ELSEVIER

Atherosclerosis 159 (2001) 1–7

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Review article

# Analytical models of atherosclerosis

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Received 8 December 2000; accepted 4 June 2001

**Abstract**

Atherosclerosis is responsible for $\approx 50\%$ of all mortalities in the USA, Europe, and Japan. An innovative approach for investigating atherosclerotic lesions using a thermodynamic model and a boundary value model and an analytical example of a human abdominal aorta vessel with an initial lesion are presented in the paper. Analytical results given by both models propose that increased transient boundary layer thickness and reduced surface energy of adhesion in regions of the arterial branch points play crucial roles in initial lesion formation. This study also improves the understanding of atherosclerotic mechanisms and helps to interpret clinical and experimental results. 

*Keywords:* Atherosclerosis; Analytical model; Thermodynamics; Surface energy of adhesion; Hemodynamics; Turbulence; Transient boundary layer; Atherosclerotic mechanism

## Nomenclature

| | |
|---|---|
| $L_a$ | axial adhesive length (cm) |
| $z_h$ | axial distance between point being studied and starting point of transient boundary layer (cm) |
| $\tau_{rz}$ | axial shear stress of plasma fluid (g/cm s$^2$) |
| $f$ | axial transient inertial force (g/cm$^2$ s$^2$) |
| $f_h$ | axial transient inertial force per unit area at border of transient boundary layer (g/cm s$^2$) |
| $u_z$ | axial velocity of plasma fluid (cm/s) |
| $u_b$ | axial velocity of plasma fluid at border of transient boundary layer (cm/s) |
| $F_e$ | body force vector (g/cm$^2$ s$^2$) |
| $A$ | contact area between lesion and endothelium (cm$^2$) |
| $\rho$ | density of liquid (g/cm$^3$) |
| $v_e$ | eddy velocity (cm/s) |
| $a$ | inner radius of tube (cm) |
| $F_a$ | interfacial shear resistance (g/cm s$^2$) |
| $E_k$ | kinetic energy of lesion (g cm$^2$/s$^2$) |
| $\omega$ | mean transient frequency (Hz) |
| $\bar{u}$ | mean velocity of blood flow in abdominal aorta (cm/s) |
| $P$ | pressure vector (g/cm s$^2$) |
| $F(z)$ | shear force (g/cm s$^2$) |

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0021-9150/01/$ - see front matter 
PII: S0021-9150(01)00655-4

$E_{sl}$ surface energy of adhesion ($g/s^2$)
$\gamma_l$ surface free energy of liquid ($g/s^2$)
$\gamma_{sl}$ surface free energy of liquid–solid interface ($g/s^2$)
$\gamma_s$ surface free energy of solid ($g/s^2$)
$h(z)$ thickness of transient boundary layer (cm)
$u$ velocity vector of fluid (cm/s)
$u_l$ velocity vector of lesion (cm/s)
$\mu$ viscosity of liquid (g/s cm)
$V$ volume of lesion ($cm^3$)

## 1. Introduction

Atherosclerosis is characterized by the thickening, hardening, and loss of elasticity of the inner arterial walls. These changes in the walls can lead to the obstruction of coronary bloodstreams. The earliest atherosclerotic lesions, called fatty streaks, are simple deposits of low-density lipoproteins (LDL) on the aortic endothelium. These streaks occur at a universal age of ten, but progress to more advanced stages at different rates in different people. In the second stage, the lesions are called fibrous plaques because they contain not only more smooth muscle cells, but also more collagens and elastic tissues. The final stage is the complex lesions that are of thrombus formation with deposits of fibrins and platelets. The American Heart Association (AHA) committee has defined a new classification of the human atherosclerotic phases from the fatty streaks to the complex lesions [1].

Since atherosclerosis is a major cause of mortality and morbidity in the world, a huge volume of research has been focused on the disease [1–18]. These research have been concerned mainly with dieting, environment, genetics, and immunity. A number of studies also attempted to identify the components and characteristics of lesions at various stages. Ross [2] contributed his response-to-injury hypothesis to the understanding of cellular and molecular mechanisms of atherosclerosis. These investigations indicated that hemodynamics might be closely related to atherosclerosis.

Atherogenesis is related to nanoscale fluid dynamics and macromolecular transport at the arterial endothelium [3]. The behavior of atherosclerosis is time-dependent and the dominant phenomena may occur in the range of 0–100 Å from the endothelium. The location of atherosclerosis is also associated with flow separation and turbulence. These factors cause the study of the effects of hemodynamics on atherosclerosis to be rather complex. Early works on these effects focused on endothelial transportation using excised tissue. Fry [19,20] initiated studies on the effect of increased shear stress on the endothelium and showed that endothelial cells remodel their shapes when the direction of flow is changed. Caro et al. [21,22] found that lesions occur in areas experiencing low and fluctuating wall shear stress. Recent reports discussed the progress in the studies of the effects of hemodynamics on atherosclerosis [23–29].

Fung [28] summarized these hemodynamic effects and pointed out that the most intriguing feature of atherosclerosis is its appearance only at certain arterial branch points. It is known that many factors influence atherogenesis including dieting, environment, diabetes, high blood pressure, genetics, and exercise. These factors, however, affect not only the special branch locations, but also the entire body. Then why will only a few feet, in miles of blood vessels in the human body, be destined to have atherosclerosis? Why do only LDL deposit on some arterial walls and not others? What is so unique about these locations? Throughout the history of the study of atherosclerosis, many researchers have been focusing on the understanding of these fundamental natures of atherosclerosis. This paper proposes some answers to these fundamental questions.

An innovative approach for investigating atherogenesis is developed using a thermodynamic model and a boundary value model. Conclusions given by this study propose two new factors in atherogenesis: increased transient boundary layer thickness and reduced surface energy of adhesion in regions of arterial branch points, which play crucial roles in atherogenesis.

## 2. Thermodynamic model

### 2.1. Thermodynamic model of an atherosclerotic lesion

The arterial endothelium is always in direct contact with the blood flow and is borne by hemodynamic forces. Endothelial cells have synthetic and metabolic capabilities and act as selectively permeable barriers for the transportation of macromolecules. The interfacial forces acting on the endothelium can change endothelial functions and structures including increased molecular permeability, LDL accumulation, and endothelial

cell damage. In this model, an initial lesion adhered on the endothelium is investigated using thermodynamics and energy conservation principles.

Let us consider the blood flow through a branched circular arterial tube of internal radius $a$ under an axial transient inertial force $f$, where $(r, \theta, z)$ is a set of cylindrical polar coordinates with the $z$-axis coinciding with the axis of the tube. Taking a small fluid element near the inner tube wall at a branch point where $r = a$ and $z = 0$, the kinetic energy of the element $E_k$ is $\frac{1}{2}\cdot\rho\cdot V\cdot u_l^2$, where $\rho$ is the density of the fluid, $V$ is the volume of the element, and $u_l$ is the velocity vector of the element. If an initial lesion occupies the element, $E_k$ becomes the kinetic energy of the lesion. This lesion is characterized by volume $V$, axial adhesive length of the lesion on the endothelium $L_a$, contact area between the lesion and the endothelium $A$, surface free energy $\gamma_{sl}$, velocity vector $u_l$, and interfacial shear resistance $F_a$ that is the force resisting the movement of the lesion (Fig. 1). All symbols of the paper are denoted in the nomenclature.

### 2.2. Energy equation

The adherence of an initial lesion on a plasma–endothelial interface can be treated as a thermodynamic problem in a mixing system because thermodynamics deals with macroscopic and statistical behaviors of interfaces rather than with details of their molecular structures. Surface energy of adhesion $E_{sl}$, one of thermodynamic terms, is the energy that is required to bring LDL from the interior of the plasma fluid onto the arterial endothelium and form an interface. Blood flow is to obey the principles of conservation of energy, mass, and momentum.

Consider a lesion under an axial transient inertial force $f$ (Fig. 1). Based on thermodynamics and energy conservation principles, the energy equations for the lesion are created as

$$E_k = \frac{1}{2}\cdot F_a\cdot L_a\cdot A, \tag{1}$$

$$E_{sl} = \frac{1}{2}\cdot F_a\cdot L_a, \tag{2}$$

$$E_k = E_{sl}\cdot A, \tag{3}$$

where $E_{sl} = \gamma_s + \gamma_l - \gamma_{sl}$ [30].

Eq. (1) describes the equivalence between the kinetic energy of a lesion $E_k$ and the work done by the total interfacial shear resistance $F_a\cdot A$ along the adhesive length $L_a$. Eq. (2) represents the equivalence between the surface energy of adhesion $E_{sl}$ and the work done by $F_a$ at a liquid–solid interface. Substitution of Eq. (2) into Eq. (1) yields Eq. (3).

If $E_k$ is greater than $E_{sl}\cdot A$, then the lesion will not form because the kinetic energy of the lesion $E_k$ overcomes the total energy of adherence $E_{sl}\cdot A$ before the adherence of the lesion can occur.

## 3. Dynamic boundary value model

### 3.1. Governing equation

Studies of hemodynamics [21–23,28,31–35] suggest that atherosclerotic lesions are located in regions of reduced shear stress of the fluid, which is often associated with flow separation and turbulence. A transient boundary layer, led by the flow, occurs in these regions. The studies also indicated that blood flow near inner arterial walls consists mainly of plasma fluids.

In the dynamic model, the plasma viscous flow in the transient boundary layer near the inner tube wall at an arterial branch point is investigated because lesions arise from this layer. Since plasma fluid is known to be Newtonian, the flow is governed by the Navier–Stokes equation. The following restrictions are imposed to simplify the dynamic model.

1. The plasma may be treated as an incompressible, homogenous fluid.
2. The flow is laminar.

Let us consider an incompressible laminar flow through a circular tube. The governing equation is

$$\rho\cdot\frac{du}{dt} = F_e - \text{grad } P + \mu\cdot\nabla^2\cdot u, \tag{4}$$

where $u$ is the velocity vector of the fluid, $F_e$ is the body force vector, $P$ is the pressure vector, $\mu$ is the viscosity of the fluid, $\rho$ is the density of the fluid, and $\mu\cdot\nabla^2\cdot u$ is the viscous force.

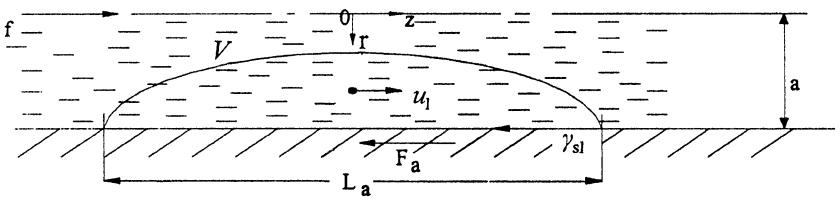


Fig. 1. Axial cross-section of a lesion called a fatty streak adhered on the arterial endothelium.

### 3.2. Assumptions

The following assumptions are imposed to simplify the boundary value model.

1. The gravitational potential in the fluid has a negligible effect because the transient boundary layer is thin.
2. The rate of flow is steady, and there is a constant pressure flow.
3. The flow does not slip at the inner wall of the tube.
4. The length of the tube is long compared to the region being studied, so that edge effects become negligible.
5. The diameter of the tube does not vary with internal pressure.
6. There is no convection in the flow.

These assumptions and previous restrictions are valid in most studies of hemodynamics [28,35,36].

### 3.3. Simplified governing equation

Let us use the same notations and consider an incompressible plasma flow in a circular arterial tube with ranges $(a-h(z)) \leqslant r \leqslant a$, $0 \leqslant \theta \leqslant 2\pi$, and $-\infty < z < \infty$, where $h(z)$ is the thickness of the transient boundary layer. Using cylindrical polar coordinates ($r$, $\theta$, $z$), we yield $\mu \cdot \nabla^2 \cdot u = \frac{\mu}{r} \cdot \frac{\mathrm{d}}{\mathrm{d}r}\left(r \cdot \frac{\mathrm{d}u_z}{\mathrm{d}r}\right)$, where $u_z$ is a function of $r$ only.

Following the above assumptions, Eq. (4) is simplified to

$$f = \frac{1}{r} \cdot \frac{\mathrm{d}}{\mathrm{d}r}(\tau_{rz} \cdot r) \tag{5}$$

and

$$\tau_{rz} = -\mu \cdot \frac{\mathrm{d}u_z}{\mathrm{d}r}, \tag{6}$$

where $u_z$ is the axial velocity component of the plasma fluid, $\tau_{rz}$ is the axial viscous shear stress of the fluid, and $f$ is the axial transient inertial force.

### 3.4. Boundary condition

According to previous assumptions, the boundary conditions of the model are

$$u_z = 0 \quad \text{at } r = a, \tag{7}$$

$$\tau_{rz} = F(z) \quad \text{at } r = a, \tag{8}$$

where $F(z)$ is the shear force acting on the inner wall of the tube.

If a fatty streak appears at $r = a$ and $z = 0$, we can substitute $F(z) = F_a$ into Eq. (8) to yield

$$\tau_{rz} = F_a \quad \text{at } r = a,\ z = 0, \tag{9}$$

where the interfacial shear resistance $F_a$ is defined in the previous model. Through Eq. (9), we can now join the thermodynamic model and the boundary value model.

### 3.5. Compatibility condition

As stated previously, there is often separation and turbulent flow at the location of atherosclerosis. The flow at these sites consists of two different types. The first is the plasma flow in the transient boundary layer that is governed mainly by the viscous force. The second is the blood flow in the rest of the regions of the tube that is governed by the axial transient inertial force. Hence, the viscous force and the transient inertial force must equal at the border of the layer for a unique analytic solution. The compatibility condition is created as

$$\tau_{rz} = f_h \quad \text{at } r = a - h(z), \tag{10}$$

where $f_h$ is the axial transient inertial force per unit area. We may take $f_h = f \cdot (a - h(z))$.

### 3.6. Analytical solutions

Eqs. (5) and (6) combined with Eqs. (7), (8) and (10) yield the axial shear stress of the plasma fluid $\tau_{rz}$, the axial velocity component $u_z$, and the compatibility equations. (Detailed derivations are omitted due to limited space.)

$$F(z) = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right), \tag{11}$$

$$u_z = \frac{f}{4\mu} \cdot (a^2 - r^2) + \frac{f}{2\mu} \cdot (a - h(z))^2 \cdot \ln\left(\frac{a}{r}\right), \tag{12}$$

$$\tau_{rz} = \frac{f}{2r} \cdot (a - h(z))^2 + \frac{r \cdot f}{2}. \tag{13}$$

Substitution of $F(z) = F_a$ into Eq. (11) yields

$$F_a = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right). \tag{14}$$

Substitution of Eq. (2) into Eq. (14) yields

$$E_{sl} = \frac{1}{2} \cdot L_a \cdot f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right). \tag{15}$$

### 3.7. The effects of turbulence eddies on atherosclerosis

Turbulence eddies do not originate in the transient boundary layer, however, these eddies may enter the layer from the side $r < (a - h(z))$ [37,38]. If we consider the effect of the eddies in the layer on atherosclerosis, the thickness of the layer $h(z)$ in the region near the branch point can be expressed approximately as

$$h(z) \approx B \cdot v_e, \tag{16}$$

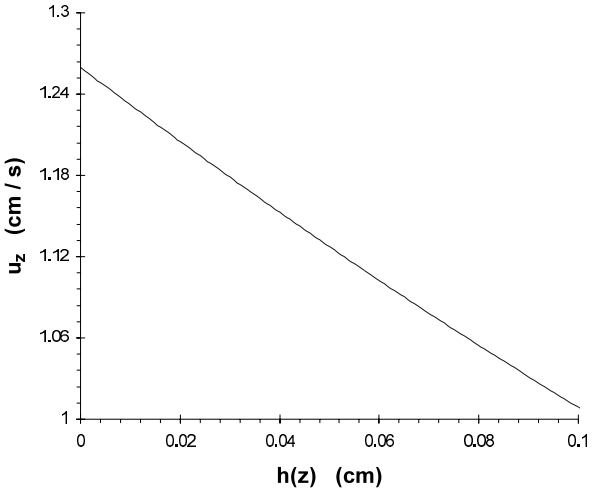


Fig. 2. The relationship between the axial velocity of the plasma fluid and the thickness of the transient boundary layer.

where eddy velocity $v_e$ is a weak function of $z$ and varies with $r$. Parameter $B$ is determined by the axial velocity $u_b$ of the plasma fluid at the border of the layer and the axial distance $z_h$ between the point being studied and the starting point in the layer.

The transfer of macromolecules in the fluid to a liquid–solid interface may be closely related to $v_e$. Eq. (16) indicates that increased $h(z)$ involves increased $v_e$, which implies that LDL in the plasma fluid is more likely to be drawn onto the endothelium. Increased thickness of the transient boundary layer $h(z)$ and increased eddy velocity $v_e$ in regions of the arterial branch points are risk factors in atherogenesis.

## 4. Conclusions

### 4.1. Analytical example

We can obtain representative results using some average numbers for a human abdominal aorta vessel [28] by taking the mean internal radius of the vessel $a = 0.5$ cm, mean transient axial velocity $\bar{u} = 15$ cm s$^{-1}$, mean transient frequency $\omega = 2$ Hz, density $\rho = 1.0$ g cm$^{-3}$, plasma viscosity $\mu = 1.2$ g s$^{-1}$ cm$^{-1}$, adhesive length $L_a = 0.2$ cm, and the range of the thickness of the transient boundary layer $0 \leqslant h(z) \leqslant 0.1$ cm. Since $f = \rho \cdot \omega \cdot \bar{u}$, we obtain the axial transient inertial force $f = 30$ g cm$^{-2}$ s$^{-2}$. Substitutions of $a = 0.5$ cm, $\mu = 1.2$ g s$^{-1}$ cm$^{-1}$, $f = 30$ g cm$^{-2}$ s$^{-2}$, $r = 0.4$ cm into Eq. (12) yield Fig. 2 for the boundary value model. Substitutions of $a = 0.5$ cm, $f = 30$ g cm$^{-2}$ s$^{-2}$, $L_a = 0.2$ cm into Eq. (15) yield Fig. 3 for the thermodynamic model.

### 4.2. Conclusions

(1) From Eq. (6), Figs. 2 and 3, we find that the shear stress of the plasma fluid $\tau_{rz}$ is proportional to the surface energy of adhesion $E_{sl}$ and inversely proportional to the thickness of the transient boundary layer $h(z)$. This means that reduced $\tau_{rz}$ results in increased $h(z)$ and reduced $E_{sl}$.

(2) Fig. 3 and Eq. (16) indicate that increased $h(z)$ involves reduced $E_{sl}$ and increased eddy velocity $v_e$. Increased $h(z)$ in regions of the arterial branch points is a dominant factor in the formation of initial lesions because, based on both of the previous models, reduced $E_{sl}$ and increased $v_e$ lead to atherosclerosis more easily.

(3) Clinical and experimental results [21–23,28] suggest that atherosclerosis occurs in regions of reduced $\tau_{rz}$. According to Con. 1 and Eq. (16), reduced $\tau_{rz}$ involves reduced $E_{sl}$ and increased $v_e$. This suggests that LDL in the fluid is more prone to be drawn onto the plasma–endothelial interface, and initial lesions form more easily in regions of reduced $\tau_{rz}$.

(4) Clinical and experimental results [31–35] show that locations of atherosclerosis are associated with flow separation and turbulence. Based on Con. 1 and Eq. (16), lesion formation occurs at these locations because it is stimulated by increased $h(z)$ and $v_e$.

(5) Clinical results [5,24] show that no endothelial defects occur during the formation of initial lesions. According to Con. 1 and Eq. (2), reduced $\tau_{rz}$ involves reduced interfacial shear resistance $F_a$, and since endothelial defects are closely dependent on $F_a$ [21–23], a lower $F_a$ value in the lesion formation area than those of its neighboring sites is therefore not the cause of endothelial defects initially.

(6) Clinical results [3–5] show that atherogenesis is caused by depositions of LDL on the arterial endothe-

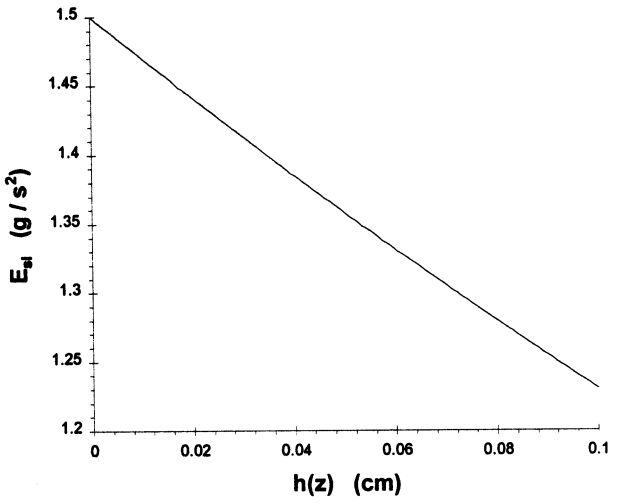


Fig. 3. The relationship between the surface energy of adhesion and the thickness of the transient boundary layer.

lium. According to the thermodynamic model and Eq. (3), LDL rather than HDL (high-density lipoproteins) are drawn from the interior of the plasma fluid onto the plasma–endothelial interface because the lower density of LDL yields a lower $E_{sl}$ than the $E_{sl}$ for HDL deposition. Therefore, reduced $E_{sl}$ and less energy required for LDL deposition leads to atherogenesis.

(7) Clinical results [4,5,28,35] show that initial lesions do not appear in veins and capillary vessels even though there is a lower $\tau_{rz}$ in veins than there is in arteries. This phenomenon can be explained by the lack of a transient boundary layer in veins and capillary vessels. The presence of a transient boundary layer is important to initial lesion formation.

## 5. Mechanism of atherosclerosis

The above conclusions propose that locations of atherosclerotic lesions are associated with regions of increased transient boundary layer $h(z)$ and reduced surface energy of adhesion $E_{sl}$, which lead to atherogenesis in only a small region of the vast systems of blood vessels. Analytical results of both models predict that increased eddy velocity $v_e$ and reduced $E_{sl}$ in these regions of the arterial branch points are main causes for the formation of initial lesions.

More specifically, increased $h(z)$ in regions of the arterial branch point is responsible for increased $v_e$ and reduced viscous shear stress $\tau_{rz}$. Reduced $E_{sl}$ and increased $v_e$ contribute to bring LDL from the interior of the plasma fluid to the plasma–endothelial interface, which lead to the formation of a lesion. The LDL then passes through the arterial endothelium and stimulates monocytes to enter this area. The monocytes may then engulf cholesterol, and the lesion progresses to a more advanced stage.

## 6. Discussions and prospects

In this paper, the viscous flow of the plasma fluid in an arterial vessel is characterized by using symbols $u_z$, $\tau_{rz}$, $h(z)$, $v_e$, $a$, $f$, $\gamma_l$, $\mu$, and $\rho$. The plasma–endothelial interface is characterized by using symbols $E_{sl}$, $\gamma_s$, $\gamma_{sl}$, $F_a$, $L_a$, and $A$. An initial lesion is characterized by using symbols $\rho$, $V$, $E_k$, $E_{sl}$, $\gamma_{sl}$, $u_l$, $A$, and $L_a$. The interfacial shear resistance is characterized by using symbols $F_a$, $L_a$, and $A$. The interactions among the plasma flow, interfacial shear resistance, and endothelial cells at a plasma–endothelial interface are investigated using Eqs. (1)–(16). Analytical results show that atherosclerosis and endothelial defects are closely dependent on $h(z)$, $E_{sl}$, $v_e$, and $F_a$. Increased thickness of the transient boundary layer $h(z)$ and reduced surface energy of adhesion $E_{sl}$ are controlling factors in atherogenesis.

The conclusions given by this study offer some insight to the understanding of the fundamental behaviors of atherosclerosis. These conclusions are supported by clinical and experimental results [3–5,21–23,28,31–35], which indicate that the analytical method used is successful as a potential tool in the study of atherosclerosis and other human lesions. This approach may help studies in the effects of interfacial shear resistance $F_a$ and shear stress of the fluid $\tau_{rz}$ on the molecular biology of endothelial cells, LDL accumulation, molecular permeability, stress-sensitive gene expression, and signal transduction.

Future works also include:

1. Investigating the intermediate lesions in transition between the fatty streaks and fibrous plaques using analytical methods because these lesions represent the critical stage in the acceleration of atherosclerosis.
2. Analyzing the effects of turbulence eddies on atherosclerosis because the transfer of macromolecules from the interior of the blood fluid into the arterial endothelium are closely dependent on these eddies.

These works will enable us to study environmental, dieting, lifestyle, high blood pressure, exercise, and genetic factors associated with atherosclerosis when the reward of prevention and the potential for regression is maximal.

## Acknowledgements

The author wishes to express his cordial thanks to Dr X.F. Wang for the discussions concerning the dynamic boundary value model of the paper.

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