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Forum Review

Oxygen Distribution and Respiration by the Microcirculation

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ABSTRACT

Longitudinal and radial oxygen gradients in the microcirculation due to oxygen release from arterioles show that in some tissues oxygen is primarily supplied by arterioles and secondarily by capillaries. In several tissues, the arteriolar rate of oxygen exit is too large to be explained by diffusion alone, indicating that in these tissues oxygen consumption of the arteriolar wall *in vivo* is much greater than that shown in *in vitro* studies of endothelium and vascular smooth muscle, a phenomenon that may be related to the synthesis autocoids by the endothelium *in vivo*. The functional significance of the high metabolic rate of the arteriolar vessels may be related to the need of providing a metabolic barrier for protecting the parenchymal tissue from high oxygen levels in arterial blood, thus reducing formation of oxygen free radicals in the perivascular tissue, a supposition supported by the finding that the radial oxygen gradient at the microvascular wall and therefore its rate of oxygen consumption are proportional to local blood oxygen partial pressure (pO_2). Oxygen consumption by the endothelium and/or smooth muscle is also a factor in causing terminal lymphatic pO_2 to have the lowest oxygen level in the tissue, rendering this compartment most vulnerable in hypoxic conditions. *Antioxid. Redox Signal.* 6, 1011–1018.

INTRODUCTION

THE PRIMARY FUNCTION OF THE CIRCULATION is undoubtedly the supply of oxygen to the tissues, a process whose energy requirement is supposed to be restricted to the mechanical energy expenditure of the heart and the lung, whereas the energy expenditure in the remainder of the circulation is assumed to reflect the oxygen metabolism of the blood vessel as a tissue mass. Given that blood vessels represent ~8% of the tissue of the organism (3), the oxygen requirement of this compartment would appear to be relatively modest if vessel wall tissue had the oxygen consumption characteristics of skeletal muscle at rest.

Data on the respiration of vascular tissue are mostly derived from isolated vessel segments, slices, or rings, and deal primarily with the oxygen consumption of smooth muscle, with no particular attention to the status of the endothelium. Howard *et al.* (11) utilizing the Cartesian diver technique were the first to report on the respiration of isolated arterioles of the hamster cheek pouch and mesenteric arterioles (65–150-μm diameter), indicating that these vessels consumed oxygen at the rate of 0.1 ml of O_2/min/g. This value is similar to that found by Sussman *et al.* (27) in isolated cerebral microvessels whose O_2 consumption ranged from 0.03 to 0.09 ml of O_2/min/g. Paul (19) extensively reviewed the respiration of vascular tissue and reported that the majority of measured values lie between 1.1 and 4.5×10^{-3} ml of O_2/min/g, a value that is comparable to the oxygen consumption of the human body as a whole, which is $\sim 0.2 \times 10^{-3}$ ml of O_2/min/g (37).

The idea that vascular tissue is a comparably small consumer of oxygen was challenged by the findings by Bruttig and Joyner (2), who used a manometric method to determine respiration of the endothelium and found that cultures with cell density of 6×10^5 cells/5 cm^2 consumed oxygen at the rate of 2.5 $\times 10^2$ ml of O_2/min/g. This rate of oxygen consumption was clearly out of proportion with oxygen consumption of the organism, which led these authors to propose that "organized tissue can inhibit potential cellular metabolism as much as 5,000-fold." This finding has been difficult to reconcile with similar data that subsequently became available, particularly the study

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of Kjellström *et al.* (13), who found that oxygen consumption of the endothelium in cell cultures ranged between 1.6 and 8 × 10^{-2} ml of O_2/min/g, depending on origin and species, and Motterlini *et al.* (18), who measured 5.6 × 10^{-2} ml of O_2/min/g for endothelial cells from the pig aorta.

Taken as a whole, these studies tend to support the concept of a relatively normal level of oxygen consumption for the endothelium. Thus, the two major active cellular components of the vascular wall, *i.e.*, smooth muscle and endothelium, would appear to present essentially normal rates of oxygen consumption. However, the data supporting this conclusion are derived entirely from experiments that measure respiration in cell cultures. It is clear that a manometric experiment of oxygen consumption of a blood vessel *in vivo* is not a practical approach; however, it is possible to determine with some reliability the compartments where oxygen is consumed in the tissue by methods of mass balance and the analysis of oxygen distribution in the tissue.

In this review, we present the current status of studies on the partition of oxygen between the blood compartment, the vascular wall, and the tissue, at the level of the microcirculation, where most of vascular tissue is located.

THE OXYGEN DELIVERY PARADOX

The classical scheme for tissue oxygenation is based on the observation that lung capillaries at the interface between the atmosphere and the circulation are the organic structures that bring oxygen into blood. The finding that capillaries permeate all amphibian and mammalian tissues led to the "mirror image" conclusion that these conduits, where red blood cells transit single file, reverse their function, releasing the oxygen acquired in the lung to the tissues (vice versa for carbon dioxide). This concept was reenforced upon the realization that both systems of capillaries from tissue and lungs present large surface areas for exchange. However, exchange is also determined by the oxygen concentration gradients that drive the material transfer. Capillary/tissue O_2 gradients are maximal in the lung (50 mm Hg/μm) and minimal in the tissues (0.5 mm Hg/μm). This large disparity is in part compensated for by the larger tissue versus lung capillary surface area, showing that tissue and lung respiration are quantitatively different. Thus, the possibility exists that they may also be qualitatively different.

Direct examination of the role of capillaries in tissue is elusive due to the lack of adequate experimental techniques. Lung capillaries are equally intractable from an experimental viewpoint; however, the lung presents defined gas and blood inputs and outputs, providing a basis for modeling lung capillary transport events. This situation is not present in tissues, and the gas exchange within the tissue has relied on theoretical analysis (15) focused on how gases are exchanged between blood flowing in a cylindrical conduit, the single capillary, and a surrounding tissue cylinder. Understanding of the process of tissue oxygenation has been extrapolated from the characteristics of this model. A critical assumption is that most of the oxygen is exchanged at this level, which implies the existence of large blood/tissue oxygen gradients in a substantial portion of tissue capillaries. Most capillaries, however, as a consequence of the extreme surface-to-volume ratio, are in near oxygen concentration equilibrium with the tissue and therefore lack the oxygen gradient necessary to deliver oxygen.

The necessary oxygen gradients for driving oxygen into the tissue are present in arterioles. In most tissues, average capillary partial pressure of oxygen (pO_2) is ~ 25 mm Hg, a value that must be viewed in relation to the shape of the oxygen dissociation curve for hemoglobin, which shows that, for most mammals, 50% of the oxygen in blood is released when blood pO_2 is 28 mm Hg. Therefore, at least half of the oxygen in blood exits the blood vessels prior to arrival in the tissue, and as venular (and venous) pO_2 is higher, little or no oxygen is contributed by the capillaries. It is to date an open question: what is the oxygen distribution in the heart? It would seem unlikely that entrance capillary pO_2 is at the level of arterial blood, and most likely the oxygen pO_2 distribution follows the same pattern as in other tissues. In the heart, the extensive capillary network may be a mechanism for insuring uniformity of tissue pO_2 rather than the supply of oxygen; however, to date, there are no data describing the path that oxygen follows in arriving in the heart tissue.

Fifty percent of the oxygen in blood is delivered to the tissue by arteriolar and arterial vessels. Furthermore, tissue pO_2 has seldom been reported to be <20 mm Hg in normal conditions, at which value capillary blood, presumably in oxygen equilibrium with the tissue, is 30% saturated. Therefore, capillaries, in general, deliver at most 20% of the oxygen in blood; however, this value, as we will show, may be overestimated.

In general, arterioles are as important as capillaries in supplying oxygen to the tissue and, in some instances and tissues, they may have the principal role. This result was implicit to the work of Duling and Berne (6), who measured the distribution of pO_2 in the microvascular network of skeletal muscle with polarographic microelectrodes and found that a substantial amount of oxygen exited the microvessels prior to blood arriving in the capillaries. This finding, subsequently verified by Pittman and Duling (20), using a spectrophotometric technique for measuring blood pO_2, when combined with local blood flow measurements showed that arterioles release oxygen at a greater rate than that predicted by the oxygen gradients measured by microelectrodes in the surrounding tissue (21). This phenomenon was verified by Intaglietta *et al.* (12), using a newly developed optical technique (28) that allows the measurement of pO_2 in the microvessels' blood and the surrounding tissue. Information showing that arterioles are major oxygen suppliers to the tissue has been available since measuring techniques for mapping oxygen in the microcirculation became available; however, the universal perception reported in the physiology texts is that capillaries are the structures oxygenating the tissue, a concept based on the purely theoretical work of Krogh (15) and which has not been experimentally verified by direct measurements.

CURRENT FINDINGS ON MICROVASCULAR AND TISSUE pO_2

The presently available technology of phosphorescence quenching for measuring pO_2 optically in the microvessels and the surrounding tissue (26, 28, 36) has allowed for *in vivo* analysis of the assumptions in the Krogh model. Results for skeletal muscle at rest, subcutaneous muscle, and connective tissue of the hamster model (12) and the rat mesentery (9) show the following:

(A) Capillary blood pO_2 is only slightly higher (~5 mm Hg) than tissue pO_2.
(B) Arterio/venous capillary pO_2 differences are small, because tissue pO_2 is uniform, and capillaries are close to pO_2 equilibrium with the tissue.
(C) The only tissue domain where pO_2 exhibits large gradients is the immediate vicinity of the microvessels, a tissue compartment whose main constituent is the microvascular wall.
(D) A major portion of blood oxygen is delivered to the tissue by the arterioles.
(E) Terminal lymphatic fluid has the lowest oxygen tension of the tissue.

Some of these findings have been previously reported, but have lain dormant because they were not available from measurements based on a single methodology or experimental setting, and consequently did not present a cohesive perspective. In the following, we discuss the salient features of the distribution and consumption of oxygen in the microcirculation.

OXYGEN GRADIENTS IN THE MICROVASCULAR WALL

Development and implementation of the phosphorescence-decay oxygen-measuring optical technology allowed for the first time an accurate mass balance analysis to be made on the decrease of oxygen content in the arterioles and to establish how this was related to the diffusional flux of oxygen out of the microvessels determined by the oxygen gradients in the surrounding tissue (Fig. 1). These measurements, made simultaneously inside and outside the microvessels (24, 32), show that oxygen exit from microvessels is driven by steep oxygen gradients at the microvascular wall (Fig. 2), a feature consistent with the hypothesis that the consumption of oxygen by the microvascular wall is high, and therefore it is a large oxygen sink. These steep gradients are present in arterioles, and to a lesser degree in capillaries and venules. The steep gradient could also be due to the presence of a large resistance to diffusion in the vessel wall (10), but this would not make it possible for oxygen to exit at the rates that have been measured.

Large oxygen consumption should be evident in terms of a measurable biological activity. In the case of endothelium, although their mitochondrial density is not very high, the many biochemical functions of these cells require oxygen (13). The biochemical functions of these cells include synthesis and secretion of renin, prostaglandins, collagen, endothelin, prostacyclin, endothelial relaxing factor, interleukin, factor VIII, degradation of bradykinin and prostaglandins, clearance of proteins, lipids, and lipoproteins, conversion of angiotensin I to II, expression of antigens, and mechanical work in contracting against blood pressure.

Smooth muscle may also participate in this metabolic process although a steady level of contraction is presumed to be maintained by a non–energy-consuming latch mechanism. It should be noted that this ratchet-like mechanism only saves

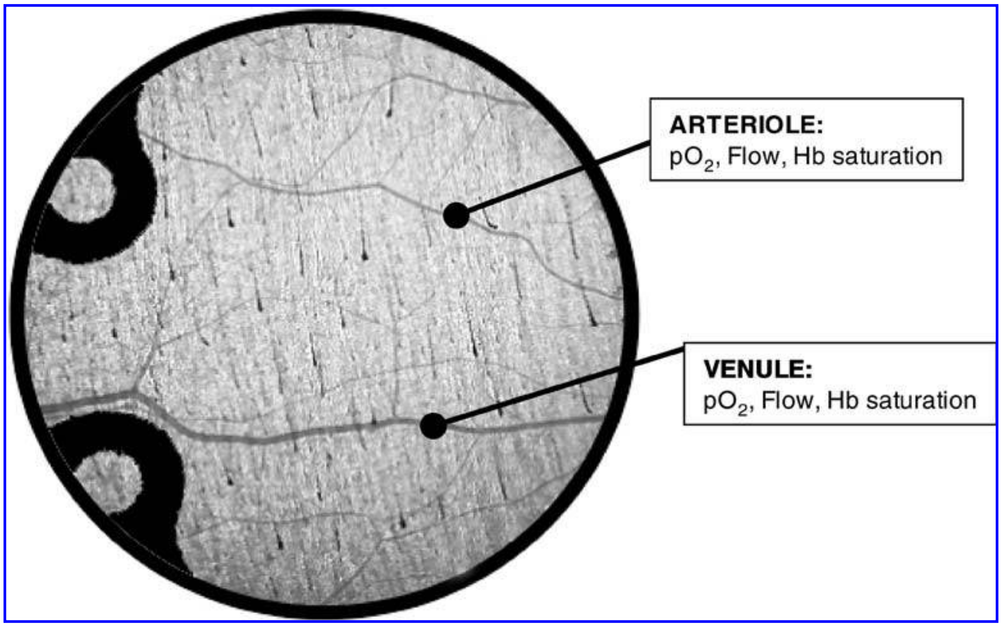

FIG. 1. Methodology for carrying out mass balance calculation in the microcirculation. The preparation of choice is the hamster chamber window model, which allows the observation of the microcirculation for periods of up to 1 week without anesthesia, and prevents exposure of the tissue to the environment. Blood and tissue pO_2 can be measured along any segment of the microvasculature, across the microvasculature, and in the tissue. These data are used to determine the oxygen-carrying capacity of blood and then, when coupled with the vessel diameter and red blood cell velocity measurements, which allow for the determination of local blood flow, the precise oxygen mass balances at all microvascular branching levels and for the whole microvascular network are calculated. Hb, hemoglobin.

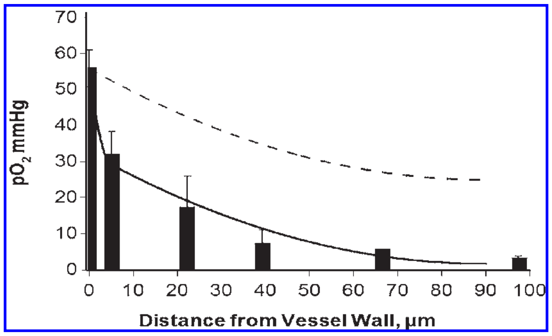

FIG. 2. pO_2 profile in the immediate vicinity of the arterioles in the rat mesentery. Fitting of these data to the oxygen profile deduced by solving the diffusion equation shows that the medium beyond the blood/tissue interface must be divided into two zones with significantly different rates of oxygen consumption, where the outside of the vessel wall rate is two orders of magnitude higher than that in the remainder of the tissue. The shaded area represents the portion of the tissue that is occupied by the vessel wall. The dotted line represents the oxygen gradient in the tissue in the absence of oxygen consumption at the vessel wall. Data are from Tsai *et al.* (32).

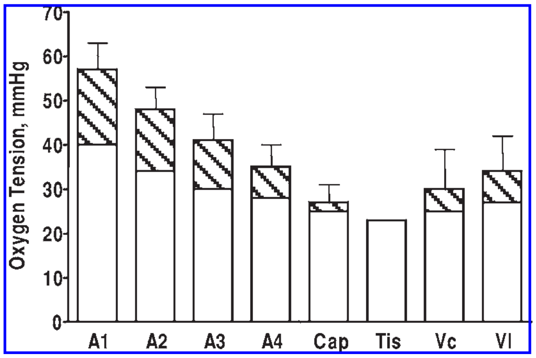

FIG. 3. Distribution of oxygen in the microcirculation of the hamster window chamber preparation. Intravascular pO_2 values are shown as height of the bars, and extravascular values immediately outside the wall are shown as open bars. The shaded portion of the bar represents the difference between the intravascular and perivascular pO_2. The vessel diameters for each order of branching are as follows (µm, mean ± SD): A1, 85.1 ± 23.1; A2, 28.4 ± 11.7; A3, 9.8 ± 3.2; A4, 6.4 ± 2.1; Vc, 21.0 ± 5.9; Vl, 88.7 ± 34.5. It should be noted that the source of oxygen to the tissue is not blood, but the blood/blood vessel combination taken as a unit. Therefore, the pO_2 that determines the rate of transfer of oxygen from the blood vessel to the tissue is the pO_2 at the outer microvessel surface, a parameter that is more directly related to tissue oxygenation than blood pO_2. Data are from Intaglietta *et al.* (12). A1–A4, arteriolar orders; Cap, capillary; Tis, tissue; Vc, collecting venule; Vl, large venule.

energy in steady contraction, and not in conditions of steady-state variability of microvessel diameter termed vasomotion, which is consistently observed in *in vivo* investigation of the microcirculation (4). The continuous modulation of vessel wall diameter causes a steady rate of mechanical energy expenditure by the vessel wall as its moves against blood pressure when the diameter decreases.

Taken as a whole, this ensemble of data leads to generalizations not contemplated within the current paradigms of oxygen management at the microscopic level of the tissue. Consequences arising from this analysis are as follows:

(A) Endothelium and smooth muscle act as a barrier to the passage of oxygen from blood to tissue, protecting the tissue from the high oxygen content (pO_2) of blood by consuming the oxygen that exits the arterioles.
(B) One of the goals of basal tissue perfusion is to supply oxygen to the endothelium and smooth muscle.
(C) Oxygenation of working tissue (exercising skeletal muscle) results from:
    (a) Lowering of the vessel wall oxygen consumption barrier.
    (b) Increased perfusion with oxygenated blood.
    (c) Deployment of a biochemical process that protects the tissue from high pO_2 levels.
(D) Under basal conditions, tissue capillaries only partially serve to supply oxygen to the tissue. They may be a structure to expose the endothelium to blood in order to fulfill the large oxygen demand of these cells, and provide for the extraction of CO_2 and other products of tissue metabolism, such as lactic acid.

A key question is whether endothelium has the same oxygen requirements throughout the organism, such as in the venular and lymphatics systems. If we analyze the distribution of pO_2 in the microcirculation, it becomes apparent that, in most tissues, blood pO_2 increases in the venular circulation as blood moves from the collecting venules to the larger venular vessels (Fig. 3). In other tissues (33), the venular pO_2 is uniform as blood progresses along the venular circulation. Both pO_2 distributions require the presence of a convective and/or diffusional oxygen shunt. Such a mechanism may be fortuitous, but may also be necessary to insure an adequate oxygen supply to the venular and venous endothelium.

THE LYMPHATIC ENDOTHELIUM COMPARTMENT

The endothelium and smooth muscle of the lymphatic system present a special case, because they derive their oxygen supply from the abluminal side of the vessels, a compartment with limited oxygen supply capacity. This situation suggests that as the lymphatic cellular lining has no direct access to oxygen sources other than the tissue, it may have a lower metabolism than the vascular counterpart, a condition that may be related to its lack of exposure to significant levels of fluid-induced shear stress.

Our studies show that endothelial lymphatic cells and smooth muscle are a metabolically active compartment because measurements of tissue/lymph pO_2 differences in the mesentery are of the order of 10–11 mm Hg in collecting lymphatic vessels, endowed with smooth muscle (9). Terminal lymphatic vessels whose primary cellular component is endothelium only show a difference of 3 mm Hg across their vessel wall. Therefore, smooth muscle and endothelium in the lymphatic systems appear to be adapted to a regime of oxygen consumption that is significantly different from that of similar cells placed next to the oxygen source in the tissue.

In a physiological context, Krogh (15), in his analysis of the distribution of tissue pO_2 in the vicinity of capillaries, proposed the existence of a specific region of tissue that has the lowest tissue pO_2, leading to the definition of the "lethal corner," namely, the midpoint in the tissue at the exit of a parallel array of capillaries. This conceptualization, based on a model of tissue oxygenation by parallel capillaries of concurrent flow, showed that this portion of the tissue was the least oxygenated locality, and therefore the most vulnerable to reduced oxygen delivery. This concept was superseded by the work of Ellsworth *et al*. (7), who showed that the random disposition of capillaries and directions of blood flow led to a mostly uniform pO_2 distribution in the tissue.

Oxygen consumption by the lymphatic system cellular components is the most probable cause for the lymph fluid pO_2 to be uniformly lower than tissue pO_2; however, the rate of oxygen consumption by the lymphatic microvessel is a small fraction of the total oxygen requirements for the organism. This fraction can be estimated considering that lymph flow in an adult individual is about a whole body blood volume per day, or 5 L per 24 h. As the oxygen solubility in lymph is the same as in water (2.14×10^{-5} ml of O_2/cm^3), then extrapolating this local microvascular finding to the whole system shows that the magnitude of this process is ~1 ml of O_2 per day. This low rate of oxygen consumption is commensurate with a low oxygen availability for this system; thus, if a highly metabolic cellular species such as lymphatic metastasis or bacterial infection were to develop in this system, it is likely that anaerobic conditions might develop.

REGULATION OF ARTERIOLAR VESSEL WALL OXYGEN CONSUMPTION

The arteriolar vessel wall appears to constitute an active gate for the passage of oxygen. In terms of the mechanism that controls this gate, *i.e.*, vessel wall oxygen utilization, there is evidence from cell cultures, whole organ studies, and whole body studies showing that nitric oxide (NO) is directly involved in the control of mitochondrial activity, acting to reduce cell respiration. Inhibition of NO production significantly increases oxygen respiration by the tissue through a mechanism that affects mitochondria (8, 38). Vallet *et al.* (35) and Shen *et al.* (23) reported increases in whole organ and body oxygen consumption as large as 30% due to NO inhibition. However, their experiments could not differentiate between the respiration of the vessel wall and that of the tissue *per se*.

A better understanding of how vessel wall respiration is regulated by NO can be obtained by examining how the vessel wall gradient changes when the production (and availability of NO) is blocked. In our experiments with the inhibition of NO production with N^{ω}-nitro-L-arginine methyl ester (L-NAME) in the hamster skin fold preparation, it was shown that this process causes vasoconstriction and elevation of mean arterial blood pressure from 100 to 120 mm Hg. The vessel wall gradient in 50-μm diameter arterioles increased from 18.4 mm Hg in control to 26 mm Hg, whereas tissue pO_2 decreased from 24 to 21 mm Hg.

Our experiments show that vessel wall oxygen gradients increase with vasoconstriction, which correlates directly with measurements in whole organs (39), whereas vasodilation reduces the vessel wall gradient to that characteristic for the oxygen expenditure of the surrounding tissue (this phenomenon was observed by us in the arteriolar network during preliminary studies with the systemic administration of prostaglandin E_2, which causes both vasoconstriction and vasodilation of arterioles without a change in tissue pO_2).

An alternative to the inhibition of NO production is NO scavenging by free hemoglobin in the circulation. This process is particularly relevant to the development of molecular hemoglobin-based oxygen-carrying blood substitutes, which in most instances produce vasoconstriction by a mechanism presumed to be directly related to NO scavenging. Our experiments show that substitution of 60% of the original red blood cell mass with 10% *O*-raffinose cross-linked human hemoglobin (Hemolink®, Hemosol, Inc., Toronto, ON, Canada) during hemodilution increases the wall gradient of 50 μm arterioles to 23 mm Hg (control 18 mm Hg), and reduces tissue pO_2 to 17 mm Hg. Substitution of 80% of the natural blood with the same solution increases the wall gradient to 28 mm Hg and reduces the tissue pO_2 to 5 mm Hg. These results suggest that NO scavenging by free hemoglobin has a direct effect in increasing endothelial oxygen consumption.

EVIDENCE OF VASCULAR AND MICROVASCULAR RESPIRATION FROM WHOLE ORGAN STUDIES

Curtis *et al.* (5) denuded the endothelium from the vasculature of the dog hind limb using a detergent and found that oxygen consumption of the preparation decreased by 35%. These authors analyzed in detail the causes of this phenomenon and concluded that the observed changes were due to an overall decrease in oxygen consumption by the tissue under study. Considering that the endothelium is on the order of 0.1% of the tissue mass, it appears that its oxygen consumption *in situ* is ~350 times higher than that of the remainder of the tissue, an estimate similar to that of Tsai *et al.* (32) obtained at the level of single arterioles.

Ye *et al.* (39) perfused the rat hind limb, kidney, intestine, and mesentery at constant flow, and found that vasoconstriction induced by the administration of noradrenaline or vasopressin significantly increased oxygen consumption, *i.e.*, the amount of oxygen extracted from the perfusion solution. Direct measurements of blood oxygen extraction established that blood vessels in the mesentery consumed oxygen at the rate of 115 μmol/h/g wet weight of blood vessels at 25°C, and that this value increased by 75% upon constriction. These same authors reported that the basal oxygen consumption of the rat hind limb is 14.5 ± 0.3 μmol/h/g. As vasoconstriction *per se* lowers tissue perfusion in terms of functional capillary density (31), it is not likely that the increased oxygen consumption was due to improved perfusion of the tissue due to increased arterial pressure.

Marshall and Davies (17) reported a significant increase in oxygen consumption in the hind limb of the rat adapted to chronic systemic hypoxia when these rats breathed room air. The increase in consumption was attributed to the vascular tissue, corresponding to a respiration rate of 0.18 ml of O_2/min/g. The exact interpretation of this result is in part dependent on the portion of vasculature that is assumed to consume oxygen. These authors used the number of 3.4% as the ratio of vascular tissue to whole tissue mass (19); however, if oxygen consumption occurs mainly in the arterioles representing only ~0.4% of the tissue mass, then the oxygen consumption of the arterioles is 1.53 ml of O_2/min/g, a value similar to that of Tsai *et al.* (32).

FUNCTIONAL ASPECTS OF ARTERIOLAR WALL OXYGEN CONSUMPTION

Oxygen consumption by the endothelium is presumably directly related to its viability as a tissue; therefore, injury and/or functional disruption would decrease the oxygen metabolism of these cells. This effect can be demonstrated by damaging the *in vivo* endothelium by using a light/dye combination method to disable endothelial function by means of oxygen free radicals liberated from injected fluorescein exposed to sufficiently high intensity illumination to cause this dye to fluoresce. This is a technique used for abolishing NO release from the endothelium in studies of flow-induced vasodilation (14). In these experiments, under normal conditions 30-µm diameter arterioles have an intravascular pO_2 of 31 ± 4 mm Hg, a wall gradient of 14 ± 3 mm Hg, and tissue pO_2 of 17 ± 4 mm Hg. As shown in Fig. 4, when the endothelium is disabled with the light/dye technique, blood pO_2 remains the same, the oxygen gradient falls to 7 ± 2 mm Hg, and the perivascular tissue pO_2 rises to 24 ± 6 mm Hg. In these experiments, there is no evidence of changes in the untreated tissue region adjacent to the arteriole. These results support the concept that the vessel wall/endothelium of arterioles is a region of high oxygen consumption, and that when this oxygen consumption is decreased (or eliminated), the perivascular oxygen level increases.

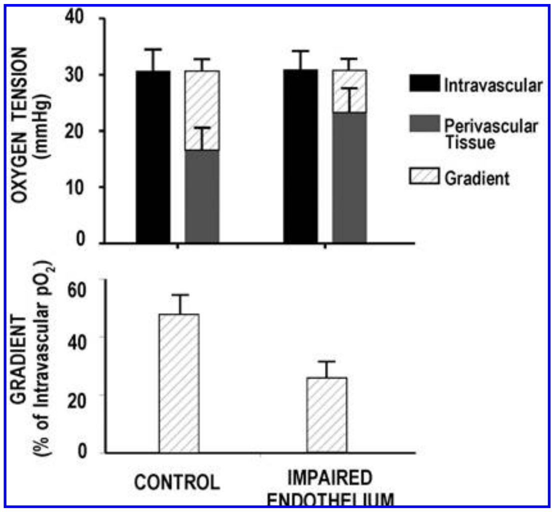

FIG. 4. Vessel wall gradient in arterioles of the hamster window preparation. Under normal conditions, the wall gradient for the size vessel studied is 14 mm Hg. Exposing the endothelium to a phosphorescent dye and illuminating a portion of the vessel disables the endothelium and reduces the wall gradient, increasing tissue pO_2 because oxygen consumption by the vessels wall is decreased. The treated vessel segment shows no response to acetylcholine and dilates when treated with papaverine, indicating that smooth muscle in the affected region was functional, whereas the endothelium did not provide the conventional responses.

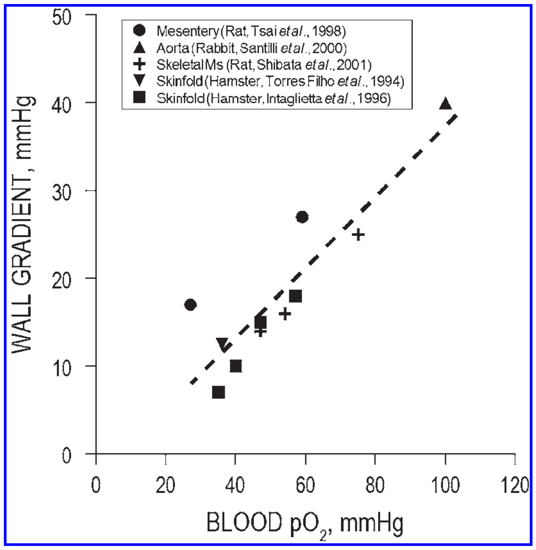

FIG. 5. Difference in oxygen tension across the arteriolar wall/endothelium as a function of blood pO_2. The trend of the data suggests that the difference in pO_2 that is directly proportional to the rate of oxygen consumption near the endothelial layer of the vessel wall is a function of the blood pO_2 that is in contact with the endothelial layer. ●, mesentery (32); ▲, aorta (22); +, skeletal muscle (25); ▼ and ■, skinfold (12, 30).

There is evidence that the oxygen loss in the arteriolar network depends on the metabolic activity of the organ/tissue involved, the vessel wall oxygen consumption being steepest in regions with low rates of metabolic activity (34) and vice versa. The functional significance of this extraordinarily high metabolic rate of the arteriolar vessel wall remains to be determined, but it may provide a metabolic barrier to protect the parenchymal tissue from the high oxygen level of arteriolar blood and, for instance, reduce the formation of oxygen free radicals in the perivascular tissue (1, 16). In this context, it should be noted that the radial oxygen gradient and therefore the rate of oxygen consumption of the blood/tissue interface for all vessels are directly proportional to the level of blood oxygen, as shown in Fig. 5.

SUMMARY AND CONCLUSIONS

Detailed analysis of the distribution of oxygen at the microscopic level shows that, in the major tissue masses of the organism at rest, oxygen is delivered by arterioles, and this delivery is modulated by the arteriolar vessel wall oxygen consumption. The capillary circulation may serve to distribute oxygen, particularly when the tissue is active, as in exercising skeletal muscle; however, its function at rest is predominantly to extract from the tissue slowly diffusible byproducts of metabolism. Capillaries may also serve as the supporting scaffolding for providing the endothelium with a maximal exposure to the oxygen supply, needed to support the large biochemical activity of this tissue. This new approach and interpretation of the oxygen transport in tissue became possible when new techniques were applied to the analysis of oxygen distribution in the microvasculature and the surrounding tissue (29). This approach reveals the presence of substantial gradients in the vicinity of microvessels, a configuration that corresponds to comparatively large oxygen consumption by the endothelium and/or smooth muscle. Vascular responses that lead to vasoconstriction can increase vessel wall oxygen consumption and lower functional capillary density. NO appears to be an important modulator of tissue oxygenation because of its dual action in controlling blood and tissue respiration, particularly the oxygen consumption of the arteriolar vessel wall. Vasoconstriction increases vessel wall oxygen consumption, and vasodilation may have the opposite effect, with direct consequences on tissue oxygenation.

The hypothesis that the arteriolar microvascular vessel wall is an important oxygen sink may provide the explanation for the clinical observation that tissue that appears to be normally perfused from macroscopic considerations, such as diabetic ulcers, does not heal due to the lack of microscopic tissue oxygenation. It may lead to a broader concept for the treatment of ischemia, which would involve lowering vessel wall (or endothelial cell) oxygen consumption as a method for increasing tissue oxygenation. It may help to explain why currently developed hemoglobin-based plasma expanders do not provide oxygen in proportion to the blood's hemoglobin content, and show how to improve their efficacy. In summary, we show that tissue oxygenation requires both the presence of oxygen delivery capacity and the control of the oxygen consumption by the microvasculature.

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ABBREVIATIONS

NO, nitric oxide; pO_2, partial pressure of oxygen.

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