Original research

# Impact on collateral flow of devices used for endovascular treatment of stroke: an in-vitro flow model

Manuel Requena ,[1,2,3] Jiahui Li,[3,4] Riccardo Tiberi ,[3,5] Pere Canals,[3] Marta Olive Gadea ,[1,3] Marta de Dios Lascuevas,[2,3] Magda Jabłońska ,[3,6] Judith Cendrero,[1,3] Alvaro Garcia-Tornel ,[1,3] Alejandro Tomasello ,[1,3] Marc Ribo [1,3,4]

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[1]Stroke Unit, Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Catalunya, Spain
[2]Neuroradiology, Vall d'Hebron University Hospital, Barcelona, Catalunya, Spain
[3]Stroke Research, Vall d'Hebron Research Institute, Barcelona, Spain
[4]Department of Neurology, Autonomous University of Barcelona, Barcelona, Spain
[5]Universitat Politècnica de Catalunya, Barcelona, Spain
[6]Department of Radiology, Gdanski Uniwersytet Medyczny, Gdansk, Poland

**Correspondence to**
Dr Marc Ribo, Stroke Unit, Neurology, Hospital Vall d'Hebron, Barcelona 08035, Spain; marcriboj@hotmail.com

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## ABSTRACT

**Background** Collateral blood supply of distal vessels has been linked to clinical outcome, infarct volume and recanalization rates in patients with large vessel occlusion. Our study aimed to explore the effects of catheterization during mechanical thrombectomy in collaterals.

**Methods** We quantified the flow diversion effect secondary to arterial occlusions in an in vitro model which was connected in a flow-loop setup with a saline reservoir and a pump supplying pulsatile flow. Clot analogs were embolized to the middle cerebral artery (MCA) M1 or M2 segments. We used the same model with a clamped anterior communicating artery (AComA) to simulate its absence. An ultrasound flow sensor was placed at the vessel of interest. Flow rates and pressures were evaluated according to the following catheter locations: baseline (1) before and (2) after the occlusion; (3) 8F guiding catheter at the internal carotid artery (ICA) bulb; (4) at the cavernous segment; (5) at the cavernous segment a 0.071" distal access catheter at proximal M1; (6) 8F balloon guide catheter inflated.

**Results** Collateral blood flow measured at distal anterior cerebral artery (ACA) (M1-MCA occlusion) and M2-MCA (M2-MCA occlusion) was progressively reduced as catheters were advanced through the ICA and MCA. In the lacking AComA model, the flow was further diminished as compared with the model with a patent AComA.

**Conclusion** Our in vitro study showed a progressive reduction of collateral blood flow due to the advance of catheters during mechanical thrombectomy.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Collateral blood supply is associated with functional outcome, infarct volume and rate of recanalization among patients with acute stroke and a large vessel occlusion. It is influenced by several factors.

### WHAT THIS STUDY ADDS

⇒ While catheters are advanced through the internal carotid artery during mechanical thrombectomy collateral blood supply suffers a progressive reduction in an in vitro model. The patency of the anterior communicating artery might have an influence on this phenomenon.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings might be relevant for device selection and positioning at different stages of the procedure with the aim of minimizing the impact on collateral circulation.

## INTRODUCTION

Collateral blood supply of vessels distal to a large vessel occlusion has been linked to stroke severity, infarct volume, clinical outcome[1 2] and rate of recanalization.[3] In the event of a large vessel occlusion, an increased flow, known as flow diversion, in the remaining patent branches can be observed in accordance with the increased parenchymal volume now supplied by the given artery. The collateral supply can partially or completely compensate the regional cerebral blood flow improving the neurological symptoms and the progression of the infarct. Different factors such as systemic blood pressure, cardiac output, or head position may influence collateral circulation during the initial hours after stroke onset.[4]

To achieve complete recanalization with the minimum number of attempts,[5] the mechanical thrombectomy technique has evolved to use progressively larger aspiration catheters[6–9] and/or proximal balloon-guide catheters,[10 11] capable of inducing substantial regional flow restrictions. When performing endovascular stroke treatment, the presence of such devices in the cervical and cerebral arteries may affect blood flow diversion, collateral circulation and potentially the patient's neurological status both before and eventually following final recanalization.

Our study aimed to assess how collateral circulation in a neurovascular in vitro model is affected by different catheter placements within the cerebral vasculature.

## METHODS

### Neurovascular model

The in vitro neurovascular model featuring a complete circle of Willis (Flowcat, Barcelona,

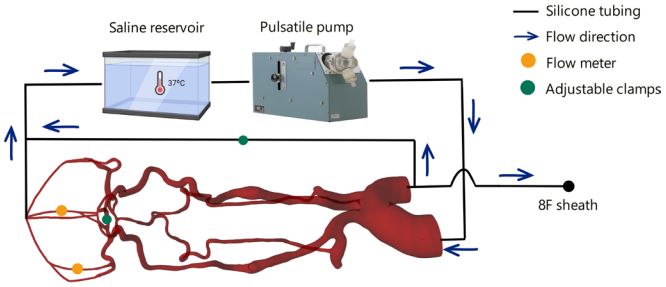


**Figure 1** Diagram of the benchtop setup.

Spain) was fabricated in-house based on the vascular anatomies extracted from anonymized computed tomography (CT) angiography images (vessel diameters are reported in online supplemental table s1). The manufacturing procedure comprises the following steps: image segmentation to generate the preliminary three dimensional (3D) geometry of the vascular anatomy, mesh modeling to simplify the anatomy and prepare a printable model (Meshmixer, Autodesk, Inc., California, USA), 3D printing using a commercially available resin and printer (Elastic 50A, Form 3 SLA Printer, Formlabs, Inc., MA, USA), post-printing processing, and manual assembly. In terms of elasticity, the printing material exhibits a hardness of 50A, approximating a Young's Modulus of 1.7 MPa. The model includes the aortic arch, bilateral common and internal carotid arteries, middle cerebral arteries (MCA, up to two distal M2-MCA branches), anterior cerebral arteries (up to proximal A2-ACA segment), anterior communicating artery (AComA), posterior communicating arteries, vertebral, basilar, and posterior cerebral arteries (up to proximal P2-PCA segments) (figure 1).

### Experimental setup

The neurovascular model was connected in a flow-loop setup with a saline reservoir at 37±1°C and a pump (Pulsatile Blood Pump Model 1423, Harvard Apparatus, MA, USA) supplying pulsatile flow at approximately 1050 mL/min (70 bpm, 15 mL/stroke). To simulate the transfemoral access, an 8F sheath attached to a silicone tubing was connected to the descending aorta. The connection diagram of the benchtop setup is depicted in figure 1. The flow rate in the model was adjusted within the physiological range by partially clamping the tubing simulating descendant aorta and monitored by a flow meter (ME2PXL, Transonic, NY, USA). Clot analogs with different predefined sizes were injected from the external carotid artery to the internal carotid artery to embolize the target vessel: M1-MCA or M2-MCA segments.

The ultrasound flow sensor was placed at the vessel of interest to characterize the collateral circulation: distal ACA if M1-MCA was occluded and patent M2-MCA if M2-MCA was occluded (figure 1). Baseline parameters were recorded before (A), and after (B) the occlusion and continuously monitored while catheters were advanced through the model: (C) 8F guide catheter in the ICA bulb; (D) 8F GC at the cavernous segment and (E) 0.071" distal access catheter at proximal M1. Finally, an 8F balloon guide catheter was inflated in the cervical ICA to assess collateral circulation under complete ICA flow arrest without a distal access catheter (F). After clamping the anterior communicating artery, all measures were repeated in the same model to characterize the collateral circulation in its absence. In each experiment, five readings were recorded over a minute: mean and standard deviation (SD) values are reported.

We used t-tests to assess the statistical significance of flow differences while catheters were advanced.

## RESULTS

### Collateral circulation at baseline

At baseline, the determined measures were: with patent AComA, ACA flow was 110±1.6 mL/min and M2-MCA flow 48.8±1.5mil/min; in absence of AComA, mean ACA flow was 77.4±1.1 mL/min and mean M2-MCA flow 54.4±1.1 mL/min.

After M1-MCA occlusion, mean ACA flow was 202±1.0 (82.3% increase) with patent AComA and 150.6 (1.8) (94.6% increase) in its absence.

**Table 1** Flow rates at the vessel of interest during catheters advance

| | Baseline | Occlusion | Catheter ICA bulb | Catheter ICA cavernous | DAC in proximal M1 | BCG inflated in ICA | Baseline | Occlusion | Catheter ICA bulb | Catheter ICA cavernous | DAC in proximal M1 | BCG inflated in ICA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **M1 occlusion** | **AComA patent** | | | | | | **AComA absent** | | | | | |
| **A2-ACA flow (ml/min) (mean, SD)** | 110.8 (1.6) | 202 (1.0) | 195.4 (2.3) | 173.8 (1.1) | 167.2 (0.45) | 155.6 (1.5) | 77.4 (1.1) | 150.6 (1.8) | 148 (2.0) | 63.6 (2.4) | 46.4 (0.89) | 39.2 (1.3) |
| %change from baseline | | +82.3% | +76.4% | +56.9% | +50.9% | +40.4% | | +94.6% | +91.2% | 17.8% | 40.0% | 49.4% |
| **M2 occlusion** | **AComA patent** | | | | | | **AComA absent** | | | | | |
| **Patent M2-MCA flow (ml/min) (mean, SD)** | 48.8 (1.5) | 64.8 (0.8) | 62.6 (0.5) | 39.2 (0.8) | 34.4 (0.5) | 38.6 (0.5) | 54.4 (1.1) | 72.8 (0.8) | 71.4 (0.5) | 22.2 (0.8) | 29.8 (1.8) | 17.0 (0.7) |
| % change from baseline | | +32.8% | +28.3% | 19.7% | 29.5% | 20.9% | | +33.8% | +31.3% | 59.2% | 45.2% | 68.8% |
| **A2-ACA flow (ml/min) (mean, SD)** | 110.8 (1.6) | 136.4 (0.5) | 137.8 (1.9) | 114.6 (2.9) | 125.0 (3.7) | 117 (3.7) | 77.4 (1.1) | 107.0 (4.9) | 100.0 (2.0) | 36.8 (0.8) | 26.6 (0.5) | 30.6 (2.4) |
| % change from baseline | | +23.1% | +24.4% | +3.4% | +13.5% | +5.6% | | +38.2% | +29.2% | 52.4% | 65.6% | 60.4% |

ACA, anterior cerebral artery; AcomA, anterior communicating artery; BCG, balloon cathether guide; DAC, distal aspiration catheter; ICA, internal carotid artery; MCA, middle cerebral artery.; SD, standard deviation.

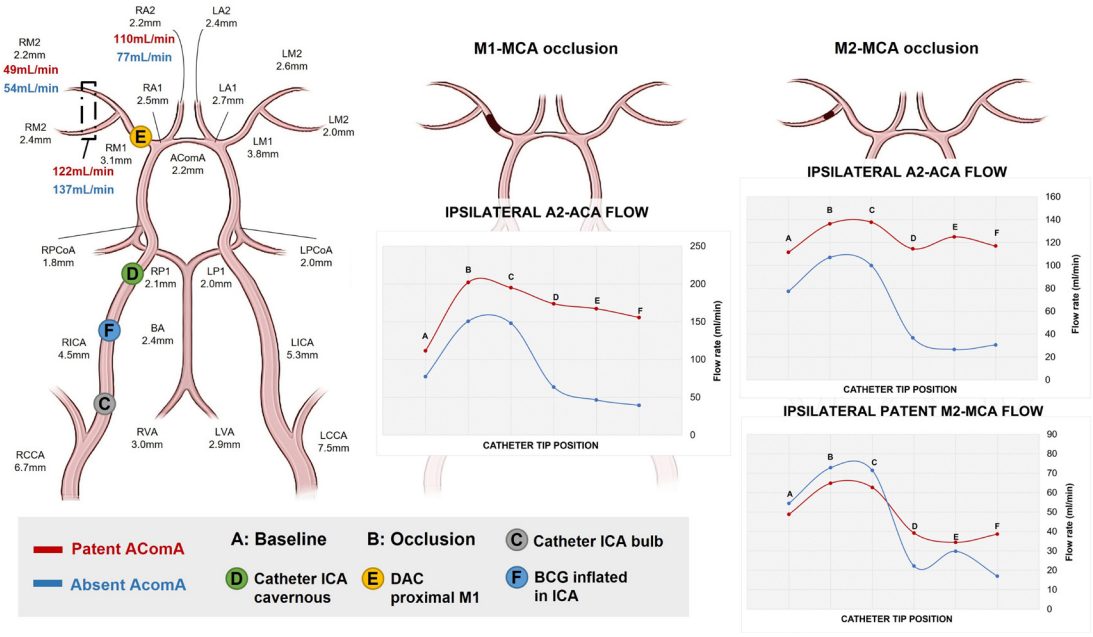


**Figure 2** Schematic diagram of anatomical model. Measured diameter of model vessels and flow rate with patent (red) or absent (blue) of anterior communicating artery at baseline (A), after occlusion (B) and when the tip of the catheters reached: 8F guide catheter in ICA bulb (C), 8F guide catheter at cavernous segment (D), 0.071″ distal access catheter at proximal M1 (E), finally, 8F balloon guide catheter was inflated in the cervical ICA (F).

After M2-MCA occlusion, mean ACA flow was 136.4±0.5 (23.1% increase) with patent AComA and 107.0±4.9 (38.2% increase) in its absence and patent mean M2-MCA flow was 64.8±0.8 (32.8% increase) with patent AComA and 72.8±0.8 (33.8% increase) in its absence (table 1, figure 2).

### Collateral circulation during catheterization

The measured flow rates progressively decreased as the catheters were advanced in the neurovascular model and the BGC was inflated (table 1, figure 2).

No significant differences according to the presence or absence of AComA were observed after the guide catheter was advanced to the ICA bulb.

For M1-MCA occlusion, with patent AComA, flow in the ACA increased+56.9% (p<0.01) from baseline when the guide catheter was advanced to the ICA cavernous segment to+40.4% (p<0.01) when the balloon was inflated in the ICA. In contrast, in the absence of AComA, the flow was reduced by −17.8% (p=0.04) as compared with baseline when the guide catheter was in the ICA cavernous segment and −49.4% (p=0.05) when the balloon was inflated in the ICA (figure 2).

For M2-MCA occlusion: flow in the patent M2 branch, with patent AComA, changed from −19.7% (p<0.01) when the guide catheter was advanced to the ICA cavernous segment to −29.5% (p<0.01) when the distal aspiration catheter was placed in proximal M1; in the absence of AComA, the reduction ranged from −59.2% (p<0.01) when the guide catheter was in the ICA cavernous segment to −68.8% (p<0.01) when balloon was inflated in the ICA. Flow in the ACA increased, with patent AComA, +3.4% (p=0.041) from baseline when the guide catheter was advanced to the ICA cavernous segment to+13.5% (p<0.01) when the distal aspiration catheter was placed in proximal M1-MCA; in contrast, in the absence of AComA, the flow was reduced by −52.4% (p=0.08) as compared with baseline when the guide catheter was in the ICA cavernous segment and −65.6% (p=0.08) when the distal aspiration catheter reached proximal M1 (table 1, figure 2).

## DISCUSSION

Our study suggests that the presence of devices and catheters in the cervical and cerebral arteries negatively impact the collateral supply to the cerebral tissue at risk. The collateral flow gradually decreased as the devices progressively occupied the intravascular space reaching minimal values when the BGC is inflated. The negative impact on collateral flow is especially pronounced in the absence of the AComA.

The rate of infarct growth is associated with multiple modifiable and unmodifiable factors.[4] The main collateral supply of cortical blood in the scenario of middle cerebral artery occlusion depends on the anterior cerebral artery, and it is considered one of the most important predictors of long-term clinical outcomes.[1 2] Collateral status may be influenced by age, previous vascular risk factors, etiology of the occlusion, blood pressure, and the presence of thrombectomy catheters in ICA as shown in the present work.

Our findings suggest that during the neurointerventional procedure, navigation of devices can induce critical changes potentially shifting slow progressors (good collaterals) into fast progressors (poor collaterals).[4] In these patients ascending catheters from proximal ICA to M1-MCA will progressively reduce the collateral supply resulting in a sudden acceleration of infarct progression during thrombectomy mainly in the absence of AComA.

Those findings could have a special impact in patients with a proximal vessel occlusion and low National Institutes of Health Stroke Scale scores or absence of brain infarct who can experience a clinical worsening during thrombectomy due to this phenomenon.[12] The ultimate goal of mechanical thrombectomy should be complete reperfusion in the shortest time,[13] meaning the interventionalist should select as frontline option

the combination of devices that in their opinion will ensure the highest chances of success in each case scenario. However, according to our results, device selection, navigation and positioning during the procedure should also consider clinical status, collateral supply, and patency of AComA, and all efforts should be adopted to minimize the impact on collateral flow.

Recently, several studies have promoted the use of large bore distal aspiration catheters and/or balloon guide catheters claiming higher first pass recanalization rates and distal emboli reduction. The deleterious effect of impairing flow diversion and pressure in the ACA due to the use of such catheters should be explored to confirm their safety, mainly in patients with good baseline collateral supply.

Some strategies may reduce the collateral supply impairment seen during catheterization. The use of devices or strategies (as anchoring with stent retriever) which have shown easier and faster catheterization may shorten the time of pathway flow arrest in collaterals.[14] Other strategies may reduce the collateral flow impairment. Examples include the use of smaller bore catheters which may allow collateral flow or stent-BGC with short inflation of the balloon during selected maneuvers (microcatheterization and clot retrieval).

It remains unclear if the effect of catheters in collateral supply may be irreversible by inducing a definitive collapse of the involved supplying vessels despite recanalization is achieved at a later point. The reversibility could be related to the duration and degree of the collateral circulation reduction. Therefore, neurointerventionalists should be aware of the impact they can have on collateral supply and as far as possible try to minimize the time the devices interfere with collaterals.

Our findings are based on an in vitro experiment. Going forward, these findings need to be confirmed in clinical conditions (online supplemental figure S1). Ideally these should be in prospective studies assessing fluctuations of neurological status during thrombectomy related to variables such as the presence of a patent AComA and the positioning of the devices and the length of the procedure.

Our study has several limitations associated with the model: First, anastomosis of external carotid artery with the anterior cerebral circulation were not studied and its relevance was neglected.[15] However, a clinical study examining the blood flow distribution in 1000 patients with >70% ICA stenosis reported an approximate 4% increase in external carotid artery flow rate (5–20 mL/min).[16] Based on this observation, we believe that, in most cases, the immediate compensatory increase in ECA flow during catheterization of the ICA, would not be enough to significantly compensate the induced flow reduction. Additionally, it is important to note that this benchtop study was unable to replicate the physiological phenomenon of reactive microvascular dilation, which has the potential to partially compensate the flow reduction by decreasing the arteriolar flow resistance. However, the mentioned arteriolar dilation is believed to be triggered, most often immediately after the occlusion occurs in order to promote collateral flow. Therefore, by the time the endovascular treatment is performed the compensatory capacity of cerebral vasoreactivity should be minimal or exhausted. We also used a single size of DAC (0.071'') and did not explore the impact of other sizes. Finally, our model was based in inferring the collateral supply from the flow of distal ACA which is a simplification of the biological phenomenon.

**Twitter** Marc Ribo @marcriboj

**Contributors** JL, RT, PC, MOG and MRi directly participated in the experiments and recorded data. MReq, JL and MRi wrote the first draft of the manuscript. JL and MReq designed the figures. All authors performed a critical review of the study.

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**Competing interests** AT reported receiving personal fees from Anaconda Biomed, Balt, Medtronic, Perflow, and Stryker outside the submitted work. MRi reported receiving personal fees from Anaconda Biomed, AptaTargets, Cerenovus, Johnson & Johnson, Medtronic, Methinks, Philips, Sanofi, Stryker, and Rapid AI outside the submitted work and is co-principal investigator of the WE-TRUST trial (NCT04701684).

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**Data availability statement** Data are available upon reasonable request. Data for collaborative studies can be obtained by contacting the corresponding author.



**ORCID iDs**
Manuel Requena http://orcid.org/0000-0002-5671-6484
Riccardo Tiberi http://orcid.org/0000-0002-1296-3731
Marta Olive Gadea http://orcid.org/0000-0003-4637-1598
Magda Jabłońska http://orcid.org/0000-0002-6108-7977
Alvaro Garcia-Tornel http://orcid.org/0000-0003-3633-3002
Alejandro Tomasello http://orcid.org/0000-0002-6736-1535
Marc Ribo http://orcid.org/0000-0001-9242-043X

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# Impact on collateral flow of devices used for endovascular treatment of stroke: an in-vitro flow model – **Supplementary material.**

| Vessel location | Mean diameter +/- standard desviation (mm) |
|---|---|
| Ascending aorta | 23.05 +/- 7.81 |
| Left subclavian artery | 7.99 +/- 2.88 |
| Left common carotid artery | 7.51 +/- 0.62 |
| Left external carotid artery | 6.44 +/- 1.80 |
| Left internal carotid artery | 5.26 +/- 1.48 |
| Brachiocephalic artery | 15.71 +/- 8.69 |
| Right subclavian artery | 8.30 +/- 1.31 |
| Right common carotid artery | 6.75 +/- 0.99 |
| Right external carotid artery | 6.08 +/- 1.24 |
| Right internal carotid artery | 4.47 +/- 1.31 |
| Right vertebral artery | 3.06 +/- 1.22 |
| Left vertebral artery | 3.21 +/- 0.84 |
| Basilar artery | 2.42 +/- 0.41 |
| Left P1 posterior cerebral artery | 1.99 +/- 0.39 |
| Right P1 posterior cerebral artery | 2.07 +/- 0.56 |
| Left posterior communicanting artery | 1.99 +/- 0.69 |
| Right posterior communicantin artery | 1.83 +/- 0.44 |
| Left M1 middle cerebral artery | 3.82 +/- 0.38 |
| Left M2 middle cerebral artery (dominant) | 2.58 +/- 0.64 |
| Left M2 middle cerebral artery (no-dominant) | 2.02 +/- 0.61 |
| Right M1 middle cerebral artery | 3.06 +/- 0.16 |
| Right M2 middle cerebral artery (dominant) | 2.37 +/- 0.52 |
| Right M2 middle cerebral artery (no-dominant) | 2.17 +/- 0.73 |
| Left A1 anterior cerebral artery | 2.72 +/- 0.44 |
| Right A1 anterior cerebral artery | 2.53 +/- 0.27 |

**Table S1.** Means and standard desviations of vessel diameters from anonymized CT angiography images used to feature the vascular model.

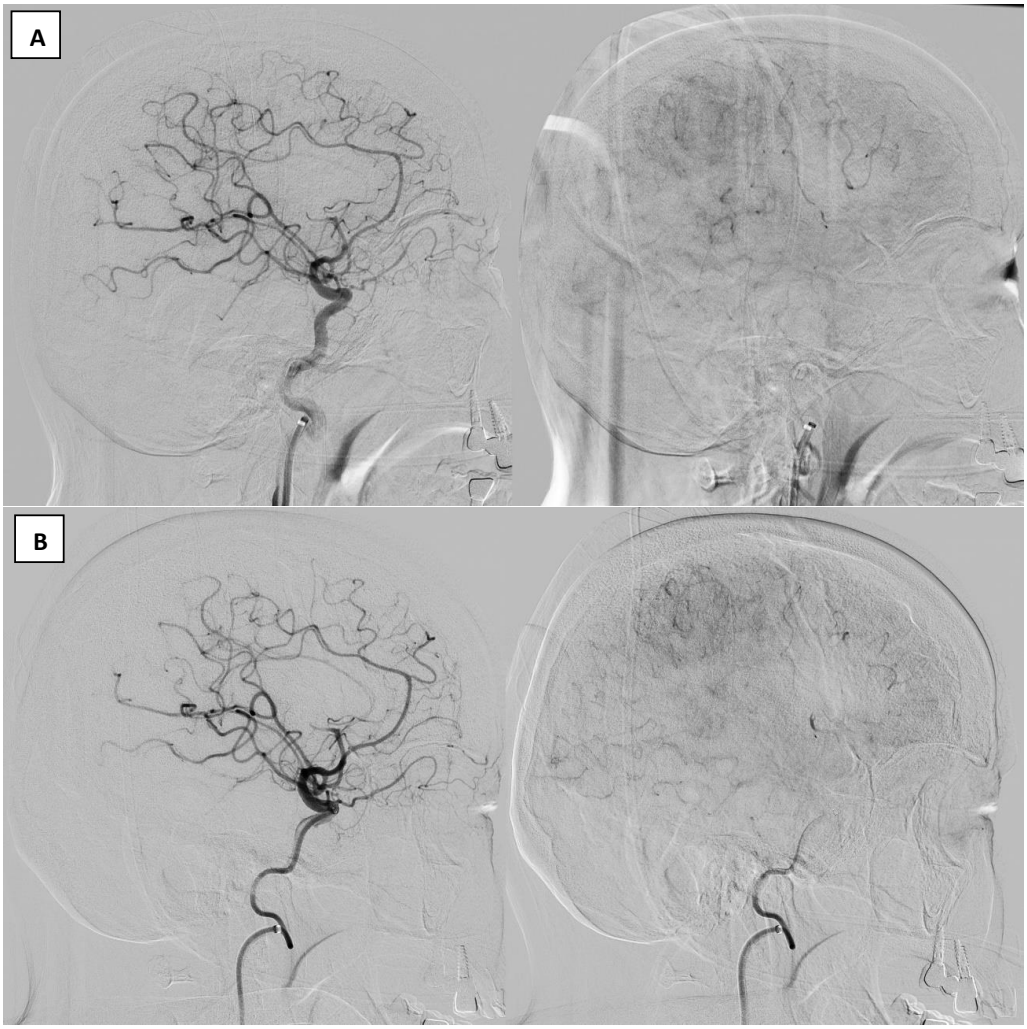


**Figure S1.** Impairment (A to B) of distal collateral blood supply after 0.072'' distal access catheter at ophtalmic segment of internal carotid artery.