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CFD SIMULATION OF PLASMA LEAKAGE AND FLUID FLOW ON DENGUE VIRUS INFECTED-ENDOTHELIAL CELLS

Nur Kaliwantoro[1], Marsetyawan HNE Soesatyo[2], Indarto[3], Mohammad Juffrie[4], Rini Dharmastiti[5], Mohammad Tauviqirrahman[6] and Zainal Arifin[7]
[1]Biomedical Engineering, Graduate School, Gadjah Mada University, Indonesia
[2]Histology and Cells Biology Department, Medical Faculty, Gadjah Mada University, Indonesia
[3]Mechanical Engineering Department, Engineering Faculty, Gadjah Mada University, Indonesia
[4]Pediatric Department, Medical Faculty, Gadjah Mada University, Indonesia
[5]Industrial Engineering Department, Engineering Faculty, Gadjah Mada University, Indonesia
[6]Laboratory for Engineering Design and Tribology, Mechanical Engineering Department, Diponegoro University, Indonesia
[7]Mechanical Engineering Department, Sebelas Maret University, Indonesia
E-Mail: kaliwantoro@yahoo.com

ABSTRACT

Plasma leakage is one of the pathological features in dengue infection and may cause fatal condition to the patients. In this study, the investigations of the plasme leakage and fluid flow around the dengue virus infected-endothelial cells were conducted using computational fluid dynamic (CFD) based on in vitro experiments of HUVEC (human umbilical vein endothelial cell) culture on the permeable membrane. Fluid velocity profiles and wall shear stress (WSS) values were computed in each surface of endothelial cells. Fluid flow was assumed as a fully developed incompressible Newtonian flow. It was shown that the leakage flow occurs due to the increase in the gap between the cell-cell junctions of the dengue virus-infected cells. The peaks of the wall shear stress distribution occur at the cell's tip, where the cell-cell junction starts its origin.

Keywords: computational fluid dynamic, endothelial cell, plasma leakage, wall shear stress.

INTRODUCTION

Dengue infection is the most common arboviral infection of humans in subtropical and tropical countries. The WHO estimates that 2.5 billion people are risk from dengue with 50 million dengue infections each year. In many cases, the death in dengue is characterized by plasma leakage caused by the increase of acute vascular permeability due to disfunction of endothelial cells infected by dengue virus [1]. The presence of circulating endothelial cells in the peripheral blood as the evidence of vascular damage in DHF patients has been reported [2]. The increase of cell permeability as well as the presence of plasma leakage will interfere the fluid flow and the wall shear stress (WSS) on the cell surface [3]. Understanding the wall shear stress which occurs on the endothelial cells is essential to reduce the plasma leakage on the dengue infection.

Wall shear stress (WSS) plays a significant role in endothelial homeostatis. It highly depends on the velocity, blood viscosity and integrity of endothelial cell structure [4]. Other molecules expressed and have strong correlation to the interaction of WSS and endothelial cells are the cell matrix and cell-cell junction molecules including integrin, PECAM-1, VE-cadherin, tyrosine kinase, caveolin-1 and glycocalix [5]. Mitchell and King [6] found that WSS can be used to control the cancer cell COLO 205 and prostate cancer cell PC-3 by inducing the interaction of cancer cells with apoptotic agent such as tumor necrosis factor apoptosis-inducing ligand (TRAIL). It was reported that the shear stress can be used to inhibit adhesion molecules expression in vascular endothelial cells, like VCAM and ICAM that has strong correlation to dengue infection [7].

Recently, the characterization of cells with respect to the plasma leakage had paid much attention to the researchers regarding with the explanations of many unsolved problems in dengue infection pathology. The complexity and the limitations of *in vivo* and *in vitro* experiments are noted in analysing the wall shear stress of the endothelial cells in more detail. Although it is difficult to verify conclusively such relationships, CFD (computational fluid dynamic) techniques can give an excellent research means to help understand these underlying issues. Some works in CFD have been performed to simulate the flow field around the stem cells [8], cells adhered on the wall of micro vessel [9] and cell-cell interaction in Malaria pathogenesis [10] with good results according to the experiments. The aim of the present work is to apply CFD to the investigation of the plasma leakage phenomena around the endothelial cells. The WSS, the velocity magnitude, and the pressure are of particular interest.

METHOD

Governing Equations

The general mathematical statements of fluid flow are the conservation equations: mass, momentum and

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energy. Since blood flow in arterial segments is adiabatic, the energy equation can be ignored, leaving the continuity and momentum equations as the governing relations for flows of interest in the present study. The Navier–Stokes equations were solved over the domain using a finite-volume method with the CFD code developed in commercial software FLUENT. The equations were applied with constant viscosity and density, without body force, while the blood is assumed as incompressible and steady flow.

CFD Model

The model developed based on the in vitro experiment exposing dengue infected endothelial cells culture by culture media in parallel plate flow chamber (Figure-1). In the in vitro experiment, human umbilical vein endothelial cells (HUVEC) were cultured on the transwell permeable membrane made of polyester (Figure-2). After the cell culture reaches its confluence, the cell was infected by dengue virus for 2 h. The media contains dengue virus was then removed, and the cells was washed by Phosphate balanced salt (PBS) for 3 times and then placed into the parallel plate flow chamber. After that, media which contains bovine serum albumin (BSA) was flowed on the cell culture surface. The albumin which migrates into the subluminal section of the transwell was then measured.

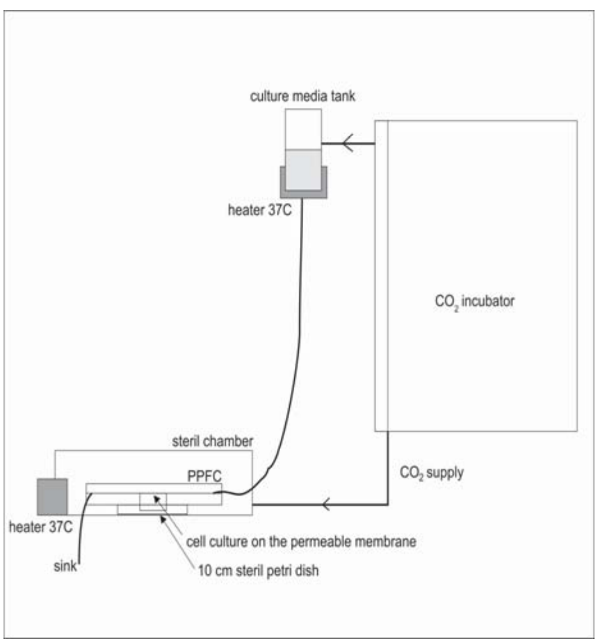

Figure-1. Experimental setup.

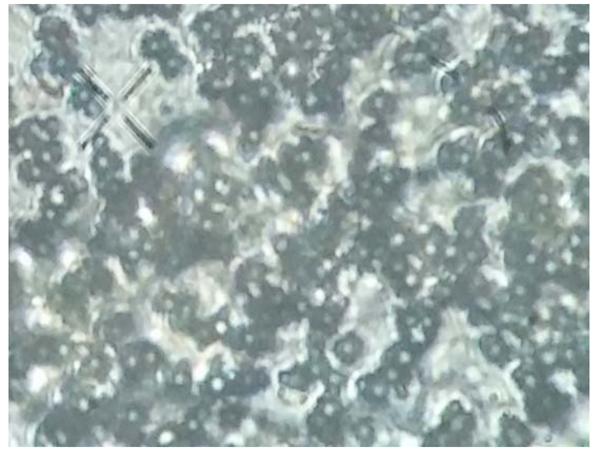

Figure-2. Microscopic view of cells culture on the polyester permeable membrane.

Based on these conditions, in the present paper the CFD model has been proposed to characterize the flow pattern around the endothelial cells. The computational domain consists of four endothelial cells placed on permeable membrane (Figure-3). In this work, membrane was represented by numbers of rectangular.

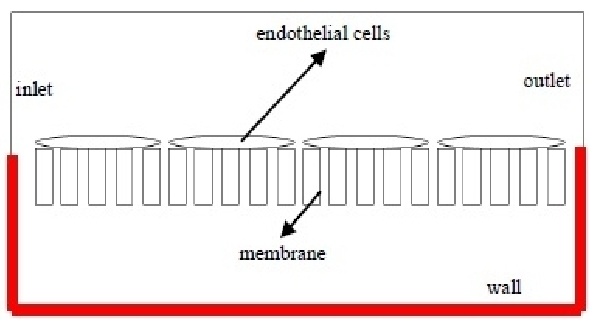

Figure-3. Schematic representation of fluid flow around endothelial cells cultured on the permeable membrane for simulation.

RESULT AND DISCUSSIONS

In the present research, several numerical results have been obtained, for example, as can be seen in Figure-4. In this figure, the velocity magnitude contours over the HUVEC cell cultured on the permeable membrane is shown. Clearly, the plasma leakage occurs in the gap area among the endothelial cells. From this figure, it is also observed that two types of leakage flow are detected. First, the main leakage which is denoted as A as shown in Figure-4. This leakage occurs due to the increase in the gap length of cell-cell junction. This finding matches well with the published works [11, 12]. However, the dengue infection causes not only the increase in cell-cell's gap, but also the loss of the attachment of some of the cell's tips on the membrane. Such leakage, in this case, is denoted as "B" and its effect leads to new gap between the

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cell and the membrane (see Figure-4). The leakage capacity due to the loss of the attachment of the cell's tips becomes significant since its flow into both sides of the membrane.

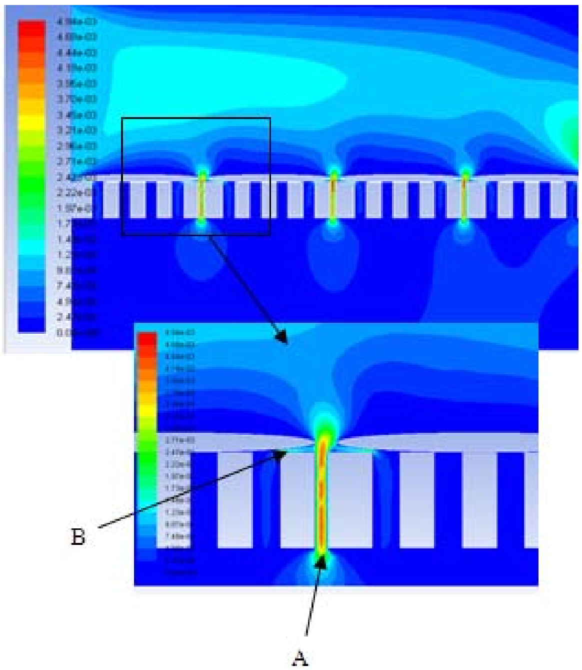

Figure-4. Velocity magnitude contours over the HUVEC cell cultured on the permeable membrane.

In the in vitro experiment the increase in albumin leakage occurs in the 48h post infection, where the attachment of some cells on the permeable membrane is disturbed due to dengue virus infection on the cells (Figure-5).

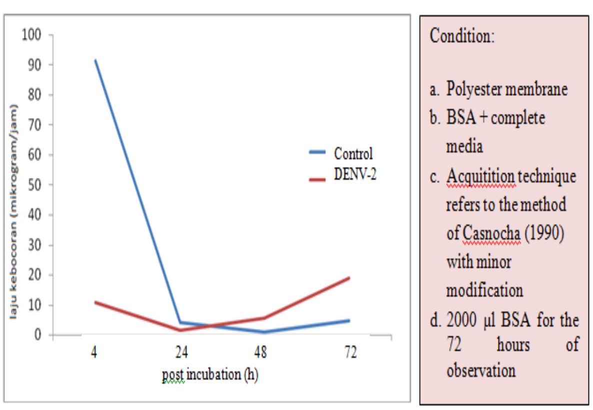

Figure-5. In vitro experiment of plasma leakage on the dengue virus infected - cells.

In order to explain why the plasma leakage could occur in the cell culture based on the physical point of view, the dynamic pressure distribution of the dengue infected cells is shown in Figure-6. It can be observed that the pressure in the cell-cell junction is the highest in the system. Such condition occurs due to the small gap between cells, which in turn will increase the pressure. This high pressure difference among narrow locations leads to the occurrence of the widening gap.

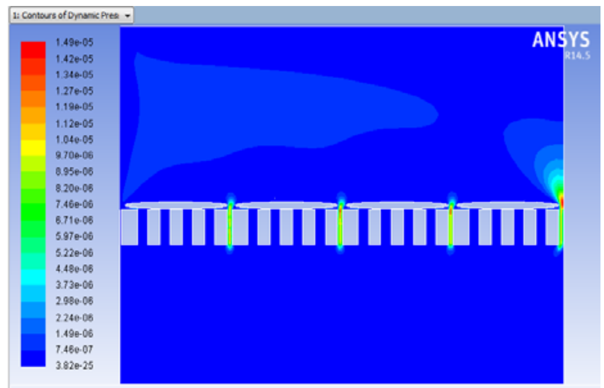

Figure-6. Dynamic pressure distribution on the system.

Figure-7 depicts the wall shear stress distribution. It is shown that the wall shear stress value on the surface of the cell body is very low, in contrast to the leading and trailing edge of the cells. The high WSS at the both cell edges occurs because of the leakage flow of the fluid between cells. The most possible explanation is that the wall shear stress value over each cell tends to decrease due to the lack of shear. The decline of the wall shear stress will ease the dengue virus to attach and infect another healthy endothelial cells on the vasculature, and make the plasma leakage becomes larger and threatens the patient life. Thus, an appropriate therapy is necessary to return the value of the wall shear stress to its normal value for reducing the ability of dengue virus to attach on the cell surface.

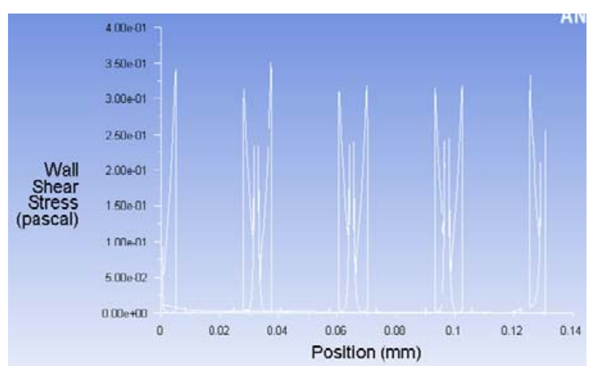

Figure-7. Distribution of the wall shear stress on the cell culture.

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CONCLUSIONS

In this work, the investigation of the plasma leakage around the endotheleal cells was investigated using computational fluid dynamic (CFD) approach. It was shown that analyses of wall shear stress distribution between endothelial cells are essential in affecting the plasma leakage. This finding may have useful implications for preventing the plasma leakage due to dengue infection through manipulation the wall shear stress.

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