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Original Article

Patency of the supraclinoid internal carotid artery branches after flow diversion treatment. A meta-analysis



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ABSTRACT

Background and purpose. – Placement of flow-diverters across the ostia of major ICA branches carries a risk of arterial occlusion. We determined the rate of occlusion of the supraclinoid ICA branches and the related symptoms, following coverage with flow-diverters.

Materials and methods. – A systematic search was performed in PubMed, MEDLINE, and EMBASE. We selected studies reporting treatments with flow-diverters in which the device was placed across the ostium of the OphtA, PcomA, or AchorA. Random-effects meta-analysis was used to pool the following outcomes: rate of arterial occlusion, diminished flow, incidence of related symptoms, factors associated with arterial occlusion.

Result. – Twenty-one studies evaluating 1152 supraclinoid ICA branches were included in the meta-analysis. The incidence of OphtA occlusion and associated symptoms was 5.9% (95 CI = 3.1–8.6%) (incidence rate = 6% per patient-year), and 0.8% (95 CI = 0.1–1.4%) (incidence rate = 0.8% per patient-year), respectively. Although asymptomatic in all cases, PcomA showed a higher occlusion rate (20.7%, 95 CI = 8.9–32.4%) (incidence rate = 19.5% per patient-year). AchorA was occluded in 1% (95 CI = 0.3–2.4%) of cases, with approximately 1% (95 CI = 0.4–2.3%) of transient neurological symptoms (incidence rate = 0.96% per patient-year). There was a trend toward higher odds of arterial patency among arteries arising from the aneurysm (OR = 2.94, $P = 0.06$). Demographic factors and multiple stents were not associated with higher risk of arterial impairment. Adequate collateral circulation was reported in 94.5% of patients with arterial occlusion.

Conclusions. – During aneurysm treatment, the ostium of the supraclinoid ICA branches can be covered with flow-diverter devices with low rates of neurological symptoms related to arterial occlusion.

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Introduction

Flow-diverter stents are increasingly being used in the treatment of cerebral aneurysms, giving a high rate of aneurysm shrinkage and occlusion. A large number of aneurysms in the supraclinoid internal carotid artery (ICA) are amenable to flow-diverter treatment [1–3]. However, an important concern is the patency

of side branches covered by the device [4–6]. Although in vitro studies and experimental models have demonstrated long-term patency rates of arterial side vessels covered with a flow-diverter [7,8], the rate and clinical consequence of ICA side branch occlusion after coverage with the stent remains not completely defined [9–11]. We performed a systematic review and meta-analysis of all the published studies examining the patency of the ophthalmic artery (OphtA), the posterior communicating artery (PcomA), and the anterior choroidal artery (AchorA) after coverage with flow-diverter devices. The purpose of our study was to determine the rate of OphtA, PcomA, and AchorA occlusion and the relative clinical sequelae.

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Materials and methods

Literature search

A comprehensive literature search of PubMed, Ovid MEDLINE, and Ovid EMBASE was conducted for studies published from 2008 to May 2017. PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed [12]. The keywords “flow-diverter”, “flow-diversion”, “side branches”, “intracranial aneurysms”, “pipeline”, were used in both “AND” and “OR” combinations. The inclusion criteria were the following: (1) studies reporting clinical and radiological outcomes of patients treated with flow-diverter in which the device was placed across the ostium of the OphtA, PcomA, or AchorA. Exclusion criteria were the following: (1) studies with < 4 covered vessels; (2) case reports; (3) review articles; (4) studies published in languages other than English; (5) in vitro studies, animal studies, mathematical models. In cases of overlapping patient populations, only the series with the largest number of patients or most detailed data were included. Two reviewers independently selected the included studies, and a third author solved discrepancies.

Data collection

From each study, we extracted the following information: (1) number of OphtAs, PcomAs, and AchorAs covered with flow-diverters; (2) rate of arterial occlusion, diminished flow and related symptoms; (3) factors related to arterial occlusion. In addition, we collected: (1) demographic data of patients; (2) aneurysm char-

acteristics; (3) type and number of stents; (4) treatment-related outcomes. Factors associated to ICA branch occlusion were divided in three categories: demographic, technical, and anatomical factors.

Outcomes

The primary objectives were to determine: (1) the incidence of supraclinoid ICA branch occlusion, and related symptoms; (2) the factors related to the risk of arterial occlusion.

Quality Scoring

The Newcastle–Ottawa Scale [13] was used to assess the quality of the included studies (Supplemental Table 2). This was done by assessing the patient selection criteria, comparability of the study groups, as well as the outcome and exposure assessment. Criteria for “High-quality” were: (1) presence of a predefined study protocol; (2) defined inclusion and exclusion criteria; (3) clearly defined imaging protocol; (4) adequate assessment of arterial flow changes; and (5) adequate length of follow-up. A star rating of 0 to 9 was allocated to each study based on these parameters. The quality assessment was performed by 2 authors independently. When discrepancies arose, papers were re-examined by the third author. Studies receiving 6 or more stars are considered “high-quality”.

Statistical analysis

We estimated from each cohort the cumulative prevalence and 95% confidence interval for each outcome. Rates of each

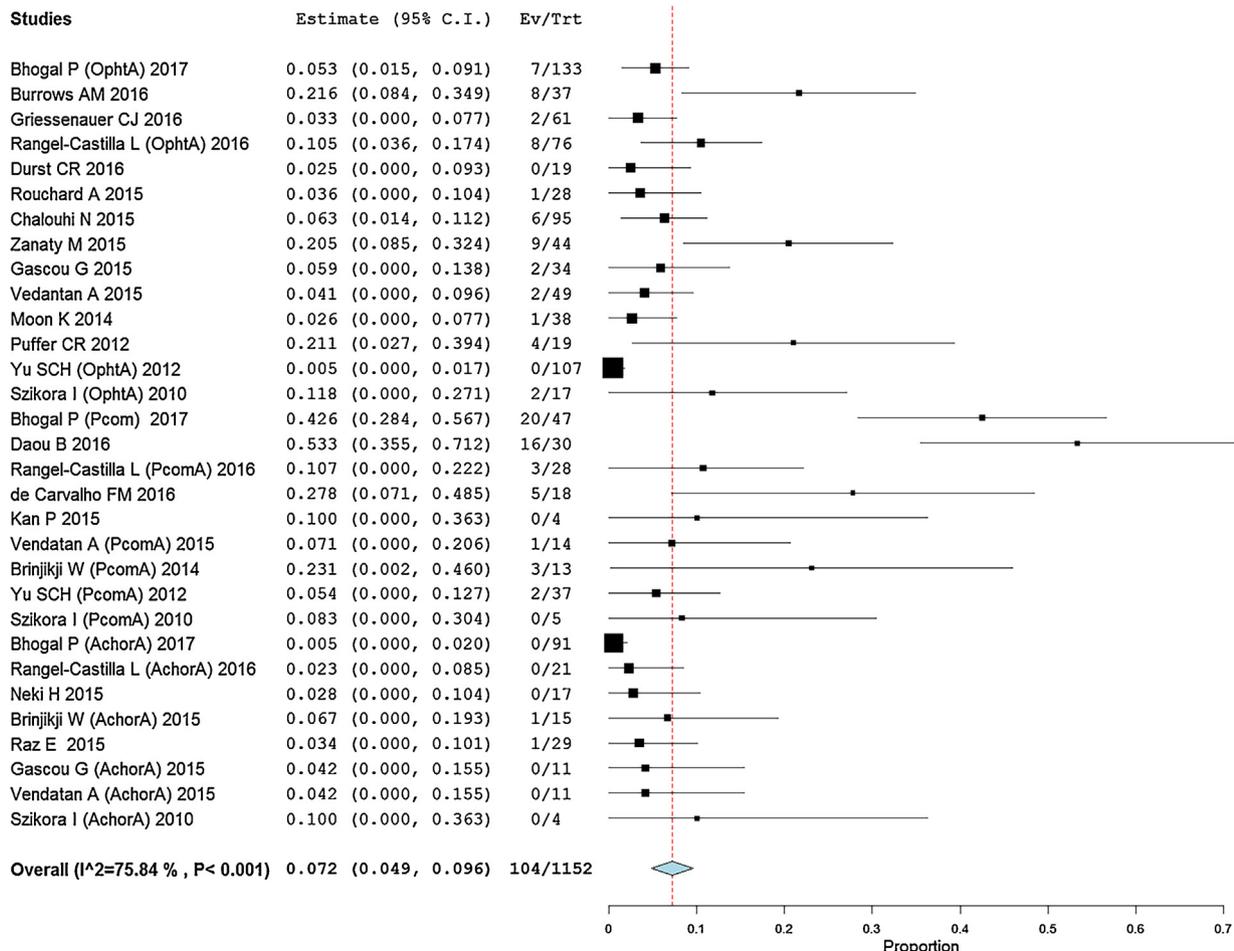


Fig. 1. Forest plot demonstrating the overall rate of internal carotid artery (ICA) branches occlusion (OphtA, PcomA, AchorA) following flow-diversion treatment.

outcome were pooled in meta-analysis across studies using the random-effects model [14]. We chose this model a priori because it incorporates both within-study variance and between-studies variance. This is recommended when data are heterogeneous. The heterogeneity of treatment effect across studies was evaluated using the I-squared (I^2) statistic, in which an I^2 value greater than 50% suggests substantial heterogeneity [15]. Chi² analysis was used to compare outcomes between groups when appropriate. Statistical analysis was performed using the software program OpenMeta [Analyst] (<http://www.cebm.brown.edu/openmeta/>).

Results

Literature review

The search strategy is summarized in Supplemental Table 1, and the included studies are reported in Supplemental Table 2. The search flow diagram is shown in Supplemental Fig. 1. The assessment of arterial occlusion and slow flow, and the relative radiological criteria, are summarized in Supplemental Table 3.

A total of 21 studies and 1152 supraclinoid ICA branches covered with a flow-diverter were analyzed. The included articles were divided into three groups: 14 studies for the OphtA, 9 for the PcomA, and 8 for the AchorA. Six articles reported information about all of the 3 arteries, and the data were analyzed separately in each of the 3 groups.

Quality of studies

Regarding the OphtA groups, 10 articles were considered “high-quality”, whereas 4 studies were “low-quality”. Among the PcomA group, 5 out of the 9 studies were rated “high-quality”. In the AchorA group’s studies, half of the reported studies were considered “high-quality”.

Patient population and aneurysm characteristics

The mean age of patients was 54 years (range 17–75), and the male/female ratio was 0.17 (Supplemental Table 4). Overall, 93.5% (95% CI=91–95.3%) of ICA aneurysms treated with the flow-diversion technique were unruptured, whereas 6.5% (95% CI=4.6–6.9%) were previously ruptured and were treated with coils or clipping in the acute phase. The proportion of saccular and fusiform aneurysms was 97.7% (95% CI=96.3–98.6%), and 2.3% (95% CI=1.3–3.7%), respectively. The mean size of aneurysms was 8.5 mm (range: 3–38).

Treatment characteristics and radiological follow-up

The most common device was PED (95.8%, 95% CI=96.3–98.6%), and most of the aneurysms were treated with one device (number of flow-diverters/aneurysm=1.2). Flow-diversion was used as first treatment modality in 92.5% of cases (95% CI=89.4–95%) (Supplemental Table 4).

Mean clinical and radiological follow-up was 12 months (range: 6–29). In about 90% of the reported patients, digital subtraction angiography (DSA) was performed during the early and long-term radiological follow-up. All cases of arterial flow changes were detected by DSA. In approximately 10% of cases, MRA or CTA were performed during the long-term radiological follow-up.

Outcome of the Supraclinoid ICA Side Branches Covered with Flow-diverting Stents

During a mean radiological follow-up of 12.3 months (median: 12, range: 6–29), the overall rate of supraclinoid ICA branches

occlusion was 7.2% (95% CI=4.9–9.6%) (incidence rate=7% per patient-year of follow-up) (Fig. 1).

Overall, 757 covered OphtAs were observed during a mean follow-up of 11.9 months (median 10.75, range: 6–29) (Table 1). The rate of OphtA occlusion was 5.9% (95% CI=3.1–8.6%) (incidence rate=6% per patient-year), whereas 1.6% (95% CI=0.5–2.8%) (incidence rate=1.6% per patient-year), of cases showed diminished flow (Supplemental Fig. 2 A, B). The incidence of immediate post-operative occlusion or diminished flow after flow-diversion was 1.2% (95% CI=0.2–2.6%) (Supplemental Fig. 3 A). No cases of symptomatic diminished flow were reported. On the contrary, 0.8% (95% CI=0.1–1.4%) (incidence rate=0.8% per patient-year), of treated patients were symptomatic after OphtA occlusion (monocular blindness or visual field deficit) (Supplemental Fig. 4A).

Of the 196 PcomAs covered with stents, 20.7% (95% CI=8.9–32.4%) were occluded during a mean follow-up of 12.7 months (median 12, range 6–22.5) (incidence rate=19.5% per patient-year), whereas 6.3% (95% CI=1.8–10.9%) showed diminished flow (incidence rate=5.9% per patient-year), (Supplemental Fig. 5A, B). Immediate post-operative flow changes were present in 4.4% of cases (95% CI=1.6–10.5%) (Supplemental Fig. 3B). No patients reported symptoms related to flow changes of the PcomA.

Overall, 199 AchorAs covered by the device were available during a mean follow-up of 12.5 months (median 12, range 6–22.3). The incidence of occlusion was 1% (95% CI=0.3–2.4%) (incidence rate=0.96% per patient-year) (Supplemental Fig. 6A). Similarly, arterial narrowing was reported in the same percentage of treated patients (Supplemental Fig. 6B). No cases of immediate arterial flow changes were reported. The incidence of symptoms related to AchorA occlusion was 1% (95% CI=0.4–2.3%) (transient hemiparesis and hemianopsia) (incidence rate=0.96% per patient-year) (Supplemental Fig. 4B).

Factors related to arterial flow changes

The mean age of patients with arterial flow changes was 52.4 years, whereas the mean age of patients with normal flow was 55.5 years ($P=0.3$) (Supplemental Table 5). The M/F ratio among patients with arterial occlusion or diminished flow was 0.1. However, the prevalence of female patients in the group with arterial flow changes compared to the group with normal flow was not statistically significant (90% vs 80%, $P=0.43$). Similarly, the prevalence of flow changes after coverage with single or multiple flow-diverters was comparable ($P=0.8$). There was a trend toward higher odds of arterial patency among arteries arising from the aneurysm (neck or dome) (OR=2.94, $P=0.06$). Overall, 94.5% (95% CI=82.2–99.4%) of patients with arterial occlusion presented adequate collateral circulation.

Study heterogeneity

Significant heterogeneity was noted in the analysis of the overall rate of arterial occlusion. Among the OphtA group, significant heterogeneity was noted in the analysis of the OphtA occlusion during follow-up. Small heterogeneity was reported in the analysis of diminished flow of covered PcomA. Finally, significant heterogeneity was reported for the rates of PcomA occlusion during follow-up and immediate occlusion or slow flow during treatment.

Discussion

Flow-diversion devices are widely used in the treatment of ICA aneurysms, allowing a high rate of angiographic success with a relatively low incidence of complications [1,16,17]. However, there are important concerns regarding possible occlusion of side branches, when the device is placed across the origin of the major supracli-

noid ICA vessels [4,5]. One mechanism involved in the arterial side branch occlusion is the “flow competition” of the collateral supply pathways of the cerebral vasculature. Due to the high density of the mesh, the pressure gradient into the artery is decreased after stent coverage: consequently, the blood flow through the collateral arterial networks becomes increased. This results in a further decrease of the pressure gradient across the jailed artery, with a possible risk of occlusion [18]. The effect of flow-diversion also depends on the local stent porosity that is influenced by the stent sizing. Berg et al. [19], in an animal model study, demonstrated that undersized stents are associated with a shorter deployment, more condensed pores, and higher mesh density, resulting in increased risks of side branch occlusion. In addition, in case of tortuous parent arteries, such as carotid siphon, the local stent deformation can influence the density of the pores, resulting in tighter mesh in the inner curves, with higher flow attenuation [20]. Our meta-analysis of nearly 1200 supraclinoid ICA vessels covered with flow-diverter stents demonstrated that the overall incidence rate of OphtA, PcomA, and AchorA occlusion was 7% per patient-year of follow-up. However, the meta-analysis showed important differences among occlusion rates, diminished flow, and related clinical events among each specific artery.

Ophthalmic artery

Of the 757 OphtA covered, roughly 6% were occluded (arterial occlusion rate of 6% per patient-year), with a low rate of clinically relevant related symptoms (0.8% among treated patients). The most important mechanism related to the branch preservation is the pressure gradient between the parent artery and its branches. This allows an aspiration effect that preserve the flow after coverage with the stent [21–23]. However, in case of significant collateral circulation, the pressure gradient across the device is usually not enough and lead to branch occlusion [24]. The OphtA presents a consistent, distal collateral circulation from the external carotid artery and this supports the low rate of clinically overt visual symptoms in cases of branch occlusion [25,26]. However, the correlation between OphtA occlusion and visual outcome is difficult, and the rate of symptoms related to flow-diverter placement across the ostium could be underestimated. Vedantam et al. [11], in a series of 49 OphtAs, reported 4% of asymptomatic OphtA occlusion. However, 6 patients experienced new visual symptoms at follow-up related to thromboembolic events after OphtA coverage. Similarly, Rouchaud et al. [20], in a recent series of 28 patients, after a complete and extensive neuroophthalmological examination, reported 21.4% and 17.9% of transient and permanent complications after coverage of the OphtA with flow-diverting stents, respectively [20]. In addition, the origin of the artery from the aneurysm dome appear associated with a trend toward visual ischemic symptoms [21,20]. Accordingly, although clinically well tolerated, the OphtA flow change may not be the only predictor of visual outcome after coverage with a flow-diverter stent.

Posterior communicating artery

Overall, nearly 20% and 6% of covered PcomA will undergo occlusion or will show diminished flow, respectively. In no cases were PcomA occlusion or slow flow associated with clinical symptoms. The aforementioned theory of gradient pressure may explain the high rate of occlusion of PcomA. In the most common pattern of posterior circulation, when the P1 artery is well represented, the direct connection to PcomA and the anastomotic circulation may explain the trend toward thrombosis of the PcomA [27]. Accordingly, the presence of a fetal variant, because PcomA represents the major supply to the posterior cerebral artery, creates a pressure gradient across the artery that preserves the flow and the

patency of the PcomA. Accordingly, all of the studies included in our meta-analysis reported 100% of patency of the fetal variant after placement of flow-diverter stents [6,28–29]. Interestingly, PcomA showed higher rates of immediate occlusion or diminished flow after treatment, compared to the other locations. Similarly, Brinjikji et al. [30] reported that initial post-angiographic flow reduction was significantly associated with occlusion of the PcomA in the long-term follow-up. In conclusion, the incidence of symptoms after coverage of PcomA with flow-diverter stents is rare, even with the high rate of related occlusion and slow flow.

Anterior choroidal artery

While the anastomotic support of the OphtA and PcomA is well defined, the collateral supply of the AchorA remains not fully predictable, and coverage of the arterial ostium is strategically limited, giving the neurological eloquence of this vascular territory [31–34]. Meta-analysis of the included studies showed a 1% incidence of AchorA occlusion with an arterial occlusion rate of 0.96% per patient-year. Most important, occlusion was clinically silent in most of cases, with approximately 1% of transient related symptoms. The pattern of collateral anastomosis with posterior choroidal branches, interpeduncular plexus, and PcomA could influence the rate of symptomatic occlusion, as well as the anatomical variants of AchorA. Takahashi et al. [35] described 7 cases of ICA obstruction, in which vertebral angiography demonstrated a retrograde filling of AchorA. In a series of 20 covered AchorAs, 14 of which were long-course variants, Neki et al. [36] reported no flow changes or symptoms after stent deployment, both in patients with long-course and short-course arteries. In a recent large series of 91 AchorAs covered with flow-diverter devices, Bhogal et al. [37] reported no arterial occlusion during 2 years of follow-up. The smaller diameter of the AchorA in comparison with the parent vessel, allows rapid blood flow through the stent into the artery, with a decreased tendency of occlusion [7,38]. Accordingly, the rarity of the angiographic occlusion and the low rate of neurological sequelae, demonstrated that placement of flow-diversion devices across the ostium of AchorA, when it is mandatory during aneurysm treatment, is feasible and safe.

Factors affecting the risk of ICA branches occlusion after flow-diversion

Understanding factors associated with ICA branch occlusion is important during flow-diversion treatment of intracranial aneurysms. However, factors related to arterial occlusion are poorly investigated in the literature, and the available data is often contradictory. Our meta-analysis did not reveal any significant association between demographic factors and arterial flow changes. The number of devices is strategically limited during the treatment due to the higher mesh density across the artery. Chalouhi et al. [38] reported a higher rate of OphtA occlusion when covered by more than one device (21% vs 8%). Similarly, Puffer et al. [24] reported that the mean number of PEDs in the patients with occluded OphtA or change in flow was 2.4 vs 1.9. However, in other studies, the number of devices used during treatment was not a significant predictor of sluggish flow [28,39]. We found that the incidence of arterial occlusion or slow flow was comparable among patients treated with one or multiple devices ($P=0.8$). Contrariwise, there was a trend toward higher odds of arterial patency among arteries arising from the aneurysm (neck or dome) ($OR=2.94$, $P=0.06$). However, the persistent runoff into branches originating from the aneurysms is reported as a factor associated with lower rate of aneurysm occlusion, probably related to an incomplete neointimal response [24,28,32]. Antiplatelet therapy certainly plays an important role for the safety of the flow-diversion treatment. However,

there is scant data showing any relation between antiplatelet therapy and the risk of arterial occlusion after flow-diversion. In a recent study, Durst et al. [39] reported a higher P2Y12 reactive units (PRU) and aspirin reactive units (ARU) in the subgroup with sluggish flow, than in the subgroup of normal flow, but the results were not significant. Finally, occlusion of covered branches is also the result of the presence of robust collaterals. We found that 94% of patients with arterial occlusion showed adequate collateral, supporting the observation that only few patients developed clinical consequences [24,26,28,32,39–41].

Limitations of the study

Our study has several limitations. A language bias should be underlined because we exclusively selected studies published in English. First, I^2 were above 50% for many of the estimates, suggesting substantial heterogeneity among the analysed outcomes. The articles reported are often small, retrospective, and single-institution series. Among studies rated “poor quality”, the angiographic outcome of covered arteries could be not appropriately investigated. Accordingly, the rate of occlusion and the related symptoms could be underestimated. Although in most of the reported cases, flow-diverting stent was the first treatment, we were unable to comment about the influence of the previous treatments. Platelet responsiveness, an important factor in determining arterial patency following treatment, was not systematically assessed, due to the scant data available.

Conclusions

Our meta-analysis conclusively demonstrated that flow changes among covered ICA branches are non-worrisome after flow-diversion treatment. OphthA and AchorA showed approximately 1% of symptomatic occlusion. Flow changes of the PcomA are common after flow-diversion, and are clinically silent. Adequate collateral circulation is frequently associated with asymptomatic arterial occlusion, whereas demographic factors and multiple stents appear not to be associated with a higher risk of arterial impairment.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.neurad.2018.07.006>.

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