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Study of Hepatic Vascular Dynamics Based on Symmetrical Pulsating Perfusion

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Background: The traditionally used perfusion method is constant flow. This study proposes a novel method called Symmetric Pulsating Flow (SPF) and verified that this method is applicable.

Material/Methods: The fluid dynamic behavior of perfusate in the vessel, the shear stress, and the vascular deformation were simulated based on the bi-directional fluid-structure interaction. The differences of the fluid dynamic behaviors and the mechanical characteristics of vascular wall were studied and compared between the 2 methods during the process of hepatic perfusion. The simulations and comparisons were carried out on 3 different vascular models.

Results: Utilizing the constant flow perfusion, a double vortex clearly appeared at the rear end of the foreign matter and reflux retention can be caused by the double vortex. The reflux retention caused lower shear stress against the vascular wall and thus brought new accumulation of foreign matter. The SPF perfusion, however, prevented the double vortex, and avoided such reflux retention during the vascular perfusion. In addition, the SPF can clean the vascular wall better with a slower speed, which causes less injury to the vessel, and the pulsating effect can reduce the accumulation of new foreign matter.

Conclusions: The SPF perfusion can clean the vascular wall more thoroughly with less injury.

MeSH Keywords: **Hydrodynamics • Liver Transplantation • Pulsatile Flow**

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Background

The liver is an important organ of digestion, metabolism, and urea synthesis, and liver failure can have a disastrous effect on human health. At present, liver transplantation is an important means to treat liver failure and other end-stage liver diseases. However, the extreme shortage of donor livers and high-quality liver donors makes it necessary to use marginal livers, such as fatty livers [1]. Therefore, improving the quality of donor livers has become a key issue in liver transplantation [2,3]. Liver perfusion is key to preoperative cleaning and preservation, and method of preserving donor livers before surgery include simple cryopreservation and mechanical perfusion preservation [4]. Compared with the traditional cryopreservation method, the mechanical perfusion preservation method can reduce damage during storage and improve the viability of transplanted organs [5]. Appropriate liver perfusion not only removes foreign matter more thoroughly and reduces the occurrence of ischemic failure in liver tissue, but also avoids damage to its blood vessels and organ tissues caused by abnormal external changes, and this protection is conducive to better post-operative recovery.

Scholars have recently been studying the cleaning and preservation of pre-transplant donors to guide the preservation of kidneys, lungs, hearts, and other organs and to reduce injury during the operation [6–9]. The traditional mechanical perfusion method is carried out at low temperature, while in recent years, the normothermic liver perfusion has been proposed and studied [10,11]. Vogel et al. [12] pointed out that mechanical perfusion at body temperature can maintain the normal metabolism of cells, reduce damage in the preservation process, and assess the viability of the transplanted livers. In 2016, Ravikumar et al. [13] and Bral et al. [14] have performed liver transplantation under normothermic mechanical perfusion separately and successfully. The results show that

the method is safe and feasible, which provides a great possibility to expand the liver pool. Because the distribution of blood vessels in the liver is more complicated than in other internal organs, Liu Jun et al. [15] analyzed the dynamic characteristics of the primary vessel in perfusion process, and the result can be used in clinical operations. Han et al. [16] compared the differences between conventional perfusion methods and retrograde perfusion methods, indicating the safety and effectiveness of retrograde perfusion techniques in clinical applications, while reducing organ damage during perfusion. Some scholars have studied the effects of changes in vascular dynamics on various vascular diseases, thus providing theoretical guidance for disease treatment. George et al. [17] studied the hemodynamics of the liver using magnetic resonance imaging (MRI) and computational fluid dynamics (CFD) and obtained new parameters of MRI to distinguish between healthy groups and patients, which is helpful in monitoring disease. Hsu et al. [18] proposed an iterative method for assessing the vascular tissue pre-stress for the formation of aneurysms in the cerebrovascular anatomy, suggesting that tissue pre-stress can be used to monitor vascular dynamics and plays a role in the formation of cerebral aneurysms. Kun Yang et al. [19] proposed a novel model for the measurement of blood perfusion on the local tissue, which was more accurate than others.

In research and clinical settings, the most commonly used method is still the constant flow perfusion method [20–22]. Its main feature is strong stability, and the flushing force on the vascular wall is determined by the inlet velocity [15–18]. To completely remove the foreign matter in the blood vessels, it is necessary to improve the inlet velocity, which is likely to result in increased vascular force and deformation, and thus cause damage to the liver. Compared with constant flow, the swirling flow method [23–25] used in some studies showed better effect in removing foreign matter in the vessel. However, the swirling flow requires complex equipment and special

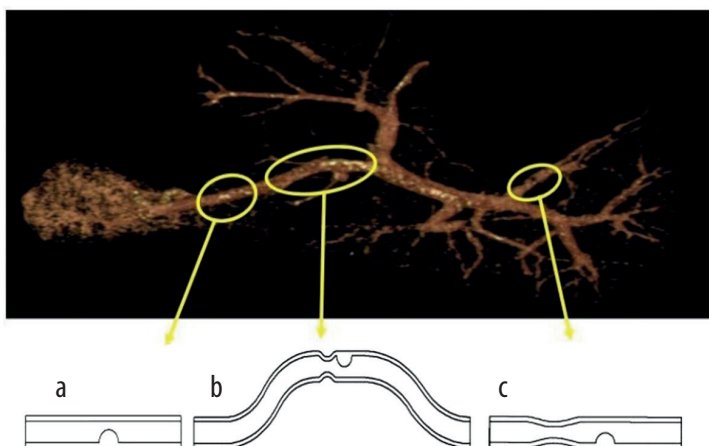


Figure 1. Liver vascular models: a) straight vessel with foreign matter, b) curved vessel with stenosis and foreign matter, c) straight vessel with stenosis and foreign matter.

operation, which makes it difficult to apply in practice. Some studies have been done on perfusion devices [26], but further studies are needed before it can be used in hepatic perfusion.

To solve the above problems, a new perfusion method called Symmetric Pulsating Flow (SPF) is proposed in this paper. In this study, the simulation was performed using three-dimensional elastic vessel models of the liver and the bi-directional flow-solid coupling method. We analyzed the dynamic characteristics, including velocity, wall shear force (WS), and vascular deformation. The results of the dynamic characteristics of the SPF were compared with the constant flow, which can be used to analyze the effect of the SPF on liver perfusion and to determine its applicability in practice.

Material and Methods

Vascular models

The models used in this study were built based on computed tomography (CT) images of liver provided by a hospital of Tianjin, China. As shown in Figure 1, 3 models were built: the straight vessel with foreign matter, the straight vessel with stenosis and foreign matter, and the curved vessel with stenosis and foreign matter. Each model has 5 types, and the thickness of the vascular wall is separated into 1.2 times, 1.1 times, 1 time, 0.9 times, and 0.8 times of the following normal value.

The parameters of the vessel are as follows [27]: The Young's modulus is 5×10^5 Pa, the vascular density is 0.941×10^3 kg/m³, and the Poisson's ratio is 0.45. The inner diameter of the vascular model is 4 mm, the outer diameter is 6 mm, and the wall thickness is 1 mm. The lengths of the vascular models shown in Figure 1 are 20 mm, 40 mm, and 50 mm, respectively. Medical studies have shown that the occurrence of spasms in the blood vessels can cause them to be in an abnormal contraction state, assuming a narrowing of about 50%, and thus the stenosis in Figure 1 appeared. The hemispheric foreign matter on the vascular internal wall is an accumulation of the necrotic muscle cells and endothelial cells, cellulose deposition, and degenerated collagen fibers, and its radius is $r=2$ mm.

Fluid control equations

Studies [28] have shown that as long as the arterial diameter is greater than 0.5 mm, the error caused by the use of Newtonian fluid instead of non-Newtonian fluid is no more than 2%. Since the vascular diameter is 4 mm in the paper, the Newtonian fluid is used in the calculation to simplify the model. The motion equation of incompressible viscous fluid is shown as follows:

$$\frac{d\mathbf{v}}{dt} = \mathbf{f} - \frac{1}{\rho} \nabla p + \nu \nabla^2 \mathbf{v} \quad (1)$$

Previous studies had revealed that the perfusate is present in turbulent form using the constant flow method [15]. The general unsteady continuous equation and the Navier-Stokes equation are also applicable to the transient motion of turbulence [29]. In order to investigate the effects of intravascular pulsations, the time averaging method and the Reynolds-averaged method were adopted, and the sum of the average values and the pulse values were used instead of the flow variable values, which are shown as follow:

$$\mathbf{u} = \bar{\mathbf{u}} + \mathbf{u}' = \begin{bmatrix} \bar{u} + u' \\ \bar{v} + v' \\ \bar{w} + w' \\ \bar{p} + p' \end{bmatrix} \quad (2)$$

where, the $u, v, w,$ and p represent the flow variables, the $\bar{u}, \bar{v}, \bar{w},$ and \bar{p} represent the average values and the u', v', w' and p' represent the pulse values.

Subtle changes in density do not have a significant effect on flow, thus ignoring the effects of density ripple. The average flow control equation of compressible turbulent flow is as follows:

$$\frac{\partial p}{\partial t} + \text{div}(\rho \mathbf{u}) = 0 \quad (3)$$

The momentum equations and equations of motion are shown below:

$$\frac{\partial(\rho u)}{\partial t} + \text{div}(\rho u \mathbf{u}) = -\frac{\partial p}{\partial x} + \text{div}(\mu \cdot \text{grad } u) + \left[-\frac{\partial(\rho \overline{u^2})}{\partial x} - \frac{\partial(\rho \overline{uv'})}{\partial y} - \frac{\partial(\rho \overline{uw'})}{\partial z} \right] + S_u \quad (4)$$

$$\frac{\partial(\rho v)}{\partial t} + \text{div}(\rho v \mathbf{u}) = -\frac{\partial p}{\partial y} + \text{div}(\mu \cdot \text{grad } v) + \left[-\frac{\partial(\rho \overline{uv'})}{\partial x} - \frac{\partial(\rho \overline{v^2})}{\partial y} - \frac{\partial(\rho \overline{vw'})}{\partial z} \right] + S_v \quad (5)$$

$$\frac{\partial(\rho w)}{\partial t} + \text{div}(\rho w \mathbf{u}) = -\frac{\partial p}{\partial z} + \text{div}(\mu \cdot \text{grad } w) + \left[-\frac{\partial(\rho \overline{uw'})}{\partial x} - \frac{\partial(\rho \overline{vw'})}{\partial y} - \frac{\partial(\rho \overline{w^2})}{\partial z} \right] + S_w \quad (6)$$

where ρ represents the fluid density, p represents the vascular pressure, $v, w,$ and u are the components of the velocity vector \mathbf{u} in the x, y and z directions, respectively, ν represents the kinematic viscosity, μ represents the dynamic viscosity of the fluid. S_u, S_v and S_w are the generalized source terms of the momentum conservation equations, where $S_u = F_x + s_x, S_v = F_y + s_y$ and $S_w = F_z + s_z$. For the incompressible fluid with a constant viscosity, we can get $s_x = s_y = s_z = 0$. F_x, F_y and F_z are the volume force on the element. Here, $F_x = F_y = 0, F_z = -\rho g$.

Solid control equations and flow-solid coupling equations

When the energy transfer between solid and fluid is ignored, the force balance equation of blood vessels can be given by Newton's second law [30]:

$$\rho_s \ddot{d}_s = \nabla \cdot \sigma_s + f_s \quad (7)$$

where σ_s represents the Cauchy's stress tensor, ρ_s represents the vascular density, \ddot{d}_s represents the local acceleration vector in solid domain, and f_s represents the volume force vector.

The bi-directional flow-solid coupling calculation also follows the energy conservation principle, so that the stress (τ) and displacement (d) are equal or conserved at the interface of the flow-solid coupling. The equations are shown as follows:

$$\begin{cases} \tau_f \cdot n_f = \tau_s \cdot n_s \\ d_f = d_s \end{cases} \quad (8)$$

where n represents the normal vector for the boundary, d represents the displacement, and subscripts s and f represent solid and fluid, respectively.

Perfusion velocity analysis of the SPF

First, the calculation method of constant flow perfusion velocity is as follows [31]: incompressible viscous fluid will cause frictional resistance and differential pressure when it flows around objects. The total resistance F_D is the sum of frictional resistance and differential pressure, assuming that it is equal to the contact friction (F_f) between the foreign matter and the vascular wall:

$$F_D = (C_f A_f + C_p A_p) \frac{\rho v^2}{2} = C_D \frac{\rho v^2}{2} A \quad (9)$$

where, C_f and C_p are the coefficients of frictional resistance and differential pressure, A_f is the effective area of shear stress, and A and A_p represent the projection area of the foreign matter in the direction of the fluid flow. C_D is the flow coefficient and is determined mainly by the Reynolds number. The value of C_D is derived according to the Reynolds number of the hepatic arterial blood, and the relation between resistance coefficient and Reynolds number, which is $C_D=0.4$.

The physical parameters of the perfusion are calculated as follows: the projection area A is calculated from the 3-D simulations and $A=2.147 \text{ mm}^2$, the quality of the foreign matter is $m=0.017 \text{ g}$, and the frictional coefficient of the vascular wall is $\mu=0.75$ [15]. Using all the parameters above, the F_D is calculated: $F_D=F_f=\mu \cdot mg=0.000017 \text{ kg} \times 9.8 \text{ m/s}^2 \times 0.75=0.000125 \text{ N}$. Therefore, the pressure needed to flush the matter away is $P=58.22 \text{ Pa}$ (the standard atmospheric pressure is assumed to be 0 Pa). Substituting all the parameters to equation (9),

the velocity can be calculated and $v=0.538 \text{ m/s}$. In the paper, the perfusate is Sodium Chloride injection of 130/0.4 Hydrocarbon ethyl starch. The Molar Substitution Degree of it is 0.38~0.45, Molar Mass 150 000 g/mol, density $\rho=1029 \text{ kg/m}^3$, and the dynamic viscosity η is 5.763 MPa·s [32]. Due to the small value of the perfusate viscosity and the small perfusion velocity, the perfusate is taken as an ideal fluid. Therefore, the heat loss caused by viscosity and the heat conduction between the perfusate and the vascular wall are neglected.

In the constant flow method, the ability of taking the foreign matter away is determined by the inlet velocity. As a result, to flush the vascular wall completely, the inlet velocity needs to be increased. However, the larger inlet velocity will increase the radial movement of the vascular wall, thereby increasing vascular deformation and damaging the tissue around the blood vessels.

The most important difference between the SPF method and the constant flow method is that the SPF will generate acceleration. The hydrodynamic theory shows that the magnitude and direction of the acceleration have a great effect on the frictional pressure drop. Thus, combining the constant flow with the pulsating flow, the perfusion method of the SPF is proposed. The perfusion cycle is set to $T=4s$ and the inlet velocity of the SPF is calculated as follows:

$$v = \begin{cases} 0.538 [m/s] \sin(2\pi t) + 0.538 [m/s], & t \in [0s, 2s] \\ 0.538 [m/s], & t \in [2s, 4s] \end{cases} \quad (10)$$

It can be seen from equation (10) that the SPF consist of the constant part and the pulsating part, and the amplitude during the perfusion may exceed the velocity of the constant flow (0.538 m/s). Under such conditions, the inlet velocity of the SPF can be reduced as long as the foreign matter can be flushed away. In this paper, the inlet velocity is set to 0.2 m/s and the inlet velocity of the SPF is as follows:

$$v = \begin{cases} 0.2 [m/s] \sin(2\pi t) + 0.2 [m/s], & t \in [0s, 2s] \\ 0.2 [m/s], & t \in [2s, 4s] \end{cases} \quad (11)$$

All the simulations of straight and curved vessels will use the inlet velocity calculated by equation (11). The velocity curve of the SPF within one cycle is shown in Figure 2.

Vascular perfusion simulation

In this paper, ANSYS is used for grid partitioning and numerical simulation is carried out in ANSYS-CFX software. All of the vascular models are discretized using hexahedral and tetrahedral mixed formats. Hexahedrons can ensure the adaptability of the mesh to the deformation of the vascular wall. The tetrahedron can optimize the irregular area. The mixing factor is set to 0.75, and the maximum residual value is set to 10^{-3} .

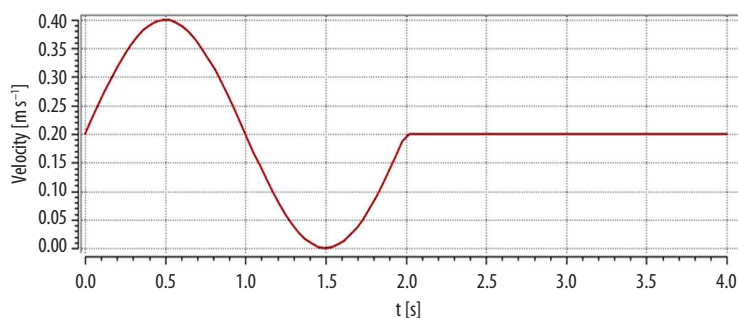


Figure 2. Velocity curve of the SPF within one cycle.

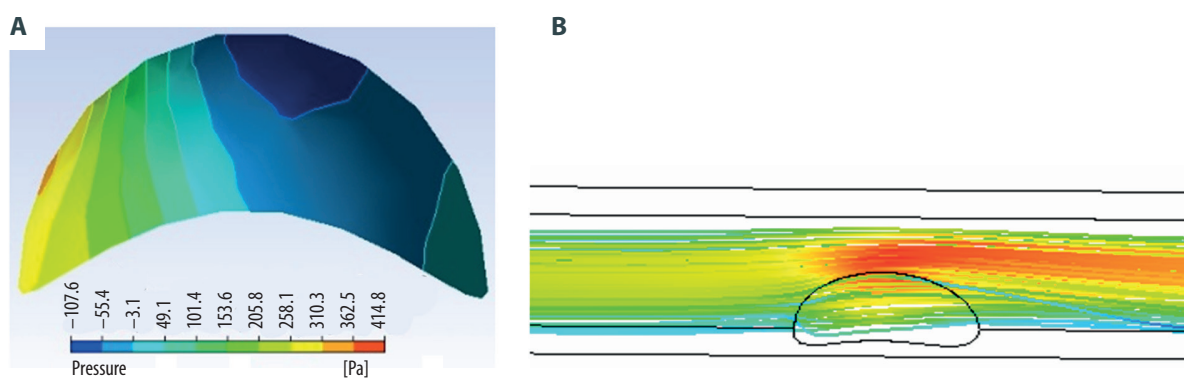


Figure 3. Simulation results of straight vessel with the SPF method (A) surface pressure distribution of foreign body (B) the velocity distribution around the foreign matter.

The number of grid nodes in the 3 models is 43 804, 117 010, and 82 950, respectively.

The bi-directional flow-solid coupling method of elastic vascular wall was used to calculate and analyze the dynamic characteristics of the 3 vascular models. Since the flow-solid coupling bi-directional analysis is transient, in order to ensure that the time steps of the 2 analyses are the same, the time step is set to 1 s. The bounding conditions are as follows: First, the inlet velocity of the constant flow is set to 0.538 m/s and the inlet velocity of the SPF is calculated using equation (11). Second, in the calculation of the flow field, the inlet pressure (i.e., the reference pressure field) is set to 0 Pa in order to obtain the actual pressure of the vascular wall. Third, according to the reference pressure field, the relative pressure at the outlet is also set to 0 Pa. Finally, the perfusate is considered as an ideal viscous fluid, and the vascular wall is considered as an ideal smooth surface. There is no relative movement at the interface between the fluid and the vascular wall.

Statistical analysis

Data were analyzed with ANSYS-workbench (Version 15.0) for calculating the wall shear stress and vascular deformations

during the process of hepatic perfusion in the 3 different vascular models. Each vascular model was simulated 5 times by using the constant flow method and the SPF method, respectively. We assessed the statistical significance of differences in the max values of vascular deformations and the wall shear force on the same perfusion method to discover the law of the change, comparing data of the same perfusion method and the different perfusion methods. The simulation results are expressed by figures in this paper.

Results

In this section, the simulation results of different models and different types of the same model are analyzed, including pressure, velocity, deformation, and wall shear stress. The feasibility of the SPF is verified by the bi-directional flow-solid coupling method and compared with the results of the constant flow.

Simulation result of the straight vessel with foreign matter

The inlet velocity is in accordance with the inlet boundary conditions and the perfusate flows from left to right. The pressure

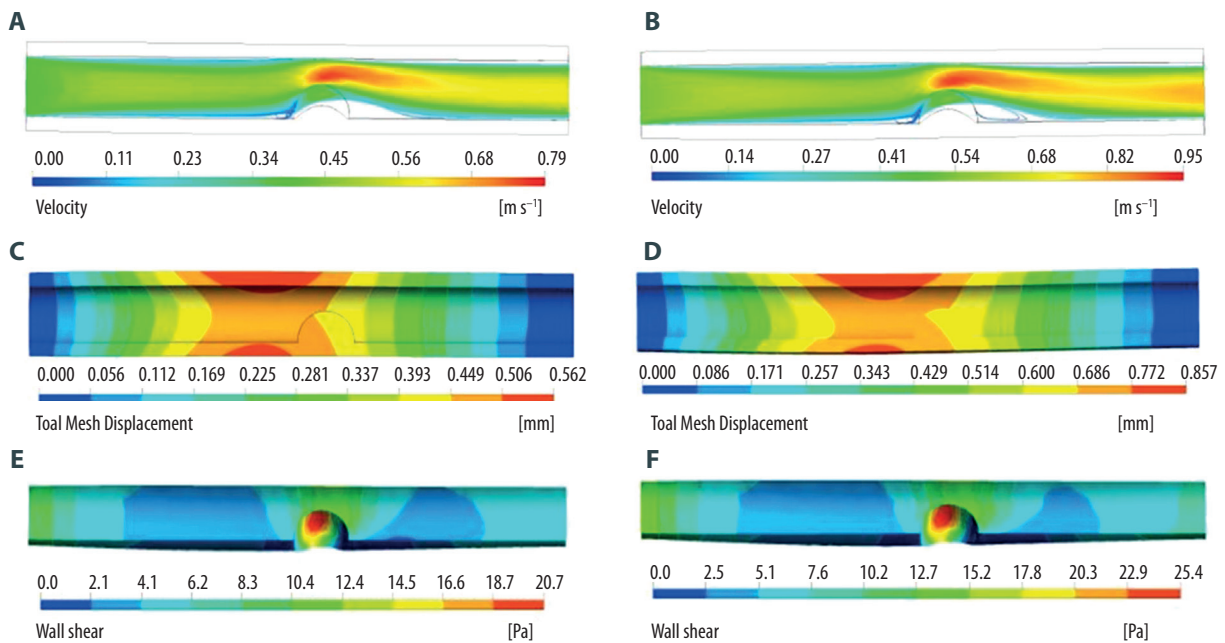


Figure 4. The hydrodynamic characteristics the SPF method and the constant flow method (A) velocity distribution of the SPF method (B) velocity distribution of the constant flow method (C) vascular deformation of the SPF method (D) vascular deformation of the constant flow method (E) WS stress distribution of the SPF method (F) WS stress distribution of the constant flow method.

and velocity distributions around the foreign matter using the SPF method are shown in Figure 3. It can be seen from Figure 3A that the pressure difference between the front and rear ends is greater than 200 Pa, which is much higher than the required pressure difference (58.22 Pa). Besides, the pressure of the rear end of the foreign matter is negative, and this phenomenon means that the SPF method can flush away the foreign matter thoroughly. Figure 3B shows the velocity distribution around the foreign matter. In the constant flow method, the back end of the foreign matter tends to have a retention zone, whereas in Figure 3B, there is no such phenomenon and the perfusate flows smoothly in the vessel.

The simulation results of the SPF method are compared with the constant flow method and the difference of dynamic characteristics is shown in Figure 4. The velocity distribution is shown in Figure 4A, 4B. The maximum velocity of the SPF and the constant flow are 0.79 m/s and 0.95 m/s, separately, and both can flush the foreign matter away. The deformation distributions are shown in Figure 4C, 4D. The peak value of the deformation is 0.562 mm using the SPF, and 0.857 mm using the constant flow. The deformation of the constant flow is greater than that of the SPF, and a greater deformation is more likely to cause damage to the vessel. Figure 4E, 4F are the WS stress distributions. The peak value of the WS stress using the constant flow method is 25.4 Pa, which is higher than with the SPF method (20.7 Pa). It can be concluded from the results

that the flow impact, vascular deformation and WS stress of SPF method are all less than the constant flow, so the SPF has less effect on blood vessels and perivascular tissue.

As seen in Figure 4C, 4D, the maximum deformation area of the SPF method is smaller than with the constant flow method, which indicates that the SPF can reduce the radial motion of the blood vessels and cause less damage to the tissue around the blood vessels.

Through the analysis of simulation results on different types of the straight vessel with foreign matter, the vascular deformations decrease with increasing the thickness of the vascular wall, and the max values of vascular deformations show an approximately linear change. In addition, the wall shear force reduces with increasing the thickness of the vascular wall too, and the changes of the wall shear force display a weak non-linear relationship.

Simulation result of the straight vessel with stenosis and foreign matter

Intravascular local stenosis has a certain effect on the velocity, pressure, and wall shear of the fluid in the vessel, so the change in hemodynamic parameters plays an important role in the diagnosis and treatment of the disease [33]. The effects of localized stenosis on the flushing of foreign matter were

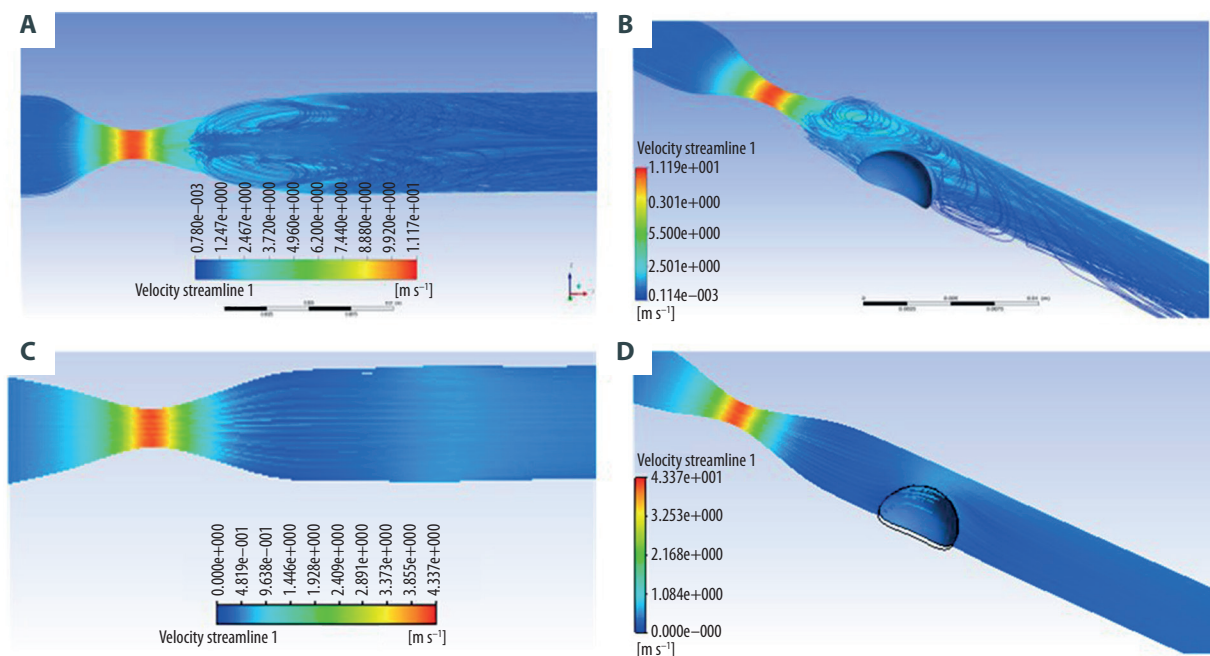


Figure 5. Velocity distribution: (A, B) velocity distribution of the constant flow method; (C, D) velocity distribution of the SPF method.

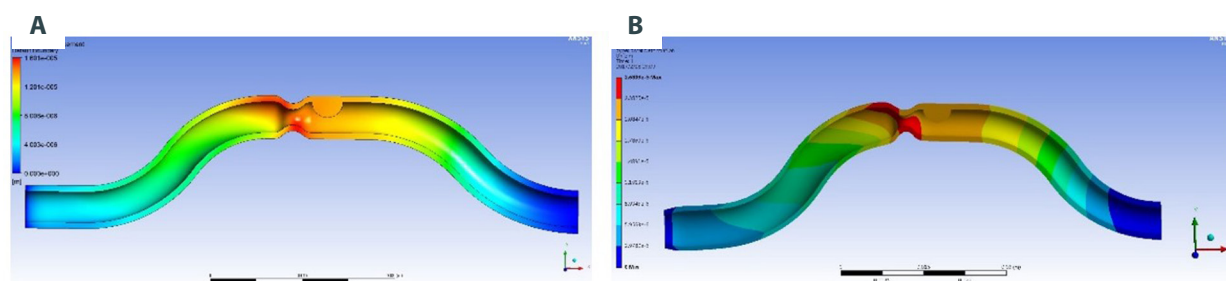


Figure 6. Vascular deformation in the simulation (A) the SPF method, (B) the constant flow method.

studied using 2 perfusion methods. The velocity field distribution is shown in Figure 5. Figure 5A, 5B are the simulation results of the constant flow. It can be seen from Figure 5A that there is a significant double vortex phenomenon in the back of the stenosis, which indicates that the Reynolds number changes when the perfusate flows through the stenosis, and the flow is in the turbulent state, and this phenomenon is called the Cat's Eye effect. Figure 5B shows that there is an obvious reflux retention zone behind the foreign matter, which can lead to a lower WS stress and form new foreign matter. When comparing Figure 5C with 5A and Figure 5D with 5B, it is clear that there is no double vortex and reflux retention zone using the SPF.

Simulation results of the curved vessel with stenosis and foreign matter

The deformation of the vessel is shown in Figure 6. The largest deformation occurs in the front of the stenosis and the foreign matter, whether using the SPF method or the constant flow method. This is because the stenosis and the foreign matter will cause higher resistance and the perfusate cannot flow through this area smoothly. However, the peak value of the deformation using the constant flow is 26.8 μm , which is much higher than the 16.1 μm achieved using the SPF. Although both methods can flush the foreign matter away, higher deformation may cause damage to the vessel. In addition, the simulation results on different types of the curved vessel with stenosis and foreign matter have similar changes with the model of the straight vessel.

Discussion

There are some similarities among the simulation results of straight vessels. First, the maximum velocity appears at the top of the foreign matter, and the velocity becomes smaller in the area near the vascular wall. Second, the largest deformation occurs in front of the foreign matter, and the deformation is smaller at both ends of the vessel. Third, the peak value of the WS stress appears at the top of the foreign matter. Comparing the SPF and the constant flow, the SPF causes smaller deformation to protect the tissue from damage. In addition, the SPF can clean the vascular wall more thoroughly and prevent the new accumulation of foreign matter. Therefore, the SPF method can provide a better perfusion quality.

According to the simulation result of the curved vessel, the deformation of the SPF method is 37% smaller than that of the constant flow method, which helps reduce the damage caused by the vascular deformation.

The biggest advantage of the SPF method is that it will not cause the double vortex behind the stenosis and the reflux

retention behind the foreign matter. The pulsation of the SPF will cause irregular velocity disturbances, which can destroy the double vortex and the reflux retention area, and then reduce the new accumulation of foreign matter.

Conclusions

In this paper, to solve the problems existing in the current constant flow and swirling flow methods, a new perfusion method called the SPF is proposed, which combines the advantages of constant flow and pulsating flow. Under the same boundary conditions, the vascular deformation of SPF is smaller than that of the traditional constant flow method. The novel SPF method reduces the radial movement of blood vessels, resulting in less flow impact and less damage to the tissues surrounding the vessels. In addition, the SPF can avoid the double vortex and the reflux retention phenomenon, and reduce the new accumulation of foreign matter. Finally, the SPF can flush the vascular wall more thoroughly and smoothly, and improve the perfusion quality remarkably.

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