Numerical investigation of carotid stenosis in three-dimensional aortic-cerebral vasculature: pulsatility index, resistive index, time to peak velocity, and flow characteristics

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\textbf{ABSTRACT}

Haemodynamic correlations among the pulsatility index (PI), resistive index (RI), time to peak velocity (TPV), and mean Reynolds number ($Re_{\text{Mean}}$) were numerically investigated during the progression of carotid stenosis (CS), a highly prevalent condition. Fifteen patient-specific CS cases were modeled in the package, SimVascular, by using computed tomography angiography data for the aortic-cerebral vasculature. Computational fluid domains were solved with a stabilized Petrov–Galerkin scheme under Newtonian and incompressible assumptions. A rigid vessel wall was assumed, and the boundary conditions were pulsatile inflow and three-element lumped Windkessel outlets. During the progression, the increase in the TPV resembled that during aortic stenosis, and the parameter was negatively correlated with PI, RI, and $Re_{\text{Mean}}$ in the ipsilateral cerebral region. The $Re_{\text{Mean}}$ was inversely related to PI and RI on the contralateral side. In particular, PI and RI in cerebral arteries showed three second-order regression patterns: 'constant (Group A)', 'moderately decreasing (Group B)', and 'decreasing (Group C)'. The patterns were defined using a new parameter, mean ratio (lowest mean index/mean index at 0\% CS). This parameter could effectively indicate stenosis-driven tendencies in local haemodynamics. Overall, the haemodynamic indices changed drastically during severe unilateral CS, and they reflected both regional and aortic-cerebral flow characteristics.

\textbf{Nomenclature}

| Haemodynamic Properties | PI | pulsatility index | Haemodynamic Structure & Arteries | ACV | aortic-cerebral vasculature |
|-------------------------|----|------------------|----------------------------------|-----|-----------------------------|
| RI                      | resistive index          | CoW | circle of Willis |
| TPV                     | time to peak velocity    | ICA | internal carotid artery |
| $Re_{\text{Mean}}$      | mean Reynolds number     | ACA | anterior cerebral artery |
| PSV                     | peak systolic velocity   | MCA | middle cerebral artery |
| EDV                     | end diastolic velocity   | PCA | posterior cerebral artery |
| $T_{PSV}$               | time at peak systolic velocity | CoA | communicating artery |
| $T_{AVO}$               | time at aortic valve opening | ACoA | anterior communicating artery |
| CA                      | carotid atherosclerosis  | PCoA | posterior communicating artery |
| CS                      | carotid stenosis         | A1  | horizontal branch of ACA |
| NASCET                  | North American           | A2  | vertical branch of ACA |
| Symptomatic Carotid     | Symptomatic Carotid      | P1  | horizontal branch of PCA |
| Endarterectomy Trial    | Endarterectomy Trial     | P2  | vertical branch of PCA |
| CTA                     | computed tomography angiography | | |

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1. Introduction

Extracranial internal carotid artery (EICA) stenosis occurs in 8.0% of all ischemic strokes (Flaherty et al., 2012), and carotid atherosclerosis (CA) is a major global burden (Song et al., 2020). In 2020, 27.6%, 21.1%, and 1.5% of the global population were estimated to have high carotid intima-media thickness, carotid plaque, and carotid stenosis (CS), respectively. The number of people with these conditions has been rapidly increasing since 2000 (Song et al., 2020). The global population affected by these conditions is estimated to be 1,067,816, and 58 million, respectively. In particular, the prevalence of carotid plaque and stenosis has an exponential relationship with age (Song et al., 2020) and it is expected to increase further in the coming decades owing to the ageing world population (United Nations, 2019).

Despite the growing incidence of CA, the impact of progressive CA on aortic-cerebral haemodynamics remains unclear. While numerous risk factors such as smoking and diabetes mellitus (de Weerd et al., 2014), and predictors such as microRNA biomarkers (Dolz et al., 2017) and inflammation (Schillinger et al., 2005) have been identified as contributing factors to the progression of CS, specific haemodynamic phenomena in vasculatures during CA or CS progression, other than the accelerative nature of CS (Cheng et al., 2004; Muluk et al., 1999; Ong et al., 2018), have not been described in sufficient detail (Chatzikonstantinou et al., 2012). A major finding by studies on progressive CS is deteriorating clinical outcomes during the progression, detected using duplex scans (Bertges et al., 2003; Sabeti et al., 2007) and through post-carotid endarterectomy analysis (Holliday, 2004; Moneta et al., 1993; Rothwell et al., 1994). Numerical studies have found various flow distributions in the circle of Willis (CoW) during the progression, despite their domains being confined to a small cerebral vasculature (Cassot et al., 1995; Cassot et al., 2000; Zhu et al., 2015). Recently, an aortic-cerebral vasculature (ACV) simulation of CS progression found that cerebral haemodynamics can show transitions in the visualized rigid-body CoW, driven by asymmetric hemispheric perfusion (T. Kang et al., 2021). An in-depth analysis of CS-induced haemodynamic phenomena can enhance the existing understanding of progressive cerebrovascular diseases at the macroscopic and regional levels.

This is the first study to investigate the effects of progressive CS conditions in relation to key haemodynamic indices – pulsatility index (PI), resistive index (RI) and time-to-peak velocity (TPV) – and flow characteristics such as mean Reynolds number (\( \text{Re}_{\text{Mean}} \)) and identify correlations among the mentioned properties. While these haemodynamic properties are numerically examined in a large three-dimensional arterial domain for the first time, the main reason is to provide an engineering background to clinical haemodynamic indices, and vice versa. This particularly is important as these properties are frequently used in the corresponding fields; \( \text{Re}_{\text{Mean}} \) is a parameter used in fluid mechanics to describe the general fluid dynamics of a problem domain, and it can be used to describe the fluid-dynamic state of stenosis-driven haemodynamics in a region. The PI is a predictor of cognitive impairment in hypertensive patients (Harris et al., 2018), and is correlated with the memory scores, processing speed, executive function (Mitchell et al., 2011), and pulse wave velocity, which is linked to arterial stiffness (Kwater et al., 2009). It also is known to respond to microangiopathic changes in the cerebral region (Lee et al., 2000), and a low PI is related to a high degree of ipsilateral CS (Bill et al., 2020). The RI is another important index in studies of abdominal arteries such as the renal artery (Ninet et al., 2015; Ohta et al., 2005; Petersen et al., 1997), and the TPV is a useful indicator of severe aortic stenosis (Kamimura et al., 2016; Kim et al., 2014) and persistent pulmonary hypertension in neonates (Gately & Patel, 2019). Revealing the impact of CS progression and their relation to both global and regional flow characteristics would not only enable the construction of predictive models using techniques like polynomial regression but also unify the different languages used in clinical and engineering fields; although no direct correlation has been found, engineering terms such as vorticity and q-criterion (Cox et al., 2019) may be alternatives for PI.

We investigated the correlations of PI, RI, TPV, and \( \text{Re}_{\text{Mean}} \) during the CS progression using a numerical method, which had the following advantages over duplex ultrasound and four-dimensional magnetic resonance imaging:

- It provides higher spatiotemporal resolution, which is helpful for obtaining a refined data grid in the arterial domain.
- It enables data acquisition in the entire region of interest by employing a fully resolved arterial domain (an advantage over duplex ultrasound).

Anatomical Orientation (Prefix)  

- LSA i ipsilateral  
- EICA c contralateral
It facilitates predictive studies on all cardiovascular diseases.

Our approach involved three-dimensional patient-specific ACV and progressive, unilateral, and symmetric CS conditions computationally imposed on the EICA, located near the carotid bifurcation (Figure 1). The arteries were classified into six (ACV perspective) and three groups (CoW perspective). From an ACV perspective, the TPV and ReMean were distinctively correlated with both PI and RI, which varied with the location of the CS. From a CoW perspective, three distinct trends – constant (Group A), moderately decreasing (Group B), and decreasing (Group C) – were observed in the PI and RI and analysed. Furthermore, lenticulostriate arteries (LSAs) were included in the analysis domain since they strongly influence by the changes in cerebral haemodynamics (Blanco et al., 2017).

2. Methods
2.1. Classification of artery groups

The changes in haemodynamics during the CS progression were complex. Hence, the artery groups were divided into two main categories based on the perspectives from ACV and CoW domain. The artery groups in one category were labeled with Roman numerals, while those in the other category were labeled with letters of the alphabet (Table 1). This approach not only helped differentiate between the macroscopic (ACV) and regional (CoW) effects of the CS but also provided insights into general haemodynamic phenomena in individual artery segments when the arteries were further classified into subgroups. The classification into subgroups was made by referring to a past study (T. Kang et al., 2021) and current simulation results. The categorization was also inspired by (Wang et al., 2016) and (Zhou et al., 2016); these studies found statistical correlations of unilateral CS with the proximal segments of the cACA and iPCoA and a correlation between CS and variations in the CoW configuration, respectively.

Specifically, a novel parameter – mean ratio – was used to characterize the subgroups in the CoW category owing to the existence of geometrical and patient-specific complexities in the arterial network. Details about the mean ratio are presented in the Methods Section. The criteria for classification in the CoW category were 35th and 60th percentiles in mean ratios, which corresponded to threshold values of 0.85 and 0.5 for the PI and 0.9 and 0.7 for the RI in mean ratios, respectively, which were chosen to reflect the haemodynamic trends in arteries. The
Table 1. Classification of arteries in the region of interest.

| Region of Interest | Group | Artery              |
|--------------------|-------|---------------------|
| Aortic-Cerebral Vasculature (ACV) | I     | DsA                 |
|                    | II    | cSA, Ceca, cMCA, cACA, cPCA, cLSA1, cLSA2 |
|                    | III   | iSA, iECA, iPCA     |
|                    | IV    | clCA, cVA, iVA      |
|                    | V     | iMCA, iACA, iLSA1, iLSA2 |
|                    | VI    | iICA                |
| CoW*               | A     | cMCA, cP1, cP2, iP2, cLSA1, cLSA2, cPCoA |
|                    | B     | cICA, BA, cA1, cA2, iP1 |
|                    | C     | iICA, iMCA, iA1, iA2, iLSA1, iLSA2, iPCoA, ACoA |

Arteries were grouped according to the tendencies of their haemodynamic indices during CS progression. LSA1, first branch of the lenticulostriate artery; LSA2, second branch of the lenticulostriate artery; A1, horizontal segment of the ACA; A2, vertical segment of the ACA; P1, horizontal segment of the PCA; P2, vertical segment of the PCA. The letters ‘i’ and ‘c’ denote ipsilateral and contralateral, respectively.

*The subgroups A, B, and C were classified on the basis of the 35th and 60th percentiles, which corresponded to mean ratios of 0.85 and 0.5 for the PI and 0.9 and 0.7 for the RI in mean ratios, respectively.

contralateral and ipsilateral cerebral arteries fell in different groups (Groups II and V), and the arteries supplying to the CoW belonged to yet another group (Group IV). Furthermore, most of the contralateral and ipsilateral cerebral arteries in the CoW group belonged to Groups A and C, respectively.

2.2. Patient-specific three-dimensional haemodynamics

Computed tomography angiography (CTA) images of patient-specific cases were acquired from a medical image database of the Screening Technology and Outcome Project (STOP), which was approved by the Institutional Review Board (Smith et al., 2009). The selection criteria included the availability of a complete upper-chest arterial domain (extending from the aorta to the CoW) and a complete set of CoWs and the existence of distinctive variance in geometrical features (Figure 1). A set of four models that were identical to those used in previous studies (T. Kang et al., 2021; Mukherjee et al., 2018; Mukherjee et al., 2016) was assessed. In particular, one model was excluded because of its potential string-like occlusive behavior in ICAs.

LSA branches were attached to the arterial domain in view of their importance in cerebral circulation (Cho et al., 2008). Unfortunately, they were hardly observed in the original image data, and hence, they were created with a reference diameter (Wardlaw, 2005) at locations with branching patterns (Cho et al., 2008; Hwang et al., 2014; Kang et al., 2005). The diameter was selected to be 0.1 cm, and two identical trunks were created on both ipsilateral and contralateral MCA branches. The trunks perforated into the brain only to a small extent to minimize artificial manipulation of the patient-specific configuration.

2.3. Model geometry

The computational arterial domains of all patient cases were constructed using the open-source package SimVascular (Updegrove et al., 2017) and CTA images with a mean voxel size of 511 mm × 511 mm × 439.7 mm (±31.8, SD) and a resolution of 0.46 mm (±0.10, SD) × 0.46 mm (±0.10, SD) × 1 mm. Conventional two-dimensional vessel segmentation (Wilson et al., 2001) was used for the construction of center-line paths in each image, and the center-line paths were combined with segmented two-dimensional contours. The generated center lines and contours were then automatically lofted to form the wall boundaries of the arterial domain. Tetrahedral grid meshing was performed by an embedded open-source mesh generator, TetGen (Si, 2015), and it completed the three-dimensional tetrahedral grid structure of the domains.

2.4. Numerical scheme

Blood was assumed to be a Newtonian fluid despite having the non-Newtonian property of haematocrit-dependent viscosity (Cho & Kensey, 1991). This is acceptable for large-artery simulations such as those involving the cerebral artery (Ku, 1997; Taylor & Figueroa, 2009; Arzani, 2018). Further, blood was assumed to be incompressible, which rendered the blood density and viscosity constants at 1.06 g·cm⁻³ (Trudnowski & Rico, 1974) and 0.04 g·s⁻¹·cm⁻¹ (Hall & Hall, 2020), respectively. The assumption of a rigid-body vessel wall was effective for simulating relatively realistic artery behavior at a reasonable computational cost. The Navier–Stokes equation, continuity equation and constitutive law for incompressible Newtonian fluids are

\[
\rho_f \left( \frac{\partial u}{\partial t} + (u \cdot \nabla u) \right) = -\nabla p + \nabla \cdot \tau + \rho_f g \tag{1}
\]
\[ \nabla \cdot u = 0 \quad (2) \]
\[ \tau = 2 \mu_f D(u) = \mu_f (\nabla u + \nabla u^T) \quad (3) \]

where \( u \) and \( p \) are the velocity and pressure fields, respectively, \( \rho_f \) is the blood density, \( \mu_f \) is the blood viscosity, \( g \) is the gravitational acceleration and \( \tau \) denotes the shear stress. The pressure and velocity fields were calculated using a Petrov–Galerkin stabilized finite element formulation with linear elements (Brooks & Hughes, 1982; Franca, Frey, Hughes, et al., 1992; Franca, Frey, & Engineering, 1992). A generalized variational form of the formulation is,

\[
\rho_f \left( \frac{w}{\partial t} \right)_\Omega + \rho_f (w, (u \cdot \nabla) u)_\Omega + 2 \mu_f (D(w), D(u))_\Omega \\
- \rho_f (w, b)_\Omega - (\nabla \cdot p)_\Omega - (\nabla q, u)_\Omega + (q, u \cdot n)_\Gamma \\
- (w, h)_{\Gamma, \epsilon} + (w, h_{\text{bd}})_{\Gamma, b} + \sum_{e=1}^{N_d} \left[ (\tau_{\text{supg}} (h^e \cdot \nabla) w^h, R^h)_{\Omega, e} \right]_{\text{SUPG stabilization}} \\
+ (\tau_{\text{pspg}} \nabla q^h, R^h)_{\Omega, e} = 0 \quad (4)
\]

where \( w \) and \( q \) are the test functions corresponding to \( u \) and \( p, \Omega \) represents the entire arterial domain used for computation, \( b \) denotes the total body force, \( h \) denotes the contributions at each Neumann boundary \( \Gamma \) of the computational domain \( \Omega \), \( D \) is the symmetry of the velocity gradient \( (\nabla u + \nabla u^T) \), \( R^h \) is the residual of the momentum equation, \( \tau_{\text{supg}} \) and \( \tau_{\text{pspg}} \) are stabilization parameters that are chosen to be functions of the element size (Franca, Frey, & Engineering, 1992; Tezduyar & Osawa, 2000) and \( h_{\text{bd}} \) is a factor representing all resistance outflow boundary conditions (Vignon-Clementel et al., 2006, 2010). This formulation was implemented in SimVascular (Updegrove et al., 2017), which has been validated for accurately setting patient-specific boundary conditions (Coogan et al., 2013; Mukherjee et al., 2018; Vignon-Clementel et al., 2006). Furthermore, the capability of a finite element solver with customized preconditioners to describe the flow in large arteries has been verified (Les et al., 2010; Mukherjee et al., 2016). The solver has been specialized with linear basis functions to optimally solve cardiovascular flows with the support of backflow stabilization (M. Esmaily-Moghadam et al., 2013), multi-scale coupling with physiological boundary conditions (Marsden & Esmaily-Moghadam, 2015), momentum coupling (Figuerola et al., 2006) and advanced numerical algorithms (Mahdi Esmaily-Moghadam et al., 2015). Further details about the solver are available in M. Esmaily-Moghadam et al. (2013). The computations were performed with SimVascular installed on a workstation with Intel Xeon CPU (E7-8890 v4@2.2 GHz with 96 cores) and 512 GB RAM, and an average of 32 cores were used per simulation. Each simulation took approximately eight days to converge, with a time step of 1 ms. Convergence occurred in the sixth cardiac cycle, and all the reported values were from the equivalent cycle.

The solver has been shown to solve the complex poststenotic flows during severe CS for non-critical stenoses (< 85% CS) reasonably well with the use of fine mesh (Kung et al., 2011), even in comparison with a large-eddy simulation turbulence model (Velde, 2018). While using the same package, we used a sufficiently dense number of elements at the stenosis region (Figure 3 in manuscript), which mesh refinement results showed convergence in the peak systolic velocity and mean arterial pressure (T. Kang et al., 2021). The blood flow in severe CS also matched important haemodynamic properties such as flow rates and the corresponding clinical measurements (T. Kang et al., 2021). While the mean Reynolds numbers in the region distal to the stenosis at severities of 75%, 85%, and 95% were about 270, 100, and 10 with the maximum Reynolds numbers at the narrowest stenotic region of about 1,420, 1,110, and 390, respectively, turbulence could develop even at such low Reynolds numbers. However, the flow would rather be vortical, involving several recirculation zones and reattachment points; such vortical structures can be seen in an experimentally validated spectral-element simulation (Griffith et al., 2009) and an in-vivo measurement (Markl et al., 2010). Furthermore, laminar flow characteristics are dominant from macroscopic artery-wise perspectives (Evju & Mardal, 2015), which minimizes the effects of any stenosis-driven near-turbulent flow in the region far distal from the stenosis.

### 2.5. Boundary conditions

The inlet face of all patient-specific geometries was an ascending aorta, and pulsatile inlet conditions identical to those used by Olufsen et al. (2000) were mapped uniformly as plug-type on the inlet surface (Seed & Wood, 1971). Lumped three-element Windkessel models were used for the distal ends of the main arterial branches for providing three patient-specific parameters, namely, \( R_p \), \( R_d \), and \( C \), which denote the proximal resistance, distal resistance, and capacitance, respectively. The total resistance \( R_t \) was calculated from the mean arterial pressure (MAP), and the total cardiac volumetric flow \( Q \) was determined using the relation \( MAP = Q \cdot R_t \). A ratio \( \alpha \), given by \( \alpha = R_p/(R_p + R_d) \), was assigned the value of 0.91. The initial value of the total capacitance
was calculated using the relation $C_{tot} = \frac{4Q}{dP}$, and the parameters $R_p$, $R_d$, and $C$ for all eleven Windkessel outlets were assigned in accordance with a cross-sectional-area rule (Coogan et al., 2013; Les et al., 2010; Mukherjee et al., 2018; Xiao et al., 2014). The optimum parameter values were then iteratively obtained using a conventional procedure (Xiao et al., 2014). The relation used for obtaining MAP was $(P_{sys} + 2P_{dia}) / 3$, where $P_{sys}$ and $P_{dia}$ are the systolic and diastolic pressures, respectively, and the flow distribution in each artery is identical to that of Mukherjee et al. (2016). Resistance values were iteratively tuned in a steady-state simulation, and capacitance values were provided by T. Kang et al. (2021).

The boundary conditions at the distal ends of the outlets were tuned in a steady-state simulation, and capacitance values were tuned to obtain acceptable pulse pressure ranges of 40–50 mmHg for the descending aorta and 30–40 mmHg for other arteries such as the carotid and cerebral arteries (Alastruey et al., 2007; Cassot et al., 1995; Ryu et al., 2015). Although we did not adopt any cerebral autoregulation models, the total cerebral blood flow (tCBF) and the collateral flow through the communicating arteries were similar to those with the autoregulation models (Cassot et al., 1995; Ryu et al., 2015); we noted this phenomenon as a bulk-autoregulatory effect of Windkessel model in a large arterial domain (T. Kang et al., 2021).

The constant-parameter assumption is also based on the fact that cerebral flow accounts for only 14% of the total cardiac output (Kety, 1950). The flow rates in major arteries leading to the circle of Willis during CS progression was also validated with the clinical data in the literature (Nicolau et al., 2001; Oktar et al., 2006). Other concerns such as acute cardiac compensation and other vascular activities such as distal collateral flow through ophthalmic and superficial temporal arteries were disregarded as the former may occur only in extreme conditions such as aortic coarctation (Coogan et al., 2013) and the latter during severe bilateral CS (Yamamoto et al., 2004); only unilateral CS was considered.

Additionally, the blood flow rate in LSAs was assumed to be approximately one twenty-fifth of the mean flow rate in the MCA, following Schnerr et al. (2017). The boundary conditions for LSAs were tuned using the procedure described in the above paragraphs and defined accordingly, and they are presented in Table 2.

### 2.6. Data analysis

#### 2.6.1. Haemodynamic indices and flow characteristics

Visualization and post-processing were performed with ParaView (Kitware, Inc., Clifton Park, NY, USA) (Schröder et al., 2004). Equations for the haemodynamic indices (PI and RI) at 0% CS and the times at which the PSV and aortic valve opening (i.e. beginning of cardiac contraction) were achieved, respectively, $\rho_f$ is the blood density, $\mu_f$ is the blood viscosity and $D_A$ is the artery diameter. $Re_{Mean}$ is the mean Reynolds number, and it reflects the general flow characteristics of the artery segment at the arterial cross section. All normalized terms were referenced to their stenosis-free values at 0% stenosis.

#### 2.6.2. Mean ratio and regression model

The haemodynamic indices of the classified artery segments showed distinctive trends. Hence, we defined a parameter ‘mean ratio’, which is the ratio between haemodynamic indices such as PI and RI at 0% CS and the severity with the lowest index value. This severity was 95% for all arteries except for the iICA, for which the lowest index value corresponded to a severity of 85%.

$$Mean\ Ratio = \frac{Lowest\ mean\ index,\ typically\ at\ 95\%\ CS}{Mean\ index\ at\ 0\%\ CS}$$

Regression models were constructed in the form of second-order polynomials by using the calculated volume data:

$$y = b_0 + b_1x + b_2x^2$$
Table 2. Windkessel RCR parameters of all patient models.

| Artery | \( R_p \) | \( C \) | \( R_d \) | \( R_p \) | \( C \) | \( R_d \) | \( R_p \) | \( C \) | \( R_d \) |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| DsA    | 0.02   | 225.4  | 0.18   | 0.02   | 221.2  | 0.19   | 0.02   | 280.1  | 0.19   |
| cACA   | 0.91   | 0.9    | 9.24   | 0.71   | 1.2    | 7.21   | 0.73   | 0.5    | 7.43   |
| cECA   | 0.44   | 2.3    | 4.42   | 0.40   | 2.5    | 4.00   | 0.28   | 2.3    | 2.80   |
| cMCA   | 0.53   | 1.0    | 5.40   | 0.57   | 0.9    | 5.78   | 0.56   | 0.8    | 5.62   |
| cPCA   | 0.78   | 0.8    | 7.85   | 1.10   | 0.5    | 11.14  | 0.82   | 0.5    | 8.26   |
| cSA    | 0.20   | 8.1    | 1.99   | 0.14   | 11.1   | 1.45   | 0.16   | 15.3   | 1.63   |
| iACA   | 0.93   | 0.8    | 9.45   | 0.78   | 1.0    | 7.85   | 0.90   | 0.4    | 9.11   |
| iECA   | 0.32   | 2.9    | 3.28   | 0.50   | 1.9    | 5.09   | 0.27   | 2.5    | 2.75   |
| iMCA   | 0.46   | 1.1    | 4.62   | 0.43   | 1.2    | 4.38   | 0.73   | 1.3    | 7.34   |
| IPCA   | 1.25   | 0.5    | 12.60  | 1.02   | 0.6    | 10.31  | 0.93   | 0.4    | 9.38   |
| ISA    | 0.13   | 11.5   | 1.34   | 0.14   | 10.9   | 1.41   | 0.16   | 16.7   | 1.59   |
| iLSA   | 13.3   | 0.044  | 135.0  | 14.3   | 0.041  | 144.4  | 13.9   | 0.046  | 140.5  |
| cLSA   | 10.7   | 0.054  | 107.8  | 10.8   | 0.053  | 109.4  | 18.1   | 0.047  | 183.4  |

\( R_p, R_d, \) and \( C \) represent the proximal resistance, distal resistance, and capacitance, respectively. The units of resistance and compliance are \( 10^9 \text{ Pa} \cdot \text{s} \cdot \text{m}^{-3} \) and \( 10^{-10} \text{ m}^3 \cdot \text{Pa}^{-1} \), respectively. The parameters from DsA to iLSA (in order) were adopted from the study of T. Kang et al. (2021).

Figure 2. Schematic of the procedure used for volume-wise analysis (basilar artery (BA) is considered as an example). A full set of diagrams and regression curves are available in Supplemental Materials (Supplemental Figures XI–XVII).

where \( y \) is the predicted polynomial outcome value, \( x \) is the variable and \( b_0, b_1, \) and \( b_2 \) are coefficients. In the present study, \( y \) was set to be a haemodynamic index such as PI or RI and \( x \) was set to be the CS severity based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) standard.

### 2.6.3. Volume-wise analysis of arterial segments

The total number of arterial segments in each patient-specific CoW domain was 20 and the arteries had distinctive geometrical features. Hence, the haemodynamic indices, PI and RI, were quantified as volumetric data for a more detailed analysis of arteries in CoWs. Subsequently, they were used to construct regression models. The arteries were segmented perpendicular to the center line, and the artery-wise perpendicular planes were created at bifurcations to minimize the volume of arteries excluded for analysis. (Figure 2). The end segments were extended to the outlet faces of the arterial network, and the segments in source arteries, ICAs and the BA, were extended to meet the range of the conventional ICA-CoW domain.

### 2.7. NASCET criterion

The present study used the NASCET criterion (Moneta et al., 1993), which can be expressed as follows:

\[
\text{NASCET} = 1 - \frac{D_s}{D_d} \times 100(\%)
\]  

where \( D_s \) and \( D_d \) represent the narrowest diameter of the stenosis and the diameter of the stenosis at its distal end, respectively. The CS was located in the right-side EICA, near the carotid bifurcation (Figure 1). A total of five severities – 0%, 50%, 75%, 85% and 95% – were imposed,
3. Results

3.1. Progressive changes in PI, RI, TPV, and $Re_{\text{Mean}}$

The following results were acquired from data obtained from all three patient models. The full data set is expressed as a bar chart in Figure 4, showing changes in the PI, the RI, the TPV and $Re_{\text{Mean}}$ during the CS progression. The values of $Re_{\text{Mean}}$ in main arteries such as the DsA, iICA and iACA are 1820, 460 and 380 at 0% CS severity, respectively, implying laminar flow characteristics. Also, when the blood density, viscosity and vessel diameter are constant, following the assumptions in our study, the $Re_{\text{Mean}}$ represents the flow rate of the artery, and a decrement of $Re_{\text{Mean}}$ is identical to a decrease in flow rate. The $Re_{\text{Mean}}$ of the iMCA falls from 500 at 0% CS to 330 at 95% CS of iICA (Figure 4), and this 30% reduction is similar to that during the occlusion of the iCCA (Ryu et al., 2015), confirming the physiological validity of our results. The details about the changes in the haemodynamic properties are discussed in Figure 5.

Figure 5 shows successive changes in the key haemodynamic properties, namely, PI in a volume contour (Figure 5A) and normalized PI, RI, TPV, and $Re_{\text{Mean}}$ in line plots (Figures 5B, C, D, and E, respectively). The full contour sets of PI and RI are presented in Supplemental Materials (Supplemental Figures I – VI), and the artery groups are presented in Section 2.5 and Table 1. Overall, the haemodynamic indices in the arteries of the Roman numeral group either did not change or showed negligible changes until the CS severity of 50% (Figure 5). Figures 5B and C show a rapid decrease in the normalized PI and RI of Groups V and VI, while the PI and RI of Group IV show a gradual decrease. For the other groups, these indices were constant throughout the CS progression. The normalized TPV in Figure 5D changed only moderately for Group V, whereas Group VI showed a large deviation at 95% CS as the iICA had a near-zero flow rate. At CS severities above 75%, the TPV for Group V was inversely correlated with both PI and RI. In Figure 5E, the flow characteristics represented by $Re_{\text{Mean}}$ are constant for Groups I, II, and III, but drastically different in Groups IV, V, and VI; $Re_{\text{Mean}}$ of Group VI drops sharply to nearly zero after 50% CS, and that of Groups IV and V changes moderately; $Re_{\text{Mean}}$ of Group IV increased but that of Group V decreased. Hence, the correlation of $Re_{\text{Mean}}$ with PI and RI was negative for Group IV, but positive for Groups V and VI. $Re_{\text{Mean}}$ fell considerably from 50% CS for Groups V and VI, implying the reduced dominance of the inertial effects of blood flow in the carotid and cerebral ipsilateral arteries. By contrast, $Re_{\text{Mean}}$ for Group IV increased significantly after 50% CS, indicating an increase in the inertial effects of blood flow.

and the lumen diameter of the target location was successively reduced to the corresponding severity to generate patient-specific CS models. The stenosis was relatively symmetric about the center line, where the narrowest CS diameter remained relatively fixed.

2.8. Grid independence test

The number of elements ranged from $6$ to $8.5 \times 10^6$, and it was similar to that in the study of Mukherjee et al. (2016). (Figure 3) This range was identical to those in some previous studies (T. Kang et al., 2021; Mukherjee et al., 2018; Mukherjee et al., 2016), and these models were verified in a previous mesh-refining study (Les et al., 2010) and an aortic coarctation study (Coogan et al., 2013). The stenosis mesh was also validated by T. Kang et al. (2021), which showed the convergence of the peak systolic velocity and mean arterial pressure of the validated mesh at 95% CS. (Table 3) In the same work, other properties such as flow rate and mean pressure in major arteries such as ICA and vertebral arteries were also compared to the clinical data and validated.

![Figure 3. Computational mesh of the patient model P01 at 95% CS. (A) A schematic of the aortic-cerebral vasculature mesh. (B) A close-up view of the ipsilateral carotid region. (C) A close-up view of the stenosis.](image-url)
Figure 4. Progressive changes in the haemodynamic indices PI, RI, and TPV as well as in $Re_{\text{Mean}}$ during CS progression. The values are area-averaged values. Changes are presented for each artery segment, and the proximal and distal parts of arteries were considered as a whole (i.e. the ACA was not segmented into A1 and A2 but integrated). The arteries were classified into the following groups: Group I, DsA; Group II, cMCA, cACA, cPCA, cLSA1, cLSA2, cSA, cECA; Group III, iECA, iSA, iPCA; Group IV, iVA, iICA; Group V, iMCA, iACA, iLSA1, iLSA2; and Group VI, iICA. DsA, descending aorta; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; LSA, lenticulostriate artery; SA, subclavian artery; ECA, external carotid artery; VA, vertebral artery; ICA, internal carotid artery. The letters ‘i’ and ‘c’ denote ipsilateral and contralateral, respectively.

3.2. Transitional changes in PI and RI of cerebral circulation

The CoW is a complex anatomical structure that functions as an effective collateral pathway during CS progression (Cassot et al., 1995; Hoksbergen et al., 2003; T. Kang et al., 2021; Mukherjee et al., 2018; Papanтечев et al., 2013). Variations of incomplete CoW anatomies are very dramatic and cause several complex transitional haemodynamic phenomena simultaneously. (T. Kang et al., 2021) An analysis of the PI and RI in Figures 6 and 7 shows that abrupt changes occurred in the PI and RI in the CoW, and the indices reached peak values or significantly low values during CS progression. A superior view of CoWs shows the difficulties faced in performing a statistical analysis for correlating haemodynamic phenomena in an arterial domain to the progression of cerebral diseases (Figure 6A and Figure 7A). As analysed in Figure 6B and Figure 7B, both PI and RI drop rapidly in all artery segments while for iA1 and cA2, both PI and RI increased sharply to significantly high values during the transition occurring at 75%, 85%, and 85% CS for P01, P02, and P03, respectively. This also implies that the transition may occur at different CS degrees in different patients.

The overall tendencies of and correlations between the PI, the RI, the TPV, and $Re_{\text{Mean}}$ were analysed using planar cross-sectional data, as shown in Figure 5. However, a holistic quantification of the haemodynamic properties in arterial segments may provide better accuracy and a better perspective for an in-depth analysis of haemodynamic tendencies and correlations. The CoW was segmented into 20 arteries. Table 4 shows the PI and RI along with the mean ratio for all arteries, and Figure 8 presents the volumetrically quantified PI of the major
artery segments, namely A1, MCA, and ICA, on both the ipsilateral and contralateral sides of the CoW of P01. Statistical data on the PI and RI for all three patient models (Table 4) showed that major differences between normal (0%) and near-occlusion (85% – 95%) occurred mostly in the ipsilateral arteries. The trend of PI of major ipsilateral CoW arteries in Figure 8 is identical, and iA1 shows overshooting behavior similar to that observed in Figures 6 and 7. Overall, the ipsilateral side showed a steady decrease in both PI and RI, while the contralateral side exhibited rather constant haemodynamic properties.

Figures for all arteries can be found in Supplemental Materials (Supplemental Figures X–XV).

### 3.3. Regression model of CoW haemodynamics

Regression models were constructed for every artery segment in the CoW by performing volume-wise analysis. The second-order regression parameters are presented in Table 5. The PI and RI of the segments showed general tendencies and the segments were divided into three groups as shown in Figure 9. The three groups – A, B,
and C – showed different tendencies: constant, moderately decreasing, and decreasing, respectively. Most of the contralateral cerebral arteries belonged to Group A, while the ipsilateral cerebral arteries were assigned to Group C. Only a few arteries, namely, cA1, cA2, cICA, iP1, and BA, belonged to Group B. These arteries were secondary collateral pathways, and they were connected to the ipsilateral hemisphere via the communicating arteries (CoA) iPCoA and ACoA, both of which belonged to Group C and were the primary collateral pathways directly supplying the rerouted ipsilateral blood to the iA1 and iICA segments. The cPCoA and other contralateral arteries had negligible impact on the unilateral CS. Hence, the unilateral CS severely affected both ipsilateral arteries and the primary and secondary collateral pathways.

The maximum $R^2$ value was 0.779 of Group C in RI. This is relatively low in terms of model validity, but in the present study, $R^2$ values represent the dispersion of the PI and RI for each group. This provides a general regression tendency for each artery group under the sole effects of unilateral CS progression.

4. Discussion

This study considered the ACV to investigate the effects of unilateral CS progression. It has been difficult to use an extensive three-dimensional domain in conventional three-dimensional stenosis progression studies because of the high computational costs involved, even though it represents more realistic haemodynamic phenomena.
In computational fluid dynamics, it is commonly held that an extended computational domain that includes distal parts far from the region of interest reduces arbitrary computational artifacts and increases the solution accuracy, at a cost of delayed cyclic convergence of the solution. Visualization through three-dimensional analysis can also provide insights into the overall phenomena, and artery-wise tendencies during progressive CS can be determined more accurately from volume data for an in-depth analysis.

4.1. Haemodynamic correlations among PI, RI, TPV, and Re\textsubscript{Mean}

The PI, the RI, the TPV, and Re\textsubscript{Mean} in the ACV showed various trends during progressive CS. In Figure 5, for Group V, the TPV has an inverse relationship with the PI, the RI, and Re\textsubscript{Mean} during severe CS. An identical observation was made by Kamimura et al. (2016) during severe aortic stenosis, implying that the same phenomenon occurs in unilateral distal arteries for extreme degrees of unilateral CS. The iICA for Group VI may have failed to show an identical phenomenon owing to severe stenosis, which significantly reduced the blood flow and rendered the flow waveform in the iICA abnormal. In Group IV, in the intermediate arteries (iVA, cICA, and cVA), both PI and RI decreased moderately, but the behavior of Re\textsubscript{Mean} was opposite to that for Group V. The increase in Re\textsubscript{Mean} compensated for the reduction in the PI and RI, and the increase was probably because of higher inertial effects of the blood flow. Overall, CS progression significantly affected the haemodynamics in
Figure 8. Box-and-whisker diagrams of the PI of the major cerebral arteries, namely A1, MCA, and ICA. The diagrams are ordered clockwise, from cA1 (A) to iA1 (F). The PI and other indices were calculated using the classification based on the CoW perspective, and therefore, they are slightly different from those in Figure 4, which was drawn for the classification based on the ACV perspective.

the ACV and altered the parameters PI, RI, TPV, and ReMean, while only the TPV in Group V changed for severe CS, having an inverse relationship with the parameters PI, RI, and ReMean. The unilateral CS affected the distal arteries in the anterior hemisphere, and ReMean in the intermediate arteries showed an inverse relationship with PI and RI. Other groups showed negligible changes.

4.2. Haemodynamic transitions at severe CS

The transitional behavior of blood flow in the CoW was first highlighted in T. Kang et al. (2021), in which the prevalence of the ‘completely recruited’ configuration of the CoW during the CS progression was discussed. The ‘completely recruited’ CoW is observed the most at 50% severity, and its occurrence is less at other severities. The overall tendency, hence, had a pulse-like trend during the CS progression, and a similar transition was observed in this study for the PI and RI, which peaked at 75% for P01 and 85% for P02 and P03 (Figures 6 and 7). While a high level of the PI generally indicates large fluctuations in the flow velocity, PI is also high when the mean velocity is significantly lower than the amplitude of the velocity profile, since $PI = (V_{max} - V_{min})/V_{Mean}$. This indicates near-reversal or even reversal of regional blood flow, which is evident in the volume contour of Figure 7A of T. Kang et al. (2021). This clearly is not a favorable situation as events such as reduced total cerebral blood flow are related to deteriorative clinical conditions such as cognitive impairments (Poels et al., 2008) and dementia (Wolters et al., 2017).

In particular, these intermediate haemodynamic changes were three-dimensional effects and thus hardly representable through one-dimensional modeling. The visualization of ACV and CoW structure helps us understand stenosis-driven macroscopic haemodynamic changes and provides insights into regional microscopic changes by providing higher resolution compared with conventional measurement techniques.

4.3. Comparison of ACV- and CoW-based analyses

The last paragraph from Section 4.2 leads to another inference: artery-wise analysis based on volume data provides highly detailed information on haemodynamic changes. While Figure 5 was prepared using ACV-based classification, Table 4 and Figures 8 and 9 were obtained using CoW-based classification. Intuitively, the three-dimensional haemodynamic domain has a more
complex structure than a one-dimensional domain and captures patient-specific features more accurately. In detail, haemodynamic phenomena were different region, where the PI and RI of cA1 (Figure 6B and Figure 7B) showed a decreasing trend while all indices of cACA (Figure 5, Group II) showed a consistent trend. The PI of iA1 (Figure 8F) increased sharply at the transitional severity of 75%. Hence, the ACV-based analysis of planar data at artery faces (Figure 5) and mean ratios (Table 4) provides general insights into upper-chest haemodynamics during CS progression, while the CoW-based analysis of volume contours (Figures 6 and 7) and box-and-whisker plots (Figure 8) provide segment-wise trends of the PI and RI in individual arteries. All box-and-whisker plots are provided in Supplemental Materials (Supplemental Figures X–XV). Overall, the indices on

Table 4. Mean values (±SD) of the PI and RI at 0% and 95% CS for all the CoW artery segments.

| Artery | Mean ± SD | Mean Ratio† | Mean ± SD | Mean Ratio† |
|--------|-----------|-------------|-----------|-------------|
| ACoA   | 2.86 ± 0.75 | 0.68 ± 0.29 | 0.24      | 0.88 ± 0.14 | 0.44 ± 0.11 | 0.50 |
| iPCoA  | 2.95 ± 0.48 | 0.83 ± 0.20 | 0.28      | 0.93 ± 0.07 | 0.52 ± 0.08 | 0.56 |
| cPCoA  | 3.07 ± 0.56 | 3.12 ± 0.76 | 1.01      | 0.88 ± 0.08 | 0.89 ± 0.08 | 1.01 |
| cA1    | 2.89 ± 0.98 | 1.62 ± 0.83 | 0.56      | 0.89 ± 0.07 | 0.67 ± 0.12 | 0.75 |
| cA2    | 2.54 ± 0.62 | 2.12 ± 0.96 | 0.83      | 0.88 ± 0.07 | 0.76 ± 0.16 | 0.86 |
| cP1    | 2.65 ± 0.53 | 2.59 ± 0.77 | 0.98      | 0.91 ± 0.08 | 0.88 ± 0.09 | 0.96 |
| cP2    | 2.59 ± 0.53 | 2.52 ± 0.56 | 0.97      | 0.92 ± 0.06 | 0.91 ± 0.07 | 0.98 |
| cMCA   | 3.05 ± 0.92 | 2.93 ± 1.09 | 0.96      | 0.92 ± 0.07 | 0.89 ± 0.08 | 0.97 |
| cICA   | 2.77 ± 0.87 | 2.08 ± 0.88 | 0.75      | 0.90 ± 0.06 | 0.78 ± 0.09 | 0.87 |
| cLSA1  | 3.61 ± 1.00 | 3.58 ± 0.98 | 0.99      | 0.97 ± 0.08 | 0.95 ± 0.08 | 0.99 |
| cLSA2  | 3.36 ± 0.99 | 3.31 ± 1.09 | 0.99      | 0.94 ± 0.09 | 0.92 ± 0.09 | 0.98 |
| iP1    | 2.61 ± 0.57 | 1.64 ± 0.49 | 0.63      | 0.91 ± 0.08 | 0.72 ± 0.10 | 0.79 |
| iP2    | 2.59 ± 0.53 | 2.24 ± 0.76 | 0.87      | 0.91 ± 0.06 | 0.84 ± 0.13 | 0.92 |
| iP1    | 2.71 ± 0.62 | 0.84 ± 0.34 | 0.31      | 0.91 ± 0.06 | 0.50 ± 0.10 | 0.55 |
| iP1    | 2.66 ± 0.63 | 1.02 ± 0.41 | 0.38      | 0.88 ± 0.06 | 0.57 ± 0.1 | 0.64 |
| iP1    | 3.54 ± 0.90 | 1.05 ± 0.42 | 0.30      | 0.95 ± 0.08 | 0.57 ± 0.12 | 0.60 |
| iP1    | 3.47 ± 0.95 | 0.85 ± 0.27 | 0.24      | 0.94 ± 0.09 | 0.52 ± 0.10 | 0.55 |
| iP2    | 2.61 ± 0.45 | 1.94 ± 0.43 | 0.74      | 0.93 ± 0.06 | 0.81 ± 0.08 | 0.87 |

The p-values were provided to show the adverse effects of occlusive CS on the local haemodynamics of the CoW. A majority of ipsilateral arteries were severely affected by occlusive CS, but its effects on the contralateral arteries were negligible. SD, standard deviation. *Mean = (lowest mean index, typically at 95% CS)/(mean index at 0% CS).

Table 5. Parameters of the second-order regression models for all artery segments in the CoW.

| Artery | Pulsatility Index | Resistive Index |
|--------|------------------|-----------------|
|        | $b_0$ | $b_1$($10^{-3}$) | $b_2$($10^{-5}$) | $b_0$ | $b_1$($10^{-3}$) | $b_2$($10^{-5}$) |
| ACoA   | 2.90  | 6.05            | -33.34            | 0.89  | 4.24            | -9.99            |
| iPCoA  | 3.00  | 31.57           | -60.88            | 0.93  | 4.97            | -10.29           |
| cPCoA  | 3.04  | 7.73            | -6.30             | 0.87  | 2.54            | -2.29            |
| cA1    | 2.90  | 6.17            | -21.59            | 0.90  | 1.35            | -4.02            |
| cA2    | 2.54  | -1.19           | -3.52             | 0.88  | 0.50            | -1.85            |
| cP1    | 2.65  | -0.47           | -0.13             | 0.91  | 0.21            | -0.60            |
| cP2    | 2.59  | -0.83           | 0.003             | 0.92  | -0.07           | -0.11            |
| cMCA   | 3.05  | 0.49            | -2.02             | 0.92  | 0.11            | -0.47            |
| cICA   | 2.90  | -2.82           | 0.97              | 0.90  | 0.65            | -2.01            |
| cLSA1  | 2.77  | 4.09            | -12.13            | 0.97  | 0.04            | -0.23            |
| cLSA2  | 3.36  | 1.58            | -2.25             | 0.94  | 0.07            | -0.26            |
| iP1    | 2.36  | 15.20           | -28.80            | 0.85  | 3.43            | -6.41            |
| iP1    | 2.36  | 1.42            | -16.78            | 0.86  | 0.91            | -4.51            |
| iP1    | 2.61  | 10.31           | -22.21            | 0.91  | 1.85            | -4.10            |
| iP2    | 2.59  | 2.80            | -7.19             | 0.91  | 0.57            | -1.50            |
| iP1    | 2.75  | 10.37           | -36.31            | 0.92  | 3.50            | -9.48            |
| iP1    | 2.70  | -3.20           | -14.79            | 0.89  | -0.45           | -2.75            |
| iP1    | 3.58  | 8.10            | -39.37            | 0.95  | 3.09            | -7.81            |
| iP1    | 3.50  | 8.85            | -41.15            | 0.95  | 3.50            | -8.67            |
| iP1    | 2.61  | 6.77            | -14.61            | 0.93  | 1.08            | -2.45            |
| Average±SD | 2.84±0.34          | -       | -       | 0.91±0.03          | -       | -       |

The regression models contained the values of all patient cases and were expressed in the second-order polynomial form $y = b_0 + b_1x + b_2x^2$.
Figure 9. Overall tendencies of the PI and RI during CS progression were analysed using a volume-wise approach. (A) A total of 20 arteries were segmented and divided into three groups, namely, A, B, and C. The tendencies of the PI for Groups A, B, and C are presented in (B, C, and D) respectively, and those for the RI for Groups A, B, and C are shown in (E, F, and G) respectively. The individual regression lines are presented in Supplemental Materials (Supplemental Figures XVI and XVII). The abbreviations ‘Const.’, ‘Mod.’, and ‘Dec.’ indicate constant, moderately, and decreasing, respectively.

the ipsilateral side tended to decrease whereas those on the contralateral side remained constant.

4.4. Haemodynamic regression model for stenosis prediction

The haemodynamic indices of CoW arteries showed distinctive tendencies. A total of 20 arteries were segmented in all patient cases, and regression models were constructed for all the cases (Supplemental Figures XVI and XVII). Although the PI and RI ranges were different in individual segments, the data showed three unique tendencies during CS progression, namely, constant (Group A), moderately decreasing (Group B), and decreasing (Group C). Interestingly, the ipsilateral arteries in the CoW and CoAs supplying to the ipsilateral hemisphere belonged to Group C, while the contralateral arteries and the cPCoA belonged to Group A. The indices of the secondary collateral pathways, cICA, BA, cA1, cA2, and iP1 in Group B showed a moderate decrease. The distal segments cA2 and iA2 followed the trends in the preceding segments cA1 and iA1, reflecting the coupled haemodynamics of segments in the same artery. The moderately decreasing group acted as a
collateral pathway during severe CS. In summary, unilateral CS progression significantly affected the ipsilateral-side arteries (Group C), but had a negligible effect on the contralateral arteries (Group A), and the secondary collateral pathways (Group B) showed changes intermediate between the changes shown by Groups A and C. The impact of the unilateral CS on the posterior part of the CoW (mostly showing constant trends) was minimal, except for iP1, suggesting that the collateral pathways, especially the primary collaterals (iPCoA and ACoA), near the ipsilateral region were prone to deteriorating haemodynamic conditions during unilateral CS.

The second-order polynomial regression model was selected after a thorough comparison of the first to fifth-order polynomial regression models. Figure 10 shows plots of the first to fifth-order regression models; the plots were used for the selection of the best-fit model, Table 6 shows the $R^2$ values for all groups in each regression order. The maximum $R^2$ values for Group A and B were generally obtained for the second-order model, but for Group C, the maximum $R^2$ values were obtained for the fourth- and fifth-order models. Group A showed almost constant tendency during the progression, and hence any regression model could be applied. The $R^2$ value for Group B, and the selection of the model did not pose any problem. The $R^2$ value for Group C, however, was the highest for the higher-order models. Statistically, higher-order regression models should be adopted for Group C, but a lower-order model has the advantages of better interpretability and simplicity. Furthermore, the difference in $R^2$ values is small, with the maximum difference being about 0.02 (Table 6), and the deviation of the second-order model is negligible compared with the fifth-order model (Figure 10). Therefore, we selected the second-order models for all groups.

![Figure 10. Comparison of regression models of PI for Group C. (A) Plots of the first to fifth order polynomial regression models. (B) Plots of the second and the fifth regression models for making a direct comparison.](image)

| Regression Order | RI | PI |
|------------------|----|----|
| Group A          | 0.0142 | 0.4238 | 0.6339 | 0.0077 | 0.3527 | 0.5861 |
| Group B          | 0.0236 | 0.5129 | 0.7787 | 0.0161 | 0.4187 | 0.6901 |
| Group C          | 0.0156 | 0.5067 | 0.7953 | 0.0256 | 0.4111 | 0.7039 |
| Group A          | 0.0079 | 0.5043 | 0.7970 | 0.0340 | 0.4086 | 0.7021 |
| Group B          | 0.0079 | 0.5043 | 0.79670 | 0.0340 | 0.4086 | 0.7021 |

### 4.5. Limitations

This study involved numerous assumptions to simplify the problem domain. First, the rigid-body assumption made the vessel wall non-deformable. Haemodynamic indices such as the pulsatility index are indeed related to arterial stiffness, which increases with age and vascular risk factor exposure (Laurent et al., 2001; Mattace-Raso et al., 2006). A computational approach involving fluid-structure interaction (FSI) would resolve the pressure and velocity fields in the vasculature more accurately, but an FSI simulation of an arterial domain ranging from the aorta to CoW requires extensive computational resources (Coogan et al., 2013); the computational cost would be enormous to complete a total of 15 patient-specific aortic-cerebral FSI simulations. The candidate models would be an arbitrary Lagrangian-Eulerian formulation (Taylor & Figueroa, 2009), boundary element method-finite element method (BEM-FEM) (Ghalandari et al., 2019), and the cut-cell immersed boundary method integrated with an adaptive mesh refinement algorithm (Salih et al., 2019).

On the other hand, rigid-body assumption simplifies the problem with reliable accuracy; Brown et al. (2012) showed that the differences in the flow fields and helical flow indices of FSI and rigid wall models are negligible.
This may be due to about 5% variations in the diameter of large arteries during pulsation. (Eriksen, 1992). For such reason, this condition is frequently used in studies using a large domain with multiple patient-specific cases. (Liu et al., 2016; Sutalo et al., 2014; Tyfa et al., 2018) Our results with rigid-wall assumption may not be identical to the measured in-vivo haemodynamic indices, but such condition was useful for isolating the effects of the progression of carotid stenosis on the haemodynamic indices (PI, RI, and TPV) and the flow characteristics (Re Mean); we could independently evaluate such effects and found that the subsequent changes of the properties during the progression are correlated to each other. We also identified that such changes are both unfavorable and drastic, supporting the accelerative nature of the stenosis progression (Cheng et al., 2004). The trends and numerical values are presented in line plots, volume contours, and regression models, which can be used as reference models in future studies while an FSI modeling on the present work is left for future work.

Second, this paper presents regression models for predicting CS progression with haemodynamic indices using only simulation data. Although the flow rate, arterial pressure and haemodynamic tendencies of the present computational models have been validated (T. Kang et al., 2021), the study does not provide any clinically measured stenosis-progressive patient-specific haemodynamic indices. The use of more patient-specific cases would also improve the present results.

Third, the consideration of few patient-specific cases and the equivalent inlet condition for all models and the disregarding of non-Newtonian effects of viscous blood are also limitations of this study. However, the use of five NASCET-based stenosis cases for each patient model and a large arterial domain (approximately seven times the height of the conventional ICA-to-CoW domain used in stenosis studies) was a major feature of this study. A future study should include more complex fluid models such as non-Newtonian haematocrit-dependent flow dynamics to develop a next-generation haemodynamic simulation.

5. Conclusion

The present study investigated the effects of progressive CS conditions on patient-specific ACV. For the first time, we show that the haemodynamic properties (the PI, the RI, the TPV, and Re Mean) change abruptly at around 75–85% CS during the CS progression and have distinctive correlations; the TPV was negatively correlated to the PI, the RI, and Re Mean in the ipsilateral region (Groups V and VI), while Re Mean was also so to the PI and the RI in the contralateral region (Group IV). Other groups (Groups I, II, and III) showed negligible changes in the PI, the RI, Re Mean, and the TPV. In general, the haemodynamics of the ipsilateral cerebral arteries (iMCA, iACA, and iLSAs) were affected the most by progressive CS conditions.

Furthermore, stenosis-predicting regression models were developed for each arterial segment in the CoW, inspired by transitional changes observed in the haemodynamic indices PI and RI in the CoW during CS progression. The transitional changes occurred at severe CS, and a regression analysis was performed on the basis of the transitional changes. Three groups – constant (Group A), moderately decreasing (Group B), and decreasing (Group C) – were identified on the basis of the variation of the PI and RI, and Groups A and C mainly comprised contralateral and ipsilateral arteries, respectively. The collateral pathways leading to the ipsilateral hemisphere were prone to deteriorating haemodynamic conditions, namely, decreasing PI and RI.

Future computational studies may adopt the constraints specified in Section 4.5 to enhance the accuracy of the numerical solution, but they may incur significantly higher computational costs. Overall, we provide numerically calculated PI, RI, and TPV values in three-dimensional aortic-cerebral vasculature and present the details of the haemodynamic correlations and trends during the CS progression. We report the regression models of PI and RI, which have not been reported in both fields (clinical and engineering fields) in the context of CS progression; these can be used as mathematical models to predict the behavior of CS and quantify its effects on the PI and RI of local arteries. As a result, the effects of CS on other parameters such as the TPV and Re Mean can be determined from changes in the PI and the RI. Our results are hence expected to be useful for both prospective and retrospective clinical and engineering studies of unilateral CS progression. In particular, they would be useful for engineering studies since large-scale vascular studies covering the region from the aorta to the cerebral vasculature are rare, especially studies involving progressive CS conditions.

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The authors declare that this section is empty.

Disclosure statement

The authors declare no conflict of interest.

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