Models for the Onset of Plasma Leakage in Dengue Haemorrhagic Fever

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Abstract

Dengue Hemorrhagic Fever (DHF) is a disease caused by Dengue virus infection. The main characteristic of the DHF is plasma leakage that leading to death. By modifying of the Navier Stokes equation, a mathematical model for blood flow conditions at the onset of plasma leakage are built. In this paper, three models of blood condition are reviewed by considering pressure variation i.e. blood flow with a constant pressure, blood flow with pressure pulsatile blood flow, and blood flow with systolic-diastolic pressure. The results indicate there are a difference in blood flux between healthy person and people who suffering DHF. In addition, plasma leakage in blood flow with constant pressure is affected by vessel radius, interference function, and blood viscosity. While the plasma leakage blood flow with pulsatile pressure and systole-diastole pressure are affected by the radius of vessel, interference function, blood viscosity, heart rate and blood density.

Mathematics Subject Classification: 76D05, 92C99

Keywords: blood flow model, dengue hemorrhagic fever, Navier-Stokes equation, onset, plasma leakage
1 Introduction

Dengue virus belongs to the family Flaviviridae, genus Flavivirus. This virus consists of four serotypes known as DEN-1, DEN-2, DEN-3 and DEN-4. The spread of this virus to humans is through certain mosquito vector, *Aedes aegypti* and *Aedes albopictus*. Infection by a virus subtype will cause a person gets lifelong immunity. However, person who infected by other subtypes, they will only obtain temporary immunity [4]. These four serotypes are sufficiently different. Therefore, there is a possibility of epidemics caused by multiple serotypes (hyperendemicity) [5].

Dengue virus infection can cause two diseases, Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF). DF has characteristics such as a sudden fever, headache, fatigue, nausea and vomiting, body aches, and rash. A clinical characteristic of DHF is rather different from the DF, which is high fever for 2-7 days, bleeding, hepatomegaly, and thrombocytopenia (platelet count < 100,000 cells/mm$^3$). Bleeding also occurs in DF patient but it is different with DHF. Plasma leakage in DHF is caused by increased vascular permeability. DHF usually occurs in a person who is infected by dengue virus for the second time from different subtypes. These infections have 5 to 500 times greater chance to develop into DHF [3]. There are two functional changes in the DHF; first, increased vascular permeability that leads to reduction in total blood volume, thus causing hemoconcentration which leads to plasma leakage, and second, shock that led by low blood pressure in the presence of hemo-concentration. In addition, there is an interference with haemostasis process [14]. Increased vascular permeability in DHF is caused by the immune system mechanisms known as Antibody Dependent Enhancement (ADE) [11].

Shortly after a person was infected with Dengue virus, the virus would have an incubation period of 3-15 days with an average of 4-7 days [4]. At this time the virus replicates. Meanwhile, the body’s immune system will respond to the subtype of dengue. Immune will response by producing antibodies at protein surfaces of that subtype, in order to prevent Dengue virus infect a targeted cells. If the same person is infected by other subtypes, then the body’s immune system is activated to attack the first subtype. Immune system is able to differentiate the four subtypes of dengue virus despite the similar surface antigen. An antibody will patch to protein surface of virus but it will not stop virus movement or kill the virus. Immune response will call macrophages, furthermore, macrophages become infected because a virus has not killed by the immune system and even cause an acute infection. Infected macrophages or infected monocytes deliver a signal to immune system in the form of antigen. This phenomenon is called antigen presentation [12, 9, 2].

Consequently, T-cell that captures signals from infected macrophages or infected monocytes becomes activated. T-cell will produce Helper T-cell and T-
cell cytotoxic. The function of cytotoxic T-cell is to destroy an infected cells as well as the virus [6, 12], while the Helper T-cell produces cytokine, a protein that regulates and helps the immune system, such as: gamma interferon(IFN-\(\gamma\)), IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-\(\alpha\), and TNF-\(\beta\) [7, 11]. The infected monocytes or infected macrophages also produce TNF-\(\alpha\), TNF-\(\beta\), IL-1, IL-1B, IL-6, and platelet activating factor (PAF) [4]. Increase in number of cytokine due to the activation of T-cell, increases vascular permeability that leads to plasma leakage [14]. There are several factors that lead to increased vascular permeability i.e. cytokine (TNF-\(\alpha\) and IL-2), chemical mediator (platelet activation factor) and complement activation (C3a and C5a). One of the manifestations of plasma leakage that is due to increased permeability of blood vessels, is an increase in hematocrit concentration by 20% or more. An increase in hematocrit as a characteristic of plasma leakage in DHF patients means increase in blood viscosity, even shortly before plasma leakage. Plasma leakage is very dangerous because it can lead to death [13].

Clinically, the pathogenesis of dengue virus infection is still a controversy. Therefore, this paper tries to utilize mathematical model to capture the phenomenon of plasma leakage by identifying the relationship between dengue virus infection and increased concentration of blood. The original construction model of blood flow has been carried out by Poiseuille. Hence, to build an infected blood flow model, a new function is added as a barrier. It is a representation of the interference by dengue virus that causes plasma leakage in DHF patient. In the next section, we present the formulation of blood flow model in DHF patient with positive-definite of time function as interference i.e. blood flow model with constant pressure with DHF intervention, blood flow model with pulsatile pressure with DHF intervention, and also blood flow model with systole-diastole pressure with DHF intervention.

## 2 Basic Equation of Viscous Fluid Motion

Equations of viscous fluids motion such as the continuity equation, Navier-Stokes equations for an incompressible fluid, which is used by Poiseuille for constructs models of normal blood flow is summarized by [10].

1. Continuity
   Continuity equation in vector form is given as 
   \[ \frac{\partial \rho}{\partial t} = \nabla \cdot (\rho \mathbf{q}) \] 
   with pressure 
   \( p = p(x, y, x, t) \), viscosity \( \rho = \rho(x, y, z, t) \), velocity \( \mathbf{q} = q(x, y, x, t) \) and 
   incompressible fluid, \( \rho = constant \), so that \( \nabla \cdot \mathbf{q} = 0 \) or 
   \[ \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0 \]

2. Navier-Stokes equation
   Vector form is given as
   \[ \rho \left( \frac{\partial}{\partial t} + (\mathbf{q} \cdot \nabla) \right) \mathbf{q} = -\nabla p + \mu \nabla^2 \mathbf{q} + \mathbf{F} \]
with \( F \) is external body force vector. If \( u \) is the only non-zero vector components of velocity, then the above equation is reduced to \( \frac{\partial p}{\partial t} + \frac{\partial (\rho u)}{\partial x} = 0 \), or if incompressible fluid \( \frac{\partial u}{\partial x} = 0 \). So, the Navier-Stokes equation can be simplified into:

\[
\rho \frac{\partial u}{\partial t} = - \frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + F_x
\]

(1)

Figure 1: flow in cylindrical tube of blood vessels

3 Mathematical models

Most of the biological fluids are non-Newtonian fluids; but theoretically, blood can be treated as a Newtonian fluid with constant viscosity. There are some assumptions that the vessels are rigid, straight, radius of vessel is same, and \( u \) is the only non zero vector in the velocity components. Dengue virus infections trigger the body’s immune system, which lead to increased vascular permeability that causes plasma leakage into the extravascular space. It decreases the blood volume in the intravascular space [4]. From that fact, the blood flow model is modified to capture the onset phenomenon of plasma leakage in DHF patient. The normal model i.e. model of constant blood flow and model pulsatile blood flow, we can see in [10].

3.1 Blood flow model with dengue haemorrhagic fever (DHF)

3.1.1 Blood flow model with constant pressure in DHF

In this section, the blood flow is constant that means not depending in time. By all disorder that occur along vessel due to dengue infection like vascular disorders, coagulation disorders, etc; we can assume the body force in the
Navier-Stokes equation is not equal to zero. It is assumed that interference came from Dengue virus. Therefore, the interference function must be representing Dengue virus condition in body. In this paper, we described the functions which capture level of hematocrit. Cinar et all [1] (1999) denote the relation between viscosity and hematocrit of blood. By choosing the right function of viscosity, it can be said that the function is represent the hematocrit level in DHF condition. We construct the interference function such as
\[ f = \frac{\mu}{\mu + k} \]
is positive definite function that reduces the velocity and \( k \) is a positive constants. From the \( x \)-component of the Navier-Stokes equations, we obtained:
\[
\rho \left( \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} \right) = -\frac{\partial p}{\partial x} + \mu \nabla^2 u - cf \tag{2}
\]
Equation 2 is simplified by utilizing the continuity equation and incompressible properties and becomes:
\[
\frac{\partial p}{\partial x} = \mu \nabla^2 u - cf \tag{3}
\]
where, \( \nabla^2 \equiv \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial \theta^2} + \frac{\partial^2}{\partial x^2} \), the equation becomes
\[
\frac{\partial p}{\partial x} = \mu \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u}{\partial r} \right) - cf \tag{4}
\]
From \( r \)-component of Navier-Stokes equations for cylindrical coordinates, we have the following equation:
\[
\rho \left( \frac{\partial}{\partial t} + (q \cdot \nabla) \right) q_r = -(\nabla t)_r + \mu \nabla^2 q_r. \tag{5}
\]
The fact that \( u \) is the only nonzero vector indicates that \( p = p(x) \), so we have
\[
\frac{dp}{dx} = \mu \frac{1}{r} \frac{d}{dr} \left( r \frac{du}{dr} \right) - cf, \tag{6}
\]
Since \( u = u(r) \) and \( p = p(x) \), using separation of variables method, it can be concluded that each term of the equation is constant so that \( \frac{dp}{dx} = \text{constant} \), which implies \( p = p_1 + \frac{p_2 - p_1}{L}x \) where \( p_1 \) is the pressure at \( x = 0 \) and \( p_2 \) is the pressure at \( x = L \). Integration to \( r \) gives
\[
\frac{du}{dr} - cf r^2 = \frac{1}{\mu} \left( \frac{dp}{dx} \right) r^2 + A, \tag{7}
\]
and higher level integration yields
\[
u = \frac{1}{2\mu} \left( \frac{dp}{dx} \right) r^2 + A \log r + B + \frac{cf r^2}{4\mu}. \tag{8}\]
Since $u$ finite at $r = 0$, then $A = 0$. And also from non-slip condition, $u = 0$ at $r = a$, then $B = -\frac{1}{4\mu}\frac{dp}{dx}a^2 - \frac{cFa^2}{4\mu}$, which gives

$$u = -\frac{1}{2\mu}\left(\frac{dp}{dx}\right)\frac{a^2 - r^2}{2} - \frac{(a^2 - r^2)}{\mu}cf$$

(9)

As a result, the flux equation is derived for constant blood flow to the intervention time function positive definite as follows

$$Q_{PL} = \frac{a^4\pi(p_1 - p_2)}{8\mu L} - \frac{a^4\pi}{8\mu}cf$$

(10)

In the case of $f = 0$, the equation replicate the Poiseuille’s law. It is apparent that a decrease in flux due to a reduction factor $\frac{a^4\pi}{8\mu}cf$ is always positive. This indicates that the volume reduction along the capillary, which is known as a case of plasma leakage.

### 3.1.2 Blood flow model with pulsatilie pressure in DHF

In this section the blood flow is depending on time, the difference with previous section lies in the pressure form and the interference function in DHF condition. This paper proposed the pressure is sinusoidal which called pulsatile pressure, this pressure more represent the real conditions. Therefore, we built the interference function that not only representing Dengue virus in DHF condition but also the pressure term. The interference function is $f(\mu, t) = \frac{\mu}{\mu + k}e^{i\omega t}$ then the blood flow equation for this case is

$$\rho\frac{\partial u}{\partial t} = -\frac{\partial p}{\partial x} + \frac{\mu}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) - cf,$$

(11)

$$-\frac{\partial p}{\partial r} = 0$$

(12)

The continuity equation gives,

$$\frac{\partial u}{\partial x} = 0$$

(13)

Equation (12) and (13) imply that $p = p(x, t)$ and $u = u(r, t)$. Therefore, the blood flow equations can be written as

$$\frac{\mu}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) - \rho\frac{\partial u}{\partial t} = \frac{\partial p}{\partial x} - cf$$

(14)

Note that the left-hand side is a function of $r$ and $t$, while the right-hand side is a function of $x$ and $t$. Hence both sides will be a function of $t$. Assume a sinusoidal pulsatile flow, the equation becomes:

$$\frac{\partial p}{\partial x} = -P_0e^{i\omega t}$$

(15)
we can see in figure 2 and 

\[ u(r, t) = U(r) e^{i\omega t} \]  \hspace{1cm} (16)

where \( P_0 = \text{constant} \), \( U(r) \) is the velocity profile across a tube with a radius.

![Figure 2: pulsatile pressure over time](image)

Assuming that the flow is identical in every part so that the waves that pass in the solution can be ignored. It is obviously that when \( \omega = 0 \) (constant case), the flow will give the same flow as previous section. The real part of equation (15) gives the flux when the pressure is \( P \cos(\omega t) \) and the imaginary part gives the flux when it is \( P \sin(\omega t) \). The equation (14) becomes

\[ \frac{\partial^2 U}{\partial r^2} + \frac{1}{r} \frac{\partial U}{\partial r} - \frac{\omega \rho i}{\mu} U = \frac{-P_0 + cf e^{-\omega it}}{\mu}, \] \hspace{1cm} (17)

The solution of (17)

\[ U(r) = AJ_0 \left( i \sqrt{\frac{\omega \rho}{\mu}} r \right) + BY_0 \left( i \sqrt{\frac{\omega \rho}{\mu}} r \right) + \frac{P_0 - cf e^{-\omega it}}{i\omega \rho} \] \hspace{1cm} (18)

Since \( U \) and \( u \) are finite at \( r=0 \), \( B = 0 \) because \( Y_0(0) \) is infinite. Using the slip boundary condition \( U(r) |_{r=a} = 0 \), we have

\[ U(r) = \frac{P_0 - cf e^{-\omega it}}{i\omega \rho} \left( 1 - \frac{J_0 \left( i^{3/2} \frac{\alpha r}{a} \right)}{J_0 \left( i^{3/2} \alpha \right)} \right) \] \hspace{1cm} (19)

\( \alpha \) is nondimensional parameter, known as Womersley parameter, \( \alpha = a \sqrt{\frac{\omega \nu}{\rho}} \) or \( \alpha = a \sqrt{\frac{\omega}{\nu}} \), where \( \nu = \frac{\mu}{\rho} \) is the kinematic viscosity. When limit \( \alpha \to 0 \), i.e., as \( \omega \to 0 \), the velocity profile becomes parabolic. Otherwise, \( \alpha \to \infty \), i.e.,
as \( \mu \to 0 \) (viscosity is neglected), it can be shown that \( \frac{J_0(i^{3/2}\alpha r/a)}{J_0(i^{3/2}\alpha)} \to 0 \). This implies that,

\[
U(r) \to \frac{P_0 - cf e^{-\omega t}}{i\omega \rho}.
\]  (20)

From equation (20) and by substituting \( f(\mu, t) = \frac{\mu}{\mu + k} e^{i\omega t} \), the pulsatile blood flow velocity that infected by DHF given as

\[
u(r, t) = \left( \frac{P_0}{i\omega \rho} - \frac{c\mu}{(\mu + k)i\omega \rho} \right) \left( 1 - \frac{J_0(i^{3/2}\alpha r/a)}{J_0(i^{3/2}\alpha)} \right) e^{i\omega t}. \]  (21)

Volume flow rate \( (Q) \) is given as \( Q = \int_a^0 2\pi r u dr \), (same as previous section).

We derive the flux of blood flow pulsatile pressure with DHF intervention as

\[
Q_{PL} = \left( \frac{\pi a^2 e^{i\omega t} P_0}{i\omega \rho} - \frac{c\mu}{i\omega \rho (\mu + k)} \right) \chi(\alpha) \]  (22)

with \( \chi(\alpha) = 1 - \frac{2J_1(\beta)}{\beta J_0(\beta)} \), and \( i^{3/2}\alpha = \beta \). In the case of \( f = 0 \), this corresponds with the pulsatile blood flow proposed by Mazumdar[10]. It is apparent that a decrease in flux due to a reduction factor \( \delta = \frac{cf \pi a^2}{i\omega \rho} \chi(\alpha) \) is always positive. This indicates that the volume reduction along the capillary is known as a case of plasma leakage.

### 3.1.3 Blood flow model with systole-diastole pressure in DHF

Human blood flows periodically in accordance with the heart rate. The heart pumps blood with a different amount for each person. This pressure depends on age, activities, and other factors. In section 3.1.2 is assumed that the pressure \( P \) is pulsatile. In this section, the assumption will be released and we will substitute \( P \) with systole-diastole pressure.

At each cardiac cycle, blood pressure changes due to atrial and ventricular, contraction and relaxation alternately, and the blood flow from areas with high pressure to areas with low pressure. The contraction in the muscular wall of the heart, increases the fluid pressure. In a normal cardiac cycle, when the atrium contracts, the ventricle relaxes, and vise versa. Systole (contraction) refers to the contraction phase, while diastole (dilatation) refers to the relaxation phase. The details of systole-diastole pressure drop as a function of \( P \) can be seen in [10]. The formulation is as follow

\[
P(t) = (P_d + A) e^{-\alpha_a t} + B \sin (\beta t - \psi), \quad 0 \leq t \leq T_s \]  (23)

where \( A = \frac{a_m^2 K}{\alpha_a^2 + \beta^2}, \quad B = \frac{a_m K}{\sqrt{\alpha_a^2 + \beta^2}}, \quad \psi = \tan^{-1} (\beta/\alpha_a) \)

The representation of systolic and diastolic pressures on real conditions can be seen in [8]. Figure 3 shows the systolic and diastolic pressures over time.
Models for the onset of plasma leakage

that shown in equation (23) as a mathematical modeling approach. To view the model of pulsatile blood flow with interference, and considering systolic and diastolic factors. By substituting the pressure on the section 3.1.2 with the pressure as describe in (23), and using the same way as in section 3.1.2, we obtained the flux of blood flow with DHF condition with systole-diastole pressure \( Q_{PL} \) and the flux without interference \( Q \) is obtained by substituting \( f = 0 \), where \( f \) is an interference. Because the equation of flux is complicated, we only show the difference flux between normal condition and DHF condition is provided. The delta of the flux is obtained as follows:

\[
\delta = Q - Q_{PL} = cf \pi a \frac{-2J_1 \left( \sqrt{-\frac{\rho \omega}{\mu}} a \right) + \sqrt{-\frac{\rho \omega}{\mu}} a J_0 \left( \sqrt{-\frac{\rho \omega}{\mu}} a \right)}{J_0 \left( \sqrt{-\frac{\rho \omega}{\mu}} a \right) \bar{p}_i \omega \sqrt{-\frac{\rho \omega}{\mu}}} 
\]  

we can simplify equation (24) to be

\[
\delta = cf \pi a^2 \frac{-2J_1 (\beta) + \beta J_0 (\beta)}{\beta J_0 (\beta) \bar{p}_i \omega} = \frac{cF \pi a^2}{\bar{p}_i \omega} \chi (\beta) 
\]  

where \( \chi (\beta) = 1 - \frac{2J_1 (\beta)}{\beta J_0 (\beta)} \), \( \beta = \alpha \alpha^2 \) and \( \alpha = a \sqrt{\frac{\omega}{\mu}} \). Equation (25) is represents the difference between normal flux condition with infected dengue virus condition.

4 Conclusions

The phenomenon of blood plasma leakage in DHF patients can be modeled by modifying Navier Stokes equations. The modification was made with considering all factors in interference blood flow along the blood vessels. Coagulation disorder and vascular damage because of immune response this resulted in a
force vector $F_x$ is no longer equal to zero. This condition can be captured by chosen $cf$ as interference function that representing Dengue virus in body. The function is positive definite which represent hematocrit level in blood flow for DHF condition as a component $F_x$. In pulsatile pressure and systole-diastole case the reduction of intravascular volume per unit time was increased and also when the blood becomes more viscous it makes the flux decreases. It can be end in fatality because the body loses the amount of plasma. Model for constant pressure, pulsatile pressure, and systole-diastole pressure shows that viscosity plays an important role in the occurrence of plasma leakage. This is in line with clinical of DHF that was presented by WHO; hematocrit level in DHF patient must be monitoring. Volume depletion due to plasma leakage in the patient DHF needs to be handled with right treatment at hospital such as intravenous fluids treatment or blood transfusion.

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