Flow around Cells Adhered to a Microvessel Wall. III. Effects of Neighboring Cells in Channel Flow*

Masako SUGIHARA-SEKI**

The flow past cells adherent to the bottom plate of a parallel-plate channel is numerically analyzed in the zero-Reynolds-number limit, and the effect of the neighboring adherent cells on the drag force exerted on an adherent cell is examined. The cells are modeled as rigid spherical particles and they are assumed to be attached to the channel wall regularly in a square array. It is found that, when the size ratio of the cell-to-channel height is smaller than approximately 0.2, the drag force exerted on an adherent cell is well approximated by a linear function of the size ratio, almost independently of the separation distances between neighboring cells except for the cases of very narrow spacing. For larger size ratios, the drag force on an adherent cell in channel flow is generally smaller than the corresponding value in tube flow, but both values vary considerably, depending on the size ratios and the separation distances.

Key Words: Adhesion, Drag, Numerical Simulation, Stress

1. Introduction

In recent years, there has been considerable interest in cell adhesion phenomena. A number of studies have been made to understand the receptor-mediated basis of cell adhesion and to estimate the magnitude of adhesion forces that are responsible for cell aggregation or cell-surface adhesion such as leukocyte adhesion to venular walls^{(1),(2)}. For the purpose of studying such cell adhesion in laboratory facilities, parallel-plate flow chambers are used extensively, where cells are attached to, or incubated on, the bottom plate of the 2D chamber, and cell deformation and dislodgement are observed closely under various flow rates⁽³⁾. If accurate information on the force acting on adherent cells exerted by the surrounding fluid is available, these *in vitro* studies are efficient to estimate the cell-surface adhesion strength and to develop insights into the adhesion mechanisms, since

the adhesive force generated by receptor-ligand bonds is balanced with the fluid force in stationary states.

In most studies, however, the drag force acting on a cell adherent to a channel wall is assumed to coincide with that for an isolated spherical particle adherent to a wall subject to a semi-infinite simple shear flow (see Eq. (3)). Apparently, this assumption is not always appropriate; in some cases, the presence of neighboring cells and the other channel wall, deformation of cells and parabolic velocity profile may be involved. Thus, it is necessary to assess the limitation of the assumption and to provide accurate information on the force acting on an adherent cell in channel flow.

Another important aspect concerning *in vitro* studies is to answer whether the results obtained in *in vitro* experiments are directly applicable to *in vivo* phenomena. From a hydrodynamic point of view, it is required to know to what extent the effect of the flow on adherent cells in vessels is simulated in flow chambers.

In order to investigate the effects of the flow on adherent cells in 2D chambers and in cylindrical tubes, we presented a numerical study of flows around adher-

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** Faculty of Engineering, Kansai University, 3-3-35 Yamate-cho, Suita, Osaka 564-8680, Japan. E-mail: sekim@kansai-u.ac.jp

Fig. 1 Schematic drawings of geometry: (a) flow over an array of rigid spherical particles which are adherent to the bottom plate of a 2D channel, and (b) flow over a line of rigid spherical particles adherent to the wall of a circular cylindrical tube

ent cells in a 2D chamber and in a tube in the zero-Reynolds-number limit^{(4),(5)}. A comparison of the two flows has revealed that, when the size ratios of the cell-to-channel height and the cell-to-tube diameter are smaller than approximately 0.2, the fluid-dynamic effects of the flow on adherent cells are almost equal in 2D channel flow and tube flow, while for larger size ratios the difference between the two flows increases drastically.

Our previous study also suggested that the presence of neighboring adherent cells affects the drag force acting on an adherent cell in a complex manner, especially in channel flows⁽⁵⁾. Since its behavior has not been reported in detail yet, the present paper presents our numerical study on the effect of neighboring adherent cells on the stresses and the drag force exerted on an adherent cell in channel flow. For simplicity, we adopt a rigid spherical particle as a model of cells, and the model cells are assumed to adhere to the bottom plate of a parallel-plate channel regularly in a square array (see Fig.1(a)). The effects of the distances between neighboring cells on the distributions of the stresses and the drag force exerted on an adherent cell are numerically studied, and the results are compared with the estimation based on Eq. (3) and the corresponding results in tube flow.

2. Methods

Consider a parallel-plate flow channel with gap distance $2h$. The presence of the side boundaries of the flow channel is neglected. We adopt a rigid spherical particle with radius a as a model of cells adherent to the bottom plate of a 2D channel, and the model cells are assumed to be positioned at the points of intersection of a square lattice as shown in Fig. 1(a). Here, the Cartesian coordinates (x, y, z) are taken such that the x -axis is along the direction of the undisturbed flow, and the xz -plane coincides with the mid-plane of the top and bottom plates of the 2D channel. The adherent particles are assumed to be aligned regularly parallel to the x - and z -axes with the distances $2d_x$ and $2d_z$, respectively. For comparison, the configuration of the corresponding tube flow is shown in Fig.1(b), where spherical particles are adherent to the wall of a circular cylindrical tube (radius r) along the undisturbed flow direction with an equal spacing 2ℓ .

In our previous study⁽⁵⁾, we considered only cases of $d_x = d_z$. In the present study, we examine the effects of each variation of d_x and d_z on the distributions of the stresses and the drag forces acting on an adherent particle, exerted by the fluid motion.

We consider the flow of an incompressible Newtonian fluid past the adherent particles. Since the Reynolds number for the blood flow through small vessels is much smaller than unity, we neglect the effect of the inertia on the motion of the suspending medium in the present study. Thus, the motion of the fluid obeys the Stokes equations and continuity equation:

$$\nabla p = \mu \nabla^2 \mathbf{u}, \quad \nabla \cdot \mathbf{u} = 0, \quad (1)$$

where $\mathbf{u}$ and p represent the velocity and the pressure, respectively, and μ stands for the viscosity of the fluid.

We adopt the non-slip boundary condition on the walls of the channel as well as on the surface of the particles. From the periodic arrangement of the configuration shown in Fig. 1(a), the flow field of the fluid is expected to be also periodic with periods $2d_x$ in the x -direction and $2d_z$ in the z -direction:

$$\begin{cases} \mathbf{u}(x, y, z) = \mathbf{u}(x + 2d_x, y, z), \\ p(x, y, z) = p(x + 2d_x, y, z) + \Delta p, \\ \mathbf{u}(x, y, z) = \mathbf{u}(x, y, z + 2d_z), \\ p(x, y, z) = p(x, y, z + 2d_z), \end{cases} \quad (2)$$

where Δp is a prescribed pressure drop over the distance $2d_x$ in the undisturbed flow direction. Then, the periodic boundary conditions are adopted in the x - and z -directions⁽⁷⁾. The motion of the suspending medium in one periodic domain is numerically analyzed by a finite element method applied to the Stokes equations and continuity equation^{(6),(7)}. From the flow

Fig. 2 Distributions of the stresses acting on the surface of an adherent particle at $a/h=0.5$ for various separation distances: (a) the normalized shear stress along the circumference at $z=0$, (b) the normalized shear stress along the circumference at $x=0$, and (c) the normalized pressure along the circumference at $z=0$. In each figure, the curves with open circles in the range of $0 < \theta$ (or φ) $< \pi$ are for various d_x/h and $d_z/h=4$, and the curves with closed circles in the other range of θ (or φ) are for various d_z/h and $d_x/h=4$.

field obtained, we calculate the distributions of the stresses and the force acting on an adherent particle.

3. Results and Discussion

For various values of the size ratio a/h and the separation distances d_x/h and d_z/h , we have computed the flow field around an adherent particle, and obtained the distributions of the stress exerted on its surface. As a typical example, the results for $a/h=0.5$ are plotted in Figs. 2(a)–(c), where the distributions of the shear stress, τ , along circumferences at $z=0$ (parallel to an undisturbed flow direction) and at $x=0$ (perpendicular to that direction), and the distribution of the pressure along a circumference at $z=0$ are shown in Figs. 2(a)–(c), respectively. Here, representing the mean pressure over the whole surface of the particle as p_0 , the values of the pressure p relative to p_0 are shown in Fig. 2(c). Apparently, 2D Poiseuille flow is realized in the channel when the adherent particles are absent. Then, the values in Figs. 2(a)–(c) are normalized by the shear stress on the channel wall for the 2D Poiseuille flow $\tau_w=3Q/4h^2dz$, where Q denotes the volumetric flow rate of the fluid across a cross-section of the channel per length $2dz$ in the z -direction. In the figure, the abscissas θ and φ denote the polar angles relative to the radius vector of the site adhering to the channel wall, with respect to the center of the particle. As evident from the consideration of symmetry of the flow geometry and linearity of the Stokes equations, the distributions of the shear stress along the circumferences at $z=0$

and $x=0$ are symmetric with respect to $\theta=\pi$ and $\varphi=\pi$, respectively, and the distribution of the pressure, $p-p_0$, is antisymmetric with respect to $\theta=\pi$. Then, in Figs. 2(a)–(c), the curves are drawn in a half range of θ or φ ; the values for various d_x/h at $d_z/h=4$ are shown in the range of $0 \leq \theta$ (or φ) $\leq \pi$, and those for various d_z/h at $d_x/h=4$ are in the range of $\pi \leq \theta$ (or φ) $\leq 2\pi$.

Figures 2(a) and (b) show that the normalized shear stress is small in the half of the particle surface nearer to the wall (i.e. θ (or φ) $< \pi/2$ and $3\pi/2 < \theta$ (or φ)), and it attains the maximum near the top portion of the particle ($\theta \sim \pi$). On each curve shown in Fig. 2(a), a point near $\theta \sim \pi/2$ or $3\pi/2$ where the shear stress vanishes marks the location of a stagnation point on the particle surface. As Pozrikidis plotted the flow pattern around an isolated adherent sphere in Fig. 10(b) of his paper⁽⁹⁾, the streamlines in the xy -plane approaching the particle above the stagnation point are ascending along the surface of the particle, and the others are descending along it. The latter explains the negative sign of the shear stress for $\theta \lesssim \pi/2$ in Fig. 2(a).

It is seen from Figs. 2(a) and (b) that the normalized shear stress decreases with decreasing d_x/h at $d_z/h=4$ while it generally increases with decreasing d_z/h at $d_x/h=4$. This statement can be more generalized for other constant values of d_z/h or d_x/h , in such a way that τ/τ_w decreases with decreasing d_x/h at constant values of d_z/h and it increases with decreasing d_z/h at constant values of d_x/h . Similar

trends are observed for the pressure distribution shown in Fig. 2(c). These behaviors are explained by considering the variations of the fluid motion with d_x and d_z . When d_x decreases at constant d_z , the velocity of the fluid placed between neighboring particles aligned in the x -direction is more slowed down, which results in a decrease in the normalized stress exerted on the particle. This feature is similar to that reported for the tube flow⁽⁴⁾. On the other hand, when d_z decreases at constant d_x , the cross-sectional area of the conduit per an adherent particle decreases, so that the normalized stress on the particles is enhanced. At very narrow spacing in the z -direction, the curves of the shear stress distribution exhibit a complex behavior as a function of φ . For example, the dotted curve at $d_z/h=11/20$ in Fig. 2(b) has a local minimum at $\varphi\sim 3\pi/2$. When the gap width between the surfaces of neighboring particles in the z -direction becomes so small, the fluid avoids flowing through the gap regions (at $\varphi\sim\pi/2$ and $3\pi/2$) and escapes to the other regions, mainly to the upper region. This decrease of the flow in the gap region reduces the normalized shear stress at $\varphi\sim\pi/2$ and $3\pi/2$, despite an augmentation of the shear stress in the remaining part.

By integrating the stresses on the surface of an adherent particle, we computed the drag force D exerted on the particle for various values of the size ratio a/h and the separation distances d_x/h and d_z/h . The drag force is normalized by the value for a spherical particle (radius a) adherent to a plane wall subject to a semi-infinite simple shear flow with shear stress $\tau^{(8)}$:

$$D_0 = 1.7005 \times 6\pi a^2 \tau. \quad (3)$$

In the normalization, as τ is adopted the shear stress at the wall of the channel in the absence of the adherent particles, τ_w . Evidently, D/D_0 coincides with unity in the limit of the size ratio a/h approaching 0.

The normalized drag force D/D_0 is plotted as a function of the separation distance d_x/h or d_z/h at several size ratios in Fig. 3. The dotted curves represent the case of various d_x/h at $d_z/h=4$, the dash-dotted curves the case of various d_z/h at $d_x/h=4$, and the solid curves the case of $d_x/h=d_z/h$. The dotted curves decrease with decreasing d_x/h while the dash-dotted curves increase with decreasing d_z/h . The solid curves are between the dotted curves and the dash-dotted curves. These behaviors are explained from the variations of the stresses on an adherent particle with d_x/h and d_z/h shown in Figs. 2(a)–(c); both of the normalized shear stress and the normalized pressure decrease with decreasing d_x/h at constant d_z/h and increase with decreasing d_z/h at constant d_x/h . The normalized drag forces on an

Fig. 3 The normalized drag force D/D_0 acting on an adherent particle versus the separation distance, d_x/h or d_z/h for channel flow and ℓ/r for tube flow. Open circles, closed circles and open rectangles represent the values at the size ratio a/h (a/r) = 0.3, 0.5 and 0.7, respectively. The solid curves denote the normalized drag force in the case of $d_x/h=d_z/h$, the dotted curves in the case of various d_x/h at $d_z/h=4$, and the dash-dotted curves the case of various d_z/h at $d_x/h=4$. The dashed curves represent the normalized drag force in tube flow.

adherent particle in tube flow are also shown in Fig. 3, for comparison⁽⁴⁾. In tube flow, the normalized drag force decreases as the particle spacing ℓ/r decreases. This tendency accords to that for channel flow in the case of decreasing d_x/h at constant d_z/h , as may be intuitively understood from a similarity of ℓ and d_x shown in Figs. 1(a) and (b).

In order to show the dependence of the drag force on the size ratio a/h , the normalized drag force D/D_0 is plotted as a function of a/h at the separation distance d_x/h (or d_z/h) = 2/3 and 4, in Fig. 4. A thin dotted straight line represents the value for an isolated spherical particle adherent to a plane wall in a semi-infinite parabolic flow in the absence of the other wall of 2D channel, under the condition that the unperturbed velocity vanishes at the location of the other wall at $y=h^{(9)}$:

$$\frac{D}{D_0} = 1 - 0.570 \left(\frac{a}{h} \right). \quad (4)$$

The second term in the right-hand side of Eq. (4) represents the effect of parabolic velocity profile on the adherent particle, which increases linearly with increasing size ratio a/h . Figure 4 shows that our results for large separation distances (open circles) are well approximated by Eq. (4), as far as the size ratio a/h is smaller than about 0.3. In addition, our results for large d_x/h and d_z/h exhibit excellent

Fig. 4 The normalized drag force D/D_0 acting on an adherent particle against the size ratio, a/h for channel flow and a/r for tube flow. The plus marks denote the values of Pozrikidis for an isolated spherical particle⁽⁹⁾, and a thin dotted straight line represents the value for an isolated spherical particle adherent to a plane wall in a semi-infinite parabolic flow in the absence of the other wall of 2D channel, as described in the text. The crosses are the results by Brooks & Tözeren⁽¹¹⁾ at $d_x/h = d_z/h = 2/3$. The asterisks denote the experimental results for a single particle in tube flow by Schmid-Schönbein et al.⁽¹⁰⁾

agreement with the corresponding values of Pozrikidis (plus marks in Fig. 4)⁽⁹⁾, who analyzed flows over an isolated axisymmetric depression or protuberance on a plane wall of a channel by a boundary-integral method.

The cases of narrow spacing: $d_x/h = 2/3$ and $d_z/h = 4$, $d_x/h = 4$ and $d_z/h = 2/3$ and $d_x/h = d_z/h = 2/3$ are represented by open rectangles, closed rectangles, and closed circles, respectively, in Fig. 4. It is seen that the values of the drag force at various separation distances are close to each other for the size ratio a/h smaller than approximately 0.2, while their differences increase significantly as the size ratio increases beyond 0.2. Figure 4 suggests that, for the size ratio larger than approximately 0.2, the normalized drag force could be larger than unity in some cases, but it also may be smaller than unity, depending on the size ratio and the separation distances.

In typical *in vitro* experiments, the drag force acting on a particle adherent to a wall of a 2D chamber is estimated by use of Eq. (3). The present study suggests that this conventional estimate is accurate only for very small particles compared to the channel height. The error increases almost linearly with increasing size ratio, up to approximately 10 percent at $a/h = 0.2$ (Eq. (4)), almost independently of the

separation distances. For size ratios larger than 0.2, the error could be more significant, depending sensibly on the size ratio and the separation distances d_x/h and d_z/h .

Comparing the values of the drag force at constant size ratios, we see that the drag force at $d_x/h = 2/3$ and $d_z/h = 4$ (open rectangles) is smaller than that at $d_x/h = d_z/h = 4$ (open circles), while that at $d_x/h = 4$ and $d_z/h = 2/3$ (closed rectangles) is larger than that at $d_x/h = d_z/h = 4$, as expected from Figs. 2(a)–(c). It is also anticipated that the drag force at $d_x/h = d_z/h = 2/3$ (closed circles) is larger than the value at $d_x/h = 2/3$ and $d_z/h = 4$, and it is smaller than that at $d_x/h = 4$ and $d_z/h = 2/3$. Figure 4 further shows that the value is above that at $d_x/h = d_z/h = 4$.

In Fig. 4, the results for tube flow in the cases of the separation distance $l/r = 2/3$ and 4 are also plotted for comparison (dashed curves)^{(4),(5)}. Experimental results for a single spherical particle adherent to a tube wall are represented by asterisks⁽¹⁰⁾. Figure 4 demonstrates that, in the case of large separation distance ($l/r = 4$ in tube flow and $d_x/h = d_z/h = 4$ in channel flow), there is a significant difference in the drag force in tube flow and channel flow for the size ratio larger than approximately 0.2, and the difference increases considerably as the size ratio increases. In contrast, comparable values of the drag force at $l/r = 2/3$ in tube flow and that at $d_x/h = d_z/h = 2/3$ in channel flow are instructive.

Brooks and Tözeren made a numerical analysis of the flow past adherent particles in a channel, whose configuration is the same as the present one, except the assumption of $d_x = d_z$ (see Fig. 1(a))⁽¹¹⁾. In Fig. 4, the normalized drag forces obtained by Brooks and Tözeren are also plotted in the case of $d_x/h = d_z/h = 2/3$. There are some discrepancies between their results (crosses) and our corresponding results (closed circles), as already pointed out in our previous study⁽⁵⁾. In spite of our detailed examination, the reason of the difference is not clarified yet.

4. Concluding Remarks

In the present study, we have shown the effect of neighboring particles on the stresses and the drag force exerted on an adherent particle in channel flow. A comparison of the flows in 2D channel and in tube shows that the drag forces acting on an adherent particle compare favorably in the two flows as far as the size ratio is smaller than about 0.2. The drag forces are well approximated by a linear function of the size ratio (Eq. (4)). For the size ratio larger than 0.2, the discrepancy is considerably enhanced, especially in the cases of large separation distances.

We have assumed that particles are adherent to

the wall periodically, infinitely long along the x - and z -directions, as shown in Fig. 1(a). In experiments, it is difficult to realize these idealized arrangements. With regard to the assumption of particle arrangements, we have shown that for tube flow, the effect of the nearest particles is the most significant so that the drag force exerted on one of the periodically arranged adherent particles in infinite number is nearly equal to that on a particle of finite number arrangements, as far as the geometrical configurations relative to the nearest neighbors are the same⁽⁴⁾. If similar arguments are possible for channel flow, the present analysis is applicable to particles in a finite number adherent to a channel wall, although more careful assessment is necessary for the application to *in vitro* experiments.

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