Functional assessment of cerebral artery stenosis: A pilot study based on computational fluid dynamics

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Abstract

The fractional pressure ratio is introduced to quantitatively assess the hemodynamic significance of severe intracranial stenosis. A computational fluid dynamics-based method is proposed to non-invasively compute the FPR_{CFD} and compared against fractional pressure ratio measured by an invasive technique. Eleven patients with severe intracranial stenosis considered for endovascular intervention were recruited and an invasive procedure was performed to measure the distal and the aortic pressure (P_d and P_a). The fractional pressure ratio was calculated as P_d/P_a . The computed tomography angiography was used to reconstruct three-dimensional (3D) arteries for each patient. Cerebral hemodynamics was then computed for the arteries using a mathematical model governed by Navier–Stokes equations and with the outflow conditions imposed by a model of distal resistance and compliance. The non-invasive P_{d-CFD} , P_{a-CFD} , and FPR_{CFD} were then obtained from the computational fluid dynamics calculation using a 16-core parallel computer. The invasive and non-invasive parameters were tested by statistical analysis. For this group of patients, the computational fluid dynamics method achieved comparable results with the invasive measurements. The fractional pressure ratio and FPR_{CFD} are very close and highly correlated, but not linearly proportional, with the percentage of stenosis. The proposed computational fluid dynamics method can potentially be useful in assessing the functional alteration of cerebral stenosis.

Keywords

Stroke, cerebral hemodynamics, cerebral blood flow, mathematical modelling, and brain ischemia

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Introduction

Arterial luminal stenosis in coronary or cerebral artery can result in insufficient blood perfusion in the heart or brain, causing ischemia and eventually heart attacks or strokes. However, the severity of stenosis does not necessarily reflect the underlying hemodynamic alteration caused by the vessel narrowness,¹ due to complex anatomic and physiologic variations. Therefore, a parameter gauging the hemodynamic significance of the stenosis is desirable to quantify its functional severity.

Fractional flow reserve (FFR) was first introduced by Pijls et al.² and has become a ‘gold standard’ in assessing

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the hemodynamic function of coronary artery stenosis and guiding the decision of revascularization.^{3–6} FFR is empirically defined as the ratio of the maximal myocardial flow in the stenotic territory and the maximal myocardial flow in the same territory with the stenosis hypothetically absent, indicating the extent of flow alteration caused by the stenosis.¹ When the ratio is close to one, the stenosis is assumed to be well tolerated with almost no hemodynamic alteration, whereas when the ratio is close to zero, the hemodynamic function of the stenotic artery is completely abolished. A ratio of 0.8 has been clinically accepted as a critical threshold for FFR-guided revascularization according to large randomized clinical trials.⁴ Since the measurement of the flow reserve is not straightforward, it was shown by Pijls et al.² that FFR can be derived from the ratio of two pressures distal and proximal to the stenosis, respectively. The measurements have to be obtained by a pressure wire, during the procedure of percutaneous coronary angiography, which is invasive and may cause periprocedural complications.

In addition to the invasive procedure, recent studies have shown that CFD can be applied to the anatomic models extracted from images of computed tomography angiography (CTA) and FFR may then be estimated non-invasively.⁷ Taylor and his group had studied and proposed a framework of this non-invasive method using 3D CFD models coupled with zero dimensional (0D) lumped parameter models for inflow and outflow boundary conditions.^{7–10} Their method has been successfully translated and was recently approved for clinical use by United States Food and Drug Administration. These techniques have substantially advanced clinical assessment and interventional management of coronary artery stenosis.

Nevertheless, studies in assessing the functional severity of cerebral artery stenosis remain scarce. Neurologists, Liebeskind and Feldmann, recently urged the introduction of a cerebral hemodynamic parameter as a new guidepost for cerebrovascular diseases and proposed the concept of fractional flow (FF) for cerebral hemodynamics.¹¹ Leng et al. applied a relatively simple CFD method to calculate the pressure ratio distal and proximal to a cerebral stenosis based on CTA data from patients with the symptomatic intracranial atherosclerosis (ICAS) and concluded that the CFD-derived hemodynamic parameter may be potentially useful in predicting subsequent stroke recurrence in patients with symptomatic ICAS.^{12,13}

In comparison with the CFD methods applied in the assessment of coronary artery stenosis, we believe that these preliminary attempts of using numerical methods for cerebrovascular diseases can be greatly improved.^{12,14} In this study, we intended to achieve the goal by (1) considering anatomic models of full

anterior or posterior circulation with primary collaterals included, (2) applying an instantaneous pulsatile inflow, and (3) incorporating a lumped parameter model to mimic the downstream effects from the distal vessels on the outlet boundaries. Instead of inducing cerebral hyperemia in patients and measuring FFR (the risk of hyperemic stimuli in cerebral artery is unclear), we measured the invasive and non-invasive fractional pressure ratios (FPR and FPR_{CFD}) using pressure wires and the improved CFD model, respectively. A statistical comparison was given to show the feasibility as well as the issues of the CFD method.

Material and methods

Clinical protocol

This cross-disciplinary study applied the same data as in the recent feasibility study of functional assessment of intracranial atherosclerosis.¹⁵ The study was approved by the ethics committee of Beijing Tiantan Hospital followed ethical guidelines of the Helsinki Declaration of 1975 (and as revised in 1983) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects, which allowed the off-label use of the pressure guide wire as an auxiliary investigation tool. Written consents were available for all of the patients included. Patients with ischemic stroke (>3 weeks after onset) caused by severe intracranial atherosclerotic stenosis were recruited during February to March 2015 if they were considered for interventional treatment (with or without stenting). A luminal narrowness $\geq 70\%$ in the intracranial large artery on digital subtraction angiography (DSA) was considered as severe stenosis. For more detailed inclusion criteria and clinical protocols, please refer to the feasibility study.¹⁵

Additionally, we further required the patients to have (1) CTA scans before and (or) after the interventional procedures allowing for a 3D reconstruction of the cerebral artery and (2) single stenosis in the intracranial large artery, more specifically, in the internal carotid artery or the middle cerebral artery or the vertebral artery or the basilar artery. There were eleven patients with all requirements qualified.

Invasive measurement of FPR

The interventional procedure was described in the feasibility study.¹⁵ Two instantaneous pressure waves, P_d and P_a , were measured simultaneously at the positions 2–3 cm distal to the stenotic lesion and in a proximal artery (the carotid or vertebral artery). The mean values of the pressure waves were calculated and the FPR was then calculated as the mean P_d divided by the mean P_a .

CFD procedure for the non-invasive measurement

Image acquisition and 3D mesh generation. CTA scans were performed for the patients before and (or) after the endovascular procedures and the data were stored in the standard Digital Imaging and Communication in Medicine (DICOM) format. The 3D geometry of vascular surfaces was then reconstructed by a suite of software, Mimics (Materialise NV, Belgium), and then examined and manually refined by two neurologists. Further processing of the vascular surface and generation of the computational domain (volume mesh) was performed using the ANSYS®ICEM CFD meshing software (ANSYS, Inc., USA). Considering the complexity of the geometry, we used the unstructured tetrahedral cell for domain discretization, and the mesh was finer nearby the vessel wall and at the stenosis where the flow field was of greater interest. The total number of elements is above 1 million and the minimum volume of the elements is about $1.0 \times 10^{-8} \text{ cm}^3$ to capture the small-scale feature of the blood flow.

3D model of blood flow. The heat transfer and the compressibility effects of the vascular wall were neglected and the blood flow was assumed to be a viscous and incompressible Newtonian fluid. The blood parameters were defined by constant density $\rho = 1.06 \times 10^3 \text{ kg.m}^{-3}$ and constant dynamic viscosity $\mu = 3.5 \times 10^{-3} \text{ kg.m}^{-1}.\text{s}^{-1}$. We chose the carotid artery diameter $D = 6.0 \times 10^{-3} \text{ m}$ and $v = 0.4 \text{ m.s}^{-1}$ as the characteristic length and velocity of the model. The Reynolds number can thus be calculated as $Re = \rho v D / \mu \approx 121$ which indicates that the flow is laminar. Finally, the governing equations of blood flow were described by 3D unsteady incompressible Navier–Stokes equations

$$\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v} \cdot \nabla) \mathbf{v} = -\frac{1}{\rho} \nabla p + \frac{\mu}{\rho} \nabla^2 \mathbf{v} + \mathbf{f} \quad (1)$$

and equation of mass conservation

$$\nabla \cdot \mathbf{v} = 0 \quad (2)$$

where $\mathbf{v}$ is the velocity vector, ρ is the density, p is the pressure, μ is the dynamic viscosity, and $\mathbf{f}$ is the body force assumed equal to 0.

The initial conditions were set to zero for all the cases, the details of inlet and outlet boundary conditions are discussed in the next section, and the vessel wall was considered as a no-slip boundary condition. The solver of the 3D blood flow is based on a finite volume approach using ANSYS CFX (ANSYS, Inc., USA) version 14.5. The numerical simulations were carried out on an AMAX server which has a

dual eight-core Intel SandyBridge E52687W@3.1 GHz processor and 240 GB of memory. A k-way Metis algorithm was applied for the mesh partition and MPI is used for communication among the processors. The total simulation time $T = 5.0 \text{ s}$ with approximately five cardiac cycles was included and each time step was 0.01s. A second-order backward Euler scheme was applied for the transient term. The relative residual target of root mean square (RMS) convergence criteria was 1.0×10^{-5} .

Boundary conditions. The boundary conditions of the CFD model include the inlet condition at the internal carotid artery or the vertebral artery and the outlet condition at the distal cerebral artery with an approximate diameter of 2.0 mm, respectively. The scheme used to set the boundary conditions is shown in Figure 1.

For the inlet boundary conditions, we defined the inflow (Q_{in}) at the internal carotid artery or the vertebral artery. As mentioned in Invasive measurement of FPR, the instantaneous P_a was measured using a pressure wire and then the velocity waveform was approximated from the P_a waveform by applying a widely used cerebral pressure–velocity transfer function^{16–18} expressed in the Z domain as

$$\frac{V(z)}{P(z)} = \frac{a + bz^{-1} + cz^{-2}}{1 + bz^{-1} + cz^{-2}} \quad (3)$$

Figure 1. The proposed settings of the inlet and outlet boundary conditions. For the outlet condition, we incorporated the outlet at distal artery with a Windkessel model (0D model) to mimic the downstream resistance R_d and compliance C to the outlet pressure P_{out} and flow Q_{out} . For the inlet condition, we transferred the waveform of P_a measured by the pressure wire into the waveform of Q_{in} . P_v and Q_v are the venous pressure and flow, respectively.

where

$$a = \left(1 - \frac{K}{f \cdot T}\right)^2, \quad b = \left(\frac{1}{f \cdot T}\right)^2 + \frac{2D}{f \cdot T} - 2, \quad c = 1 - \frac{2D}{f \cdot T} \quad (4)$$

where $f = 100$ Hz is the sampling frequency of the measured pressure, K , T , and D are three predefined constants as the gain parameter, the time constant, and the damping factor, respectively.^{16–18} We chose $K = 0.94$, $T = 1.6$, and $D = 0.65$ according to the definition of the parameters by Tiecks et al. to show a normal dynamic relationship between the cerebral blood pressure and the blood flow.¹⁹ This waveform was then considered as the waveform of the inflow, assuming cerebral blood flow velocity changes proportionally to the flow in large arteries. We then offset the waveform to match the averaged cerebral inflow from 94 subjects recently reported by Zarrinkoob et al. using high-resolution phase-contrast magnetic resonance imaging (HR PC-MRI) techniques.²⁰ More specifically, according to this recent work, the total cerebral Q_{in} is approximately $12 \text{ ml} \cdot \text{s}^{-1}$ if both anterior and posterior cerebral circulations are considered. Approximately 35% of the total Q_{in} was assigned for one intracranial carotid artery and 15% of the total Q_{in} was assigned for one vertebral artery, respectively. Note that this was only an initial guess of the inflow. In order to assure the agreement between the P_a measured by the pressure wire and the P_{a-CFD} simulated by the CFD method, the Q_{in} was then adjusted iteratively after each CFD computation until the resultant P_{a-CFD} matched the measured pressure within a difference of 5 mmHg or the computed inflow was out of the range of blood flow measured by HR PC-MRI.²⁰

For the outlet condition, we need to define the outlet pressure P_{out} . The 3D blood flow model was incorporated with a lumped parameter model to mimic the effects of the downstream resistance and the compliance on the outlet boundaries of the cerebral artery. We chose a two-element Windkessel model to simulate the hemodynamics contributed by arterioles, capillaries, and veins. The model, as shown in Figure 1, consists of a distal resistance R_d in parallel with a capacitance C to simulate the resistivity and compliance in the distal artery. The time-dependent outlet pressure $P_{out}(t)$ can then be derived from the ordinary differential equations of the Windkessel circuit.¹⁰ The parameters of this Windkessel model were adopted from a recent study of dynamic pressure-to-flow relationship of the cerebral circulation, where the total resistance of the cerebral artery is defined as the cerebrovascular index divided by the internal area of the artery, the downstream distal resistance R_d is one-third of the total resistance, and the value of the vascular

compliance C is $0.21 \text{ ml/mmHg}^{21}$. We excluded the resistance of large artery R_a as this has been replaced by our 3D CFD model.

$$P_{out}(t) = [P_{out}(0) - P_v(0)]e^{-\frac{t}{\tau}} + P_v(0) + \int_0^t \frac{e^{-\frac{t-i}{\tau}}}{C} Q_{out}(i) di, \quad \tau = R_d C \quad (5)$$

Following the assumption in Vignon-Clementel et al.'s recent work, we also assumed the distal venous blood pressure (P_v) to be zero and, as the total outflow is always equal to the total inflow, we had $Q_{out} = Q_{in}$.¹⁰ We then calculated P_{out} according to equation (5) and incorporated the 3D blood flow model with it.

Statistical analysis

With the non-invasively obtained hemodynamic parameters P_a , P_d , FPR, and the inlet blood flow Q_{in} computed by the proposed CFD method, we then tested their relationships against the invasively obtained parameters by Spearman's correlation, ρ . A p value < 0.01 was considered statistical significant. The Bland–Altman analysis was performed to demonstrate the agreement between the FPR and FPR_{CFD} .

Results

The patients' information and the results of invasive and non-invasive methods are given in Table 1. Data from 11 patients (6 males with mean age 58.6 years) were included for this study. There were two cases with intracranial stenosis in the middle cerebral artery, three cases in the internal carotid artery, one case in the basilar artery, and five cases in the vertebral artery, respectively. Of these patients, one case with favorable hemodynamics determined by DSA did not have further interventional treatment, whereas the rest had treatments with either angioplasty alone in seven cases or combination of angioplasty and stenting in three cases. We further applied the proposed CFD method to estimate P_{a-CFD} and P_{d-CFD} for each subject non-invasively. There were three cases with unqualified CTA scans before (two cases) and after (one case) the intervention, respectively, and two cases in which the patients were transferred from other hospital, therefore, with no CTA data before the intervention. This resulted in 16 qualified CTA scans from 11 patients.

In Figure 2, we demonstrate three examples of the 3D hemodynamic simulation. Panel A shows a case with 74% stenosis at the C7 segment of the left internal carotid artery (Case 1 in Table 1). In this case, bilateral anterior cerebral arteries were included in the CFD

Table 1. Patients' information and the results of the hemodynamic measures by the invasive (pressure wire) and non-invasive (CFD) methods.

No.	Gender	Age (year)	Site of intracranial stenosis ^a	Intervention	Pre /Post	Percentage of stenosis	Pressure wire			CFD			
							P_a (mmHg)	P_d (mmHg)	FPR (%)	P_{a-CFD} (mmHg)	P_{d-CFD} (mmHg)	FPR_{CFD} (%)	Q_{in} (ml/s)
1	M	63	LC6	Conservative	Pre	74%	55.9	46.9	0.84	57.6	47.8	0.83	4.7
2	F	47	LC6	Angioplasty	Pre	70%	71.2	35.4	0.50	77.0	43.2	0.56	4.3
					Post	40%	72.1	61.0	0.85	62.4	57.2	0.92	5.2
3	F	52	LV4	Angioplasty	Pre	76%	99.1	80.0	0.81	94.0	87.0	0.93	5.4
					Post	38%	89.0	84.7	0.95	83.2	79.9	0.96	6.2
4	M	53	BA	Stenting	Pre	89%	80.2	57.3	0.71	80.8	57.5	0.71	4.8
					Post	55%	88.8	74.7	0.84	84.6	70.5	0.83	6.5
5	M	54	LV4	Angioplasty	Pre	81%	67.7	41.3	0.61	68.7	46.4	0.68	4.3
					Post	42%	72.6	70.8	0.98	69.1	64.8	0.94	5.2
6	F	65	LC6	Stenting	Pre	84%	65.4	42.8	0.65	61.6	41.3	0.67	2.8
					Post	22%	61.4	58.1	0.95	63.0	59.5	0.94	4.7
7	F	75	LV4	Angioplasty	Pre	85%	67.7	46.9	0.69	67.6	47.4	0.70	2.7
8	M	64	LMI	Angioplasty	Pre	84%	71.8	28.5	0.40	85.7	28.2	0.33	2.4
9	M	61	RMI	Angioplasty	Post	15%	84.8	82.7	0.98	73.8	62.7	0.85	6.6
10	M	54	LV4	Angioplasty	Post	30%	63.1	60.5	0.96	56.7	53.6	0.95	4.5
11	F	50	LV4	stenting	Post	36%	65.4	56.1	0.86	59.2	53.7	0.91	4.5

^aAbbreviation of the types of the stenosis by R-right, L-left, C-carotid, M-middle, V-vertebral, BA-basilar and the number of arterial segment.

model as we observed the anterior communicating artery on the CTA scan. The result shows that FPR_{CFD} is 0.84 which means the patient had 84% of blood pressure preserved in the P_{d-CFD} with respect to the P_{a-CFD} . From the simulation, we speculate that there is an inverse (right-to-left) flow passing through the anterior communicating artery so as to compensate the pressure loss in the left middle cerebral artery caused by the stenosis. It is interesting to note that the clinical decision agrees with these findings. This patient was not proceeded for further interventional treatment according to the clinical criteria in the previous study,¹⁵ even though the lumen of the carotid artery is severely narrowed by the atherosclerotic lesion. Panel B and C show a luminal lesion at the basilar artery, with 89% stenosis before, and 55% stenosis after angioplasty and stenting (case 5 in Table 1). It is clear that the distal pressure loss after the invention was evidently reduced as the waveform of the P_{d-CFD} moves towards the waveform of the P_{a-CFD} , resulting in an increase of the FPR_{CFD} from 0.68 to 0.94. In the last example (case 6 in Table 1), in Panel D and E, it shows a case with stenosis at the right internal carotid artery. We only included the right anterior cerebral artery in the CFD model, as there was no the anterior communicating artery observed on the CTA scan. The result is similar to the second example. The FPR_{CFD} was increased from 0.67 to 0.94 as the stenosis

was improved from 84% to 22% by stenting. In this figure, we also gave the instantaneous pressure waves estimated non-invasively by the CFD method and the counterparts measured invasively by the pressure wire.

The statistical analysis based on the mean pressure values is given in Table 2. In the first two rows, it shows that the pressures, P_{a-CFD} and P_{d-CFD} , measured non-invasively by the CFD method are highly correlated with the ones, P_a and P_d , measured invasively by the pressure wire. The ratios, FPR and FPR_{CFD} , in the third row are thus also significantly correlated. They are significantly correlated with the percentage of stenosis and the inflow Q_{in} estimated non-invasively by the CFD method shown in the last four rows. In order to further elucidate if the percentage of stenosis and the FPR is nonlinearly correlated, we fitted the data by first- and second-degree polynomials, respectively, and calculated the root-mean-square-errors (RMSE). Shown in Table 2, the highest RMSE difference is between the percentage of stenosis and the FPR, suggesting that a nonlinear curve (a second order polynomial in this case) is more appropriate to describe the relationship between the percentage of the stenosis and the FPR than a straight line. The data with the fitted curves are plotted in Figure 3. The results of the Bland-Altman analysis are shown in Figure 4, where the mean difference (bias) between the FPR and FPR_{CFD} is

Figure 2. (a), (b, c), and (d, e) are three examples referring to the case 1, 5, and 7 in Table 1, respectively. The blood pressure distribution and the corresponding instantaneous pulsation at P_{a-CFD} (red lines) and P_{d-CFD} (blue lines) simulated by the CFD method (dashed lines) and measured by the pressure wire (solid line) are shown. (a) The case 1 was with 74% stenosis at C7 segment in the internal carotid artery. We found the pressure loss after the stenosis was not significant, as both the FPR and FPR_{CFD} was above 0.8 measured either by the pressure wire or CFD method shown in Table 1. (b) The case 5 was with 89% stenosis at the basilar artery and (c) after stenting. (d) and (e) are the case 7 with stenosis at C6 segment in the internal carotid artery before and after stenting, respectively.

Table 2. Statistical analysis of the results.

Variable 1	Variable 2	Coefficient	p	$RMSE_{1st}^a$	$RMSE_{2nd}^a$	RMSE Diff.
P_a	P_{a-CFD}	0.84	$<10^{-4}$	1.45 mmHg	1.44 mmHg	1%
P_d	P_{d-CFD}	0.94	$<10^{-8}$	1.55 mmHg	1.45 mmHg	7%
FPR	FPR_{CFD}	0.86	$<10^{-8}$	0.0139	0.0136	2%
Stenosis%	FPR_{CFD}	-0.71	$<10^{-2}$	4.51%	4.10%	9%
Stenosis%	FPR	-0.82	$<10^{-4}$	3.82%	2.80%	27%
Q_{in}	FPR_{CFD}	0.63	$<10^{-3}$	0.22 ml/s	0.22 ml/s	<1%
Q_{in}	FPR	0.69	$<10^{-2}$	0.22 ml/s	0.22 ml/s	<1%

^a $RMSE_{1st}$ and $RMSE_{2nd}$ are the root-mean-square-error for the first- and second-degree regressions, respectively.

0.0083 and the 95% limits of agreement are -0.11 to 0.12 , respectively.

Discussion

Main findings

According to our study, the proposed CFD simulation achieved comparable results with the invasive measurements. The computed pressure ratios are highly correlated with the ones measured by the pressure wires ($r=0.88$, $p<0.001$) and the Bland–Altman analysis shows excellent agreement of the invasive and non-invasive measurements. The numerical simulation results also revealed a significant relationship ($r=0.68$, $p=0.0019$) between the pressure ratios and the computed carotid artery (inlet) blood flow which is, however, less correlated with the percentage of stenosis ($r=-0.59$, $p=0.009$). This agrees with the findings in coronary arteries²² where the hemodynamic alteration is only partly determined by the percentage of the luminal stenosis.

Figure 4. The results of the Bland–Altman analysis are demonstrated. The differences ($FPR - FPR_{CFD}$) are denoted by circles. The mean difference (bias) between the FPR and FPR_{CFD} is 0.0083 (solid line) and the 95% limits of agreement are -0.11 to 0.12 (dotted line), respectively. Note that two cases at approximately 0.84 (x-axis) are almost overlapped.

Figure 3. The plots of statistical analysis of the results are given. (a) The invasive blood pressures, P_a and P_d , against the non-invasive pressures, P_{a-CFD} and P_{d-CFD} , were plotted in circles and pluses. The solid regression line is for the circles while the dash-dotted one is for the pulses. (b) The FPR versus the FPR_{CFD} were shown in circles. (c) The relationship between the percentage of stenosis and FPR (or FPR_{CFD}) was demonstrated in circles (or triangles). The solid and dash-dotted lines are two second-degree polynomials fitted in a least-square manner for the circles and triangles, respectively. (d) Instead of the percentage of stenosis, the relationship between the Q_{in} and FPR (or FPR_{CFD}) was also shown with the same line types and plot symbols as in (c).

Improvement of the CFD model

Incorporation of a two-element Windkessel model to the outlet boundary of the 3D CFD model is more realistic than using a constant or a fixed pulsation of blood pressure which ignores the downstream effects. Our results showed that, by this means, the non-invasive hemodynamic parameters, P_a , P_d , and FPR are all significantly correlated with the non-invasive ones measured by pressure wires. Although the exact values of the downstream resistance and the compliance in stroke patients have not been reported, previous study of pulsatility index (PI) using transcranial Doppler, however, suggested that significant changes of the distal resistance occurs only in patients with highly severe stenosis or substantial changes of ICP.^{23,24} These conditions do not apply to the patients in this study. We thus adopted the downstream parameters from a previous study of a model of cerebral circulation in healthy subjects.²¹

Another realistic consideration was the inclusion of primary collateral arteries that allow for mimicking the hemodynamic function of the communicating artery. This may help in some extent to explain our findings that the pressure drop distal to the stenosis was not entirely determined by the stenosis. In Figure 3(c), we found that it was more appropriate to describe the relationship between the percentage of the stenosis and the FPR by a nonlinear relationship than a linear regression. On contrast, in Figure 3(d), the FPR was linearly correlated with the inlet blood flow of the cerebral artery, indicating that this parameter is more directly related to the hemodynamic changes than the anatomic changes caused by atherosclerosis. One typical example is in Figure 2(a) where the patient had only 17% (FPR=0.83) blood pressure lost across the stenosis with 74% luminal narrowing at C7 of the left internal carotid artery. The CFD simulation showed that there is a right-to-left blood flow across the anterior communicating artery, resulting in asymmetric inlet blood flow at 6.5 ml/s and 2.2 ml/s on the right and the left carotid arteries, respectively. It is evident that the right anterior circulation compensates the reduced blood flow in the stenotic left ICA, through increased flow in right ICA and the right-to-left flow via the anterior communicating artery.

The computation of the pulsatile pressure with the high temporal resolution at a sampling rate of 100 Hz provides instantaneous information of cerebral hemodynamics. We can then derive the hemodynamic parameters, P_a , P_d , and FPR from the pulsatile pressures exactly as the derivation of the invasive parameters. In Figure 3, we show the significant correlation and good instantaneous agreement between the non-invasive and invasive pulsatile pressures. Interestingly, we also noted that the pulse

waves of P_a and P_d present almost no phase shift. This means that a rapid pulse transit time from P_a to P_d , therefore suggesting insignificant compliance of the large cerebral artery. This agrees with the findings by Giller et al. who reported the insignificant change of the diameter of large cerebral arteries despite induced alterations of arterial blood pressure or CO_2 ,²⁵ which validates the assumption of rigid vessel wall in modeling large cerebral artery in this study.

Relation of FF, FPR, and FFR and their clinical implications

Liebeskind and Feldmann first proposed the concept of FF, adapted from the coronary circulation, to indicate the hemodynamic significance of cerebral artery stenosis.¹¹ It can be interpreted as a parameter without considering the potential blood flow reserve. In this study, we however used FPR which is equal to FFR if the blood flow reserve is taken into account. According to the assumptions of FFR,^{1,2} we deduced simplified mathematical relations in Supplementary information (available online). It turns out that $\text{FF} \geq \text{FPR} \geq \text{FFR}$ without hyperemia induced and $\text{FF} = \text{FPR} = \text{FFR}$ with distal artery maximally dilated, suggesting that FPR is a closer parameter to FFR than FF, though they both converge to FFR when the resistance of the distal artery is reduced to minimum.

Indeed, in this study, both the computational method and the interventional method suggested that the FPR is a functional parameter of cerebral hemodynamic, which is different from the severity of stenosis. In Figure 3(c), the values of FPR from the patients with severe stenosis (>70% luminal stenosis) were scattered transversely, implying that the patients even with high degree of stenosis could have blood pressure preserved sufficiently. This agrees with the findings in the study of FFR in coronary artery diseases (CAD).¹ However, FPR is not equal to FFR unless the distal arteries are maximally dilated. Although hyperemic stimulus is required for FFR in CAD, the potential risks in cerebrovascular diseases have not been sufficiently assessed and it is therefore of great concern. We thus suggest that FPR is used as a functional parameter that shows hemodynamic alteration without considering the potential reserve of the blood flow, and further speculate that FPR might be a good approximation of FFR in patients with symptomatic intracranial artery stenosis as blood flow reserve is likely consumed in this condition. Indirect evidence may be found in autoregulation, as previous study showed significant impairment of cerebral autoregulation in patients with stenosis, suggesting significant dilation of the resistance vessels.^{26,27}

Limitations

Despite the excellent agreement of our computational results and the clinic measurements, we recognize the following limitations in this study. (1) Possible changes of downstream vessel resistance were not considered. There was thus no effect of cerebral autoregulation simulated when stenosis presented. (2) Only limited collateral information was provided by the CTA source images. This might explain the relatively large difference between the invasive and non-invasive measurements in the cases (case 8 and 9 in Table 1) with stenosis in the middle cerebral artery where the downstream flow can be supplied by pial collaterals which are not considered in the proposed CFD model. We note that some recent studies applied the phase-contrast MRI based imaging techniques to measure intracranial hemodynamic information with good temporal resolution.^{20,28} These techniques need to be considered in the future CFD simulation.

Conclusions

In this paper, we introduce a parameter, the fractional pressure ratio, which can be obtained invasively or non-invasively and we show that the parameter reflects the hemodynamic significance of the stenosis. A CFD-based method is proposed to compute FPR, and the value of the computed FPR_{CFD} is close to the value obtained with the invasive measurement. This CFD-based method is therefore being potentially useful in the non-invasive assessment of the functional alteration caused by cerebral luminal stenosis. The numerical simulation also helps in elucidating that the pressure ratio is more closely related to the hemodynamics than the percentage of stenosis. Further refinement of the CFD-based method, together with clinical studies of the functional assessment of stenosis, is necessary in order to achieve more accurate estimate under more general situations and for the technique to become clinically practical.

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Declaration of conflicting interests

The author(s) declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this paper.

Authors' contributions

JL and XCC proposed and designed the CFD model for this study. LL designed the clinical experiment. JL, XCC and LL

wrote the manuscript. ZY and WSS implemented the CFD method. YP and XLi collected the CTA images. JW and RC reconstructed the 3D artery from the CTA images and transferred the 3D artery into meshes. XLe and HQ performed the statistical analysis. BJ, LS, YW (for Yilong Wang), ZM, and YW designed and implemented the interventional measurement.

Supplementary material

Supplementary material for this paper can be found at <http://jcbfm.sagepub.com/content/by/supplemental-data>

References

1. Bruyne BD and Sarma J. Fractional flow reserve: a review. *Heart* 2008; 94: 949–959.
2. Pijls NH, van Son JA, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993; 87: 1354–1367.
3. Pijls NH, Bech GJW, Bruyne BD, et al. Clinical assessment of functional stenosis severity: Use of coronary pressure measurements for the decision to bypass a lesion. *Ann Thorac Surg* 1997; 63: S6–S11.
4. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360: 213–224.
5. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; 367: 991–1001.
6. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; 371: 1208–1217.
7. Taylor CA, Fonte TA and Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve. *J Am Coll Cardiol* 2013; 61: 2233–2241.
8. Vignon-Clementel IE, Alberto Figueroa C, Jansen KE, et al. Outflow boundary conditions for three-dimensional finite element modeling of blood flow and pressure in arteries. *Comput Meth Appl Mech Eng* 2006; 195: 3776–3796.
9. Kim HJ, Vignon-Clementel IE, Figueroa CA, et al. On coupling a lumped parameter heart model and a three-dimensional finite element aorta model. *Ann Biomed Eng* 2009; 37: 2153–2169.
10. Vignon-Clementel IE, Figueroa CA, Jansen KE, et al. Outflow boundary conditions for 3D simulations of non-periodic blood flow and pressure fields in deformable arteries. *Comput Meth Biomech Biomed Eng* 2010; 13: 625–640.
11. Liebeskind DS and Feldmann E. Fractional flow in cerebrovascular disorders. *Interv Neurol* 2012; 1: 87–99.
12. Leng XY, Scalzo F, Ip HL, et al. Computational fluid dynamics modeling of symptomatic intracranial atherosclerosis may predict risk of stroke recurrence. *PLoS ONE* 2014; 9: e97531.

13. Leng XY, Wong KS and Liebeskind DS. Evaluating intracranial atherosclerosis rather than intracranial stenosis. *Stroke* 2014; 45: 645–651.
14. Qi XL, Zhou FY, Wan J, et al. Noninvasive assessment of cerebral artery stenoses from anatomic computed tomography angiography. *Adv Interv Cardiol* 2015; 10: 18–20.
15. Miao Z, Liebeskind DS, Lo W, et al. Fractional flow assessment for the evaluation of intracranial atherosclerosis: a feasibility study. *Interv Neurol* 2016; 5: 65–75.
16. Aaslid R, Lindegaard KF, Sorteberg W, et al. Cerebral autoregulation dynamics in humans. *Stroke* 1989; 20: 45–52.
17. Zhang R, Zuckerman JH, Giller CA, et al. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol – Heart Circ Physiol* 1998; 274: H233–H241.
18. Panerai RB, Dineen NE, Brodie FG, et al. Spontaneous fluctuations in cerebral blood flow regulation: contribution of PaCO₂. *J Appl Physiol* 2010; 109: 1860–1868.
19. Tiecks FP, Lam AM, Aaslid R, et al. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995; 26: 1014–1019.
20. Zarrinkoob L, Ambarki K, Wåhlin A, et al. Blood flow distribution in cerebral arteries. *J Cereb Blood Flow Metab* 2015; 35: 648–654.
21. Zhang R, Behbehani K and Levine BD. Dynamic pressure–flow relationship of the cerebral circulation during acute increase in arterial pressure. *J Physiol* 2009; 587: 2567–2577.
22. Bruyne BD, Pijls NHJ, Bartunek J, et al. Fractional flow reserve in patients with prior myocardial infarction. *Circulation* 2001; 104: 157–162.
23. Lim M-H, Cho YI and Jeong S-K. Homocysteine and pulsatility index of cerebral arteries. *Stroke* 2009; 40: 3216–3220.
24. Akopov S and Whitman GT. Hemodynamic studies in early ischemic stroke serial transcranial Doppler and magnetic resonance angiography evaluation. *Stroke* 2002; 33: 1274–1279.
25. Giller CA, Bowman G, Dyer H, et al. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993; 32: 737–742.
26. White RP and Markus HS. Impaired dynamic cerebral autoregulation in carotid artery stenosis. *Stroke* 1997; 28: 1340–1344.
27. Guo Z-N, Liu J, Xing Y, et al. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. *PLoS ONE* 2014; 9: e93213.
28. Peng S-L, Su P, Wang F-N, et al. Optimization of phase-contrast MRI for the quantification of whole-brain cerebral blood flow. *J Magn Reson Imag* 2015; 42: 1126–1133.