

## Apport de l'imagerie multimodale avancée au bloc de neuroradiologie interventionnelle

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## Apport de l'Imagerie Multimodale Avancée au Bloc de Neuroradiologie Interventionnelle

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#### JURY

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A mes Parents, A Bénédicte.



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## Résumé

Les deux piliers de la Neuroradiologie Interventionnelle (NRI) sont depuis la naissance de cette spécialité dans les années 1960-70 : la technicité des « outils » employés et le guidage par l'image.

Grace à des avancées technologiques majeures, nos cathéters nous autorisent désormais à naviguer dans n'importe quelle artère du cerveau. Et l'ensemble des dispositifs de NRI existants nous permet de désobstruer une artère occlue, emboliser une lésion à risque de saignement ou bien reconstruire des vaisseaux pathologiques.

En revanche, si la résolution de l'angiographie numérique s'est progressivement améliorée au fil des années, nous ne disposions encore récemment que de peu d'éléments pour planifier et évaluer précisément nos traitements, ceci directement au bloc de NRI.

La première partie de ce travail a consisté à démontrer le potentiel d'une technologie largement disponible mais sous-employée. L'imagerie volumique par faisceau conique (*Cone-Beam CT*) est en effet une aide précieuse pour imager les dispositifs faiblement radio-opaques. Dans un deuxième temps, nous exposons au travers de plusieurs modèles précliniques, le potentiel extraordinaire de l'imagerie intra-vasculaire par tomographie en cohérence optique (*Optical Coherence Tomography*). Non utilisée en pratique clinique NRI jusqu'à ce jour, cette imagerie à très haute résolution a le potentiel de devenir un véritable microscope vasculaire utilisable in vivo.

Enfin, après la description des ces modalités morphologiques nous nous sommes efforcés de démontrer la valeur ajoutée des imageries fonctionnelles lors du traitement des pathologies neurovasculaires.

Nous illustrerons cette progression dans les techniques d'imagerie au travers de deux techniques très différentes pour le traitement des anévrismes intracrâniens; l'une endosacculaire (*WEB*) et l'autre pariétale (stents à diversion de flux).

Au total, l'importance de l'imagerie dans notre spécialité est encore en train de se renforcer, en raison de sa diversification. Il ne fait aucun doute que dans un avenir proche, la multiplicité des informations fournies sera disponible, en temps réel, par réalité augmentée, à la manière d'un pilote d'avion. Dans le futur, c'est même par l'imagerie que nous réaliserons nos interventions ; quand les systèmes à résonnance magnétique permettront de guider, à distance les cathéters jusqu'à leur cible.

*Mots clés* : *Radiologie, Imagerie médicale, Angiographie numérisée, Imagerie volumique par faisceau conique, Tomographie en cohérence optique, Mécanique des fluides numérique, Anévrisme cérébral.* 

## Summary

Since the very beginning of Interventional Neuroradiology (INR), the two pillars of this young specialty born in the 1960-70 have been both technological innovation and imaging.

Thanks to numerous evolutions, we now can navigate our catheters anywhere in the brain. And all the available devices allow us to open an obstructed artery, occlude an hemorrhagic lesion or reconstruct a pathological vessel.

The resolution of digital subtraction angiography has gradually improved over the years but up until recently we did not benefit from diverse options to plan and evaluate our treatments.

The first part of this work consisted in demonstrating the clinical potential of a widely available but underused modality, the Cone Beam Computed Tomography. It allows a very good visualization of devices presenting a low radiodensity.

In a second part, we exposed through multiple preclinical models, the potential impact of intravascular imaging with optical coherence tomography. Only used in the cardiology field, it could become an in vivo microscope for the analysis of neurovascular diseases and their treatment.

Finally, after the description of morphological imaging modalities, we demonstrated the interest of functional imaging for the treatment planning of the cerebrovascular diseases managed by INR.

We will illustrate this imaging progression through two very different approaches to treat intracranial aneurysms ; one endosaccular (*WEB device*) the other parietal (*Flow diverter stents*).

In total, the importance of imaging is continuously growing in our field, because of the diversification of INR imaging. There is no doubt that in few years from now the multiplicity of these data will be provided through advanced reality systems similarly with pilots helmet mounted displays. In the future, it is possible that treatments will even be performed through imaging when magnetic resonance system will allow the remote navigation of catheters up to their pathological target.

**Key Words :** Radiology, Medical Imaging, Digital subtraction angiography, Cone bean CT, Optical Coherence tomography, Computational fluid dynamics, Intracranial aneurysm, Arterio-venous malformation, Stroke.

## Liste des Abréviations

Angiographie 3D Rotationnelle				
Accident Vasculaire Cérébral				
Cone-Beam Computed Tomography				
Computational Fluids Dynamics				
Cellules Musculaires Lisses				
Flow Diverter Stent – Stent à Diversion de Flux				
Malformation Artério-Veinseuse				
Microscopie Electronique à Balayage				
Neuroradiologie Interventionnelle				
Hyperplasie Intimale				
Optical Coherence Tomography				
Thrombectomie Mécanique				
Ratio de Couverture de la Surface du Collet				
Woven EndoBridge				

We must try to expand the boundaries of human wisdom, empathy and perception, and there is no way of doing that except through education.

SENATOR J. WILLIAM FULBRIGHT

# Apport de l'Imagerie Multimodale Avancée au Bloc de Neuroradiologie Interventionnelle

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## Préambule

Basé sur des travaux de recherche clinique hospitaliers et de recherche expérimentale en laboratoire animalier, ce travail a pour but d'exposer la valeur des techniques avancées d'imagerie vasculaires neuroradiologiques. Avec les progrès de l'imagerie nous assistons à une très importante amélioration de la résolution spatiale avec désormais un accès possible aux caractéristiques fonctionnelles du réseau vasculaire.

- Nous montrerons tout d'abord le potentiel maximal d'une technique rayons-X actuellement largement disponibles dans les blocs de Neuroradiologie Interventionnelle, *la tomographie volumique à faisceau conique*.
- Ensuite nous aborderons une technique d'imagerie intravasculaire haute résolution à très fort potentiel mais jusqu'à ce jour encore inexistante en NRI clinique, *la tomographie en cohérence optique*.
- Enfin en complément de ces techniques d'imagerie morphologique nous évoquerons des techniques d'imagerie fonctionnelle désormais disponibles directement au bloc NRI.

Les travaux basés sur l'imagerie rayon-X ont été réalisés dans le service de Neuroradiologie du Professeur Spelle, tout d'abord à l'hôpital Beaujon puis à l'hôpital Bicêtre. La recherche basée sur l'imagerie optique a été conduite à l'université du Massachusetts dans le laboratoire du Professeur Gounis grâce à l'obtention d'une bourse d'échange Franco-Américaine Fulbright. Enfin les travaux sur les simulations de flux ont été menés en partenariat avec l'université de Waseda au Japon.

L'ensemble de ces travaux a abouti à la publication de 8 articles dans des revues internationales à comité de revue.

## Introduction

### **1. INTRODUCTION**

#### 1.1 La Neuroradiologie Interventionnelle

#### 1.1.1 Généralités

La Neuroradiologie Interventionnelle (NRI) est une spécialité née dans les années 1960-70 qui s'est rapidement développée notamment grâce aux progrès de l'imagerie médicale (**Fig. 1**). L'arrivée au début des années 1990, des coils à détachement contrôlé a fait de l'approche endovasculaire, la référence pour le traitement des anévrismes intracrâniens, remplaçant ainsi les indications neurochirurgicales, plus invasives car nécessitant une craniectomie. L'étude randomisée ISAT<sup>1</sup> a d'ailleurs démontré la supériorité de l'approche endovasculaire pour les anévrismes rompus pouvant être traités par les deux techniques.

Depuis la publication en 2015 de cinq études randomisées positives,<sup>2</sup> la NRI est au cœur de la prise en charge de l'accident vasculaire (AVC) ischémique. Quand un caillot sanguin occlut une artère encéphalique, il risque d'entraîner un infarctus cérébral. La thrombectomie mécanique (TM) consiste à retirer ce caillot sanguin par l'intermédiaire du cathétérisme des artères encéphaliques, ceci sous guidage radiologique.<sup>3</sup> La TM est devenue en association à la thrombolyse intraveineuse, le traitement de référence des accidents ischémiques cérébraux par l'occlusion d'une artère proximale. Cette « révolution »<sup>4</sup> dans le traitement des AVC conduit actuellement à un deuxième essor mondial de la NRI.



Figure 1. Système Angiographique Biplan au bloc de NRI de l'hôpital Bicêtre

#### 1.1.2 Anévrismes artériels

Dans ce travail de thèse nous allons nous focaliser sur le traitement des anévrismes artériels intracrâniens. Celui-ci encore exclusivement chirurgical jusqu'à la fin des années 1980. La chirurgie ayant pour but d'exclure l'anévrisme de la circulation sanguine en plaçant

un clip au niveau de son collet. L'idée d'une approche endovasculaire, et donc moins invasive, s'est ensuite développée.

Le traitement endovasculaire d'un anévrisme consiste en la mise en place en son sein d'un matériel thrombogène qui va conduire à son occlusion puis à sa « cicatrisation ». Des innovations technologiques successives ont permis l'exclusion sélective des anévrismes : initialement à l'aide de ballons largables<sup>5</sup> puis par des spires métalliques (coils)<sup>6</sup> et maintenant par des cages métalliques préformées (WEB).<sup>7</sup>

Les anévrismes peuvent également être traités grâce à l'utilisation de prothèses endovasculaires, se présentant sous la forme de structures tubulaires composées de fils métalliques (stents).

Récemment développés, les stents à diversion de flux ou flow-diverter stents (FDS) permettent la déviation du flux sanguin intra-anévrismal vers la lumière de l'artère porteuse en aval et vont donc promouvoir la thrombose de l'anévrisme grâce à la stagnation du flux sanguin à l'intérieur de celui-ci (**Fig. 2**).<sup>8-10</sup>



**Figure 2. Traitements modernes des anévrismes intracrâniens**. Technique chirurgicale : A) Clipping Techniques endovasculaires : B) Coiling C) Stent Flow-diverter D) WEB

L'approche Neuroradiologique interventionnelle a ainsi permis de réduire les taux de morbidité et de mortalité associés au traitement des anévrismes intracrâniens rompus, tout en améliorant significativement la qualité de vie des survivants.<sup>11</sup>

## Imagerie au Bloc NRI

## **2. IMAGERIE AU BLOC NRI**

#### 2.1 Angiographie Digitale avec Soustraction

La numérisation des images radiologiques, initiée dans les années 1970, a permis le développement de l'angiographie numérisée. Celle-ci consiste en l'acquisition d'une série d'images fluoroscopiques soustraites, pixel par pixel, à partir d'une image de référence, appelée masque.<sup>12</sup> Pendant cette séquence, si aucune modification de luminosité n'est intervenue en aucun point de la région étudiée, l'image résultante affichée sur l'écran apparaîtra blanche. A l'inverse si l'on injecte par voie intravasculaire un produit de contraste, les vaisseaux apparaîtront sur l'image soustraite en raison de l'augmentation de l'absorption des rayons X.

La finalité de l'angiographie numérisée soustraite est de supprimer tous les éléments qui sont invariables au cours de la séquence, c'est à dire les structures denses qui se projettent sur les vaisseaux (**Fig. 3**).



**Figure 3**. A) Radiographie du crâne de profil qui va servir de masque B) Même incidence après soustraction des structures radio-opaques et injection de produit de contraste iodé dans la carotide interne.

L'angiographie numérisée est utilisée au quotidien en NRI afin d'obtenir des cartographies vasculaires pour guider le cathétérisme des artères cérébrales et ainsi permettre le traitement de diverses pathologies neurovasculaires.

Toutefois cette technique présente plusieurs limitations. Il s'agit d'une imagerie de projection donc elle ne permet pas une représentation aisée de la complexité de l'anatomie vasculaire dans les trois dimensions de l'espace. Aussi, contrairement à ses résolutions temporelles et spatiales qui sont excellentes, la résolution en contraste de l'angiographie numérisée est limitée pour les structures et implants faiblement radio-opaques. En NRI, la plupart des dispositifs utilisés sont difficilement visibles en raison de leur taille extrêmement réduite (de l'ordre de quelques millimètres) et des alliages utilisés, peu absorbants.<sup>13-15</sup>

Au contraire de l'os, les structures biologiques peu denses comme le parenchyme cérébral, sont très mal visualisées avec les systèmes fluoroscopiques utilisés au bloc de NRI. Ainsi les premiers systèmes angiographiques ne permettaient pas de dépister certaines des complications ; comme par exemple une hémorragie cérébrale ou bien la phase initiale du développement d'un thrombus dans une artère.

#### 2.2 Tomographie Volumique par Faisceau Conique

Pour pallier ces limitations, les différents constructeurs ont progressivement intégré à leurs systèmes, des solutions d'acquisitions rotationnelles. L'objectif étant de proposer, directement au bloc de NRI des techniques d'imagerie à projections multiples, similaires à la tomodensitométrie en coupe, aussi appelée scanographie ou scanner.

Dans les années 1990, la technologie des capteurs plans a été initialement développée pour améliorer la qualité d'image des radiographies standard acquises par le biais du couple écranfilm.<sup>16, 17</sup> Le capteur plan comprend un nombre important de détecteurs individuels, chacun capable de stocker une charge électrique en réponse à une exposition aux rayons X. Chaque élément de détection comprend à la fois une diode photosensible et un composant électronique permettant la digitalisation directe du signal (**Fig. 4**).



**Figure 4**. **Technologie du capteur plan**. Un écran fluorescent composé d'un cristal d'iodure de césium transforme l'énergie des rayons X en lumière. Une matrice de photodiodes va ensuite transformer la lumière en signal électrique (*dans Kalender*<sup>16</sup>).

La lecture numérique sans conversion, associée à une cadence de plusieurs images par seconde ont également fait des capteurs plans une technologie idéale pour la fluoroscopie. Au début des années 2000, leur usage s'est généralisé à l'ensemble des salles d'angiographie.

La tomographie volumique par faisceau conique ou *Cone Beam Computed Tomography* (CBCT) est une technique développée au début des années 2000. C'est une modalité d'imagerie fluoroscopique dynamique qui permet la couverture d'un grand volume lors d'une rotation d'environ 200°. On peut la décrire simplement comme un scanner multi-détecteurs dans lequel les rangées de détecteurs ont été remplacées par une surface de détection (**Fig. 5**).<sup>18</sup>



Figure 5. Principe de la Tomographie volumique à faisceau conique (dans Gupta<sup>18</sup>)/

Pour répondre aux besoins de l'activité dans un bloc de Radiologie Interventionnelle, les constructeurs ont réalisé l'intégration commune sur un portique en forme de bras en « C », d'un capteur plan et d'un tube à rayon-X à faisceau conique (**Fig. 6**).



Figure 6. Bloc NRI. Système fluoroscopique par capteur plan, monté sur un portique en « C » suspendu. La résolution spatiale de la tomographie volumique par faisceau conique est supérieure à celle du scanner conventionnel, ce qui en fait une technique idéale pour étudier les structures bien contrastées comme la vascularisation cérébrale après injection de produit de contraste (**Fig. 6**).



Figure 6. Acquisition angiographique rotationnelle 3D. Elle permet de mesurer très précisément un anévrisme dans les trois plans de l'espace et ainsi choisir le dispositif d'embolisation le plus adapté.

Malgré une résolution en contraste légèrement inférieure à celle du scanner conventionnel, l'imagerie volumique par faisceau conique permet toutefois d'obtenir directement au bloc de NRI des images en coupe du parenchyme cérébral dont la qualité est en amélioration constante (**Fig 7**).



Figure 7. Etude en coupe du parenchyme cérébral. A) CBCT B) Scanner.

#### 2.3 Tomographie en Cohérence Optique

#### 2.3.1 Technologie

La tomographie en cohérence optique, *Optical Coherence Tomography* (OCT) est une technique d'imagerie médicale haute résolution qui utilise la réflexion de la lumière proche des infra-rouges pour produire des images en coupe des tissus biologiques avec une résolution de l'ordre du micromètre.

Le principe physique de l'OCT est similaire à celui de l'échographie. L'OCT est basé sur la mesure du retard et de l'intensité des échos optiques pour créer une image de la microstructure des tissus en fonction de la profondeur.

Cette très haute résolution est idéale pour étudier l'aspect de tissus biologiques à disposition en couches fines ainsi que les micro-caractéristiques des implants médicaux. La première application de l'OCT fut l'étude de l'œil, notamment de la cornée et de la rétine.<sup>19</sup> Quelques années plus tard l'incorporation de la fibre optique dans les systèmes OCT a permis de développer des cathéters pour l'imagerie intravasculaire des artères coronaires.<sup>20</sup>

L'OCT intravasculaire (**Fig. 8**) nécessite l'utilisation d'une fibre optique et d'un dispositif imageant (fine lentille de focalisation). Ce dernier est utilisé pour illuminer puis collecter la lumière rétrodiffusée par la paroi artérielle. L'acquisition des images a lieu lors du recul du cathéter lors d'une rotation à très haute vitesse du système optique.



Figure 8. Système OCT cardiologique.<sup>21, 22</sup> A) Schéma de la lentille de focalisation, B) Système de visualisation des images, C) Catheter OCT, D) Distalité du cathéter, E) Schéma de l'exploration d'une sténose athéromateuse.

#### 2.3.2 Application à la NRI

La faisabilité de l'utilisation de l'OCT intravasculaire a été démontrée en cardiologie au début des années 2000.<sup>23</sup> La haute résolution de cette technique autorise une analyse précise de la géométrie de la lumière et des sténoses artérielles. L'OCT permet une excellente étude de la structure des plaques athéromateuses (morphologie, biométrie, composition, érosion) ainsi que de l'interaction entre les stents et la paroi vasculaire, ce qui n'était jusqu'alors pas réalisable.<sup>20</sup>

De très rares études cliniques rapportent l'utilisation in vivo, en NRI de l'OCT. Elles suggèrent le potentiel de l'OCT pour évaluer l'athérosclérose intracrânienne,<sup>24</sup> le traitement des anévrismes cérébraux<sup>25,26</sup> et des AVC.<sup>27</sup> Mais cet usage est toujours extrêmement limité en NRI car les cathéters d'OCT ne sont pas optimisés pour la tortuosité de la navigation intracrânienne.<sup>28</sup>

En collaboration avec l'université du Massachusetts, un système optique spécialement conçu pour la NRI a été développé. Il peut être introduit au travers d'un microcathéter standard (0,017 inch de diamètre interne). La résolution approche 10  $\mu$ m et le champ de vue permet d'imager dans un rayon de 8 mm.

Dans un manuscrit soumis pour publication (Ughi GJ, Marosfoi M, King RM, **Caroff J** et al. *High-Frequency Optical Coherence Tomography enables in Situ Cerebrovascular Microscopy*), nous nous sommes efforcé de démontrer la faisabilité d'un système optique spécifiquement dédié à la NRI, l'OCT à haute fréquence.<sup>29</sup>

La vascularisation cérébrale est significativement plus tortueuse que les artères coronaires. Afin de tester les capacités de navigation de ce système HF-OCT dédié aux applications neurologiques nous avons utilisé un modèle porcin dans lequel les membres antérieurs ont été positionnés en hyperflexion afin de reproduire des courbes semblables à celles d'un siphon carotidien humain.<sup>30</sup> Dans notre étude, la navigation distale a été possible dans tous les cas. Et lors des tests de retrait, nous n'avons mis en évidence aucun artefact de distorsion. Ils sont liés à une friction excessive sur les composants internes du cathéter lors de la rotation et classiquement retrouvés avec les systèmes cardiologiques.<sup>20, 31</sup>

Si l'OCT n'est pas encore une technique d'imagerie de pratique clinique en NRI. Le développement de systèmes HF-OCT destinés à la navigation intracrânienne, autorisant l'accès a des artères tortueuses et de petit calibre permet donc d'envisager très prochainement un usage large de cette technologie dans le champ de la NRI.

Nous allons exposer dans les chapitres suivants comment ces techniques d'imagerie s'appliquent aux techniques les plus récentes et innovantes dans le traitement des anévrismes intracrâniens. En ouverture nous évoquerons également pour chacune l'apport potentiel de modalités d'explorations fonctionnelles.

## Dispositifs Intra-sacculaires

### **3. DISPOSITIFS INTRA-SACCULAIRES**

Les dispositifs intra-sacculaires à diversion de flux sont une toute nouvelle approche pour le traitement endovasculaire des anévrismes intracrâniens, apparue il y a moins de 10 ans.<sup>32</sup> Il s'agit de cages métalliques très finement tressées qui entraînent une modification du flux sanguin au niveau du collet anévrismal et ainsi une thrombose progressive de l'anévrisme. Le WEB<sup>®</sup> (*Woven Embolization System*) est actuellement le système le plus utilisé (**Fig. 9**). Il a été initialement conçu pour le traitement des anévrismes de bifurcation à collet large, son utilisation est en pleine expansion.<sup>33</sup>



Figure 9. WEBs. A) Forme en baril, B) Forme sphérique.

#### 3.1 Visualisation – Apport du CBCT

#### ✓ Problématique

Le WEB possède une structure micro-tressée, constituée de fils de nitinol de très fin diamètre (19 à 38 microns), d'où sa très faible visibilité en angiographie numérique (**Fig. 10**). La structure du WEB a récemment été améliorée avec l'ajout d'un cœur de platine dans chacun des fils de nitinol.<sup>34</sup> Malgré cela et notamment pour les plus petits dispositifs, la radio-opacité du WEB demeure très faible.

Le but de notre étude était de démontrer le potentiel du CBCT comme méthode de contrôle du bon positionnement du WEB au sein de l'anévrisme, avant et après son détachement.<sup>15</sup>



**Caroff J**, Mihalea C, Neki H et al. Role of C-Arm VasoCT in the Use of Endovascular WEB Flow Disruption in Intracranial Aneurysm Treatment. *AJNR Am J Neuroradiol. 2014 Jul 15;35(7):1353–7* 

#### ✓ Résultats

Nous avons mis au point un protocole d'acquisition CBCT permettant à la fois la bonne visualisation du dispositif WEB mais également des artères intracrâniennes :

La rotation du bras en « C » à 200° permet d'acquérir 620 images de projections. Le WEB est positionné au centre de l'image, la taille du détecteur est fixée à 22 cm de diamètre, la taille des pixels à 0,154 mm, autorisant ainsi des reconstructions à haute résolution. La résolution spatiale obtenue est de 0,109 mm, supérieure à celle d'un scanner conventionel.<sup>35</sup>

Entre Mars 2012 et Juillet 2013, 13 anévrismes traités par WEB ont été inclus. L'angiographie numérisée et le CBCT ont été évalués et comparés par deux lecteurs. Le CBCT a été jugé de qualité informative dans 91% des cas.



#### Figure 10. WEB déployé dans un anévrisme sylvien droit.

Mal visualisé en A) angiographie soustraite et en B) radiographie. Alors que par C) CBCT, on visualise précisément la structure du WEB et son rapport au collet de l'anévrisme.

#### ✓ Impact clinique

Dans cette étude pilote, le contour du dispositif était bien visible dans tous les cas. Une protrusion du dispositif a été démontrée dans 5 cas, conduisant à un repositionnement ou une modification de la taille du WEB. L'absence de groupe contrôle ne permet pas de démontrer ici l'impact clinique direct du CBCT sur la sureté et l'efficacité du WEB.

Toutefois nous avons observé que à partir des informations du CBCT la stratégie thérapeutique initiale a été modifiée dans presque 40 % des cas. Ceci pour un faible « coût » en temps, rayons et produit de contraste reflétant probablement son grand intérêt clinique.

#### ✓ Conclusion

Au contraire de l'angiographie conventionnelle, le CBCT est un excellent outil pour évaluer le déploiement et le positionnement du WEB. Le CBCT permet une excellente évaluation du dimensionnement du WEB et de sa relation avec les artères porteuses. Cette information est très probablement à même d'améliorer la sûreté du dispositif en évitant de potentielles protrusions de WEB dans une artère porteuse, à risques de complications thrombo-emboliques.

#### 3.2 Evaluation clinique

#### ✓ Problématique

L'évaluation clinique du WEB a tout d'abord démontré qu'il s'agissait d'un dispositif faisable et sûr pour traiter les anévrismes de bifurcation.<sup>7, 36, 37</sup> En revanche, l'efficacité de cette nouvelle approche est toujours en cours d'évaluation. En raison de l'aspect innovant du WEB, les échelles d'évaluation de l'occlusion anévrismale existantes, créées pour l'évaluation du coiling, n'apparaissent pas ici adaptées.<sup>38</sup>

Le CBCT, qui permet d'analyser le positionnement du WEB avant son détachement lors du traitement d'un anévrisme, est également un excellent outil lors du suivi, afin d'évaluer la qualité de l'occlusion anévrismale.

Le but de notre étude était de proposer une nouvelle classification pour l'évaluation de l'occlusion anévrismale, dans laquelle le CBCT aurait une place centrale.<sup>39</sup>



**Caroff J**, Mihalea C, Tuilier T et al. Occlusion assessment of intracranial aneurysms treated with the WEB device. *Neuroradiology; 2016 Jun 15;58(9):1–5* 

#### ✓ Résultats

Nous avons décrit une échelle à 5 grades (Bicêtre Occlusion Score Scale - BOSS). Elle a la particularité d'être parfaitement adaptée à l'usage spécifique du WEB (**Fig. 11**). Par exemple on considère l'opacification du récessus proximal du WEB comme une occlusion complète et non pas comme un collet résiduel. Sont également décrits, les cas d'opacifications intra-dispositif résiduelles isolées, situations propres au WEB.

Nous avons fourni trente imageries de suivi après embolisations par WEB à sept utilisateurs expérimenté du dispositif. Nous leur avons demandé d'évaluer l'occlusion selon les échelles BOSS et WOS, tout d'abord en ne disposant que des images d'angiographie numérique. Dans un deuxième temps les relecteurs disposaient d'images CBCT supplémentaires.



**Figure 11**. **Bicêtre Occlusion Score Scale.** 0 = Occlusion complète 0' = Cupule proximale 1 = Opacification intra WEB 2 = collet résiduel 3 = Anévrisme résiduel

Nous avons montré que le CBCT permettait d'améliorer la concordance inter-observateurs lorsque la classification BOSS était utilisée, mais aussi lorsque des classifications plus simples en 3 ou 2 grades étaient utilisées (**Tableau 1**).

Kappa values	5-point BOSS scale	3-point WOS scale	2-point dichotomized scale	WEB persistent filling
Without VasoCT	0.52 SE = 0.04, 95 % CI = 0.48 to 0.57	0.57 SE = 0.029, 95 % CI = 0.52 to 0.63	0.82 SE = 0.040, 95 % CI = 0.81 to 0.96	$0.48 \\ SE = 0.040, \\ 95 \% \\ CI = 0.41 \\ to 0.56$
With VasoCT	$0.55 \\ SE = 0.023, \\ 95 \% \\ CI = 0.51 \\ to 0.60 \\ \end{bmatrix}$	0.59 SE=0.029, 95 % CI=0.53 to 0.65	$0.88 \\ SE = 0.040, \\ 95 \% \\ CI = 0.74 \\ to 0.90 \\ \end{cases}$	$0.61 \\ SE = 0.040, \\ 95\% \\ CI = 0.54 \\ to 0.67$



Le CBCT démontre ici toute sa valeur car la visualisation en coupe des images acquises permet notamment une meilleure différenciation entre les opacifications intra-anévrismales et les opacifications uniquement intra-WEB, dont la prise en charge diffère.

#### ✓ Limites à l'application clinique

A ce jour, l'échelle la plus couramment utilisée, est celle en 3 points (WEB Occlusion Scale - WOS).<sup>40</sup> C'est une méthode reproductible pour l'évaluation des résultats angiographiques du WEB.

L'échelle BOSS peut paraître plus complexe, mais elle identifie des catégories de patients avec probablement des problématiques cliniques différentes. Si l'accord inter-observateurs est apparu relativement faible dans notre étude. Il faut toutefois noter qu'il l'était également avec l'échelle WOS de référence et que l'apport du CBCT a permis de légèrement réduire cet écart entre les deux classifications.

Suite à la parution de notre manuscrit nous avons publié une lettre afin d'expliciter l'intérêt de notre classification.<sup>41</sup>

#### ✓ Conclusion

Notre échelle en 5 points permet d'identifier des sous-groupes d'anévrismes avec des risques différents (de récurrence ou de resaignement). Ils nécessitent probablement d'être séparés, alors que nous sommes encore à la phase initiale de l'évaluation du WEB. Quelle que soit l'échelle utilisée, le CBCT a une très nette valeur ajoutée, en améliorant la reproductibilité et donc en permettant une analyse plus précise.

#### 3.3 Evaluation du pronostic angiographique par OCT

#### ✓ Problématique

L'embolisation par coils des anévrismes rompus est actuellement la technique de référence.<sup>42</sup> Toutefois, l'une des limitations de l'embolisation par coiling est le risque de recanalisation ; soit en raison d'une cicatrisation incomplète, d'une compaction des coils ou bien d'une croissance continue de l'anévrisme. De ce fait une surveillance au long terme est nécessaire pour ces patients.<sup>11, 43</sup> Les données cliniques montrent qu'environ 20% des patients vont présenter une recanalisation de leur anévrisme et que 10% des anévrismes coilés nécessiteront un deuxième traitement.<sup>42</sup> Des taux plus élevés de recanalisation ont été décrit dans les anévrismes à collet large, probablement en raison d'une moins bonne couverture du collet.<sup>44</sup>

Des études précliniques ont montré in vitro que lors de l'utilisation de flow-diverters intrasacculaires autres que le WEB, la reconstruction du collet anévrismal était une composante fondamentale afin d'obtenir une réduction satisfaisante du flux intra-anévrismal.<sup>45</sup> Les nouvelles générations de coils<sup>46</sup> et les dispositifs intra-sacculaires à diversion de flux ont le potentiel technologique<sup>7</sup> pour améliorer la couverture du collet.

Le but de notre étude était d'évaluer l'homogénéité de la couverture du collet anévrismal par HF-OCT lors de l'utilisation de coils à diversion de flux, puis d'étudier son importance dans la guérison angiographique lors du suivi.<sup>47</sup>



King RM, Marősfoi M, **Caroff J** et al. High frequency optical coherence tomography assessment of homogenous neck coverage by intrasaccular devices predicts successful aneurysm occlusion. *Journal of NeuroInterventional Surgery. 2019 Apr 29* 

journal of Neuronnervencional Surgery. 20197

#### ✓ Résultats

Pour cette étude, nous avons créé chirurgicalement des anévrismes de bifurcations et des anévrismes latéraux dans un modèle canin (n=11). Sept étaient traités par un dispositif endosacculaire de nouvelle génération (DENG) similaires à des coils à diversion de flux et quatre par des coils standard en platine selon la technique de référence.

Une étude HF-OCT permettait d'évaluer la couverture du collet après implant et lors du suivi. Une segmentation automatique des images a permis d'individualiser les interstices les plus larges dans cette couverture afin de les corréler à l'occlusion anévrismale à 3 mois.

Il n'y avait pas de différence dans les taux d'occlusion entre les deux techniques (P=0,045).

Nous avons retrouvé que lors de l'utilisation de DENG, un défaut de couverture du collet  $>1mm^2$  était corrélé à un défaut d'occlusion à 3 mois (p=0.047). Et ce seuil permettait de prédire l'échec dans tous les cas.



**Figure 12**. **Analyse HF-OCT en rendu de volume 3D (rangée supérieure) et en coupe 2D.** Endothélialisation progressive d'un collet complétement et homogènement couvert.



#### Figure 13. Anévrisme de bifurcation embolisé par un DENG.

 A) L'angiographie semble montrer un positionnement satisfaisant du dispositif au sein de l'anévrisme. B) L'étude HF-OCT montre toutefois un espacement significatif dans la couverture du collet (flèche). C) Le contrôle à 3 mois montre une opacifiaction persistante du sac anévrismal à ce niveau.

#### ✓ Impact clinique

Dans cette étude, nous avons démontré qu'une couverture uniforme du collet est indispensable pour obtenir un bon résultat angiographique. L'HF-OCT elle la seule technique qui permet actuellement de réaliser cette évaluation très précise immédiatement au bloc opératoire lors du traitement (**Fig. 12 et 13**).

Ceci avec l'impact potentiel pour l'opérateur de renforcer ou de modifier immédiatement le traitement réalisé afin d'assurer un bon résultat angiographique lors du suivi.

#### ✓ Conclusion

Lorsque des nouveaux dispositifs intra-sacculaires sont utilisés pour l'embolisation des anévrismes intracrâniens, l'HF-OCT autorise une analyse précise de leur positionnement dans l'anévrisme. L'OCT permet de dépister de fins intervalles dans la couverture du collet.

Nous avons montré, in vivo dans un modèle animal que la présence d'une couverture inhomogène du collet était prédictive d'une occlusion incomplète lors du suivi.

#### 3.4 Imagerie fonctionnelle – Simulations de flux

#### ✓ Problématique

Si les résultats initiaux du WEB sont très encourageants.<sup>37, 48</sup> Un rapport clinique récent a décrit dans certains cas, lors du suivi, une dégradation de la qualité de l'occlusion anévrismale par rapport au résultat initial ; en raison d'une modification de la forme du dispositif.<sup>49</sup> En effet, Cognard et al. ont rapporté une « rétraction » du dispositif dans 64% des cas.

Les mécanismes à l'origine de ce phénomène sont à ce jour inconnus. Le flux sanguin

pulsatile pourrait être à l'origine d'une compaction du WEB. Toutefois lors du suivi on visualise parfois une diminution de hauteur du WEB du dôme vers le centre, c'est-à-dire de la face non exposée au flux sanguin. Ainsi certains auteurs suspectent que cela soit la rétraction du caillot à l'intérieur du WEB qui entraîne sa rétractation.<sup>50</sup>

La NRI est une spécialité basée sur la morphologie, celle des vaisseaux. La taille, la tortuosité et les bifurcations des artères sont pour nous des routes d'accès plus ou moins aisées que nous traçons grâce aux rayons X. Nous étudions la morphologie des vaisseaux pour adapter au mieux nos dispositifs d'embolisation. Mais la vascularisation cérébrale n'est pas un système inerte à la façon d'un modèle en silicone que l'on imprime maintenant en 3D en quelques minutes.

Nous savons qu'il ne suffit pas de bien remplir un anévrisme avec des coils pour obtenir un résultat satisfaisant au long terme. En effet certains auteurs ont montré que la densité de la masse de coils n'était pas corrélée aux taux de recanalisation.<sup>51</sup>

Il y a des mécanismes biologiques (croissance de l'anévrisme lui-même, mauvaise cicatrisation du thrombus sacculaire, absence de formation de néointima) et hémodynamiques (pulsatilité sanguine) impliqués<sup>52</sup> qu'il faudrait savoir évaluer pour les intégrer à notre stratégie thérapeutique et ainsi garantir un résultat durable.

C'est pourquoi nous avons besoin d'une imagerie plus performante, qui nous apportera en plus d'une étude morphologique précise, des informations sur la fonctionnalité du réseau vasculaire cérébral.

Les simulations de flux ou *Computational Fluid Dynamics* (CFD) sont utilisées depuis de nombreuses années en NRI, le plus souvent dans le but de prédire le risque de rupture d'un anévrisme cérébral découvert fortuitement.<sup>53</sup>

Le but de notre étude était d'utiliser des simulations de flux simples et disponibles directement au bloc NRI afin de déterminer si les modifications de forme des WEB pouvaient être imputées, au moins en partie au flux sanguin.<sup>54</sup>



**Caroff J**, Mihalea C, Da Ros V et al. A computational fluid dynamics (CFD) study of WEB-treated aneurysms: Can CFD predict WEB "compression" during follow-up? *J Neuroradiol. 2017 Jul;44(4):262–8* 

✓ Résultats

Nous avons analysé les imageries 3D rotationnelles pré-opératoires de 22 anévrismes consécutifs traités par WEB. Nous avons calculé le ratio entre le flux sanguin entrant dans l'anévrisme et le flux dans l'artère porteuse afin d'estimer simplement l'exposition de chacun des anévrismes au flux sanguin (**Fig. 14**).

La modification de forme du WEB lors du suivi n'était pas corrélée au volume de l'anévrisme, à l'aspect ratio ni à la taille du collet. En revanche il existait une corrélation significative avec l'exposition au flux sanguin (p<0,018).



Figure 14. Anévrisme sylvien traité par WEB.

A) Angiographie avant traitement, B et E) occlusion complète immédiate.C et F) le contrôle à 6 mois montre que le WEB a pris une forme en papillon.D) l'analyse CFD montre un anévrisme fortement exposé au flux de l'artère porteuse.

✓ Application clinique

Les techniques de CFD sont souvent très consommatrices en temps, en raison du prétraitement manuel des données et puis du temps de calcul par l'ordinateur. Nous avons ici utilisé une solution logicielle développée en partenariat avec l'université Waseda au Japon (*https://hemoscope.com*). L'avantage ici est que l'ensemble de la procédure est simplifié, automatisé et réalisable en quelques minutes directement au bloc NRI, notamment pendant la planification du traitement. Cette technologie ouvre la voie à un usage large des simulations de flux dans le cadre de nombreuses applications NRI.

Ce travail préliminaire peut paraître limité car il ne rapporte pas les conséquences cliniques pour les patients de ces phénomènes de modification de forme du WEB lors du suivi. Toutefois le but de cette étude était plus physiopathologique que clinique, d'ailleurs certains auteurs ont déjà consacré des registres cliniques à la problématique de la rétraction des WEBs.<sup>55, 56</sup>

De plus nous avons complété cette étude par une analyse exhaustive des images CBCT lors du suivi pendant de plus de deux ans de 60 anévrismes traités par WEB dans notre institution. Cette analyse rapporte précisément la fréquence du phénomène, ses liens avec l'anatomie et le sizing des WEB. Ce travail vient d'être présenté en Octobre 2019 lors du congrès de la *World Federation of Interventional and Therapeutic Neuroradiology*.

#### ✓ Conclusion

Les mécanismes à l'origine de la modification de forme des WEB lors du suivi sont probablement multifactoriels. La rétraction du caillot en cours de formation au sein de l'anévrisme en est probablement le mécanisme principal. Mais il apparaît d'après notre étude que l'exposition à un important afflux sanguin soit au moins en partie impliquée dans ce phénomène.

Les explorations fonctionnelles hémodynamiques ne sont pas à proprement parler une technique d'imagerie mais plutôt une technique basée sur l'imagerie. Elles semblent en tout cas à même d'apporter des informations utiles à l'établissement de la meilleure stratégie thérapeutique en NRI (choix du type dispositif, de sa taille....).

## Stents à Diversion de Flux
## 4. STENTS A DIVERSION DE FLUX

L'utilisation des stents intracrâniens pour le traitement des anévrismes est en nette croissance depuis une dizaine d'années car ils permettent de palier certaines limites du traitement conventionnel par coils.<sup>57</sup>

Les stents *sans effet de diversion de flux* rendent accessible au traitement endovasculaire des anévrismes à collet large auparavant uniquement pris en charge par chirurgie.<sup>58-60</sup> Ils sont utilisés afin de permettre le maintien des coils dans le sac anévrismal, sans risquer une protrusion dans l'artère porteuse. Ils ont également démontré leur efficacité pour réduire les taux de recanalisation.<sup>57</sup>

Les stents à diversion de flux ont introduit une approche thérapeutique complètement innovante.<sup>9</sup> Après leur déploiement en regard de l'anévrisme, le flux intra-anévrismal va être considérablement réduit et une thrombose intra-sacculaire va s'initier. Dans un deuxième temps, la couverture du stent par une néo-endothélialisation va entraîner l'exclusion défintive de l'anévrisme de la circulation systémique et donc sa guérison. L'utilisation des FDS est associée à des taux de guérison très élevés notamment pour des anévrismes de grande taille, jugés auparavant très difficiles à traiter.<sup>61</sup>

### 4.1 Apport du CBCT pour le suivi des FDS

### ✓ Problématique

Une des limites à l'utilisation des stents en NRI est leur faible radio-opacité. Il est donc difficile de juger de leur bon positionnement en utilisant uniquement la fluoroscopie. Nous savons qu'un mauvais positionnement peut être source de complication<sup>62</sup> et aussi qu'une bonne apposition à la parois est fondamentale afin d'obtenir la guérison de l'anévrisme.<sup>63</sup> C'est pourquoi progressivement, l'usage de l'imagerie volumique par capteur plan s'est imposée après l'implantation des stents intracrâniens afin de vérifier leur bon positionnement.<sup>13, 64, 65</sup> En revanche, lors du suivi post-opératoire, l'utilisation du CBCT n'est que très peu répandue.

L'hyperplasie intimale (HI) est une réaction excessive de la paroi des vaisseaux qui est fréquente après traitement par FDS<sup>66-68</sup> et qui peut parfois être la cause d'accident ischémique.<sup>69</sup> Dans des modèles animaux, le CBCT a été validé pour la mesure de l'hyperplasie intra-stent.<sup>66</sup>

# Le but de notre étude était de démontrer l'intérêt de l'usage systématique du CBCT lors du suivi des anévrismes traités par FDS pour dépister l'HI.<sup>10</sup>



**Caroff J**, Iacobucci M, Rouchaud A et al. The occurrence of neointimal hyperplasia after flow diverter implantation is associated with cardiovascular risks factors and the stent design. *Journal of NeuroInterventional Surgery; 2019 Jun;11(6):610–3* 

### ✓ Résultats

Nous avons étudié une cohorte de 148 patients traités par FDS et suivis par CBCT dans notre département.

En plus de montrer l'intérêt du CBCT pour chaque individu, afin de dépister la présence d'HI ; ceci avec un très bon agrément entre les observateurs (kappa=0,88) (**Fig. 15**). Cette étude a également permis pour la première fois dans la littérature de déterminer plusieurs facteurs de risque de développement d'HI intra FDS.

Il est apparu que la survenue de l'HI n'était en rien corrélée aux caractéristiques anévrismales. En revanche il existe une nette association avec les facteurs de risque cardio-vasculaires du patient (tabac, dyslipidémie, HTA) lors du suivi précoce (< 12 mois). Egalement, la survenue d'HI était plus fréquente lorsqu'un FDS en nitinol (*SILK stent* = 68%) était utilisé, par rapport à un stent en Chrome-Cobalt (*Pipeline stent* = 38%) (P<0,02).



**Figure 15**. A) L'angiographie numérisée ne permet pas de visualiser une fine hyperplasie intimale développée sur toute la longueur du FDS, B) au contraire du CBCT (flèche).

### ✓ Application clinique

Après la pose d'un FDS, la néo-endothélialisation est une réaction normale mais ambivalente. D'une part elle est souhaitable et contribue à la cicatrisation du collet, donc à la guérison de l'anévrisme. Mais si elle est excessive, elle risque d'entraîner une réduction du flux sanguin, voir l'occlusion d'une branche artérielle recouverte par le stent.

Ce travail a un intérêt clinique évident en décrivant pour la première fois les facteurs individuels et opératoires prédisposant à la survenue de ce phénomène. En fonction, le clinicien pourra être amené dans certaines situations à privilégier une autre stratégie que la mise en place d'un FDS.

### ✓ Conclusion

Nous avons montré grâce à la précision de l'étude CBCT que l'hyperplasie intimale est une complication qui peut être anticipée et peut être même évitée en traitant les facteurs de risque cardiovasculaires des patients.

Le design des FDS et notamment les matériaux utilisés impactent directement le risque de survenue d'HI lors du suivi.

### 4.2 Apport de l'OCT pour le suivi des FDS

### 4.2.1 L'OCT pour évaluer l'hyperplasie intimale

### ✓ Problématique

Nous avons vu précédemment que l'HI est fréquemment retrouvée durant le suivi des anévrismes traités par FDS (55% à 1 an) et peut parfois conduire à des complications ischémiques retardées.<sup>10</sup> Nous avons également démontré que les différents matériaux utilisés pour produire les FDS influençaient le développement d'HI.

Les FDS avec un revêtement à la phosphorylcholine ont fait preuve d'une thrombogénicité réduite à la fois in vitro,<sup>70</sup> et in vivo.<sup>71</sup> Il est possible que ces nouveaux FDS soient donc associés à une HI réduite.

Le CBCT est un bon outil pour dépister l'HI excessive, notamment car il est largement disponible. Toutefois, sa résolution spatiale est tout de même limitée et ne permet pas de mettre en évidence de faible variations d'HI.

Après implantation d'un stent coronarien, la mesure de l'HI in vivo par OCT est fortement corrélée aux mesures histologiques (gold standard).<sup>72, 73</sup>

Les FDS et les stents coronariens ont des designs très différents. La porosité du FDS est nettement inférieure et ses mailles sont beaucoup plus fines.

Le but de notre étude était d'évaluer la faisabilité de la mesure de l'HI des FDS in vivo par OCT afin d'étudier la réponse vasculaire à un nouveau FDS recouvert par un revêtement bio-modulateur.<sup>74</sup>



**Caroff J**, Tamura T, King RM et al. Phosphorylcholine surface modified flow diverter associated with reduced intimal hyperplasia. *Journal of NeuroInterventional Surgery. 2018 Nov;10(11):1097–101* 

### ✓ Résultats

Dans cette étude nous avons utilisé un modèle anévrismal lagomorphe et deux types de FDS, l'un avec et l'autre sans revêtement à la phosphorylcholine. L'incubation d'élastase dans l'artère carotide commune droite du lapin induit après ligature distale la formation d'un anévrisme. Celui-ci est traité dans un deuxième temps par la mise en place d'un FDS dans l'artère sous-clavière droite.

Nous avons ensuite mesuré à 30 jours l'HI in vivo par OCT. Après prélèvement chirurgical du segment artériel stenté, l'HI a également été évaluée en histologie. L'épaisseur maximale de l'HI était mesurée par les deux techniques au niveau de 5 localisations précises (**Fig. 16**).



**Figure 16**. **Photographie de l'artère sous-clavière après prélèvement chirurgical.** L'épaisseur de l'HI a été mesurée aux deux extrémités du stent (1,5), à hauteur de l'anévrisme (2a, b,c), en aval de l'anévrisme (3) et au niveau de l'ostium de la vertébrale (4).

L'OCT a été utilisé pour mesurer l'HI dans 227 localisations. Les mesures OCT étaient fortement corrélées avec les mesures histologiques ( $r^2=0.83$ ; pente=0.988; P<0,0001). Les stents avec revêtement à la phosphorylcholine présentaient significativement moins d'HI qu'un FDS standard (p<0,0001).



Figure 17. Comparaison entre une coupe histologie (gauche) et OCT (droite).

### ✓ Potentiel clinique

En recherche préclinique, l'OCT apparaît comme une technique innovante extrêmement utile pour le développement et la caractérisation de nouveaux implants chirurgicaux endovasculaires. L'OCT permet en effet des mesures in vivo, précises et répétées ; ce que n'apporte à ce jour aucune autre technique d'imagerie (**Fig. 17**).

La mise à disposition prochaine en pratique clinique d'une telle modalité intravasculaire à très haute résolution permettra ainsi de réaliser un suivi très précis après mise en place d'un FDS. On évaluera la croissance tissulaire au collet, qui conduit à la guérison de l'anévrisme. Et l'HI intra-stent qui peut entrainer une sténose et une réduction du flux sanguin en aval.

Dès aujourd'hui, ces stents traités à la phosphorylcholine sont disponible, et doivent probablement être favorisés pour les populations à risque d'HI (identifiées dans le travail précédent).

### ✓ Conclusion

L'OCT est une technique qui permet le monitoring in vivo de la réponse endothéliale après pose de FDS.

Dans un modèle animal, le revêtement des FDS par phosphorylcholine permet de réduire le développement de l'hyperplasie intimale.

### 4.2.2 L'OCT pour évaluer l'endothélialisation normale / modèle de bifurcation

### ✓ Problématique

La diversion de flux représente un changement de paradigme pour le traitement endovasculaire des anévrismes intracrâniens. Pour les anévrismes larges du siphon carotidien les résultats ont prouvé être excellents.<sup>61</sup>

Désormais, de plus en plus d'usages « *off-label »* sont décrits dans la littérature. Les FDS sont maintenant utilisés pour des anévrismes petits,<sup>75</sup> distaux,<sup>76</sup> et de bifurcation.<sup>77</sup> Toutefois, l'usage des FDS dans les bifurcations reste très controversé, avec des taux élevés de complications ischémiques dans le territoire recouvert par le stent.<sup>77-81</sup>

Malgré cet usage croissant, les mécanismes de guérison des FDS ne sont que partiellement compris. Il est suggéré qu'il s'agisse d'une endothélialisation continue des mailles du stent, en combinaison avec une thrombose progressive du sac.<sup>9</sup>

Mais, cette néo-endothélialisation peut également être un mécanisme néfaste. En effet la croissance tissulaire sur le stent au niveau des ostia des branches couvertes est la cause principale de complication ischémique retardée après usage de FDS.<sup>82</sup>

S'il est possible de dépister par CBCT une réaction intimale marquée et excessive,<sup>10</sup> toutefois en raison d'une résolution insuffisante, les systèmes basés sur les rayons X ne permettent pas le monitoring du processus normal d'endothélialisation.

L'HF-OCT autorise désormais une visualisation sans précédent de l'interaction entre les dispositifs endovasculaires de NRI et la paroi vasculaire, ceci avec une résolution approchant les 10 microns.<sup>29, 83</sup>

Le but de notre étude était de monitorer précisément la néo-endothélialisation des FDS dans un modèle animal de bifurcation artérielle.<sup>84</sup>



**Caroff J** et al. Longitudinal Monitoring of Flow-diverting Stent Tissue Coverage After Implant in a Bifurcation Model Using Neurovascular High-Frequency Optical Coherence Tomography. *Neurosurgery 2020* 

### ✓ Modèle et méthode

Nous avons ici, utilisé 6 lapins et déployé par voie fémorale six FDS dans 6 bifurcations aortiques. Quatre animaux ont reçu le traitement antiplaquettaire standard (double anti-agrégation). Afin d'étudier l'impact de ce traitement sur l'endothélialisation et dans le but de reproduire des situations pathologiques nous avons utilisé deux animaux contrôles, l'un recevant uniquement de l'aspirine et le dernier ne recevant aucun traitement antiagrégant.

Une acquisition HF-OCT était obtenue in vivo juste après la pose du FDS puis à deux autres moments lors du suivi. Pour chaque section 2D passant au travers de l'ostium de la bifurcation aortique, nous avons segmenté manuellement, d'une part la surface libre de l'ostium et de l'autre celle couverte (par les mailles du stent ou du tissu). Nous avons ainsi déterminé le ratio de couverture de surface de l'ostium (RCSO) (**Fig. 18**).

Après 60 jours, les segments artériels ont été prélevés chirurgicalement et des images par microscopie électronique à balayage (MEB) ont été obtenues.



# Figure 18. Schéma du modèle animal (gauche) et Segmentation manuelle du ratio de couverture de la surface de l'ostium (droite).

Nous avons fait le rapport entre la somme des angles d'ouverture des segments couverts (rouges en B) sur l'angle d'ouverture total de l'ostium (A) ; ceci coupe par coupe.

Le résultat, le RCSO est la moyenne de l'ensemble de ces ratios pour un ostium à un moment précis du suivi.

### ✓ Monitoring de l'endothélialisation

1) Entre 0 et 30 jours après l'implant, l'analyse HF-OCT a montré que la couverture tissulaire de l'ostium de l'artère iliaque gauche est significativement plus importante en l'absence de double antiagrégation plaquettaire (p < 0.0001).

2) En revanche, après 30 jours, les vitesses de progression de l'endothélialisation sont similaires et une couverture importante de 90% est ainsi obtenue dans tous les groupes (Fig. 19).



La très bonne corrélation entre les images in vivo et la MEB montre que l'HF-OCT permet également de décrire précisément la morphologie et le type de la couverture tissulaire des implants intracrâniens.

Il était possible ici, de différencier deux types de couvertures cellulaires des FDS. L'une fine, irrégulière et majoritairement située entre les mailles, correspondant probablement à une trame de cellules inflammatoires et de cellules musculaires lisses (CML).<sup>85</sup> L'autre, épaisse et

régulière correspondant plus probablement à une néo-endothélialisation complète, comme illustré par MEB (**Fig. 20**).



Figure 20. Couverture de l'ostium de la bifurcation iliaque à 60 jours après pose de FDS. A) La MEB montre deux types de couvertures : 1) épaisse et régulière 2) fine entre les mailles. B) L'HF-OCT retrouve également ces deux types de couvertures.

### ✓ Physiopathologie de la néo-endothélialisation

Nous avons également étudié la distribution de la croissance tissulaire au niveau de l'ostium couvert par le FDS (proche du centre vs proche de la périphérie de l'ostium). Ainsi nous avons pu montrer une prédominance de la couverture du FDS en périphérie à 13 jours mais à aucun des autres points de suivi (**Fig. 21**).

Immédiatement après implant, la couverture initiale du stent consiste en une couche de cellules inflammatoires issues de la circulation systémique,<sup>9</sup> ce qui pourrait expliquer l'homogénéité de la couverture à 6 jours.

Chez le lapin, le pic de la prolifération de CMLs a lieu à J14.<sup>86, 87</sup> L'origine de ces CMLs qui vont venir recouvrir les FDS avant endothélialisation finale reste source de controverse. On pense soit qu'elles migrent à partir de la paroi vasculaire adjacente ou bien qu'elles dérivent de la différenciation de cellules progénitrices circulantes (issues de la moelle osseuse). Des études récentes suggèrent qu'il pourrait s'agir d'un mélange de ces deux mécanismes.<sup>88</sup>

Bien que nous ne puissions pas tirer de conclusion définitive à partir de notre étude, toutefois la prédominance périphérique de la couverture observée à J13 suggère la prépondérance du mécanisme par contiguïté à la phase initiale de l'endothélialisation.



Figure 21. Corrélations entre l'importance de la couverture tissulaire du FDS et la proximité de la coupe OCT avec le centre ou bien la périphérie de l'ostium.

### ✓ Utilisation des FDS pour des anévrismes de bifurcation

Bien que les publications concernant de l'utilisation des FDS dans les bifurcations soient de plus en plus nombreuses,<sup>81</sup> la sûreté et l'efficacité de cette procédure reste controversée.

Une méta-analyse récente<sup>81</sup> a montré un taux non négligeable de complications (20%). Dans cette analyse, le flux sanguin dans la branche couverte était altéré lors du suivi dans 36% des cas (flux ralenti ou occlusion de la branche), conduisant à un déficit neurologique dans 5,3% des cas. Les auteurs, suggèrent donc de réserver l'utilisation des FDS dans les bifurcations à des indications très limitées, ceci en l'absence d'autre option thérapeutique.

Ces complications retardées ont été rapportées à la survenue d'une endothélialisation progressive du FDS, elle-même conduisant à un rétrécissement du calibre de l'ostium de la branche de bifurcation couverte et ainsi à une réduction du flux sanguin.<sup>81</sup> Dans notre étude, la surface perméable de l'ostium couvert n'était après 60 jours, plus que 10% de la surface initiale avant la mise en place du stent.

Shapiro et al.<sup>89</sup> ont montré qu'après le déploiement d'un FDS, le taux de couverture par le métal était en moyenne de 30% en regard des branches artérielles couvertes. Ils rapportent que ce RCSO est supposé être hémodynamiquement bien toléré quelle que soit la taille du FDS, le diamètre de l'artère ou la collatéralité artérielle. Ils montrent ensuite que lorsqu'un RCSO de 90% est atteint (comme dans notre modèle), le flux sanguin traversant l'ostium de la branche couverte n'est plus que 15% de son débit initial.

Donc dans les cas ou la circulation collatérale n'est pas suffisante, l'endothélialisation progressive des stents et la réduction de flux qui en découle pourraient mettre le patient dans une situation à risque de complication ischémique.

### ✓ Application clinique : HF-OCT pour une médecine personnalisée

Les antiagrégants sont connus pour être la cause potentielle de complications hémorragiques mineures et parfois majeures.<sup>90</sup> Toutefois, la double thérapie antiagrégante est indispensable après la pose d'un FDS.<sup>91</sup> Les protocoles antiagrégants sont très hétérogènes d'une équipe à l'autre. Leur durée peut en effet varier de 3 mois à toute la vie.<sup>92</sup>

Dans un futur proche on peut imaginer que le traitement antiagrégant soit modulé en fonction des résultats de l'HF-OCT. Ainsi la démonstration d'une endothélialisation complète permettrait d'interrompre ce traitement de façon sûre et donc de ne pas le prolonger inutilement. Au contraire, en l'absence d'endothélialisation complète, la protection par antiagrégant serait maintenue afin d'éviter une complication thrombotique.

### ✓ Conclusion

L'HF-OCT permet le suivi et la caractérisation précise de l'endothélialisation des mailles des FDS.

L'utilisation des FDS dans les bifurcations artérielles est à risque d'induire une réduction drastique de la surface des ostia des branches recouvertes par le stent.

### 4.3 Imagerie fonctionnelle de perfusion

### ✓ Problématique

Nous avons précédemment vu que l'HI, voir même l'endothélialisation normale pouvaient être la source de perturbations du flux sanguin.

En raison de la richesse et de la complexité des anastomoses vasculaires cérébrales, le lien entre une réduction localisée du flux sanguin artériel et son retentissement clinique est difficile à extrapoler à partir de la seule morphologie des vaiseaux.

Récemment, la faisabilité de la mesure de la perfusion cérébrale directement au bloc de NRI, par CBCT a été démontrée (**Fig. 22**).<sup>93, 94</sup> Une fois optimisée, cette technique pourrait s'intégrer parfaitement dans l'évaluation hémodynamique d'une sténose intra-FDS ou bien dans l'étude immédiate du retentissement de la couverture d'une branche de bifurcation par un FDS.



**Figure 22**. **Mesure de la perfusion cérébrale par CBCT.** Perfusion réduite en frontal antérieur gauche (bleu).

En raison de plusieurs limitations intrinsèques, l'étude de la perfusion cérébrale par capteur plan est à ce jour encore loin d'être validée et disponible en routine. Le principe physique de la mesure précise du volume sanguin cérébral (VSC) nécessite un état d'équilibre de l'opacification vasculaire pendant toute l'acquisition rotationnelle.<sup>95</sup>

Le but de notre étude était d'analyser les paramètres influençant l'état d'équilibre du rehaussement de la vascularisation cérébrale avant mesure du VSC par CBCT.<sup>96</sup>



**Caroff J**, Jittapiromsak P, Ruijters et al. Use of time attenuation curves to determine steady-state characteristics before C-arm CT measurement of cerebral blood volume. *Neuroradiology. 2014 Mar;56(3):245–9* 

### ✓ Méthode

La confirmation de cet état d'équilibre avant la mesure du VSC est rarement rapportée dans la littérature. En son absence, ce qui sera mesuré ne reflétera pas uniquement le VSC (qui correspond au cœur de l'infarctus). En effet, les mesures seraient affectées par les potentielles voies de collatéralité du patient, conduisant ainsi à sur ou sous-estimer l'étendue des potentielles lésions cérébrales définitives.

Dans cette étude, nous avons analysé des courbes d'atténuation (rehaussement cérébral) en fonction du temps, après injection d'un bolus de produit de contraste iodé. Nous avons varié

les sites d'injection (artériels ou veineux), les volumes et les débits lors d'études chez des patients atteints de diverses pathologies neurovasculaires (n=24) (**Fig. 23**).



Figure 23. Analyse de l'atténuation après injection d'un bolus de produit de contraste. A) une région d'intérêt est positionnée au niveau du parenchyme cérébral en évitant les gros vaisseaux (cercle). B) L'état d'équilibre est ici considéré comme la durée pendant laquelle le rehaussement est au moins supérieur à 85% des valeurs maximales.

### ✓ Résultats

Le résultat principal est que l'analyse des courbes a montré que quelle que soit la méthode, lorsque l'on utilise des quantités de produit de contraste compatibles avec la pratique clinique, la durée réelle de l'état d'équilibre est relativement courte, en moyenne inférieure à 10 secondes.

### ✓ Perspectives

Depuis la publication de cet article en 2014, des progrès technologiques autorisent des rotations multiples avec des vitesses de l'ordre de 8 secondes ou moins. Une méta-analyse récente rapporte une corrélation correcte avec les mesures de perfusion par scanner mais toutefois une tendance à la surestimation des lésions en CBCT.<sup>97</sup> Les auteurs concluent que l'obtention de l'état d'équilibre par l'optimisation des protocoles d'injections et des délais d'acquisition est la clé afin d'obtenir des résultats fiables.

### ✓ Conclusion

En pratique clinique, l'état d'équilibre du rehaussement du parenchyme cérébral est court, parfois plus court que les durées de rotation des protocoles CBCT au moment de la réalisation de cette étude.

Des développements en cours, basés sur l'optimisation des protocoles d'injection et l'augmentation des vitesses de rotation permettront peut-être dans l'avenir la généralisation de la mesure de la perfusion cérébrale en salle d'angiographie.

# **5. CONCLUSIONS ET PERSPECTIVES**

L'imagerie qui est au cœur de notre spécialité depuis ses origines voit aujourd'hui son importance encore se renforcer du fait de sa diversification. C'est un outil évidemment indispensable au Neuroradiologue interventionnel pendant une procédure, mais une imagerie performante est tout autant indispensable en amont pour la planification et ensuite lors suivi. S'il est nécessaire d'exploiter au maximum les systèmes angiographiques actuels, nous ne devrions pas nous restreindre aux technologies basées sur les rayons X.

**I.** Le CBCT est largement disponible. C'est un excellent outil pour étudier les dispositifs faiblement radio-opaques. Et il nous semble que son usage devrait être encore plus répandu.

**II.** Les cathéters d'OCT conçus spécifiquement pour la NRI ne sont pas encore cliniquement disponibles. Mais l'HF-OCT a le potentiel de devenir bientôt un véritable microscope vasculaire utilisable in vivo.

**III.** L'imagerie morphologique ne reflète pas la complexité des mécanismes à l'origine des pathologies prises en charge en NRI. L'analyse de la perfusion cérébrale, de la collatéralité vasculaire et de la mécanique des fluides devraient potentiellement participer à une meilleure compréhension physiopathologique avec le potentiel d'aider à établir une meilleure stratégie thérapeutique.

Dans un avenir plus ou moins proche, de véritables révolutions sont attendues dans les blocs de NRI :

**IV.** Les casques de réalité augmentée<sup>98, 99</sup> vont probablement bientôt transformer l'environnement de travail au bloc, en rendant obsolète les écrans géants qui encombrent l'espace. L'opérateur pourra bénéficier en temps réel de nombreuses informations afin de guider son geste ; notamment l'affichage des résultats des simulations informatiques préopératoires que l'on réalise déjà directement au bloc.<sup>100</sup>

**V.** Les procédures endovasculaires assistées par robotique sont déjà une réalité en cardiologie.<sup>101, 102</sup> L'opérateur, guidé uniquement par les images pourra ainsi réaliser les procédures à distance.

**VI.** Dans un avenir plus lointain on peut imaginer que les salles d'angiographie rayons X vont être supplantés par des systèmes non irradiants. L'utilisation de la résonnance magnétique autoriserait en plus de la cartographie vasculaire, une analyse exceptionnelle du parenchyme cérébral. Aussi, il serait ainsi possible d'utiliser les champs magnétiques pour diriger en temps réel les cathéters jusqu'à la cible du traitement.<sup>103, 104</sup>

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# 7. ANNEXES

- I. Role of C-Arm VasoCT in the Use of Endovascular WEB Flow Disruption in Intracranial Aneurysm Treatment. Caroff J, Mihalea C, Neki H et al. *AJNR Am J Neuroradiol. 2014 Jul 15;35(7):1353–7*
- II. Occlusion assessment of intracranial aneurysms treated with the WEB device.
   Caroff J, Mihalea C, Tuilier T et al. Neuroradiology; 2016 Jun 15;58(9):1–5
- III. High frequency optical coherence tomography assessment of homogenous neck coverage by intrasaccular devices predicts successful aneurysm occlusion.

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- IV. A computational fluid dynamics (CFD) study of WEB-treated aneurysms: Can CFD predict WEB "compression" during follow-up? Caroff J, Mihalea C, Da Ros V et al. J Neuroradiol. 2017 Jul;44(4):262–8.
- V. The occurrence of neointimal hyperplasia after flow diverter implantation is associated with cardiovascular risks factors and the stent design. Caroff J, Iacobucci M, Rouchaud A et al. Journal of NeuroInterventional Surgery; 2019 Jun; 11(6):610–3
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- VII. Longitudinal Monitoring of Flow-diverting Stent Tissue Coverage After Implant in a Bifurcation Model Using Neurovascular High-Frequency Optical Coherence Tomography Caroff J et al. Neurosurgery 2020
- VIII. Use of time attenuation curves to determine steady-state characteristics before Carm CT measurement of cerebral blood volume. Caroff J, Jittapiromsak P, Ruijters et al. Neuroradiology. 2014 Mar; 56(3):245–9.

# Role of C-Arm VasoCT in the Use of Endovascular WEB Flow Disruption in Intracranial Aneurysm Treatment

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#### ABSTRACT

**BACKGROUND AND PURPOSE:** The WEB aneurysm embolization system is still under evaluation but seems to be a promising technique to treat wide-neck bifurcation aneurysms. However, this device is barely visible using conventional DSA; thus, high-resolution contrastenhanced flat panel detector CT (VasoCT) may be useful before detachment to assess the sizing and positioning of the WEB. The purpose of this study was to evaluate the interest of VasoCT during WEB procedures.

**MATERIALS AND METHODS:** From March 2012 to July 2013, twelve patients (10 women and 2 men; age range, 44–55 years) were treated for 13 intracranial aneurysms with the WEB device. DSA and VasoCT were used and compared to depict any protrusion of the device in parent arteries before detachment. Two neuroradiologists reviewed each VasoCT scan, and the quality was graded on a subjective quality scale.

**RESULTS:** The mesh of the WEB was very well-depicted in all cases, allowing a very good assessment of its deployment. Device protrusion was clearly detected with VasoCT in 5 cases, leading to WEB repositioning or size substitution. During follow-up, VasoCT also allows good assessment of eventual residual blood flow inside the aneurysm or the WEB device.

**CONCLUSIONS:** Unlike DSA, VasoCT is an excellent tool to assess WEB deployment and positioning. In our experience, it allowed a precise evaluation of the WEB sizing and its relation to the parent vessel. Such information very likely enhances the ability to safely use this device, avoiding potential thromboembolic events in cases of protrusion in the parent arteries.

**ABBREVIATIONS:** WEB = Woven EndoBridge Embolization System

The Woven EndoBridge Embolization System (WEB; Sequent Medical, Aliso Viejo, California) is a 2-compartment intrasaccular flow disrupter, particularly dedicated to the treatment of intracranial wide-neck bifurcation aneurysms. This device has an attenuated microbraided mesh structure constructed from a large number of nitinol wires (ranging from 19 to 38 microns). This mesh is almost not visible with standard DSA because of the small diameter of nitinol wires, so 3 platinum markers represent the proximal, middle, and distal parts of inner and outer braids (Fig 1).<sup>1,2</sup> The first clinical results suggest a high feasibility of the treatment with acceptable morbidity and mortality.<sup>3-5</sup>

Flat panel detector CT has proved to be a very accurate tool to assess the structure and deployment of intracranial stents.<sup>6,7</sup> VasoCT (Philips Healthcare, Best, the Netherlands) provides simultaneous detailed visualization of neurovascular stents and parent arteries.<sup>8,9</sup>

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We present here our experience using VasoCT as a systematic method to control WEB deployment before and after its detachment.

### MATERIALS AND METHODS

#### Population

Between March 2012 and July 2013, twelve patients were treated for 13 intracranial aneurysms with the WEB device in our hospi-



**FIG 1.** *A*, Photograph of the WEB device. *B*, Corresponding nonenhanced VasoCT clearly depicts the 2 different compartments and the 3 markers (*arrows*).

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tal. All subjects gave informed consent for the treatment. There were 10 women and 2 men with a mean age of 52 years (range, 44–55 years).

#### Treatment Technique

Endovascular treatment was performed by using a biplane flat panel angiographic system (Allura Xper 20/10; Philips Healthcare). Endovascular procedures were performed with the patient under general anesthesia and systemic heparinization.

A guiding catheter, FargoMax 6F (Balt, Montmorency,



**FIG 2.** Central section of the VasoCT conebeam reconstruction of a line-pair phantom. The numbers at the left and right side indicate the line pairs per millimeter.



**FIG 3.** *A*, DSA before detachment of a WEB positioned in a left MCA bifurcation aneurysm. It is impossible to depict any protrusion of the device in the parent artery because only the 3 markers are seen and the mesh is almost not visible. *B*, Corresponding unsubstracted image. *C*, VasoCT confirms correct positioning of the WEB without any protrusion. *D*, Three-month control VasoCT shows residual flow in the proximal compartment (*arrow*).

France) was advanced in the internal carotid or vertebral artery. To deliver the WEB, we used different microcatheters and placed them at the base of the aneurysmal sac: Rebar 27 (Covidien, Irvine, California), DAC 38 (Concentric Medical, Mountain View, California), Headway 27 (MicroVention, Tustin, California), and Via 27 or 33 (Sequent Medical). The microcatheter was chosen according to the WEB size. The WEB size choice was based on 3D rotational angiography performed during treatment.

Control DSA and VasoCT were performed before delivery. If the position was not satisfactory, the WEB was resheathed and repositioned. If the sizing was not adequate, the WEB was removed and another device was used. At the end of the procedure, both DSA and VasoCT were repeated after detachment of the WEB.

#### **High-Resolution Flat Panel Detector CT**

For high-spatial-resolution imaging of intravascular devices and their parent vessel lumen, a dedicated iodine contrast-enhanced conebeam CT protocol was developed (VasoCT). It is acquired by using a neuroangiographic x-ray C-arm (Allura Xper FD20; Philips Healthcare) equipped with a cesium iodide–amorphous silicon flat panel detector. The sensor area of the flat detector measures approximately  $30 \times 40$  cm and consists of  $1920 \times 2480$ pixels. The conebeam acquisition consists of a rotational trajec-

> tory over a 200° arc while acquiring 620 projection images at a fixed source-todetector distance of 1195 mm. The objects of interest should be positioned in the center of the rotation, 810 mm from the source. The x-ray tube voltage is set to 80 kV; the focal spot, to 0.4 mm, while no copper filter is used. The associated radiation dose ranges from 45 to 49 mGy CT dose index. The imaged detector area is fixed to a diameter of 22 cm, which enables an unbinned pixel size of 0.154 mm, allowing very high-spatialresolution 3D reconstructions. The 3D reconstruction is obtained by using the Feldkamp-Davis-Kress method.<sup>10</sup> Preprocessing steps of the projection images include gain correction, scatter correction, water beam-hardening correction, and Parker weighting. The WEB VasoCT was reconstructed with a 5123 matrix covering a cubic FOV of 34.44 mm in each dimension.

> Figure 2 shows a VasoCT reconstruction of a line-pair phantom. As can be seen, up to 4.6 line pairs per millimeter (lp/mm) can be distinguished, which correspond to an intrinsic resolution of 0.109 mm according to the following formula: Resolution Intrinsic Millimeter = 0.5 [lp / mm].

> The spatial resolution is substantially higher than the resolutions reported for

<sup>2</sup> Caroff Jul 2014 www.ajnr.org











**FIG 5.** *A*, DSA anteroposterior view of a basilar tip aneurysm. *B*, Control angiogram and corresponding unsubtracted view (*C*) prior to detachment of the WEB. Some contrast agent stagnation is visible in the second layer. It is impossible to analyze the good positioning of the device; no flow abnormality is depicted in the left P1 segment. *D*, VasoCT clearly shows the protrusion in the left P1 segment. The WEB was then retrieved and replaced by a smaller one.

multisection CT. For 64-section CT, a resolution of approximately 1.5 lp/mm has been reported.<sup>11</sup> The high spatial resolution of VasoCT allows imaging the stent struts of intracranial nitinol stents.<sup>9</sup> To visualize the vessel lumen and the intravascular devices simultaneously, we used a diluted iodine contrast agent with 20% iodixanol (Visipaque 270; GE Healthcare, Mississauga, Ontario, Canada) and 80% saline solution. The total volume used was 90 mL at the injection rate of 3 mL/s. In case of streaking artifacts caused by nearby metal (eg, coils), the image quality can be improved by applying a metal-artifactsreduction algorithm in a second-pass reconstruction.<sup>12</sup> Data were analyzed with MPR and MIP reconstructions.

#### **Quality Assessment**

VasoCT scans were reviewed in consensus by 2 interventional neuroradiologists. For every case, the quality of visualization of the WEB and the parent vessels was scored in ordered scales from 1 to 3. A score of 1 indicated that visualization was insufficient for evaluation; a score of 2 was given if the visualization was good; and a score of 3, if excellent. Metal artifacts from the WEB device and microcatheter, if present, were also evaluated. A score of 3 was given when no artifacts were depicted; a score of 2, if mild artifacts were observed. A score of 1 indicated severe artifacts, making evaluation of the WEB positioning impossible.

Those scores were added to obtain a global quality score on a 9-point subjective scale. Global VasoCT quality scores were compared with WEB dimensions by using the Pearson correlation coefficient.

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**FIG 6.** A, DSA working projection of a large-neck anterior communicating artery aneurysm. B, After placement of a  $9 \times 7$  mm WEB, the control DSA shows the occlusion of the right A2 segment and a narrowing of the left A2. C, VasoCT confirms the occlusion and that the WEB is not properly deployed. It is in a heart-shaped configuration with a distal trough; the 2 distal markers are attached (*arrow*). This "heart sign" depicts an inappropriate width of the WEB regarding aneurysm dimensions. It was then replaced by a correctly deployed  $7 \times 6$  cm WEB.



**FIG 7.** Nonenhanced VasoCT. It is very important to consider the acquisition plane to avoid the projection of any metal artifacts over the region of interest. Here, the angulation of the head of the patient was modified so that coil artifacts from a previously treated basilar tip aneurysm do not superimpose on the MCA bifurcation.

Additionally, reviewers had to evaluate whether any protrusion, clotting, vessel occlusion, or residual neck was present.

#### RESULTS

Most treated aneurysms were unruptured (3 ruptured cases), with an unfavorable wide-neck anatomy (mean dome/neck ratio = 1:1). The mean aneurysm size was 7.3 mm (range, 5-11 mm).

WEB placement was not possible in 1 case because of the unavailability of an appropriate-sized device. Device protrusion was clearly detected with VasoCT in 5 cases, leading to WEB repositioning or size substitution (Figs 3 and 4). The average number of WEBs used to obtain good sizing was 1.3 per procedure.

The total number of VasoCT scans reviewed was 31, with an average number of 2.4 VasoCT scans performed per procedure. The mean quality score was 6.6  $\pm$ 1.4 (range, 4–9). Visualization of the WEB and/or the parent vessel was insufficient for evaluation in 3 cases of VasoCT (9%).

Quality score was significantly and inversely correlated to the WEB height (r = 0.78, P < .0001).

#### DISCUSSION

The visibility of the WEB is very poor with conventional angiography (Fig 5). Unlike DSA, VasoCT offers a very good visualization of the microbraided mesh structure and shape of the WEB

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device. It allows a precise study of its relationship with the parent arteries. This is fundamental before detachment of this completely retrievable device to avoid potential thromboembolic complications due to protrusion (Fig 6).

We have encountered some differences in VasoCT image quality. Some features seem to be significantly influencing the visibility of the WEB. The device should always be placed in the isocenter of the acquired volume. All movements of the patient have to be limited; therefore, apnea is required during acquisition. No geometric disturbances should occur; these can be seen when the C-arm hits the infusion stand or table. High-attenuating items need to be avoided in the reconstruction plane of the WEB by positioning the head of the patient so that coils or clip streak artifacts appear in another plane (Fig 7). Metal artifacts reduction may be useful in some cases, especially when WEB-marker artifacts are projected over the parent artery (ie, MCA bifurcation aneurysms) (Fig 8).

WEB markers made of iridium and platinum alloy generate significant metal artifacts (unlike nitinol mesh). We have noticed that distal markers of the delivery microcatheter, made with the same iridium and platinum alloy, also induce artifacts; they can be avoided by retrieving the catheter proximally in the parent artery.

The quality score was inversely correlated to the WEB height. This observation can be explained first because the diameter of nitinol wires is variable (ie, smaller for the smallest WEB). Thus, the largest WEB sizes are more radiodense and easily assessed. This feature should encourage manufacturers to increase the visibility of the smaller devices. Second, the distance between the markers is small for the small WEB, leading to overlapping metal streak artifacts that are summed, deteriorating the visualization of the parent arteries.

We advise a systematic calibration of the angiographic suite prior to each acquisition. When the system is used for a long time with a reduced FOV (as is usual during a procedure), then the pixels that have been irradiated within this image format have a different response than the ones that were not irradiated. The calibration corrects this phenomenon, allowing an optimal image quality.

Some authors report the use of 3D rotational angiography to control WEB positioning.<sup>5</sup> There are similarities and differences



**FIG 8.** A, VasoCT of an MCA aneurysm treated with a WEB. Marker artifacts are projecting over the parent vessels. B, A new reconstruction with a metal-artifacts-reduction algorithm clearly improves the image quality and the visualization of the bifurcation.

between VasoCT and 3D rotational angiography. Both protocols are optimized for visualization of iodine contrast; hence, both use approximately 80 kV for the x-ray tube and both are optimized for high-resolution reconstructions (either volume-rendering or multiplanar mode). While VasoCT is meant for small contrast differences (with diluted contrast medium), 3D rotational angiography is meant for larger contrast differences (with pure contrast medium). To achieve the high contrast resolution, VasoCT acquires 620 images, whereas 3D rotational angiography records 120 images in the rotation. As a result, the VasoCT acquisition takes longer (20 versus 4 seconds); and because of the larger number of images, the reconstruction times for VasoCT are also longer (approximately 26 seconds versus 5 seconds for 256<sup>3</sup>). Because of its superior contrast resolution, VasoCT is the most appropriate technique for use with the WEB device.

VasoCT x-ray skin dose calculated from simulations amounts to 0.89 mSv, and the effective dose is 0.51 mSv. For comparison, the standard brain CT effective dose average is 1.5 mSv.<sup>13</sup>

While VasoCT appears essential during endovascular treatment, it is also very useful during follow-up. It can be performed with the patient under local anesthesia, and it allows the assessment of any residual flow inside the 2 separate layers (Fig 3).

#### CONCLUSIONS

Unlike DSA, VasoCT is an excellent tool to assess WEB deployment and positioning. In our experience, it allows a precise evaluation of the WEB sizing and its relation to the parent vessel. Such information likely enhances the ability to use this device safely, avoiding a potential thromboembolic event in cases of protrusion in the parent arteries.

Disclosures: Daniel Ruijters—UNRELATED: Employment: I am a Philips Healthcare employee. Jacques Moret—UNRELATED: Consultancy: Covidien, MicroVention.

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INTERVENTIONAL NEURORADIOLOGY

## Occlusion assessment of intracranial aneurysms treated with the WEB device

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#### Abstract

*Introduction* The Woven EndoBridge (WEB) system is an innovative device under evaluation for its capacity to treat wide-neck bifurcation intracranial aneurysms. The purpose of this study is to evaluate the use of the different occlusion scales available in clinical practice.

*Methods* Seven WEB-experienced neurointerventionalists were provided with 30 angiographic follow-up data sets and asked to grade each evaluation point according to the Bicêtre Occlusion Scale Score (BOSS), firstly based on DSA images only then using additional C-Arm VasoCT analysis. This BOSS evaluation was then converted into the WEB

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Occlusion Scale (WOS) and into a dichotomized scale (complete occlusion or not). To estimate the inter-rater agreement among the seven raters, an overall kappa coefficient [1] and its standard error (SE) were computed.

*Results* Using the five-grade BOSS, raters showed "moderate" agreement (kappa = 0.56). Using the three-grade WOS, agreement appeared slightly better (kappa = 0.59). Strongest inter-rater agreement was observed with a dichoto-mized version of the scale (complete occlusion or not), which enabled an "almost perfect" agreement (kappa = 0.88). VasoCT consistently enhanced the agreement particularly with regards depicting intra-WEB residual filling.

*Conclusion* The WOS is a consistent means to angiographically evaluate the WEB device efficiency. But the five-grade BOSS scale allows to identify aneurysm subgroups with differing risks of recurrence and/or rehemorrhage, which needs to be separated especially at the initial phase of evaluation of this innovative device. The additional use of VasoCT allows better inter-rater agreement in evaluating occlusion and specially in depicting intra-WEB persistent filling.

Keywords Endovascular treatment  $\cdot$  Intracranial aneurysms  $\cdot$  Woven EndoBridge device  $\cdot$  WEB  $\cdot$  Flow disruption

#### Introduction

The Woven EndoBridge (WEB; Sequent Medical, Aliso Viejo, California, USA) was initially developed to treat wide-neck bifurcation intracranial aneurysms. With such aneurysms that are typically challenging to treat with standard coiling, the WEB has proven to be a highly feasible and safe technique [2–5].

The results of this innovative device are still under evaluation, yet classical endovascular evaluation scales used for

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coiling [6, 7] are not appropriate. The WEB Occlusion Scale (WOS) [8], a Raymond-inspired scale, is up to now the most frequently used for WEB angiographic evaluation, but it may not be optimal for this device. Indeed, the new concept of intrasaccular flow-disruption introduces new analytical issues, such as proximal recess appearance, residual filling of the WEB, and device compression [9], which require consideration.

To account for those issues introduced with the WEB device, we have described a novel angiographic assessment of occlusion scale, which we named the Bicêtre Occlusion Scale Score (BOSS) [10]. The purpose of the present study was to assess the reproducibility of this scale, and others previously reported with special attention to intra-device residual opacification and the potential benefit of using VasoCT.

#### Materials and methods

#### Database

An electronic portfolio consisting of 30 angiographic followup evaluations of WEB-treated aneurysms was elaborated. It consisted of one three-dimensional rotational angiographic view of the aneurysm and one or two digital subtraction angiography (DSA) working projections (subtracted and unsubtracted images) before treatment and at the >6-month follow-up (total three to five images for one case). One author (J.C.) selected and assembled the images for the portfolio, attempting to include one third of aneurysm recurrences, one sixth of intra-WEB opacifications, one third of immediate results, and one third of cases that were "difficult to judge or unclear." These proportions were chosen to (1) cover a wide spectrum of difficulties in interpretation of results and (2) to minimize well-known paradoxes of *k*-statistics [11].

Informed consent was obtained in each case. Images were de-identified and compiled in a powerpoint file (Microsoft, Redmond, Washington, USA). This was then addressed to seven expert neurointerventionalists (from six different centers in France), each highly experienced (>15 personal WEB cases) in the use of the WEB device. They all did independently reviewed all images of 30 cases regardless of clinical information. Once each neurointerventionalist had fulfilled a first evaluation, one complementary selected VasoCT image [12] was given (mostly corresponding to the best working projection view) and they were asked to confirm or modify their first evaluation.

#### **BOSS classification**

The BOSS used to assess the occlusion achieved with the WEB device is scaled as follows: 0 = no residual flow inside the aneurysm or the WEB; 0' = opacification of the proximal

recess of the WEB; 1 = residual flow inside the WEB; 2 = neck remnant; 3 = aneurysm remnant; and 1 + 3 = contrast agent media depicted inside and around the device. (Fig. 1). The scores 0 and 0' are being considered as complete occlusion.

#### Other classifications

From the reviewers' evaluation (so without additional review from the experts), we could also regroup BOSS types and transform the results from the BOSS into the WOS because of similarities. WOS is described as follows: WOS 0 = noresidual flow inside the aneurysm or the WEB, or



Fig. 1 WEB occlusion scale. Grade 0 indicates complete occlusion. Grade 0' is similar but with opacification of the proximal recess and is also considered as complete occlusion. Grade 1 signifies opacification inside the WEB. Grade 2 denotes a neck remnant. Grade 3 indicates an aneurysm remnant with contrast agent inside the sac between the wall and the WEB device. In grade 1+3, contrast agent is depicted inside and around the device

opacification of the proximal recess of the WEB; WOS 1 = neck remnant; and WOS 2 = aneurysm remnant.

As some studies' endpoint is the complete occlusion of the aneurysm, we decided also to evaluate a two-grade dichotomized scale, i.e., complete versus non-complete occlusion.

#### Data analysis

To estimate the inter-rater agreement among the seven raters, an overall kappa coefficient [1] and its standard error (SE) were computed. Landis and Koch's table was used to interpret kappa values [13]. The BOSS scores 0 and 0' were gathered, both being considered as complete occlusion.

#### Results

#### Five-grade BOSS classification

Without VasoCT, raters showed moderate agreement (kappa = 0.52, SE = 0.04, 95 % CI = 0.48 to 0.57). Inter-rater agreement was slightly better when the raters had access to VasoCT to complete their evaluation (kappa = 0.56, SE = 0.023, 95 % CI = 0.51 to 0.60) (Table 1).

#### Persistent opacification

Inter-rater agreement for persistent intra-WEB opacification (BOSS 1 and BOSS 1+3) was moderate without VasoCT (kappa = 0.48, SE = 0.040, 95 % CI = 0.41 to 0.56) but "substantial" after adding the VasoCT dataset to the evaluation portfolio (kappa = 0.61, SE = 0.040, 95 % CI = 0.54 to 0.67) (Fig. 2).

#### Three-grade WOS classification

Without VasoCT, raters showed moderate agreement (kappa = 0.57, SE = 0.029, 95 % CI = 0.52 to 0.63). When

 Table 1
 Inter-observer agreements

Kappa values	5-point BOSS scale	3-point WOS scale	2-point dichotomized scale	WEB persistent filling
Without VasoCT	0.52 SE=0.04, 95 % CI=0.48 to 0.57	0.57 SE = 0.029, 95 % CI = 0.52 to 0.63	0.82 SE=0.040, 95 % CI=0.81 to 0.96	0.48 SE = 0.040, 95 % CI = 0.41 to 0.56
With VasoCT	0.55 SE = 0.023, 95 % CI = 0.51 to 0.60	0.59 SE = 0.029, 95 % CI = 0.53 to 0.65	0.88 SE = 0.040, 95 % CI = 0.74 to 0.90	$0.61 \\ SE = 0.040, \\ 95 \% \\ CI = 0.54 \\ to 0.67$

the raters had access to VasoCT to complete their evaluation, inter-rater agreement was kappa = 0.59, SE = 0.029, 95 % CI = 0.53 to 0.65.

#### Two-grade dichotomized classification

Strongest inter-rater agreement was observed with the dichotomized scale (complete occlusion or not) which allowed an "almost perfect" agreement. It was better with VasoCT (kappa = 0.88, SE = 0.040, 95 % CI = 0.81 to 0.96) than without VasoCT (kappa = 0.82, SE = 0.040, 95 % CI = 0.74 to 0.90).

#### Discussion

#### Inter-observer variability

In our current study, we have demonstrated that use of the five-graded BOSS allowed moderate inter-rater agreement (kappa = 0.56), but not really dissimilar to that described with coiling evaluation scales. In a large meta-analysis, Ernst et al. [11] reported an estimated average kappa of 0.65. It should also be noted that the vast majority of authors used a three-grade scale and none used a five-grade scale.

In this study, the agreement with the WOS kappa was probably not statistically different than with the BOSS (0.59, 95 % CI = 0.53 to 0.65 vs 0.56, 95 % CI = 0.51 to 0.60). The disagreement between readers mostly came because of the lack of precise distinction between a large neck remnant and an aneurysm remnant and not from persistent opacifications.

One should notice that in the article by Fiorella et al. [8] regarding the use of the WOS, the kappa reported was higher 0.70. This could be caused by differences in the reviewers' training with the WEB, but in both studies they were highly experienced with the device. The kappa difference with Fiorella et al. was rather due to the *k*-statistic paradoxes [14]. It means that the clarity and complexity of the selected cases included in the different portfolios can influence the results. Ernst et al. observed that in studies using DSA, inter-observer agreement was significantly better in samples with a higher proportion of completely occluded aneurysms [11].

#### **Interest of BOSS scale**

To evaluate the efficiency of the WEB device, we have proposed the BOSS, a Raymond-modified scale which we have previously reported [6]. We admit that this classification may first appear too complex. But this five-grade scale sought to identify aneurysm subgroups with differing risks of recurrence and/or rehemorrhage, which needs to be separated especially at the initial phase of evaluation of this innovative device.

The main difference between BOSS and WOS is that it takes into account situations where the WEB itself remains

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Fig. 2 DSA before detachment of a WEB positioned in a left MCA bifurcation aneurysm (a). With the 6-month follow-up DSA, b it is difficult to analyze the neck region of the treated aneurysm. Whereas the VasoCT study c clearly depicts a residual filling in the proximal compartment of the WEB-DL (*arrow*)



filled with contrast media. *BOSS 1* corresponds to opacification of the WEB alone whereas *BOSS 1 + 3* indicate conditions in which residual opacification of the aneurysmal sac can be seen in addition. This appears to be an important difference between the scales, which should be considered not least because instances of WEB devices remaining filled with contrast media on follow-up evaluation are far from rare. In a previously published WEB study [15], short-term imaging follow-up at an average of 3.3 months was available in 70 % of cases. At these early evaluation stages, *BOSS 1* or *BOSS 1 + 3* was found in 15 % of cases.

Moreover, we contend on the importance of differentiating aneurysm remnants (*BOSS 3*) from an isolated residual filling of the WEB (*BOSS 1*). Although in most cases *BOSS 1 + 3* remnants should be considered for retreatment (additional stent-assisted coiling or flow-diverter stent), the aneurysm rupture risk in *BOSS 1* cases is probably low and complete occlusion may be observed during the subsequent follow-up.

However, in the very particular situation of WEB treatment for ruptured aneurysms, the depiction of those showing persistent intra-device filling is fundamental meanwhile the prevention of rebleeding from WEB treatment is strongly reported in the literature. Furthermore, identifying persistent filling of the WEB may also be of great interest to understand the underlying phenomenon of WEB delaying compression [9] as some authors suggest it could result from clot retraction.

Unsurprisingly, observer variability has been shown to substantially reduce with the use of scales that offer fewer observer responses [16]. However, scales with fewer grades may not identify aneurysm subgroups with different clinical management issues. Also, as many studies about WEB evaluation are ongoing, a more detailed scale could lead to a more detailed evaluation.

#### Additional value of VasoCT

Considering a dichotomous endpoint (i.e., complete occlusion or not), we found substantially better agreement in our study than that previously published in studies using a dichotomous scale. Fiorella et al. [8] reported kappa = 0.78, and in their animal study Rouchaud et al. [17] reported kappa = 0.63.

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The main difference was that only in our study did the reviewer have access to a VasoCT dataset.

VasoCT appeared paramount in our study and, in 24 % of cases, drove reviewers to change their initial evaluation. The additional use of VasoCT allowed better inter-rater agreement with the use of both dichotomized and non-dichitomized scales. The benefit from additional VasoCT data did appear even greater with regards the detection of intra-WEB persistent fillings.

As often encountered in occlusion assessment studies, the reviewers did not have here access to the full DSA and VasoCT data set but only to preselected images, and this could have affected the results.

In light of our findings, we would recommend the use of the BOSS classification system, rather than the WOS in the ongoing studies by which to evaluate the WEB device in all its aspects. We believe that the BOSS allows a better understanding of the WEB aneurysm occlusion mechanism by identifying the persistent device fillings.

The dichotomized version would be a very reproducible method for further angiographic evaluation of the long-term efficiency of WEB devices specially to face other validated strategies as surgical clipping.

The WOS is probably a sufficient way to evaluate occlusion rates in everyday practice.

VasoCT should be systematically performed, not only at the end of the procedure to ensure good positioning before detachment but also during the follow-up period to evaluate the extent of occlusion.

#### Conclusion

The WOS is a consistent means to angiographically evaluate the WEB device efficiency. But the five-grade BOSS scale allows to identify aneurysm subgroups with differing risks of recurrence and/or rehemorrhage, which needs to be separated especially at the initial phase of evaluation of this innovative device. The additional use of VasoCT allows better inter-rater agreement in evaluating occlusion and specially in depicting intra-WEB persistent filling. **Compliance with ethical standards** We declare that all human and animal studies have been approved by the local ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest CC, LP, JM and LS consult for Sequent Medical.

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### ORIGINAL RESEARCH

# High frequency optical coherence tomography assessment of homogenous neck coverage by intrasaccular devices predicts successful aneurysm occlusion

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#### ABSTRACT

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Neuroradiology, NEURI Center, Bicêtre Hospital, Le Kremlin**Background** High frequency optical coherence tomography (HF-OCT) is a novel intravascular imaging technology developed for use in the cerebral vasculature. We hypothesize that HF-OCT characterization of intrasaccular device neck coverage can prognosticate exclusion of the aneurysm from the circulation.

**Methods** Bifurcation and sidewall aneurysms were made in six dogs. Seven aneurysms were treated with next generation intrasaccular devices (NGID) and four with traditional platinum coils. HF-OCT was performed to interrogate gaps in the neck coverage, coil herniation, or acute thrombus formation. Animals were re-imaged at 7, 30, 90, and 180 days following aneurysm embolization. An automated image processing method segmented the devices at the neck of the aneurysm and quantified neck coverage. The largest coverage gap was used to predict aneurysm occlusion at 180 days.

**Results** No difference was found in occlusion rates between the coil and NGID groups (P=0.45). Successful segmentation of the NGID construct was achieved in all cases. A coverage gap >1 mm<sup>2</sup> was found to predict failed aneurysm occlusion (P=0.047). This threshold was able to predict all cases of failed occlusion. The average number of devices needed to treat the aneurysm was lower in the NGID group (1.9 vs 6.75, P=0.009). HF-OCT showed strong agreement with scanning electron microscopy (bias 0.0024 mm<sup>2</sup> (95% CI -0.0279, 0.0327)).

**Conclusions** HF-OCT enables precise and accurate measurement of coverage gaps at the neck of aneurysms treated with intrasaccular devices in vivo. We provide in vivo evidence that uniform aneurysm neck coverage by intrasaccular devices is critical for aneurysm occlusion.

aneurysms due to poor neck coverage.<sup>4</sup> Although this issue is now often addressed by flow diversion or stent assisted coiling (SAC),<sup>7-9</sup> these techniques can incur additional risks of thromboembolic complications or complications associated with administration of dual antiplatelet therapy.<sup>10</sup> Next generation coil<sup>11</sup> or intrasaccular flow disruption<sup>12</sup> designs have the potential to improve neck coverage and reduce the need for SAC.

Newly developed intrasaccular devices may improve neck coverage and following positive trials have received Food and Drug Administration approval. Preclinical studies in vitro showed that the reconstruction of the aneurysm neck is a critical component for achieving intra-aneurysmal flow reduction.<sup>13</sup> High frequency optical coherence tomography (HF-OCT), a catheter based imaging technique specifically designed for use in tortuous neurovasculature, was recently introduced.<sup>14</sup> Using near infrared light, HF-OCT acquires three-dimensional information from cerebrovascular arteries, providing micron level details of the arterial lumen morphology, intraluminal objects (eg, neurovascular devices and presence of thrombus), and the vessel wall microstructure. With a resolution approaching 10 µm, HF-OCT images can characterize in extraordinary detail the device and its relationship to the aneurysm neck at the time of implantation.

In this study, we hypothesized that gaps in the neck coverage visualized by HF-OCT at the time of implantation, but not visible by traditional X-ray imaging modalities (ie, DSA and CT), are predictive of failure of aneurysm occlusion. This would inform the need for modification of the treatment to ensure eventual aneurysm exclusion.

#### Check for updates

#### INTRODUCTION

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BMJ

#### Coil emboliza

Coil embolization of brain aneurysms is a widely established technique with level 1 evidence for ruptured aneurysms.<sup>1</sup> However, one of the major concerns of coil embolization is recanalization due to incomplete healing, coil compaction, or aneurysm regrowth, warranting long term follow-up imaging.<sup>23</sup> This is especially applicable for large and giant aneurysms,<sup>4</sup> particularly those that are partially thrombosed.<sup>5</sup> Clinical data have shown that approximately 20% of embolized aneurysms will recur, with up to 10% of all coiled aneurysms needing retreatment.<sup>6</sup> Higher rates of recanalization are found in wide neck

#### **METHODS**

#### **Experimental procedures**

All animal research procedures were approved by our university's institutional animal care and use committee. Six purpose bred hound cross dogs (sex male, weight 20–25 kg) were used in this study. On the day of surgery, the animals were sedated and pretreated with intramuscular injections of a single dose of acepromazine (0.06 mg/kg), buprenorphine (0.02 mg/kg), and glycopyrrolate (0.01 mg/ kg). Anesthesia was induced with an intravenous dose of propofol (3–4 mg/kg), and the animal was



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intubated. Anesthesia was maintained by mechanical ventilation of 1-3% isoflurane in oxygen. Additionally, ECG, SpO2, invasive or non-invasive arterial blood pressure, rectal temperature, and end tidal CO, were continuously monitored and recorded every 15 min. Fentanyl patches (75 µg/hour) were used to manage postoperative pain following the aneurysm creation procedure. For subsequent interventional procedures, analgesia was provided with local administration of bupivacaine. Both sidewall and bifurcation anatomical variants were surgically created from a venous pouch, based on a previously described model.<sup>15</sup> <sup>16</sup> In brief, the midsection of the left common carotid artery was ligated, transected, and tunneled beneath the trachea where it was anastomosed end-to-side with an arteriotomy to the midsection of the right common carotid artery. A segment of the external jugular vein was anastomosed to the junction of the two arteries. The lateral wall aneurysm was constructed approximately 10 cm cranial to the newly constructed bifurcation aneurysm on the right common carotid artery. A total of six sidewall and six bifurcation aneurysms were created.

Aneurysm treatment was initiated at a minimum of 21 days post aneurysm creation. A 2:1 randomization was used to determine device selection: either embolization with a next generation intrasaccular device (NGID) or traditional coil embolization (Axium; Medtronic Neurovascular, Irvine California, USA). For traditional coil embolization, aneurysms were packed to achieve complete obliteration of the aneurysm with the goal of preventing herniation. We did not permit assist devices (balloon remodeling or stents) to reduce confounding variables, as well as determine the ability of the NGID to reconstruct the aneurysm neck. For NGID embolization, one or two devices were inserted at the discretion of the neurointerventional surgeon. Once the aneurysm was considered successfully packed, a prototype HF-OCT imaging device (Vis-M<sup>TM</sup>; Gentuity LLC, Sudbury Massachusetts, USA) compatible for delivery through a 0.017 inch microcatheter, was navigated distal to the aneurysm. A 6 F balloon catheter was then inflated in the proximal right common carotid artery and the HF-OCT pullback was performed concurrently with contrast injection (5 mL/s for 20 mL), clearing the artery of residual blood. A balloon catheter was used to arrest very high afferent flow through the remaining carotid artery for approximately 5 s. HF-OCT images were generated real time, and displayed live during image acquisition. After both aneurysms were treated and imaged, DSA and high resolution cone beam CT (VasoCT)<sup>17</sup> data were acquired for each aneurysm. DSA, HF-OCT, and VasoCT imaging was repeated at 7, 30, 90, and 180 days following implant to interrogate progressive healing of the aneurysm and capture conformational changes of the devices.

At day 180, the animals were euthanized and perfused with saline followed by 4% paraformaldehyde. After overnight immersion fixation in 2.5% glutaraldehyde, the explants were rinsed in 0.1 M cacodylate buffer. The arteries were longitudinally cut under a dissecting microscope to expose the neck of the aneurysm, and then dehydrated through a graded series of ethanol concentrations (up to 100%) followed by critical point drying in carbon dioxide. The arterial samples were mounted on to aluminum stubs, grounded with silver conductive paste, sputter coated with gold/palladium, and imaged with scanning electron microscopy (SEM) (Quanta 200 MKII FEG; FEI, Hillsboro, Oregon, USA).

#### Image analysis

For quantification of HF-OCT datasets, an inhouse developed automated segmentation algorithm was applied to classify image pixels into three categories: lumen pixels, clot or tissue, and device. First, the neck of the aneurysm was found by manually tracing the vessel wall and identifying the neck. Once the neck was located, the images were remapped into polar coordinates



**Figure 1** High frequency optical coherence tomography (HF-OCT) cross sectional images before (A) and after (B) the segmentation procedure, illustrating an accurate classification of the implant: (\*) denotes the aneurysm. HF-OCT shows a small gap on the side of the neck (arrow), filled with uncleared blood.

to proceed with the classification. A multi-parametric classification method based on the local gradient, threshold signal value, shadows trailed by objects that completely block the HF-OCT emitted light, and the cumulative sum of the pixel value from the center point was applied. An example of the classification results is shown in figure 1. Once the classification was complete, the results were reviewed and approved by an expert image reader. All gaps in the coverage of the entire neck of the aneurysm were identified, and from this, the largest gap was measured. Being a high resolution imaging modality (ie, with a spatial resolution approaching  $10 \,\mu$ m),<sup>14</sup> HF-OCT could depict and quantify the presence of both large and minor gaps, that cannot be visualized by DSA or VasoCT.

The primary outcome of the study was aneurysm occlusion determined using DSA after 180 days. The occlusion score was dichotomized to a good outcome (fully occluded) or bad outcome (any residual filling) and compared with Fisher's exact t test. The number of devices implanted was compared with a non-parametric Mann–Whitney U test due to the non-normal distribution of the number of coils used. A threshold analysis of HF-OCT prediction of occlusion was applied and Fisher's exact t test was used to determine if HF-OCT predicted occlusion of the aneurysm assessed with DSA. Finally, a Bland–Altman graph was generated to look at the bias and limits of agreement between HF-OCT and SEM. All statistical calculations were done in R 3.5.1 (the R Foundation).

#### RESULTS

All aneurysms were successfully treated (n=11) except for one sidewall aneurysm (n=1) that was partially thrombosed on the day of surgery and therefore excluded from the study. Baseline aneurysm characteristics between the aneurysms treated with NGID and coils were found to be not significantly different (table 1). Aneurysms treated with coils trended towards a slightly higher occlusion score immediately following implant although it was not significantly different (P=0.09) (table 2). The number of devices deployed was greater for the aneurysms coiled than those treated with NGID (6.75 vs 1.9, respectively; P=0.009, Mann-Whitney U test). The NGID formed a stable construct at the level of the neck with no case of herniation into the parent artery whereas there was evidence of coil herniation in 75% of aneurysms (P=0.024). On final follow-up 180 days after treatment, DSA occlusion scores were not statistically different between coils and the NGID device (P=0.45, Fisher's exact t test).

HF-OCT findings showed that all gaps of neck coverage larger than  $1 \text{ mm}^2$  at the time of the implant were predictive of

Table 1         Baseline aneurysm characteristics and device implant location								
	Sidewall			Bifurcation				
Animal No	Dome diameter (mm)	Height diameter (mm)	Neck width (mm)	Device	Dome diameter (mm)	Height diameter (mm)	Neck width (mm)	Device
Animal No 1	4.58	4.55	<1	Not treated	11.14	11.09	5.12	Coils
Animal No 2	9.22	6.67	2.88	Coils	8.75	8.21	3.60	NGID
Animal No 3	7.11	6.24	3.28	Coils	8.01	7.99	3.60	NGID
Animal No 4	8.80	7.24	5.12	NGID	9.78	6.96	3.90	NGID
Animal No 5	5.27	3.52	3.44	NGID	8.13	8.91	4.24	Coils
Animal No 6	5.07	3.20	4.00	NGID	9.92	6.96	4.10	NGID

NGID, next generation intrasaccular device.

persistent aneurysm dome filling culminating in device compaction at 6 months (P=0.047, Fisher's exact t test) (table 2). A representative set of treated bifurcation aneurysms is shown in figure 2. All aneurysms with a large coverage gap failed to occlude (contrast penetration into the aneurysm dome) at 6 months whereas uniform coverage resulted in complete occlusion within 30 days that remained stable throughout the duration of surveillance (figure 3).

SEM and HF-OCT findings at 180 days were qualitatively and quantitatively compared. Measurement of the coverage gaps in the NGID construct were obtained for both modalities. HF-OCT was found to have a very high level of agreement with SEM (figure 4), with no bias, small limits of agreement (bias 0.0024 mm<sup>2</sup>; 95% CI -0.0279, 0.0327), and no significant difference. Qualitative analysis showed that when small areas of incomplete endothelization of the NGID device on SEM were identified, and the corresponding slices from the HF-OCT were examined, the images showed similar findings (figures 4 and 5).

#### DISCUSSION

Coiling of intracranial aneurysms has been shown to be a safe and effective treatment. Despite an excellent safety profile, there is a known risk of recurrence and potential need of retreatment. The balloon remodeling technique remains an important option for coiling wide neck aneurysms.<sup>18</sup> <sup>19</sup> To reduce the chances of aneurysm recanalization, SAC has often been adopted. However, SAC techniques may lead to an additional chance of thrombotic complications, as high as 16%.<sup>20</sup> The development of new intrasaccular devices offers potential for safer aneurysm treatment that avoids the use of dual antiplatelet therapy, uses fewer devices, and may reduce procedure time. As an additional benefit, intrasaccular devices often require fewer implants than traditional aneurysm coils (1.9 vs 6.75 in this study). Preliminary experience with these devices has shown promising results<sup>21</sup> but also concerns regarding recurrence, particularly when only one device is used.<sup>22</sup> The specific mechanism for intrasaccular device failure to achieve occlusion may be related to lack of mechanical support from tight packing to resist transient hemodynamic forces leading to fatigue, failure to reconstruct the neck, or related to patient specific factors. In a controlled experiment, we show that small gaps in neck coverage delay aneurysm healing and lead to device compaction.

Following coil treatment, current predictive tools of aneurysm occlusion include packing density, aneurysm volume, and Raymond-Roy classification,<sup>23</sup><sup>24</sup> with post-treatment angiographic classification showing the greatest OR. Due to photon starvation in a densely packed aneurysm, contrast penetration into the aneurysm neck and dome may not be fully appreciated, a limit of current imaging capabilities. Furthermore, given the reduced X-ray attenuation of these newer intrasaccular devices, a new classification paradigm may be required for outcome prediction. In this study, we have shown that the measurement of the largest gap in the neck coverage, obtained using high resolution intravascular imaging, predicts the efficacy of aneurysm embolization. Altogether, the results of this study illustrated the

Table 2 Largest coverage gap in the next generation intrasaccular device construct as it compares wth the implant, and final DSA occlusion scores

500.05							
Animal No	Location	Device	No of implants	Herniation (Y/N)	Largest coverage gap at implant (mm <sup>2</sup> )	Implant DSA score <sup>3</sup>	180 day DSA outcome score <sup>3</sup>
Animal No 1	Bifurcation	Coils	11	Y	N/A	2	2
Animal No 2	Sidewall	Coils	6	Ν	N/A	2	1
	Bifurcation	NGID	2	Ν	1.57	3	3
Animal No 3	Sidewall	Coils	4	Υ	N/A	2	1
	Bifurcation	NGID	2	Ν	0.18	3	1
Animal No 4	Sidewall	NGID	1	Ν	0.55	2	1
	Bifurcation	NGID	2	Ν	1.30	3	3
Animal No 5	Sidewall	NGID	3	Ν	0.09	3	1
	Bifurcation	Coils	6	Υ	N/A	3	1
Animal No 6	Sidewall	NGID	2	Ν	0.08	3	1
	Bifurcation	NGID	1	Ν	0.12	3	1

Due to artifacts in imaging, it was not possible to perform this analysis on the standard coils. NGID, next generation intrasaccular device.

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**Figure 2** Control angiography of a bifurcation aneurysm after next generation intrasaccular device (NGID) embolization (A). High frequency optical coherence tomography (HF-OCT) shows a gap in the neck coverage (B, arrow), leading to an aneurysm neck remnant at day 180 (C) and compaction of the device. Angiography of a second bifurcation aneurysm embolized with a NGID (D). Three-dimensional HF-OCT data show evidence of complete and uniform neck coverage (E). The aneurysm was fully occluded after 30 days and remained stable throughout the observation period of 180 days (F).

potential benefits of performing HF-OCT acquisition prior to device detachment to further inform treatment decisions. Using in vitro vascular models, it was shown that effective neck coverage of intrasaccular devices is critical for hemodynamic modification,<sup>13 25</sup> a finding consistent with the in vivo results presented herein. As such, the use of HF-OCT imaging combined with the ability to modify device placement can provide procedural guidance for an optimized deployment, significantly increasing the chances of obtaining complete aneurysm occlusion.

Numerical simulations have also been proposed to predict recurrence following coil embolization and applied successfully to clinical cases.<sup>26</sup> These approaches rely on important procedural information as well as certain assumptions about the implant (such as uniform distribution or resistance to flow). Herein, we demonstrate that HF-OCT can provide imaging data for subsequent quantitation of spatial variations in aneurysm neck coverage. These data



**Figure 3** High frequency optical coherence tomography (HF-OCT) imaging of progressive in vivo aneurysm neck remodeling: baseline versus 7, 30, and 180 days following implantation. Three-dimensional HF-OCT data acquired at baseline show complete coverage of the aneurysm neck (A). Follow-up at 7 days shows healing progression with a significant amount of uncovered struts exposed to the blood flow (B, arrows). HF-OCT imaging at 30 days shows tissue growth over the device (C); the arrow points to a small area of an uncovered metallic strut. HF-OCT imaging at 180 day shows additional healing progression and no neck remnants (D).



**Figure 4** High frequency optical coherence tomography (HF-OCT) (A, B) and scanning electron microscopy (SEM) (C) images of the next generation intrasaccular device, 180 days following implant. Images show a small area of incomplete tissue coverage (A, solid arrows) and an uncovered metallic strut (B, open arrow). En face SEM imaging of the device (C); open arrow, uncovered strut, and solid arrow, gap in tissue coverage, confirms these findings. Bland–Altman plot of HF-OCT versus SEM for the measurement of the coverage gap at 180 days.

may well complement numerical strategies by providing essential information for accurate modeling.

This study was limited by a relatively small sample size. Despite the low number of NGID devices, a threshold of  $1 \text{ mm}^2$  gap correctly classified the two cases in which the treatment failed. Furthermore, the remaining five cases with successful occlusion did have gaps in neck coverage but not exceeding this threshold and were therefore also correctly classified. Using a larger sample size



**Figure 5** Control angiography following implant (A) showing contrast entering the dome of the aneurysm treated with a next generation intrasaccular device. Follow-up angiogram at 180 days demonstrates residual filling of the aneurysm dome and compaction of the device (B). Scanning electron microscopy (SEM) reveals a coverage gap at the neck (C, open arrow), and uncovered struts (solid arrow). Day 0 high frequency optical coherence tomography (HF-OCT) (D) shows a large coverage gap (D , open arrow) at the aneurysm neck (defined by the small, solid arrows). HF-OCT at day 180 clearly depicts the neck coverage gap (E, open arrow) and the uncovered struts (E, solid arrow) seen on the post mortem SEM.

#### **Basic Science**

will enable a more sensitive threshold to be established. Traditional coils often herniated from these wide neck aneurysms inhibiting a full three-dimensional reconstruction of the coil structure at the level of the neck due to imaging catheter positioning in the vessel lumen and optical attenuation by the coils. Image quality coupled with a limited sample size did not allow a meaningful analysis of traditional coil embolization in all cases.

#### CONCLUSIONS

With the advent of HF-OCT, an informed and accurate prediction of treatment efficacy may be possible. In this study, HF-OCT enabled a quantitative analysis of the aneurysm neck for a new class of intrasaccular devices that is predictive of aneurysm occlusion. We showed that the presence of gaps with an area larger than 1 mm<sup>2</sup> leads to persistent aneurysm filling and that homogenous neck reconstruction with no gaps larger than this threshold reliably predicts aneurysms occlusion. The results of this study demonstrate the feasibility of high resolution intravascular imaging for the assessment of acute device implantation, procedural guidance, and ability to prognosticate complete aneurysm occlusion.

**Contributors** RMK: performed the experiments, analyzed and interpreted the data, wrote the manuscript, and approved the final manuscript. MM: performed the experiments, interpreted the data, revised the manuscript, and approved the final manuscript. JC: performed the experiments, analyzed and interpreted the data, and approved the final manuscript. GJU: performed the experiments, interpreted the data, revised the manuscript. DMG: performed the experiments and approved the final manuscript. MJG: designed the study, designed and performed the experiments, analyzed and interpreted the data, drafted the manuscript, approved the final manuscript, and agrees to be accountable for the accuracy and integrity of the work. ASP: designed the study, interpreted the data, revised the manuscript, and approved the final manuscript.

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**Competing interests** MM: fee for service consulting for Stryker Neurovascular and InNeuroCo Inc. JC has received educational scholarships from Medtronic Neurovascular and Microvention/Terumo. GJU is an employee of Gentuity LLC and holds stock in Gentuity LLC. ASP: consultant for Medtronic Neurovascular and Stryker Neurovascular; and research grants from Medtronic Neurovascular and Stryker Neurovascular. MJG has been a consultant on a fee per hour basis for Cerenovus, Imperative Care, MIVI Neurosciences, Phenox, Route 92 Medical, and Stryker Neurovascular; holds stock in Imperative Care and Neurogami; and has received research support from the National Institutes of Health (NIH), the United States– Israel Binational Science Foundation, Anaconda, Cerenovus, Cook Medical, Gentuity, Imperative Care, InNeuroCo, Magneto, Microvention, Medtronic Neurovascular, MIVI Neurosciences, Neuravi, Neurogami, Philips Healthcare, Rapid Medical, Route 92 Medical, Stryker Neurovascular, Syntheon, and the Wyss Institute.

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**Original Article** 

### A computational fluid dynamics (CFD) study of WEB-treated aneurysms: Can CFD predict WEB "compression" during follow-up?

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#### ABSTRACT

Background. - Recent reports have revealed a worsening of aneurysm occlusion between WEB treatment baseline and angiographic follow-up due to "compression" of the device. Objective. - We utilized computational fluid dynamics (CFD) in order to determine whether the underlying

mechanism of this worsening is flow related.

Methods. - We included data from all consecutive patients treated in our institution with a WEB for unruptured aneurysms located either at the middle cerebral artery or basilar tip. The CFD study was performed using pre-operative 3D rotational angiography. From digital subtraction follow-up angiographies patients were dichotomized into two groups: one with WEB "compression" and one without. We performed statistical analyses to determine a potential correlation between WEB compression and CFD inflow ratio.

Results. - Between July 2012 and June 2015, a total of 22 unruptured middle cerebral artery or basilar tip aneurysms were treated with a WEB device in our department. Three patients were excluded from the analysis and the mean follow-up period was 17 months. Eleven WEBs presented "compression" during follow-up. Interestingly, device "compression" was statistically correlated to the CFD inflow ratio (P=0.018), although not to aneurysm volume, aspect ratio or neck size.

Conclusion. - The mechanisms underlying the worsening of aneurysm occlusion in WEB-treated patients due to device compression are most likely complex as well as multifactorial. However, it is apparent from our pilot study that a high arterial inflow is, at least, partially involved. Further theoretical and animal research studies are needed to increase our understanding of this phenomenon.

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#### Introduction

The WEB intra-saccular flow disrupter (Sequent Medical, Alisa Viejo, California) is a novel endovascular approach to treat broad base intracranial aneurysms. A recent report has demonstrated a worsening of aneurysm occlusion between postoperative baseline and follow-up due to "compression" of the device [1]. Cognard et al. described a worsening between the post-procedural and follow-up angiographies in 10 of 14 cases (71.5%) and a "compression" of the WEB in 9 of 14 cases (64.3%) (Fig. 1). In a larger series, other authors [2] demonstrated that this phenomenon was not infrequent with a WEB shape modification in 32% of cases.

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Yet the underlying mechanisms are still unknown. The WEB device is expected to better resist arterial flow due to its volumetric shape and radial force, therefore some suspect that WEB shape is modified by clot retraction [3].

However, neither mechanism has yet been demonstrated. Here, we sought to determine whether the reported worsening of aneurysm occlusion is flow related using computational fluid dynamics (CFD) technology.

#### Material and methods

#### Data collection

From our prospectively maintained database, we retrospectively extracted all consecutive patients treated with a WEB device in our institution between July 2012 and June 2015 for either a

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**Fig. 1.** A. Right 6.5 mm MCA aneurysm (A). DSA (B) and VasoCT (E) showing immediate and complete occlusion obtained after WEB-SL delivery. At the 6-month follow-up, DSA (C) and VasoCT (F) depict a small recanalization with an opacification of the proximal recess (arrow in C) due to WEB shape modification with a "butterfly" aspect. The pre-operative CFD analysis (D, inflow view) calculated a high inflow ratio: 1.02, thus a high "compression" risk.

middle cerebral artery (MCA) or basilar tip aneurysm, that were unruptured, untreated and without partial thrombosis. Informed consent was obtained in each case. The study was conducted under the rules of local ethics committee. Patients with obvious bad technical results were excluded, i.e. absence of neck sealing and blood flow penetrating inside the aneurysm around the WEB due to an undersized device. Patients without follow-up imaging were also excluded.

Pre-operative 3D rotational angiography (3DRA) acquisitions and follow-up digital subtraction angiography (DSA) were recorded. Morphological parameters (aneurysm volume, neck size, aspect ratio defined as depth/neck ratio) were measured from 3DRA. Contrast enhanced high resolution cone-beam CT (VasoCT [4]) was systematically used at the end of the procedure and during follow-up angiographies. Angiographic follow-up was performed at 6, 18 and 32 months after treatment.

Two authors (J.C and C.M.) blind reviewed all follow-up imaging from CFD data to determine the presence or absence of WEB device shape modification (defined as a shortening of the distance between the proximal and distal WEB markers between postoperative images and follow-up). The analysis was based on 2D images and VasoCT systematically performed during follow-up. Reviewers also analyzed and the presence or absence of complete aneurysmal occlusion. Differences between the results of the 2 observers were discussed in an additional meeting to reach consensus.

The anatomical results were evaluated using the Bîcetre occlusion scale score (BOSS) [5].

#### Treatment technique

Endovascular treatment was performed using a biplane flat panel angiographic system (Allura Xper 20/10; Philips, Best, Netherlands). Endovascular procedures were performed under general anesthesia and systemic heparinization. WEB-DL, WEB-SL and WEB-SLS were used at the operator's discretion.

#### CFD analysis

CFD analysis was carried out using a novel CFD package (*hemoscope* v1.4, EBM Corp., Japan) that was developed specifically for aneurysmal flow research by medical professionals as previously reported [6].

#### Vascular geometry

Initially, a three-dimensional geometry of the vascular lumen was constructed by a medical-image processing package (Ziostation2, Ziosoft, Inc., Japan). Input images came from 3DRA. The reconstructed slice images gave a spatial resolution of approximately 0.2 mm. The region of interest in anterior circulation included the internal carotid artery, anterior cerebral artery A1 segment, MCA M1 and M2 segments. The posterior circulation included the basilar artery, superior cerebellar artery, and posterior cerebral artery P1 segment. These major arteries and other branches were included in CFD if the diameter of each artery was greater than 1.0 mm. Hence, the diameter denotes the median of equivalent circle diameters scan-measured along a center line at each segmented vessel. The vascular lumens were defined as those of a single threshold or greater. The threshold was represented as a half of the peak intensity in M1 and P1 segments, in anterior and posterior circulation, respectively. With these thresholds, the software allowed polygonised surface geometries to be obtained using a marching-cube method.

#### Preprocessing

Subsequently, *hemoscope* software automatically enabled the following processing. First, these vascular geometries were filled with unstructured cells. The shape was mainly composed of hexahedrons, and their sizes were approximately 0.25 mm in far-wall, and 0.125 (width) and 0.05 (height) mm in near-wall regions. Nearwall meshes consisted of three layers. The inlet and outlet vessels were extended by 5 and 10 times greater than their diameters, respectively. The blood density ( $\rho$ ) and viscosity ( $\mu$ ) were set as:  $\rho = 1050 \text{ kg/m}^3$  and  $\mu = 0.004$  Pas. The boundary conditions were determined in accordance with a constant wall-shear-stress theory. Specifically, flow rates of inlet and outlet vessels were calculated using the following equation:

$$Q = \frac{\tau\pi}{32\mu} D^3 \tag{1}$$

where Q,  $\tau$ ,  $\mu$ , D denotes flow rate, wall shear stress, fluid viscosity and vascular diameter, respectively. This equation is a well-known theoretical basis of a fully developed laminar pipe flow. Herein, the wall shear stress was set to be  $\tau = 1.5$  Pa [7]. After calculating total inflow at an inlet vessel, the amount of inflow were distributed at each outlet vessel according to equation (1), and the specified boundary condition of inlet and outlet vessels were pressure and velocity boundary conditions, respectively. The present computation adopted a steady flow, and thus the inlet pressure was set at 100 mmHg

#### Computation

Governing equations of fluid flow were solved in a threedimensional unsteady fashion using the finite volume method. The fluid blood was assumed to be incompressible and Newtonian fluid, and the nature of flow was allowed to have transient behaviors. The Euler and 2nd-order upwind schemes were adopted for discretizing unsteady and convective acceleration terms. The convergent criteria were set to  $10^{-4}$ .

#### Post-processing and inflow ratio

Computed velocity information allowed us to visualize aneurysmal flow structures by streamlines and the inflow environments were characterized by an aneurysmal inflow rate. The aneurysmal inflow rate was a net flow rate entering an aneurysm through a user-defined aneurysmal neck.

In order to quantity the strength of inflow, the aneurysmal inflow ratio was defined as a ratio of flow going inside the aneurysm over parent artery flow:

$$\Phi = \frac{Q_a}{Q_p}$$

where  $Q_a$  and  $Q_p$  were aneurysmal inflow rate and parent artery flow rate, respectively (Fig. 2). For M1 tip and BA tip aneurysms treated herein, parent arteries were defined as distal M1 and mid BA segments, respectively.

Thus, a high inflow ratio (around 1) corresponded to most of the proximal parent arterial flow entering into the aneurysmal sac. The inflow ratio can be greater than 1, in cases where the turbulent outflow re-enters inside the aneurysm through the neck.

#### Statistical analysis

The parameters of CFD inflow ratio, aspect ratio, neck size and aneurysm volume were compared between the WEB "compression" and "non-compression" populations using the Mann-Whitney *U* test. Similar analysis was repeated among groups with "complete aneurysmal occlusion" and "incomplete aneurysmal occlusion" at last follow-up. To estimate the inter-rater agreement between the two readers, an overall kappa coefficient and its standard error were computed. Statistical significance was assumed at the *P*<0.02 level. Receiver operating characteristic (ROC) curves were generated from the inflow values using XLSTAT software (Version 2016.01.26783).

#### Results

#### Demographic data

Between July 2012 and June 2015, a total of 22 unruptured MCA and basilar tip aneurysms, that had never received treatment, were operated on with a WEB device in our institution (Table 1). A total of 18 patients (15 women and 3 men; average age 64 years), with 19 WEB-treated aneurysms were included in this study. Three cases were excluded for different reasons:

- one patient had obvious post-detachment negative results (with flow around the device) and is planned to be retreated in a second session;
- another had a partially thrombosed aneurysm;
- the third case lacked imaging during follow-up.

It was determined that 15 aneurysms were located along the MCA, and 4 along the basilar artery. The maximum diameter of aneurysms varied from 4.8 to 11.6 mm (mean: 7.3 mm), neck sizes varied from 2.5 to 9.2 mm (mean: 5.5 mm) and the aspect ratio, (defined as depth/neck), varied from 0.7 to 3.12 (mean: 1.2). WEB-DL was used in 10 cases, WEB-SL in 8 cases and WEB-SLS in 1.

#### Follow-up

The average time interval from treatment to follow-up was 17 months (range: 6–28 months) and complete occlusion had occurred in 10 cases (53%).

The two raters showed a substantial agreement to determine "compression" (kappa = 0.67, SE = 0.1795% CI = 0.33 to 1.02).

WEB device "compression" was depicted in 11 cases (56%) and the following was observed within this subgroup:

- complete occlusion in 3 cases (due to initial WEB protrusion in the parent artery);
- a deep proximal recess in 2;
- an intra-device opacification in 1;
- a neck remnant in 1 and 4 cases had an aneurysm remnant.

A worsening of the anatomical result (i.e. evolution from complete occlusion to neck remnant or aneurysm remnant and from neck remnant to aneurysm remnant) was observed in 4 cases.

#### CFD analysis

CFD analysis was possible in all cases (Fig. 3). The mean inflow ratio was 0.8 (range: 0.48–1.39).



**Fig. 2.** Streamline view of two different aneurysms. White arrows illustrate the cross sections where the flow in the parent artery and through the aneurysmal neck is calculated to obtain the CFD inflow ratio. On the left, the aneurysm is exposed to high flow: all the parent artery flow is entering inside the aneurysm through the neck with associated outflow vortex re-entering inside the aneurysm (CFD inflow ratio is 1.15). On the right side is an aneurysm less exposed to flow with only less than  $\frac{3}{4}$  of the parent artery flow penetrating inside the sac (CFD inflow ratio is 0.70). Color scales are different between right and left.

#### Table 1

Aneurysms and procedural characteristics.

Aneurysm	Location	Width (mm)	Dome (mm)	WEB type	CFD inflow ratio	Complete Occlusion (yes/no)	Compaction (yes/no)
1	BA	11	11.2	DL $11 \times 9$	1.08	No	Yes
2	MCA	5.5	7.4	$DL7 \times 6$	0.7	No	Yes
3	MCA	9.9	8.5	$DL10\times7$	1.39	No	Yes
4	MCA	8.25	7.4	$DL 9 \times 6$	1.15	No	Yes
5	BA	5.95	5.7	$DL7 \times 6$	0.68	Yes	No
6	MCA	6.75	4.4	$DL6 \times 4$	0.8	Yes	Yes
7	MCA	6.85	5.3	DL $7 \times 5$	0.78	Yes	No
8	MCA	4.9	5.5	$DL 5 \times 4$	0.6	Yes	No
9	BA	6	5.5	$DL6\times4$	0.91	No	Yes
10	MCA	9.1	5.4	$DL8\times4$	1.02	No	Yes
11	MCA	4.8	4.7	SL $5 \times 4$	0.75	Yes	No
12	MCA	5.35	5.6	SL $5 \times 3$	0.61	No	No
13	MCA	6.6	5.4	SL $7 \times 4$	1.02	Yes	Yes
14	MCA	5.1	4.6	$SL 6 \times 3$	0.96	No	No
15	MCA	6.25	7.8	SLS 7	0.37	No	No
16	MCA	5	3.2	SL $5 \times 3$	1.02	No	Yes
17	BA	9.9	7.1	SL $9 \times 7$	0.58	Yes	No
18	MCA	4.9	3.7	SL $5 \times 3$	0.49	No	Yes
19	MCA	4.7	4.1	$SL4\times3$	0.69	No	Yes

MCA: middle cerebral artery aneurysm; BA: basilar tip aneurysm; DL: dual layer; SL: single layer; SLS: single layer sphere.

#### Correlations

WEB "compression" was not significantly associated with neck size (P=0.51), aspect ratio (P=0.77), aneurysm volume (P=0.43), maximum aneurysm diameter (P=0.48), maximum width (P=0.43), WEB diameter (P=0.55) or the absolute aneurysm inflow rate estimated from CFD (P=0.21) (Table 2).

WEB "compression" was significantly associated with a high inflow ratio (i.e. absolute aneurysm inflow rate/absolute

parent artery flow rate) as calculated from CFD analysis. The mean inflow ratio in the "compaction group" was  $0.93 \pm 0.25$  and the mean ratio in the "non-compaction group" was  $0.67 \pm 0.17$ ; P = 0.018.

ROC analysis is represented in Fig. 4. AUC was 8.83; 95% CI: 0.676, 0.983; P < 0.01. The optimal operating point was 0.79 (sensitivity 0.727; specificity 0.875).

Furthermore, we also found a tendency towards lower CFD inflow ratios in the "complete occlusion" group (mean

#### Table 2

Association between aneurysm characteristics and WEB "compression" during follow-up.

Aneurysm parameters	CFD inflow ratio (P)	Complete occlusion (P)	Aspect ratio (P)	Aneurysm volume (P)	Maximum diameter (P)	Maximum width (P)	WEB diameter (P)
Mann-Whitney test	0.018	0.09	0.77	0.43	0.48	0.43	0.55



Fig. 3. Results of CFD analysis. On the abscissa, each point represents an aneurysm sorted by chronological order. Red squares represent WEB "compression" and blue circles represent no WEB "compression". The CFD inflow ratio is represented on the ordinate. From ROC curve analysis (Fig. 3), the optimal operating point was determined to be 0.79 (sensitivity 0.727; specificity 0.875). It appeared that in our late experience patients – i.e. after November 2013, there were fewer WEB shape modifications during follow-up.



Fig. 4. ROC curve for the prediction of WEB "compression" according to the inflow ratio calculated by CFD.

ratio =  $0.73 \pm 0.16$ ) vs the "incomplete occlusion" group (mean ratio =  $0.92 \pm 0.3$ ), with *P* = 0.09.

#### Discussion

#### WEB "compression"

The WEB intra-saccular flow disrupter was first introduced to the market as an exciting device since it appeared to be a simple solution for managing previously difficult-to-treat wide-neck bifurcation aneurysms, in addition to a very good safety profile [8–14]. However, it has recently been described in an unexpected phenomenon: during early follow-up, a worsening of the occlusion rates, related to "compression" of the device, had been observed in up to 64% of cases [1]. Here, in this selected population, we found a similar rate of WEB shape modification during follow-up (56%). Therefore, we have tried to understand the underlying mechanisms using CFD in this study.

Here, we have shown that despite the likely multifactorial origin of device "compression", there is clearly an association with aneurysm flow exposure as represented by the CFD inflow ratio.

#### CFD inflow ratio

Modeling of flow in intracranial aneurysms requires flow information at the model boundaries. We did not find a significant correlation between the absolute value of aneurysmal flow and the appearance of WEB "compression" (P=0.21). This could be due to the fact that the absolute values greatly depend on the accuracy of boundary conditions [15,16], but the choice of modeled versus measured boundary conditions is still debated in the literature [17].

Perhaps if we had used patient-specific inlet conditions measured by phase-contrast magnetic resonance, parameters such as the aneurysm absolute neck velocity or wall shear stress might have been significantly correlated to WEB "compaction". But as we wanted to propose a clinical and fast processing CFD analysis directly in the angiosuite, we decided to use an inflow ratio. This ratio has been recently described by some authors and they have shown a significant correlation between this ratio and the recanalization of coiled basilar tip aneurysms [6]. The benefit of using a ratio is to reduce variation induced by the boundary conditions and here we found a strong correlation between WEB "compression" and the ratio between intra-aneurysmal flow and parent artery flow (P=0.018).

#### Low CFD ratio and WEB compression

However, we have described here three cases (3/19) where the inflow ratio was low (<0.6), yet WEB "compression" still occurred during follow-up. Furthermore, we noted in some cases a deepening of both the proximal and distal concave recesses of the WEB device, indicating more a "retraction" on the device rather than a "compression" phenomenon.

These findings may indicate that clot contraction is another possible mechanism involved in the worsening of occlusion rates during follow-up.

#### Aneurysm occlusion rate

In this study, we found a tendency toward an association between CFD inflow ratio and complete aneurysmal occlusion at follow-up. Although not statistically significant, there was a clear trend of lower CFD inflow ratios in the group of patients presenting a complete aneurysmal occlusion (P=0.09). The lack of statistical significance may be due to the small sample size of our study in addition to the short follow-up period. One should also note that the "compression" phenomenon is not systematically associated with a bad angiographic result. Complete occlusion could still be observed either because of a neck sealing with a distal to proximal "compression" or, more often, due to the intentional position of the device to slightly protrude into the parent artery when delivered.

A worsening of the anatomical result was observed in our series in 36% of cases at last follow-up with an "adequate occlusion" in 55% of cases in this subgroup. Although Cognard et al. [1] report a very high rate of 64% of occlusion worsening, other authors found less impact of WEB compaction over occlusion rates. Herbreteau et al. [2] described shape modifications in 31.6% of patients (similar to our results). It was then not associated with a lower rate of adequate occlusion with at short-term, midterm, and long-term follow-up, adequate occlusion obtained in 86.8, 83.3, and 87.5% of cases. A recent and large meta-analysis [9] confirmed those results with an 84% midterm adequate occlusion rate.

#### **Operators with increased WEB experience**

When patients were dichotomized between early experience (i.e. before November 2013) and late experience (after November 2013), we found no significant difference in inflow ratio between the two groups (P=0.11). In the early experience, patients "compression" occurred in 70% of cases (7/10). Interestingly, in late experience, we found a trend towards less WEB shape modification during follow-up, as it occurred in only 44% of cases (4/9).

Numerous factors could be at the origin of this finding. The fact that the operators will have gained experience and perhaps a better selection of cases could both explain the improved angiog-raphic results of the late experience patients. A third explanation could be our recent application of a principle recommended by other authors from their personal clinical experience: to oversize the device by approximately 1 mm in diameter to obtain optimal anatomical results and better flow resistance [3]. This is supported by Behme et al.'s [18] paper where they showed an important learning curve with favorable angiographic rates growing from 40 to 75% from 2012 to 2014.

Finally, this study is one of the first to use CFD simulations as a tool that can directly impact treatment planning [15]. Our purpose here is definitely not to state that cases with high inflow ratios are contraindications for WEB treatment. However, it should highlight awareness to the operator that WEB shape and size selection are paramount; and that width oversizing may increase WEB resistance to "compression", ensuring optimal follow-up angiographic results.

#### Limitations

Our study has a number of limitations. Firstly, the number of cases included is moderate since the WEB is a very recent device in treating aneurysms.

Secondly, we used only a binary scale for "compression" as it was difficult to accurately quantify the "compression" for small devices given their low radiopacity. Thus we were unable to determine whether a greater inflow would induce a greater WEB "compression".

Further pre-clinical studies are vital for an increased understanding of the underlying mechanisms behind WEB "compression" and how WEBs should be used optimally to decrease the frequency of this phenomenon. In addition, long-term follow-up clinical studies are necessary to further evaluate any impact of WEB "compression" on angiographic results.

#### Conclusion

The mechanisms underlying in WEB shape change with time, as observed in some aneurysms, are most likely complex as well as multifactorial. This device compression does not correspond to worsening of aneurysm occlusion in all cases. However, it is apparent from our pilot study that a high arterial inflow effect is, at least, partially involved. Further theoretical and animal research studies are needed to increase our understanding of this phenomenon.

#### Authors contribution

JC: project development, data collection, manuscript writing, statistical analysis, approval of final version.

TY: project development, approval of final version.

CM, VDR, MI, LI, JM, LS: data analysis, approval of final version.

#### **Disclosure of interest**

LS and JM are consultants for Sequent Medical, TY is an employee of EBM corp.

Jildaz Caroff, Cristian Mihalea, Valerio Da Ros, Marta Iacobucci, Léon Ikka declare that they have no competing interest.

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V

#### ORIGINAL RESEARCH

# The occurrence of neointimal hyperplasia after flowdiverter implantation is associated with cardiovascular risks factors and the stent design

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#### ABSTRACT

**Background** Neo-intimal hyperplasia (NIH) is frequently observed after flow-diverter stent (FDS) implantation. Although mostly asymptomatic, this vascular response can sometimes lead to delayed ischemic strokes. This study intended to evaluate the factors potentially influencing the rates of NIH following FDS treatment.

Material and Methods All aneurysm treatments performed with a Pipeline embolization device (PED) or a SILK stent from May 2011 to May 2015 were collected in a prospectively maintained database. Patient demographics, clinical, and angiographic outcomes including both digital subtraction angiography and C-arm cone-beam CT were registered. Two blind reviewers rated the presence of NIH on a binary scale (present/absent). **Results** From 148 patients, 63 datasets were available for analysis. Inter-reader agreement was excellent (Kappa=0.88). NIH was positively correlated with smoking, dyslipidemia, and high blood pressure, but not with aneurysm characteristics. At early follow-up (<12 months), NIH was more frequently associated with the use of the SILK stent (68%) rather than the PED (38%): P<0.02. At long-term follow-up, the NIH rate in the total population dropped from 55% to 26% with no more significant difference between the two stents. The

complete occlusion rate as seen in early follow-up was higher in the SILK group with 76% vs 65% but without statistical significance (P=0.4).

**Conclusion** NIH is a dual-vessel reaction after FDS implant. When planning a treatment in locations at risk of ischemic complications if severe NIH would occur, then the stent design should be considered. However, minimal NIH might also be needed as it is involved in aneurysm healing. Before treatment patients should be recommended best medical management of their cardiovascular risks factors to prevent an excessive NIH reaction.

#### INTRODUCTION

Neointimal hyperplasia (NIH) is a vessel-wall reaction frequently depicted after flow-diverter stent (FDS) treatment for intracranial aneurysm,<sup>1–3</sup> and may lead to delayed ischemic strokes.<sup>2–5</sup> C-arm cone-beam CT (VasoCT) has been validated for measurement of in-stent tissue growth.<sup>1</sup> The goal of this study is to evaluate if the FDS design and cardiovascular risks factors affect the vessel-wall reaction during follow-up using high resolution cone-beam CT.<sup>6</sup>

#### MATERIAL AND METHODS Population

Between May 2011 and May 2015, 148 consecutive patients treated with a Pipeline embolization device (PED) (Medtronic, Irvine, California, USA) or a SILK stent (Balt, Montmorency, France) were retrospectively reviewed to assess the incidence of NIH using conventional digital subtraction angiography (DSA) and cone-beam CT multiplanar reconstructions. National Commission for Data Processing and Freedom approval and informed written consents were obtained.

#### Endovascular treatment

All endovascular treatments were performed using a biplane, flat-panel detector angiography system (Allura Xper 20/10; Philips Healthcare, Best, The Netherlands). Conventional 2D DSA and VasoCT were routinely performed on the day of the procedure to confirm good wall apposition, and in the follow-up angiograms at 6, 18, and 42 months after treatment to check for any in-stent stenosis. Non-routine additional angiograms were obtained at the discretion of the physician and when unexpected clinical or angiographic findings were seen during follow-up. Informed consent was obtained from each patient.

Endovascular procedures were performed with the patient under general anesthesia and systemic heparinization. Patients were premedicated with clopidrogrel (75 mg daily) and aspirin (160 mg daily) starting 7 days before the procedure. Thrombocyte inhibition levels were confirmed using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) and four hematological laboratory tests. In cases of resistance a loading dose of plavix was given prior to intervention. The choice of stent used for treatment was dependent on the operator's choice based on anatomy and personal experience. The dual antiplatelet therapy was maintained for 3 months then discontinued, while aspirin was continued until 12 months after treatment. In cases

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#### Neuroimaging

of severe NIH the dual antiplatelet therapy was maintained until the following DSA.

#### Images analysis

A set of images was selected by a qualified interventional radiologist. It contained the best DSA and unsubtracted images with VasoCT images at the time of treatment, first and last follow-up. Blinded from the clinical data, two experienced interventional neuroradiologists rated the NIH on a 3-point scale described as follows: 0=absence of NIH; 1=minor NIH (<25%); and 2=mild and severe NIH (>25%). From this the scale was also analyzed as binary, describing the presence or the absence of NIH. Differences in image interpretation were then resolved by consensus.

#### **Inclusion criteria**

The inclusion criteria in this study were: the use of a PED or SILK FDS; and at least one available early follow-up angiogram performed between 3 and 12 months (VasoCT quality had to be sufficient for NIH analysis).

#### Cardiovascular risks factors

Smoking was defined by the status at the time of the treatment. High blood pressure and dyslipidemia were considered if the patient was at least treated with one drug for those conditions.

#### Statistical analysis

Statistical analysis was performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). NIH evaluation reported by two raters and agreement was assessed using Cohens' weighted Kappa ( $\kappa$ ) scores for both binary and 3-point scales. Comparison of categorical variables was obtained with Fisher's exact test. We performed univariate analyses using the Mann–Whitney *U* test for the comparison of continuous variables. A P-value of P<0.05 was considered statistically significant.

#### RESULTS

#### Patients' demographics

From 148 patients, 63 datasets were available for analysis. Basic demographic data and aneurysmal characteristics are summarized in tables 1 and 2. No significant difference was observed between the PED and SILK groups.

#### **Imaging analysis**

Inter-reader agreement was excellent ( $\kappa$ =0.89 and 0.81 for binary and 3-points scales respectively).

Table 1         Demographic data and aneurysmal characteristics								
	PED	SILK	P values					
Average age (years)	52	53	0.6					
Gender (male/female)	17%/83%	20%/80%	1					
Smokers	28%	56%	0.2					
High blood pressure	45%	43%	1					
DM	4%	8%	0.2					
Dyslipidemia	32%	16%	0.3					
Aneurysm location (anterior/posterior circulation)	26/3	34/0	0.1					
Max size (mm)	6.5	7.4	0.5					
Neck size (mm)	4.6	4.8	0.7					

At early follow-up (<12 months) NIH was more frequently associated with the usage of the SILK stent 68% rather than the PED (38% for both readers) with a P value =0.02 (table 3).

When present, the two readers rated the NIH as minimal (<25% stenosis) in 33% for the SILK population and 50% for the PED population.

The presence of NIH was not correlated with gender, age, or aneurysms' characteristics. But it was significantly associated with cardiovascular risk factors (smoking, high blood pressure, dyslipidemia), all with P < 0.01.

At last follow-up (average 29 months) the NIH presence rate in the total population dropped from 55% (35/63) to 26% (11/35), with no significant difference between the two stents (5/18 for the SILK and 4/17 for the PED; P=1).

#### **Occlusion** rates

At early follow-up ( $\leq 12$  months) the complete occlusion rate was higher in the SILK group with 76% (26/34) vs 65% (19/29) in the PED group without reaching significance (P=0.4).

#### **Clinical outcome**

In only one case were some clinical symptoms linked to NIH, which consisted of transient amaurosis episodes 6 months after the implant. DSA and VasoCT revealed severe NIH inside a SILK stent at the level of the origin of the patent ophthalmic artery. Symptoms resolved with the reintroduction of double antiplatelet therapy, but the 40-month follow-up demonstrated the persistence of mild NIH (figure 1).

#### DISCUSSION

#### Physiopathology

FDS have proven highly effective in treating intracranial brain aneurysms.<sup>7</sup> The vascular response (ie, neo-intimal and neo-endothelial reaction) after stent implant contribute to the long-term healing of the aneurysms.<sup>8</sup> <sup>9</sup> The NIH results from smooth muscle cell (SMC) migration from the media to the intima following an endothelium injury during FDS implantation. The exact biological mechanisms underlying this wall reaction are still unclear and probably different from the atherosclerotic vessel reaction after coronary stent implant.<sup>10</sup>

Although frequently depicted and usually asymptomatic, an excessive NIH reaction can sometimes lead to delayed ischemic complications.<sup>3 5 11</sup>

#### Cardiovascular risks factors' impact

In our study, smoking, high blood pressure, and dyslipidemia were individually strongly correlated to the presence of NIH. In a large surveillance angiographic analysis after coronary stenting, Cassese *et al* demonstrated that patient-related predictors of restenosis were diabetes mellitus and a history of bypass

Table 2         Aneurysms' location			
	PED	SILK	P values
Intracranial carotid siphon	16	21	0.6
Middle cerebral artery	6	5	0.7
Basilar	3	1	0.3
Anterior communicating artery	2	2	1
Cavernous	1	4	0.4
Pericallosal artery	1	0	0.5
Carotid terminus	0	1	1

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Table 3	3 Correlation between NIH and demographic data, aneurysm characteristics, and stent type							
	Gender	Age	Max A size	Neck size	Smoking	HBP	Dyslipidemia	Stent type
P values	1	0.2	1	1	<0.01	<0.01	<0.01	<0.05

surgery.<sup>12</sup> The population and the underlying disease in our study are different from the population in the large cardiovas-cular trials.

In 2015 the AHA/ASA recommended that patients with unruptured intracranial aneurysms should be counseled regarding the importance of smoking cessation and undergo treatment for hypertension.<sup>13</sup> The data from our study indicates that cardiovascular risks factor management could also be relevant for excessive NIH prevention.

#### Stent design effect

We found in our study that at early follow-up the SILK stent was more frequently associated with the occurrence of NIH than the PED (68% vs 38% respectively) and that it also tends to be more severe.

The results of our study cannot directly compare with previous reports because here we systematically used VasoCT to evaluate NIH, with this tool having a sensibility closer to histology than DSA to depict NIH.<sup>1</sup> We also decided to target and analyze any minimal amount of NIH detectable.

Nevertheless, the results of this work focused on NIH detection seem to be in accordance with the results of larger clinical studies on FDS. In a SILK meta-analysis of 285 patients, authors found an intra-stent stenosis in 5% of patients during follow-up,<sup>14</sup> whereas in a large meta-analysis of 1556 patients treated with PED it was described in less than 1.5% of cases.<sup>15</sup>

In a single center study John *et al*<sup>2</sup> depicted intra-stent tissue growth in 41% of cases using PED, whereas with the SILK stent Essbaiheen *et al*<sup>16</sup> reported a 44% rate and Lubicz *et al*<sup>17</sup> up to 57%.

Cohen *et al*<sup>3</sup> also reported a study focusing on in-stent proliferation rates after FDS implantation. Authors reported similar rates of in-stent stenosis for PED and SILK (39% and 38% respectively) but there were more cases of severe grade stenosis in the SILK patients.

We know that different materials used in stent manufacture can induce different host responses leading to different levels of local inflammation. Those inflammatory cells will produce platelet-derived growth factor, a key signal in smooth muscle cell proliferation and subsequent NIH.<sup>18</sup> Nickel ions are the most allergenic metal ions known and have proven to cause severe inflammation when tissue concentrations are high.<sup>19</sup> Surface treatment is essential for the optimum bioperformance of nitinol, and the nickel content in the oxide layer over the FDS will impact the levels of nickel ion release.<sup>20</sup> Aguilar Pérez et al published a series of patients treated with the p64 FDS made from nitinol and platinum similarly to the SILK stent.<sup>21</sup> They reported a 29.6% rate of NIH. The difference from our results may come from the fact that we based our analysis on VasoCT which has proven to be able to depict smaller amounts of NIH than DSA.

#### Long-term follow-up

At the late regression phase of NIH, a remodeling process has been described with a change of the SMC phenotypes from synthetic to contractile. The remodeling of the NIH is also related to a significant reduction in the SMCs' proteoglycan content with no change in SMC density.<sup>22</sup>

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In the long-term follow-up of our study, a 29% decrease in the total NIH rate was observed and the significant difference in the NIH rates between the two different FDS was no longer present.

As previously reported<sup>2 3 16</sup> no patient without evidence of NIH at the early follow-up developed NIH in the long-term follow-up. Also, no worsening of the vessel lumen caliber reduction due to NIH between early and late follow-up was depicted.

#### Dual impact of NIH

In the vast majority of cases, the NIH does not lead to any clinical complication.<sup>2</sup> <sup>21</sup> However, ischemic stroke is a rare but potential complication in cases of flow restriction related to severe stenosis and occlusions of covered branches.<sup>3 5 17</sup>

NIH is also very likely to be a key phenomenon in the physiopathology of aneurysm healing after treatment with a FDS.<sup>3</sup> The neo-endothelialization and subsequent occlusion of the aneurysm depend on an underlying SMCs substrate.<sup>23</sup> It is possible that a higher amount of NIH, especially at the level of the neck, would lead to higher occlusion rates. In our study, although it did not reach significance (probably due to the small population) we found a tendency toward more occlusion rates associated with the use of the SILK stent.



**Figure 1** A sexagenarian patient was treated with a SILK stent for an ophthalmic aneurysm, (A) postoperative DSA. This patient was admitted 6 months later because of episodes of transient amaurosis. (B) DSA and (C) VasoCT depicted a severe NIH at the level of the origin of the patent ophthalmic artery (arrow). Symptoms resolved with the reintroduction of double antiplatelet therapy, but the 40-month followup demonstrated the persistence of NIH (D).

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#### Antiplatelet therapies

Ticagrelor is a novel antiplatelet agent now being used in some centers (including ours) in association with aspirin. The pharmacodynamic effects of ticagrelor are more prompt, potent, and predictable compared with those of clopidogrel.<sup>24</sup> It has been linked to inhibition of SMC proliferation and, hence, could be associated with reduced NIH.<sup>25</sup> The impact of ticagrelor on NIH and occlusion rates should be the subject of another study.

#### Limitations

Our study limitations include the retrospective design and single-center experience. The inclusion criteria required quality VasoCT follow-up imaging which can be difficult to obtain because of motion artifact with a patient under local anesthesia.

We encountered some loss of follow-up and perhaps patients with NIH could have benefited more frequently from DSA follow-up as this could have participated in over-estimating the NIH rate.

Another bias could be attributed to the FDS type selection. We believe that the SILK offers a better navigability so operators could be more prone to using it in case of tortuous anatomy which could have affected the FDS correct apposition and the vessel wall reaction by the end.

#### CONCLUSION

NIH is a dual vessel reaction after FDS implant. When planning a treatment strategy involving a FDS in locations at risk of ischemic complications if severe NIH would occur, then the stent design should be taken into account. However, minimal NIH might also be needed as it is involved in aneurysm healing.

Before treatment, patients should be recommended best medical management of their cardiovascular risks factors to prevent an excessive NIH reaction.

**Contributors** JC: designed the study, analyzed and interpreted the data, drafted the manuscript, and approved the final manuscript. All authors: data set creation and approved the final manuscript

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Patient consent Obtained.

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VI

#### ORIGINAL RESEARCH

# Phosphorylcholine surface modified flow diverter associated with reduced intimal hyperplasia

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#### ABSTRACT

(sPED).

Background Optical coherence tomography (OCT) is

a high-resolution, intra-vascular diagnostic technique

pathologies and optimization of stent implantation

during percutaneous coronary intervention. OCT was

used to investigate the in vivo vascular response to a

new phosphorylcholine surface modified flow diverter

Methods In an in vivo rabbit aneurysmal model, we

- cPED; and sPED) with or without dual antiplatelet

therapy (four groups, n=10 per group). OCT cross-

sectional area measurements were compared with

histology in all animals. Neointimal hyperplasia (NIH)

ratio was compared between OCT and histology at five

different levels for each stent. The severity of NIH was

protocols, and vessel locations.

INTRODUCTION

with reduced NIH.

also compared between the different stents, antiplatelet

Results OCT was used to calculate in-stent hyperplasia

sections. OCT measurement strongly correlated with gold

standard histology ( $r^2=0.83$ ; slope=0.988; P<0.0001).

flow diverters (mean percent of lumen reduction 5.7%

sPED had significantly less in-stent NIH than non-treated

for sPED versus 8.9% for cPED; P<0.0001). The NIH ratio

was slightly higher with dual antiplatelet therapy (DAPT)

(NIH ratio=7.9% with DAPT versus 6.8% without DAPT;

P<0.05). Complete and near complete occlusion rates of

the aneurysms were not different with the cPED or sPED.

stent treatments. In an animal model, phosphorylcholine

stent implant without reducing aneurysm occlusion rates.

Neointimal hyperplasia (NIH) is frequently

depicted during the imaging follow-up of flow

diverter treatment,<sup>1</sup> and may lead to delayed isch-

emic strokes.<sup>2</sup> Phosphorylcholine surface modified

flow diverters (Pipeline Flex with Shield Tech-

nology, sPED) were recently developed and demon-

strated reduced thrombogenicity both in vitro<sup>3</sup> and

vivo.<sup>4</sup> We hypothesized that the improved throm-

bogenicity profile of the sPED<sup>5</sup> may be associated

vascular technique using near-infrared light reflec-

tion to generate cross-sectional, high-resolution

Optical coherence tomography (OCT) is an intra-

**Conclusion** OCT is a promising technique for

immediate and long-term evaluation of flow diverter

surface modified flow diverters induces less NIH after

in 227 different locations corresponding to histology

used two different types of flow diverters (classic Pipeline

widely used for the characterization of vascular

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To cite: Caroff J, Tamura T, King RM, et al. J NeuroIntervent Surg Epub ahead of print: [please include Day Month Year]. doi:10.1136/ neurintsurg-2018-013776 images. It is widely used during percutaneous coronary intervention to explore atherosclerotic plaques and to optimize stent placement.<sup>67</sup> Up to now, OCT has been rarely used in the neurointerventional field mostly because the design of the OCT catheter is not optimized for intracranial navigation. However, it has been recently demonstrated to be a valuable diagnostic assay for the characterization and development of novel neurointerventional devices.489 OCT has been demonstrated to strongly correlate with histology to evaluate neointimal coverage after coronary stent implantation.10 11 Flow diverters and coronary stents present very different designs. Indeed, the struts of flow diverters are thinner and the porosity is significantly reduced. We also evaluated the ability of OCT to characterize the vascular response to flow diverters compared with gold-standard histology.

#### **METHODS**

#### Aneurysm creation and study design

After Institutional Animal Care and Use Committee approval, elastase-induced aneurysms were created in 40 New Zealand white rabbits at the origin of the right common carotid artery as previously described.<sup>12</sup> A minimum of 3 weeks after creation, the aneurysms were screened with digital subtraction angiography (DSA)<sup>13</sup> and randomized to one of the following treatment groups: classic Pipeline embolization device (cPED) with animal on dual antiplatelet therapy (DAPT); sPED with DAPT; cPED without DAPT; and sPED without DAPT. Animals assigned to DAPT received oral aspirin (10 mg/kg) and clopidogrel (10 mg/kg) beginning 5 days prior to flow diverter (FD) implant and continued for the duration of the study.

#### Flow diverter implant and OCT imaging

All procedures were performed under general anesthesia. First, the animals were pre-anesthetized by a subcuticular injection of atropine (0.01 mg/kg), followed by an intramuscular injection of a mixture of ketamine (35 mg/kg) and xylazine (5 mg/kg) for anesthesia induction. The animals were intubated and mechanical ventilation was maintained with 1%-3% isoflurane.

A 6Fr introducer sheath was inserted after surgical exposure of the right common femoral artery. A Navien 072 catheter was used to navigate the FD to the right subclavian artery. Both devices were sized based on the diameter of the



BMJ



**Figure 1** Photograph of the harvested implanted artery. Each line represents a section taken for histology. 1=proximal stent, 2a, b, and c=at the level of the aneurysm neck, 3=distal to the aneurysm, 4=at the origin of the vertebral artery, 5=at the distal part of the stent.

brachiocephalic trunk proximal to the aneurysm and ranged from 3.75 to 4.5 mm. All devices were 16 mm in length. The FD was deployed under fluoroscopic guidance and implanted such that complete coverage of the aneurysm neck was achieved. Angioplasty was performed on all devices (HyperGlide 4 mm x 10 mm) to optimize apposition.

Thirty days after device implant, the animals were re-anesthetized and DSA was performed to assess the stent permeability and the aneurysm occlusion on a previously described 5-point scale.<sup>14</sup> Then OCT imaging (Dragonfly Catheter, St Jude Medical, Westford, MA, USA) were acquired with a 10 mm/s pull-back speed through 54 mm length, generating 540 frames/pull-back. For sufficient blood clearance, iodinated contrast (Omnipaque 240, GE Healthcare, Malborough, MA, USA) was administered by a power injector at a flow rate of 4 mL/s for 4 s.

#### Tissue harvesting and histology

Intimal hyperplastic response in this animal model has been reported to reach a peak at 30 days.<sup>15</sup> Therefore, following the 30-day imaging procedure, euthanasia was performed by an overdose of sodium pentobarbital (150 mg/kg). Transcardiac perfusion fixation was performed using heparinized saline (5000 U/L) followed by 4% paraformaldehyde under physiological pressure. The subclavian and innominate arteries were explanted then embedded in epoxy resin. The embedded vessels were then sectioned with a Buehler Diamond saw, lightly sanded, polished, and stained (1% toluidine blue). Seven histological sections were performed; one prior to the aneurysm; three at the neck level; one distal to the aneurysm; one at the origin of the vertebral artery; and a last one at the distal part of the stent (figure 1).

#### Images analysis

In each case, all 540 OCT images acquired were analyzed and seven cross-sections co-registered from the histology sections were selected (figure 2). In a blinded fashion, all histological and OCT images were used to measure the lumen area, the stent area (defined by the area limited by the struts of the stent), and the neointimal area (defined by stent area/lumen area), while the percent of lumen reduction related with NIH was defined as the NIH ratio (lumen area/stent area).

Over a theoretical number of 280 sections, 227 were analyzed. Some were missing either because of insufficient quality or because it was not possible to obtain three histological sections through the neck of the aneurysm or the distal landing zone did not extend beyond the vertebral artery.

#### **Statistical methods**

Statistical analysis was performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). OCT and histology images were compared using linear regression and



**Figure 2** Histological (left), and OCT (right) cross-sections at the level of vertebral and internal thoracic arteries (\*) demonstrating the correlation between the two techniques. Neointimal hyperplasia presents here an asymmetric pattern with a localized maximum thickness (line with arrows).



**Figure 3** A. Comparison between histological and OCT measurements of the percent of the lumen reduction with linear regression analysis. The red line is the best fit line for the data, with  $r^2=0.83$ ; slope=0.988 (P<0.0001). The green lines indicate 95% CI for that given best fit line. The blue lines indicate 95% confidence of the prediction interval. B. Bland–Altman analysis showing a bias of -0.15% and SD of the bias of 2.2%.

the Bland–Altman test. The NIH ratios were compared between the different types of stent, antiplatelet therapy protocol, and locations using two-way repeated measures analysis of variance (ANOVA). A Fisher's exact test was used to compare the rates of occlusion. A P value of < 0.05 was considered statistically significant.

#### RESULTS

#### Histological and OCT correlation

When compared by linear regression, OCT measurement strongly correlated with gold standard histology ( $r^2=0.83$ ; slope=0.988; P<0.0001). The Bland–Altman analysis showed that histology and OCT measurements are equivalent and free of systematic bias when measuring NIH lumen reduction (bias=-0.15%, SD of bias=2.2%, 95% CI -4.5% to 4.2%; (figure 3).

To assess the intra-observer variability of the OCT measurements, we randomly selected 30 datasets and repeated the analysis. The mean absolute difference was 1.0% (CI 95%: -0.37;2.37).

#### Effect of phosphorylcholine surface modification

Phosphorylcholine surface modified flow diverters presented less in-stent NIH than non-modified flow diverters with an average 56% reduction in NIH ratio on OCT measurements (NIH ratio were 5.7% for sPED versus 8.9% for cPED; P<0.0001).

#### Effect of DAPT

The severity of NIH was slightly more pronounced with DAPT (mean NIH ratio from OCT measurements were 7.9% for with DAPT versus 6.8% without DAPT; P<0.05).

#### Effect of location

Location had a significant effect over the NIH. The more distal location (location 5) presented the maximum NIH ratio with

Table 1   Effect of s	section	locatio	n on NI	H as me	easured	on OC	Г
Section location	1	2a	2b	2c	3	4	5
Average % of lumen reduction	6.1	5.5	5.8	5.3	5.9	8.8	14.9
Average mean stent diameter (mm)	4.13	4.18	4.16	4.23	4.06	3.68	2.85

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an average lumen reduction of 14% and a significant difference with all other section locations (P < 0.0001) (table 1).

Also, we found a linear relationship between the ratio of stent oversizing (FDS nominal size over vessel size from OCT measurement) and the NIH ratio ( $r^2$ =0.46; P<0.0001) (figure 4).

Moreover, the sPED had significantly less NIH for all locations, except location 3, as compared with cPED (table 2).

#### **Occlusion rates**

Occlusion rates were not different between the different stent types and use of DAPT (table 3).



**Figure 4** Comparison between stent oversizing (flow diverter nominal size over vessel diameter from OCT measurements) and the percent of the lumen reduction with linear regression analysis. The red line is the best fit line for the data, with  $r^2$ =0.46 (P<0.0001). The green lines indicate 95% CI for that given best fit line. The blue lines indicate 95% confidence of the prediction interval.

Table 2         Comparison of NIH ratio per section location							
Section location	1	2a	2b	2c	3	4	5
Average % of lumen reduction/cPED (mean±SD)	7.2±2.4	6.8±2.7	7.1±3.0	6.8±2.3	6.8±2.9	10.1±5.4	16.5±7.6
Average % of lumen reduction/sPED	4.9±2.0	4.2±1.6	9.8±1.3	4.0±1.4	5.1±2.6	6.9±3.0	10.9±4.8
P value	0.004	0.002	0.006	0.0005	0.06	0.02	0.02

### DISCUSSION

OCT validation

OCT has proven to strongly correlate with histology to evaluate NIH coverage after coronary stent implantation.<sup>10 11</sup> However, we sought to validate those results specific to neurointerventional devices since flow diverter design differs substantially from coronary stents.<sup>16</sup> Flow diverter struts are much smaller (~30 µm) than laser cut, coronary stents (~100 µm) requiring very high resolution to depict the device relationship with the wall. Flow diverters have a much higher metal density as well, which can induce significant optical artifacts.

In our study, OCT values correlate well with the gold standard histology (r<sup>2</sup>=0.83; P<0.0001). Recently, in a pig model, Matsuda and colleagues<sup>8</sup> described good agreement between OCT and histology for imaging flow diverters. The data presented here are in excellent agreement and our quantitative analysis in a rabbit model further validate the use of OCT to characterize tissue response to flow diverters. Image co-registration between OCT and histological photomicrographs was done manually by visualization of anatomical landmarks. It is possible that this introduced some errors in comparing the measurements. However, from the Bland-Altman analysis, the average absolute difference between the measurements was close to zero, meaning that the NIH ratio value from OCT is reliable. We believe this is an important result, as OCT may play an important role in flow diverters implant optimization as the optical engine and catheter technologies improve.

#### Phosphorylcholine surface modification effect

The Pipeline embolization device with phosphorylcholine surface modification was recently developed in order to improve the hemocompatibility of this device, and reduced thrombogenicity has been demonstrated both in vitro<sup>3</sup> and vivo.<sup>4</sup> This surface modification has already demonstrated efficacy in reducing NIH on arterial grafts.<sup>5</sup>

Although the magnitude of the absolute difference in lumen reduction between the sPED and cPED was small, the average relative reduction of NIH ratio was 56% and statistically significant. Also, despite the relatively frequent presence of NIH following FD treatment, this rarely produces clinically significant sequelae.<sup>17 18</sup> Some authors propose extending the indication of FD treatment to aneurysms beyond the circle of Willis.<sup>19</sup> In those locations, bifurcation and large side branches are frequently covered by the stent. It has been shown that for bifurcation branches, at 3 months' follow-up, the percentage of ostium surface tissue coverage ranged from 80% to 98%.<sup>20</sup> We

Table 3	Aneurysms' characteristics and occlusion rates at 30 days						
		cPED	sPED	P value			
Aneurysm i	neck (mm)	3.9	4.1	0.65			
Aneurysm width (mm)		3.5	3.58	0.83			
Aneurysm height (mm)		7.0	7.65	0.33			
Occlusion r	ate	50%	45%	0.76			

assume that even a small decrease in the NIH amount at the level of the ostia could reduce the high rate of occlusion and flow modifications of those jailed branches.<sup>21</sup>

Also, these young and healthy animals generally do not have a pronounced response to the implant. So the reduction of the NIH ratio in the sPED group could be more pronounced in clinical practice.

Recently, Matsuda et al<sup>8</sup> studied NIH evolution to flow diverters in a swine model and did not find any difference in the neointimal volume between cPED and sPED. However, in their study with variable anti-platelets, 100% of the cPED and 33% of sPED thrombosed at day 7 and were then reopened using mechanical thrombectomy. Thus, in-stent clotting and subsequent treatment may have modified the normal pathophysiology of NIH after flow diverter implant.

#### Aneurysmal healing

With flow diverters, the aneurysmal occlusion is obtained by both promotion of flow-diversion-related aneurysm thrombosis and from newly formed endothelial coverage over the device at the level of the neck.<sup>22</sup> This second step is fundamental to permanently exclude the aneurysm from the circulation. A stent design that would prevent any neointimal formation would not serve the healing purpose. The goal is to 'control' a potential excessive and harmful proliferative response to the device, while allowing effective remodeling of the vessel.

Here in our study, from OCT images in the selected sections going thru the aneurysmal neck, we found that in a very limited number of cases (2.1%; 1/47) a NIH ratio of 1% or less (meaning that the NIH coverage is minimal). Furthermore, we did not find any difference in occlusion rates with 50% of complete or near complete occlusion for cPED and 45% for sPED (P=0.8).

The severity of neo-intimal hyperplasia was slightly more pronounced with DAPT with a 1.1% increased NIH ratio. NIH development is initiated by an endothelial damage during FDS implantation and angioplasty. Platelets adhering to the subendothelial surface participate in the NIH through platelet-derived growth factors inducing a vascular smooth muscle cell proliferation.<sup>23</sup>

Aspirin has proven to inhibit early platelet thrombus formation.<sup>24</sup> While the interference with platelet function reduces intimal hyperplasia in human and primate studies, in rabbit models it has shown to fail to prevent platelets and fibrin deposition after wall injury,<sup>25</sup> and also it may increase the NIH ratio.<sup>26 27</sup> We selected a 10 mg/kg dose of aspirin based on prior literature;<sup>28</sup> however, this dose represents an approximately 10-fold increase over the common dose used in humans. Future studies should evaluate the effect of aspirin dosing on NIH formation in this model. In some animal models, clopidogrel was sometimes found ineffective to prevent NIH,<sup>23</sup> highlighting the role of other factors than platelets alone in NIH formation, such as leukocytes.<sup>29</sup>

From our data, we have showed that there is a linear relationship between the device oversizing and the amount of NIH. As the device radial force is low we suspect that the increased vessel metal coverage due to flow diverter oversizing would be responsible for higher NIH. This parameter should be taken into account when sizing flow diverters in situations where the distal and proximal vessel caliber are significantly different (ie, in case of dysplastic vessels or when the FDS has to be anchored in a smaller branch as the middle cerebral artery to treat siphon aneurysms).

Our model was limited to saccular aneurysms. Although it is true that we did not find any significant difference in aneurysm occlusion rates between the different groups, it would be of interest to repeat these experiments in different models, such as fusiform aneurysms.<sup>30 31</sup>

Our study has several limitations. To assess the margin of error of repeated OCT measurements, we did not perform multiple pullbacks since the contrast load would have been too great for 3 kg rabbits. In half of the cases we did not use DAPT in order to maximize the potential differences between the device types, but that does not correspond to the standard clinical practice. Moreover, the use of balloon angioplasty of FD is not clinical standard-of-practice and may alter NIH patterns. However, despite these departures from clinical routine to enhance NIH in this model we did not encounter a single stent occlusion and that may reflect some difference between human and rabbit biology. Thus, the effects of the phosphorylcholine surface treatment in flow diverters should be confirmed in human studies.

#### CONCLUSION

OCT is a promising technique for the immediate and long-term evaluation of flow diverter treatments. In an animal model, phosphorylcholine surface modified flow diverters (sPED) induces less NIH after stent implant without reducing aneurysm occlusion rates.

**Contributors** Study design: JC, RMK, ETL, JMW, FC, MM, MJG, and ASP. Data acquisition: JC, TT, RMK, ETL, FC, MM. Literature research: JC, RMK, MM, MJG. Data analysis and interpretation: JC, TT, RMK, PNL, FC, LS, MM, MJG, and ASP. Manuscript preparation: JC and RMK. Revision of manuscript for important intellectual content: FC, MM, MJG, and ASP. Approval of final version of manuscript: all authors.

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### **Basic science**

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# VII

## Longitudinal Monitoring of Flow-Diverting Stent Tissue Coverage After Implant in a Bifurcation Model Using Neurovascular High-Frequency Optical Coherence Tomography

**BACKGROUND:** Tissue growth over covered branches is a leading cause of delayed thrombotic complications after flow-diverter stenting (FDS). Due to insufficient resolution, no imaging modality is clinically available to monitor this phenomenon.

**OBJECTIVE:** To evaluate high-frequency optical coherence tomography (HF-OCT), a novel intravascular imaging modality designed for the cerebrovascular anatomy with a resolution approaching 10 microns, to monitor tissue growth over FDS in an arterial bifurcation model.

**METHODS:** FDS were deployed in a rabbit model (n = 6), covering the aortic bifurcation. The animals were divided in different groups, receiving dual antiplatelet therapy (DAPT) (n = 4), aspirin only (n = 1), and no treatment (n = 1). HF-OCT data were obtained *in vivo* at 3 different time points in each animal. For each cross-sectional image, metal and tissue coverage of the jailed ostium was quantified. Scanning electron microscopy images of harvested arteries were subsequently obtained.

**RESULTS:** Good quality HF-OCT data sets were successfully acquired at implant and followup. A median value of 41 (range 21-55) cross-sectional images were analyzed per ostium for each time point. Between 0 and 30 d after implant, HF-OCT analysis showed a significantly higher ostium coverage when DAPT was not given. After 30 d, similar growth rates were found in the DAPT and in the aspirin group. At 60 d, a coverage of 90% was reached in all groups.

**CONCLUSION:** HF-OCT enables an accurate visualization of tissue growth over time on FDS struts. The use of FDS in bifurcation locations may induce a drastic reduction of the jailed-branch ostium area.

**KEY WORDS:** Intracranial aneurysm, Flow diverter, Optical coherence tomography, Endothelialization

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low diversion represents a paradigm shift for the endovascular treatment of intracranial aneurysms. In large carotid siphon aneurysm indications, the long-term flow diverting stents (FDS) results have proven to be excellent<sup>1</sup>; their use in small,<sup>2</sup> distal,<sup>3</sup> and bifurcation aneurysms is increasingly

ABBREVIATIONS: DSA, digital subtraction angiography; DAPT, dual antiplatelet therapy; FDS, flow diverting stents; HF-OCT, high-frequency optical coherence tomography; OSCR, ostium surface coverage ratio; PED, pipeline embolization device; SEM, scanning electron microscopy; 2D, 2-dimensional reported.<sup>4</sup> However, the use of FDS in bifurcation aneurysms is controversial, and high rates of ischemic complications have been reported in the jailed territory.<sup>4-8</sup>

Despite an increased usage, their healing mechanism is only partially understood. It is thought to be a continuous endothelialization of the device struts, in combination with a progressive aneurysm thrombosis.<sup>9</sup> However, neointima formation over jailed branches can be harmful, causing delayed ischemic complications following treatment.<sup>10</sup>

Although associated with hemorrhagic complications, dual antiplatelet therapy (DAPT) is required to prevent FDS thrombosis and it

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is considered mandatory.<sup>11</sup> Nevertheless, the existing antiplatelet protocols are highly heterogeneous among different centers, with treatment durations that may vary from 3 mo to life-long. Existing imaging tools allow the monitoring of an excessive neointimal reaction,<sup>12</sup> however, due to insufficient spatial resolution, conventional x-ray based systems do not allow the evaluation of the device endothelialization process.

Intravascular imaging techniques have been extensively adopted for the investigation of peripheral and coronary arteries,<sup>13</sup> but existing devices are unsuitable for use in tortuous neurovasculature.<sup>14</sup> High-frequency optical coherence tomography (HF-OCT) is a novel modality designed for intravascular use in the cerebrovascular anatomy. With a spatial resolution approaching 10 microns, HF-OCT allows the user to visualize fine details about the interaction between the endovascular devices and the arterial wall, unprecedented in the field of neurovascular imaging.<sup>15,16</sup> In this study, we sought to evaluate the use of HF-OCT to monitor tissue growth over FDS in an arterial bifurcation rabbit model.

#### **METHODS**

The Institutional Animal Care and Use Committee (IACUC) approved all animal research activities. Six New Zealand White rabbits (n = 6; sex: either, weight range 3.0-4.0 kg) were included in this study.

#### **Antiplatelet Regimen**

Four animals (n = 4) were premedicated with a standard of care DAPT regimen consisting of oral administration of aspirin (10 mg/kg/d) and clopidogrel (10 mg/kg/d), beginning at least 5 d prior to implant, and continued for the duration of the study.<sup>17</sup> Two animals were used as controls: one was given only aspirin (10 mg/kg/d), and the other one did not receive any antiplatelet therapy.

#### FDS Implant

All procedures were performed under general anesthesia using a strict aseptic technique. Prior to all surgical procedures, the animals were pre-anesthetized by a subcuticular injection of atropine (0.01 mg/kg) and given an intramuscular dose of sustained-release buprenorphine (0.03 mg/kg) for pain management. Anesthesia was induced by an intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg) and maintained with mechanical ventilation of 1% to 3% isoflurane. The physiologic status of the animal was assessed using continuous monitoring of respiration rate, heart rate, oxygen saturation level, end-tidal  $CO_2$  level, and temperature.

Once anesthetized, the right femoral artery was exposed through a 2 cm incision. A 6-French introducer sheath was inserted over a guidewire and through an arteriotomy of the femoral artery. A Navien-072 guide catheter (Medtronic Neurovascular; Medtronic, Dublin, Ireland) was positioned in the right iliac artery. A pipeline embolization device (PED) (Medtronic Neurovascular) was deployed without any compression and in a way that its center was covering the aortic bifurcation (Figure 1). PED length was 20 mm and diameter chosen in a 3.25 to 3.75 mm range based on digital subtraction angiography (DSA) measurements. After implant, DSA and HF-OCT acquisitions were performed, then the femoral artery was ligated.



#### Follow-up Imaging

Under the same conditions of the FDS implant, 2 different imaging procedures were performed for the 2 different follow-up time points. For the first procedure, the left carotid artery was exposed through a 2 cm incision. A 6-French introducer sheath was subsequently inserted over a guidewire and through an arteriotomy of the carotid artery. A Navien-072 catheter was then positioned at the level of the proximal end of the FDS and used to perform HF-OCT and DSA studies. For the second follow-up imaging procedure, this technique was repeated through the right cervical carotid artery.

#### **HF-OCT Imaging Technique**

HF-OCT data sets were acquired at the time of the implant, at 14 d, and at 60 d for all control animals (n = 2) and for a first group of the DAPT animals (n = 2). The remaining animals receiving DAPT (n = 2) underwent HF-OCT imaging at implant, at 6 d, and at 27 d. Imaging time points were chosen as follows: 14 d because it is known to be the peak for smooth muscle cell proliferation<sup>18</sup>; 30 d because it is known to be the peak for intimal hyperplasia<sup>18</sup>; 60 d in order to obtain a late evaluation, as tissue growth is usually slower on covered branches.

To acquire the HF-OCT data sets, an intravascular imaging prototype (Vis-M<sup>™</sup>, Gentuity LLC, Sudbury, Massachusetts) was navigated distally through the flow-diverter under fluoroscopy guidance. To displace the blood from the arterial lumen, iodine contrast (Omnipaque 240; GE Healthcare, Marlborough, Massachusetts) was injected at a continuous rate of 4 mL/s for approximately 4 to 5 s through the Navien-072. During the contrast injection, the Vis-M device was automatically retracted at a constant speed, and the HF-OCT data acquired. The HF-OCT system processes the data in real time, the images are displayed live during the pullback, and are immediately available for review.



**FIGURE 2.** Segmentation of the FDS covered segments. **A**, measurement of the ostium opening angle; **B**, determination of the OSCR. This procedure was repeated for all the HF-OCT cross-sections acquired over the bifurcation ostium and averaged for each follow-up study (ie, 3 different time points). Red area demarcates the tissue covered area of the device, and green where there remain open spaces. Scale bars are 1 mm.

#### **HF-OCT Data Analysis**

HF-OCT data were processed to quantify the percentage of the ostial surface covered by metal and tissue by the means of software ImageJ (National Institutes of Health, Bethesda, Maryland). Three-dimensional data analysis was achieved by performing a sequential analysis of stacked 2-dimensional (2D) cross-sectional images. Specifically, the center of gravity of the vessel lumen was determined for each of the HF-OCT 2D images, and the full extension of the ostium was quantified using an angular measurement (Figure 2A). Subsequently, the covered and open fractions of the ostium angle were identified (Figure 2B). The extension of the coverage was quantified (%) for each section, as the ratio between the sum of covered angles (by tissue and/or struts) and the opening angle of the covered branch. This procedure was repeated for all the HF-OCT cross sectional images acquired over the left iliac artery ostium. The average of all 2D measurements was calculated to determine the 'ostium surface coverage ratio' (OSCR) and quantify the volumetric percentage of covered ostium for each animal at each different time points.

#### **Scanning Electron Microscopy**

After the final follow-up imaging procedure, the animal was euthanized and perfused with saline, followed by a 4% paraformaldehyde solution. After overnight immersion fixation in a 2.5% glutaraldehyde solution, the explants were rinsed in 0.1 M cacodylate buffer. The FDS were longitudinally cut under a dissecting microscope to expose the aortic bifurcation, and then dehydrated through a graded series of ethanol with concentrations up to 100%, followed by critical point drying in carbon dioxide. The samples were mounted on aluminum stubs, grounded with silver conductive paste, sputter coated with gold/palladium, and imaged using a FEI Quanta 200 MKII FEG SEM (Figure 3).

#### **Statistical Analysis**

Statistical analysis was performed using Prism software version 8.1 (GraphPad, San Diego, California). A normality test was applied to assess the Gaussian distribution of data in all cases. Results are shown as mean  $\pm$  SD deviation. The medians of 2 independent groups, if nonnormal distributions, were analyzed using the Mann–Whitney *U* test. Correlations were determined using Spearman correlation coefficients and *P*-values were considered significant if < .05.

#### RESULTS

#### **DSA Analysis**

For all the animals treated with at least one antiplatelet medication, DSA imaging did not reveal any occlusion of the jailed branch. The development of collateral circulation was not observed in any of the cases (n = 6).

In the control animal without any antiplatelet therapy (n = 1), DSA at day 14 showed slow filling of a narrowed jailed branch and vessel occlusion. In this case, the ostium coverage ratio was quantified to be equal to 98% (Figure 4) and the animal was subsequently sacrificed as it reached one of the study endpoints.

# Percentage of Bifurcation Coverage as a Function of Time

Good quality HF-OCT data sets were successfully acquired in all cases. Approximately 41 OCT cross-sectional images were

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detail of the tissue covering the ostium of the iliac artery in vivo. **B**, ex vivo SEM imaging shows a high-degree of correlation with the HF-OCT findings. The arrow in panel **A** indicates the presence of a thrombus (having a darker appearance than the surrounding tissue) covering a portion of the jailed ostium, that is no longer visible after harvest and processing of the specimen for ex vivo imaging with SEM. **C**, high-resolution detail of the tissue covering the ostium of the aortic bifurcation (arrowheads). **D**, HF-OCT cross-sectional imaging showing micron-resolution detail of the clot over the flow-diverter struts (arrows). Scale bars are 1 mm.

analyzed per ostium for each time point (median value equal to 41, with a range between 21 and 55).

Due to a risk of contrast overload, HF-OCT was not performed at the time of the implant in 2 animals. Given that the ostium coverage at baseline is only due to metallic struts, the missing baseline values were approximated in Figure 5 by averaging the OSCR values from the HF-OCT datasets acquired in the other 4 animals. This procedure resulted in an average post implant OSCR equal to 39% (range = 36%-41%).

In the DAPT group, the OSCR was quantified to be 62% at day 6 (n = 2), 67% at day 13 (n = 2), 85% at day 27 (n = 2), and 90% at day 60 (n = 2) (Figures 4 and 5). In the aspirin-only control animal, the OSCR was found to be equal to 81% at day 14 (n = 1), and 91% at day 60 (n = 1). For the animal that did

not receive any antiplatelet therapy, the OSCR was 98% at day 14 (n = 1). Compared with the DAPT group, the ostium coverage was significantly higher at day 14 (+/- 1) in the aspirin group (P < .0001) but not at day 60 (Figure 5).

To analyze the antiplatelet effect on stent coverage, we measured the FDS coverage for each HF-OCT cross-section over the ostium and performed a comparison between all images from the aspirin and those from the DAPT regimen groups. At 14 d ( $\pm$ 1), we found a mean ostium slice coverage ratio of 81% and 67% for the aspirin (over a total of n = 31 sections) and the DAPT groups (n = 75 sections), respectively (P < .0001). At 60 d, no difference was found (P = .2), with a mean OSCR of 91% for the aspirin group (n = 41 sections), and 90% for the DAPT group (n = 104 sections).



branch. **B**, after 14 d, DSA shows a caliber reduction of the left iliac artery (arrowhead), associated with an impaired flow and the occlusion of the distal end of the FDS (arrow). **C**, Three-dimensional HF-OCT data rendering depicting an almost complete occlusion of the jailed ostium (98% OSCR) and presence of clots.

#### **Endothelialization Patterns**

For each 2D cross-section, the OSCR was correlated with the location of the cross-section within the ostium (center vs periphery). For cross-sections closer to the center (Figure 6), the ostium shows a wide angle. In the periphery, the ostium shows a narrower angle. In the DAPT group, a significant peripheral coverage dominance at day 13 was found (Spearman r = -0.41, P < .0002) (Figure 7) meaning that after implant the neointima formation follows a centripetal pattern. This dominance was no longer observed after 13 d.

#### DISCUSSION

#### FDS use in Bifurcation Aneurysms

Although the use of FDS in bifurcation cases is increasingly reported,<sup>8</sup> the safety and efficacy of these procedures are still controversial. A recent meta-analysis showed a non-negligible rate of treatment-related complications (20%), suggesting that FDS in bifurcation should only be considered as an alternative treatment when conventional treatment methods are unfeasible.<sup>8</sup> In this analysis, the overall rate of flow impairment in the jailed branch

(defined as a diminished flow or an artery occlusion) was 36%, with a 5.3% related incidence of symptoms.

It has been suggested that immediate ischemic complications are often related to flow diversion in the covered branch. These complications can be prevented with an optimal antiplatelet regimen, accurate blood pressure management, and using GP IIb/IIIa inhibitors.<sup>19</sup>

Delayed complications, however, have been related to progressive endothelialization leading to a drastic narrowing of the jailed ostium.<sup>8</sup> In this study, the ostial tissue-free surface was observed to be only 10% of the original area after 2 mo. Notably, since the tissue growth along the surface of the flow diverter is below the resolution DSA, stenosis is not depicted and vessels appear patent on DSA.

In a study by Shapiro et al,<sup>19</sup> at the time of the implant, a metal coverage ratio up to 30% (for jailed bifurcation branches) was found. The authors reported that this coverage ratio is expected to be well-tolerated regardless of the device size, the artery diameter, or the availability of immediate collateral support. They also demonstrated that when an OSCR of 90% is reached, the flow going through the FDS is only 15% or less of its initial value. Thus, for cases with insufficient collateral circulation, the

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progressive endothelialization and the subsequent flow reduction can put the patient at risk for a delayed ischemic lesion.

#### **New Zealand White Rabbit Bifurcation Model**

In a swine bifurcation model, Iosif et al<sup>20</sup> have reported similar rates of ostial coverage between 81% and 98%. However, in this model, the vascular territory supplied by the ascending pharyngeal artery presents an extensive collateral supply. It is possible to theorize that the presence of such extensive collaterals might have caused the elevated coverage ratio observed at 3 mo.

Our study corroborated those results using a high-flow, terminal artery, jailed by the device trying to reproduce the normal response of human intracranial bifurcations. The development of this model was uniquely possible using the reduced profile of the imaging probe provided with the HF-OCT system, as compared with conventional OCT solutions designed for use in the coronaries.<sup>21</sup>

#### **HF-OCT Monitoring of Jailed Ostia**

HF-OCT allowed detailed longitudinal monitoring of the tissue coverage over the jailed ostia. We have observed that DAPT induces a slower coverage formation over the stent struts. This finding reinforces the idea that an efficient antiplatelet therapy is required not only in acute settings but also for months following when treating arterial bifurcations with FDS. It is possible to speculate that a slower coverage formation might allow collateral pathways to fully develop and balance the flow reduction related to a high OSCR.

In the control group without antiplatelet medication, DSA at day 14 demonstrated slow filling and reduced caliber of the jailed iliac artery. HF-OCT showed a very high ostium coverage ratio. This rabbit model, in combination with HF-OCT, can be used in the near future to evaluate the new coated FDS (developed for providing lower thrombogenicity) without antiplatelet medication.<sup>22</sup> Furthermore, a high correlation with scanning electron microscopy (SEM) demonstrated that HF-OCT can accurately depict the tissue coverage morphology and micro-structure, differentiating between 2 different patterns. One is a thin, irregular and mostly interstruts coverage possibly corresponding to a scaffold of inflammatory and smooth-muscle cells.<sup>23</sup> The second pattern is a thick and more regular coverage, likely to correspond to neo-intima formation as illustrated by SEM (Figure 8).

#### Pathophysiology

Based on the coverage distribution observed over the ostium, we have found a statistically significant, peripheral predominance that can be observed after day 13, but at no other time point. After implant, early stage coverage largely consists of inflammatory cell layers<sup>9</sup> that may arise from the circulation and possibly explaining the homogeneous coverage distribution observed at day 6.

In rabbit models, the smooth muscle cell proliferation is known to peak at day 14.<sup>18,24</sup> However, the origin of the endothelial cells covering the FDS still remains controversial. They are either believed to migrate from the adjacent parent artery or to arise from differentiation of circulating bone marrow-derived endothelial progenitor cells. Recent studies are suggesting that it is likely a result of both mechanisms.<sup>25</sup> No definitive conclusion can be drawn from the findings presented by this study, but the peripheral distribution we observed at day 13 could be related to a dominance of the contiguous mechanism in the early phase. If this trend is confirmed, it could reinforce the idea that the correct



peripheral 2D HF-OCT section is to the ostium center (rea dot) the water the opening angle of the ostium is. A, peripheral 2D HF-OCT section with a narrow opening angle. B, Corresponding 3-dimensional HF-OCT rendering, illustrating the section location on the proximal border of the ostium. C and D, images of a central section with a large opening angle. Scale bars represent 1 mm.

apposition of FDS to the arterial wall is a key parameter for the healing of aneurysms,<sup>26,27</sup> as it would facilitate the migration of cells. This finding may support the future concept of performing a careful analysis of wall apposition by the means of a high-resolution imaging modality, and advocates for the use technical solutions where indicated (eg, balloon angioplasty).

#### **HF-OCT for Personalized Care**

Antiplatelet therapy is known to be a frequent source of both minor and major patient complications.<sup>28</sup> Despite the widespread use of FDS, no consensus can be found on optimal antiplatelet management. In some clinical centers, DAPT is often prescribed

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FIGURE 7. Correlation between the coverage values and the location of the HF-OCT images (ie, their proximity to the isocenter or to the periphery of the ostium). The data scatter plot shows the OSCR value on the vertical y-axis vs the location of the cross-section (horizontal x-axis). The wider the ostium opening angle is (x-axis), the closer it is to the isocenter of the ostium. Each plot corresponds to a unique HF-OCT cross-sectional image from animals in the DAPT group. Data collected at day 13 show a statistically significant peripheral predominance of the OSCR.



for no more than 3 mo and aspirin is prescribed for 1 yr<sup>11</sup>; other centers may prescribe DAPT for a period of 6 mo, followed by aspirin indefinitely.<sup>29</sup> In the near future, it is possible to imagine that optimal antiplatelet therapy can be modulated through an informed decision based on high-resolution imaging data, and that HF-OCT evidence of complete FDS endothelialization may allow the discontinuation of this medication.

#### Limitations

This study is limited by the small sample size. However, due to the very high resolution of HF-OCT, it was possible to quantify the ostium coverage in a large number of individual cross-sections in both the DAPT group (n = 355), and in the non-DAPT group (n = 93), allowing for a statistical comparison. Furthermore,

although limited by potential differences between the human and rabbit biology, the results presented in this manuscript suggest a promising role for HF-OCT in the field of neuroendovascular surgery.

#### CONCLUSION

HF-OCT enables accurate visualization and quantification of tissue growth over FDS struts at the orifice of jailed arteries as a function of time. The use of FDS in bifurcation locations may induce a drastic reduction of the jailed-branch ostium area. In the near future, HF-OCT could potentially contribute to personalized care, helping the physician to determine the ideal antiplatelet regimen for each patient.

#### Disclosures

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#### NEUROSURGERY

# VIII

FUNCTIONAL NEURORADIOLOGY

### Use of time attenuation curves to determine steady-state characteristics before C-arm CT measurement of cerebral blood volume

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#### Abstract

*Introduction* Cerebral blood volume (CBV) measurement by flat panel detector CT (FPCT) in the angiography suite seems to be a promising tool for patient management during endovascular therapies. A steady state of contrast agent distribution is mandatory during acquisition for accurate FPCT CBV assessment. To the best of our knowledge, this was the first time that steady-state parameters were studied in clinical practice.

*Methods* Before the CBV study, test injections were performed and analyzed to determine a customized acquisition delay from injection for each patient. Injection protocol consisted in the administration of 72 mL of contrast agent material at the injection rate of 4.0 mL/s followed by a saline flush bolus at the same injection rate. Peripheral or central venous accesses were used depending on their availability. Twenty-four patients were treated for different types of neurovascular diseases. Maximal attenuation, steady-state length, and steady-state delay from injection were derived from the test injections' time attenuation curves.

*Results* With a 15 % threshold from maximum attenuation values, average steady-state duration was less than 10 s. Maximum average steady-state duration with minimal delay variation was obtained with central injection protocols.

*Conclusion* With clinically acceptable contrast agent volumes, steady state is a brief condition; thus, fast rotation speed acquisitions are needed. The use of central injections

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decreases the variability of steady-state's delay from injection. Further studies are needed to optimize and standardize injection protocols to allow a larger diffusion of the FPCT CBV measurement during endovascular treatments.

Keywords Flat detector computed tomography  $\cdot$  Perfusion imaging  $\cdot$  Cerebral blood flow  $\cdot$  Endovascular therapy  $\cdot$  Steady state

#### Introduction

Recently, the feasibility of flat panel detector CT (FPCT) cerebral blood volume (CBV) measurement within the angiographic suite has been described in acute ischemic stroke patients [1, 2] (Fig. 1). This technique may also be of great interest during the endovascular management of other neurovascular diseases. Regarding brain arteriovenous malformations (AVM), the use of perfusion CT showed different perfusion patterns that could correspond to different pathological mechanisms and could lead to different treatment strategies [3]. After the use of flow-diverter stents, some adverse events are still not fully understood and may be due to perfusion abnormalities [4].

The principle of the FPCT CBV technique requires a steady state of brain parenchyma enhancement during whole acquisition [5, 6]. This steady state is a major prerequisite to ensure the reliability of the CBV assessment. CBV measurement using C-arm CT is not an everyday tool, and the acquisition protocol has not yet been codified. Various protocols have been described using either venous or arterial injections [1, 2, 7]. The reality of the steady state during CBV acquisition is usually assumed but not verified, and this could be the cause of errors in measurements. The purpose of this study is to

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Fig. 1 A 55-year-old patient presenting with acute aphasia. Intracranial bleeding was ruled out by a CT scan, and then the patient was admitted in the angiographic suite for endovascular early stroke therapy. Pre-interventional FPCT CBV measurement shows a decreased CBV area in the left middle cerebral artery anterior territory



determine if a standard injection protocol ensures enough steady-state time for a reliable CBV measurement.

#### Materials and methods

#### Patient characteristics

Between May 2012 and January 2013, 24 patients (14 female, 10 male; age range, 19–84 years; median, 39 years) referred for endovascular treatment were prospectively enrolled for this study performed according to the guidelines of our institution; informed consent was obtained for each procedure. CBV studies were acquired in the angiographic suite during 10 brain AVM endovascular treatments and 14 intracranial aneurysm flow-diverter stent-assisted treatments.

#### Test acquisitions

Before the CBV runs were acquired, a test perfusion acquisition was performed at a static posteroanterior viewing incidence in order to obtain the time attenuation curves (TAC) of tissue enhancement in brain parenchyma. It corresponded to a three image per second subtracted fluoroscopic acquisition during 30 s. It was initiated after an 8-s delay for central injections and a 12-s delay for peripheral injections in order to minimize the X-ray dose.

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#### FPCT CBV measurement

Both endovascular treatment and perfusion study were performed on a biplane angiographic system (Allura Xper FD20/10, Philips Healthcare, Best, the Netherlands) under general anesthesia. FPCT CBV was assessed before embolization for brain AVM and after stent delivery for aneurysms.

The CBV acquisitions on a C-arm system consist of two FPCT runs: a mask run without contrast and a contrastenhanced run during the steady state. The difference in attenuation per volume element between these runs corresponds to the contrast enhancement of the parenchyma. FPCT CBV measurement was performed as previously reported [5], but with a 5-s rotation time and a tailored acquisition delay from injection, i.e., calculated from test acquisition.

#### Injection protocols

Injection protocols were identical for test acquisition and for CBV measurement. Contrast media injections were performed either through a 4F intra-atrial venous pigtail catheter or through a peripheral cubital vein access when central access was not available. We have used a literature inspired protocol [2], consisting in the injection of 72 mL of iodixanol (Visipaque 270, GE Healthcare, Mississauga, Canada) at the injection rate of 4 mL/s, followed by a saline flush at the same rate.

**Fig. 2** A *circle region* of interest is drawn in a brain anteroposterior projection to obtain the TAC using the 2D perfusion software. From this, the steady-state's characteristics are determined with a threshold of 15 % from the peak attenuation value



#### Post-processing

Data from test injections were analyzed by using commercially available software, *2D Perfusion* (Philips Healthcare, Best, the Netherlands) and exported to *Excel* software (Microsoft, Redmond, Washington, USA). From a large region of interest drawn in the non-pathological hemisphere and avoiding major vessels the 2D Perfusion software provides TAC with a 0.33-s time resolution (Fig. 2). As steady state required strictness for the FPCT CBV measurement that has not been previously evaluated in the literature, we have arbitrarily chosen a 15 % tolerance threshold from peak attenuation value. From this, the steady-state length and the delay from injection to the steady-state's beginning were measured.

Raw data from test injections (i.e., digital subtraction angiography) were secondarily analyzed by two neuroradiologists (20 and 5 years of experience). They determined delay from injection to full opacification of venous sinuses; this is called the "bolus watching" technique and it would be related to the steady-state's beginning according to some authors [1, 2, 8] (Fig. 3). When using the bolus watching technique, the rotational acquisition is manually initiated after contrast agent injection when the superior sagittal sinus is opacified. Finally, data from CBV acquisition were analyzed using the CBV prototype software (Philips Healthcare, Best, the Netherlands) in order to obtain CBV color maps.

#### Statistical analysis

Statistical analysis was performed using commercial statistical software SPSS (version 12.0, Statistical Package for the Social Science, Chicago, IL). Average steady-state's length from different injection protocols were compared using Mann-Whitney U test. Correlations between the two readers using bolus watching technique and the measured steady-state delay from TAC were performed using Spearman correlation coefficient.

#### Results

TAC analyze was possible in every case. Twenty patients were explored using central venous injections and four using peripheral injections (Table 1). There were no statistical differences between mean peak values of the two different protocols (central=212, peripheral 72/72=201). With central injections, mean lengths of the steady state was  $9.5\pm1.4$  s (range 5.9-11.9) versus  $8.2\pm0.9$  s (range 6.9-8.9) with peripheral injections.

Central venous injections are associated with a longest mean steady state (central injections, 9.5 s; peripheral injections, 8.2 s; p < 0.047) with a mean difference of 1.3 s (14 %). The central protocols are also associated with less timing variation from injection to steady



Fig. 3 Homogeneous opacification of the venous sinuses is considered by some authors to reflect the steady-state's beginning. Superior sagittal sinus (*black arrow*) and lateral sinus (*white arrow*) opacified

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Table 1
 Injection protocols

	Number of patients	Average age	Aneurysm/AVM
Central injections	20	40.5	13/7
Peripheral injections	4	43	1/3

state when compared with peripheral injections. Mean delays are, respectively, 20.8 versus 27.2 s and standard deviations are 2.0 versus 5.0 s (Table 2). When using peripheral access, the delay between injection and the beginning of the steady state was nearly 7 s later than with central injections. This is logical and corresponds to the time the contrast agent goes from the forearm to the right atrium.

When considering central venous injections, there was a significant agreement between the two readers regarding the timing determination of full opacification of venous sinuses according to concept of the bolus watching technique (correlation coefficient r=0.78; p<0.005). Delays from visual triggering and the steady-state's delay measured on the TAC were correlated (r=0.75; p<0.005), but in few cases, we have noticed significant differences with a maximum of 6 s.

### Discussion

The steady state of brain parenchyma contrast enhancement during whole acquisition is a key parameter to ensure the reliability of the CBV measurement in the angiographic suite. Most of the recent publications on the subject only assume the reality of this condition during FPCT CBV acquisition. However, if the steady state is not reached during acquisition, the CBV measurement could be underestimated leading to a "pseudo-CBV abnormality" [9].

To determine temporal characteristics of tissue enhancement and then apply a tailored timing for the CBV acquisition, we have used test injections at a price of a larger use of contrast media. The same volume was used for test injection and for final acquisition because it has been shown that if a smaller volume was used during the test injection, the measured delay would not be correlated to the final injection delay [10].

 Table 2
 Characteristics of the steady states

Length (s)	Delay (s)	Peak value
9.5±1.4	20.8±2.0	212
8.2±0.9	$27.2 \pm 5.0$	201
	Length (s) 9.5±1.4 8.2±0.9	Length (s)         Delay (s)           9.5±1.4         20.8±2.0           8.2±0.9         27.2±5.0

From this, we first see that the steady state is a brief condition with an average duration shorter than 10 s in our study. It implies that acquisition time for the CBV measurement should be as short as possible, this being for the moment a technological limitation from the C-arm rotation speed. Depending on manufacturers, some actual angiographic suites allow 5 s rotation acquisition.

The optimal bolus geometry is an immediate increase in the enhancement of the tissues just before the acquisition of data, followed by a steady state in which the enhancement is stable during the whole acquisition. In reality, the actual bolus geometry is a gradual increase in the enhancement until a peak and then a gradual decrease.

Parameters influencing bolus geometry are described in the literature review by Cademartiri et al. [10]. Several studies report that time between injection and maximal attenuation is not affected by age, weight, height, body surface, blood pressure, heart rate, or gender. A porcine study showed that a decrease in cardiac output produces a proportionally longer time to reach the maximal attenuation peak. Consequences of bolus characteristics have also been described in this article. When the injection rate is increased, the time to peak is shortened and the maximal attenuation is increased. This corresponds to a sharper TAC and a shorter steady-state length. Thus, with the same amount of contrast media, injection rates faster than 4 mL/s would induce steady states shorter than in our study.

Bae [11] showed that with fixed injection rates, time to peak enhancement in the aortic arch is determined by the volume and the traveling time of contrast media. With central venous injections, this traveling time is significantly reduced (7 s in our study). The variability between patients due to different circulatory speeds is reduced when the traveling time is shorter, which means that the delay from injection to steady state is more reproducible.

The bolus watching technique is actually mostly used for CBV measurements by flat panel detector [1, 2, 8]. After the FPCT mask run has been acquired, the C-arm returns to the start position, and a standard 2D digital subtraction angiography is initiated. The second rotation is manually initiated when large dural sinuses opacification is observed, assuming it to reflect the beginning of the steady state in the brain parenchyma. To our knowledge, this relationship does not seem to have been validated in humans. In our study, there is a correlation between sinuses' opacification and the steady state, but it may not be the guarantee for a FPCT acquisition during steady state, as in some cases, the timing difference with the actual beginning of the steady state can be as much as 6 s.

From our data, we could determine for central injections a probabilistic timing with a 5-s acquisition initiated 24 s after contrast media injection and it would correspond to an acquisition during steady state for the majority of the patients of our study.

There are several limitations in our study. First, there are a small number of patients in this study, and the validation of the FP CBV measurement was not the purpose of this preliminary work. Secondly, the strictness of the steady state required for precise CBV measurement has not been determined in the literature, so we have arbitrarily chosen 15 %. Logically, the steady-state length would increase with a raise of the tolerance threshold. For example, in our study, the average gain would be 1.7 s (+ 15 %) if the threshold were increased from 15 to 20 %. Thirdly, those results may not be applicable to stroke patients because of vessel occlusion and slow flow blood supply from collaterals. This could be responsible of a different steady state of contrast enhancement in comparison with normal tissues resulting in possible "pseudo-CBV abnormalities".

Finally, there are variety of ways to extend the steady state by manipulation of the injection protocol, and for example, it would be of great interest to study slower injection rates because with an equivalent volume of contrast agent, it should not only induce a longest steady state but also a lower peak enhancement and therefore a lower signal to noise ratio for FPCT CBV measurement.

#### Conclusion

Perfusion maps of CBV can be obtained in the angiographic suite using FPCT with a steady state of contrast enhancement of the brain parenchyma, but with clinically acceptable contrast agent volumes, steady state is a brief condition; thus, fast rotation speed acquisitions are compulsory. The use of central venous injections decreases the variability of steady-state's delay from injection. The bolus watching technique is an interesting way to overcome interindividual variability but may not always be the guarantee for steady state during the whole acquisition.

Further studies are needed to optimize and standardize injections protocols to allow a larger diffusion of the FPCT CBV measurement during endovascular stroke therapy.

**Conflict of interest** DR is employed by Philips Healthcare, Netherlands.

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## Résumé

Les deux piliers de la Neuroradiologie Interventionnelle (NRI) sont depuis la naissance de cette spécialité née dans les années 1960-70 : la technicité des « outils » employés et le guidage par l'image.

Grace à des avancées technologiques majeures, nos cathéters nous autorisent désormais à naviguer dans n'importe quelle artère du cerveau. Et l'ensemble des dispositifs de NRI existants nous permet de désobstruer une artère occlue, emboliser une lésion à risque de saignement ou bien reconstruire des vaisseaux pathologiques.

En revanche, si la résolution de l'angiographie numérique s'est progressivement améliorée au fil des années, nous ne disposions encore récemment que de peu d'éléments pour planifier et évaluer précisément nos traitements, ceci directement au bloc de NRI.

La première partie de ce travail a consisté à démontrer le potentiel d'une technologie largement disponible mais sous-employée. L'imagerie volumique par faisceau conique (*Cone Beam CT*) est en effet une aide précieuse pour imager les dispositifs faiblement radio-opaques.

Dans un deuxième temps, nous exposons au travers de plusieurs modèles précliniques, le potentiel extraordinaire de l'imagerie intra-vasculaire par tomographie en cohérence optique (*Optical Coherence Tomography*). Non utilisée en pratique clinique NRI jusqu'à ce jour, cette imagerie à très haute résolution a le potentiel de devenir un véritable microscope vasculaire utilisable in vivo.

Enfin, après la description des ces modalités morphologiques nous nous sommes efforcés de démontrer la valeur ajoutée des imageries fonctionnelles lors du traitement des pathologies neurovasculaires.

Nous illustrons cette progression dans les techniques d'imagerie au travers de deux approches différentes pour le traitement des anévrismes intracrâniens ; l'une endosacculaire (*WEB*) et l'autre pariétale (stents à diversion de flux).

Au total, l'importance de l'imagerie dans notre spécialité est encore en train de se renforcer, en raison de sa diversification. Il ne fait aucun doute que dans un avenir proche, la multiplicité des informations fournies sera disponible, en temps réel, par réalité augmentée, à la manière d'un pilote d'avion. Dans le futur, c'est même par l'imagerie que nous réaliserons nos interventions ; quand les systèmes à résonnance magnétique permettront de guider, à distance les cathéters jusqu'à leur cible.

# Mots Clés

Radiologie, Imagerie médicale, Angiographie numérisée, Imagerie volumique par faisceau conique, Tomographie en cohérence optique, Mécanique des fluides numérique, Anévrisme cérébral.

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