

## MASS TRANSPORT IN ARTERIES AND THE LOCALIZATION OF ATHEROSCLEROSIS IN HUMAN

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### ABSTRACT

Atherosclerosis is a disease of the large arteries that involves a characteristic accumulation of high-molecular weight lipoprotein in the arterial wall. This research focuses on the mass transport processes that mediate the focal accumulation of lipid in arteries and places particular emphasis on the role of fluid mechanical forces in modulating mass transport phenomena as well as analysis of the Damkholer numbers within the arterial surfaces. Blood phase controlled hypoxia was considered in the mass transport mechanisms that emerge in the localization of atherosclerosis. The results of the analysis of Damkholer numbers indicated that there were no significant difference between the model derived values of the Damkholer numbers and the corresponding simulated values. Measured values ( $D_{ar} = 17.7$  for ATP,  $D_{ac} = 0.02 - 1.0$  for LDL,  $0.027 - 0.10$  for albumin,  $D_{aw} = 10.8 - 49.0$  for oxygen) and simulated value ( $D_{ar} = 7.762$  for oxygen,  $D_{ac} = 1.214$  for LDL,  $D_{aw} = 14.58$  for oxygen); where  $D_{ar}$  is Damkholer number,  $D_{ac}$  is Damkholer number based on endothelial permeability and  $D_{aw}$  is Damkholer number based on the wall consumption. The heat generation rate in tissue was calculated as  $4.0342 \times 10^2 \text{ w/m}^3$  and heat generation due to consumption of oxygen is  $2.09 \times 10^7 \text{ J/m}^3$ . The surface reaction rate constant,  $K_r$  and fluid-phase mass transfer coefficient,  $K_L$  are calculated as  $0.003198 \text{ mol.m/s}$  and  $0.000123 \text{ mol.m/s}$  respectively.

### 1. INTRODUCTION

Atherosclerosis is a disease of the coronary, carotid, and other proximal arteries that involves a distinctive accumulation of low-density lipoprotein (LDL) and other lipid-bearing materials in the arterial wall. Atherosclerosis is the leading cause of morbidity and mortality in Western societies. It is a progressive disease characterized by localized plaques that form within the artery wall. As the disease progresses, these plaques enlarge and either directly or indirectly lead to impairment of blood flow (Kaazempur, 2005).

In the advanced stages of atherosclerosis, various complications may occur. One of the most serious of these complications occurs when a blood clot forms in the narrowed artery. Unless the clot is dissolved or is removed through surgery, it may cut off the flow of blood to the tissue normally supplied by the artery, resulting in the death of the affected tissue. This kind of complication often occurs in the major arteries that carry blood to the brain and to the extremities.

The disease tends to be localized in regions of curvature and branching in arteries where fluid shear stress (shear rate) and other fluid mechanical characteristics deviate from their normal spatial and temporal distribution patterns in straight vessels. Because of the association of disease with regions of altered fluid mechanics, the role of blood flow in the localization of atherosclerosis has been debated for many years. Among the first mechanisms proposed to relate blood flow to the localization of atherosclerosis was one in which the fluid (blood)-phase resistance to transport of low-density lipoprotein or other atherogens was controlled by the local wall shear rate. Studies by Caro and Nerem (1973), however, suggested that the uptake of lipids in arteries could not be correlated with fluid-phase mass transport rates, leading to the conclusion that the wall (endothelium) and not the blood was the limiting resistance to transport. This implied that fluid-flow effects on macromolecular transport were mediated by direct mechanical influences on the transport systems of the endothelium. Somewhat later, attention was drawn to the fact that accumulation of macromolecules in the arterial wall depends not on the ease by which materials enter the wall, but also on the hindrance to passage of materials out of the wall offered by underlying layers. This brought into focus the possibility that the sub endothelial intima and media layers could be important structures contributing to local macromolecular uptake patterns (Nerem, 1995).

This paper determined the mass transport processes that mediate the focal accumulation of lipids in arteries with particular emphasis on the role of fluid (blood) in modulating mass transport phenomena and the localization of atherosclerosis. Model equations of the transport processes to the endothelial cell surfaces in human arteries were developed. The model equations include the effect of regions of curvature and branching in arteries, where fluid

shear stress and other fluid mechanical characteristics, deviate from their normal spatial and temporal distribution patterns in straight vessels. Also, the role of fluid (blood) flow in the localization of atherosclerosis was determined.

## 2. MODELING

Mathematical modeling constitutes a potential technique to contribute and investigate arterial flow dynamics and mass transport. Arterial blood flow dynamics and mass transport phenomena are of great interest in vascular physiology and biology. The main interest concerns the relation between hemodynamic and mass transport and the genesis of diseases (atherosclerosis and thrombosis) in arteries. Modeling helps to gain an insight into areas where the complete flow field over the vessel space, the shear stress at the fluid endothelium interface and the concentration field of dissolved gases and macro-molecules can be analysed.

### 2.1 MATHEMATICAL MODELS OF TRANSPORT TO THE ENDOTHELIAL CELL SURFACE IN HUMAN

Here, three common situations for transport that utilized the entire endothelial surface; the reactive surface, the permeable surface, and the reactive wall are modeled to estimate and evaluate the importance of fluid-phase transport relative to other transport processes, kinetics, and mass transfer coefficient.

#### 2.1.1 Reactive Surface

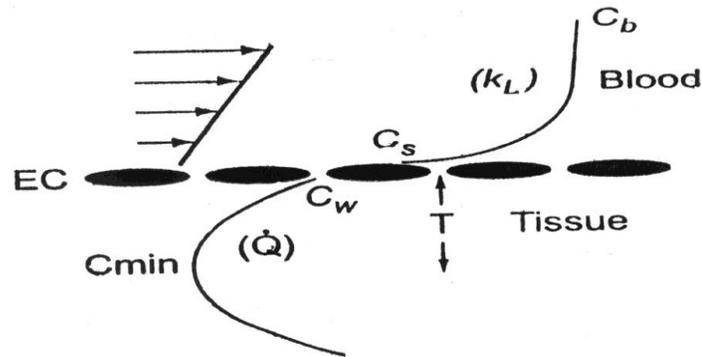


Figure 1. Schematic diagram of arterial wall transport processes.

Figure 1 shows a schematic diagram of arterial wall transport processes showing the concentration profile of a solute that is being transported from blood, where its bulk concentration is  $C_b$ , to the surface of the endothelium where its concentration is  $C_s$ ; then, across the endothelium, where the sub-endothelial concentration is  $C_w$ ; and finally to a minimum value within the tissue,  $C_{min}$ . It is assumed that the species of interest is transported from the blood vessel lumen, where its bulk concentration is  $C_b$ , to the blood vessel surface, where its concentration is  $C_s$ , by a convective-diffusive mechanism that depends on the local fluid mechanism and can be characterized by a fluid-phase mass transfer coefficient,  $K_L$ . The species flux,  $J_s$  (mass flow rate divided by surface area) in the blood phase is given by

$$J_s = K_L(C_b - C_s) \quad (1)$$

At the endothelial surface where the species undergo enzyme catalyzed surface reaction, can be modeled using Michaelis-Menten kinetics, where the rate  $V$ , is given as;

$$V = \frac{V_{max} C_s}{K_m + C_s} \quad (2)$$

When  $C_s \ll K_m$  as is often the case, the reaction rate is pseudo-first order.

$$V = K_r C_s \quad (3)$$

The rate constant for the reaction is given by

$$K_r = \frac{V_{max}}{K_m} \quad (4)$$

Where  $V_{max}$  is Maximum rate and  $K_m$  is Michaelis constant.

At steady state the transport to the surface is balanced by the reaction at the surface so that

$$K_l(C_b - C_s) = K_r C_s \tag{5}$$

We can now cast equation (5) into a dimensionless form by multiplying by  $d/D$ :

$$Sh(C_b - C_s) = D_{ar} C_s \tag{6}$$

and

$$Sh = \frac{K_l d}{D} \tag{7}$$

$$D_{ar} = \frac{K_r d}{D} \tag{8}$$

Solving equation (6) for surface concentration one finds

$$\frac{C_s}{C_b} = \frac{1}{1 + D_{ar}/Sh} \tag{9}$$

When  $D_{ar} \ll Sh$ ,

$$C_s = C_b \tag{10}$$

And the process is termed “Wall-limited” or “reaction-limited”. On the other hand, when  $D_{ar} \gg Sh$ ,

$$C_s = \frac{Sh}{D_{ar}} C_b \tag{11}$$

### 2.1.2 Permeable Surface

Many species will permeate the endothelial without reacting at the luminal surface (e.g. albumin, LDL) and their rate of transport (flux) across the surface layer can be described by

$$J_s = P_e(C_s - C_w) \tag{12}$$

If the resistance to transport offered by endothelium is significant, then

$$C_s \ll C_b \tag{13}$$

So that at steady state when the fluid and surface fluxes balance,

$$K_l(C_b - C_s) = P_e C_s \tag{14}$$

Multiplying equation (14) by  $\frac{d}{D}$  to introduce dimensionless parameter and then solving for the surface concentration leads to

$$\frac{C_s}{C_b} = \frac{1}{1 + D_{ac}/Sh} \tag{15}$$

Where  $Sh$  is defined in equation (7) and

$$D_{ac} = \frac{P_e d}{D} \tag{16}$$

### 2.1.3 Reactive Wall

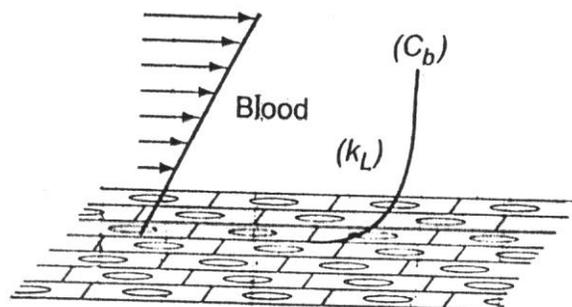


Figure 2: Schematic diagram of fluid-phase solute transport to a vessel wall.

Figure 2 shows a schematic diagram of fluid-phase solute transport to a vessel wall. The endothelial cells are shown conceptually, aligned in the longitudinal direction of the flow field with intercellular clefts elongated in the direction of flow. The concentration profile of a solute being transported from the blood is shown where  $C_b$  is its bulk concentration. The fluid-phase mass transport to the cleft is characterized by the mass-transfer coefficient  $K_L$ . The intercellular clefts are assumed to be the only route for the solute uptake. Oxygen is transported readily across the endothelium, but unlike most protein, it is rapidly consumed by the underlying tissue. In this case, endothelial transport resistance is neglected (assume  $C_w = C_s$ ), and then equating the rate of transport to the wall with the zeroth order consumption rate,

$$K_L(C_b - C_s) = QT \quad (17)$$

Where Q is Tissue consumption rate and T is Tissue thickness.

For a specific case of  $O_2$  transport, concentration (C) is replaced by the partial pressure (P) through the Henry's law relationship,  $C = KP$ , where K is Henry's law constant and invoking this relationship and rearranging equation (17) into a dimensionless rate, we have:

$$\frac{P_s}{P_b} = 1 - D_{aw} / sh \quad (18)$$

$$D_{aw} = \frac{QTd}{KDP_b} \quad (19)$$

Where  $P_b$  and  $P_s$  are bulk partial pressure and surface partial pressure respectively.

Clearly, when  $D_{aw} \ll sh$ , the process is wall limited. But, as  $D_{aw} \rightarrow sh$ , the process becomes limited by transport in the fluid phase ( $P_s \rightarrow 0$ ) and fluid mechanics plays a role.

### 3. RESULTS

The mathematical modeled equations describing the mass transport processes to the entire endothelial cell surface which enhances the development of atherosclerosis in arteries were developed. The Damkholer numbers for the reactive surface,  $D_{ar}$  the permeable surface,  $D_{ac}$  and the reactive wall  $D_{aw}$  were solved analytically.

$D_{ar} = 7.762$  for oxygen,  $D_{ac} = 1.214$  for LDL and  $D_{aw} = 14.58$  for oxygen. The solved model of the transport processes verified our assumption that the reaction rate obeys pseudo-first order kinetics. Our aim is to show that the developed equations produce results that are similar to the measured results. The diameter, d of the large artery is 2.5 cm and 5  $\mu$ m for small artery. The lengths and diameters were based on magnetic resonance measurements. At locations where measured data are not available, concentrations were estimated from combined literature data with measured and computed data. The blood flow rate of the subject in question is  $2.1753 \times 10^{-4} m^3 / sm^3$ . Under normal condition, the average blood flow rate for a human is  $5 \times 10^{-4} m^3 / sm^3$  tissue, under basal resting condition (Simant and Ayodeji, 2003). The heat generation rate in tissue was calculated to be  $4.0342 \times 10^2 w / m^3$ , which is within the range of  $3.2336 \times 10^2 - 5.2309 \times 10^2 w / m^3$  for humans (Simant and Ayodeji, 2003). The average oxygen level of the subject was  $0.17 m^3 O_2 / m^3$ , and the calculated heat generation due to consumption of oxygen was  $2.09 \times 10^7 J / m^3$ . Total plasma cholesterol concentration (LDL) of the subject was less than 200 mg/100 ml which is considered desirable (EST, 2002). The Sherwood number, Sh is 114 for LDL, 79.2 for albumin, 41.8 for ATP and 31.1 for oxygen. Reynolds number,  $R_e$  is 250 and Schmidt number,  $S_c$  is 3000 for both ATP and free oxygen in blood. The protein concentration (The Plasma phospholipids transfer protein, PLTP) is 12.6 mg/l, which is in the range of 4.9-20.5 mg/l for a normal subject, EST (2002). The permeability coefficient was assumed to be 0.9 mm/s. For a normal subject it is between 0.5mm/s and 2.5mm/s (Tarbell, 2003). Tissue thickness, T was measured as 0.5  $\mu$ m for heparinase treatment plasma labeling, and hematocrit measurement. Diffusion coefficient, D of concentration transport from was estimated to be  $2.06 \times 10^{-9} m^2/s$ . The Surface reaction rate constant,  $K_r$  and endothelial transport resistance,  $K_L$  are calculated as  $0.003198 mol.m/s$  and  $0.000123 mol.m/s$  respectively.

#### 4. DISCUSSION OF RESULTS

The results shown in Table 1 are Damkholer numbers for the transport processes in human arteries, obtained using the model equations which are similar to those derived from estimation techniques (literature values) for low-density lipoprotein (LDL) and oxygen transport as shown in Table 2. The Damkholer number for LDL show that fluid-phase transport of these solutes to intercellular junctions is not a limiting factor in arteries, but may be important in capillaries.

Table 1. Damkholer number from mathematical model (simulated)

Parameter	LDL	Albumin	ATP	Oxygen
$D_{ac}$	1.214	-	-	-
$D_{ar}$	-	-	-	7.762
$D_{aw}$	-	-	-	14.58

Table 2. Measured Damkholer numbers for the transport processes in human arteries

Damkholer Numbers	LDL	Albumin	ATP	Oxygen
$D_{ac}$	0.02-1.0	0.027-0.10	-	-
$D_{ar}$	-	-	17.7	-
$D_{aw}$	-	-	-	10.8-49.0

But it is clear that since the Damkholer number is much greater than Sherwood number, the process is termed “transport-limited” or “fluid-phase-limited”. Hence, the modeled equations are true representation of the biological system. However, a synthesis of these basic mass transport processes in relation to pattern of macromolecular uptake improve the localization of atherosclerosis and is presented in the form of several plausible mechanisms of atherogenesis in which mass transport plays a central role. High-molecular-weight species, such as LDL and albumin, are not limited by the fluid phase. Oxygen transport, however, may be fluid-phase limited in regions of low fluid-phase mass transfer rates (Sherwood number,  $sh$ ), such as the outer walls of bifurcations and the inner walls of curved vessels where enhanced LDL uptake and atherosclerotic lesions localize. Hypoxia in such regions has been confirmed by direct measurement in the carotid bifurcations, around vascular graft anastomoses and in other vessels. Hypoxia in the arterial wall has for many years been implicated in the development of atherosclerosis. Local hypoxia can affect the uptake of LDL and other macromolecules by the arterial wall through several mechanisms: (a) Hypoxia can break down the endothelial barrier and form interendothelial gaps leading to increased macromolecular transport. (b) Hypoxia also induces endothelial cell apoptosis, which can increase LDL transport through leaky junctions. The uptake of LDL is controlled by the endothelium, not the fluid phase, and leaky junctions, not tight junctions, would appear to constitute the principal pathway for transport of LDL across the endothelial layer. Leaky junctions are associated with cell in a state of turn over (mitosis) or death (apoptosis), and these processes are affected by local fluid mechanics. Elevated steady shear stress tends to suppress both mitosis and apoptosis, whereas low shear stress is separated or disturbed flow increase in these processes. Therefore, it is expected that leaky junctions would be more prevalent in regions of low shear stress and separated flow than in regions of higher, uni-directional shear stress. These are precisely the regions where atherosclerotic plaques tend to be localized at the carotid bifurcation, in coronary arteries, and the aortic bifurcation. For large macromolecules, such as LDL, that have a low endothelial permeability ( $P_e$ ) relative to volume flux ( $J_v$ ), an increase in  $J_v$  with fixed  $P_e$  will reduce the accumulation of solute beyond the endothelial layer (intima/media), by convectively clearing (flushing) out the region beyond the high resistance endothelial barrier. If we assume that a macromolecule crosses the endothelial primarily through leaky junctions, and that volume flux (primarily water flux) is controlled principally by the intercellular junctions that have a much greater total area than the leaky junctions, then factors that affects  $J_v$  but not  $P_e$  can influence the accumulation of macromolecules within the wall.

#### CONCLUSION

The accumulation of Lipoprotein in the arterial intima is a hallmark of atherosclerosis. Low density-lipoprotein (LDL) is the most abundant atherogenic lipoprotein in plasma and high plasma levels of LDL are casually related to the development of atherosclerosis. The results of the analysis indicated that there were no significant difference between the model derived values of the Damkholer numbers and the corresponding simulated values. Model values

( $D_{ar} = 17.7$  for ATP,  $D_{ac} = 0.02 - 1.0$  for LDL,  $0.027 - 0.10$  for albumin,  $D_{aw} = 10.8 - 49.0$  for oxygen) and simulated value ( $D_{ar} = 7.762$  for oxygen,  $D_{ac} = 1.214$  for LDL,  $D_{aw} = 14.58$  for oxygen). The flux of LDL into the arterial wall depends on the plasma concentration and permeability,  $P_e$  which for human aorta is between the range of  $5 \times 10^{-4} - 2.5 \times 10^{-3} m/s$ . Thus, a correlation between  $P_e$  and plasma concentration then enhances the localization of atherosclerotic plaques. Subjects with high permeability and plasma protein concentrations are prone to atherosclerotic plaques. Research has improved our understanding of this disease, which necessitated the evaluation of the mathematical models equations for mass transport in arteries. The mathematical models in turn are used to suggest better treatments, such as the administration of aspirin to reduce the risk of blood clots forming on the damaged artery lining and surgical treatment such as coronary angioplasty, which improve the state of the patients suffering from this disease.

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