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Journal of
NeuroInterventional Surgery

**The role of distal cerebral vasculature in vessel constriction
after aneurysm treatment with flow-diverter stents**

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Keywords:	Blood Flow, Aneurysm, Flow Diverter, Ultrasound

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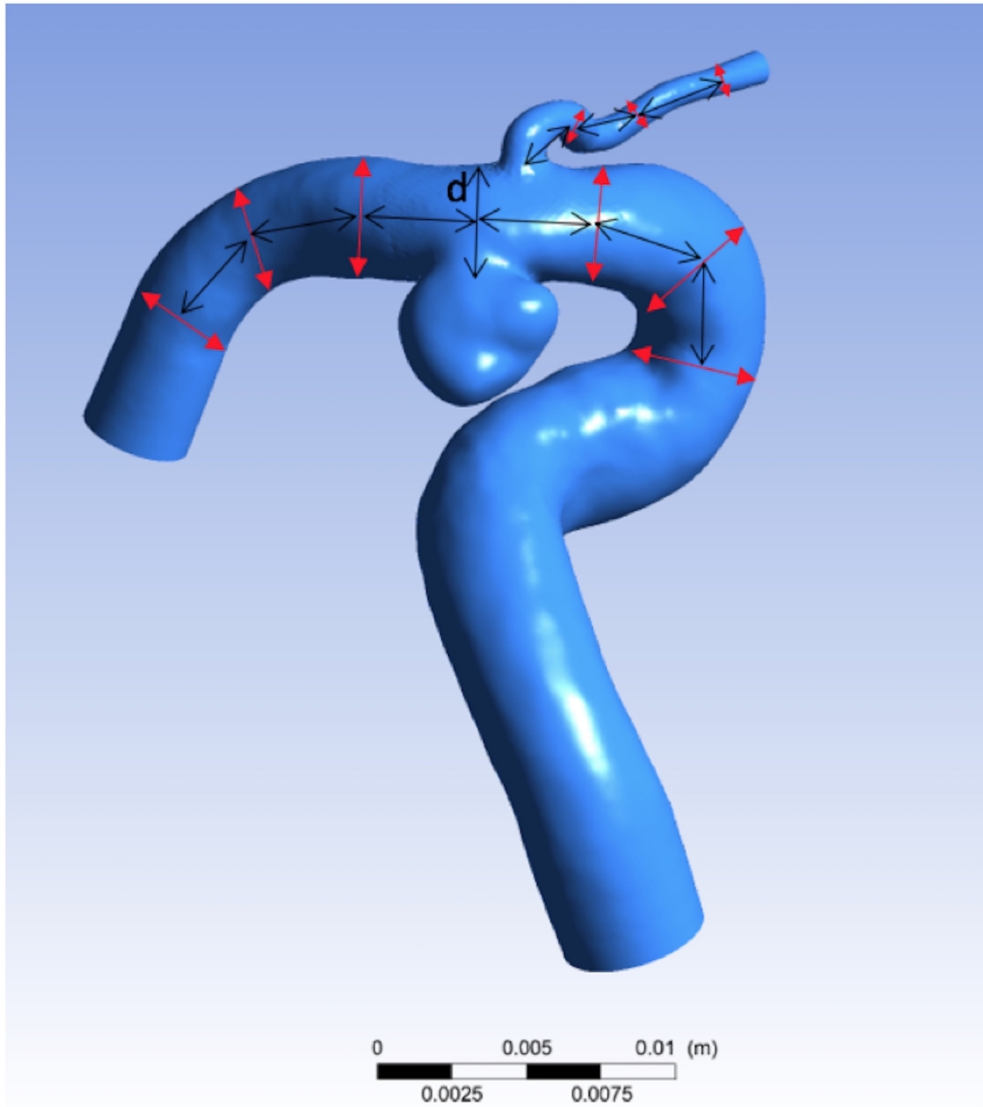


Fig 1 (online suppl.) Measurement protocol followed to extract bifurcation-vessel diameter values. Red arrows indicate approximate locations of measurements, black arrows indicate approximate distances (d = parent vessel lumen diameter at aneurysm location) among consecutive measurements locations. A similar measurement protocol was followed for aneurysms at other locations.

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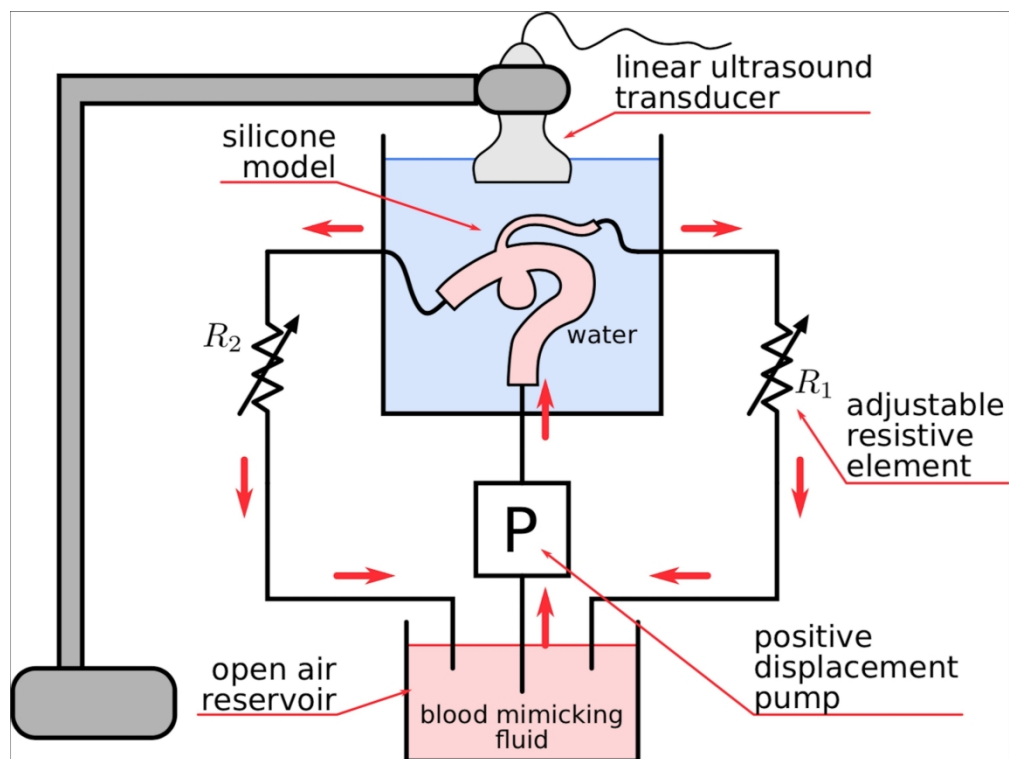


Fig 2 (online suppl.) Closed loop circuit filled with ultrasound compatible blood mimicking fluid and connected to a programmable pump. Silicone models were produced based on patient-specific geometry.

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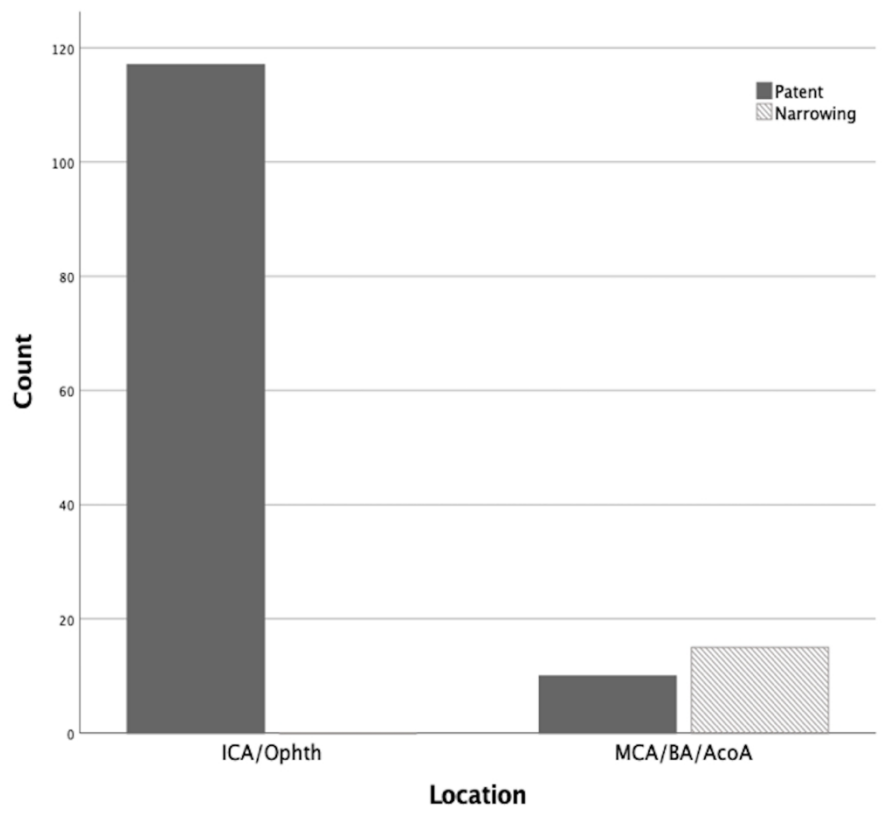


Fig 3 (online suppl.) Graph showing distribution of vessel narrowing (shadowed grey) and patent (dark grey) jailed vessels subgroup by location of aneurysm in internal carotid artery (ICA)/ophthalmic artery (OphthA) (left) and in middle cerebral artery (MCA)/basilar artery (BA)/anterior communicating artery (AcoA) bifurcations (right).

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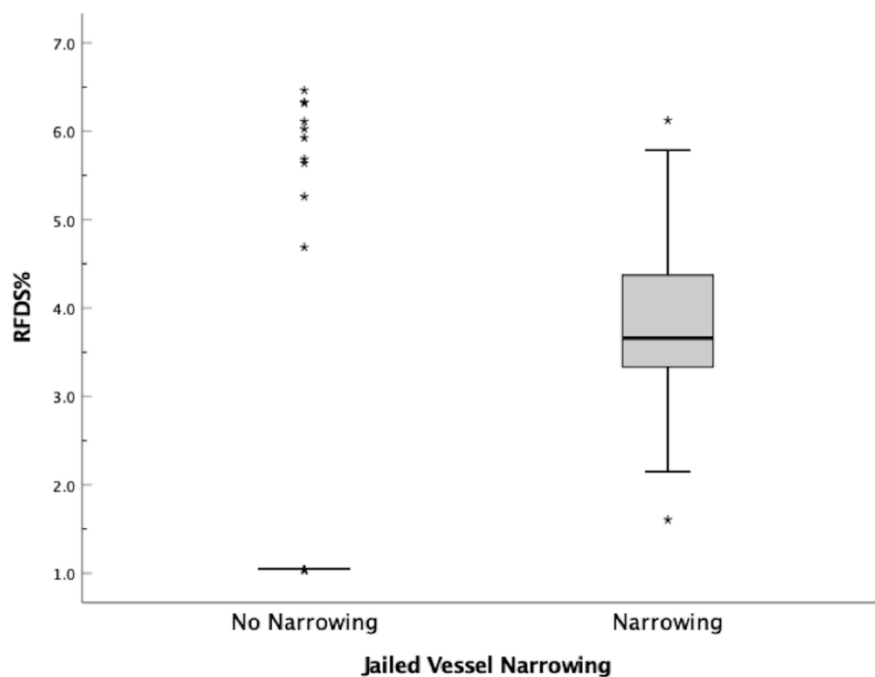


Fig 4 Whisker plots showing distribution of FDS resistance to flow as a percentage of overall jailed vessel vascular resistance (RFDS%) for datasets showing jailed vessel patency (left, mean = 1.048, lower bound = 1.046, upper bound = 1.05) and narrowing (right, mean = 3.7, lower bound = 3.33, upper bound = 4.5).

Solid lines within the boxes indicate median values. Each boxplot describes first quartile values (bottom black line), median values (middle black line), and third quartile values (top black line). Error bars (whiskers) show minimum (bottom black bar) and maximum (top black bar) values. Stars denote outliers identified by using the maximum normed residual test.

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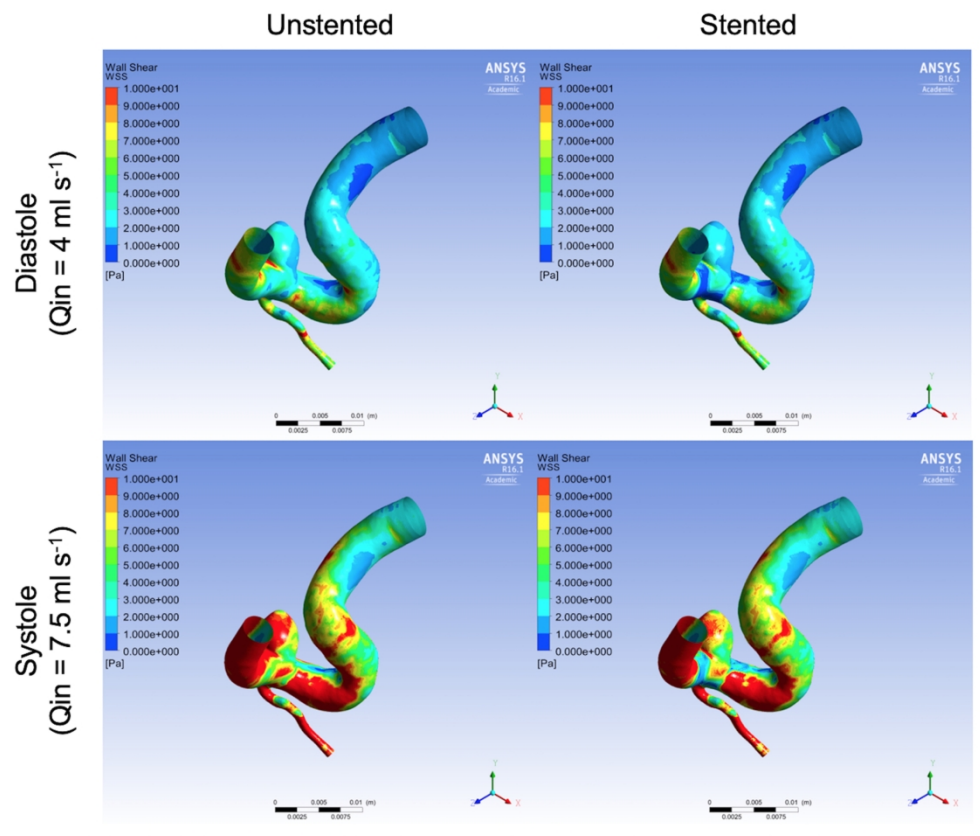


Fig 5 WSS contours at peak systole ($Q_{in} = 7.5 \text{ ml s}^{-1}$) for the unstented (top left) and stented (top right) models. WSS contours at end diastole ($Q_{in} = 4 \text{ ml s}^{-1}$) for the unstented (bottom left) and stented (bottom right) models.

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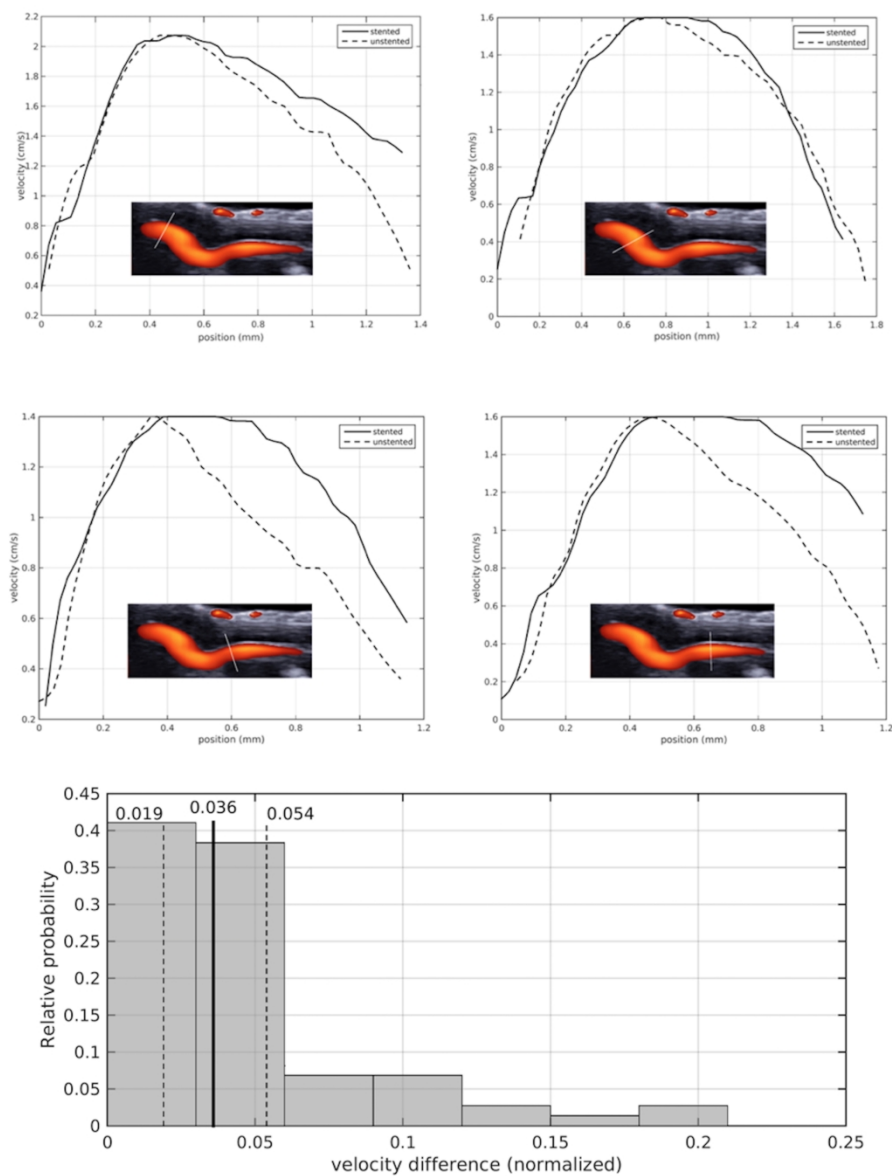


Fig 6 (Top) Velocity profile PD-US measurements (for $Q_{in} = 4 \text{ ml s}^{-1}$) for the unstented (dashed line) and stented (solid line) replicas. The in-box images show the PD-US images and the locations along the OphthA where the velocity measurements were extracted (flow in OphthA directed left-to-right in in-box images). (Bottom) Normalized velocity discrepancy obtained from 75 measurements taken at different locations along the OphthA. The continuous line indicates the median value and the dashed lines represent quartiles Q1 and Q3.

101x128mm (600 x 600 DPI)

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3 **Fig 1** (online suppl.) Measurement protocol followed to extract bifurcation-vessel diameter
4 values. Red arrows indicate approximate locations of measurements, black arrows indicate
5 approximate distances (d = parent vessel lumen diameter at aneurysm location) among
6 consecutive measurements locations. A similar measurement protocol was followed for
7 aneurysms at other locations.
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15 **Fig 2** (online suppl.) Closed loop circuit filled with ultrasound compatible blood mimicking
16 fluid and connected to a programmable pump. Silicone models were produced based on
17 patient-specific geometry.
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23 **Fig 3** (online suppl.) Graph showing distribution of vessel narrowing (shadowed grey) and
24 patent (dark grey) jailed vessels subgroup by location of aneurysm in internal carotid artery
25 (ICA)/ophthalmic artery (OphthA) (left) and in middle cerebral artery (MCA)/basilar artery
26 (BA)/anterior communicating artery (AcomA) bifurcations (right).
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33 **Fig 4** Whisker plots showing distribution of FDS resistance to flow as a percentage of overall
34 jailed vessel vascular resistance (RFDS%) for datasets showing jailed vessel patency (left,
35 mean = 1.048, lower bound = 1.046, upper bound = 1.05) and narrowing (right, mean =3.7,
36 lower bound = 3.33, upper bound = 4.5). Solid lines within the boxes indicate median values.
37 Each boxplot describes first quartile values (bottom black line), median values (middle black
38 line), and third quartile values (top black line). Error bars (whiskers) show minimum (bottom
39 black bar) and maximum (top black bar) values. Stars denote outliers identified by using the
40 maximum normed residual test.
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51 **Fig 5** WSS contours at peak systole (Q_{in} = 7.5 ml s⁻¹) for the unstented (top left) and stented
52 (top right) models. WSS contours at end diastole (Q_{in} = 4 ml s⁻¹) for the unstented (bottom
53 left) and stented (bottom right) models.
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3 **Fig 6** (Top) Velocity profile PD-US measurements (for $Q_{in} = 4 \text{ ml s}^{-1}$) for the unstented
4 (dashed line) and stented (solid line) replicas. The in-box images show the PD-US images and
5 the locations along the OphthA where the velocity measurements were extracted (flow in
6 the locations along the OphthA where the velocity measurements were extracted (flow in
7 OphthA directed left-to-right in in-box images). (Bottom) Normalized velocity discrepancy
8 obtained from 75 measurements taken at different locations along the OphthA. The
9 continuous line indicates the median value and the dashed lines represent quartiles Q1 and
10 Q3.
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Table 2 Quantification of FDS-induced changes to haemodynamic variables extracted from OphthA bifurcation at peak systole (peak) and end diastole (dia). Avg WSS is the space-averaged WSS extracted from the OphthA. ICA and Ophth outflow are the volumetric flow rates calculated at the outlet of the ICA and OphthA, respectively.

	<i>Unstented</i> [peak/dia]	<i>Stented</i> [peak/dia]	<i>Diff</i> [peak/dia]	<i>%Diff</i> [peak/dia]
<i>Avg WSS [Pa]</i>	11.56/5.30	10.98/5.04	-0.58/-0.26	-5.0/-4.7
<i>ICA outflow [ml/s]</i>	7.20/3.80	7.19/3.82	-0.01/-0.02	0.1/0.5
<i>Ophth outflow [ml/s]</i>	0.38/0.20	0.38/0.201	0.0/0.001	0.0/0.5

Dataset	Location	J-Ves Narrowing	J-Vess Diam [mm]	J-Vess R [mmHg s ml ⁻¹]	Periph R [mmHg s ml ⁻¹]	R _{FDS} [mmHg s ml ⁻¹]	%R _{FDS}
1	ICA	NO	1.09	8	470	5	1.04
2	ICA	NO	1.05	10	470	5	1.04
3	ICA	NO	1.08	9	470	5	1.04
4	ICA	NO	1.07	9	470	5	1.04
5	ICA	NO	1.08	9	470	5	1.04
6	ICA	NO	1.16	6	470	5	1.05
7	ICA	NO	1.07	9	470	5	1.04
8	ICA	NO	1.24	5	470	5	1.05
9	ICA	NO	1.06	9	470	5	1.04
10	ICA	NO	1.13	7	470	5	1.05
11	ICA	NO	1.23	5	470	5	1.05
12	ICA	NO	1.09	8	470	5	1.05
13	ICA	NO	1.30	4	470	5	1.05
14	ICA	NO	1.14	7	470	5	1.05
15	ICA	NO	1.11	8	470	5	1.05
16	ICA	NO	1.13	7	470	5	1.05
17	ICA	NO	1.17	6	470	5	1.05
18	ICA	NO	1.21	6	470	5	1.05
19	ICA	NO	1.17	6	470	5	1.05
20	ICA	NO	1.11	8	470	5	1.05
21	ICA	NO	1.15	7	470	5	1.05
22	ICA	NO	1.15	7	470	5	1.05
23	ICA	NO	1.27	5	470	5	1.05
24	ICA	NO	1.15	7	470	5	1.05
25	ICA	NO	1.19	6	470	5	1.05
26	ICA	NO	0.98	13	470	5	1.04
27	ICA	NO	1.10	8	470	5	1.05
28	ICA	NO	1.16	6	470	5	1.05
29	ICA	NO	1.16	7	470	5	1.05
30	ICA	NO	1.19	6	470	5	1.05
31	ICA	NO	1.10	8	470	5	1.05
32	ICA	NO	1.18	6	470	5	1.05
33	ICA	NO	1.14	7	470	5	1.05
34	ICA	NO	1.01	11	470	5	1.04

Table 1 Demographic constitution and anatomical data of patients' population. J-Vess Diam = jailed vessel diameter, J-Vess R = jailed vessel vascular resistance, Periph R = peripheral resistance, R_{FDS}= FDS-induced resistance to flow, % R_{FDS}= FDS-induced resistance to flow given as a percentage of overall resistance (FDS plus vascular plus peripheral).

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35	ICA	NO	1.18	6	470	5	1.05	
36	ICA	NO	1.17	6	470	5	1.05	
37	ICA	NO	1.12	7	470	5	1.05	
38	ICA	NO	1.30	4	470	5	1.05	
39	ICA	NO	1.14	7	470	5	1.05	
40	ICA	NO	1.22	5	470	5	1.05	
41	ICA	NO	1.27	5	470	5	1.05	
42	ICA	NO	1.07	9	470	5	1.04	
43	ICA	NO	1.22	5	470	5	1.05	
44	ICA	NO	1.15	7	470	5	1.05	
45	ICA	NO	1.23	5	470	5	1.05	
46	ICA	NO	1.26	5	470	5	1.05	
47	ICA	NO	1.13	7	470	5	1.05	
48	ICA	NO	1.08	9	470	5	1.04	
49	ICA	NO	1.25	5	470	5	1.05	
50	ICA	NO	1.10	8	470	5	1.05	
51	ICA	NO	1.25	5	470	5	1.05	
52	ICA	NO	1.13	7	470	5	1.05	
53	ICA	NO	1.11	8	470	5	1.05	
54	ICA	NO	1.10	8	470	5	1.05	
55	ICA	NO	1.19	6	470	5	1.05	
56	ICA	NO	1.05	10	470	5	1.04	
57	ICA	NO	1.12	8	470	5	1.05	
58	ICA	NO	1.15	7	470	5	1.05	
59	ICA	NO	1.12	8	470	5	1.05	
60	ICA	NO	1.09	8	470	5	1.04	
61	ICA	NO	1.20	6	470	5	1.05	
62	ICA	NO	1.13	7	470	5	1.05	
63	ICA	NO	1.17	6	470	5	1.05	
64	ICA	NO	1.09	8	470	5	1.05	
65	ICA	NO	1.14	7	470	5	1.05	
66	ICA	NO	1.00	12	470	5	1.04	
67	ICA	NO	1.13	7	470	5	1.05	
68	ICA	NO	1.12	8	470	5	1.05	
69	ICA	NO	1.14	7	470	5	1.05	
70	ICA	NO	1.16	6	470	5	1.05	
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72	ICA	NO	1.12	7	470	5	1.05	
73	ICA	NO	1.11	8	470	5	1.05	
74	ICA	NO	1.18	6	470	5	1.05	
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	78	ICA	NO	1.05	10	470	5	1.04
	79	ICA	NO	1.17	6	470	5	1.05
	80	ICA	NO	1.12	7	470	5	1.05
	81	ICA	NO	1.14	7	470	5	1.05
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	84	ICA	NO	1.05	10	470	5	1.04
	85	ICA	NO	1.19	6	470	5	1.05
	86	ICA	NO	1.05	10	470	5	1.04
	87	ICA	NO	1.14	7	470	5	1.05
	88	ICA	NO	1.13	7	470	5	1.05
	89	ICA	NO	1.15	7	470	5	1.05
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	91	ICA	NO	1.20	6	470	5	1.05
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	94	ICA	NO	1.13	7	470	5	1.05
	95	ICA	NO	1.03	11	470	5	1.04
	96	ICA	NO	1.16	7	470	5	1.05
	97	ICA	NO	1.13	7	470	5	1.05
	98	ICA	NO	1.11	8	470	5	1.05
	99	ICA	NO	1.11	8	470	5	1.05
	100	ICA	NO	1.07	9	470	5	1.04
	101	ICA	NO	1.12	8	470	5	1.05
	102	ICA	NO	1.17	6	470	5	1.05
	103	ICA	NO	1.03	10	470	5	1.04
	104	ICA	NO	1.13	7	470	5	1.05
	105	ICA	NO	1.16	6	470	5	1.05
	106	ICA	NO	1.09	8	470	5	1.05
	107	ICA	NO	1.13	7	470	5	1.05
	108	ICA	NO	1.17	6	470	5	1.05
	109	ICA	NO	1.17	6	470	5	1.05
	110	ICA	NO	1.13	7	470	5	1.05
	111	ICA	NO	1.14	7	470	5	1.05
	112	ICA	NO	1.17	6	470	5	1.05
	113	ICA	NO	1.02	11	470	5	1.04
	114	ICA	NO	1.13	7	470	5	1.05
	115	ICA	NO	1.11	8	470	5	1.05
	116	ICA	NO	1.15	7	470	5	1.05
	117	ICA	NO	1.11	8	470	5	1.05
	118	MCA	YES	1.05	62	75	5	3.66

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119	ACOM	YES	1.05	62	75	5	3.66
120	MCA	YES	1.6	11	75	5	5.79
121	MCA	YES	1.05	62	75	5	3.66
122	BA	YES	1.15	43	75	5	4.24
123	MCA	YES	1.04	64	75	5	3.60
124	MCA	NO	1.55	13	75	5	5.68
125	MCA	NO	1.53	14	75	5	5.64
126	MCA	YES	1.2	36	75	5	4.50
127	MCA	NO	2.06	4	75	5	6.32
128	MCA	NO	2.37	2	75	5	6.46
129	MCA	YES	0.83	158	75	5	2.15
130	MCA	NO	1.82	7	75	5	6.11
131	BA	YES	0.75	237	75	5	1.60
132	MCA	YES	1.83	7	75	5	6.12
133	BA	NO	2.08	4	75	5	6.33
134	BA	NO	1.39	20	75	5	5.26
135	MCA	YES	1.04	64	75	5	3.60
136	BA	YES	0.96	88	75	5	3.06
137	BA	NO	1.24	32	75	5	4.69
138	MCA	NO	1.68	9	75	5	5.92
139	MCA	YES	1.1	51	75	5	3.96
140	MCA	YES	1.6	11	75	5	5.79
141	ACOM	NO	1.75	8	75	5	6.03
142	MCA	YES	0.88	125	75	5	2.50

The role of peripheral vasculature in vessel constriction after aneurysm treatment with flow-diverter stents

Abstract

Background Treatment of intracranial aneurysms with flow diverter stents (FDS) can lead to calibre changes of jailed vessels. The reason some branches remain unchanged and others are affected by narrowing remains unknown.

Objective This study investigates the influence of resistance to flow from distal vasculature on stent-induced haemodynamic modifications affecting bifurcating vessels.

Materials and methods Radiological images and demographic data were acquired for 142 aneurysms treated with FDS. Vascular resistance values were estimated from patient-specific anatomical data. Correlation analysis was used to identify correspondence between anatomical data and clinical outcome. Computational Fluid Dynamics was performed on a typical patient-specific model to evaluate FDS-specific influence on flow. Relevant haemodynamic variables along the bifurcating vessels were quantitatively analysed and validated with *in vitro* data obtained using power Doppler ultrasound.

Results Statistical analysis showed a correlation between clinical outcome and FDS resistance to flow considering overall jailed-vessel vascular resistance ($r=0.5$, $p<0.001$). Computational predictions of blood flow showed that haemodynamics is minimally affected by FDS treatment in the OphthA.

Conclusions Jailed vessels are affected by narrowing when resistance to flow from the FDS constitutes a larger proportion of overall vessel resistance to flow. This knowledge may contribute to better understanding of intracranial hemodynamic after FDS procedure and reinforce indications of flow diversion in the treatment of intracranial aneurysms.

INTRODUCTION

Flow diverter stent (FDS) procedures for proximal internal carotid artery (ICA) aneurysms are a frequent treatment with high aneurysm obliteration rates. Neurological impairment remains relatively low considering that FDS covers not only the aneurysm neck but also side wall arteries like ophthalmic (OphthA) and anterior choroidal arteries [1]–[3], that seem to be less affected than bifurcating arteries when jailed by FDS [4]–[12]. Narrowing and occlusion are a frequent event after FDS procedure for middle cerebral artery (MCA) and some anterior cerebral artery (ACA) bifurcation aneurysms (MCA and ACA bifurcations without opposite A1) and anatomic parameters could be involved in hemodynamic changes that affect the vessel wall. Asymmetry of branches, hemodynamic alterations and clinical outcome after treatment with FDS for bifurcation aneurysms have been correlated in a study that identified an anatomical threshold of the daughter vessel diameter ratio (0.7) below which FDS-induced alterations of volumetric flow rates and significant changes in wall shear stress (WSS) correlate to poor clinical outcome[13]. It is difficult to apply this theory in the context of proximal ICA aneurysms considering that the ratio between OphthA and ICA are lower than 0.7, and jailed OphthA remains mostly patent. Iosif and colleagues evaluated the presence of collaterals converging to the same territory of the jailed artery to explain the narrowing process, however this hypothesis does not explain OphthA permeability after FDS procedures as collaterals are often present in this territory too [14].

In an attempt to explain this phenomenon, Cebal et al.[15] proposed the role of high peripheral vascular resistance (R_{PER}) as the most significant factor affecting hemodynamics and possibly vessel calibre changes after FDS treatment. Their study showed that computational estimations of blood flow patterns in the jailed arteries are only

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3 minimally affected by the small perturbation imposed by the FDS and mainly influenced by
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5 the much larger resistance to flow imposed by the peripheral bed distal to these small
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7 arteries. Blood flow distribution throughout the cardiovascular system is highly influenced by
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9 R_{PER} , which can be described as the viscous impediment to blood flow in a vessel as
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11 described by the Hagen-Poiseuille relationship that links pressure to flow [16]. This
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13 relationship shows that resistance, or impediment to flow, increases with higher values of
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15 blood viscosity (hematocrit), vessel length and smaller vessel radii.
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20 The aim of this study is to perform a quantitative estimation of the factors affecting
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22 hemodynamics of FDS-jailed arteries, with a focus on the quantification of the impediment
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24 to flow from the FDS (R_{FDS}) in relation to the overall artery resistance (R_{TOT}) to flow, and for a
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26 larger cohort of datasets. The study also includes an experimental validation of our
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28 theoretical and numerical observations using power doppler-ultrasound (PD-US).
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36 MATERIALS AND METHODS

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38 The hypothesis of this study is that clinical outcome and FDS-induced hemodynamic
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40 alterations depend on the relative significance of R_{FDS} to flow with respect to overall artery
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42 resistance ($R_{TOT} = R_{FDS} + R_{JV} + R_{PER}$) in the jailed artery (local jailed artery resistance = R_{JV}). The
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44 methodology of this study was developed to test this hypothesis and organized within 3
45
46 different phases: Phase I=analysis of clinical data (radiological and demographic) for
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48 estimation of vascular resistances and possible associations with clinical outcomes; Phase
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50 II=patient-specific computational fluid dynamics (CFD) analysis of flow through a typical
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52 OphthA aneurysm to analyze and illustrate the effect of R_{FDS} to flow at a location normally
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3 less affected by vessel narrowing; Phase III=validation of numerical predictions through
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5 experimental analysis.
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10 11 **Phase I**

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15 Clinical data from 142 patients were retrospectively collected upon appropriate
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17 ethical approval and patient consent. Bifurcation aneurysms from middle cerebral artery
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19 (MCA), basilar artery with hypoplasia of posterior communicating artery and anterior
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21 communicating artery aneurysms with agenesis of contra-lateral anterior cerebral artery and
22
23 treated with FDS between December 2010 and December 2015 were included (25
24
25 aneurysms from 25 patients). OphthA aneurysms data were collected from December 2014
26
27 to December 2017 (117 aneurysms from 117 patients). All patients included had 3D-
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29 angiography prior to FDS positioning and at 3-6 months follow-up. Images were acquired
30
31 using a biplane X-ray system (General Electric Healthcare Innova IGS 650, Marlborough,
32
33 Massachusetts, USA) and were obtained during a 240 degrees rotation for a duration of 5
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35 seconds and for a total of 244 projections. This resulted in a 3D volume dataset of
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37 512x512x512 voxels covering a field of view of 116 mm.
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45 Table 1 (online suppl.) illustrates the demographic constitution of the data together
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47 with jailed-vessel outcomes, anatomic information (lumen diameter) and estimations of
48
49 local resistance to flow. Resistances were calculated from jailed-vessel patient-specific
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51 diameter values using Hagen-Poiseuille's theory $R = 8 \mu L / (\pi r^4)$, where $\mu=0.0035 \text{ Pa s}$ is
52
53 whole blood viscosity, L is vessel length and r is lumen radius. Typical values of vessel length
54
55 for jailed arteries and R_{PER} values were taken from Reymond et al.[17]. Three vessel diameter
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57 values were taken from radiological images by two fully trained neuroradiologists along the
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3 vessels of each bifurcating branch (Fig 1, online suppl.), reporting only its arithmetic average
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5 value and their standard deviation to quantify interobserver variability. OsiriX was used to
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7 measure vessel diameters from 2D acquisitions by digital subtraction angiography and 3D-
8
9 angiography images. 2-way, mixed intra-class correlation coefficients was used to assess the
10
11 reliability of measurements with 95% confidence interval. 2-tailed Pearson correlation
12
13 analysis was performed to identify associations between clinical outcome, anatomical data
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15 and estimation of vascular and relative R_{FDS} to flow. Although normally a probability value of
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17 $p < 0.05$ is sufficient to test correlation significance, for our relatively small cohort, we
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19 wanted to test our hypothesis to a more stringent significant region and decided to set 0.01
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21 as probability value threshold.
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28 **Phase II**

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31 For the patient-specific CFD analysis, an aneurysm located at OphthA segment was
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33 selected. Medical image segmentation and surface reconstruction were performed using the
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35 @neurIST computational toolchain[18]. Blender® was used for removal of artefacts and
36
37 further surface mesh refinements. FDS was deployed virtually, in accordance with clinical
38
39 procedures, and using the process described by Larrabide et al [19]. The FDS model
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41 represents a typical Surpass FDS (Stryker, Kalamazoo, MI, USA) of 4 mm diameter with 72
42
43 wires. For the same patient-specific geometry we run several analyses, with and without
44
45 stent, and for different flow conditions.
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51 The equations governing the physics of steady laminar flow were solved by using
52
53 ANSYS CFX (ANSYS, Canonsburg, Pennsylvania). Blood was assumed incompressible (density
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55 $\rho = 1050 \text{ kg m}^{-3}$) and Newtonian (viscosity $\mu = 0.0035 \text{ Pa s}$). Appropriateness of modelling
56
57 approaches and accuracy of the numerical solutions was ensured by adopting methodologies
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3 already reported in the literature[13], [18], [20], [21]. The mesh used for the unstented
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5 model comprised approximately 0.8 million nodes (4 million nodes for stented model) and
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7 2.7 million elements (19 million elements for stented model), resulting in a mesh volumetric
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9 density of 2.7 thousand elements mm^{-3} (19 thousand el. mm^{-3} for stented model). Typical
10
11 volumetric flow rates, time-averaged along the cardiac cycle, were imposed at inlet in the
12
13 form of a fully developed parabolic velocity profile to mimic peak systolic ($Q_{\text{in}} = 4 \text{ ml s}^{-1}$) and
14
15 end diastolic ($Q_{\text{in}} = 7.5 \text{ ml s}^{-1}$) conditions. Outlet boundary conditions were imposed by
16
17 mimicking typical resistance to flow imposed by the peripheral networks distal to the ICA
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19 and OphthA [22]. R_{PER} at distal ICA outlet boundary was set to $R_{\text{ICA}} = 25 \text{ mmHg s mL}^{-1}$,
20
21 whereas resistances at the OphthA outlet were set to $R_{\text{OphthA}} = 470 \text{ mmHg s mL}^{-1}$. CFD
22
23 analysis and results were also used to obtain values of resistance to flow caused by the FDS
24
25 by extracting values of pressure drops and flow across the wires and calculating resistance as
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27 $R = \Delta P / Q$, where ΔP is the pressure drop measured across the stent wires, and Q the flow rate
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29 across the same location.
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40 Phase III

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43 CFD data were validated via PD-US measurements from life-size silicone replicas
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45 purposely produced for the study. Two silicone replicas of the geometry used in the CFD
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47 analysis were produced. The difference between the surfaces of the produced replicas and
48
49 their target STL surfaces was evaluated quantitatively using a position error index method
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51 [23]. This resulted in a median value for the distribution of position errors across the surface
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53 mesh below $70 \mu\text{m}$. One of the replicas received an FDS Surpass (Stryker, Kalamazoo, MI,
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55 USA) 4mm diameter by 20mm length with 72 wires, deployed by a senior intervention
56
57 neuroradiologist (APN) carefully placing the stent to match with CFD model. Both replicas
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3 were connected to a closed loop circuit filled with ultrasound compatible blood mimicking
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5 fluid and connected to a programmable pump (CompuFlow 1000, Shelley Medical Imaging
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7 Technologies, Toronto, Canada).
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10 An Ultrasound System (Aixplorer® Multiwave Supersonic Imagine, S.A.; Aix-en-
11
12 Provence, France) equipped with a 256-element (SL15–4) 7.5-MHz linear-array transducer
13
14 was used to take PD-US measurements of velocity magnitude along the OphthA from both
15
16 replicas. Velocities profiles were extracted from PD-US along the OphthA and compared to
17
18 identify FDS-induced changes and validation of CFD data (Fig 2, online suppl.).
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25 RESULTS

26 Phase I: Clinical data analysis results

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28 Reports of the incidence of vessel narrowing per location, showing a higher
29
30 incidence of clinical complications for vessels jailed by the FDS in bifurcating aneurysms and
31
32 no complications for FDS-treatment of aneurysms at OphthA location at 3 months follow up
33
34 are shown in Fig 3 (online suppl.). The intra-class correlation and Pearson correlation
35
36 performed to assess the reliability of the anatomical measurements showed high interclass
37
38 correlation coefficient (ICC=0.97, CI 95%, lower bound = 0.95, upper bound = 0.998,
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40 $p < 0.0001$ and Pearson Correlation Coefficient $r = 0.743$, $p < 0.0001$). Mortality was not
41
42 considered as only patients with control at 3 months follow-up were included.
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51 Box-plots graphs in Fig 4 show relation between R_{FDS} to flow and R_{TOT} ($R_{FDS} + R_{JV} + R_{PER}$)
52
53 for cases showing patency (no narrowing) and narrowing of the jailed vessel. The graphs
54
55 clearly indicate that those cases where median R_{FDS} to flow is low compared with R_{TOT} are
56
57 also the cases presenting no complications (Fig 4, patent group, mean=1.05). On the
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3 contrary, cases with relatively higher R_{FDS} to flow are also the cases presenting vessel
4 narrowing (Fig 4, narrowing group, mean=3.6). This correlation is statistically significant as
5
6 narrowing (Fig 4, narrowing group, mean=3.6). This correlation is statistically significant as
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8 showed by the Pearson correlation analysis reporting a Pearson correlation coefficient of
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10 $r=0.5$ ($p<0.0001$).
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12 **Phase II: CFD analysis**

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16 The CFD results obtained for the patient-specific analysis of flow through an OphthA
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18 showed that FDS-induced changes mostly affect values within the aneurysm sac and parent
19
20 vessel, and not visibly affect values in the jailed OphthA (Table 2 and Fig 5). Table 2 reports
21
22 FDS-induced changes on flow redistributions (ICA and OphthA outflow) at peak systole
23
24 (peak) and end diastole (dia), showing values below 0.5%. FDS-induced changes on WSS
25
26 space-averaged across the OphthA show reduction in values below 5%. In accordance with
27
28 the quantitative values reported in Table 2, Fig 5 shows the spatial distribution of WSS
29
30 magnitude across the patient-specific model, indicating that FDS-induced changes mostly
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32 affect values within the aneurysm sac and parent vessel, and not visibly affect values in the
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34 jailed OphthA, both at peak systole and end diastole.
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44 **Phase III: Validation results**

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46 Velocity profiles from both replicas were obtained from PD-US measurements.
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48 Profiles at the same positions along the OphthA were extracted and the changes were
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50 quantified using a normalized discrepancy index $D = \frac{|V_{unstented} - V_{stented}|}{\max(V_{unstented})}$. Profiles at four
51
52 different positions are presented in Fig 6. The discrepancy index, D , was computed up to
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54 0.4mm deep into the vessel due to limitations in accuracy in the PD-US approach. Fig 6
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56 presents the histogram of the discrepancy D ($N=75$ samples). The median of the discrepancy
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3 is 3.6%, in agreement with CFD analysis. The measurements corroborate that FDS does not
4
5 induce significant changes to the flow in the jailed OphthA.
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11 12 13 14 15 **DISCUSSION**

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17 The aim of the study was to investigate, for a cohort of 142 aneurysm datasets, the
18 role of resistance to flow in the context of flow changes induced by FDS treatment that may
19 relate to vessel narrowing/occlusion in a subacute phase. The effect of FDS on flow
20 distribution at symmetric and asymmetric bifurcations was studied in the past, but this was
21 contrasted to a small number of cases (25) which was not enough to explain the changes in
22 vessel diameter [13].
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32 The statistical analysis results of this study showed significant correlations between
33 flow resistance attributed to the presence of the FDS and vessel narrowing at follow-up.
34 Analysis of R_{FDS} were considered as values relative to the overall resistance to flow, R_{TOT} ,
35 encountered by the viscous flow of blood through the jailed vessel and distal R_{PER} . R_{FDS}
36 estimated from the CFD simulations in the OphthA were almost negligible (1%) when
37 compared to R_{TOT} , mostly due to a large R_{PER} . Correlation was found with the CFD analysis,
38 which showed that WSS values and flow redistributions were only marginally affected by the
39 presence of the stent (changes ranging from 0 to 5%). Experimental data obtained with PD-
40 US on a silicon replica of a typical OphthA found similar alterations to flow (median value =
41 3.6%). The importance of R_{PER} in side-wall branches after stenting was also highlighted by
42 Appanaboyina et al.[24] in their analysis of blood flow in three patient-specific models.
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3 The study presented here goes one step further by estimating not only R_{PER} but all
4 resistances encountered by blood as it flows through the jailed vessels and how these relate
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6 to the additional resistance to flow imposed by the stent. For these calculations lumen
7
8 caliber data were derived from imaging data of 142 datasets. It is well established that flow
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10 distribution and WSS are heavily dominated by vessel anatomy and the viscous nature of
11
12 blood as smaller vessels, such as the OphthA, will oppose higher resistance to flow than
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14 relatively larger vessels like MCA branches. So the presence of a FDS will not affect the
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16 resistance in the OphthA because it is already high.
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23 The distribution of R_{FDS} to flow as a percentage of R_{TOT} between cases showing jailed
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25 vessel patency and narrowing/occlusion was much higher (2 to 6 fold) in this latter group. In
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27 the not narrowing cases, a series of outliers ranging from 4.5 to 6.5 fold the $R_{FDS}\%$ can be
28
29 observed. This can be explained by the fact that the data have been collected from follow up
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31 images. The narrowing is a biological response to a change in flow, which is not
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33 instantaneous and might take different times depending on the physiological condition of
34
35 the patient, or might not happen at all.
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40 This study has some limitations that should be highlighted. Some of the data used
41
42 to compute vascular resistance (eq. 2) were typical values from the literature (i.e. blood
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44 viscosity, vessel length), and vessel tortuosity and its effect on flow resistance was not
45
46 considered. This might result in some discrepancies between our estimations and the real
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48 values. However, these discrepancies could be negligible as the most influential parameter
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50 to flow resistance (lumen radius) was patient-specific. CFD simplifying assumptions included:
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52 Newtonian, incompressible and stationary fluid, which were adopted following previous
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54 results in the literature, where it was observed that CFD variables like velocity and WSS
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56 resulting from steady state simulations were equivalent to averaging the same variables over
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3 the cardiac cycle for a transient simulation [25]. In this study we are assessing pressure drop,
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5 velocity, mass inflow, and WSS at specific locations for a period of time that is considerably
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7 longer than a single cardiac cycle. Therefore, the use of steady state instead of transient CFD
8
9 simulations is safe, with additional benefit of a considerable computational time reduction.
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11 The non-Newtonian effect on the above mentioned variables is observed for shear rates at a
12
13 much lower regime than considered in this study [26]. Vascular remodeling is a complex
14
15 biological process strongly related to fluid-wall mechanics and their interaction. The study of
16
17 vascular wall remodeling and wall change over time has been modelled computationally in
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19 the past with promising results [27]. Still, the complexity of determining personalized wall
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21 properties and associated mechanobiological parameters makes the use of such models non
22
23 practical in the cases studied, which is a limitation. The link of such models to local
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25 hemodynamic parameters (WSS) that might induce vascular changes and remodeling should
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27 be a subject of future studies, to help further understand the reasons for these changes at
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29 follow-up.
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40 **CONCLUSIONS**

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42 Observations of FDS procedures in some bifurcation aneurysms and side-wall arteries seem
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44 to have different arterial narrowing/occlusion rates of the jailed arteries by the stent. This
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46 study identified statistically significant correlations between flow resistance and vessel
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48 narrowing that could explain large patency rates in OphthA in a cohort of 142 aneurysms.
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50 This was further supported by a numerical and experimental analysis of blood flow through a
51
52 typical OphthA that were used to identify and illustrate the mechanisms explaining these
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54 correlations. A complete understanding of the phenomena at play will only be possible when
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56 mechanobiological pathways linking hemodynamics alterations to endothelial cells and
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3 arterial wall response (vasoconstriction or remodeling) are also considered. It is necessary a
4
5 better understanding of intracranial hemodynamic after FDS procedure to reinforce
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8 indications of flow diversion in the treatment of intracranial aneurysms.
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Confidential: For Review Only

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Dataset	Location	J-Ves Narrowing	J-Vess Diam [mm]	J-Vess R [mmHg s ml ⁻¹]	Periph R [mmHg s ml ⁻¹]	R _{FDS} [mmHg s ml ⁻¹]	%R _{FDS}
1	ICA	NO	1.09	8	470	5	1.04
2	ICA	NO	1.05	10	470	5	1.04
3	ICA	NO	1.08	9	470	5	1.04
4	ICA	NO	1.07	9	470	5	1.04
5	ICA	NO	1.08	9	470	5	1.04
6	ICA	NO	1.16	6	470	5	1.05
7	ICA	NO	1.07	9	470	5	1.04
8	ICA	NO	1.24	5	470	5	1.05
9	ICA	NO	1.06	9	470	5	1.04
10	ICA	NO	1.13	7	470	5	1.05
11	ICA	NO	1.23	5	470	5	1.05
12	ICA	NO	1.09	8	470	5	1.05
13	ICA	NO	1.30	4	470	5	1.05
14	ICA	NO	1.14	7	470	5	1.05
15	ICA	NO	1.11	8	470	5	1.05
16	ICA	NO	1.13	7	470	5	1.05
17	ICA	NO	1.17	6	470	5	1.05
18	ICA	NO	1.21	6	470	5	1.05
19	ICA	NO	1.17	6	470	5	1.05
20	ICA	NO	1.11	8	470	5	1.05
21	ICA	NO	1.15	7	470	5	1.05
22	ICA	NO	1.15	7	470	5	1.05
23	ICA	NO	1.27	5	470	5	1.05
24	ICA	NO	1.15	7	470	5	1.05
25	ICA	NO	1.19	6	470	5	1.05
26	ICA	NO	0.98	13	470	5	1.04
27	ICA	NO	1.10	8	470	5	1.05
28	ICA	NO	1.16	6	470	5	1.05
29	ICA	NO	1.16	7	470	5	1.05
30	ICA	NO	1.19	6	470	5	1.05
31	ICA	NO	1.10	8	470	5	1.05
32	ICA	NO	1.18	6	470	5	1.05
33	ICA	NO	1.14	7	470	5	1.05
34	ICA	NO	1.01	11	470	5	1.04
35	ICA	NO	1.18	6	470	5	1.05
36	ICA	NO	1.17	6	470	5	1.05
37	ICA	NO	1.12	7	470	5	1.05

Table 1 (online suppl.) Demographic constitution and anatomical data of patients' population. J-Vess Diam = jailed vessel diameter, J-Vess R = jailed vessel vascular resistance, Periph R = peripheral resistance, R_{FDS} = FDS-induced resistance to flow, % R_{FDS} = FDS-induced resistance to flow given as a percentage of overall resistance (FDS plus vascular plus peripheral).

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80	ICA	NO	1.12	7	470	5	1.05	
81	ICA	NO	1.14	7	470	5	1.05	
82	ICA	NO	1.20	6	470	5	1.05	
83	ICA	NO	1.14	7	470	5	1.05	
84	ICA	NO	1.05	10	470	5	1.04	
85	ICA	NO	1.19	6	470	5	1.05	
86	ICA	NO	1.05	10	470	5	1.04	
87	ICA	NO	1.14	7	470	5	1.05	
88	ICA	NO	1.13	7	470	5	1.05	
89	ICA	NO	1.15	7	470	5	1.05	
90	ICA	NO	1.05	10	470	5	1.04	
91	ICA	NO	1.20	6	470	5	1.05	
92	ICA	NO	1.17	6	470	5	1.05	
93	ICA	NO	1.12	8	470	5	1.05	
94	ICA	NO	1.13	7	470	5	1.05	
95	ICA	NO	1.03	11	470	5	1.04	
96	ICA	NO	1.16	7	470	5	1.05	
97	ICA	NO	1.13	7	470	5	1.05	
98	ICA	NO	1.11	8	470	5	1.05	
99	ICA	NO	1.11	8	470	5	1.05	
100	ICA	NO	1.07	9	470	5	1.04	
101	ICA	NO	1.12	8	470	5	1.05	
102	ICA	NO	1.17	6	470	5	1.05	
103	ICA	NO	1.03	10	470	5	1.04	
104	ICA	NO	1.13	7	470	5	1.05	
105	ICA	NO	1.16	6	470	5	1.05	
106	ICA	NO	1.09	8	470	5	1.05	
107	ICA	NO	1.13	7	470	5	1.05	
108	ICA	NO	1.17	6	470	5	1.05	
109	ICA	NO	1.17	6	470	5	1.05	
110	ICA	NO	1.13	7	470	5	1.05	
111	ICA	NO	1.14	7	470	5	1.05	
112	ICA	NO	1.17	6	470	5	1.05	
113	ICA	NO	1.02	11	470	5	1.04	
114	ICA	NO	1.13	7	470	5	1.05	
115	ICA	NO	1.11	8	470	5	1.05	
116	ICA	NO	1.15	7	470	5	1.05	
117	ICA	NO	1.11	8	470	5	1.05	
118	MCA	YES	1.05	62	75	5	3.66	
119	ACOM	YES	1.05	62	75	5	3.66	
120	MCA	YES	1.6	11	75	5	5.79	
121	MCA	YES	1.05	62	75	5	3.66	

122	BA	YES	1.15	43	75	5	4.24
123	MCA	YES	1.04	64	75	5	3.60
124	MCA	NO	1.55	13	75	5	5.68
125	MCA	NO	1.53	14	75	5	5.64
126	MCA	YES	1.2	36	75	5	4.50
127	MCA	NO	2.06	4	75	5	6.32
128	MCA	NO	2.37	2	75	5	6.46
129	MCA	YES	0.83	158	75	5	2.15
130	MCA	NO	1.82	7	75	5	6.11
131	BA	YES	0.75	237	75	5	1.60
132	MCA	YES	1.83	7	75	5	6.12
133	BA	NO	2.08	4	75	5	6.33
134	BA	NO	1.39	20	75	5	5.26
135	MCA	YES	1.04	64	75	5	3.60
136	BA	YES	0.96	88	75	5	3.06
137	BA	NO	1.24	32	75	5	4.69
138	MCA	NO	1.68	9	75	5	5.92
139	MCA	YES	1.1	51	75	5	3.96
140	MCA	YES	1.6	11	75	5	5.79
141	ACOM	NO	1.75	8	75	5	6.03
142	MCA	YES	0.88	125	75	5	2.50

Table 2 Quantification of FDS-induced changes to haemodynamic variables extracted from OphthA bifurcation at peak systole (peak) and end diastole (dia). Avg WSS is the space-averaged WSS extracted from the OphthA. ICA and Ophth outflow are the volumetric flow rates calculated at the outlet of the ICA and OphthA, respectively.

	Unstented [peak/dia]	Stented [peak/dia]	Diff [peak/dia]	%Diff [peak/dia]
Avg WSS [Pa]	11.56/5.30	10.98/5.04	-0.58/-0.26	-5.0/-4.7
ICA outflow [ml/s]	7.20/3.80	7.19/3.82	-0.01/-0.02	0.1/0.5
Ophth outflow [ml/s]	0.38/0.20	0.38/0.201	0.0/0.001	0.0/0.5