Cardiovascular Responses to Exercise

Second Edition

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ABSTRACT

Exercise is the act of increasing metabolic rate for the purpose of enhancing physical fitness. Exercise can be one of the most stressful physiological responses that the body undertakes. With exercise, there are increases in metabolic rate, heart rate, blood flow (hyperemia), respiration, and heat production. The increased metabolic requirement during exercise is well met by an increased blood flow (functional hyperemia) and oxygen supply to the exercising tissue, which is regulated by multiple local and systemic mechanisms. The local mechanisms (factors) are responsible for mediating the muscle homeostasis and vascular conductance to match the increased metabolic requirement, whereas the systemic mechanisms are responsible for the maintenance of blood pressure and global cardiovascular homeostasis, including the increase in and redistribution of cardiac output, which is mainly mediated by sympathetic activation. For instance, the substantial decreases in vascular resistance and resultant large increase in blood flow during exercise require higher blood pressure and more cardiac output, such that the metabolically active muscle can be perfused with adequate blood flow. This book will provide an overview of the cardiovascular responses to exercise under physiological conditions as well as some pathological circumstances.

KEYWORDS

exercise, blood flow, vasodilation, hyperemia, microcirculation, circulation, sympathetic activity, blood pressure, heart rate, cardiac output, cardiovascular homeostasis

Contents

Preface

The second edition of Cardiovascular Responses to Exercise includes corrections, updates, and clarifications in many sections of the original chapter, making the chapter easier to follow for readers with different levels of background in medical science. We also added a new section "Pulmonary Hemodynamics in Response to Exercise", in which pulmonary ventilation, blood flow, oxygen uptake, oxygen partial pressure, exercise capacity, and their relationships are described.

CHAPTER 1

Capillary Perfusion in Skeletal Muscle during Exercise

Arteries branch and narrow into arterioles and downstream capillaries, where oxygen, nutrients, and metabolites are exchanged between blood stream and tissue. The capillaries then join and widen to become venules and downstream veins, which return blood to the heart. Exercise induces alterations in the distribution and magnitude of blood flow in skeletal muscle microcirculation via a coordinated interplay among arterioles, capillary, and venules. In general, the arterioles regulate blood flow while the capillaries are the major site of diffusion. Constructed of single-layer endothelial cells, the capillary is highly permeable due to the pores (space) between endothelial cells, through which nutrients and metabolites can be quickly exchanged between tissue and blood stream along the net filtration pressure (Figure 1.1). With a lack of smooth muscle cells, the capillary perfusion is

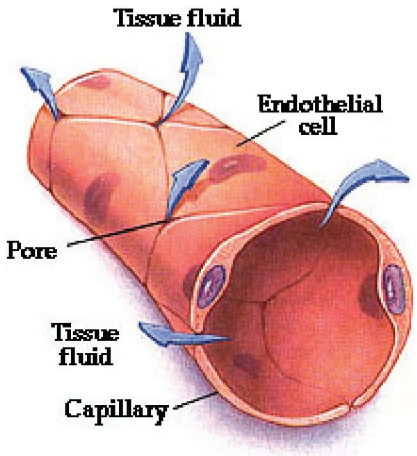

FIGURE 1.1: The capillary is constructed of single-layer endothelial cells of highly permeable due to the pore between endothelial cells (http://www.physioweb.org/circulation/blood_vessels.html).

determined by its upstream arterioles (or precapillary sphincters), which regulate the blood flow via relaxation or contraction based on local metabolic rate. Thus, the anatomical organization of capillary and the regulation of its perfusion by arterioles according to metabolic demand are the key to balance metabolic rate and oxygen delivery in exercising muscle.

1.1 CAPILLARY PERFUSION AT REST

The regulation of capillary perfusion in skeletal muscle is tightly correlated with the metabolic demand of local muscle fibers both at rest and during exercise. Capillaries (or downstream venules) lack intrinsic vasomotor ability, and the regulators of capillary perfusion exist in the precapillary vessels and upstream feed arterioles. Figure 1.2 shows a typical microvasculature bed including capillary, precapillary (terminal) arterioles, and the upstream arteriole (feed arteriole) that supplies and regulates blood flow into the terminal arterioles and capillaries. This section introduces the major characteristics of capillary hemodynamics and the corresponding anatomical regulation at rest:

1.1.1 Capillary Vasomotion

At rest, not all the capillaries are open, and the blood flow is not continuous but displays intermittency, varying from seconds to minutes. This characteristic of capillary perfusion (vasomotion) was first dem-

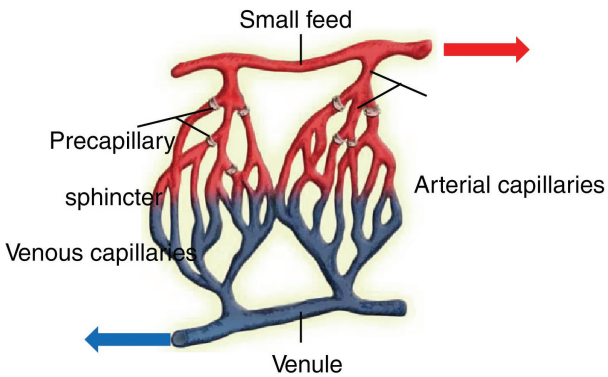

FIGURE 1.2: Microvasculature and regulation of capillary perfusion (drawn by Mohamad Sebai).

onstrated by August Krogh showing that at rest, there were more capillaries in muscle than were actually perfused, with the number of opened capillaries varying constantly [131, 132]. These observations suggest that the mechanisms mediating capillary perfusion and recruitment exists in microcirculation itself. Several major mechanisms have been postulated for the regulation of capillary perfusion:

(a) Precapillary sphincters: A sphincter function at the origin of capillary was first hypothesized by Zweifach et al. in the 1940s. The precapillary sphincter was proposed as a localized band of smooth muscle that would open and close to allow capillary flow by which capillary perfusion is controlled. However, in skeletal muscle, no precapillary sphincters have been found via microscopic observation.
(b) Passive sphincter: In some cases, the flow ceases in capillaries but not in the parent terminal arterioles, indicating a functional "passive sphincter" [122].
(c) Simple closure of the terminal arterioles: in most tissues, the terminal arteriole, an arteriole that divides into capillaries, acts like a precapillary sphincter, such that any decrease in arteriolar diameter along the length of the arteriole will modulate capillary perfusion. This mechanism is particularly interesting since an altered capillary perfusion would occur in groups of capillaries (microvascular units) rather than individual capillaries.

In addition to the capillary vasomotion, it should be realized that not every feed arteriole is perfused at rest. For example, an intravital study of the hamster cremaster muscle demonstrated that ~34% of the total feed arterioles were relatively unperfused at rest. These unperfused vessels at rest provide an important reserve for the large increase in blood flow during exercise (see REGULATION OF CAPILLARY PERFUSION DURING EXERCISE).

1.1.2 Microcirculatory Units

Another important characteristic of microcirculatory anatomy for blood flow control in the skeletal muscle are microvascular units (modules), which consist of a parent terminal arteriole and a group of capillaries running parallel to muscle fibers (Figure 1.3) and ending to a common venule [33, 44]. Relaxation of terminal arteriole increases the perfusion of downstream capillary group. This functional unit is the smallest element of control for capillary perfusion in skeletal muscle. During exercise, the increase in blood flow (hyperemia) requires the perfusion of many microvascular units as well as corresponding parent arteriolar dilation (see REGULATION OF CAPILLARY PERFUSION DURING EXERCISE).

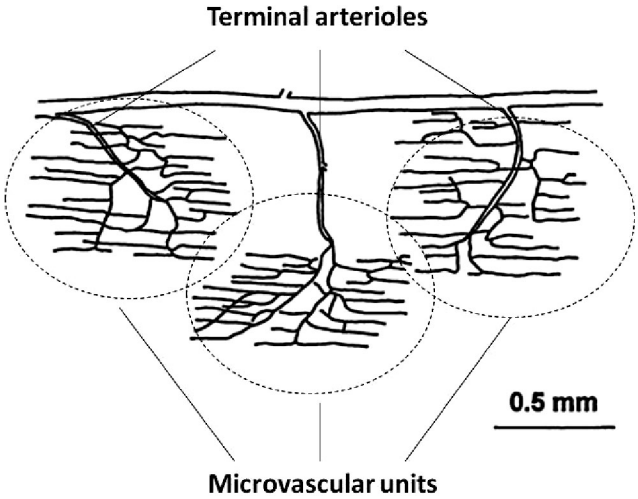

FIGURE 1.3: Microvascular units arise from consecutive terminal arterioles along parent arteriole in hamster retractor muscle. The muscle fibers are horizontal and parallel to capillaries. Adapted from [Ref 44], Figure 2A.

1.2 REGULATION OF CAPILLARY PERFUSION DURING EXERCISE

1.2.1 Capillary Perfusion during Exercise

Blood flow to microvascular units is increased in proportion to the metabolic requirements of the respective contracting muscle fibers. In most tissues, any alteration in arteriolar tone along the length of the arteriole will modulate capillary perfusion and blood flow. Since capillaries are constructed of single-layer endothelial cells, the increase in blood flow into exercising muscle is mainly achieved by increasing the number of perfused capillaries rather than "capillary dilation." The increased capillary "numbers" during exercise was first reported by Krogh. In cross-sections of freeze clamped canine gracilis muscle, the density of erythrocyte-containing capillaries was lowest through entire skeletal muscle fibers at rest and was increased about 3-fold during exercise [96], suggesting an increased total capillary perfusion. Thus, a match between blood flow in capillary and oxygen delivery into the skeletal muscle fiber is achieved. This increased total capillary perfusion in exercising muscle may involve two possible hemodynamic changes:

(a) The relaxation of terminal arteriole (or precapillary sphincters) during exercise diminishes the individual capillary vasomotion that occurs at rest. Thus, the passive hemodynamic effect

due to terminal arteriolar dilation results in a "full perfusion" in all the capillaries within the microvascular unit.

(b) The vasodilation of feed arterioles during exercise (see Chapter 2) increases blood flow to many microvascular units and thus increases the total capillary perfusion in the exercising tissue. Thus, as compared with terminal arterioles, the feed arterioles are more important in mediating the muscle blood flow during exercise.

Notably, the terminal arteriolar dilation in response to muscle fibers contraction is supposed to increase the perfusion of all the downstream capillaries within the microvascular unit that may also encompass the non contracting fibers. However, an "over-perfusion" to the non exercising fibers does not occur during exercise, suggesting a distinct mechanism for the capillary perfusion during exercise.

An intravital study of hamster cremaster muscle demonstrated that half of the terminal arterioles exhibited approximately a 25-fold increase in blood cell flux from rest to hyperemia. However, the blood cell flux heterogeneity in feed arterioles was decreased significantly from rest to hyperemia, whereas the corresponding decrease in blood cell flux heterogeneity in terminal arterioles was not significant. Thus, unperfused feed arterioles instead of terminal arterioles are present in a proportion reflecting capillary recruitment and independently modulate flow distribution distally in hamster cremaster [231], while the terminal arterioles are the major site controlling capillary perfusion and blood cell influx. Another study in dog gracilis muscles showed that the blood flow or capillary density was controlled independently by feed or terminal arterioles, respectively [95]. In addition, it has been shown that a low-intensity muscle contraction recruited capillaries without any change in flow [93], while a higher contractile intensity increased muscle blood flow with a little elevation in capillary perfusion, suggesting an upstream feed arteriolar dilation [95, 96]. Therefore, during a mild exercise, the terminal arterioles increase the number of perfused capillaries, resulting in increased surface area for exchange and O_2 diffusion. As a result, the metabolic requirement could be met with little change in blood flow during mild exercise [3, 95]. In response to a higher intensity of exercise and O_2 consumption, however, the feed arterioles will dilate to increase blood flow and oxygen supply into the exercise muscle fibers correlated with muscle fiber type, oxidative capacity, and patterns of muscle type recruitment [6, 34, and 138].

In summary:

(1) In response to exercise, terminal arterioles control capillary perfusion, while upstream or feed arterioles determine the blood flow distribution in terminal arterioles and downstream capillary groups (Figure 1.3).

(2) In response to mild exercise, terminal arterioles may regulate capillary perfusion and increase oxygen delivery without increasing blood flow.
(3) In response to high level of exercise, both upstream arterioles and terminal arterioles have to dilate to increase tissue blood flow and oxygen supply.

1.2.2 Factors Determining Capillary Perfusion

As shown in Figure 1.2, within a functional microvascular unit, the capillary group is supplied by a terminal arteriole, and the relaxation of which increases the total blood flow in downstream capillary group. Although a typical arrangement of a capillary bed is not found, the terminal arterioles are always in close contact with the tissue they serve, suggesting that the terminal arteriole is an important site in mediating capillary perfusion and blood flow within the exercising muscle (see REGULATION OF CAPILLARY PERFUSION DURING EXERCISE).

The relaxation of terminal arterioles during muscle contraction can be mediated by multiple factors such as the local concentrations of O_2, CO_2, H^+, and metabolic end products (see Chapter 2). One of the most important factors proposed to regulate the terminal arteriolar diameter is tissue oxygen concentration [O_2]. During skeletal muscle contraction, the decreased [O_2] leads to relaxation of terminal arterioles, thereby allowing more oxygen and nutrients delivery and an increased metabolite removal. In a theoretical model, the microvascular units can sense oxygen levels and transmit this information to the upstream feed arterioles via conducted responses (see Chapter 2); thus, the fraction of perfused capillaries increases gradually during muscle activation [148]. Since the feed arterioles are more important in mediating the muscle blood flow during exercise, a majority of studies in the feed arterioles have been performed to determine the mechanisms responsible for the blood flow control during exercise (see Chapter 2).

Capillary density and capillary-active muscle fiber distance are also factors affecting the total perfusion and oxygen delivery with a given arteriolar tone. An impaired oxygen delivery occurs when active muscle fibers are a distance of 50 μm or more from the nearest perfused capillary, which could be seen after microvascular rarefaction. Figure 1.4 shows the negative correlation between tissue PO_2 and its distance from the supplying capillary in rat mesentery circulation [60]. An oxidative muscle has a greater need for oxygen and thus a higher capillary density. There is evidence that capillary density in skeletal muscle determines oxidative capacity [98, 103] (maximal oxygen consumption) as well as the cardiac output in humans [161]. Oxygen consumption and cardiac output during exercise are discussed in Chapter 3. An elevated capillary density and capillary-to-fiber ratio along with improved exercise capability and functional hyperemia is reported in exercise-trained humans [221, 270]. During extreme exercise in trained athletes, the blood flow through skeletal

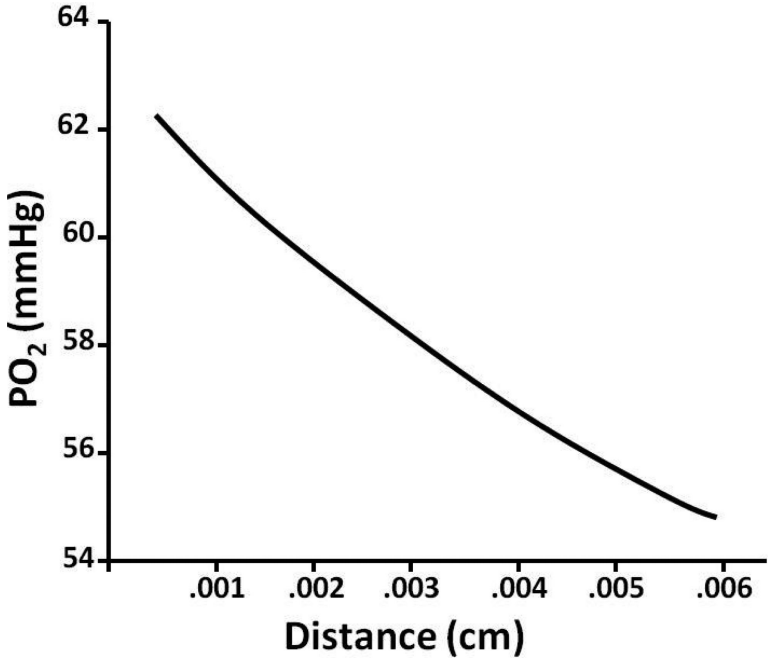

FIGURE 1.4: The PO_2 profile between a distance 5–60 μm away from the blood/wall interface. Adapted from [60], Figure 6.

muscle may increase 15 to 25 fold. It should be realized that, in addition to increased capillary density, the increased functional hyperemia following training can be also due to increased cardiac or arteriolar function. Conversely, a reduction in microvascular density of skeletal muscle has been shown to impair exercise intolerance of patients with chronic heart failure (Chapter 4) or peripheral artery disease [41, 203].

1.3 OXYGEN DELIVERY TO SKELETAL MUSCLE DURING EXERCISE

Oxygen delivery to tissues mainly occurs with capillaries and is determined by the cardiac output and oxygen content. When oxygen consumption is high (e.g., during exercise), the increased oxygen requirement is usually provided by an increased cardiac output. It is easy to understand how an

increase in cardiac output and blood flow increases oxygen delivery during exercise. If cardiac output doubles to 10,000 ml/min, then there is a corresponding doubling in oxygen delivery to tissue. The oxygen content of blood (ml O_2/100 ml) is determined by the blood hemoglobin concentration, the percentage of this hemoglobin saturated with oxygen, and the amount of oxygen dissolved in the plasma. Under normal conditions, *oxygen delivery (mls O_2/min) = Cardiac output (L/min) × Hb concentration (g/100 ml blood) × 1.34 (mls O_2/g Hb) × % saturation*. For example, a cardiac output of 5 l/min and Hb concentration of 15 g/100 ml blood with 100% saturation yields an oxygen delivery to tissue of 1000 ml O_2/min. A decreased cardiac output, a low hemoglobin concentration (anemia), or low hemoglobin O_2 saturation will result in an inadequate delivery of oxygen. The regulation of cardiac output during exercise will be discussed in Chapter 3. This section will discuss the other factors that affect the oxygen delivery from capillaries into exercising tissues.

1.3.1 Oxygen Gradient

Oxygen moves down the pressure or concentration gradient from a relatively high level in air, to the levels in the respiratory tract and then alveolar gas, the arterial, arterioles, capillaries, and finally, the cell, with the partial pressure of oxygen (PO_2) reaching the lowest level (4–20 mm Hg) in the mitochondria. This decrease in PO_2 from air to the mitochondria is known as the oxygen cascade. In capillaries, the arteriolar–venous O_2 difference is due to oxygen diffusing down the pressure gradient into the cell and mitochondria where the PO_2 is the lowest. During exercise, the increased alveolar PO_2 due to increased ventilation and the increased muscle oxygen consumption during exercise result in increased oxygen delivery from capillary into the contracting muscle (Figure 1.5) [200, 201]. A linear relationship has been found among work intensity, muscle blood flow, and O_2 uptake as well as the arterio venous O_2 difference [108].

Figure 1.7 describes how altered oxygen gradient affects oxygen delivery of capillary blood at rest and during exercise. At rest (Figure 1.6A), arterial PO_2 is 100 mm Hg and the tissue has a PO_2 of 40 mm Hg. As blood flows through the capillary, oxygen diffuses from the blood to the tissue reaching an equilibrium of 40 mm Hg as the blood leaves the tissue. At a PO_2 of 100 mm Hg, the arterial oxygen content would be 20 ml O_2/100 ml blood and a PO_2 of 40 mm Hg in the venous blood has an oxygen content of 15 ml O_2/100 ml blood. Thus, there is a net diffusion of 5 ml O_2/100 ml blood flow. During exercise, increased tissue metabolism (oxygen consumption) and the resultant fall in PO_2 increase the oxygen gradient for diffusion from blood to tissue. As shown in Figure 1.6B, tissue PO_2 falls to 20 mm Hg, and the venous blood would also reach an equilibration of 20 mm Hg. Arterial blood would still have 20 ml O_2/100 ml blood, but venous blood would now have 5 ml O_2/100 ml blood, increasing the net diffusion to 15 ml O_2/100 ml blood flow. Thus,

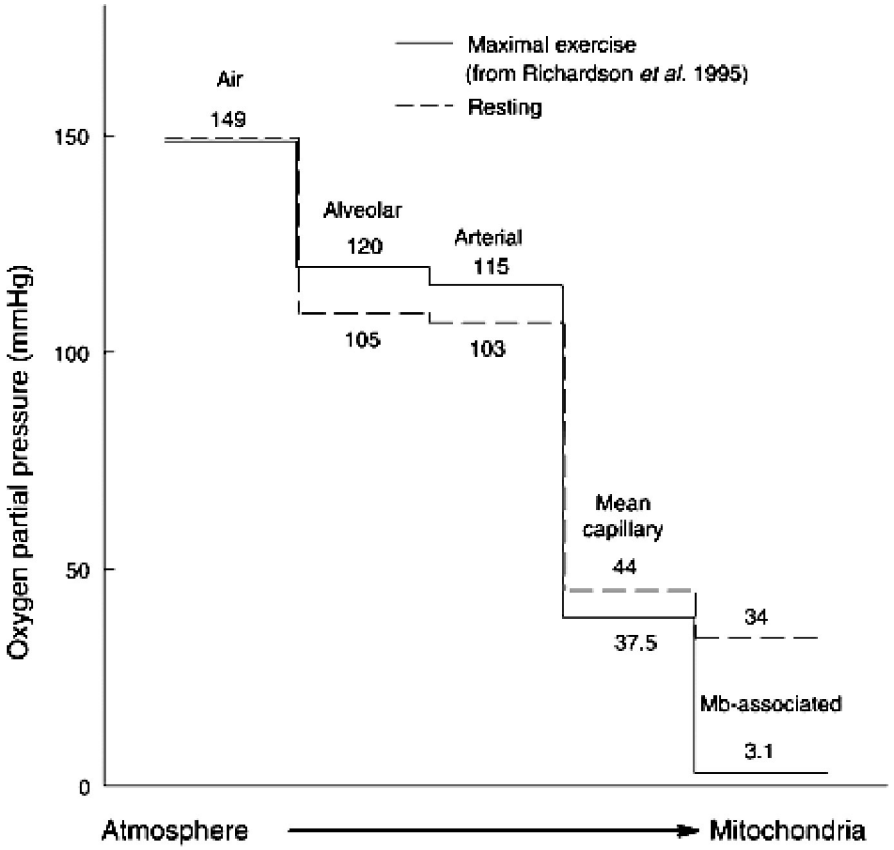

FIGURE 1.5: The O_2 cascade at rest and during maximal knee-extensor exercise in humans. Image from [200], Figure 5. Reproduced with permission from *J Physiol*, Wiley-Blackwell.

by decreasing the tissue PO_2, there can be significant increases in oxygen delivery to tissue and a greater extraction of oxygen from the blood. The increased extraction is important in skeletal muscle during increased metabolism, but is also important in tissues that exhibit a decreased blood flow during sympathetic stimulation that occurs during exercise (see Chapter 3).

1.3.2 Bohr Effect

Oxygen is carried in the blood in two forms: combined with hemoglobin (mostly) and dissolved in the plasma (small amount). Oxygen delivery to tissue is determined by the diffusion gradient from the hemoglobin to the tissue and the affinity of hemoglobin for oxygen. With a certain oxygen

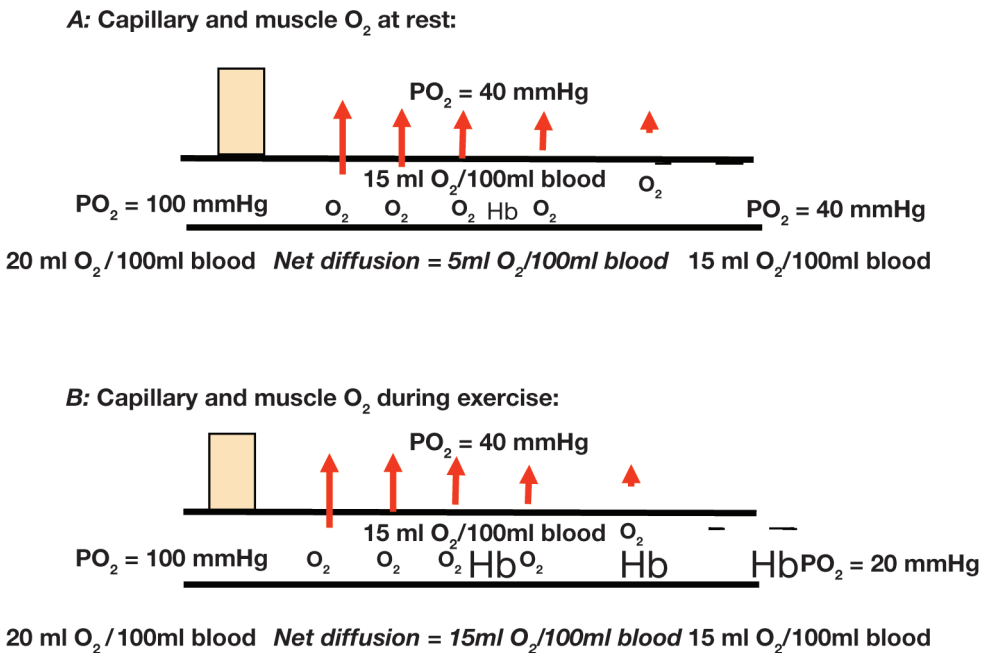

FIGURE 1.6: Oxygen delivery to tissue at rest and during exercise.

gradient, the oxygen delivery to tissue can be regulated either by altering blood flow or by altering the diffusion of oxygen from hemoglobin to tissue. For a male with normal hemoglobin concentration of 15 g/dl, there is approximately 20 ml O_2/100 ml of blood. Women with a normal hemoglobin concentration of 14 g/dl would have 19 ml O_2/100 ml blood. The Bohr Effect, first described in 1904 by the Danish physiologist Christian Bohr, states that an increasing concentration of protons and/or carbon dioxide will reduce the oxygen binding to hemoglobin. A shift in the hemoglobin dissociation curve to the right decreases affinity, allowing a greater unloading of oxygen from the hemoglobin at the same pressure gradient (Figure 1.7). It has been shown in humans that exercise decreases the capillary blood pH from 7.4 to 7.1 (continuous exercise) or 6.9 (intermittent maximal exercise) [77]. The decrease in capillary pH during maximal exercise may contribute to an elevated oxygen delivery via the Bohr Effect. Thus, during exercise, an increased metabolism and resultant production of protons and/or carbon dioxide can reduce the oxygen saturation and increase oxygen delivery. It should be realized that the Bohr Effect is more important when PO_2 is lowered. As shown in Figure 1.8, when the PO_2 = 100 mm Hg, such as in the pulmonary microcirculation or the feed arteries to skeletal muscles, the hemoglobin is the same (~98%) saturated at both pH 7.4 and

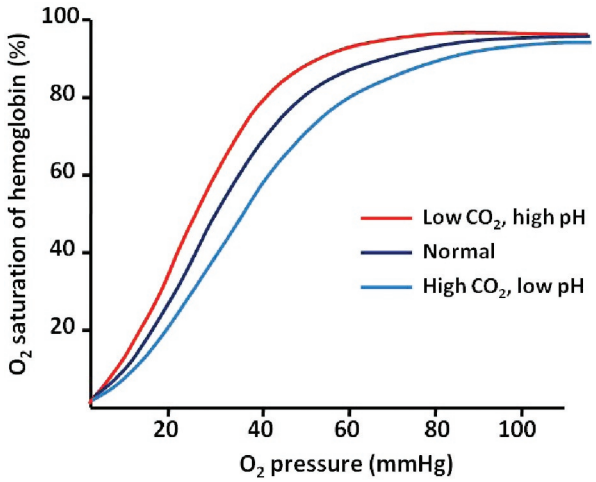

FIGURE 1.7: The effect of pH on hemoglobin dissociation curve at different PO_2 (Bohr Effect).

7.2. Thus, the binding of oxygen to hemoglobin in the lung microcirculation (gas exchange) or large arterioles in skeletal muscles is not affected by changing the pH and oxygen will load normally.

1.3.3 Oxygen Deficient at Onset of Exercise

The energy demand increases instantaneously at the onset of exercise while the actual O_2 uptake via lung lags behind for ~2 min (see Chapter 2). As shown in Figure 1.8, the gradual increase in

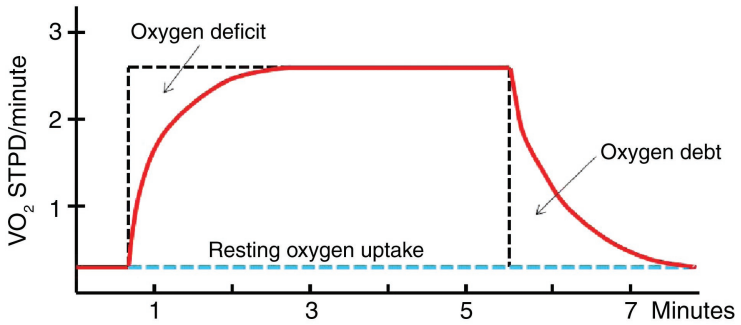

FIGURE 1.8: Oxygen uptake at standard temperature and pressure dry (STPD) during exercise. Adapted from *Textbook in Medical Physiology and Pathophysiology Essentials and Clinical Problems, 2nd Edition* (http://www.zuniv.net/physiology/book/content.htm). Used with permission from P.E. Paulev.

pulmonary oxygen uptake at the onset of exercise results in a transient "oxygen deficient" state. However, this oxygen deficiency does not cause a mismatch between metabolic requirement and oxygen delivery with exercising tissues at the onset of exercise. This is because the oxygen deficiency results in an extra increase in capillary-tissue oxygen gradient and decrease in pH, which in turn facilitate the oxygen delivery until the O_2 uptake in the lung is sufficient as seen in the steady state of exercise (see Chapter 2). In addition, as mentioned before, the microvascular units may "overperfuse" without a large increase in arteriole flow during the onset of exercise. This initial perfusion of capillaries may provide a feed-forward mechanism to minimize any delay in O_2 supply in the initial stage of exercise. The oxygen deficiency can be repaid by an extra amount of oxygen uptake in the post exercise period (oxygen debt) (Figure 1.8), which is responsible for the oxidation of 75% of the lactate produced as well as the conversion of 25% of the lactate to glycogen in the liver. However, the oxygen debt is often twice as high as the O_2 deficit.