with nearly identical  $\dot{V}O_{2max}$  values there can be a two-fold range in mitochondrial enzymes (1976). Furthermore, low-intensity training may elicit small changes in mitochondrial enzymes without any change in  $\dot{V}O_{2max}$ , and *vice versa* (38,52,64). On the other hand, there is some evidence that the increase in mitochondria play a permissive role in allowing  $\dot{V}O_{2max}$  to increase. Holloszy and Coyle (44) note that the lowest value for SDH activity in the elite runners studied by Costill (16) was still 2.5-fold greater than that found for untrained individuals in the same study. The increase in muscle mitochondria may allow a slightly greater extraction of  $O_2$  from the blood by the working muscles, thus contributing in a minor way to an increased  $\dot{V}O_{2max}$  (44).

**Capillary density.** In 1977 Andersen and Henriksson (1) showed that capillary density increases with training. Other studies noted a strong relationship between the number of capillaries per fiber in the vastus lateralis and  $\dot{V}O_{2max}$  ( $mL \cdot kg^{-1} \cdot min^{-1}$ ) measured during cycle ergometry (72). The main significance of the training-induced increase in capillary density is not to accommodate blood flow but rather to maintain or elongate mean transit time (70). This enhances oxygen delivery by maintaining oxygen extraction ( $a-\bar{v} O_2$  difference) even at high rates of muscle blood flow. The ability of skeletal muscle to adapt to training in this way is far greater than what is observed in the lung (24).

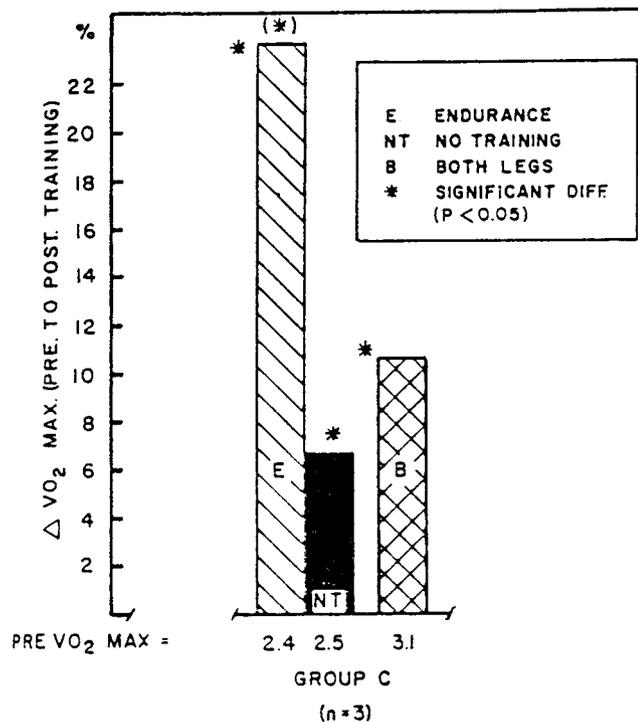
## Central or Peripheral Limitation?

The issue of central versus peripheral factors limiting  $\dot{V}O_{2max}$  has been a long-standing debate. Work conducted in the early 1970s supported the idea of central factors being limiting for  $\dot{V}O_{2max}$ . Clausen et al. (12) showed that two-legged bicycle training resulted in an increase in arm  $\dot{V}O_{2max}$ . They correctly interpreted this as evidence of a central cardiovascular training effect.

In 1976 Saltin et al. (73) examined the effects of one-legged cycle training on the increase in  $\dot{V}O_{2max}$  in a trained leg, a control leg, and 2-legged bicycling. The trained leg had a 23% increase compared with a 7% increase in  $\dot{V}O_{2max}$  in the control leg (Fig. 8). The disparity between legs was attributed to peripheral adaptations occurring within the trained skeletal muscle. The authors concluded that peripheral factors were dominant in limiting  $\dot{V}O_{2max}$ . This study was conducted during the 1970s as new discoveries about fiber type, capillary density, and oxidative enzyme activities in athletes were being made. At that time, the investigators thought that these changes were essential for increasing  $\dot{V}O_{2max}$  (73).

However, in 1985 Saltin et al. (70) performed the definitive experiment showing that  $\dot{V}O_{2max}$  is limited by blood flow. They observed what happens when a subject does maximal exercise using only a small muscle mass (i.e., knee extensions with only one leg). This allowed a greater proportion of cardiac output to be directed to an isolated area. Under these conditions, the highest  $O_2$  uptake in an isolated quadriceps muscle group was 2–3 times higher than that measured in the same muscle group during a whole-body maximum effort. They concluded that skeletal muscle has a tremendous capacity for increasing blood flow and  $\dot{V}O_2$  (70), which far exceeds the pumping capacity of the heart during maximal whole-body exercise. This experiment proved that  $\dot{V}O_{2max}$  is constrained by oxygen delivery and not by the mitochondria's ability to consume oxygen.

How can we reconcile the results of the two experiments by Saltin et al. (70,73)? In the earlier study, they measured  $\dot{V}O_{2max}$  during one-legged cycling. However, it must be remembered that maximal cardiac output is not the dominant factor limiting  $\dot{V}O_{2max}$  in exercise with an isolated muscle group (i.e., one-legged cycling) (66). Whole-body  $\dot{V}O_{2max}$  is primarily limited by cardiac output, while for exercise with small muscle groups the role of cardiac output



**Figure 8**—Effects of one-legged cycle training on  $\dot{V}O_{2\max}$  in the trained leg, untrained control leg, and both legs. Training consisted of four to five sessions of endurance training at 75%  $\dot{V}O_{2\max}$  (1 leg), 35–45 min per session, for 4 wk. This study provided support for the role of peripheral adaptations. From reference 73. Saltin, B., K. K. Nazar, D. L. Costill, et al. The nature of the training response: peripheral and central adaptations to one-legged exercise. *Acta Physiol. Scand.* 96:289–305, 1976. Used with permission.

is considerably less important (10). Since the 1976 conclusion about peripheral limitations does not apply to  $\dot{V}O_{2\max}$  measured in severe whole-body exercise, the later conclusion does not conflict with their earlier work. The current belief is that maximal cardiac output is the principal limiting factor for  $\dot{V}O_{2\max}$  during bicycling or running tests (66).

### Comparative Physiology and Maximum Oxygen Uptake

Taylor et al. (79,80,82) and Weibel (87) have studied the physiological factors limiting  $\dot{V}O_{2\max}$  from a different perspective. They examined different animal species to see what physiological factors explain the superior  $\dot{V}O_{2\max}$  of the more athletic ones. These studies in comparative physiology provide a way to test the concept of “symmorphosis” which hypothesizes that animals are built in a reasonable manner. Their underlying assumption is that all parts of the pathway for  $O_2$  (from atmosphere to mitochondria) are matched to the functional capacity of the organism. If any one system involved in the  $O_2$  pathway were overbuilt, then there would be a redundancy that would be wasteful, from an energetic standpoint.

The first series of experiments compared mammalian species of similar size, but with a 2.5-fold difference in  $\dot{V}O_{2\max}$  (dog vs goat, racehorse vs steer) (49,81). This is referred to as “adaptive variation” (adaptation was defined in the evolutionary sense, as the end-result of natural selec-

tion). The high  $\dot{V}O_{2\max}$  values in the more athletic species were accompanied by a 2.2-fold increase in stroke volume, nearly identical maximal heart rate, and a large increase in mitochondria (49,81). In general, these adaptive pairs show similar physiological differences as observed when trained and untrained humans are compared (Table 1).

A second series of experiments examined a variety of animal species ranging in size from a few grams to 250 kg (79). The difference in  $\dot{V}O_{2\max}$  seen in animals of varying body mass ( $M_b$ ) is termed “allometric variation.”  $\dot{V}O_{2\max}$  values ( $L \cdot \text{min}^{-1}$ ) increase with body mass to the power of 0.81. However, when adjusted for body mass, small animals have  $\dot{V}O_{2\max}/M_b$  values that are 8–10 times higher than large animals (Fig. 9). Across a wide range of animal species, there is a very close match between mitochondrial density and  $\dot{V}O_{2\max}/M_b$  (80). The smaller species have an abundance of mitochondria, so that the capacity of the muscles to consume oxygen is enhanced. It would be impossible for the smaller species to achieve such incredibly high metabolic rates (200 to 260  $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) without an increase in mitochondrial density. Thus, it can be said that the muscles “set the demand for  $O_2$ ” (80).

The more athletic animals also have an increase in the size of the structures involved in supplying  $O_2$  to the working muscles. Lung size and function are scaled in proportion to  $\dot{V}O_{2\max}$ . In addition, the heart’s pumping capacity is tightly coupled to  $\dot{V}O_{2\max}$ . In adaptive variation (animals of same size), the more athletic animals achieve this by an increase in heart size (80). In allometric variation, small animals achieve an increase in  $O_2$  transport with a higher maximal heart rate (1300  $\text{beats} \cdot \text{min}^{-1}$  in the shrew) ((87), p. 400). The general conclusion of these studies is that the principle of symmorphosis is upheld (80). The structures involved in the  $O_2$  pathway are scaled in proportion to  $\dot{V}O_{2\max}$ , meaning that animals are built in a reasonable manner (88).

However, there are exceptions where one sees redundancies at various levels in the pathway for  $O_2$ . For example, the mitochondria’s ability to consume  $O_2$  exceeds the ability of the cardiorespiratory system to supply it (80). To illustrate this point, in maximally exercising animals the mitochondria have a fixed respiratory capacity, with an invariant value of 4–5  $\text{mL } O_2 \cdot \text{mL}^{-1}$  of mitochondria per minute across species (80). However, the respiratory capacity of isolated mitochondria has been measured at 5.8  $\text{mL } O_2 \cdot \text{mL}^{-1}$  of mitochondria per minute (75). Using these values, Taylor and Weibel (80) conclude that animals are able to exploit 60–80% of the *in vitro* oxidative capacity when they exercise at  $\dot{V}O_{2\max}$ . The reason that mitochondria cannot fully exploit their oxidative ability is a result of the limitation on  $O_2$  delivery imposed by the central cardiovascular system.

### Reaching Consensus on Limiting Factors for Maximum Oxygen Uptake

Physiologists have often asked, “What is the limiting factor for  $\dot{V}O_{2\max}$ ?” The answer depends on the definition of

TABLE 1. Body mass and oxygen transport parameters of the cardiovascular system in horses and steers, during maximal exercise (mean  $\pm$  SD). Adapted from Jones et al. (J. Appl. Physiol. 67:862–870, 1989).

	Body mass (kg)	$\dot{V}O_{2\max}$ (mL $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup> )	HR <sub>max</sub> (beats $\cdot$ min <sup>-1</sup> )	CO <sub>max</sub> (L $\cdot$ min <sup>-1</sup> )	C <sub>a-v</sub> O <sub>2</sub> (ml O <sub>2</sub> $\cdot$ L blood <sup>-1</sup> )	Hct (%)
Horses (N = 4)	453 $\pm$ 34	134 $\pm$ 2	202 $\pm$ 7	288 $\pm$ 22	213 $\pm$ 13	55 $\pm$ 2
Steers (N = 3)	449 $\pm$ 9	51 $\pm$ 1	216 $\pm$ 5	143 $\pm$ 1	161 $\pm$ 3	40 $\pm$ 2

$\dot{V}O_{2\max}$ , maximum oxygen uptake; HR<sub>max</sub>, maximal heart rate; CO<sub>max</sub>, maximal cardiac output; C<sub>a-v</sub>O<sub>2</sub>, maximum arterio-venous oxygen difference; Hct, hematocrit.

a limiting factor and the experimental model used to address the problem (R.B. Armstrong, personal communication, February, 1999). If one talks about the intact human being performing maximal, whole-body exercise, then the cardio-respiratory system is the limiting factor (36,74,84). If one discusses the factors that limit the increase in  $\dot{V}O_2$  in an isolated dog hindlimb, then the peripheral diffusion gradient is limiting (45). If one talks about the factors that explain the difference in  $\dot{V}O_{2\max}$  across species, mitochondrial content and O<sub>2</sub> transport capacity are both important (80).

Wagner, Hoppeler, and Saltin (86) have succeeded in reconciling the different viewpoints on factors limiting  $\dot{V}O_{2\max}$ . They conclude that while  $\dot{V}O_{2\max}$  is broadly related to mitochondrial volume across a range of species, in any individual case  $\dot{V}O_{2\max}$  is determined by the O<sub>2</sub> supply to muscle. They state that in humans “. . . the catabolic capacity of the myosin ATPase is such that it outstrips by far the capacity of the respiratory system to deliver energy aerobically. Thus,  $\dot{V}O_{2\max}$  must be determined by the capability to deliver O<sub>2</sub> to muscle mitochondria via the O<sub>2</sub> transport system, rather than by the properties of the muscle’s contractile machinery (86).”

Wagner, Hoppeler, and Saltin (86) maintain that there is no single limiting factor to  $\dot{V}O_{2\max}$ . They conclude that “. . . each and every step in the O<sub>2</sub> pathway contributes in an integrated way to determining  $\dot{V}O_{2\max}$ , and a reduction in

the transport capacity of any of the steps will predictably reduce  $\dot{V}O_{2\max}$  (85,86).” For instance, a reduction in the inspired PO<sub>2</sub> at altitude will result in a decreased  $\dot{V}O_{2\max}$  (22,31,53). A reduced hemoglobin level in anemia will result in a decreased  $\dot{V}O_{2\max}$  (36,78). A reduction in cardiac output with cardioselective beta-blockade will result in a decreased  $\dot{V}O_{2\max}$  (84). There are also instances where substrate supply (not O<sub>2</sub>) is the limiting factor. For example, metabolic defects in skeletal muscle, such as McArdle’s disease (phosphorylase deficiency) or phospho-fructokinase deficiency, will result in a decreased  $\dot{V}O_{2\max}$  (54).

In the field of exercise physiology, when limiting factors for  $\dot{V}O_{2\max}$  are discussed, it is usually with reference to human subjects, without metabolic disease, undergoing maximal whole-body exercise, at sea level. Under these conditions, the evidence clearly shows that it is mainly the ability of the cardiorespiratory system (i.e., heart, lungs, and blood) to transport O<sub>2</sub> to the muscles, not the ability of muscle mitochondria to consume O<sub>2</sub>, that limits  $\dot{V}O_{2\max}$ . We conclude that there is widespread agreement with regard to the factors limiting  $\dot{V}O_{2\max}$ , and that this agreement is based on sound scientific evidence. In general, the 75 years of subsequent research have provided strong support for the brilliant insights of Hill et al. (41,42).

### PART III: DETERMINANTS OF ENDURANCE PERFORMANCE

A first principle in exercise physiology is that work requires energy, and to maintain a specific work rate or running velocity over a long distance, ATP must be supplied to the cross bridges as fast as it is used. As the duration of an all-out performance increases there is greater reliance on ATP production via oxidative phosphorylation to maintain cross bridge cycling. Consequently, the rate at which oxygen is used during prolonged submaximal exercise is a measure of the rate at which ATP is generated. In our previous paper (5) we summarized the conventional understanding of how oxygen uptake is linked to endurance running performance. A variety of criticisms were directed at our attempt, ranging from suggestions that correlation data were being used to establish “cause and effect,” to concerns that our model was not adequately explained (63). In the following paragraphs we will summarize the physiological model linking oxygen uptake with performance in distance running.

Figure 10 shows that the  $\dot{V}O_2$  maintained during an endurance run (called the “performance  $\dot{V}O_2$ ” by Coyle (19)) is equal to the product of the runner’s  $\dot{V}O_{2\max}$  and the percent of  $\dot{V}O_{2\max}$  that can be maintained during the

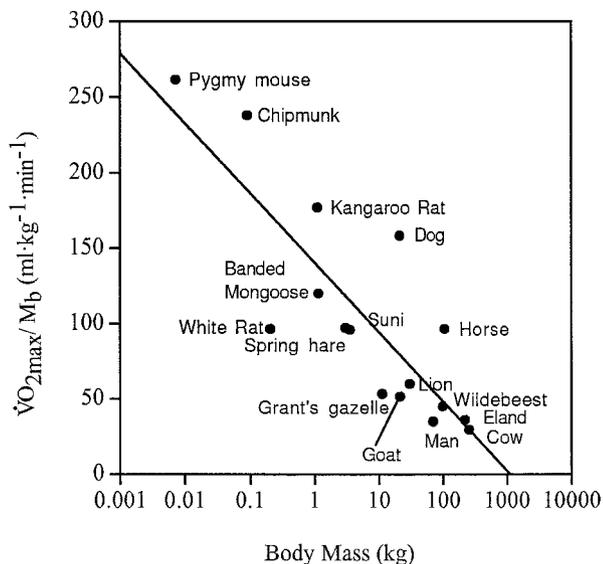
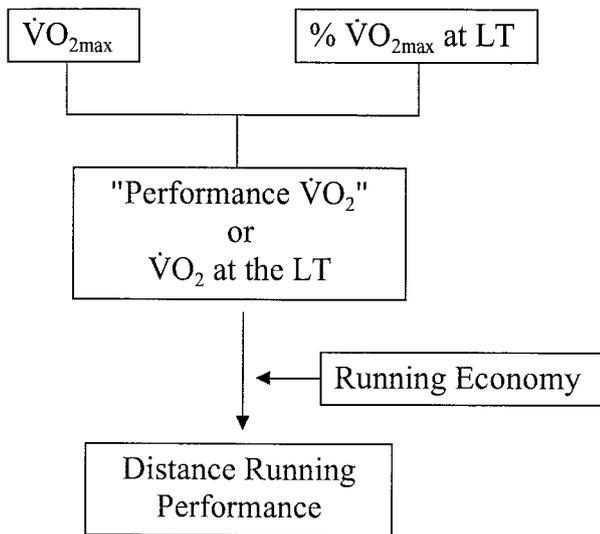


Figure 9—Maximum oxygen uptake ( $\dot{V}O_{2\max}/M_b$ , in mL $\cdot$ kg<sup>-1</sup> $\cdot$ min<sup>-1</sup>) of various animal species in relation to body mass ( $M_b$ ). The smaller animals have incredibly high  $\dot{V}O_{2\max}/M_b$  values, which are made possible by an increased mitochondrial density (which enables their muscles to consume more oxygen) as well as an increased capacity for oxygen transport.



**Figure 10**—Simplified diagram of linkages between maximal aerobic power ( $\dot{V}O_{2max}$ ), the percent of maximal aerobic power (%  $\dot{V}O_{2max}$ ) and running economy as they relate to distance running performance.

performance. The percent of  $\dot{V}O_{2max}$  is related to the  $\dot{V}O_2$  measured at the lactate threshold (LT), so that for endurance events the performance  $\dot{V}O_2$  is closely linked to the  $\dot{V}O_2$  at the LT. The  $\dot{V}O_{2max}$  is limited primarily by central cardiovascular factors (see Part II above), while the percent of  $\dot{V}O_{2max}$  that can be maintained is linked primarily to adaptations in muscles resulting from prolonged training (44). The actual running velocity realized by this rate of oxidative ATP generation (the performance  $\dot{V}O_2$ ) is determined by the individual's ability to translate energy (e.g., running economy) into performance (19,20). We will again summarize the role of each of these variables in distance running performance.

### Role of Maximum Oxygen Uptake in Running Performance

Previously we stated that " $\dot{V}O_{2max}$  sets the upper limit for performance in endurance events" (5), not that it is "the best predictor of athletic ability" ((63), p. 1381). Data of Costill et al. (17) were presented to show an inverse correlation ( $r = -0.91$ ) between  $\dot{V}O_{2max}$  and time in a 10-mile run. These investigators used subjects with a wide range of  $\dot{V}O_{2max}$  values (54.8 to 81.6 mL·kg<sup>-1</sup>·min<sup>-1</sup>) to examine this relationship. This was an appropriate research design to see whether a correlation existed between these two variables in that such a relationship must be evaluated over an appropriate range of values. If one were to narrow the range of values over which this relationship was examined, the correlation coefficient would approach zero as the range of values approaches zero. Consequently, we acknowledged the fact that  $\dot{V}O_{2max}$  was not a good predictor of performance in runners with similar  $\dot{V}O_{2max}$  values ((5) p. 598). If Costill et al. (17) had found the correlation between  $\dot{V}O_{2max}$  and time in a 10-mile run in this diverse group of runners to be  $r = -0.09$  rather than  $r = -0.91$ , there would have been little debate. We are in agreement that a high correlation

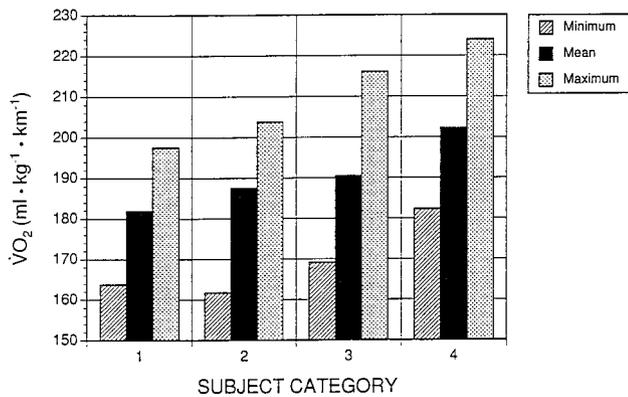
does not imply "cause and effect;" however, to simply dismiss a high correlation between two variables having high construct validity might result in an investigator missing an important point.

$\dot{V}O_{2max}$  is directly linked to the rate of ATP generation that can be maintained during a distance race, even though distance races are not run at 100%  $\dot{V}O_{2max}$ . The rate of ATP generation is dependent on the  $\dot{V}O_2$  (mL·kg<sup>-1</sup>·min<sup>-1</sup>) that can be maintained during the run, which is determined by the subject's  $\dot{V}O_{2max}$  and the percent of  $\dot{V}O_{2max}$  at which the subject can perform (Fig. 10). For example to complete a 2:15 marathon, a  $\dot{V}O_2$  of about 60 mL·kg<sup>-1</sup>·min<sup>-1</sup> must be maintained throughout the run. Consequently, even if a marathon could be run at 100%  $\dot{V}O_{2max}$ , the runner would need a  $\dot{V}O_{2max}$  of 60 mL·kg<sup>-1</sup>·min<sup>-1</sup> for the above performance. However, since the marathon is typically run at about 80–85% of  $\dot{V}O_{2max}$ , the  $\dot{V}O_{2max}$  values needed for that performance would be 70.5–75 mL·kg<sup>-1</sup>·min<sup>-1</sup>. In this way  $\dot{V}O_{2max}$  sets the upper limit for energy production in endurance events but does not determine the final performance. As we stated in the previous article (5) there is no question that runners vary in running economy as well as in the percent of  $\dot{V}O_{2max}$  that can be maintained in a run; both have a dramatic impact on the speed that can be maintained in an endurance race. These will be discussed in the following paragraphs.

### Running Economy

Mechanical efficiency is the ratio of work done to energy expended. The term "running economy" is used to express the oxygen uptake needed to run at a given velocity. This can be shown by plotting oxygen uptake (mL·kg<sup>-1</sup>·min<sup>-1</sup>) versus running velocity (m·min<sup>-1</sup>) or by simply expressing economy as the energy required per unit mass to cover a horizontal distance (mL O<sub>2</sub>·kg<sup>-1</sup>·km<sup>-1</sup>). In our previous paper we showed that running economy explains some of the variability in distance running performance in subjects with similar  $\dot{V}O_{2max}$  values (5). Data from Conley and Krahenbuhl (14) were used to show a relatively strong correlation ( $r = 0.82$ ) between running economy and performance in a 10-km run in a group of runners with similar  $\dot{V}O_{2max}$  values but with a range of 10-km times of 30.5–33.5 min. As was pointed out in the rebuttal (63), when one examines the fastest four runners (10 km in 30.5–31 min) there was considerable variability in the economy of running (45–49 mL·kg<sup>-1</sup>·min<sup>-1</sup> at 268 m·min<sup>-1</sup>), suggesting a lack of association between the variables. As mentioned above, this is to be expected. A correlation coefficient will approach zero as the range of values for one of the variables (in this case, performance times ranging from 30.5 to 31 min) approaches zero. There is little point in looking at a correlation unless the range of values is sufficient to determine whether a relationship exists.

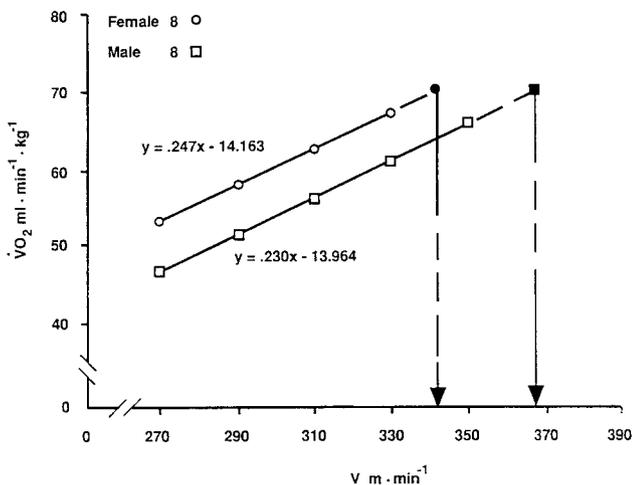
There is a linear relationship between submaximal running velocity and  $\dot{V}O_2$  (mL·kg<sup>-1</sup>·min<sup>-1</sup>) for each individual. However, there is considerable variation among individuals in how much oxygen it costs to run at a given speed,



**Figure 11**—Minimum, mean, and maximum aerobic demand running economy values for elite runners (Category 1), subelite runners (Category 2), good runners (Category 3), and untrained subjects (Category 4). From reference 59. Morgan, D. W., D. R. Bransford, D. L. Costill, et al. Variation in the aerobic demand of running among trained and untrained subjects. *Med. Sci. Sports Exerc.* 27:404–409, 1995. Used with permission.

that is, running economy (6,59). Figure 11 shows a bar graph of the variation in running economy (expressed in  $\text{mL} \cdot \text{kg}^{-1} \cdot \text{km}^{-1}$ ) among groups that differ in running ability (59). The group of elite runners had a better running economy than the other groups of runners, and all running groups were better than the group of untrained subjects. However, one of the most revealing aspects of this study was the within-group variation; there was a 20% difference between the least and most economical runner in any group (59).

One of the best descriptions of how  $\dot{V}O_{2\text{max}}$  and running economy interact to affect running velocity was provided by Daniels (20) in his description of “velocity at  $\dot{V}O_{2\text{max}}$ ” ( $v\dot{V}O_{2\text{max}}$ ). Figure 12 shows a plot of male and female runners equal in terms of  $\dot{V}O_{2\text{max}}$ , but differing in running economy (21). A line was drawn through the series of points used to construct an economy-of-running line, and was extrapolated to the subject’s  $\dot{V}O_{2\text{max}}$ . A perpendicular line was then drawn from the  $\dot{V}O_{2\text{max}}$  value

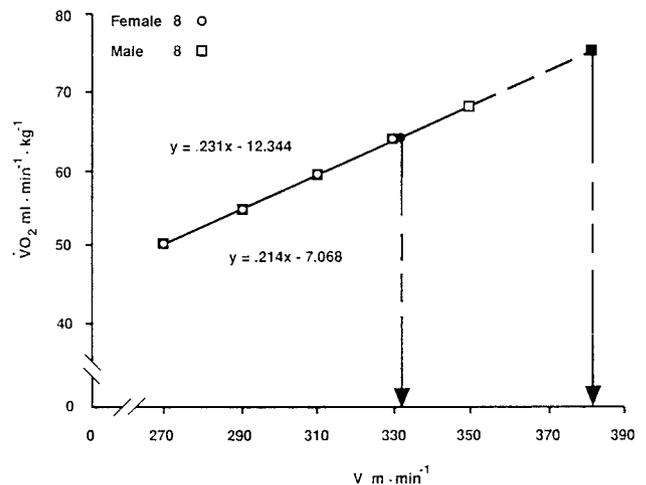


**Figure 12**—Comparison of male and female runners of equal  $\dot{V}O_{2\text{max}}$ . The males are significantly favored in economy and in  $v\dot{V}O_{2\text{max}}$  ( $P < 0.05$ ). From reference 21. Daniels, J. and N. Daniels. Running economy of elite male and elite female runners. *Med. Sci. Sports Exerc.* 24:483–489, 1992. Used with permission.

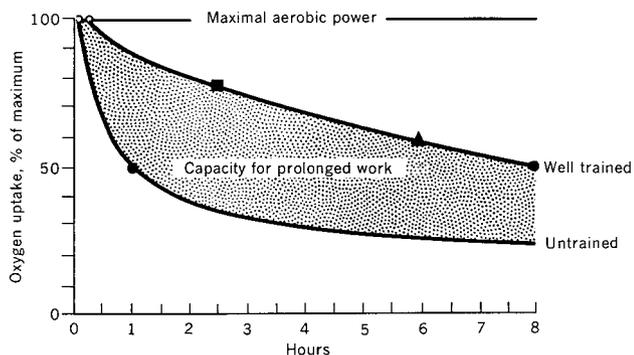
to the x-axis to estimate the velocity that subject would have achieved at  $\dot{V}O_{2\text{max}}$ . This is an estimate of the maximal speed that can be maintained by oxidative phosphorylation. In this example, the difference in running economy resulted in a clear difference in the speed that could be achieved if that race were run at  $\dot{V}O_{2\text{max}}$ . In like manner, Figure 13 shows the impact that a difference in  $\dot{V}O_{2\text{max}}$  has on the  $v\dot{V}O_{2\text{max}}$  in groups with similar running economy values. The 14% difference in  $\dot{V}O_{2\text{max}}$  resulted in a 14% difference in the  $v\dot{V}O_{2\text{max}}$ . Consequently, it is clear that both  $\dot{V}O_{2\text{max}}$  and running economy interact to set the upper limit of running velocity that can be maintained by oxidative phosphorylation. However, since distance races are not run at  $\dot{V}O_{2\text{max}}$ , the ability of the athlete to run at a high percentage of  $\dot{V}O_{2\text{max}}$  has a significant impact on running performance (17).

### Percent of Maximum Oxygen Uptake

Figure 14, from the classic *Textbook of Work Physiology* by Åstrand and Rodahl (3) characterizes the impact that training has on one’s ability to maintain a certain percentage of  $\dot{V}O_{2\text{max}}$  during prolonged exercise. Trained individuals functioned at 87% and 83% of  $\dot{V}O_{2\text{max}}$  for 1 and 2 h, respectively, compared with only 50% and 35% of  $\dot{V}O_{2\text{max}}$  for the untrained subjects. This figure shows clearly the impact that the %  $\dot{V}O_{2\text{max}}$  has on the actual (performance)  $\dot{V}O_2$  that a person can maintain during an endurance performance. In addition, Figure 15, taken from the same text, shows how  $\dot{V}O_{2\text{max}}$  and the %  $\dot{V}O_{2\text{max}}$  change over months of training.  $\dot{V}O_{2\text{max}}$  increases during the first 2 months and levels off, while the %  $\dot{V}O_{2\text{max}}$  continues to change over time. Consequently, while changes in both  $\dot{V}O_{2\text{max}}$  and the %  $\dot{V}O_{2\text{max}}$  impact changes in the performance of a subject early in a training program, subsequent changes in the performance  $\dot{V}O_2$  are caused by changes in the %  $\dot{V}O_{2\text{max}}$  alone. This classic figure is supported by later work showing that the  $\dot{V}O_2$  at the LT (%  $\dot{V}O_{2\text{max}}$  at the LT) increases much



**Figure 13**—Comparison of male and female runners of equal running economy, over common test velocities. Males are favored in  $\dot{V}O_{2\text{max}}$  and in  $v\dot{V}O_{2\text{max}}$  ( $P < 0.05$ ). From reference 21. Daniels, J. and N. Daniels. Running economy of elite male and elite female runners. *Med. Sci. Sports Exerc.* 24:483–489, 1992. Used with permission.



**Figure 14**—A graphic illustration based on a few observations showing approximately the percentage of a subject's maximal aerobic power he/she can tax during work of different duration and how this is affected by training state. From reference 3. Åstrand, P.-O. and K. Rodahl. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970, pp. 279–430. Used with permission.

more as a result of training than does  $\dot{V}O_{2max}$  (see review in (89) p. 59).

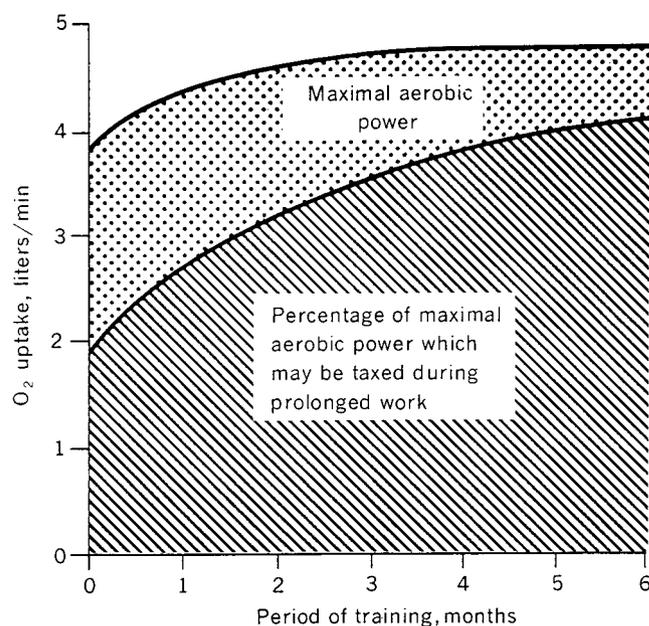
### The Lactate Threshold and Endurance Performance

The model presented earlier in Figure 10 showed how  $\dot{V}O_{2max}$  and %  $\dot{V}O_{2max}$  interact to determine the performance  $\dot{V}O_2$  and how running economy shapes the final performance. In this model the  $\dot{V}O_2$  at the LT integrates both  $\dot{V}O_{2max}$  and the %  $\dot{V}O_{2max}$ . In our previous paper (5) we used a more detailed model to show that running velocity at the LT integrates all three variables mentioned earlier (the  $\dot{V}O_{2max}$ , the %  $\dot{V}O_{2max}$ , and running economy) to predict distance running performance. We will now use that same model (Fig. 16) to expand our discussion with a focus on the lactate threshold.

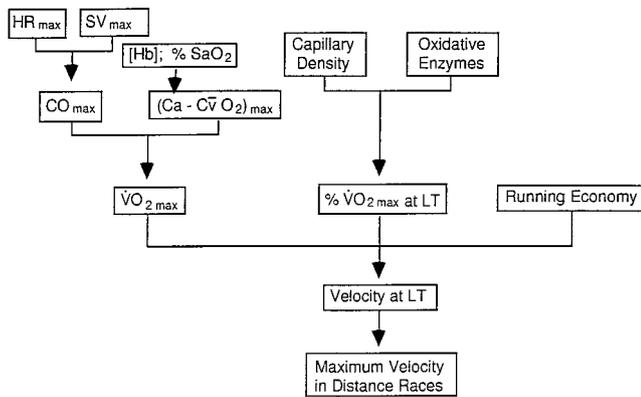
To determine a lactate threshold, a subject completes a series of tests at increasing running speeds, and after each test a blood sample is taken for lactate analysis. The speed at which the lactate concentration changes in some way (e.g., to an absolute concentration, a break in the curve, a delta amount) is taken as the speed at the LT and is used as the predictor of performance. Numerous studies have shown the various indicators of the LT to be good predictors of performance in a variety of endurance activities (e.g., running, cycling, race walking) and for both trained and untrained populations ((89) p. 49). In most of these studies the association between the LT and endurance performance was evaluated in groups of athletes that were heterogeneous relative to performance. As discussed earlier, this is an appropriate design to see whether a relationship (correlation) exists between the variables. On the other hand, if one were to narrow the range of performances (or the LT) over which this relationship were examined, one would expect the correlation to be markedly reduced. This means that even though the speed at the LT explains the vast majority of the variance in performance in distance races (30) other factors can still influence the final performance. If any model could explain all of the variance in performance, gold medals would be handed out in the lab!

The classical model that has been passed down to us revolves around the proposition that the ability to maintain a high running speed is linked to the ability to maintain a high rate of oxidative ATP production. Both logic and empirical data provide support for that proposition; to argue otherwise would suggest that “oxygen independent” (anaerobic) sources of ATP are important in such performances—a clear impossibility given the small amount of potential energy available via those processes.

It has been known for some time (43,44) that lactate production is related to a number of variables, including the mitochondrial content of muscle, as measured by mitochondrial enzyme activity. Variations in the LT across diverse groups of endurance athletes and improvements in the LT resulting from training are linked to differences and increases in mitochondrial enzyme activity, respectively ((19), (89), p. 49–59). An explanation for this connection was provided by Holloszy and Coyle in 1984 (44). When muscles contract to meet a specific submaximal power output, ATP is converted to ADP and Pi to power the cross bridges, and the latter two, in turn, drive metabolic reactions in the cell to meet the ATP demand associated with that work rate. In a muscle cell with relatively few mitochondria the ADP concentration must rise to a high level to drive the limited number of mitochondria to meet the ATP demand via oxidative phosphorylation. This high concentration of ADP also drives other metabolic pathways, including glycolysis, because of the stimulatory effect of ADP on phosphofructokinase (PFK). This results in a greater rate of carbohydrate turnover, an accumulation of pyruvate and NADH in the cytoplasm of the muscle fiber, and an increase in lactate production (44,50). Following training there is a large (50–100%) increase in the number of mitochondria in



**Figure 15**—Training causes an increase in maximal oxygen uptake. With training a subject is also able to tax a greater percentage of his/her maximal oxygen uptake during prolonged work. From reference 3. Åstrand, P.-O. and K. Rodahl. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970, pp. 279–430. Used with permission.



**Figure 16**—Summary of the major variables related to  $\dot{V}O_{2\max}$  and the maximal velocity that can be maintained in distance races. From: Bassett, D. R., Jr. and E. T. Howley. Maximal oxygen uptake: “classical” versus “contemporary” viewpoints. *Med. Sci. Sports Exerc.* 29: 591–603, 1997. Used with permission.

the muscles involved in the activity. Consequently, at the same work rate the oxygen uptake is shared by a greater number of mitochondria, and the ADP concentration does not have to rise to the same level as before training to achieve the same rate of oxidative phosphorylation ( $\dot{V}O_2$ ) after training. The lower level of ADP after training results in less stimulation of PFK and a reduction in carbohydrate turnover, and the greater number of mitochondria increases the capacity to use fat as a fuel. The result is less lactate formation (44).

As we mentioned throughout this section, the relationships between  $\dot{V}O_{2\max}$  and performance (15), running economy and performance (14), and %  $\dot{V}O_{2\max}$  and performance (30) used groups with large variations in the independent variables. As one reduces the range of each of these variables, the correlations are reduced in magnitude or eliminated, suggesting that other variables also influence performance. Instead of dismissing the relationships as having little worth, investigators have used these observations as motivation to examine other factors that might be related to endurance performance. An excellent example of taking the next step is found in an experiment by Coyle et al. (18).

Coyle et al. (18) studied 14 trained cyclists (3–12 yr of training) who were similar in terms of  $\dot{V}O_{2\max}$  (thus eliminating that as a variable) to examine the relationship between the LT and time to fatigue at 88%  $\dot{V}O_{2\max}$ . Subjects were divided into high-LT (mean = 81.5%  $\dot{V}O_{2\max}$ ) and low-LT (mean = 65.8%  $\dot{V}O_{2\max}$ ) groups. The performance test at 88%  $\dot{V}O_{2\max}$  resulted in large differences in performance (60.8 vs 29.1 min), and the postexercise lactate concentration (7.4 vs 14.7 mM) for the high-LT and low-LT groups, respectively. The difference in performance between these groups that had the same  $\dot{V}O_{2\max}$ , but differed in the %  $\dot{V}O_{2\max}$  at the LT, was consistent with the model described above. On the other hand, the fact that the vastus lateralis of both groups had the same mitochondrial enzyme activities suggested a break in the chain of evidence linking the %  $\dot{V}O_{2\max}$  at the LT and mitochondrial activity. This created a rare opportunity for the investigators to study two groups with the same  $\dot{V}O_{2\max}$  and the same mitochondrial

enzyme activity but with substantial differences in performance. The investigators examined the metabolic response of the cyclists to a 30-min test at 79%  $\dot{V}O_{2\max}$ . They found that while the low-LT group used 69% more carbohydrate during this exercise bout than the high-LT group, the low-LT group reduced its vastus lateralis muscle glycogen concentration 134% more than the high-LT group. This difference in muscle glycogen depletion (relative to total carbohydrate oxidation) suggested that the high-LT group was able to distribute the same work rate (and  $\dot{V}O_2$ ) over a larger muscle mass, resulting in less loading on the muscle fibers recruited to do the work. Use of a larger muscle mass also increased the mass of mitochondria sharing in the production of ATP by oxidative phosphorylation ((18,19) and (87) p. 131). Consequently, the study of Coyle et al. (18) indicates that the mass of muscle involved in the activity (in addition to mitochondrial density) contributes to the %  $\dot{V}O_{2\max}$  at the LT (as well as performance), in a manner consistent with the above model.

## LT, THE CLASSICAL MODEL, AND ENVIRONMENTAL FACTORS

Noakes has asked, “. . . why should prolonged endurance exercise in which the oxygen consumption is not maximal and therefore not limiting be determined by the oxygen delivery to the active muscle?” ((63) p. 1393). This is a good question because a marathon runner can certainly run at faster speeds and higher  $\dot{V}O_2$  values over shorter distances—but not without some metabolic consequences. During submaximal exercise, oxygen delivery to muscle is closely tied to the mitochondrial oxygen demand which is driven by the cellular charge (i.e., [ADP + Pi]) provided by the exercise. As mentioned earlier, this same cellular charge also drives other metabolic pathways, notably, glycolysis. If a marathoner chose to run at a speed above the LT, the increased cellular charge needed to drive the  $\dot{V}O_2$  to the higher level would also speed up glycolysis. This would deplete the limited carbohydrate store at a faster rate; the resulting increase in blood lactate accumulation would be caused by both an increase in lactate formation and a decrease in lactate removal (7,50). Given the obligatory need for carbohydrate at high exercise intensities (13) and the negative impact of hydrogen ion accumulation on muscle function (29,56,57,60), neither of these changes are consistent with being able to maintain the faster pace over a marathon distance.

In this and our previous paper (5) we attempted to explain how the variables of  $\dot{V}O_{2\max}$ , the percentage of  $\dot{V}O_{2\max}$ , and running economy can account for the vast majority of the variance in distance running performances (30,89). In addition, the model also accounts for the impact of certain environmental factors on endurance performance. Acute exposure to moderate altitude results in a decrease in arterial oxygen saturation and  $\dot{V}O_{2\max}$  (22,53). Consequently, the “performance  $\dot{V}O_2$ ” is decreased even though runners can still perform at a similar percentage of  $\dot{V}O_{2\max}$ , and performance in endurance events is adversely affected (22,31).

Historically, this effect of a lower PO<sub>2</sub> causing a shift in the LT was interpreted as an “oxygen lack” at the muscle. However, it is now recognized that the lower PO<sub>2</sub> results in a higher cellular charge to achieve the same steady state  $\dot{V}O_2$  at a fixed submaximal work rate (50). These circumstances will result in a higher rate of glycolysis, an accumulation of NADH<sup>+</sup>, and an increase in lactate production.

Performance times in the marathon are adversely affected by high environmental temperatures, with race times being optimal at a temperature of 12–13°C (34), and a decrement of 40 s expected for every 1°C rise in temperature (33). Exercise in the heat increases the rate of carbohydrate oxidation, leading to a faster rate of muscle glycogen depletion and higher blood lactate concentrations during prolonged work (32). Consequently, changes in metabolism resulting from acute exposure to heat or altitude are associated with a decrease in endurance performance, consistent with the model.

## Postscript

In summary, the “classical” model of  $\dot{V}O_{2max}$  passed down by Hill et al. (41,42) has been modified and expanded upon by numerous investigators. We now have a much more complete understanding of the determinants of endurance performance than did exercise scientists from the 1920s. In hindsight, Hill et al. (41,42) were wrong about some of the details, such as the notion of a strict 1:1 ratio of O<sub>2</sub> deficit:O<sub>2</sub> debt. However, Hill deserves recognition for his

major role in the discovery of nonoxidative pathways in isolated frog muscle and the application of this discovery to the exercising human (9,51). Hill’s work shaped the emerging discipline of Exercise Physiology (37,48), and his ideas continue to be influential even to this day.

Hill welcomed challenges to his theories and urged others to critically analyze scientific beliefs ((40) p. 363). It is clear that he viewed errors in interpretation and scientific debate over the merits of competing theories to be a necessary part of progress ((51) p. 82). In *Trails and Trials in Physiology*, Hill stated that, “Knowledge advances by continual action and reaction between hypothesis on the one hand and observation, calculation, and experiment on the other ((40), p. 361).” In contrast to the view that the classical theory represents an “ugly and creaking edifice” (62), we have arrived at a very different point of view. Our conclusion is that Hill’s theories have served as an ideal theoretical framework. The work that has built upon this framework has allowed exercise scientists to learn much about the physiological factors governing athletic performance.

Support was provided by the University of Tennessee, Knoxville, Exhibit, Performance, and Publication Expense (EPPE) Fund.

Address for correspondence: David R. Bassett, Jr., Department of Exercise Science and Sport Management, University of Tennessee, 1914 Andy Holt Ave., Knoxville, TN 37996. E-mail: [DBassett@utk.edu](mailto:DBassett@utk.edu)

## REFERENCES

- ANDERSEN, P. and J. HENRIKSSON. Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. *J. Physiol.* 270:677–690, 1977.
- ÅSTRAND, P.-O. *Experimental Studies of Physical Working Capacity in Relation to Sex and Age*. Copenhagen: Ejnar Munksgaard, 1952, pp. 23–27.
- ÅSTRAND, P.-O. and K. RODAHL. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970, pp. 279–430.
- ÅSTRAND, P. O. and B. SALTIN. Oxygen uptake during the first minutes of heavy muscular exercise. *J. Appl. Physiol.* 16:971–976, 1961.
- BASSETT, D. R. and E. T. HOWLEY. Maximal oxygen uptake: “classical” versus “contemporary” viewpoints. *Med. Sci. Sports Exerc.* 29:591–603, 1997.
- BRANSFORD, D. R. and E. T. HOWLEY. Oxygen cost of running in trained and untrained men and women. *Med. Sci. Sports Exerc.* 9:41–44, 1977.
- BROOKS, G. Anaerobic threshold: review of the concept and directions for future research. *Med. Sci. Sports Exerc.* 17:22–31, 1985.
- BUICK, F. J., N. GLEDHILL, A. B. FROESE, L. SPRIET, and E. C. MEYERS. Effect of induced erythrocythemia on aerobic work capacity. *J. Appl. Physiol.* 48:636–642, 1980.
- CASTIGLIONI, A. *A History of Medicine*. New York: Alfred A. Knopf, 1947, pp. 942–943.
- CERRETELLI, P. and P. E. DI PRAMPERO. Gas exchange in exercise. In: *Handbook of Physiology*. A. P. Fishman, L. E. Farhi, S. M. Tenney and S. R. Geiger (Eds.). Bethesda, MD: American Physiological Society, 1987, pp. 297–339.
- CHRISTENSEN, E. H. Beitrage zur Physiologie schwerer körperlicher. IV: Mitteilung: die Pulsfrequenz während und unmittelbar nach schwerer körperlicher Arbeit. *Arbeits Physiol.* 4:453–469, 1931.
- CLAUSEN, J. P., K. KLAUSEN, B. RASMUSSEN, and J. TRAP-JENSEN. Central and peripheral circulatory changes after training of the arms and legs. *Am. J. Physiol.* 225:675–682, 1973.
- COGGAN, A. R. and E. F. COYLE. Carbohydrate ingestion during prolonged exercise: effect on metabolism and performance. *Exerc. Sport Sci. Rev.* 19:1–40, 1991.
- CONLEY, D. L. and G. KRAHENBUHL. Running economy and distance running performance of highly trained athletes. *Med. Sci. Sports Exerc.* 12:357–360, 1980.
- COSTILL, D. L. Metabolic responses during distance running. *J. Appl. Physiol.* 28:251–255, 1970.
- COSTILL, D. L., W. J. FINK, and M. L. POLLOCK. Muscle fiber composition and enzyme activities of elite distance runners. *Med. Sci. Sports* 8:96–100, 1976.
- COSTILL, D. L., H. THOMASON, and E. ROBERTS. Fractional utilization of the aerobic capacity during distance running. *Med. Sci. Sports Exerc.* 5:248–252, 1973.
- COYLE, E. F., A. R. COGGAN, M. R. HOPPER, and T. J. WALTERS. Determinants of endurance in well-trained cyclists. *J. Appl. Physiol.* 64:2622–2630, 1988.
- COYLE, E. F. and J. O. HOLLOSZY. Integration of the physiological factors determining endurance performance ability. In: *Exercise and Sport Sciences Reviews*. J. O. Holloszy (Ed.). Baltimore, MD: Williams & Wilkins, 1995, pp. 25–63.
- DANIELS, J. A physiologist’s view of running economy. *Med. Sci. Sports Exerc.* 17:332–338, 1985.
- DANIELS, J. and N. DANIELS. Running economy of elite male and female runners. *Med. Sci. Sports Exerc.* 24:483–489, 1991.
- DANIELS, J. and N. OLDRIDGE. The effects of alternate exposure to altitude and sea level on world-class middle-distance runners. *Med. Sci. Sports* 2:107–112, 1970.
- DAVIDSON, A. C., R. LEACH, R. J. D. GEORGE, and D. M. GEDDES. Supplemental oxygen and exercise ability in chronic obstructive airway disease. *Thorax* 43:965–971, 1988.
- DEMPSEY, J. A. Is the lung built for exercise? *Med. Sci. Sports Exerc.* 18:143–155, 1986.

25. DEMPSEY, J. A., P. HANSON, and K. HENDERSON. Exercise-induced arterial hypoxemia in healthy humans at sea-level. *J. Physiol. (Lond.)* 355:161–175, 1984.
26. DUNCAN, G. E., E. T. HOWLEY, and B. N. JOHNSON. Applicability of  $\dot{V}O_{2\max}$  criteria: discontinuous versus continuous protocols. *Med. Sci. Sports Exerc.* 29:273–278, 1997.
27. EKBLUM, B., P. O. ÅSTRAND, B. SALTIN, J. STENBERG, and B. WALLSTROM. Effect of training on circulatory response to exercise. *J. Appl. Physiol.* 24:518–528, 1968.
28. EKBLUM, B., G. WILSON, and P. O. ÅSTRAND. Central circulation during exercise after venesection and reinfusion of red blood cells. *J. Appl. Physiol.* 40:379–383, 1976.
29. FABIATO, A. and F. FABIATO. Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscle. *J. Physiol.* 276:233–255, 1978.
30. FARRELL, P. A., J. H. WILMORE, E. F. COYLE, J. E. BILLING, and D. L. COSTILL. Plasma lactate accumulation and distance running performance. *Med. Sci. Sports Exerc.* 11:338–344, 1979.
31. FAULKNER, J. A., J. KOLLIAS, C. B. FAVOUR, E. R. BUSKIRK, and B. BALKE. Maximum aerobic capacity and running performance at altitude. *J. Appl. Physiol.* 24:685–691, 1968.
32. FINK, W., D. L. COSTILL, and P. J. V. HANDEL. Leg muscle metabolism during exercise in the heat and cold. *Eur. J. Appl. Physiol.* 34:183–190, 1975.
33. FOSTER, C. and J. DANIELS. Running by the numbers. *Runners World* 10:14–17, 1975.
34. FREDERICK, E. C. Hot times. *Running* 9:52, 1983.
35. GLEDHILL, N. Blood doping and related issues: a brief review. *Med. Sci. Sports Exerc.* 14:183–189, 1982.
36. GLEDHILL, N. The influence of altered blood volume and oxygen-transport capacity on aerobic performance. *Exerc. Sport Sci. Rev.* 13:75–93, 1985.
37. HAMLEY, E. J. A. V. Hill, C. H., F. R. S.: an appreciation. *Br. J. Sports Med.* 10:195, 1976.
38. HENRIKSSON, J. and J. S. REITMAN. Time course of changes in human skeletal muscle succinate dehydrogenase and cytochrome oxidase activities and maximal oxygen uptake with physical activity and inactivity. *Acta Physiol. Scand.* 99:91–97, 1977.
39. HERBST, R. Der Gasstoffwechsel als Mass der körperlichen Leistungsfähigkeit. I. Mitteilung: die Bestimmung des Sauerstoffaufnahmevermögens beim Gesunden. *Deut. Arch. Klin. Med.* 162: 33–50, 1928.
40. HILL, A. V. *Trails and Trials in Physiology: a Bibliography, 1909–1964, with Reviews of Certain Topics and Methods and a Reconnaissance for Further Research.* Baltimore, MD: Williams and Wilkins, 1966, pp. 359–368.
41. HILL, A. V., C. N. H. LONG, and H. LUPTON. Muscular exercise, lactic acid and the supply and utilisation of oxygen: Parts VII–VIII. *Proc. Roy. Soc. B* 97:155–176, 1924.
42. HILL, A. V. and H. LUPTON. Muscular exercise, lactic acid, and the supply and utilization of oxygen. *Q. J. Med.* 16:135–171, 1923.
43. HOLLOSZY, J. O. Biochemical adaptations to exercise: aerobic metabolism. *Exerc. Sport Sci. Rev.* 1:45–71, 1973.
44. HOLLOSZY, J. O. and E. F. COYLE. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J. Appl. Physiol.* 56:831–838, 1984.
45. HONIG, C. R., R. J. CONNETT, and T. E. J. GAYESKI.  $O_2$  transport and its interaction with metabolism: a systems view of aerobic capacity. *Med. Sci. Sports Exerc.* 24:47–53, 1992.
46. HOWLEY, E. T., D. R. BASSETT, and H. G. WELCH. Criteria for maximal oxygen uptake: review and commentary. *Med. Sci. Sports Exerc.* 27:1292–1301, 1995.
47. ISSEKUTZ, B., N. C. BIRKHEAD, and K. RODAHL. Use of respiratory quotients in assessment of aerobic capacity. *J. Appl. Physiol.* 17:47–50, 1962.
48. JOKL, E. 90th Birthday of Professor A.V. Hill. *J. Sports Med.* 16:349, 1976.
49. JONES, J. H., K. E. LONGWORTH, A. LINDHOLM, et al. Oxygen transport during exercise in large mammals. I. Adaptive variation in oxygen demand. *J. Appl. Physiol.* 67:862–870, 1989.
50. KATZ, A. and K. SAHLIN. Regulation of lactic acid production during exercise. *J. Appl. Physiol.* 65:509–518, 1988.
51. KATZ, B. ARCHIBALD VIVIAN HILL. *Biographical Memoirs of Fellows of the Royal Society* 24:71–149, 1978.
52. KLAUSEN, K., L. B. ANDERSEN, and I. PELLE. Adaptive changes in work capacity, skeletal muscle capillarization, and enzyme levels during training and detraining. *Acta Physiol. Scand.* 113:9–16, 1981.
53. KOLLIAS, J. and E. BUSKIRK. Exercise and altitude. In: *Science and Medicine of Exercise and Sport.* W. R. Johnson and E. R. Buskirk (Eds.). New York: Harper and Row, 1974, pp. 211–227.
54. LEWIS, S. F. and R. G. HALLER. Skeletal muscle disorders and associated factors that limit exercise performance. *Exerc. Sport Sci. Rev.* 17:67–113, 1989.
55. LINDHARD, J. Ueber das minutenvolum des herzens bei ruhe und die muskellarbeit. *Arch. F. D. Ges. Physiol.* 1915, clxi:233–383, 1915.
56. METZGER, J. M. and R. L. MOSS. Depression of  $Ca^{2+}$  insensitive tension due to reduced pH in partially troponin-extracted skinned skeletal muscle fibers. *Biophys. J.* 54:1169–73, 1988.
57. METZGER, J. M. and R. L. MOSS. Greater hydrogen-ion induced depression of tension and velocity in skinned single fibres of rat fast than slow muscles. *J. Physiol. (Lond.)* 393:727–742, 1987.
58. MITCHELL, J. H., B. J. SPROULE, and C. B. CHAPMAN. The physiological meaning of the maximal oxygen intake test. *J. Clin. Invest.* 37:538–547, 1958.
59. MORGAN, D. W., D. R. BRANSFORD, D. L. COSTILL, J. T. DANIELS, E. T. HOWLEY, and G. S. KRAHENBUHL. Variation in the aerobic demand of running among trained and untrained subjects. *Med. Sci. Sports Exerc.* 27:404–409, 1995.
60. NEKAMARU, Y. and A. SCHWARTZ. The influence of hydrogen ion concentration on calcium binding and release by skeletal sarcoplasmic reticulum. *J. Gen. Physiol.* 59:22–32, 1972.
61. NOAKES, T. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.* 20:319–330, 1988.
62. NOAKES, T. D. Challenging beliefs: ex Africa semper aliquid novi. *Med. Sci. Sports Exerc.* 29:571–590, 1997.
63. NOAKES, T. D. Maximal oxygen uptake: “classical” versus “contemporary” viewpoints: a rebuttal. *Med. Sci. Sports Exerc.* 30: 1381–1398, 1998.
64. ORLANDER, J., K.-H. KIESSLING, J. KARLSSON, and B. EKBLUM. Low intensity training, inactivity and resumed training in sedentary men. *Acta Physiol. Scand.* 101:351–362, 1977.
65. POWERS, S. K., J. LAWLER, J. A. DEMPSEY, S. DODD, and G. LANDRY. Effects of incomplete pulmonary gas exchange of  $\dot{V}O_{2\max}$ . *J. Appl. Physiol.* 66:2491–2495, 1989.
66. RICHARDSON, R. S. and B. SALTIN. Human muscle blood flow and metabolism studied in the isolated quadriceps muscles. *Med. Sci. Sports Exerc.* 30:28–33, 1998.
67. ROOYACKERS, J. M., P. N. DEKHUIZEN, C. L. VAN-HERWAARDEN, and H. T. FOLGERING. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur. Respir. J.* 10:1278–84, 1997.
68. ROWELL, L. B. *Human Circulation: Regulation During Physical Stress.* New York: Oxford University Press, 1986, pp. 213–286.
69. ROWLAND, T. W. Does peak  $\dot{V}O_2$  reflect  $\dot{V}O_{2\max}$  in children?: evidence from supramaximal testing. *Med. Sci. Sports Exerc.* 25:689–693, 1993.
70. SALTIN, B. Hemodynamic adaptations to exercise. *Am. J. Cardiol.* 55:42D–47D, 1985.
71. SALTIN, B., B. BLUMQUIST, J. H. MITCHELL, R. L. JOHNSON, K. WILDENTHAL, and C. B. CHAPMAN. Response to submaximal and maximal exercise after bed rest and after training. *Circulation* 38(Suppl.7):1–78, 1968.
72. SALTIN, B., J. HENRIKSSON, E. NYGAARD, and P. ANDERSEN. Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners. *Ann. N. Y. Acad. Sci.* 301:3–29, 1977.
73. SALTIN, B., K. NAZAR, D. L. COSTILL, et al. The nature of the training response; peripheral and central adaptations to one-legged exercise. *Acta Physiol. Scand.* 96:289–305, 1976.
74. SALTIN, B. and S. STRANGE. Maximal oxygen uptake: “old” and “new” arguments for a cardiovascular limitation. *Med. Sci. Sports Exerc.* 24:30–37, 1992.

75. SCHWERZMANN, K., H. HOPPELER, S. R. KAYAR, and E. R. WEIBEL. Oxidative capacity of muscle and mitochondria: correlation of physiological, biochemical and morphometric characteristics. *Proc. Natl. Acad. Sci. USA* 86:1583–1587, 1988.
76. SHEPHARD, R. *Endurance Fitness*, 2nd Ed. Toronto and Buffalo: Univ. of Toronto Press, 1977, pp. 64–103.
77. SPRIET, L. L., N. GLEDHILL, A. B. FROESE, AND D. L. WILKES. Effect of graded erythrocythemia on cardiovascular and metabolic responses to exercise. *J. Appl. Physiol.* 61:1942–1948, 1986.
78. SPROULE, B. J., J. H. MITCHELL, and W. F. MILLER. Cardiopulmonary physiological responses to heavy exercise in patients with anemia. *J. Clin. Invest.* 39:378–388, 1960.
79. TAYLOR, C. R. and E. R. WEIBEL. Design of the mammalian respiratory system I-IX. *Respir. Physiol.* 44:1–164, 1981.
80. TAYLOR, C. R. and E. R. WEIBEL. Learning from comparative physiology. In: *The Lung: Scientific Foundations*. J. B. W. R.G. Crystal, et al. (Ed.) New York: Raven Press, 1991, pp. 1595–1607.
81. TAYLOR, C. R., E. R. WEIBEL, R. H. KARAS, and H. HOPPELER. Adaptive variation in the mammalian respiratory system in relation to energetic demand I-VIII. *Respir. Physiol.* 69:1987.
82. TAYLOR, C. R., E. R. WEIBEL, J.-M. WEBER, et al. Design of the oxygen and substrate pathways I-VII. *J. Exper. Biol.* 199:1643–1709, 1996.
83. TAYLOR, H. L., E. BUSKIRK, and A. HENSCHEL. Maximum oxygen intake as an objective measure of cardio-respiratory performance. *J. Appl. Physiol.* 8:73–80, 1955.
84. TESCH, P. A. Exercise performance and beta-blockade. *Sports Med.* 2:389–412, 1985.
85. WAGNER, P. D. Gas exchange and peripheral diffusion limitation. *Med. Sci. Sports Exerc.* 24:54–58, 1992.
86. WAGNER, P. D., H. HOPPELER, and B. SALTIN. Determinants of maximal oxygen uptake. In: *The Lung: Scientific Foundations*. R. G. Crystal, J. B. West, et al. (Eds.) New York: Raven Press, 1991, pp. 1585–1593.
87. WEIBEL, E. R. *The Pathway for Oxygen: Structure and function in the Mammalian Respiratory System*. Cambridge, MA: Harvard University Press, 1984, pp.1–425.
88. WEIBEL, E. R. A tribute to Charles Richard Taylor. *J. Exper. Biol.* 199:i-iv, 1996.
89. WELTMAN, A. *The Blood Lactate Response to Exercise*. Champaign, IL: Human Kinetics, 1995, pp.1–117.