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Numerical modeling of fluid and oxygen exchanges through microcirculation for the assessment of microcirculation alterations caused by type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus (DM2) is frequently accompanied by microcirculation complications, including structural and functional alterations, which may have serious effects on substance exchanges between blood and interstitial tissue and the health of organs. In this paper, we aim to study the influence of microcirculation alterations in DM2 patients on fluid and oxygen exchanges through a model analysis.

A fluid flow and oxygen transport model were developed by considering the interplay between blood in capillary network and interstitial tissue. The two regions were separately represented by 1D network model and 3D volume model, and the immersed boundary method (IBM) was adopted to solve fluid and mass transfer between these two regions. By using the model, the steady flow field and the distributions of oxygen in capillary network and surrounding tissue were firstly simulated. In the interstitial volume, fluid pressure and oxygen tension decreased with the increase of distance from the network; in the network, oxygen tension in blood plasma dropped from 100 mm Hg at the entrance to about 40 mm Hg at the exit. We further tested several structural and functional disorders related to diabetic pathological conditions. Simulated results show that the impaired connectivity of the network could result in poor robustness in maintaining blood flow and perfused surface; under high fluid permeability conditions of capillary walls, the pressure gradient was much larger around the capillary bed, and this alteration led to a saturation level of the interstitial pressure when lymphatic flow drainage can't work effectively; the variations in network connectivity and permeability of capillary wall also had unfavorable influence on oxygen distributions in interstitial tissue. In addition, when the oxygen releasing capacity of hemoglobin was confined by glycosylated hemoglobin (HbA1) in the case of diabetes, the plasma could not be complemented with adequate oxygen and thus the hypoxic tissue range will be extended.

This study illustrates that when microcirculation disturbances, including the structure of capillary network, the wall osmosis property and the capacity of blood binding oxygen occur in DM2, some negative impacts are raised on microvascular hemodynamics and metabolism circumstance of interstitial tissue.

1. Introduction

Peripheral vascular complications often appear in the early stage of DM2, showing alterations in microvascular hemodynamics and substance exchange with tissue. Through clinical microcirculation observations, the most obvious structural changes in the case of DM2 include the thickening of the capillary basement membrane, diminished capillary size, and pericyte degeneration (Chao and Cheing, 2009). Benedict et al. (2011) observed that a significant 37% decrease in microvascular branching and a 19% decrease in microvessel length density associated with the onset of DM2 via detailed measurements of microvascular network connectivity and geometric structure in control rats and in rats before and after developing DM2. They also predicted that the changes in DM2 capillary connectivity can result in a significant 44% decrease in capillary flow. By using the imaging method of adaptive optics scanning laser ophthalmoscopy, Lu et al. (2016) constructed parafoveal capillary network models from healthy and diabetic retinopathy eyes. It is found that the vasculature for diabetic

Abbreviations: PO_2, partial pressure of oxygen; Hb, hemoglobin; SO_2, oxygen saturation; DM2, Diabetes mellitus type 2; FDM, finite difference method; IBM, immersed boundary method; VEGF, vascular endothelial growth factor; VCCC, vanished cross-connecting capillaries; RBC, red blood cell; LDF, laser doppler flowmetry; DR, diabetic retinopathy; NO, nitric oxide

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retinopathy eyes is more tortuous. Additionally, the microvascular density in papillary dermis and the expression of vascular endothelial growth factor are found to be reduced in diabetic foot ulcer patient (Mai et al., 2014).

Functional changes in microcirculation in DM2 include altered microvascular blood flow, vascular resistance, tissue PO_2, and characteristics of vascular permeability. Padilla et al. observed that there was a significant attenuation in RBC flux and velocity in the muscle capillaries of diabetic rats. They further estimated that theses alterations would reduce convective and diffusive O_2 transport (Padilla et al., 2006). In a research about retinal vessel alteration in Chinses DM2 patients, Dong et al. used noninvasive retinal oxymetry to analyze the vessel diameter and oxygen saturation for different groups of diabetic patients from fundus images and found that all of the diabetic patients showed smaller arterioles and wider venules. Meanwhile, the oxygen saturations in arterioles and venules for diabetic patients were both higher than that in normal subjects (Dong et al., 2016). The experiment of Khoobehi et al. supports the finding as well (Khoobehi et al., 2013). It is demonstrated that the change of glycocalyx structure under hyperglycaemia can lead to an increase of vascular permeability to water. Additionally, platelets of diabetic individuals more easily adhere to endothelium (Perrin et al., 2007). In addition to microvascular alterations, non-enzymatic glycation of proteins is involved in DM2 complications. Glycated hemoglobin levels can be elevated from 4 – 6% under normal conditions to 10 – 20% of the total hemoglobin under diabetic condition, which result in weakened capacity of releasing oxygen into plasma (Guo and Ren, 2005). Hua et al. investigated the correlations of oxygen saturation of retinal vessels and diabetic retinopathy (DR) stages or HbA1c level in patients with DR through experimental statistical analysis. They found that there was a positive correlation between the levels of HbA1c and retinal vessel oxygen saturation.

Despite the findings of structural and functional alterations in diabetes, the mechanisms of the alterations are still not extremely clear. Hyperglycemia is the central causative factor in vascular abnormalities induced by diabetes, including impaired vascular permeability, vascular tone, and the auto-regulation of blood flow. The modeling work has shown that the periodic variation of nitric oxide (NO) concentration is consistent with the periodic vasomotion of arteriole diameter and consists of dynamic regulating process which is caused by the feedback control of shear stress (Tang and He, 2017). Meanwhile, oxygen reaction rate with NO and the characteristics of membrane of red blood cells have significant impacts on NO concentration in capillary lumen (Wei et al., 2017).

To date, as far as we know, little work can qualitatively or quantitatively assess these alterations theoretically from their influence on fluid and oxygen transport of diabetic tissue. Fluid and mass transfer occurs mainly in capillaries and postcapillary venules in most microcirculatory beds (Hall, 2016), which is an import assurance for physical functions of tissues and organs. Capillary wall consists of a unicellular layer of endothelial cells surrounded by a thin basement membrane, which is permeable to some substances. By far the most important means by which substances are transferred between the plasma and the interstitial fluid is diffusion (Hall, 2016). Water-soluble substances, like water molecules and sodium ions, can diffuse through intercellular “pores” in capillary membrane; lip-soluble substances, like oxygen and carbon dioxide, can diffuse directly through cell membranes of capillary endothelium. Fluid filtration across capillaries can be described by Starling's law (Popel, 1989). Meanwhile, excess interstitial fluid and dissolved solute that leaking from the blood into the interstitial spaces can be absorbed by lymphatic system to maintain pressure balance. Due to the complex process of fluid transport in tissue, multiscale modeling method is frequently employed, where blood flow is modeled as Poiseuille flow through a permeable wall and interstitial and lymphatic flow are modeled as transport in porous media (Pozrikidis, 2013; Pozrikidis, 2010a, b; Cattaneo and Zunino, 2014a, 2014b; Shipley and Chapman, 2010). Cattaneo and Zunino (2014a) have developed a computational model for fluid exchange between microcirculation and tissue interstitium, where the capillaries and interstitial volume were described as two independent structure and immersed boundary method was adopted to couple the 1D flow through the network and 3D flow through the interstitial volume. They further expanded the model to drug delivery through microcirculation to compare different tumor treatments (Cattaneo and Zunino, 2014b). It is considered that the work of Cattaneo et al. is the most comprehensive since it includes the influence of lymphatic flow which was not frequently taken into accounted in other models.

On the other hand, oxygen in blood is carried in two forms: as free oxygen dissolved in plasma and oxygen bound to hemoglobin (Hb) within red blood cells. Only about 1.5% of oxygen is in the dissolved form. The oxygen affinity of Hb can be evaluated by P_{50}, which is defined as the plasma PO_2 at which Hb is 50% saturated with oxygen. The affinity is increased when P_{50} decreases and vice versa. For human blood P_{50} is approximately 26 mm Hg (Popel, 1989). The oxyhemoglobin curve, including the value of P_{50}, can be affected by many factors. Moore and Ethier (1997) modeled the transport of oxygen transport in large arteries, including the physiologically important effects of oxygen transport by hemoglobin in the blood and wall tissue, and metabolic consumption of oxygen by the wall. Their research indicated that the role of oxygen binding by hemoglobinis was of extreme importance in oxygen transport.

The Krogh tissue cylinder model of oxygen transport between capillaries and tissue has been broadly used for prediction of oxygen distribution in tissue, however, it can't estimate oxygen transport in tissue with unevenly spaced vessels (Krogh, 1919). Secomb et al. (2004, 1998) theoretically simulated oxygen transport to tumors through microvessel networks by using Green's function methods. Relative to finite difference methods, the Green's function approach reduces the number of unknowns in the numerical formulation and allows rapid computations even for complex vascular geometries. Fraser et al. (2015) analyzed the impact of incremental perfusion loss on oxygen transport in a tissue with a real capillary network model, where the influence of blood flow and oxygen saturation were considered in different occluded capillary network, but they didn't considered the influences of interstitial and lymphatic flow on oxygen transport. Chen et al. (2007) investigated the complex co-transport of nitric oxide and oxygen in a paired arteriole-venule, surrounded by capillary-perfused tissue using a 3D model. Their results predicted that the capillary bed facilitated the release of oxygen from the vessel pair to the surrounding tissue. The modeling strategy of the hybrid model (Fang et al., 2008) of oxygen distribution is basically the same as that of Fraser (Fraser et al., 2015) and Cattaneo (Cattaneo and Zunino, 2014a, 2014b), where1D/3D advection–diffusion coupling method was employed.

In spite of little theoretical work for diabetic microcirculation, some latest published papers have focused on the issue. Causin et al. (2016) presented a multiscale model describing the coupling effect between blood flow and oxygen transport in the retina. Blood flow in the vascular tree network is modeled as one-dimensional two-phase flow including plasma and red blood cells. The retinal tissue consists of 6 layers with different oxygen consumption rate, where capillary plexus are embedded in the 4 and 6 layer. This may be the first thorough model for retinal microcirculation and oxygen transport. Lu et al. (2016) employed three-dimensional computational method to analyze capillary velocity, wall shear stress, and capillary prefusion pressure in real structural parafoveal capillary networks, which provides another noninvasive method for characterizing microcirculation in healthy and diabetic patients. In the modeling work of Fu et al. (2016), they simulated the progress of diabetic capillary occlusion and oxygen distribution by coupling the variation of the level of vascular endothelial growth factor (VEGF). Although these works provide useful insight into understanding the influences of blood rheology and vascular alterations on microcirculation under diabetic condition, the relationship between oxygen saturation, capillary occlusion, and tissue hypoxia under