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Vessel calibre and flow splitting relationships at the internal carotid artery terminal bifurcation

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Abstract

Objective: Vessel lumen calibres and flow rates are thought to be related by mathematical power laws, reflecting the optimization of cardiac vs. metabolic work. While these laws have been confirmed indirectly via measurement of branch calibres, there is little data confirming power law relationships of flow distribution to branch calibres at individual bifurcations.

Approach: Flow rates and diameters of parent and daughter vessels of the internal carotid artery terminal bifurcation were determined, via robust and automated methods, from 4D phase-contrast magnetic resonance imaging and 3D rotational angiography of 31 patients.

Main Results: Junction exponents were 2.06±0.44 for relating parent to daughter branch diameters (geometrical exponent), and 2.45±0.75 for relating daughter branch diameters to their flow division (flow split exponent). These exponents were not significantly different, but showed large inter- and intraindividual variations, and with confidence intervals excluding the theoretical optimum of 3.

Power law fits of flow split vs. diameter ratio and pooled flow rates vs. diameters showed exponents of 2.17 and 1.96, respectively. A significant negative correlation was found between age and the geometrical exponent (r=-0.55, p=0.003) but not the flow split exponent. We also found a dependence of our results on how lumen diameter is measured, possibly explaining some of the variability in the literature.

Significance: Our study confirms that, on average, division of flow to the middle and anterior cerebral arteries is related to these vessels’ relative calibres via a power law, but it is closer to a square law than a cube law as commonly assumed.
1. Introduction

Blood is transported from the heart to the capillary beds through the cardiovascular tree. This complex biological system is constituted by a tree architecture composed of a number of arteries that split the flow, typically via bifurcations, to perfuse distal territories. At each bifurcation, a ‘parent’ vessel typically splits in two ‘daughter’ vessels, increasing the number of vessels while resulting in a progressive reduction of their calibre, all while conserving the total flow rate. In order to transport blood through this system, energy expenditure is needed because of the frictional/viscous losses. Although bigger vessels incur less frictional losses, the metabolic cost of maintaining the blood volume will rise. This begs the question of the existence of optimum laws enforcing a certain architectural design and blood distribution while ensuring an optimal function of the whole biological system.

Assuming that such biological system follows an optimal design to ensure a minimum energy cost while transporting blood, Murray (1926) modelled this system by expressing a cost function taking into account the competition between the energy needed to transport the blood and the metabolic cost needed to maintain this biological system. Under the simplifying assumptions of Poiseuille flow, a constant metabolic rate, and a constant blood viscosity, Murray demonstrated that the optimal design led to a cubic power law relationship among the vessel calibres, such that the cubed diameter of the parent vessel equates to the sum of the cubes of each daughter vessel’s diameter. Similarly, a functional relation between vessel calibre and flow rate exists such as the flow rate ratio between the two daughter vessels must equate to the cubed ratio of their diameters.

Since Murray’s work, studies have tried to improve the accuracy of these power law models. Notably, setting aside the key assumption of Poiseuille flow in the derivation of Murray’s laws, Uylings (1977) showed that the power law exponent might vary between 2.33 and 3 depending on whether the flow is turbulent or laminar. Others have shown that the exponent might be between 2.42 and 3 when the non-Newtonian behaviour of the blood is accounted for (Revellin et al., 2009). Besides these theoretical studies, experimental measurements have reported values ranging between 2 and 3 on diverse cardiovascular territories, and using diverse methodologies (Beare et al., 2011; Finet et al., 2008; Ingebrigtsen et al., 2004; Mittal et al., 2005; Rossitti and Lofgren, 1993b; van der Giessen et al., 2011). With rare exceptions (e.g. Riva et al., 1985), these investigations have been limited to measurement of the vessel calibres only, leaving untested their nominal relationship to the blood flow distribution. These experimental studies have shown a significant scatter, confirming the idea that the power law exponent may vary along the cardiovascular tree. For example, Sherman (1981) concluded that Murray’s cube law is not obeyed in the largest, most proximal bifurcations of aorta,
the pulmonary trunk, the vena cavae, and the pulmonary veins. Murray’s Law also implies a constant wall shear stress (WSS) throughout the cardiovascular system; however, in-vivo measurements in recent studies (Cheng et al., 2007; Reneman et al., 2009) have shown that the assumption of constant WSS throughout the body seems unrealistic. These findings further support the idea that the exponent of the power law is not constant throughout the vascular tree, and only tends toward a cube law closer to the arterioles, where Murray’s simplifying assumptions (e.g., Poiseuille’s law) are better met.

Besides their obvious fundamental physiological relevance, laws governing blood distribution and cardiovascular architecture have a clinical relevance, playing a role in a variety of vascular pathologies. In the cerebrovasculature in particular, pathogenesis and pathophysiology of diseases such as intracranial aneurysms are thought to be linked to vascular architecture and flow distribution among the cerebral arteries. Vessel calibre power laws have been used to study the deviation from this assumed optimum and its assumed link to aneurysm initiation (Baharoglu et al., 2014; Bor et al., 2008). In addition, these laws have been extensively used to estimate outlet boundary conditions for computational fluid dynamics models (Janiga et al., 2015) or for other applications such as segmentation or generation of model of cerebrovascular branching (Jiang et al., 2011; Rempfler et al., 2015). In the cerebrovasculature, studies have reported that carotid arteries and their daughter branches followed the Murray’s law (Rossitti and Lofgren, 1993a, b), while others have shown that they do not (Beare et al., 2011; Ingebrigtsen et al., 2004). In addition, while the cerebrovasculature architectures are often readily available from clinical angiography, study of both the architecture and the blood flow distribution is rarely possible in vivo, limiting those studies to the vascular geometry only.

Therefore, questions remain concerning the validity of this principle of optimality, since findings are discordant, and have concentrated only on the relationship of the relative calibres of parent and branch vessels, not the flow rates themselves. Taking unique advantage of a cohort that had both 3D angiography and phase-contrast MRI data available, the present study investigated the power law relationships among vessel calibres and flow rates based on these in vivo measurements at a particular site: the internal carotid artery (ICA) terminus, where the C7 segment of the ICA bifurcates to the anterior cerebral artery (ACA) and middle cerebral artery (MCA). With these in vivo data, we could directly test the validity of the Murray’s “cube law” for a representative large artery bifurcation and, more generally, inter- and intraindividual variations in power laws.
2. Materials and Methods

2.1. Patient population and imaging

The study focused on consecutive patients enrolled in a study that evaluated the value of phase contrast MRI (PC-MRI) velocity measurement on the prediction of outcomes for brain aneurysms intended to be treated by endovascular approach (Pereira et al., 2015). Patients with carotid or intracranial stenosis or vascular abnormalities were excluded. A total of 31 patients were included prospectively after institutional ethical board approval (NEC 07-056), having aneurysms at the ICA (N=27), MCA (N=1), or anterior communicating artery (N=3). Patient age ranged from 27 to 79 years (mean 53) and 77% female.

The patients were imaged prior to the treatment, with phase-contrast magnetic resonance (PC-MRI). Briefly, PC-MRI measures the blood flow velocity by means of bipolar magnetic field gradients inducing an additional phase to the excited spins proportional to the velocity component in the gradient direction (Bryant et al., 1984). In time-resolved 3D (i.e., 4D) PC-MRI, the three components of the full velocity field are assessed by imposing subsequently three orthogonal gradients as described in detail, with various applications, in Markl et al. (2012). The 4D PC-MRI flow sequence was adapted for intracranial flow investigations: field-of-view 190x210mm with acquisition (reconstruction) voxel size of 1mm isotropic (0.8mm isotropic); 32 slices (adjusted according to volume-of-interest size) of thickness 1mm spaced by 1mm; SENSE acceleration factor 2; repetition/echo times of 4.6/2.9ms (shortest); flip angle 5°; and background phase error correction. The volume of interest enclosed the whole aneurysm volume and adjacent parent vessel. The sequence was triggered with heartbeat using a peripheral pulse unit. A balanced (Hadamard) velocity encoding insured an isotropic variance on the velocity magnitude while the Velocity Sensitivity Encoding parameter was set to 80 cm/s, as recommended for intracranial arteries to minimize possible aliasing artefacts without degrading the signal to noise ratio. For a typical heart rate of 65 beats per minute (bpm), the number of cardiac phases was 16 and the acquisition time was about 13 minutes. In addition, for each patient, a 3D rotational angiogram (3DRA) of the ICA carrying the aneurysm was acquired during the endovascular procedure. Angiograms were performed with a biplane C-arm (Allura FD20 - Philips Healthcare, Best, The Netherlands) made of 180 projection images covering 210° around the region of interest while injecting the contrast agent in the ICA.

2.2. Measurements of geometrical and flow quantities

For each subject, cycle-averaged volumetric flow rates and cross-sectional areas were measured. The mean flow rate was measured by integrating, over the cardiac cycle, the through-plane velocity over the lumen cross-sectional area at every time frame using a recently-described method (see Bouillot
et al., 2017). In this method, the partial volume artefacts affecting 4D PC-MRI velocities were detected and subsequently corrected using the complementary 3DRA vessel geometry information, ensuring robust blood flow derivation. Measurement slices (illustrated in Figure 1a) were placed at the terminal part of the (parent) ICA, corresponding to the C7 level downstream of the posterior communicating and anterior choroidal arteries; and at the two daughter branches, namely the M1 segment of the MCA and the A1 segment of the ACA. The slices used for measurements were oriented perpendicularly to the vessel centerline with 1mm inter-plane distance. Depending on the branch geometries and lengths, three to five measurements for each branch were made. For each branch, the average of these measurements was used for the present study, with the standard deviations quantifying measurement variability.

Although 3D time-of-flight MRA were acquired along with PC-MRI for each patient, the vessel lumen was digitally reconstructed from the 3DRA images acquired during the intervention, owing to their superior spatial resolution and contrast, which is especially important for accurate measurement of the smaller ACA and MCA diameters. An interactive watershed analysis on the image gradient was applied, which depends minimally on the operator. Each reconstructed 3D lumen was then subjected to a novel fully-automated geometric characterization. As illustrated in Figure 1b, centrelines were first generated in the lumen model and were used to identify the branching points of the bifurcations. Cross-sectional areas were computed at each bifurcation point and converted to diameter under the assumption of a circular cross-section. Further details of these robust, automated techniques are provided in Chnafa et al. (2017b). In order to mitigate the local variations in diameters and the vessel flare at the bifurcation, the diameters were averaged from the bifurcation point to a point placed two diameters from the bifurcation, either upstream (for the parent artery) or downstream (for the daughter arteries). If a new branch arose before that point, the point was placed at this bifurcation point.

2.3. Determination of junction exponents

As detailed in the Introduction, it has been suggested that arterial bifurcations are designed to minimize the work required for blood to flow throughout the cardiovascular network. The theoretical basis for this optimality principle of minimum work was initially described by Murray (1926). The relationship between blood flow rate (Q) and internal vessel diameter (D) is expressed as a power law, i.e. \( Q = k D^n \), where k is a constant encompassing the patient characteristics (e.g., blood viscosity, metabolic cost for maintaining blood and vessel wall tissue, etc.), while the junction exponent n is an indirect measure of the division of flow at the bifurcation. Assuming k is the same for all branches, it
follows from the conservation of flow rate among the branches that the junction exponent $n$ is
defined by the equation,

$$D_{ICA}^n = D_{ACA}^n + D_{MCA}^n,$$

where the indices refer to the physiological names of the branches in our particular case. We will
refer to this equation as the geometrical relationship and the exponent of this relation as the
generical exponent. But thanks to the assumed power law relationship between the blood flow
rate ($Q$) and the internal vessel diameter ($D$), ratios can be derived from it, one of them being:

$$\frac{Q_{ACA}}{Q_{MCA}} = \left(\frac{D_{ACA}}{D_{MCA}}\right)^n$$

We will refer to this equation as the flow split relationship and the exponent of this relation as the
flow split exponent. (Note that this particular equation requires no information about the parent
artery, compared to the previous equation which does, an observation that will be discussed later.) If
the assumptions of Murray are valid for this arterial territory, the exponent should be $n=3$ for both of
these equations. Using the measured diameter and flow rate data, we solved these equations for $n$,
for each subject, using numerical root finding methods.

2.4. Statistical analyses

Paired t-tests were used to test the significance of the differences between the geometrical and flow
split exponents. Power law relationships between diameters and flow rates (or their ratios) were
determined using least-squares linear regressions on the log-transformed data. Linear regressions
and/or Pearson correlation analyses were used to test for relationships between other selected
variables. All statistical analyses were performed using Prism 6.0 (Graphpad Software, San Diego,
CA). Significance was assumed at the level of $p<0.05$.

3. Results

Of the 31 cases, three were excluded because the aneurysmal sac was present within the integration
length; one was excluded because of a hypoplastic branch; and another because the M1 could not be
reliably segmented owing to the presence of a closely adjacent vessel, which would have impacted
the computation of the MCA diameters. We therefore analysed 26 bifurcations at this C7 junction
(age=53±11 years, range: 33-79; 73% female). Of these, in two cases we could not reliably quantify
the flow rates in one of the daughter branches, meaning we could compute the flow split for only 24
bifurcations. The resulting 3DRA diameter and 4D PC-MRI flow measurements are shown in Table 1,
and were well within the physiological ranges usually reported (Fahrig et al., 1999; Krejza, 2006). At
the C7 junction, the geometrical exponent was 2.06 ± 0.44 (95% CI: 1.89-2.24) and the flow split exponent was 2.45 ± 0.75 (95% CI: 2.21-2.77). Note that these both exclude the theoretical optimum exponent of 3, and are significantly lower.

Figure 2a shows that, *intraindividually*, there was no obvious relationship between the geometrical and flow split exponents. Moreover, it shows the wide *interindividual* variation of these exponents among the subjects, ranging from 1.24 to 3.46 for the geometrical exponent, and 1.23 to 3.95 for the flow split exponent. On the other hand, Figure 2b shows that the flow split between the ACA and MCA was well predicted by a power law fit to the diameter ratio, with exponent n=2.17 (95% CI: 1.87-2.47, R²=0.63). As shown in Figure 3a, some of the wide *interindividual* variation in the geometrical exponent could be explained by a significant (p=0.003) inverse relationship with age; however, per Figure 3b, there was no such age dependence for the flow split exponent (p=0.45). Finally, Figure 4, shows that when parent and daughter vessels were pooled together (N=71), flow rates were strongly predicted by diameter via a power law, with exponent n=1.96 (95% CI: 1.70-2.22, R²=0.77).

4. Discussion

4.1. Summary

To our knowledge, this work constitutes the first human study of both geometrical and flow rate characteristics of the ICA terminal bifurcation, and on the relation between the diameter and flow ratios of the daughter branches. As expected for a large artery bifurcation such as this, our findings are at odds with Murray’s “cube law” (Murray, 1926; Sherman, 1981), since confidence intervals for power law fits to flow split vs. diameter ratio and flow rate vs. diameter both excluded n=3. On the other hand, the confidence intervals included n=2, quantitatively supporting the validity of a “square law” at the ICA terminal bifurcation. In addition, our data showed age dependence for the geometrical exponent, but not the flow split exponent. In addition to providing insight into cerebrovascular physiology, these findings may be used to estimate flow rates in ‘patient-specific’ cerebrovascular models when only the vascular anatomy is measured (e.g., Chnafa *et al.*, 2017a).

4.2. Interindividual relationship

Paired t-tests revealed no significant difference between the means of the geometrical and flow split exponents (p=0.055). Therefore our data would seem to suggest that, for a broader population, the same power law holds for the parent vs. daughter diameters on the one hand, and the daughter flow split vs. daughter diameters on the other. This result hinges on the presumed power-law relationship between blood flow rate and internal vessel diameter (Q = k Dⁿ). Differences between geometrical
and flow split exponents would mean that this relationship varies for each vessel and/or subject. The assumptions of a constant exponent and constant coefficient k boils down to assuming that the characteristics of a population can be encoded into simple population-averaged parameters, which seems to be the case here, at least in an average sense. On the other hand, even if the means of the two different junction exponents were not significantly different, for each exponent (i.e. geometrical based or flow based), wide interindividual differences were observed (see Figure 2), something that has previously been reported based on magnetic resonance angiography of healthy volunteers (Mut et al., 2014). The implication of this is that the mechanisms of adaptation of vessel calibres to flow can vary widely depending on the individual, as can the flow rate distributions themselves.

### 4.3. Intraindividual relationship

Similarly, the present data have demonstrated wide intraindividual differences in diameter-based vs. flow-split-based relationships – at least wide with respect to variations that could be attributed to uncertainty in imaging and reconstruction processes. As clearly seen in Figure 2a, the two junction exponents showed no significant relationship (i.e., R²<10⁻²). These intraindividual differences imply that the in vivo conditions can vary widely from the assumptions made by Murray. This is understandable, since cerebral arteries at this location feature curved geometries with non-uniform cross sections; blood flow is pulsatile with potential flow instabilities (Khan et al., 2017); and the vessel walls are compliant. Especially within the tortuous ICA, the velocity profile can differ greatly from a parabolic profile. Obviously, Murray’s principle is derived from an optimum model, based on an abstraction of a complex biological system; an absolute accuracy is not expected, and the influence of the pulsatility (Painter et al., 2006), flow regime (Uylings, 1977), or blood rheology (Revellin et al., 2009) have been shown before.

### 4.4. Age and exponents relationship

Interestingly, per Figure 3a, a significant inverse relationship between age and the geometrical exponent was present in our data (Pearson r=-0.55, p=0.003). This was found to be a consequence of the positive correlation of the C7 (i.e., distal ICA) diameter with age (Pearson r=0.40, p=0.042), since there was no significant correlation with age for either ACA or MCA diameters, i.e. because of the polynomial relationship among the different diameters of the bifurcation, an increased C7 diameter with age means a reduced geometrical exponent. This is consistent with a report of age-related reduction in carotid terminal bifurcation area ratio (i.e., ACA+MCA areas divided by C7 area), which was driven by a significant increase in C7 diameter with age (Ozdogmus et al., 2008). An age-related increase of the common carotid artery diameter has also been reported previously (Bonithon-Kopp et al., 1996; Denarie et al., 2000), although it is unclear whether this reflects atherosclerotic changes in the wall or vascular remodelling responsible for loss of vessel elasticity with age. Since we did not
control for traditional cardiovascular risk factors in our sample, it is possible that any age-related increase in C7 diameter may simply reflect the fact that endothelial dysfunction and/or arterial stiffness are more likely to be found in older subjects. Interestingly, however, the flow split exponent was not affected by the age since, as noted above, we found no significant correlation between age and the diameters of the ACA or MCA, nor any age-dependence of ICA, ACA or MCA flow rates. This reinforces an advantage of the flow split power law noted in the Methods, namely that, unlike the geometrical power law, it does not depend on measurements from the parent artery.

4.5. Relationship between vessel diameter and flow rate

Since the two equations used in this study come from assumptions linking the blood flow rate to lumen diameter ($Q = k D^n$), it was interesting to see that when diameters and flow rates were pooled together, they were fit well by something very close to the square law (Figure 4). This seems to contradict a previous study (Cebral et al., 2008), which demonstrated a cube law fit ($R^2=0.81$) between flow rates and diameters of the left and right ICA and vertebral arteries (VA) based on PC-MRI measurements of 11 normal subjects. A possible explanation for this discrepancy is the diameter (actually, area) measurements in that study were derived as a by-product of a pulsatility-based segmentation technique, which while robust for measuring flow rates, may be more susceptible to overestimation of areas for the smaller VA vs. the larger ICA, something that could serve to distort the overall shape of the fitted curve. This is in contrast to the present study, which used high-resolution 3DRA for lumen boundary segmentation and diameter measurement. Furthermore, as pointed out by Valen-Sendstad et al. (2015): “Reanalyzing the data by separating VA and ICA measurements, we found a power law coefficient of $n=3.1\pm0.4$ for the VA and $n=1.8\pm1.0$ for the ICA. Although suggestive of cube and square laws, respectively, these power law coefficients were not statistically significantly different.”

Fitting a power law to each group of arteries in the present study, the ACA showed a square law fit, with $n=1.98$ (95% CI: 1.29 to 2.67, $R^2=0.62$), whereas there was no significant relationship between flow rates and diameter for either the MCA and ICA, i.e., the confidence intervals on the exponents included zero. So while pooled artery data may be well represented by a simple power law relationship between diameter and flow rate, an individual artery’s flow rate cannot necessarily be estimated from its diameter via a simple power law. Several effects might add up, e.g. the constant $k$ might actually depend on the artery. However, if $k$ really were different for the different vessels, i.e., different for ICA vs. MCA vs. ACA, then the $k$’s would not cancel out of the flow split or the geometrical equations. On the other hand, if $k$ would vary only interindividually, that would not affect the flow split and geometrical equations since, again, the individual’s $k$ would cancel out, but it
would affect the plot of \( Q \) vs. \( D^n \) when all the individuals are considered. Thus, it may not be the ‘k’ that is the problem, but rather just the physiological scatter from the simplistic power law model.

These points warrant further investigation since, as discussed below, they have implications for computational fluid dynamics (CFD) modelling, where estimations of flow rate from diameter are routinely relied upon. It is also interesting to note the increasing scattering of the flow rates with the larger diameters i.e. for MCA and especially ICA in comparison with ACA. This scatter implies that for the ICA, and to a lesser extent the MCA, the blood flow rate cannot be encoded in simple population averaged scaling parameters. The local hemodynamics may be responsible for this, since secondary flows induced by the curvature in the ICA, which has wide variation interindividually (Sangalli et al., 2009), will affect the blood flow velocity profile to differing degrees, and thus the suitability of a simple power law.

4.6. Implications and relationship to previous studies

As noted above, a direct application of our results stems from the need, in the hemodynamics research community, for modelling outflow splitting. Recently, retrospective studies using image-based CFD of cerebral aneurysms have demonstrated associations between local hemodynamic features and rupture status (Cebral et al., 2011; Miura et al., 2013; Xiang et al., 2011). One of the major advantages of such studies is that they allow for the indirect estimation and spatial distribution of WSS. These local blood features are, however, impacted by various modelling assumptions and uncertainties (Kallmes, 2012). The emulation of in vivo conditions is restricted notably by the fact that patient-specific flow rates are rarely available, and most investigations resort to diameter-based scaling laws to estimate them. Here, our observation that the flow splitting can be predicted robustly by a power law even if the individual flow rates themselves cannot provides a rationale for the development of models computing the flow splitting locally at each bifurcation; like here at the C7 territory (i.e., Figure 3b), our data also show that this relationship at the terminal ICA bifurcation does not depend on age, and thus can be used generally.

Even though our mean flow split exponent of 2.45 suggests something between a square and cube law, the power law fits between diameter and flow ratios on the one hand (\( n=2.17 \), per Figure 2b) and diameters and flow rates on the other (\( n=1.96 \), per Figure 4) point to a square law. As hinted at by Zamir et al. (1992) and then demonstrated by Valen-Sendstad et al. (2015), a cube law would tend to accentuate the effect of extreme ratios of diameters. In this regard, it is instructive to consider measured flow rates reported in the literature, and especially the flow rate ratio between the ACA and MCA daughter branches. Per Table 2, the sample-size-weighted average ratio from those studies is 0.59 (95% CI: 0.52–0.66). Interestingly, for the cases in the present study, the ACA/MCA flow ratio
based on the mean of their diameter ratio (i.e., 0.75, per Table 1) comes out to 0.56 using a square law, but only 0.42 using a cube law. So, in addition to avoiding the larger variance of the results inevitable with a cube law, the square law shows better accuracy against values from healthy subjects in the literature. Thus, use of a square law results in flow splits that demonstrably fall within a physiological range, whereas non-physiologically (or at least unlikely) skewed values are observed if the flow splitting is based on the cube law. In short, the literature also supports our observation of the suitability of a square law versus a cube law.

On the other hand, our findings appear to be at odds to those for Ingebrigtsen et al. (2004), who reported a geometrical exponent of $1.7 \pm 0.8$ for the ICA terminal bifurcation, which has a lower mean and higher standard deviation compared to our finding of $2.06 \pm 0.44$. Although this could be attributed to the different cohorts, we noted that those authors measured diameter at a single location for each branch (two diameters upstream or downstream of the bifurcation). Following their point-wise definition of diameter (c.f., our approach based on averaging over a two-diameter-long segment, per Figure 1b), we obtained, for our cohort, a lower geometrical exponent of $1.82 \pm 0.73$, which is closer to that of Ingebrigtsen et al., and also a significantly larger standard deviation than the results using our averaging method (F-test, $p=0.018$). Furthermore, using their point-wise approach to measure diameter, the significant relation we found between age and the geometrical exponent disappeared because of the wider scattering of the geometrical exponent ($0.80-3.70$ vs. $1.24-3.46$). In past studies, vessel diameters have been measured at a variety of locations, typically defined in terms of some nominal distance from a user-identified landmark like the bifurcation apex, and often varying in definition from study to study. In short, the above discussion highlights that the choice of diameter measurement method can have an appreciable impact on the derived power law exponent, something we attempted to ameliorate in our study by using robust and objective averaging approach to avoid the potential pitfalls of subjectively-chosen point-wise values. Likewise, we took advantage of state-of-the-art 3D imaging modalities, and robust segmentation and flow rate assessment methods in order to minimize the potential methodological biases.

4.7. Limitations

It might be perceived that a limitation, or at least an inconvenience, of our method is its reliance on cross-sectional areas to compute the mean diameters. We therefore also redid our analyses using the diameters of maximally inscribed spheres, which are conveniently provided as a by-product of the Vascular Modelling ToolKit (VMTK; www.vmtk.org)-based centreline algorithm that we used, and are equivalent to the minimum projected diameter of a vessel. This approach actually gave more robust results (e.g. cases with fused arteries could be treated) since variations of the lumen diameter
along the vessel are more weakly taken into account. However, this technique underestimated the 
diameters (e.g. for the ICA, by 15%), which is a trade off for robustness. Overall, however, the 
conclusions did not change and results were not significantly different. Thus, as the impact was 
considered negligible, we chose to base our analyses on the more accurate cross-sectional areas.

The present study has several other potential limitations. The sample size is relatively small, 
constituted mainly by females, and the subjects were patients who harbour aneurysms. Owing to 
relatively long scan times, it is difficult to acquire 4D PC-MRI data for large cohorts in a clinical 
setting, and, obviously, it would have been impossible to acquire 3DRA data for control healthy 
subjects. However, the flow split seemed not be affected by the presence of the aneurysm since, as 
shown in Table 2, our results were similar, on average, to those from studies of normal subjects. 
Moreover, as highlighted by the dark (red) circles in Figure 2, four cases with aneurysms more distal, 
at the MCA or anterior communicating artery, seemed to overlap with the (majority of) cases having 
ICA aneurysms. In addition, the vessel diameters we reported fall into the range of other 
physiological measurements (Fahrig et al., 1999). Ingebrigtsen et al. (2004) also showed that the 
bifurcation exponent was not predictive of the presence of aneurysm, reinforcing the confidence in 
our results. We also took care to exclude cases for which the aneurysmal sac was too close of the ICA 
terminal bifurcation. We note, however, that those excluded cases did feature larger daughter 
vessels downstream of the sac, as reported by Baharoglu et al. (2014) and thus abnormally high 
geometrical exponents (n>4). Baharoglu et al. suggested that these bifurcations with abnormal 
geometrical exponents might be prone to a shift toward abnormal hemodynamics, possibly causing 
endothelial damage and eventual aneurysm formation, thus constituting a means of evaluation of 
aneurysm initiation. Given the wide range of exponents shown in the present study, and also by 
Ingebrigtsen et al. (2004), and the fact that abnormally high exponents seem to be mostly due to the 
presence of the sac, we would be cautious to conclude anything concerning a causative role of 
geometrical exponent in aneurysm initiation. Another point giving confidence in our results is that 
we found the ratio of daughter flow rates to be close to literature values from normal subjects, which 
suggests that aneurysmal cases keep the same mean ratio. This encourages the broad application of 
our findings to cerebrovascular model studies, whether of aneurysmal or normal cases. This also 
need not be limited to 3DRA, since diameter measurements, when carefully performed and 
calibrated, could be derived from 3D MR or CT angiography.

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Table 1: Geometrical and flow measurements (mean ± standard deviation).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>mean±stdev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameters [mm]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>26</td>
<td>3.52 ± 0.34</td>
</tr>
<tr>
<td>ACA</td>
<td>26</td>
<td>2.09 ± 0.33</td>
</tr>
<tr>
<td>MCA</td>
<td>26</td>
<td>2.80 ± 0.26</td>
</tr>
<tr>
<td>Diameter ratio (D_{ACA}/D_{MCA})</td>
<td>26</td>
<td>0.75 ± 0.13</td>
</tr>
<tr>
<td>Geometrical exponent (n)</td>
<td>26</td>
<td>2.06 ± 0.44</td>
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<tr>
<td>Flow rates [mL/s]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>23*</td>
<td>3.25 ± 0.77</td>
</tr>
<tr>
<td>ACA</td>
<td>24</td>
<td>1.09 ± 0.40</td>
</tr>
<tr>
<td>MCA</td>
<td>24</td>
<td>2.09 ± 0.45</td>
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<tr>
<td>Flow ratio (Q_{ACA}/Q_{MCA})</td>
<td>24</td>
<td>0.53 ± 0.19</td>
</tr>
<tr>
<td>Flow split exponent (n)</td>
<td>23†</td>
<td>2.45 ± 0.75</td>
</tr>
</tbody>
</table>

*For one case the C7 flow rate could not be measured.
†For one case with diameter and flow ratio close to 1, flow split exponent could not be defined.

Table 2: Literature review of the ratio of flow rates going through the A1 and M1 segments of the ACA and MCA. The average is weighted by the number of subjects (N) of each study. When left and right sides were reported, a mean ratio has been computed.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>94</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>14</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>Q_{ACA} / Q_{MCA}</td>
<td>0.56</td>
<td>0.72</td>
<td>0.58</td>
<td>0.64</td>
<td>0.60</td>
<td>0.69</td>
<td>0.56</td>
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</table>
Figure 1: Definition of the vessel-specific characterization. (a) Vessels reconstructed from 3DRA and illustration of the 4D PC-MRI flow rate measurements on four slices for the MCA. (b) The reported diameters are computed from measurements starting at the bifurcation point (red spheres) to a distance L (black spheres) equivalent to two bifurcation diameters (subscripted 0). Note that for these ICA cases, the path of integration of the diameter does not reach the (proximal) aneurysm location; otherwise this case would have been excluded from the study.
Figure 2: (a) Wide interindividual and intranindividual variations in geometrical and flow split exponents. Shown also is the line of unity. (b) Flow division between ACA and MCA is well predicted by their diameter ratio via a power law. For both plots: error bars were calculated as the standard deviation of the within-subject flow measurements; and the dark (red) symbols highlight the subset of four cases with an aneurysm at a territory other than ICA (see Discussion).

Figure 3: (a) Significant inverse dependence of the geometrical exponent with age. (b) Lack of relationship between the flow split exponent and age. Shown in both plots are the linear regressions, with $R^2$ at top right.
Figure 4: Cycle-average flow rate (Q) vs. diameter (D) for parent and branch data pooled together. The solid line is the best-fit power law.