Active oxygen transport in tissue by interstitial flow

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Key points

1. Interstitial flow plays a key role in active O_2 transport in tissue due to its high Prandtl number $\nu/D \sim 10^3$;
2. O_2 transport in tissue is balanced by both active convection and passive diffusion transport.
3. Interstitial flow in form of active convective transport can pump more than hundred times of O_2 into tissue than those by passive diffusion transport due to the concentration gradient.
4. Active convection transport can be triggered by external pressure, which is crucial for damage tissue recovery.

Abstract:

Oxygen (O_2) transport through diffusion from capillary to tissue has long been established by Krogh. However, the interstitial fluid in the interspace between tissue and capillary has a high Prandtl number around 10^3 and hence its convective mass transport is more efficient than its diffusive transport. The interstitial flow drained by the initial lymphatics contributes to the convective transport of O_2 through tissue, which can be modeled as aligned blood capillaries in parallel and the initial lymphatics. It is found that both the O_2 concentration distribution and the total O_2 flux are sensitive to the flow rate of interstitial fluid. The convection contribution has been evaluated based on the Peclet number, feature flow rate, and convection-diffusion boundary. At the same interstitial flow rate, convection delivers more O_2 to type I muscle fibers with a higher concentration of myoglobin than to type IIX muscle fibers. Even with a small external

force, tissue with a higher specific hydraulic conductance (permeability) has a larger interstitial flow rate and a higher O_2 transport rate than those in healthy tissue. Hence, the overall O_2 transport from capillary to tissue includes two components, i.e., active convection transport by interstitial flow due to pressure gradient and passive diffusion transport due to concentration gradient. The active convective O_2 transport is crucial for the recovery of damaged tissue where the contribution from passive diffusion transport is constrained by regulation of capillary opening. The convection facilitated O_2 transport can be the basis for cell differentiation, morphogenesis, and therapeutic effects of massage and acupuncture.

Keywords: Active oxygen transport, interstitial flow, convective transport, diffusive transport, capillary, initial lymphatics

1. Introduction

Human bodies rely on oxygen metabolism in mitochondria to produce the cellular energy adenosine triphosphate (ATP). During respiration, oxygen (O_2) is uptaken by the hemoglobin forming Fe-O_2 bond inside red blood cells. It is, then, circulated through blood streams to capillaries in peripherals. In capillaries, O_2 dissociates from hemoglobin and dissolved in plasma, diffuses through the endothelium of capillaries. Finally, it reaches tissue and transports to mitochondria to participate in the ATP production. From the capillary to the tissue, O_2 confronts the highest transport resistance due to its low solubility in the body fluid (Popel, 1989; Widmaier *et al.*, 2007).

Krogh (Krogh, 1919b, a) introduced a model to describe the oxygen transport from capillary to tissue based on the passive diffusion of O_2 inside the tissue. He also discovered the capillary regulation of opening and close at rest that governs this passive diffusion. Since then, the subsequent models have been developed in different scales from tissue to organs (Rakusan *et al.*, 1984; Lagerlund & Low, 1987; Popel, 1989), with various geometries (Hill, 1928) in multiple types of muscles and tumors (Wittenberg *et al.*, 1975; Honig *et al.*, 1984; Secomb *et al.*, 2004). Similarly, all these models are constrained to pure diffusive transport, driven by the concentration gradient, without consideration of the O_2 convective transport, i.e., the contribution of the body fluid movement.

The passive diffusive O_2 transport only is difficult to recover the damaged tissue. As O_2 consumptions can dramatically increase in sports as an example, opening more capillaries to enhance blood volume has been considered as the main strategy to produce more ATP to fulfill the O_2 demands. However, if the tissue is in fatigue with lactic acid byproducts or even injured, the O_2 transport is inhibited by a reduced mitochondria metabolism. At such conditions, O_2 reimbursement is a perquisite to recovering the damaged tissue back to health. Diseases, such as covid-19, which directly attack the respiration system and reduce the total O_2 uptake in body, could leave a damaged tissue with pulmonary fibrosis in patients. The passive O_2 diffusion transport only depends on the demand, *i.e.*, the concentration gradient. However, the damaged tissue with impeached mitochondria metabolism cannot retrigger the O_2 demand

automatically. It means that, unless with certain assistance of active O_2 transport, the damaged tissue cannot recover only by passive O_2 diffusion.

The O_2 transport from the capillary to the tissue is conveyed by the interstitial fluid, a dynamic movement flow for maintaining nutrition metabolism of body. In the interstitial fluid, the Prandtl number, ν/D, of O_2 is ~10^3, where, $\nu = 10^{-6}$ m^2/s is the viscosity of interstitial fluid and $D_{O2} = 1.6\times10^{-9}$ m^2/s is the O_2 diffusion coefficient. The large Prandtl number indicates that convective transport in the interstitial fluid is more effective than diffusive transport even low flow rates (Levich, 1962). Hence, the convective transport of interstitial fluid should be included in the O_2 transport from the capillary to tissue.

The interstitial flow is a one-way movement from the capillary to the initial lymphatics. The interstitial fluid includes blood plasma, water, proteins, and electrolytes leaked from capillary (Guyton & Hall, 2006). For a healthy tissue, 10-20 % of the excess interstitial fluid is drained by the initial lymphatics and the rest is reabsorbed by the venous capillaries. Hence, the lymph formation and the lymph flow rate regulate the flow rate of interstitial fluid (Breslin *et al.*, 2018; Goswami *et al.*, 2020). Lymphatic vessels locate inside the connective tissues and distribute across the entire muscle tissues correlated with arcading arterioles and veins (Skalak *et al.*, 1984). In muscle tissues, the initial lymphatics has a luminal size about 10-100 μm with an average distance of several hundred micrometers (Skalak *et al.*, 1984; Schmid-Schonbein, 1990). However, the initial lymphatics does not have smooth muscles, and thus cannot contract spontaneously. Their openness is controlled by contraction of surrounding muscle fibers and arterial pulsations (McMaster & Parsons, 1938; Skalak *et al.*, 1984; Mazzoni *et al.*, 1990). The typical interstitial flow rate, $\boldsymbol{u}$, is in the range of 0.1-2 μm/s (Swartz & Fleury, 2007). During exercises, the lymph flow can increase by more than 10-30 folds (Havas *et al.*, 1997; Guyton & Hall, 2006). At the lymphedema condition due to disease or injury, the lymph flow is almost ceased, rendering the interstitial fluid and tissue swollen (Schmid-Schonbein, 1990; Swartz, 2001). Therefore, the interstitial flow maintains nutrition and body fluid metabolism. The entire process is balanced by the venous pressure, interstitium composition, interstitial pressure, and pressure inside lymphatic vessels (Granger, 1979; Aukland & Reed, 1993; Swartz & Fleury, 2007).

The interstitial flow through tissue has been found to facilitate protein transport, drug deliveries, and therapeutics (Reddy *et al.*, 2006a; Reddy *et al.*, 2006b; Dukhin & Labib, 2013). The convection is an active process prone to local external force offered by, such as, massage and body stretch (Olszewski & Engeset, 1980; Guyton & Hall, 2006). The interstitium can tune its porosity and permeability responding to tissue deformation and compression (Zhang *et al.*, 2000; McGuire *et al.*, 2006). Furthermore, manipulating large molecules through interstitium to tumor sites by enhancing its convective transport has been investigated as an effective way in cancer therapies (Heldin *et al.*, 2004; Dreher *et al.*, 2006). In addition, the convective transport of interstitial flow is important in nutrition delivery for cartilage and bone modeling (Piekarski & Munro, 1977; Evans & Quinn, 2006). For soft tissue, the interstitial flow is very sensitive to local pressure and permeability of the tissue. The morphogenesis, differentiation, and regeneration of cells closely correlate to the interstitial flow (Fleury *et al.*, 2006; Goldman *et al.*, 2007; Rutkowski & Swartz, 2007). Moreover, the interstitial flow has been correlated to the meridian channel theory (Li *et al.*, 2008; Zhang *et al.*, 2015; Li *et al.*, 2020). Therefore, the convective transport is a crucial mass transport process in interstitial fluid.

In this work, the convection-diffusion transport process has been thoroughly solved in a one-dimensional (1D) framework by introducing a critical flow rate, u_{dc}, and a spatial convection-diffusion boundary, x_0. The muscle tissue with different muscle fibers is represented by varying the myoglobin concentration. Darcy's law is introduced to state the relationship between tissue permeability and local pressure gradient. A comprehensive picture of O_2 transport in tissue is presented by considering the convective component of the interstitial flow and the diffusive component driven by concentration gradient.

2. Convective and diffusive transport of O_2 inside tissue

The O_2 flux from the capillary to the tissue, J_{total}, includes two parts: molecular diffusion, J_D, and convection of interstitial flow, J_{conv}.

$$J_{total} = J_D + J_{conv} \tag{1}$$

The O_2 diffusion across a surface of unit area per unit time is described by Fick's first law:

$$J_D = -D_{O2}\nabla C_{O2} \tag{2}$$

where, C_{O2} is O_2 concentration gauged by its partial pressure (O_2 tension) P_{O2}. $C_{O2}=\alpha P_{O2}$, α is the solubility coefficient of the body fluid (1.23 mol/m^3 torr). The convective transport by the interstitial fluid flow of rate $\boldsymbol{u}$ [m/s] is:

$$J_{conv} = C_{O_2}\boldsymbol{u} \tag{3}$$

Assuming a homogeneous consumption of O_2 inside the tissue by mitochondria with a rate of M_0 [mol·m^{-3}s^{-1}], the O_2 transport in a volume tissue is equal to the O_2 flux through the tissue boundary and the consumption within the tissue volume, which can be described by Fick's second law:

$$\frac{dC_{O_2}}{dt} = D_{O_2}\nabla^2 C_{O_2} - \boldsymbol{u}\nabla C_0 - M_0 \tag{4}$$

For impressible fluid, $\nabla\cdot\boldsymbol{u} = 0$. At steady state, $dC_{O2}/dt = 0$, and the above equation can be simplified as:

$$D_{O_2}\nabla^2 C_{O_2} - \boldsymbol{u}\nabla C_{O_2} - M_0 = 0 \tag{5}$$

It is difficult to solve equation (5) in two-dimensional (2D) or three-dimensional (3D) domains. However, it can be solved analytically in a 1D domain where the capillary is assumed to lie in parallel to the initial lymphatics with distance b and the following boundary conditions: at $x = 0$ (location of the capillary), $C_{O2} = C_0 = \alpha P_0$; at $x = b$ (location of the initial lymphatics), $\nabla C = 0$, as shown in **Fig. 1**. Although the analytical solution is approximate and not so accurate as the 3D result, the 1D model suffices to provide critical insights into the physics of convection and diffusion of O_2, a vital element in human body. Note that the interstitial flow is a one-way movement from the capillary to the initial lymphatics. The close form of solution of equation (5) is:

$$C(x) = C_0 - \frac{M_0}{\boldsymbol{u}}x - \frac{DM_0}{\boldsymbol{u}^2}\exp\left(-\frac{\boldsymbol{u}}{D}b\right)\left[1 - \exp\left(\frac{\boldsymbol{u}}{D}x\right)\right] \tag{6}$$

Substituting equation (6) into equation (1-3), J_D and J_{conv} can be obtained as follows:

$$J_D = -D_{O_2}\nabla C_{O_2} = \frac{M_0 D}{\boldsymbol{u}}\left\{1 - \exp\left[-\frac{\boldsymbol{u}}{D}(b - x)\right]\right\} \tag{7}$$

$$J_{conv} = C_{O_2}\boldsymbol{u} = C_0\boldsymbol{u} - M_0 x + \frac{DM_0}{\boldsymbol{u}}\exp\left(-\frac{\boldsymbol{u}}{D}b\right)\left[\exp\left(\frac{\boldsymbol{u}}{D}x\right) - 1\right] \tag{8}$$

$$J_{total} = J_{conv} + J_D(O_2) = C_0\boldsymbol{u} + \frac{DM_0}{\mathbf{u}}\left[1 - \exp\left(-\frac{\boldsymbol{u}}{D}b\right)\right] - M_0 x \tag{9}$$

Details in mathematical derivations can be found in Appendix. The O_2 concentration distribution along x can be resolved, so does the convective and diffusive transport

fluxes. Since the actual distance between the capillary and the initial lymphatics is around several hundred micrometers, a typical value of b = 1 mm is selected in our calculation. In addition, a 1D numerical simulation is implemented by using COMSOL Multiphysics. The related parameters used in the calculation and simulation are listed in **Table 1**.

3. Results:

The distribution of O_2 tension across the tissue is shown in **Fig. 2**(A), without considering the fluid movement, *i.e.*, convention. The penetration length of O_2 is determined by $L_p = (2DC_0/M_0)^{1/2}$ (Hill, 1928) (see Appendix). If b is less than, *i.e.*, $b < L_p$, the O_2 flux can reach the initial lymphatics by diffusion; while, if $b \geq L_p$, O_2 is extinguished by mitochondria consumption before reaching the initial lymphatics. In this situation, part of the tissue is under the condition of hypoxia and fatigue. Therefore, the critical initial O_2 tension with $b = L_p$ is $P_{O2}(L_p) = b^2M_0/(2D\alpha C_0)$. As the interstitial fluid flow increases, the O_2 concentration gradient decreases but the O_2 concentration at the lymphatic capillary ($x = b$) increases, as shown in **Fig. 2**(B). Hence, $\boldsymbol{u}$ changes the diffusive transport of O_2 and accelerates the O_2 flux through the tissue.

The normalized O_2 flux at $x = 0$ is used to characterize the total O_2 input into the entire tissue region (from 0 to b) as shown in **Fig. 3**(A). At very small flow rate, *i.e.*, $u <$ 0.1 μm/s, the total O_2 flux into the tissue remains almost unchanged. However, it grows exponentially when the flow rate increases further. The ratio of the O_2 convective flux to the total flux is displayed in **Fig. 3**(B). Three regions of O_2 transport can be discerned: **i**) convection wherein the O_2 transport is predominated by the interstitial fluid movement and the total O_2 flux is linearly dependent on the flow rate; **ii**) convection-diffusion in which both the interstitial fluid movement and the concentration gradient have large effects on the O_2 transport and the total O_2 flux into the tissue increases dramatically with the flow rate; and **iii**) diffusion where the flow rate of interstitial fluid is too small to affect the concentration gradient of O_2 and the O_2 transport is dominated by diffusion.

Normally, the convection and diffusion contributions can be evaluated by the Peclet number, $\boldsymbol{Pe} = \boldsymbol{u}b/D$. However, even with a small $\boldsymbol{Pe}$ number, the flow rate of the

interstitial fluid can influence the concentration gradient due to different O_2 tension conditions as shown in **Fig. 3**(B). Hence, the total O_2 consumption in the tissue (bM_0) and L_p. are included in the following discussion.

i) **Convection regime** (***Pe*** > 1)

In the convection regime, $\boldsymbol{u}b >> D$, $\exp(-\boldsymbol{u}b/D) \sim 0$, $J_D = DM_0/\boldsymbol{u}$, and $J_D \sim 0$. Thus, the O_2 concentration is constant across the tissue. Then, the O_2 transport solely relies on the interstitial fluid movement expressed as:

$$J_{conv} = C_{O_2}\boldsymbol{u} = C_0\boldsymbol{u} - M_0 x \tag{10}$$

At $x = 0$, the O_2 flux into the tissue is $J_{conv} = J_{total} = C_0\boldsymbol{u}$, with $J_{conv}/J_{total} = 1$. The total O_2 flux into the tissue depends on the initial O_2 tension and u.

ii) **Convection-diffusion regime** (***Pe*** ~ 1)

At $x = 0$, equation (5) becomes:

$$J_D = -D_{O_2}\nabla C_{O_2} = \frac{M_0 D}{\boldsymbol{u}}\left[1 - \exp\left(-\frac{\boldsymbol{u}}{D}b\right)\right] \tag{11}$$

$$J_{conv} = C_0\boldsymbol{u} \tag{12}$$

$$J_{total} = C_0\boldsymbol{u} + \frac{DM_0}{\boldsymbol{u}}\left[1 - \exp\left(-\frac{\boldsymbol{u}}{D}b\right)\right] \tag{13}$$

In this region, $J_D/J_{conv} \sim \boldsymbol{u}^{-2}$. The concentration gradient is very sensitive to $\boldsymbol{u}$. The total input flux into the muscle increases with $\boldsymbol{u}$, while the gradient of the concentration decreases as a result of a higher convective contribution. In the convection-diffusion regime, both diffusive and convective fluxes are correlated to the body fluid flow rate. Hence, the total flux is sensitive to the body flow rate.

iii) **Diffusion/convection-diffusion regime** (***Pe*** < 1)

If ***Pe*** < 1, the transport is dominated by the diffusive transport. However, if the flow rate is large enough to modify the concentration gradient, convection can also contribute significantly to the O_2 transport inside the tissue.

In this region, $\boldsymbol{u} < D/b$, $1-\exp(-\boldsymbol{u}b/D) = \boldsymbol{u}b/D$. Then, equation (5) becomes:

$$J_{total} = J_{conv} + J_D(O_2) = C_0\boldsymbol{u} + M_0(b - x) \tag{14}$$

$$J_D = M_0(b - x) \tag{15}$$

$$J_{conv} = C_0\boldsymbol{u} \tag{16}$$

At $x = 0$, $\boldsymbol{u} < u_{dc}$, J_D/J_{conv} can be expressed as a sigmoid function:

$$\frac{J_{conv}}{J_{total}} = \frac{\boldsymbol{u}/u_{dc}}{1+\boldsymbol{u}/u_{dc}} \tag{17}$$

$$u_{dc} = \frac{M_0 b}{C_0} \tag{18}$$

where, u_{dc} is the critical flow rate at which the O_2 delivery by the interstitial flow into the tissue is equal to that by the concentration-gradient induced diffusion. For $M_0 b = 10^{-7}$ mol/m^2 s, $C_0 = \alpha P_0$ (50 torr) = 6.2×10^{-2} mol/m^3 and u_{dc} = 1.6 μm/s.

Hence, for low flow rate, the diffusive flux of O_2 is a function of the distance inside the tissue, x. The boundary between the convection dominated region and the diffusion dominated region is expressed by x_0:

$$x_0 = b\left(1 - \frac{\boldsymbol{u}}{\boldsymbol{u}_{dc}}\right) \tag{19}$$

At $x = x_0$, $J_D = J_{conv}$. The amount of O_2 molecules delivered by the interstitial flow is the same as the amount by diffusion. For $x < x_0$, $J_D > J_{conv}$. The mass transport of O_2 to the site is prevalent by diffusion. For $x > x_0$, $J_D < J_{conv}$. The O_2 transport to the site mainly relies on convection.

However, for $b > L_p$, the diffusive flux is determined by the O_2 consumption rate, $L_p M_0$:

$$u_{dc} = \frac{M_0 L_p}{C_0} = \sqrt{\frac{2DM_0}{C_0}} \tag{20}$$

then

$$x_0 = L_p\left(1 - \frac{\boldsymbol{u}}{u_{dc}}\right) \tag{21}$$

It can be found in **Fig. 4**(A) that u_{dc} drops as the O_2 tension of capillary increases. Furthermore, x_0 moves from the initial lymphatics to the capillary as $\boldsymbol{u}$ rises from 0 to u_{dc}, as shown in **Fig. 4**(B). In the hypoxia condition, *i.e.*, $b > L_p$, the O_2 gradient cannot provide enough O_2 reaching the tissue in the deep. Hence, the hypoxia region is sensitive to the fluid movement in which the O_2 delivery relies mainly on the interstitial fluid. Therefore, it is difficult to recover the O_2 metabolism in tissue only unless there is an external force to drive the interstitial flow.

Muscle types

Inside muscle fibers, myoglobin can store O_2 and facilitate O_2 transport at the same time (Popel, 1989). Muscle type I fiber has the largest concentration of mitochondria and myoglobin, while muscle type IIX fiber has the lowest concentration. The

concentration of the O_2 loaded myoglobin ($C_{Mb\text{-}O2}$) can be expressed as a function of C_{O2} according the Hill equation (Hill, 1910):

$$C_{Mb-O_2} = \frac{C_{Mb}^{T} K C_{O_2}}{1+KC_{O_2}} \tag{22}$$

where, C_{Mb}^{T} is the total concentration of uniformly distributed myoglobin (0-1 mM) and K is the reaction equilibrium constant. Assuming the muscle tissue with uniform myoglobin distribution allows to evaluate the effects of myoglobin concentration on the O_2 transport. Substituting equation (22) into (1), the diffusive flux of O_2 becomes:

$$J_D = -D_{O_2}\nabla C_{O_2} - D_{Mb-O_2}\nabla C_{Mb-O_2} \tag{23}$$

$$J_{conv} = C\boldsymbol{u},\ \ C = C_{O_2} + C_{Mb-O_2} \tag{24}$$

where, D_{Mb} (1×10^{-6} cm^2/s) is the diffusion coefficient of myoglobin (Covell & Jacquez, 1987) by assuming $D_{Mb} = D_{Mb\text{-}O2}$.

It is clear that u_{dc} is linearly dependent on the myoglobin concentration, as shown in **Fig. 5**(A). u_{dc} reduces to 0.16 μm/s as the concentration of the myoglobin increases to 1 mM. It means that at the same interstitial flow and O_2 tension, the convective transport contributes more O_2 flux to the slow-twitch muscle tissue with type I muscle fiber than that to the fast-twitch muscle tissue with type IIX fiber. The convective flux ratio of the total O_2 flux with and without myoglobin can be found in **Fig. 5**(B). The convection-diffusion region shifts to smaller u_{dc} as the myoglobin concentration increases.

Tissue permeability

Darcy's law is usually used to describe porous media. Hence, the flow is directly proportional to pressure gradient and $\boldsymbol{u}$ through the tissue can be expressed as follows:

$$\boldsymbol{u} = \frac{\kappa}{\mu}\nabla \boldsymbol{P} = \frac{\kappa}{\mu}\frac{\boldsymbol{P}}{b} \tag{25}$$

where, κ is the tissue permeability or specific hydraulic conductivity of tissue, in unit of [m^2], μ is the dynamic viscosity of u and $\mu = 1\times10^{-3}$ [Pa s] for water, and $\boldsymbol{P}$ is the pressure exerted at $x = 0$. The value of κ depends on the tissue type, the hydrate of the interspace, pressure, and interestitium composites such as proteins, collagen fibers, *etc*. (Guyton *et al.*, 1966; Levick, 1987)

The linear relationship between the pressure gradient and tissue permeability κ is shown in **Fig. 6**, without considering the pressure dependence of the tissue permeability. At the same pressure, the flow is much easier to go through the tissue with lower κ. Typical tissue permeability κ values are in the range of 10^{-11} to 10^{-15} m^2 (Swartz & Fleury, 2007). But tissue permeability can increase by more than 10^5 times above the atmospheric pressure (Guyton *et al.*, 1966), for example, in acute edema conditions. Therefore, the interstitial flow in tissue with acute edema is sensitive to the external force, which suggests that even a small force can achieve high flow rate and regulate O_2 transport inside the tissue.

4. Discussion

The O_2 transport inside the muscle tissue is here modeled by including the convection transport of the interstitial flow with the diffusion transport. It has now been established that the interstitial flow plays a key role in the O_2 transport in tissue through convective transport. The O_2 transport due to convection can be evaluated by examining **P**e, u_{dc}, and x_0. At the large flow rate, $\mathbf{u} >> u_{dc}$ (**P**e>>1), the convection by the interstitial flow can pump hundreds times O_2 flux into the tissue than those by the passive diffusion transport. As for small flow rate, $\boldsymbol{u} < u_{dc}$ (**P**e<1), contribution of convection transport can be expressed by a sigmoid function: $J_{conv}/J_{total} = (\boldsymbol{u}/u_{dc})/(1+\boldsymbol{u}/u_{dc})$. In addition, x_0 defines the spatial contribution of the convective O_2 transport in tissue for $\boldsymbol{u} < u_{dc}$. As $\boldsymbol{u}$ increases from 0 to u_{dc}, x_0 moves from the initial lymphatics distance towards the capillary. This movement reflects that diffusion is more effective in transport near the capillary for $\boldsymbol{u} < u_{dc}$. In contrast, the convective transport is crucial for the O_2 delivery to any point far from the capillary. Moreover, if there is a fatigue region due to the low O_2 tension, the initial lymphatics is much easy to reach the hypoxia condition because the diffusion penetration length is insufficient to delivery O_2 to the initial lymphatics. Thus, the convective transport with a faster flow is required to recover the ATP production near the initial lymphatics due to its higher u_{dc}.

For muscle tissues, interstitial flow has large accelerating effects on the O_2 transport in the slow twitch muscle with type I fiber than on the fast twitch muscle due to its higher myoglobin concentration. The tissue permeability and the magnitude of pressure

gradient in tissue are crucial to driving the interstitial flow. For the tissue with a higher tissue permeability such as in the edema condition, a small external force can change the O_2 transport through the tissue.

In this model, the interstitial flow is through the entire tissue, a uniform porous media, including muscle fibers. Here, the cell permeability of water molecules is converted into the apparent tissue permeability. The effect of myoglobin concentration on O_2 transport in muscle tissues is highlighted by ignoring the fact that myoglobin molecules are only located inside the muscle fiber not in the interstitial interspace. This difference could affect the net calculated O_2 input flux in tissue but has nothing to do with its effects on the O_2 transport.

Interstitial flow with capillary regulation and O_2 influx into tissue

The correlation between the interstitial flow and O_2 influx to tissue is schematically shown in **Fig. 7**. At the balanced metabolism, the interstitial flow is leaked from the capillary and drained by the initial lymphatics. Therefore, the interstitial flow provides a positive and negative feedback for the blood stream in the capillary and the O_2 influx into the tissue, respectively. If interstitial flow $\boldsymbol{u}$ increases, both the lymph formation and the O_2 convective transport are enhanced. The speedy O_2 transport from the capillary also accelerates the O_2 dissociation from hemoglobin (Hb-O_2) in red blood cells. Consequently, the faster interstitial flow further increases the hydraulic and osmosis pressure gradient between the inside (②) and outside (③) of the capillary shown in **Fig. 7**, and causes more plasma leak from the capillary. In sequence, more plasma leaking from the capillary reduces the local hydraulic pressure inside the capillary (②)and builds up a large hydraulic pressure gradient (ΔP) from upstream (①) inside the capillary, and thus drives more blood stream to the local capillary. Hence, the O_2 mitochondria metabolism can benefit from the fast convective O_2 transport and the blood volume increases due to the positive feedback of interstitial flow $\boldsymbol{u}$.

If interstitial flow $\boldsymbol{u}$ becomes low, a negative feedback leads to a sluggish blood stream and an inactive O_2 mitochondria metabolism. Moreover, the static interstitial fluid may accumulate in the tissue and causes further edema.

Model of active and passive O_2 transport inside tissue

For tissue metabolism, both the convective transport by interstitial flow and the diffusive transport by concentration gradient play a key role in the O_2 transport in tissue. The diffusive O_2 transport is governed by the capillary regulation and the O_2 tension inside the capillary, which corresponds to the microcirculation and system metabolism of the body. The convective transport is governed by the interstitial flow and can be tuned by a local pressure gradient and drainage of the initial lymphatic. To restore the O_2 mitochondria metabolism of damaged tissues, it is convenient by stimulating an active interstitial flow to facilitate the O_2 transport by a local pressure gradient. Hence, the convective contribution by the interstitial flow resembles an active O_2 transport that can be triggered by exerting an external force, while the diffusive contribution by the concentration gradient is a passive O_2 transport governed by the capillary regulation.

Hence, O_2 transport from capillary to mitochondria in tissue follows active and passive routes as summarized in **Fig**. 8. The passive diffusive O_2 transport in tissue is driven by the concentration gradient, and the corresponding model has been established by Krogh about 100 years ago. The active convective O_2 transport in tissue is determined by the interstitial flow, which can be caused by pressure gradient.

During a balanced metabolism, the diffusive transport can provide sufficient O_2 flux for mitochondria near the capillary. However, this passive supply is insufficient for the distant mitochondria. The convective transport by the interstitial flow can delivery O_2 effectively to the distant mitochondria in tissue, since the moment transfer is more rapid than molecular mass transfer in form of diffusion due to a high Prandtl number of $\nu/D \sim 10^3$ in the interstitial fluid. For damaged tissues, capillaries are in regulation to respond to the reduced O_2 mitochondria metabolism. Thus, a concentration gradient cannot sustain enough O_2 to the far end of the tissue as what the interstitial flow can. Therefore, the convective transport by the interstitial flow is crucial for recovery of damaged mitochondria metabolism, which can be activated by external forces.

The significance of active O_2 transport in tissue

For microcirculation metabolism, the interstitial flow through tissue is driven by the drainage of the initial lymphatics. This interstitial flow drainage may be easily blocked

by damaged tissues and constrained by the dysfunctional local muscle contraction, render that the passive O_2 diffusion transport is the only route to maintain the tissue metabolism in damaged tissue. Therefore, driving the interstitial flow through tissue could enable O_2 redistribution and reimburse O_2 deficiency of tissue.

Hence, the O_2 transport through convection is very import for tissues in fatigue and during excise. In fatigue tissues where lactic acids accumulate locally or tissues damaged by injury inducing the regulation of capillaries, the diffusive transport cannot provide enough O_2 for the tissues to recover with closed capillaries and reduced O_2 demand of mitochondria. Thus, an external force is needed to drive the interstitial flow, and facilitate the O_2 transport through tissue to recover the tissue metabolism. During exercises, muscle tissues demand O_2 rapidly, and O_2 stored in the myoglobin can only last for few seconds during long time aerobic exercise such running and swimming. It has been observed that the lymphatic flow can increase by more than 10 folds from the level in the resting condition. Concurrently, the blood volume increases with more capillaries being opened to deliver more O_2. Based on our convective-diffusion model of the O_2 transport inside the tissue, the physiology mechanism behind the significant enhancement of interstitial flow is to trigger the active convection O_2 transport in tissue to sustain the sudden O_2 demand of tissue during exercises.

The interstitial flow provides an additional route for O_2 transport through tissue, accompanying with diffusion. It can be used to explain the phenomena that interstitial flow can influence cell morphogenesis and differentiation even with small flow rate. Since the interstitial flow facilitates not only the nutrition delivery but also O_2 transport, it provides more ATP for cell morphogenesis and differentiation along the interstitial flow and orientated by ATP production and O_2 metabolism of mitochondria.

Perspective of active and passive O_2 transport in tissue

ATP produced by mitochondria for O_2 metabolism is the main energy source for tissue. Our convection-diffusion model of O_2 transport shows that the lymphatic drainage of the interstitial flow is a crucial driving force for the O_2 transport through tissues besides its function of nutrition delivery. Typically, $\boldsymbol{u}$ is around 0.1-2 μm/s. This range is close to u_{dc} at which both diffusion and convection play the similar role for the

O_2 transport. Hence, the O_2 transport through convection and diffusion is sensitive to $\boldsymbol{u}$ in this flow range *i.e*, small fluctuation of the interstitial flow can impact the O_2 transport in tissue.

A local pressure gradient can stimulate the active O_2 transport through tissue and promote microcirculation. Traditional therapies, such as massage and cupping, provide local force to the tissue so as to enhance the local interstitial fluid, enhance the O_2 transport, and rebuild the local O_2 metabolism. Physical exercises, such as yoga, Taichi, and other stretching movements, would stimulate the contraction of lymphatic vessels with smooth muscles and directly facilitate the lymphatic flow (Guyton & Hall, 2006). All this results in a fast drainage of the interstitial fluid and a high-flux rate O_2 delivery. For covid-19 patients, as an example, it could be possible for a therapy route to recover the O_2 deficiency of local tissues if a suitable way can be found to trigger the active O_2 transport in pulmonary tissues, in addition to enhancing the O_2 intake by using a ventilator.

5. Conclusion

The interstitial flow provides an alternative active route for the O_2 transport from capillary to tissue along with its counterpart of diffusion. It also provides a perspective to understand the morphogenesis and differentiation of cells. Moreover, the comprehensive picture of the O_2 transport suggests that the traditional therapies, such as massage and stretch, could facilitate the O_2 transport from capillary to tissue to promote the tissue recovery from hypoxia. Based on this mechanism, acupuncture with magnetic needles can drive the interstitial flow to enhance the O_2 flux and rebuild the O_2 metabolism of tissue, which can be found in our follow-up paper.

Appendix

1. O_2 diffusive transport

The capillary is parallel the lymphatic capillary with the distance b. The tissue has a constant O_2 consumption rate M_0 by the mitochondria. From Fick's first law, if no convection contribution, the O_2 flux per area per second is:

$$J_D = -\mathrm{D}_{O_2}\nabla \mathrm{C}_{O_2} \tag{A1}$$

The flux into the tissue per second can be expressed by Fick's second law:

$$\frac{dC_{O_2}}{dt} = D_{O_2}\nabla^2 C_{O_2} - M_0 \tag{A2}$$

Equation (A1) and (A2) can be solved at the steady state $dC_{O2}/dt = 0$ with the boundary condition: $C_{O2} = C_0 = \alpha P_0$, at $x = 0$, and $\nabla C = 0$, at $x = b$.

$$C_{O2} = C_0 + \frac{M_0}{2D}x(x - 2b) \tag{A3}$$

The total O_2 flux J_{total} into the tissue from the capillary is corresponding to the O_2 flux at $x = 0$. Substituting equation (A3) into equation (A1), we can obtain:

$$J_D = M_0(b - x) \tag{A4}$$

At $x = 0$, $J_D = M_0 b$.

2. Including O_2 convective transport

If the total flux is determined by the gradient of concentration and the body fluid flow $\boldsymbol{u}$, the total O_2 flux becomes

$$J_{total} = J_D + J_{conv} = -D_{O_2}\nabla C_{O_2} + C_{O_2}\mathbf{u} \tag{A5}$$

$$\frac{dC_{O_2}}{dt} = D_{O_2}\nabla^2 C_{O_2} - \mathbf{u}\nabla C_0 - M_0 \tag{A6}$$

The liquid is impressible and $\nabla\cdot\boldsymbol{u} = 0$. At the steady state, with the boundary conditions are: $C_{O2} = C_0 = \alpha P_0$, at $x = 0$, and $\nabla C = 0$, $x = b$. The equation can be solved at steady state. Let

$$y = \frac{dC}{dx} + \frac{M_0}{\mathbf{u}} \tag{A7}$$

Equation (A6) becomes:

$$0 = D_{O_2}\nabla y - \mathbf{u}y \tag{A8}$$

$$y = A\exp(\frac{\mathbf{u}}{D}x) \tag{A9}$$

where, A is a constant. With the boundary condition $\nabla C = 0$ at $x = b$, we can obtain

$$A = \frac{M_0}{\mathbf{u}}\exp(-\frac{\mathbf{u}}{D}b) \tag{A10}$$

$$y = \frac{M_0}{\mathbf{u}}\exp(-\frac{\mathbf{u}}{D}(b - x)) \tag{A11}$$

Substituting equation (A11) into equation (A7),

$$\frac{M_0}{\mathbf{u}}\exp\left(-\frac{\mathbf{u}}{D}(b - x)\right) = \frac{dC}{dx} + \frac{M_0}{\mathbf{u}} \tag{A12}$$

$$C = \frac{M_0}{\mathbf{u}}\left(-x + \frac{D}{\mathbf{u}}\exp\left(-\frac{\mathbf{u}}{D}(b - x)\right)\right) + B \tag{A13}$$

The constant B can be determined by the boundary condition $C_{O2} = C_0$ at $x = 0$.

$$B = C_0 - \frac{DM_0}{\mathbf{u^2}} \exp\left(-\frac{\mathbf{u}}{D} b\right) \tag{A14}$$

Thus, equation (A13) becomes:

$$\mathrm{C} = \mathrm{C}_0 - \frac{M_0}{\mathbf{u}} x - \frac{DM_0}{\mathbf{u^2}} \exp\left(-\frac{\mathbf{u}}{D} b\right)\left(1 - \exp\left(\frac{\mathbf{u}}{D} x\right)\right) \tag{A15}$$

The diffusion flux component is:

$$J_D = -\mathrm{D}_{O_2} \nabla \mathrm{C}_{O_2} = \frac{M_0 D}{\mathbf{u}}\left(1 - \exp\left(-\frac{\mathbf{u}}{D}(b - x)\right)\right) \tag{A16}$$

The convection flux component is:

$$J_{conv} = \mathrm{C}_{O_2}\,\mathbf{u} = \mathrm{C}_0\mathbf{u} - M_0 x + \frac{DM_0}{\mathbf{u}} \exp\left(-\frac{\mathbf{u}}{D} b\right)\left(\exp\left(\frac{\mathbf{u}}{D} x\right) - 1\right) \tag{A17}$$

The total flux is:

$$\mathrm{J} = J_{conv} + \mathrm{J}_D(O_2) = \mathrm{C}_0\mathbf{u} + \frac{DM_0}{\mathbf{u}}\left(1 - \exp\left(-\frac{\mathbf{u}}{D} b\right)\right) - M_0 x \tag{A18}$$

If $\boldsymbol{u}b < \mathrm{D}$, following the first order expansion,

$$1 - \exp\left(-\frac{\mathbf{u}\boldsymbol{b}}{D}\right) = 1 - \left(1 - \frac{\mathbf{u}\boldsymbol{b}}{D}\right) = \frac{\mathbf{u}b}{D} \tag{A19}$$

$$\mathrm{C} = \mathrm{C}_0 - \frac{M_0}{\mathbf{u}} x - \frac{DM_0}{\mathbf{u^2}} \exp\left(-\frac{\mathbf{u}}{D} b\right)\left(1 - \exp\left(\frac{\mathbf{u}}{D} x\right)\right)$$

$$\mathrm{C} = \mathrm{C}_0 - \frac{M_0}{\mathbf{u}} x - \frac{DM_0}{\mathbf{u^2}}\left(1 - \frac{\mathbf{u}\boldsymbol{b}}{D}\right)\left(1 - \exp\left(\frac{\mathbf{u}}{D} x\right)\right)$$

$$\mathrm{C} = \mathrm{C}_0 - \frac{M_0}{\mathbf{u}} x - \frac{DM_0}{\mathbf{u^2}}\left(1 - \exp\left(\frac{\mathbf{u}}{D} x\right)\right) + \frac{bM_0}{\mathbf{u}}\left(1 - \exp\left(\frac{\mathbf{u}}{D} x\right)\right) \tag{A20}$$

$$\left(\exp\left(-\frac{\mathbf{u}}{D} b\right) - \exp\left(-\frac{\mathbf{u}}{D}(b - x)\right)\right) = \left(1 - \frac{\mathbf{u}\boldsymbol{b}}{D}\right) - \left(1 - \frac{\mathbf{u}}{D}(b - x)\right) = -\frac{\mathbf{u}x}{D} \tag{A21}$$

$$\mathrm{J} = J_{conv} + \mathrm{J}_D(O_2) = \mathrm{C}_0\mathbf{u} + \frac{DM_0}{\mathbf{u}}\left(\frac{\mathbf{u}}{D} b\right) - M_0 x = \mathrm{C}_0\mathbf{u} + M_0(b - x) \tag{A22}$$

$$\mathrm{J}_D = M_0(b - x) \tag{A23}$$

At $x = 0$,

$$J_{total} = \mathrm{C}_0\mathbf{u} + \frac{DM_0}{\mathbf{u}}\left(1 - \exp\left(-\frac{\mathbf{u}}{D} b\right)\right) \tag{A24}$$

$$J_{conv} = \mathrm{C}_0\mathbf{u} \tag{A25}$$

$$\mathrm{J}_D = \frac{M_0 D}{\mathbf{u}}\left(1 - \exp\left(-\frac{\mathbf{u}}{D} b\right)\right) \tag{A26}$$

For $\mathbf{u}b < \mathrm{D}$, $J_\mathrm{D} = M_0 b$.

$$\frac{J_D}{J_{conv}} = \frac{M_0 b}{\mathrm{C}_0 \mathbf{u}} \tag{A27}$$

Authors contributions:

Z.L. conceived the idea. Z.L. discussed with C.W. on the physiology aspects of the idea and with S.-L.Z. on the physics aspects. Z.L. worked on model design, mathematical derivations, data analysis, and drafted the manuscript. C.W. built the COMSOL model. All authors contributed to the manuscript revision.

Funding: Financial support from Chinese oversea program CSC foundation 201907035003 and Faculty fund of Uppsala University.

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Table 1. Parameters used in the COMSOL simulation (Covell & Jacquez, 1987)

k_1	24×10^{3} m^{3} mol^{-1} s^{-1}	$K = k_1/k_2$	3.69×10^{2} m^{3} mol^{-1}
k_2	65 s^{-1}	α	1.23×10^{-3} mol m^{-3} torr^{-1}
C_{Mb}^{T}	0 - 1 mM	P_0	50 torr^{-1}
D_{O2}	1.6×10^{-9} m^{2} s^{-1}	b	1 mm
D_{Mb}	10^{-10} m^{2} s^{-1}	M_0	10^{-4} mol m^{-3}s^{-1}

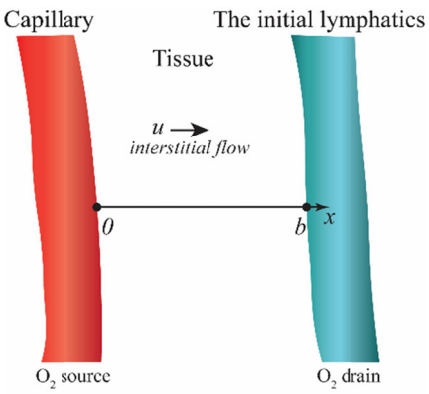

Figure 1. Illustration of a 1D model for the O_2 transport from the capillary (x = 0) to the initial lymphatics (x = b)

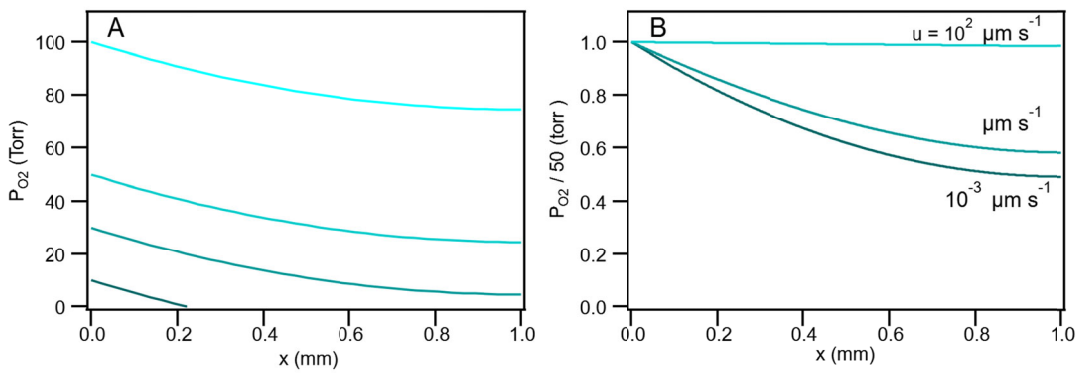

Figure 2. Concentration profile at different (A) O_2 tension of capillary and (B) fluid flow rate (10^{-9}, 10^{-6} and 10^{-4} m/s) at Po_2= 50 torr.

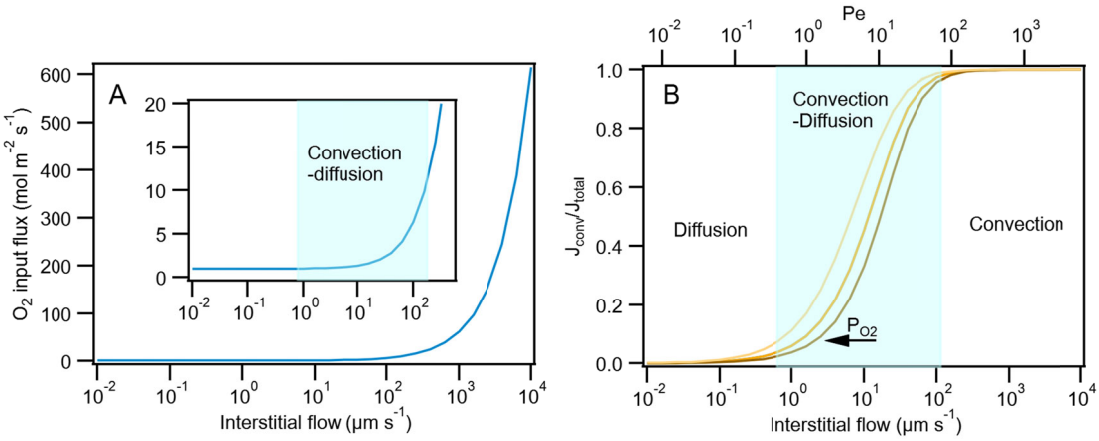

Figure 3. At $x = 0$, (A) the ratio plot of J_{tconv}/J_{total} ($\boldsymbol{u} = 0$) as a function of the fluid flow with the inset for an enlarged image; (B) the ratio of J_{conv}/J_{total} as a function of the interstitial flow, at $P_{O2} = 30$, 50, and 100 Torr from right to left.

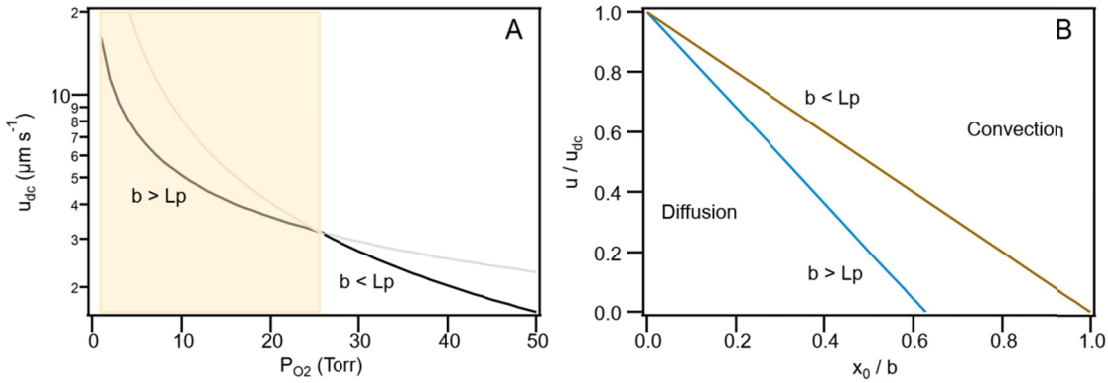

Figure 4. For $b < L_p$ and $b > L_p$, (A) $\boldsymbol{u}_{dc}$ as a function of the O_2 tension of capillary and (B) the normalized $\boldsymbol{u}$ and x_0.

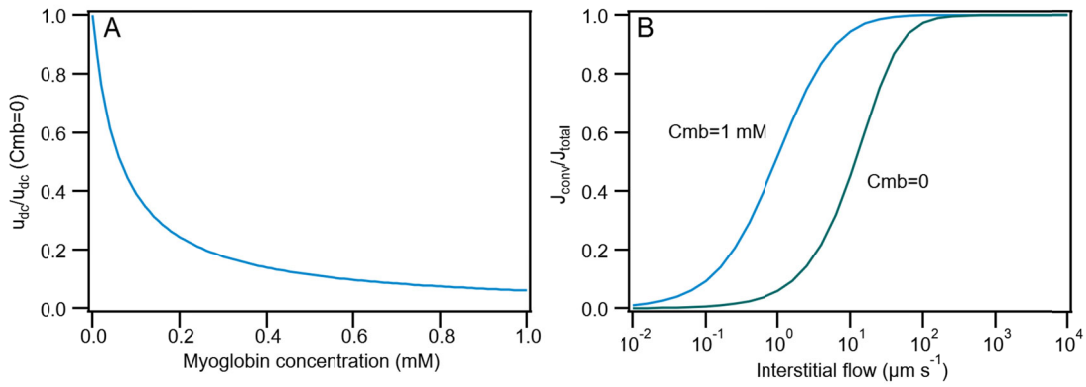

Figure 5. (A) The interstitial fluid $\boldsymbol{u}_{dc}$ as a function of myoglobin concentration, C_{mb}; (B) the ratio of J_{conv}/J_{total} at x = 0 as a function of the interstitial flow with and without myoglobin.

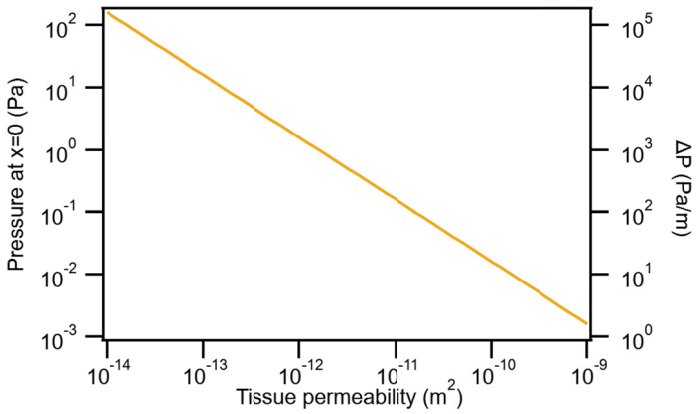

Figure 6. Pressure (P) and pressure gradient *vs.* permeability at $\boldsymbol{u}$ = 1.6 μm/s.

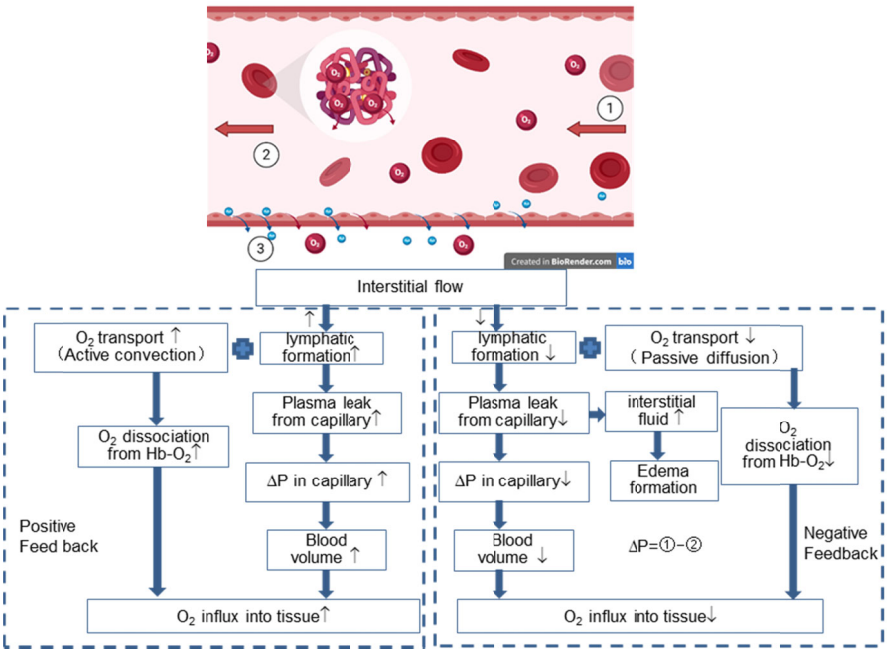

Figure 7. Influence of the interstitial flow on the O_2 influx into tissue.

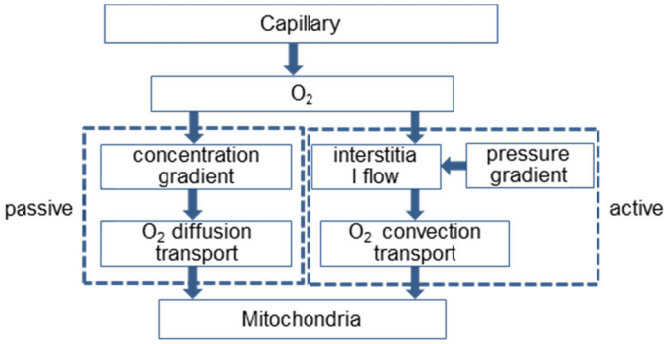

Figure 8. Summary of the active and passive O_2 transport routes in tissue.