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Does the Vessel Wall Partition Oxygen Away from the Tissue?

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ABSTRACT

The microvascular wall is metabolically active and plays a key role in maintaining homeostasis. Additionally, it regulates the delivery of nutrients to the tissue and removal of its byproducts. Large oxygen gradients have been found to occur across the vessel wall. By using pharmacologic challenges, studies have demonstrated that the vascular wall regulates oxygen release from the blood to the tissue. Thus, these findings lead to the hypothesis that vasoactive substances used clinically may inadvertently partition proportionately more oxygen to the vascular wall and reduce the amount received by the tissue, leaving it potentially at risk. *Antioxid. Redox Signal.* 9, 985–989.

MICROVESSELS are not static tubes that exist merely to perfuse the tissue with blood, but instead, they actively function to regulate blood flow for homeostasis. They are the interface between the blood and the tissue and comprise a single layer of endothelium and variable layers of smooth muscle, except in capillaries, where only a single layer of endothelium is found. This partition constitutes one of the most biologically active regions for the chemical production of many vasoactive substances that require oxygen. These components of the vascular wall continuously interact and produce physical changes in response to blood flow and shear stress in the form of biochemical products that play a major role in maintaining the tissue conditions within the homeostatic range. They regulate the flow of oxygen into the tissue by physically redistributing the blood to the tissue dynamically, thus increasing or decreasing their own metabolic rate, which allows the tissue to receive lower or higher amounts of oxygen.

Earliest studies to determine the respiratory rate of the vessel wall focused on the role of the smooth muscle. Excised vessel segments from various tissues studied with the cartesian diver microrespirator technique showed an oxygen consumption rate directly proportional to the vessel diameter (10). The studies reported that active and passive contractions of excised vessels were proportional to the tissue's metabolic rate (13). An extensive review (19) of the energetics of smooth muscle indicates that the oxygen-consumption rate of vascular tissue is in the range of $1.1–4.5 \times 10^{-3}$ ml O_2/min/g. The oxygen-consumption rate of endothelial cells measured in cell cultures is in the range of $2–8 \times 10^{-2}$ ml O_2/min/g, depending on origin and species. The oxygen consumption rate of endothelial cells from the pig aorta was 5.6×10^{-2} ml O_2/min/g when measured by using the phosphorescence technique (17). Whole-body oxygen consumption is estimated to be about 0.2×10^{-3} ml O_2/min/g (31). These findings were obtained from experiments using isolated vessels and cell cultures; however, these conditions do not completely reproduce those of the intact vasculature *in vivo.*

OXYGEN LOADING AND RELEASE

Delivery of oxygen to tissue is one of the most important tasks for the circulatory system, but how oxygen is finally distributed to the tissue after loading in the lung is not completely understood. The hemoglobin is saturated with oxygen in the lung capillaries with a large capillary/tissue oxygen concentration gradient (50 mm Hg/μm), and then, following the oxygen–hemoglobin dissociation curve, is off-loaded to the tissue where a small oxygen-concentration gradient is found

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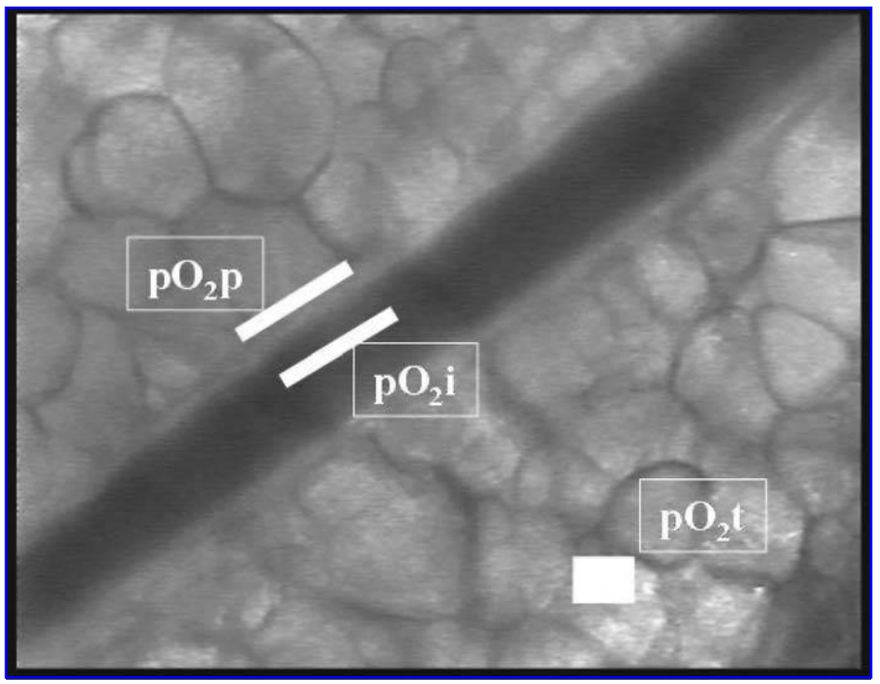

FIG. 1. Phosphorescence-quenching technique for intravascular (pO_2i) and extravascular (perivascular, pO_2p; tissue, pO_2t) pO_2 measurements. Solid white bars, site of oxygen measurement, and the size of the measurement area can be adjusted. The measurements are made in the hamster window model. The diameter of the arteriole is ~50 μm.

(0.5 mm Hg/μm). Therefore, tissue capillaries may not be sufficient for ensuring oxygen delivery to the tissue, suggesting that oxygen release from blood to other portions of the vasculature likely occurs.

The classic Krogh cylinder model, in which oxygen is diffused from the blood directly into the surrounding tissue, led to the concept of capillary density and anoxic regions in the tissue termed the "lethal corner" (14). The major assumption in this model is that capillary blood pO_2 is high enough to cause a substantial diffusion of oxygen from blood in these vessels to the tissue. However, because of the large surface-to-volume ratio found between capillaries and the tissue, oxygen concentration in the capillaries is in near equilibrium with that in the tissue, and therefore, the oxygen gradient necessary to drive oxygen from the blood in large amounts is not present at the capillary level in many tissues (28).

Longitudinal oxygen gradients were found when intravascular oxygen distribution was measured by using polarographic microelectrodes in the hamster cheek pouch (21). These measurements show that at least 67% of the oxygen loaded in the lung exited before blood arrived at the capillaries, indicating that capillaries are not the sole suppliers of oxygen to the tissue. A similar longitudinal gradient was found in the awake hamster model by Kerger *et al.* (11) by using the phosphorescence-decay technique in which the greatest decrease in pO_2 was in the arteriolar network. The conclusion from these findings is that the majority of oxygen delivered to these tissues is supplied by the arteriolar network, and the capillaries do not play a role in this process. Thus, the idealized situation proposed by Krogh, in which capillaries are the sole supplier of oxygen to the tissue, has not been corroborated experimentally.

Experimental and theoretic studies of oxygen delivery focused on understanding and accounting for the substantial oxygen loss from the arterioles. Shunting of oxygen from arterioles to parallel venules was shown to account for some of the oxygen lost during normal conditions (22). Arteriolar oxygen diffusion to over- and underlying capillaries was found to account for no more than 40–50% of the arteriolar loss (5). Studies on the variability of the diffusivity of oxygen in the vessel wall could account for only an increase of 10–15%.

Development of optical noninvasive phosphorescence quenching microscopy (PQM) (27) allows quantification of both intravascular and perivascular pO_2 with high resolution. By knowing the location of the measurement, this technique also allows estimation of oxygen extraction within a microvascular network from the difference between the oxygen delivery to the feeding arterioles and the draining venules. Figure 1 illustrates typical placement of the measurement window to assess oxygen at the microvascular level. Studies in the microvasculature of the hamster window-chamber model, rat mesentery, and cremaster muscle have led to several new concepts of how oxygen is delivered to the tissue. The arterioles and not the capillaries are the main suppliers of oxygen to the tissue. The largest gradient of oxygen is between the blood and the perivascular tissue. The tissue pO_2 is nearly the same as that of the capillaries; thus, most oxygen is not transferred from the capillaries to the tissue because of the lack of a diffusion gradient.

THE VASCULAR WALL AS AN OXYGEN SINK

Phosphorescence-quenching microscopy provides a new direction in the analysis of oxygen transport to tissue because it allows simultaneous optical measurement of pO_2 in microvessels and the surrounding tissue (26, 27, 30). The power of this technique was realized when it was used to calculate the mass balance of oxygen from *in vivo* measurements to determine

oxygen loss, a measurement not possible with earlier methods. Mass-balance analysis equates the difference between the oxygen delivered upstream and downstream (longitudinal convective loss) to the amount exiting the vessel in the radial direction (diffusion and consumptive loss). Measurements in the rat mesentery (29) and skeletal muscle (23) found large radial gradients and, concomitantly, a longitudinal gradient, which confirmed that oxygen indeed exits into the tissue. Furthermore, the diffusive resistance to transport hypothesized to exist from engineering and mathematical models were shown not to exist *in vivo* under normal conditions. The steep radial gradients at the vessel wall in combination with the measured high rates of oxygen exit show that the vascular wall is an oxygen sink and thus has a high oxygen-consumption rate. The gradient is essential to promote oxygen exit from the arterioles by diffusion to the tissue.

The use of PQM technique to measure pO_2 in the tissue was at first rejected because the albumin–porphyrin was thought not to be able to extravasate. There were also technical problems related to the use of very high light excitation, which consumed oxygen and rendered the phosphorescence signal undetectable. Improvements in the technique currently provide reliable tissue measurements, including measurements in the lymphatic vessels (8).

OXYGEN CONSUMPTION BY THE VESSEL WALL

Oxygen consumption is usually directly related to the number of mitochondria (18). The number of mitochondria within the endothelial cell is not high enough to be consistent with the high oxygen gradient across the vessel wall. However, the biochemical functions of the endothelial cells, many directly involved with autoregulation, require oxygen. These molecules include synthesis and production of nitric oxide, prostaglandins, renin, collagen, endothelin, prostacyclin, interleukin, reactive oxygen species, factor VIII, degradation of bradykinin and prostaglandins, expression of antigens, conversion of angiotension I to II, and mechanical work to contract against blood pressure. Experiments in the hamster window-chamber model, in which a light-dye technique is used to disable a segment of the arteriolar endothelium, found a decrease in vessel-wall gradient by 50% in comparison to an unaffected segment of the same vessel, supporting the concept that the endothelium consumes a portion of the oxygen exiting the vessel (28). Smooth muscle may also consume more oxygen than expected at the microvascular level, because these vessels are subjected to constant cycles of contraction and dilation to regulate the distribution of blood in the network. This dynamic modulation of vessel diameter against the blood pressure (3) is different from the static contraction of muscle, which has been thought to reduce the rate of oxygen consumption (20).

WHOLE-ORGAN STUDIES

Removal of the endothelial cells by using a detergent agent in an isolated dog hindlimb model reduced the oxygen consumption rate by 34% (4). Induced vasoconstriction by administration of noradrenaline and vasopressin significantly increased the amount of oxygen extracted from the perfusate to the isolated hindlimb, kidney, intestine, and mesentery of the rat (32). Oxygen-consumption rate was found to increase in rats adapted to prolonged systemic hypoxia when these rats were exposed to the stress of room air (16).

OXYGEN RELEASE AND WALL CONSUMPTION DURING VASOACTIVITY

By using PQM, the difference between the intravascular pO_2 and perivascular pO_2 just adjacent to the vessel wall is measured. This radial gradient is directly proportional to the rate of vessel-wall consumption per unit volume of the tissue (29).

A change in vascular tone is usually a response to maintain homeostatic conditions in the tissue. However, a change in tone will likely affect the vessel-wall oxygen-consumption rate and thus regulate the amount of oxygen available to the interstitial tissue. Acute changes in vascular tone with pharmacologic agents have been used as a tool to investigate the variability in the vessel-wall consumption and how this redistributes oxygen away from the interstitial tissue, changing interstitial pO_2 levels.

Vasodilation was induced with a continuous administration of verapamil (L-type Ca^{2+} blocker), and this significantly reduced arteriolar vessel-wall gradient with a concomitant increase in tissue pO_2 in the hamster window-chamber model (9). A similar result was obtained with papaverine-induced vasodilation, a nonspecific Ca^{2+} blocker, in the cremaster muscle of the rat (24). The reduction in vascular tone of the arteriolar walls by topical application of papaverine resulted in a decreased vessel-wall gradient in all segments of the arteriolar network, but was most prevalent in the feeding A1 arterioles relative to normal tissue. Interestingly, the site of high-oxygen wall consumption found in these studies, the A1 vessels, coincides with the most active vessel in the microvasculature and has the highest smooth muscle per volume tissue in the network.

Prostaglandin E_1 (PGE1) was used to determine if relaxation of vessel-wall vascular smooth muscle through vasodilation would affect wall oxygen consumption. PGE1 causes vasodilation through the adenylate cyclase system in the smooth muscle, and thus tries to delineate the oxygen consumption of the muscle and the endothelium of the vessel wall. With a continuous infusion of PGE1, the arteriolar wall gradient and consumption rate was reduced by 20%. In this study, adjusting for the effect of the cylindrical geometry of the vessels showed that the actual vessel-wall oxygen consumption was lowered to 50% of baseline (6).

Nitric oxide (NO) inhibition and production was found to modulate both vessel tone and vessel-wall gradient. In studies performed in the rat cremaster muscle, L-NAME was used to inhibit NO synthesis, which increased the oxygen consumption of arteriolar walls by 42%, whereas the flow-induced NO release decreased it by 34% (25). The relation between NO production on the vessel-wall consumption was also studied in endothelial nitric oxide synthase (eNOS)–deficient mice with the window-chamber model (1). The vessel-wall gradient was reduced in these animals relative to the wild-type animals, suggesting that the genetically impaired endothelium

used a lower amount of oxygen when not producing NO. The perivascular tissue oxygen utilization was increased in these animals when compared with the wild-type animals but resulted in a lower tissue pO_2 level, likely because of the increase in respiratory rate by the tissue to produce NO *via* the NOS-3 pathway to compensate for lack of eNOS production.

Vasoconstriction was induced by using a continuous infusion of arginine vasopressin (AVP, the antidiuretic hormone) in the hamster window-chamber model with the objective of studying the contribution of smooth muscle cells to the oxygen consumption of the microvascular wall (7). Results show that a reduced tissue pO_2 and an increased vessel-wall gradient are compatible with the concept that vasoconstriction increases oxygen consumption by the vessel wall. Oxygen release during AVP treatment was increased in both arterioles and capillaries relative to control. The increased oxygen release did not result in an increase in tissue pO_2. The O_2 released from blood was used by the increased oxygen consumption by the vessel wall noted experimentally as an increased vessel-wall gradient. These measurements show that increased oxygen release does not necessarily result in increased tissue pO_2 (6).

ANALYSIS OF CONSUMPTION BY VASCULAR-WALL COMPONENTS

The light-dye technique (12) was used temporarily to eliminate the function of the endothelium at specific sites along arteriolar segments *in vivo*. The endothelium is damaged by release of oxygen free radicals when injected fluorescein is excited by high-intensity Hg illumination. An adjustable aperture defined the site where the endothelium was treated. Papaverine and acetylcholine were used to elicit vasodilation and estimate the level of induced damage. The oxygen gradient measured by using the PQM across the vessel wall at these sites was reduced by 50% relative to normal segments of the same vessel (28).

In the rat cremaster muscle preparation, NO-dependent and NO-independent vasodilation was found to reduce the vessel-wall oxygen consumption. This led to the conclusion that NO decreased vessel-wall oxygen consumption by decreasing vascular smooth muscle mechanical work rather than a change in the consumption by the endothelium, the other major component of the wall (25).

In summary, the techniques of phosphorescence decay microscopy provide sufficient resolution to obtain pO_2 measurements within the vessel wall and establish the relative consumption rates of the endothelium and smooth muscle. All studies support the concept that arteriolar walls consume a significant amount of oxygen compared with the surrounding tissue (25).

CLINICAL IMPACT OF OXYGEN VESSEL-WALL CONSUMPTION

Vasopressors are commonly used in critical care medicine as a second-line treatment for vasodilatory shock after administration of fluid and inotropic agents. The goal is to prevent hypotension by increasing systemic pressure so that this is transmitted to the periphery, promoting perfusion. The direct correlation of perfusion pressure and microvascular perfusion was initially observed when a systematic occlusion of the feeding vessel to a microvascular network reduced capillary perfusion (15). Recently, micropipette measurements of microvascular pressure distributions have confirmed a direct correlation between RBC-perfused capillaries and the incoming arteriolar pressure (2). This effect does not always have a beneficial outcome, and a strong vasopressor such as AVP increases central pressure and vascular tone, but to a point at which microvascular perfusion, defined by the number of capillaries perfused with RBCs, and oxygen tension in the tissue are significantly reduced (7).

The use of vasopressors in critically ill patients with severe vasodilatory shock, already suffering from peripheral malperfusion due to their critical illness, may result in worsening of perfusion, aggravating the deficit in tissue oxygen supply by causing the vessel walls to consume more oxygen. Therefore, the objective of attaining a sufficient mean arterial pressure necessary to sustain organ perfusion may be negated by the reduction of oxygen delivery to the tissue, by the combined effect of increased peripheral vascular resistance, and increased vessel-wall oxygen consumption.

CONCLUSION AND OPEN QUESTIONS

Studies on the rate of oxygen consumption by the vessel wall led to a reevaluation of our understanding of oxygen delivery to the tissue. Results from these studies show a higher oxygen requirement for the vessel wall than the rest of the tissue. The rate of oxygen consumption by the vessel wall is found to relate directly to the amount of oxygen released from the blood into the tissue, blood pO_2, and vessel tone. Vasoconstriction increases blood-vessel oxygen consumption, and *vice versa*. In the healthy organism in normal conditions, blood oxygen availability exceeds the combined requirements of blood vessels and the tissue. Problems arise when the oxygen supply to the tissue is limited, because blood vessels are first in line to use the available oxygen.

Many clinical conditions involve the use of vasopressors to increase blood pressure, under the assumption that this increases the oxygen supply to the tissue. The current findings indicate that the clinical success of this intervention depends on attaining a balance between the improvement resulting from higher driving pressure for blood, the restriction of blood flow due to vasoconstriction, and the additional limitation arising from the reduction of oxygen delivery to the tissue due to the increased oxygen consumption by blood vessels as they expend energy in maintaining vascular tone. Further investigation to understand the interaction of the local oxygen distribution and the vessel wall will allow more effective use of vasoactive drug therapy.

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ABBREVIATIONS

AVP, arginine vasopressin; eNOS, endothelium-derived nitric oxide synthase; L-NAME, *N*-omega-nitro-L-arginine methyl ester hydrochloride; NO, nitric oxide; PGE1, prostaglandin E_1, pO_2, partial pressure of oxygen; PQM, phosphorescence-quenching microscopy.

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