Medizinische Fakultät
der
Universität Duisburg – Essen

Aus der Klinik für Neuroradiologie
Neurozentrum, Klinikum Stuttgart

Animal experiments, in-vitro study and clinical use of a new device for the endovascular treatment of intracranial wide necked bifurcation aneurysms (pCONus®)

Inaugural-Dissertation
zur
Erlangung des Doktorgrades der Medizin
durch die Medizinische Fakultät der Universität Duisburg – Essen

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2014

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Tag der mündlichen Prüfung: 26. Juni 2015

Aguilar-Pérez, M., Kurre, K., Fischer, S., Bäzner, H., Henkes, H. (2014) Coil occlusion of wide-neck bifurcation aneurysms assisted by a novel intra- to extra-aneurysmatic neck-bridging device (pCONus®): initial experience. AJNR Am. J. Neuroradiol. 35, 965-71.

Gory, B., Aguilar-Pérez, M., Pomero, E., Turjman, F., Weber, W., Fischer, S., Henkes, H., Biondi, A. (2015) pCONus device for the endovascular treatment of wide-neck middle cerebral artery aneurysms. AJNR Am J Neuroradiol. (e-pub ahead of print)

Content

1. Scales

1.1. modified Rankin Scale (mRS)

mRS 0	no symptoms at all
mRS 1	no significant disability despite symptoms; able to carry out all usual duties and activities
mRS 2	slight disability; unable to carry out all previous activities, but able to look after own affairs
mRS 3	moderate disability; requiring some help, but able to walk without assistance
mRS 4	moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
mRS 5	severe disability; bedridden, incontinent and requiring constant nursing care and attention
mRS 6	death

1.2. Hunt & Hess (HH)

HH 1	asymptomatic or minimal headache and slight neck stiffness
HH 2	moderate to severe headache; neck stiffness; no neurologic deficit except cranial nerve palsy
HH 3	drowsy; minimal neurologic deficit
HH 4	stuporous; moderate to severe hemiparesis; possibly early decerebrate rigidity and vegetative disturbances
HH 5	deep coma; decerebrate rigidity; moribund

1.3. Fisher Grade: appareance of SAH on CT scan

Fisher I	no hemorrhage evident
Fisher II	subarachnoid hemorrhage less than 1 mm thick
Fisher III	subarachnoid hemorrhage more than 1 mm thick
Fisher IV	intraventricular hemorrhage or parenchymal extension

2. Introduction

Coil occlusion of intracranial aneurysms, both ruptured and unruptured, is safe and efficacious if patient selection and endovascular treatment are carried out adequately (Raymond et al. 1997, Roy et al. 2001, Pierot et al. 2008, Spetzler et al. 2013). A major limitation for this treatment modality is related to the geometry of the target aneurysm. A neck of ≥ 4 mm and a fundus width/neck ratio ≤ 1 mm are unfavorable for simple coiling (Brinjikji et al. 2009). Intraluminal flow diversion has solved this issue for sidewall aneurysms (Fischer et al. 2011). Intraaneurysmal flow disrupter (e.g., WEB, Sequent Medical; LUNA, nFocus/Covidien) are promising but not yet fully established devices for selected bifurcation aneurysms (Klisch et al. 2011, Pierot et al. 2012, Lubicz et al. 2013, Pierot et al. 2013). For WNBAs, the techniques to assist coil occlusion include single or crossing stent deployment and balloon remodeling (Lubicz et al. 2009, Moret et al. 1997), both requiring catheter access to at least one efferent vessel of the bifurcation. This catheterization can sometimes be difficult. Coil assist techniques without efferent vessel access include TriSpan device (Raymond et al. 2001), which is no longer available, and the deployment of self-expanding stents with their distal end inside the aneurysm, the so-called “waffle cone” technique (Horowitz et al. 2006). The stents used for the “waffle cone” technique (e.g., Solitaire AB, Covidien; Enterprise, Codman) are not optimized for this purpose and are far from ideal. pCONus® (phenox) is a dedicated neurovascular device, which was designed to address the functional needs of an extra-intrasaccular neck bridging aneurysm implant to assist the coil occlusion of WNBAs.

The present thesis summarizes the *in vitro* study of the device, its initial use in 9 New Zealand White Rabbits as well as the angiographic and clinical results in the endovascular treatment of 50 intracranial aneurysms. In the clinical use of pCONus® we refer to the initial state of the patient, the angiographic outcome of the treatment session, possible complications and clinical outcome after the treatment. The results of the follow-up, the

necessity and, if necessary, subsequent treatments, and in turn, their clinical outcome are presented elsewhere.

3. Device description

The pCONus® (phenox GmbH, Bochum, Germany) was developed as an endovascular implant for the bridging of intracranial WNBAs to enable aneurysm coiling.

pCONus® is a stent-like lasercut vessel implant made of Nitinol with 4 loops (petals) at its distal end, which are flared in the radial direction (Figure 1).

The distal inner diameter of the pCONus® is additionally crossed by 6 nylon fibers creating a mechanical barrier between the aneurysm and the parent vessel (Figure 2). The biocompatibility of these fibers is certified and the same material was used for coils with attached nylon fibers (ev3).

The proximal end of the pCONus® implant as well as the 4 distal loops carry segmental radiopaque markers made of Platinum-Iridium wire. They allow visual control of the otherwise none radiopaque device under fluoroscopy. pCONus® ends proximally in one eccentric strut, which carries a detachment element connected to an insertion wire made of stainless steel. This insertion wire is 180 cm long, has a diameter of 0.42 mm (0.0165 inch) and is conically shaped at its distal end. A 30 mm long radiopaque marker made of Platinum-Iridium wire at the distal tip of the insertion wire allows alignment with the two markers of the delivery microcatheter. The detachment element consists of a Cobalt Chromium wire, which can be dissolved electrolytically by direct electric current using available coil detachment generator devices.

The distal diameters of the expanded petals are available in 5, 6, 8, 10, 12 and 15 mm. The stent-like shaft has a 4 mm diameter and is 20 or 25 mm long (Table 1). This product range allows the implantation into target vessels with a diameter between 2.5 and 3.75 mm, covering aneurysm necks of 4 to 14 mm diameter.

The radial force of the device is in between the radial forces of other intracranial stents like Solitaire AB (ev3/Covidien) or Neuroform (Stryker).

pCONus® is compatible with standard microcatheters with an inner diameter of 0.021” or 0.027” (e.g., RapidTransit, Codman Neurovascular; Marksman, Covidien). We always used 0.021” microcatheters for easier access.

The device allows controlled insertion, deployment and eventual withdraw into the microcatheter. The radiopacity is sufficient for a visual control of deployment under high quality fluoroscopy but does not impair the visualization of the device using flat panel detector CT (e.g., DynaCT, Siemens; XperCT, Philips).

Figure 1: (A) The pCONus® is a self-expanding, completely retrievable, electrolytically detachable device with a proximal shaft (similar to stents) and 4 distal petals at its distal end. The proximal end (yellow asterisk) as well as the 4 distal petals (red asterisks) contain radiopaque markers. (B) Similar to the waffle cone technique, the 4 distal loops of the pCONus® are deployed inside the aneurysm at the level of the neck (red arrow), assisting coil occlusion. The proximal detachment element consists of a Cobalt Chromium wire, which can be dissolved electrolytically (yellow arrow).

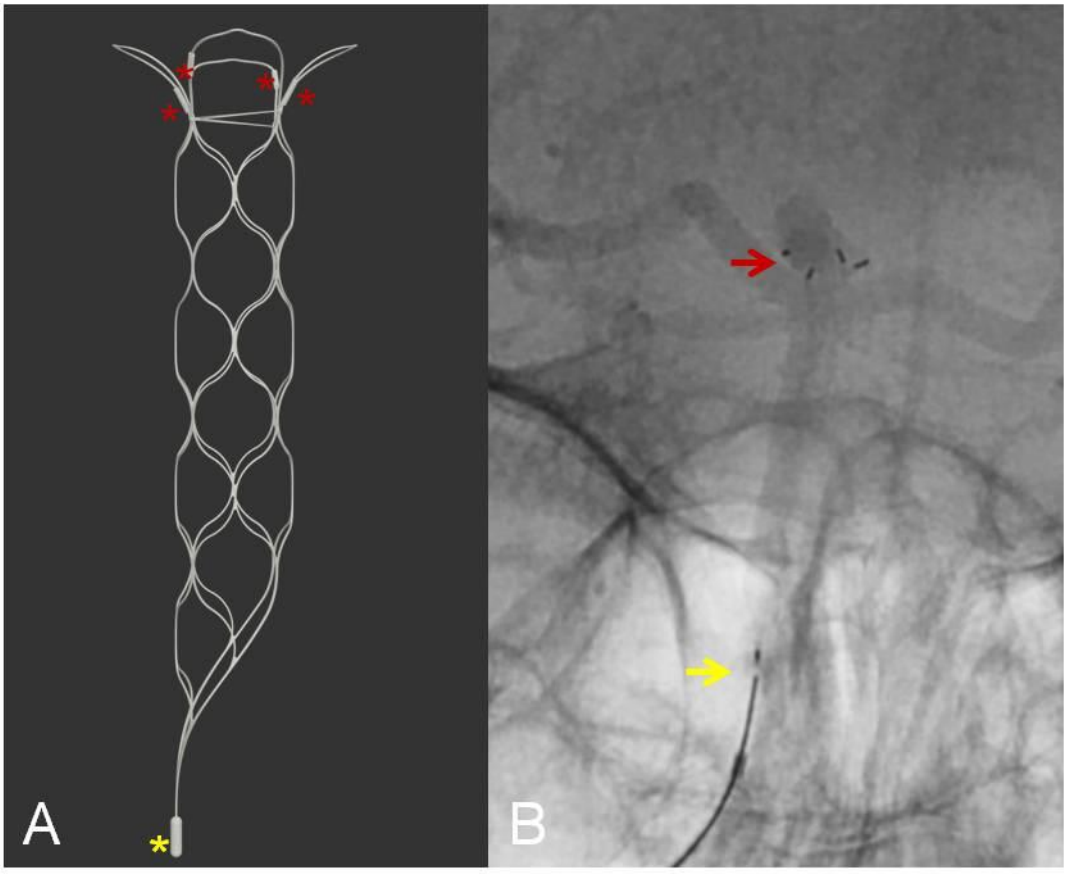


Figure 2: Six Nylon fibers cross the distal inner diameter of the pCONus® (red dashed lines), creating a mechanical barrier between the aneurysm and the parent vessel, and preventing coil protrusion into the shaft of the device.

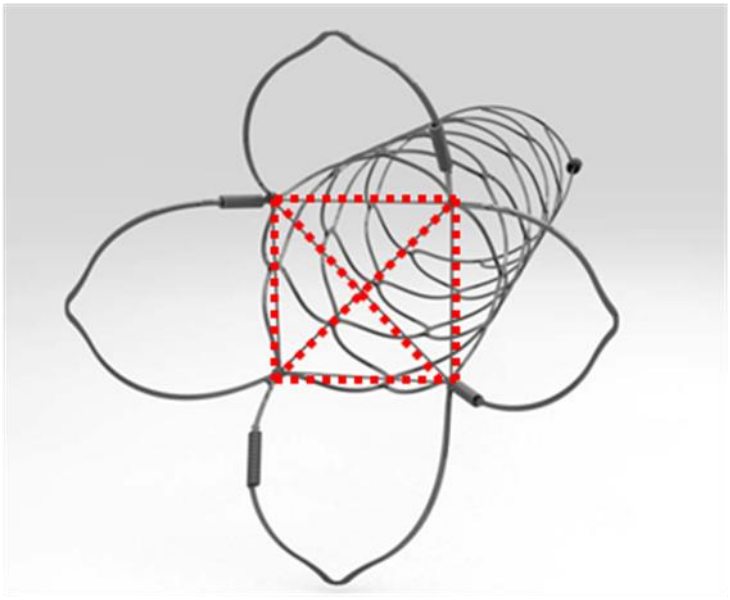


Table 1: Available pCONus® sizes.

pCONus®	Stent-shaft diameter	Stent-shaft length	Petals diameter
	4 mm	20 mm	5 mm
			6 mm
			8 mm
		25 mm	10 mm
			12 mm
			15 mm

4. Animal experiments

As a part of the design validation process of the device an *in vivo* study was conducted using New Zealand White Rabbits with microsurgically created common carotid artery wide neck bifurcation aneurysms between August 2011 and April 2012.

The study was conducted in the animal laboratories of the “Allgemeines Krankenhaus der Stadt Wien”, Medical University of Vienna, Austria, in cooperation with PD Dr. Camillo Sherif, neurosurgeon at “Krankenanstalt Rudolfstiftung”, Vienna, and managing partner NVtec Neurovascular Technologies GmbH, Vienna, and member of the Cerebrovascular Research Group at the Department of Biomedical Research at the Medical University of Vienna. These animal experiments were registered under the number 66.009/0215-II/10b/2008.

The purpose of this *in vivo* study was to assess the acute therapeutic success and chronic functional success of the pCONus® for the treatment of bifurcation aneurysms as support for coiling procedures.

At the end of the follow-up period the aneurysms were explanted for complete histological and pathological analysis in order to evaluate the biocompatibility and hemocompatibility of the device.

4.1. Animal aneurysm preparation

Wide-neck aneurysms (n = 9) were created according the procedures published by Sherif et al. and Marbacher et al. using New Zealand White Rabbits (Sherif et al. 2011, Marbacher et al. 2011).

The aneurysm pouch was made using a 1 cm long segment of the external jugular vein, which was cut longitudinally (1), folded along its transverse axis (2) and sutured at proximal and distal ends (3). After that this pocket was sutured to the artificial bifurcation of both common carotid arteries (Figure 3 and 4).

Figure 3: Creation of the aneurysm pouch in rabbits.

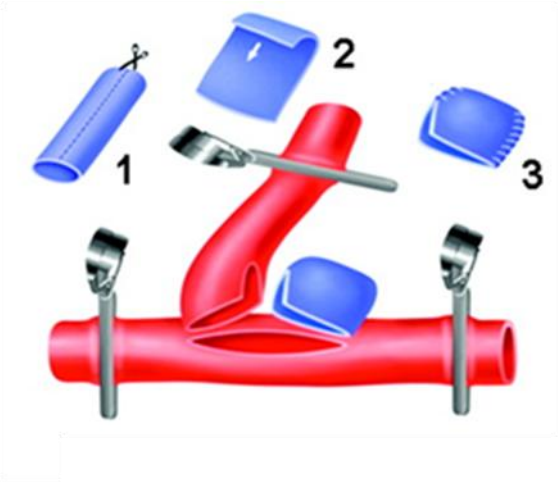
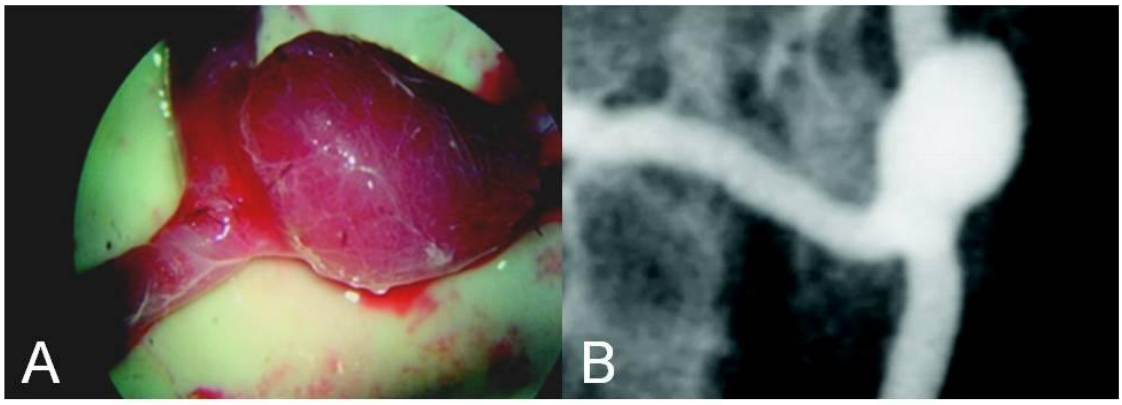


Figure 4: (A) Photograph during the operation. (B) Aneurysm visualized by MR angiography.



4.2. Aneurysm embolization and ongoing animal care

At least 3 weeks passed between aneurysm creation and embolization. The animal received 10 mg/kg of acetylsalicylic acid and clopidogrel at least 3 days before the treatment. Anesthesia was induced by using 50 mg/kg of ketamine, 2 mg/kg xylazine, and 1.2% isofluran, and was maintained by using ketamine and xylazine via perfusor with ECG and SiO2 monitoring.

A surgical cut-down of the right femoral artery was performed, and a 4F sheath was inserted. A 4F guide catheter (Tempo4; Cordis) was placed into

the carotid artery just proximal to the target aneurysm. Heparin (100 U IV) was administered, and then a microcatheter (Prowler Select Plus; Codman Neurovascular) was placed over a microguidewire (Traxcess14; MicroVention Terumo) inside the aneurysm, about 3 mm distal to the aneurysm neck in order to insure the desired placement position of the pCONus®.

The pCONus® size was selected to match the aneurysm neck with a pCONus® plate diameter that had nearly the same neck size. The wire was removed, and the pCONus® device was advanced into the aneurysm cavity and deployed. After a DSA the pCONus® was electrolytically detached. Thereafter the pCONus® was carefully passed with a second microcatheter, placing the tip inside the aneurysm, about 3 mm distal of the aneurysm neck. After coiling, the microcatheter was removed and a DSA of the common carotid artery was performed (Figure 5).

The sheath was removed and the femoral artery was ligated over the site to obtain hemostasis. The incision in the groin was closed with sutures. At this point the anesthesia was discontinued and the animal was returned to its pen.

Postmedication included antiplatelet therapy with 10 mg/kg of acetylsalicylic acid and clopidogrel per os.

4.3. Angiographic evaluation

All animals were followed for a nominal period of 3 months or longer. This period is the target endpoint and subject to minor duration fluctuations based on the availability of the animal laboratory facility. At this point, the aneurysms were evaluated angiographically. The follow-up angiography was performed with a sheath in the ear vein.

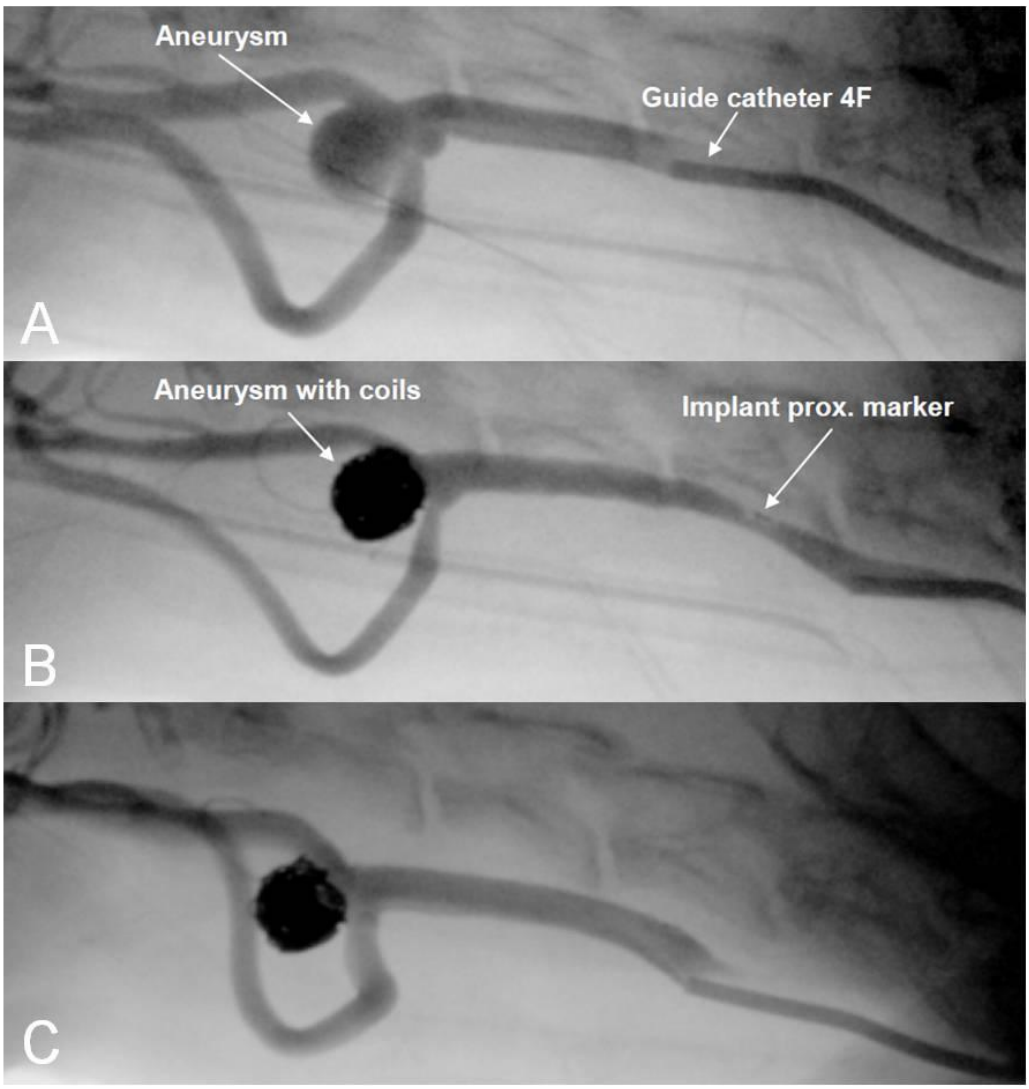
Aneurysm dimensions (neck width, aneurysmal height and width) were determined with DSA measurements, which were adjusted by using an external sizing device of known diameter. Angiographic evaluation was

performed by angiographic analysis conducted immediately after device implantation as well as prior to euthanasia.

The degree of aneurysm occlusion was assessed by using the 3-point Raymond scale (Raymond et al. 2003): grade 1: complete occlusion; grade 2: neck remnant; grade 3: incomplete occlusion.

Interval changes were registered by comparing the 3-point occlusion scale results of individual aneurysms immediately after implantation with a separate 3-point scale indicating that the aneurysm was stable, recanalized, or progressively thrombosed.

Figure 5: Animal No. 31: (A) Vessels with aneurysm before implantation. (B) Implant and coils directly after implantation. (C) Final DSA before termination.



4.4. Euthanasia

At the time of sacrifice, animals were deeply anesthetized. Animals were then humanely euthanized with a lethal injection of pentobarbital. Harvested aneurysms with implant and sufficient artery length distal and proximal to the implant were immediately covered with a 5% formalin solution.

Explanted aneurysms were forwarded to the appropriate laboratory for evaluation.

4.5. Conventional histopathological processing

The histopathologic study was performed in the “Labor für medizinische Materialprüfung GmbH”, technological medical center of Aachen, Germany, in order to evaluate the biocompatibility of the device.

Various sections from the distal and proximal part of delivered test items of each specimen without implant were placed in HistoTec® boxes. Parts with implants were prepared for polymer embedding (Figure 6).

Tissue samples with implants were dehydrated in alcohol and embedded in plastic Technovit 7200 VLC. After the steps of polymerization the specimens were placed in an incubator at 50 degrees Centigrade for up to 12 hours to complete the polymerization. After that several sections of the specimens were grinded and stained with hematoxylin and eosin (H&E) (Figure 7).

The explanted aneurysms were reviewed for any protrusions into the parent vessel as well as thrombus formation, recanalization, intimal hyperplasia, elastic lamina disruption, foreign body giant cell reaction, and signs of inflammation.

Figure 6: Photographic documentation of the sample P0384-09/12 (left). Photographic documentation of the sample P0384-09/12 after embedding with marked grinding surface (right).

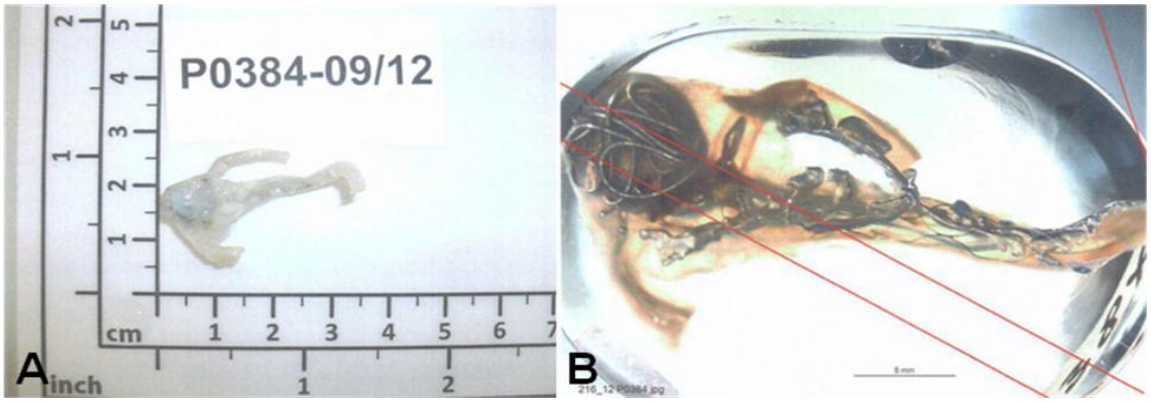
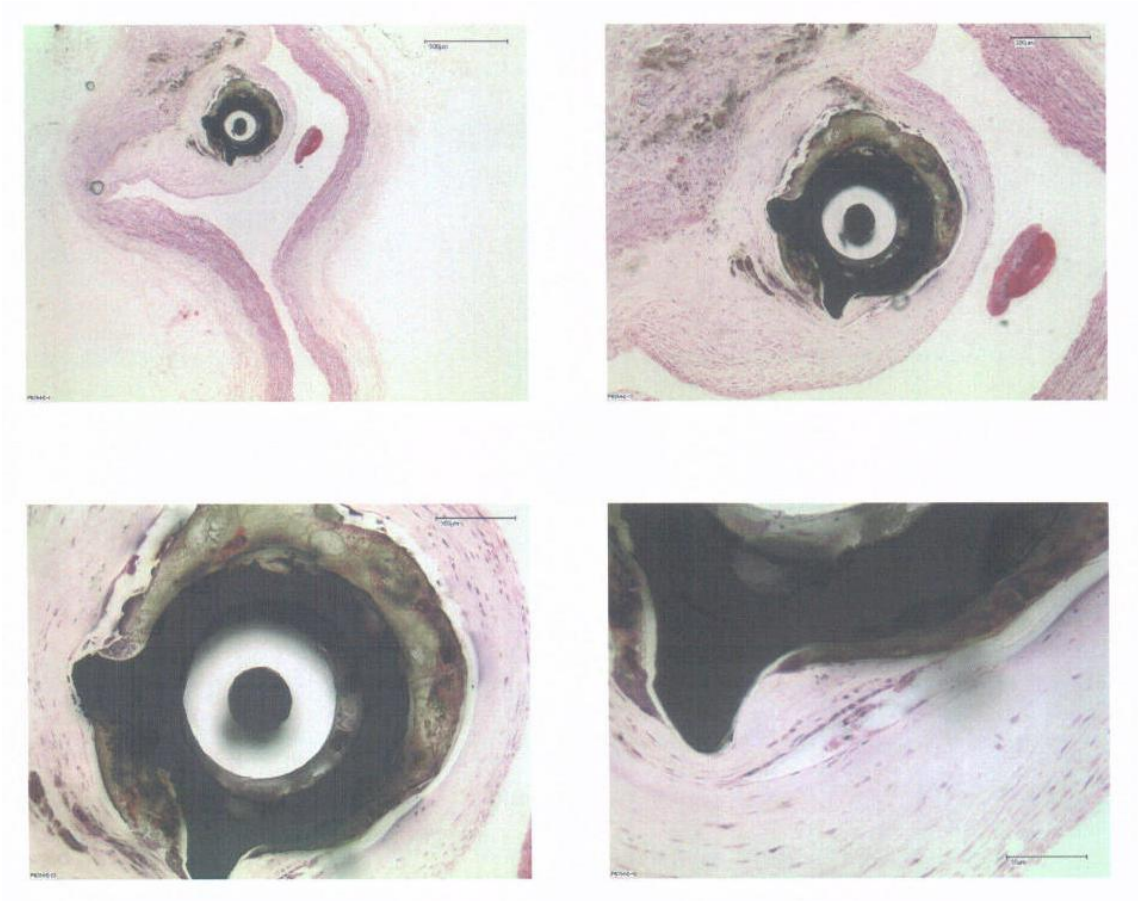


Figure 7: Microscopic documentation of the sample P0384-09/12 with implant, grinding surface detachment element; magnifications x 40, x 100, x 200, x 400 (H&E).



4.6. Angiographic and technical results

In the course of this *in vivo* study 9 New Zealand White Rabbits with venous pouch aneurysms were treated with a pCONus® implant to enable subsequent coiling.

In all these cases, handling and behavior of the pCONus® implant was within expectation. The self-expansion, deployment and detachment functioned very well. The implants did not migrate inside the target vessel and did not cause perforation, ruptures or vessel diameter changes.

The implant could be easily passed by the coil delivery microcatheter. Structural and material damages of the implant could not be observed.

One coiling procedure ended up with minor vasospasm that was medically treated and is a common reaction of vessels after excessive mechanical manipulation.

At the end of the procedure (Table 2), complete occlusion (grade 1) was achieved in 5/9 aneurysms (55.6%). 2/9 aneurysms (22.2%) were graded as neck remnant (grade 2) and another 2 aneurysms (22.2%) as incompletely occlusion (grade 3).

Table 2: Initial angiographic results after pCONus® assisted coiling in 9 rabbits with venous pouch aneurysms using the 3-point scale.

Occlusion rates	n	%
1 – complete occlusion	5	55.6
2 – neck remnant	2	22.2
3 – incomplete occlusion	2	22.2

Five animals (55.5%) were terminated after a period of 3.4 to 11.5 months and demonstrated that the treated aneurysms were very well occluded. Four animals (44.4%) died before the end of the study due to various reasons:

- stroke in another artery after extended anaesthesia duration (n = 1), one day after embolization treatment
- extended anaesthesia duration (n = 1), on same day of embolization treatment
- urinary hemorrhage due to excessive antiplatelet effects (n = 1), 21 days after embolization treatment
- unknown reasons (n = 1), 1.5 months after embolization treatment. Autopsy did not show any device related reason.

From the 5 cases with follow-up (Table 3), one aneurysm presented coil compaction (20%) and two (40%) minor neck remnants after the coiling procedures, which would have required additional coiling treatments.

Table 3: Angiographic follow-up results after pCONus® assisted coiling in 5 out of 9 rabbits with venous pouch aneurysms using the 3-point scale.

Occlusion rates	n	%
1 – complete occlusion	2	40
2 – neck remnant	2	40
3 – incomplete occlusion	1	20

The most important criteria and results of the *in vivo* tests are summarized in table 4.

Table 4: Criteria and results of 9 New Zealand White Rabbits with venous pouch aneurysms treated with pCONus® assisted coil occlusion.

Animal No.	**23**	**22**	**31**	**29**	**27**	**26**	**25**	**38**	**41**
Aneurysm creation	11.8.11	10.8.11	27.10.11	11.10.11	30.9.11	28.9.11	26.9.11	15.3.12	19.4.12
Date of treatment (embolization)	13.9.11	13.9.11	05.12.11	06.12.11	06.12.11	06.12.11	3.02.11	15.5.12	15.5.12
Main vessel-Ø [mm]	2,5	2,0	2,5	2	2,5	2,5	2,5	2,6	2,5
Side vessel-Ø [mm]	1,7	0,5	2,1	1,8	2,2	1,5	2,0	2,0	2,0
Side vessel-Ø [mm]	1,8	1,3	2,0	1,9	2,2	1,7	1,8	2,5	2,0
Height of aneurysm [mm]	8,4	8,0	5,0	4,0	7,5	12,0	16,2	12,0	9,0
Width of neurysm [mm]	5,0	4,0	6,0	4,0	5,5	5,0	9,3	6,0	5,0
Aneurysm neck [mm]	3,5	4,0	5,0	5,0	6,0	4,0	7,9	5,0	4,0
Deployment and detachment of pCONus®	Very good	Very good	Very good	Very good	Very good	Very good	Very good	Very good	Very good
Negative incidents	No	No	No	No	No	No	No	No	No
Passing through pCONus®	Easy	Easy	Some attempts needed	Easy	Easy	Some attempts needed	Easy	Some attempts needed	Easy
pCONus® migration	No	No	No	No	No	2-3 mm	No	No	No
Postoperative blood flow in aneurysm	No, 100% occlusion	No, 100% occlusion	No, 100% occlusion	No, 100% occlusion	No, 100% occlusion	No, but stasis in proximal portion	Flow 15%, occlusion 85%	Remnant neck, 100% occlusion	Minimal neck remnant, 100% occlusion
Postoperative blood flow in vessel	Yes	Yes	Yes	Yes: Main vessel & 1 side vessel; BUT: 1 side vessel occluded	Yes	Yes	Yes	Yes	Yes
Postoperative negative incidents	No	No	No	No	No	No	No	No	No
Variations of the protocol	Spasm after coiling	No	No	No	No	No	No	No	No

Animal No.	23	22	31	29	27	26	25	38	41
Preterm death	14.9.11 1 day after treatment	No	No	06.12.11 same day of treatment)	27.12.11 21 days after treatment	19.01.12 1,5 months after treatment	No	No	No
Reason of preterm death	Stroke in VA	-	-	Long anesthesia duration	Urinary Hemorrhage	Unknown	-	-	-
Post embolization follow-up	-	16.1.12	16.1.12	-	-	16.1.12	4.6.12	No	No
Follow-up period	-	4 months	4 months	-	-	40 days	4 months	-	-
MRA blood flow in vessels	-	Yes	Yes	-	-	Yes	Yes	-	-
Remarks		Fill of aneurysm cannot be evaluated by MRA	Fill of aneurysm cannot be evaluated by MRA			Fill of aneurysm cannot be evaluated by MRA	Fill of aneurysm cannot be evaluated by MRA		
Final follow-up date	-	24.8.12	24.8.12	-	-	-	24.8.12	24.8.12	31.8.12
Follow-up period	-	11,5 months	8,8 months	-	-	-	6,8 months	3,4 months	3,6 months
DSA blood flow in vessels	-	Yes	Yes	-	-	-	Yes	Yes	Yes
Success rate	-	80% occlusion	100% occlusion	-	-	-	100% occlusion	100% occlusion	100% occlusion
Remarks		Re-coiling needed due to coil compaction						Neck remnant might need re-coiling	Little neck remnant might need re-coiling

4.7. Histological findings

Available were 9 specimens fixed in buffered 5% formalin. The investigated specimens were taken after 4.3 to 11 months after implantation.

Conventional histopathology showed an increased vessel diameter due to the stenting procedure. Corresponding to the macroscopic aspect, the microscopy also revealed no tissue defect and no penetrating wall defects.

The pCONus® stent filaments showed no or only minor foreign body reaction with some macrophages in the interface filament-vessel wall, low neointima

formation without significant reduction of the vessel lumen, partial atrophy of the muscle layer of the vessel wall. No thrombus formation and no vasculitis were encountered (Table 5).

Cross-sections of the coil area revealed a more complex form of neointima formation resulting in a subtotal or total occlusion of the aneurysmatic vessel segment.

In cross-sections of the detachment element again a mild neointima could be observed. The interface indicated no or only a mild foreign body reaction.

In none of the specimens signs of infection and degradation of the vessel wall (calcification and atherosclerotic changes) could be observed.

Table 5: Results of the histological evaluation of the test items in 5 venous pouch aneurysms after pCONus® assisted coil occlusion

0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = extensive; () = with tendency to

Sample No.	Inflama-tory infiltate	Giant Cells	Granulo-cytes	Lympho-cytes	Macro-phages	Plasma cells	Infection	Fibrosis	Calci-fication	Necrosis	Degene-ration
P0378-09/12	0-1	0	0	0	0-1	0	0	1	0	0	0
P0380-09/12	0-1	0	0	0	0-1	0	0	1	0	0	0
P0384-09/12	0-1	0	0	0	0-1	0	0	1	0	0	0
P0385-09/12	0-1	0	0	0	0-1	0	0	1	0	0	0
P0386-09/12	0-1	0	0	0	0-1	0	0	1	0	0	0

As result, the application of the pCONus® implant in investigated specimens provides a tissue compatible stenting procedure covering the inner vessel wall of the artery without stenosis and without thrombus formation.

The biocompatibility and hemocompatibility of the pCONus® implant in these cases were considered as excellent with no or only minimal foreign body reaction in the interface and with an overall low neointima formation.

5. *In vitro* study

In order to investigate and quantify the intra-aneurysmal flow modification induced by pCONus®, different devices, including pCONus®, were tested during an *in vitro* experience in Geneva in cooperation with Professor Vitor Mendes Pereira, director of the unit of interventional neuroradiology at the University Hospital of Geneva.

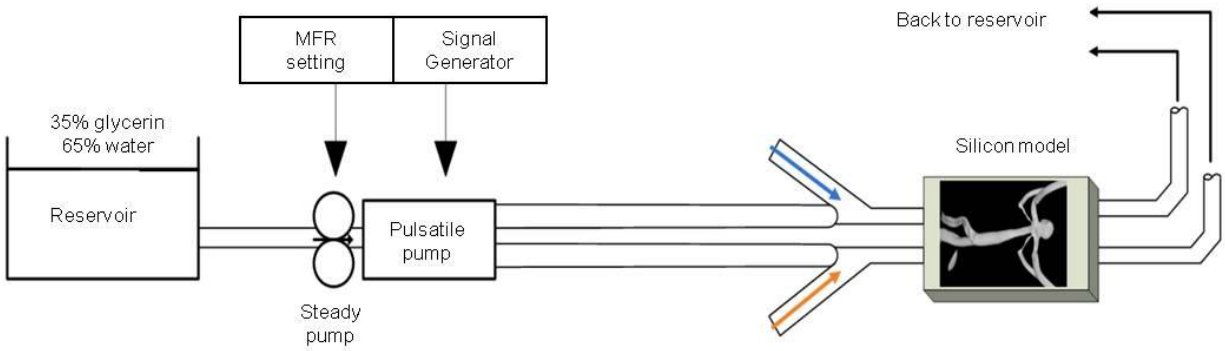
In a circulating *in vitro* closed set-up, a patient specific silicon model mimicking a basilar artery bifurcation aneurysm was used to evaluate different devices dedicated to endovascular treatment of intracranial aneurysms.

An imaging flow prototype, based on DSA images and optical flow imaging, developed by Philips Healthcare, was used to quantify intra-aneurysmal flow modification induced by the different devices.

5.1. Experimental set-up

Experimental set-up (Figure 8) consists of a reservoir, which contains a mixture of water and glycerin (Water 65% - glycerin 35%) simulating human blood, a continuous flow pump, which is modulated by a pulsatile system and creates conditions similar to arterial flow, a vascular phantom, and a closed circuit.

Figure 8: Experimental set-up for the *in vitro* testing of the hemodynamic effects of pCONus®.



As vascular phantom, we used a silicon model simulating a wide-necked basilar artery bifurcation aneurysm. The size of the aneurysm neck was 4.02 / 5.7 mm, the aneurysm height was 6.37 mm and the aneurysm width 7.37 / 6.43 mm.

The silicon model (Figure 9 and 10) contains 2 inlets (simulating right and left vertebral arteries). One inlet is used for imaging, while the other one is used for device implantation. The inlet used for device implantation is clipped during imaging to avoid reflux during contrast agent (CA) injection.

Figure 9: Silicon model for the *in vitro* testing of the hemodynamic effects of pCONus®.

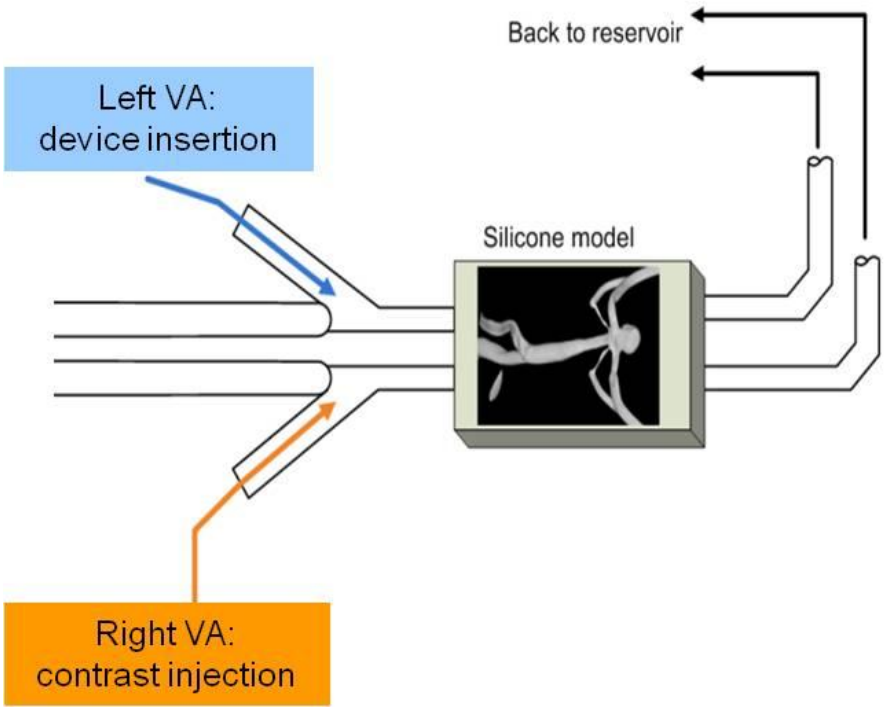
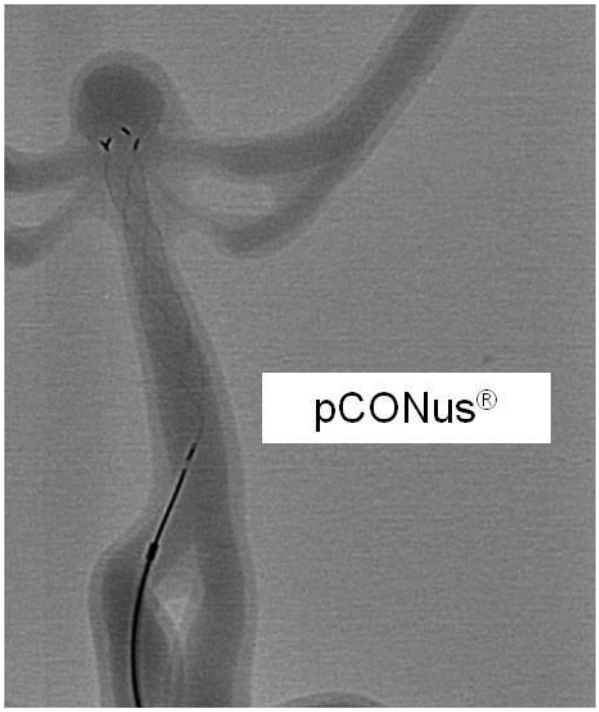


Figure10: Silicon model with a pCONus® device in place.



5.2. Imaging

The study was performed on a monoplane flat panel digital subtraction angiography (DSA) unit (Allura FD20, Philips Healthcare, Einthoven, The Netherlands).

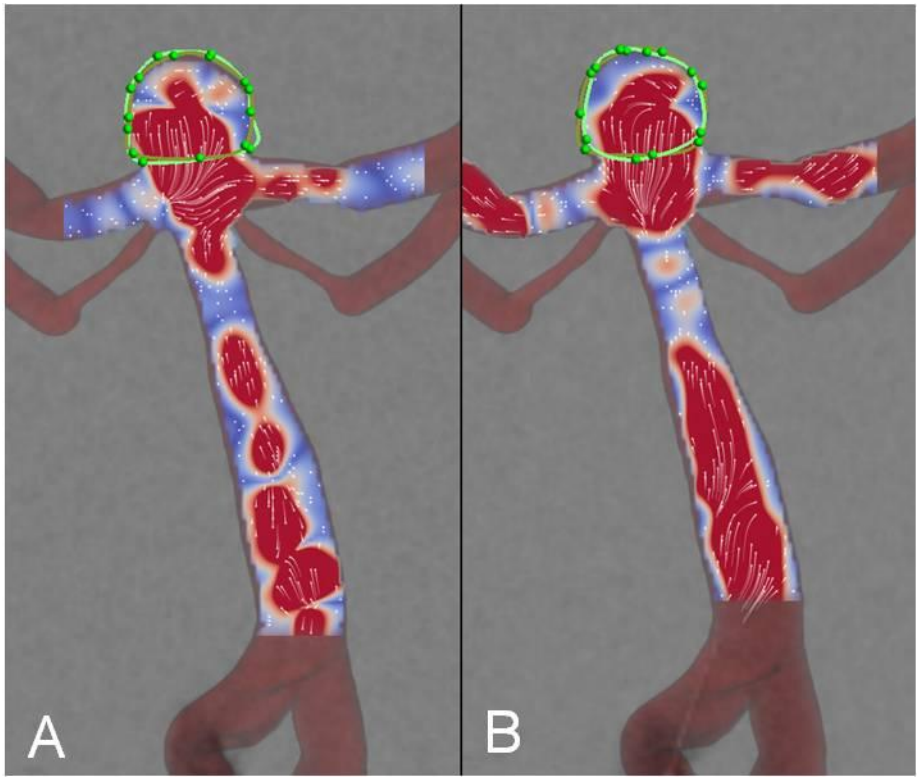
The angiographic sequences were acquired with a 60 images/second frame rate. Flow reduction analysis with MAFA (Mean Aneurysm Flow Amplitude) and MAFA ratio calculation was performed with the flow prototype from Philips Healthcare.

Two different CA injection rates (2 and 3 cc/s) were applied for each projection view (AP and lateral). Consequently, for each configuration, 2 angiographic sequences were acquired.

5.3. Flow analysis

The method used to evaluate the flow modification is based on optical flow principles applied to DSA sequences and was developed by Philips Healthcare. This tool called “angio flow” is still in development. The velocity fields could be visualized as vectors or streamlines projected in the line of sight of the detector (Figure 11).

Figure 11: “Angio flow” method. (A) Velocity fields without device. (B) Velocity fields after device implantation.



Furthermore, time average velocities can be computed from a region of interest covering the aneurysm region from which the mean aneurysm flow amplitude (MAFA) before and after stenting could be computed.

After that, a pre and post implantation ratio ***R*** can be calculated as following:

$$R = \frac{MAFA(post)}{MAFA(pre)}$$

5.4. Results

Pre and post implantation MAFA values were evaluated and the corresponding ratio R for each tested device was calculated. These values were acquired from the AP view with 2 cc/s injection rate.

Since flow rate and waveform is not expected to change in experimental conditions, pre and post stent sequences could be considered to have been acquired in the same flow conditions.

Consequently R reflects only the flow changes induced by the device.

- R>1 corresponds to an increase of the intra-aneurysmal flow after device implantation.
- R<1 reflects a reduction of intra-aneurysmal flow.

Device	MAFA pre/post	R
pCONus®	3.5/3.5	1

Based on R, the pCONus® device has, quantitatively, no influence on the intraaneurysmal blood flow.

6. Clinical experience

6.1 Material and methods

The results presented below are based on the retrospective analysis of all wide-necked intracranial bifurcation aneurysms treated with pCONus® between February 2012 and April 2014.

All the procedures included in this series were performed in the “Klinik für Nueroradiologie” of the Katharinenhospital Stuttgart by a team of four interventional neuroradiologists, and always under the supervision of the director of the clinic.

Procedures were performed on biplane flat panel digital subtraction angiography (DSA) units (Axiom Artis, Siemens).

The endovascular treatment was either proposed to the patient as a result of an interdisciplinary discussion or offered on the basis of the *a priori* preference of the patient.

In elective procedures, all patients had comprehensive consultations prior to the procedures, which included an explanation of the disease, all therapeutic options, and their respective chances and risks. Microsurgery and conservative management were discussed with all elective patients. In patients in the acute phase after SAH, endovascular treatment including the use of pCONus® was carried out as an emergency measure and whenever possible, was explained to the relatives. Written informed consent was obtained from all elective patients.

The decision to use a pCONus® was in all patients based on anatomical features of the target aneurysm. In all aneurysms, a wide neck in a vessel bifurcation or a diffuse vessel bifurcation enlargement was expected not to allow safe and sufficient unassisted coil occlusion. Single vessel stenting was always weighted against pCONus® usage. Kissing- or crossing-stents was not considered as a preferred alternative to pCONus®.

6.1.1 Elective cases (Table 6)

Patients undergoing elective treatment were premedicated at least 1 day prior to the treatment with a single loading dose of 500 mg acetylsalicylic acid and 600 mg clopidogrel (n = 27) or 180 mg ticagrelor (n = 4). Each patient was tested before the endovascular treatment for sufficient inhibition of the platelet function with Multiplate® (Roche). Six patients were found to be non-responders to clopidogrel and were re-loaded with 30 mg prasugrel (n = 2) or 180 mg ticagrelor (n = 4).

Patient No. 1 had a diagnostic angiography on a Friday with subsequent consultation and asked for endovascular treatment, was scheduled for the endovascular treatment for the forthcoming Monday and planned for loading, but bled prior to the intake of the medication and was therefore treated under emergency conditions.

6.1.2 *Emergency cases* (Table 7)

Patients with severe SAH underwent ventricular shunting prior to diagnostic angiography and eventual endovascular treatment. The decision for an endovascular treatment was in all cases based on an interdisciplinary discussion between the board-certified neurosurgeon on call and the interventional neuroradiologist in charge. Arguments in favor of an endovascular approach were poor clinical condition after SAH (Hunt and Hess IV-V) or anticipated surgical difficulty (e.g., basilar artery aneurysms).

As soon as the decision was made to use a pCONus®, patients received either 600 mg clopidogrel (n = 7) or 180 mg ticagrelor (n = 4) via a nasogastric tube. As soon as the pCONus® was deployed, 500 mg acetylsalicylic acid was given intravenously. Patient No. 2 suffered severe SAH (Fisher IV) due to a ruptured AcomA aneurysm. The poor clinical condition (HH V) was in favor of an endovascular treatment and the patient was medicated only with 1000 mg acetylsalicylic acid intravenously.

In the patient No. 17, a local thrombus formation was observed during the procedure, which completely resolved after administration of a bolus dose of

eptifibatide. After this case, if a patient did not receive a loading dose before the treatment, a body weight adapted bolus dose of eptifibatide was applied intravenously per protocol.

After SAH, Patient No. 44 had a diagnostic angiography the day of the hospital admission. After angiographic confirmation of a wide-necked basilar tip aneurysm and subsequent consultation with the neurosurgeon on call, the patient was scheduled for endovascular treatment for the forthcoming day. The patient received 500 mg acetylsalicylic acid IV and 180 mg ticagrelor *per os* early in the morning. The treatment was performed 5 hours later after confirmation of sufficient inhibition of the platelet function.

Table 6: Premedication in elective cases (n = 37) prior to pCONus® assisted coil occlusion of a *non-ruptured* intracranial aneurysm.

Premedication	n	%
ASA p.o. and clopidogrel p.o.	27	73
ASA p.o.and ticagrelor p.o.	4	10.8
ASA p.o., clopidogrel p.o. and ticagrelor p.o.	4	10.8
ASA p.o., clopidogrel p.o. and prasugrel p.o.	2	5.4

Table 7: Premedication in emergency cases (n = 13) prior to pCONus® assisted coil occlusion of a *ruptured* intracranial aneurysm.

Premedication	n	%
ASA i.v. and clopidogrel p.o.	5	38.5
ASA i.v., ticagrelor p.o. and eptifibatide i.v.	4	30.8
ASA i.v., clopidogrel p.o. and eptifibatide i.v.	2	15.4
ASA i.v. and ticagrelor p.o.	1	7.7
ASA i.v.	1	7.7

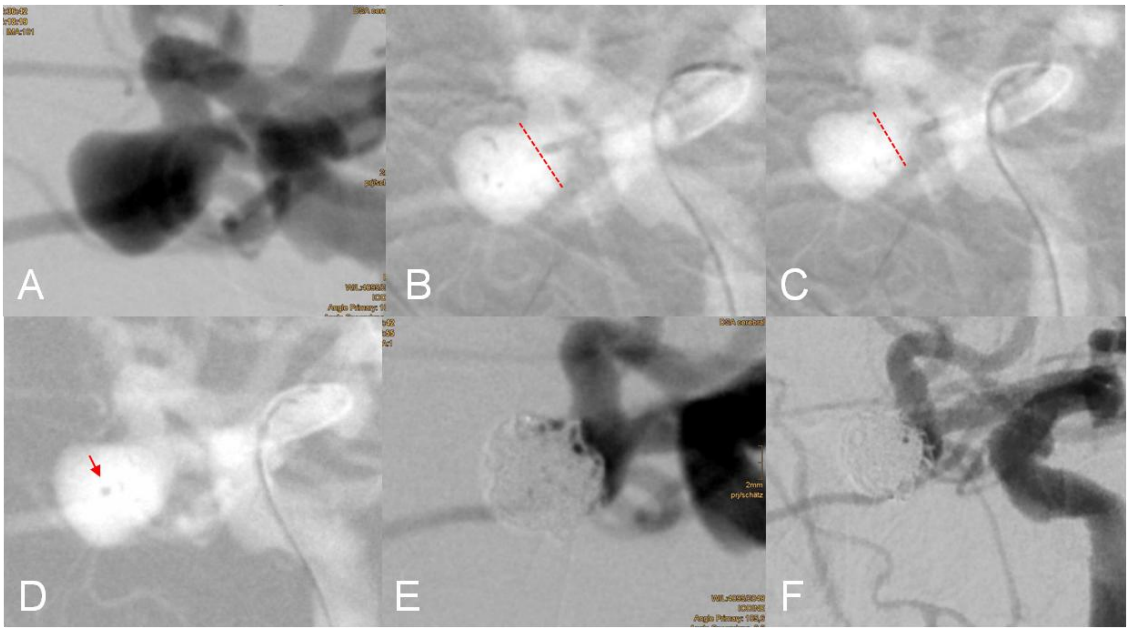
6.1.3 Procedure

All patients were treated under general anesthesia using a biplane DSA unit (Axiom Artis, Siemens). An intravenous bolus of heparin (5,000 IU) and 500 mg acetylsalicylic acid were given at the beginning of the procedure. Activated clotting time was not routinely measured.

Via a femoral access, a 6F or 8F guiding catheter was inserted into the respective cervical vessel. In a suitable working projection, showing the aneurysm neck and the efferent vessels, calibrated measurements were used to determine the neck width, the aneurysm width and the aneurysm height (Brinjikji et al. 2009).

The pCONus® size was selected in a way that a complete coverage of the aneurysm neck by the pCONus® petals could be expected. A 0.021´´ microcatheter (e.g., RapidTransit or Prowler Select Plus, Codman) was chosen. The distal end of the pCONus® was deployed in the middle of the aneurysm fundus, avoiding any impact to the aneurysm wall. As soon as the four petals were fully open, the microcatheter was gently pulled back bringing the pCONus® petals more proximal to the neck of the aneurysm. Without further movement of the pCONus®, the insertion wire of the pCONus® was kept in place and the microcatheter was pulled back with complete deployment of the shaft of the pCONus®. Thereafter a second microcatheter was inserted through the shaft of the pCONus® into the aneurysm fundus (e.g., Echelon10, ev3/Covidien; Excelsior SL10, Stryker). Coil occlusion started with the attempt to create a frame or basket with the first coil (e.g., Morpheus coil, Covidien; Framing coil, MicroVention). The residual space was filled with long and soft coil (e.g., Hypersoft, MicroVention). As soon as the aneurysm fundus was considered completely occluded, the coil catheter was withdrawn and the pCONus® was electrolytically detached (Figure 12).

Figure 12: (A) Unruptured aneurysm of the MCA bifurcation on the left side. (B) The distal end of the pCONus® is deployed in the middle of the aneurysm fundus. (C) As soon as the four pCONus® petals are fully open, the microcatheter is gently pulled back bringing the petals more proximal to the neck of the aneurysm (dotted red line). (D) A second microcatheter is inserted through the shaft of the pCONus® into the aneurysm fundus. (E) Coil-occlusion of the aneurysm (Raymond 1). (F) Angiographic follow-up after 3 months showing complete occlusion of the aneurysm (Raymond 1).



6.1.4 Postprocedure management

SAH patients were managed according to widely accepted SOPs. Patients with unruptured aneurysms underwent a MRI examination within 48 hours after the procedure. If MRI was not possible, a CT scan was performed. Angiographic follow-up was scheduled for 3 and 9 months after treatment and yearly thereafter.

Post-procedural medication (Table 8) included a daily lifetime dose of 100 mg acetylsalicylic acid and 75 mg clopidogrel for three months. Nonresponders to clopidogrel or patients directly premedicated with another

antiplatelet drug were continued with 10 mg prasugrel (n = 3) or 2x 90 mg ticagrelor (n = 11).

Table 8: Postmedication after pCONus® assisted coil treatment of an intracranial aneurysm (n = 50).

Postprocedural medication	n	%
ASA p.o. & clopidogrel p.o.	36	72
ASA p.o.& ticagrelor p.o.	11	22
ASA p.o.& prasugrel p.o.	3	6

6.1.5 Procedure and postprocedural evaluation

Patients, aneurysms and procedures were evaluated for:

- age, gender, history of previous subarachnoid hemorrhage, previous treatments of the aneurysms, treatment during the acute phase after subarachnoid hemorrhage, and clinical condition at the time of treatment according to the mRS (Jenneth et al. 1975)
- ruptured or unruptured nature of the target aneurysm, long axis, short axis, neck size, and location of the aneurysm
- ability to insert and deploy the pCONus® properly
- occurrence of aneurysm or target vessel perforation due to the pCONus® usage
- ability to catheterize the aneurysm through the deployed pCONus®
- coil retention inside the aneurysm, as a function of the pCONus®, and its ability to prevent the inadvertent occlusion of the efferent vessels
- degree of aneurysm occlusion achieved by coiling (Roy et al. 2001)
- clinical condition of the patient at discharge.

At follow-up patients and aneurysms were clinically and angiographically evaluated for:

- stability of aneurysmal coil occlusion (Raymond et al. 2003)
- occurrence of intimal hyperplasia inside the stent shaft
- ability to perform re-coiling of partially reperfused aneurysms as far as necessary, in the presence of the previously implanted pCONus®
- clinical condition of the patients during follow-up.

6.2 Results

This retrospective series includes 50 consecutive patients, 25 female (50%) and 25 male (50%), and 50 aneurysms treated with pCONus® between February 2012 and April 2014. The median age was 59.3 years (range: 25-76 years).

The medians and ranges for the aneurysm sizes were: neck width 6.2 mm (range: 2.8 – 13.8 mm), fundus width 6.6 mm (range: 3.2 – 15.5 mm), fundus height 7.8 mm (range: 2.7 – 17.4 mm).

The location of the treated aneurysms is summarized in table 9. 39/50 aneurysms (78%) were located in the anterior circulation, and 11/50 (22%) in the posterior circulation.

Of these 50 aneurysms, 18 were right-sided aneurysms, 10 aneurysms on the left side, and 22 aneurysms located in the midline.

Table 9: Location of 50 aneurysms treated with pCONus® assisted coil occlusion.

Location	n	%
Middle cerebral artery	27	54
AcomA	11	22
Basilar tip artery bifurcation	9	18
Anterior cerebral artery (A2-segment)	1	2
Basilar artery trunk (fenestration)	1	2
Posterior cerebral artery (P2- segment)	1	2

Of the 50 treated aneurysms, 28 (56%) were found incidentally, 13 (26%) were detected due to an acute subarachnoid hemorrhage from the treated aneurysm, 2 (4%) caused cerebral ischemia (transient ischemic attack - TIAs), 1 (2%) was related with blurred vision, and 1 (2%) was detected due to a seizure (Table 10). Five out of 50 aneurysms (10%) had been previously treated by coiling and showed a major recurrence, which required retreatment, 2 of them from previously ruptured aneurysms.

Table 10: Symptoms related to 50 intracranial aneurysms treated by pCONus® assisted coil occlusion.

Initial symptoms	n	%
No symptoms	33	66
Acute SAH	13	26
TIAs	2	4
Seizure	1	2
Blurred vision	1	2

The treatment of ruptured aneurysms was mostly carried out within the first two days after the initial subarachnoid hemorrhage (median 1.7 days, range: 0 - 7 days).

The distribution of Hunt and Hess grades at the time of treatment in the ruptured aneurysm group (n = 13) is shown in table 11.

The distribution of Fisher grades at the time of treatment in the ruptured aneurysm group (n = 13) is summarized in table 12.

Thirty-seven aneurysms (74%) were unruptured. The clinical condition of the concerning patients was graded according to the modified Rankin Scale (mRS) at the time of treatment in the unruptured aneurysm group (n = 37) and is listed in table 13.

Table 11: Distribution of Hunt and Hess grades after the rupture of 13 intracranial aneurysms prior to pCONus® assisted coil occlusion.

Clinical condition (Hunt & Hess)	n	%
HH I	4	30.8
HH II	3	23.1
HH III	1	7.7
HH IV	4	30.8
HH V	1	7.7

Table 12: Amount of intracranial blood, graded according to the Fisher grading scale, in 13 ruptured aneurysms that were treated with pCONus® assisted coil occlusion.

Amount of blood on CT scan (Fisher)	n	%
Fisher I	0	0
Fisher II	2	15.4
Fisher III	2	15.4
Fisher IV	9	69.2

Table 13: Clinical condition of 37 patients with unruptered intracranial aneurysms prior to pCONus® assisted coil occlusion.

modified Rankin Scale (mRS)	n	%
mRS 0	32	86.5
mRS 1	1	2.7
mRS 2	2	5.4
mRS 3	1	2.7
mRS 4	1	2.7
mRS 5	0	0

In 45 out of 50 aneurysms (90%), a single pCONus® alone retained the coils inside the aneurysm sac and protected the efferent vessels from occlusion.
In two patients (4%) two pCONus® deployed in a crossing position were necessary to protect the neck region of the aneurysm. For this purpose, a special version without distal nylon cross was used to allow telescoping of the two devices. Patient No. 26 (Figure 13) presented a large unruptured aneurysm of the basilar tip, which incorporated both PCAs and both SCAs origins. The aneurysm was directed posteriorly towards the brainstem, with a 90° angle between the axes of the basilar artery and the aneurysm fundus. Patient No. 43 (Figure 14) presented a large unruptured aneurysm of the right MCA. The aneurysm neck was asymmetric with the superior trunk of the right MCA originating from the aneurysm sac. In both cases, two pCONus® were deployed in a crossing position to protect the neck region of the aneurysm.
In three patients (6%) another device aside from pCONus® was necessary to prevent the occlusion of the efferent vessels. Patient No. 19 (Figure 15) presented a giant partially thrombosed MCA aneurysm. The already deployed 12 mm pCONus® was withdrawn because the stabilization of the coils appeared insufficient to protect both M2 origins. A 16 mm TriSpan coil (Boston Scientific) was inserted and the petals were subsequently intermingled with the coil loops. This construct of TriSpan and coils was fixated by the pCONus®, which was redeployed at the end of the procedure. Patient No. 23 (Figure 16) presented a fusiform upper basilar trunk aneurysm with both PCAs and SCAs originating from the posterior aspect of the aneurysm. A 12 mm pCONus® was inserted into the aneurysm but appeared alone insufficient to protect the PCAs and SCAs origins. Two Y-crossing Solitaires only in both PCAs were expected to incompletely protect the SCAs, with difficult control of the coil occlusion of the saccular component of the aneurysm. After positioning of the pCONus® petals within the lumen of the aneurysm, the left PCA was catheterized and a Solitaire AB stent (4/20 mm) was deployed from the left PCA to the basilar artery trunk.

After the detachment of this stent, the right PCA was catheterized through the shaft of the pCONus® and the first Solitaire AB stent and a second stent was deployed from the right PCA to the basilar artery trunk. The resulting structure of pCONus® and Y-stenting was stable and allowed for a well-controlled coil occlusion of the aneurysm protecting both PCAs and SCAs. Patient No. 29 presented a wide-necked AcomA aneurysm. An Enterprise Stent was deployed from the left A1 to the left A2-segment in order to protect the left ACA. Thereafter, 6 mm pCONus® was inserted into the aneurysm from the right side allowing aneurysm occlusion.

Figure 13: Patient No. 26: 25 year old male with a large unruptured basilar tip aneurysm. (A) Axial T2WI shows the mass effect to the brainstem. (B) Initial 3D reconstruction image of rotational angiogram shows both PCAs and SCAs originating from the aneurysm sac. (C) Right vertebral artery injection, lateral view, demonstrating the aneurysm. (D) DynaCT showing the crossing pCONus® (2x 15 mm). (E-F) Right vertebral artery injection, frontal and lateral view, after coiling.

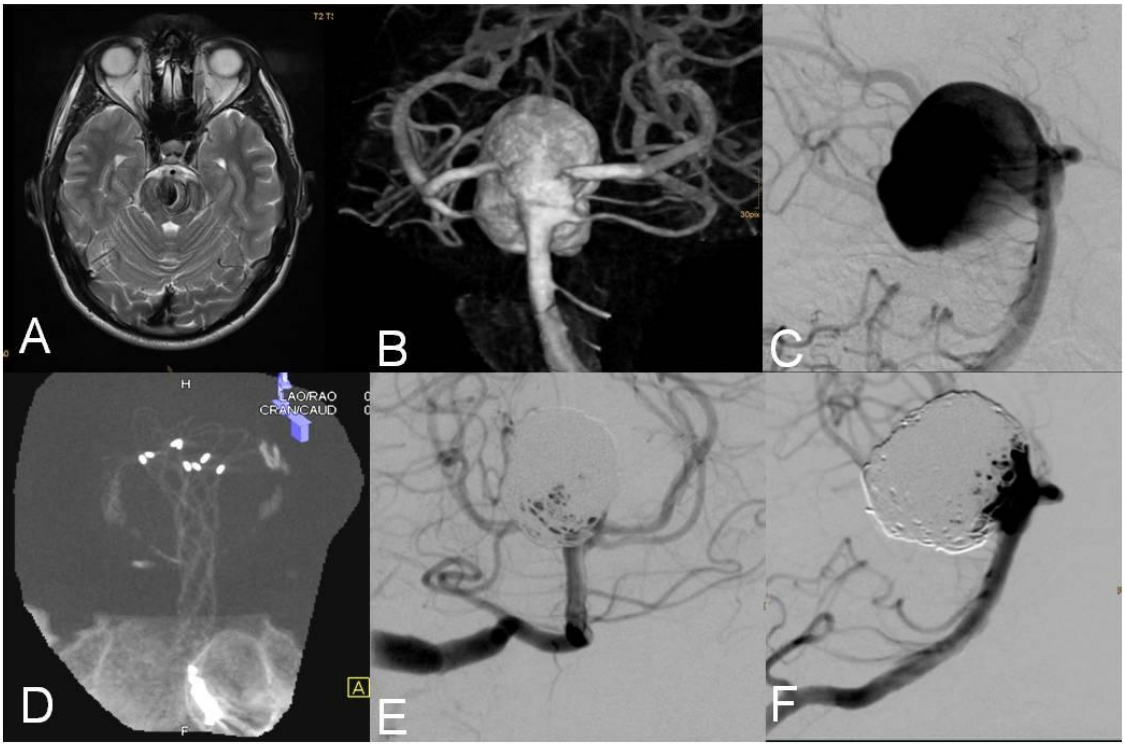


Figure 14: Patient No. 43: 68 year old female with a large unruptured MCA-aneurysm. (A) Right carotid artery injection showing the aneurysm. (B) Roadmap in the working projection with a 15 mm pCONus® in place. The superior trunk of the MCA is still not protected from coil protrusion (black asterisk). (C) Unsubtracted view, after deployment of a second 12 mm pCONus®, showing the crossing pCONus®. (D) Right carotid artery injection after coil occlusion.

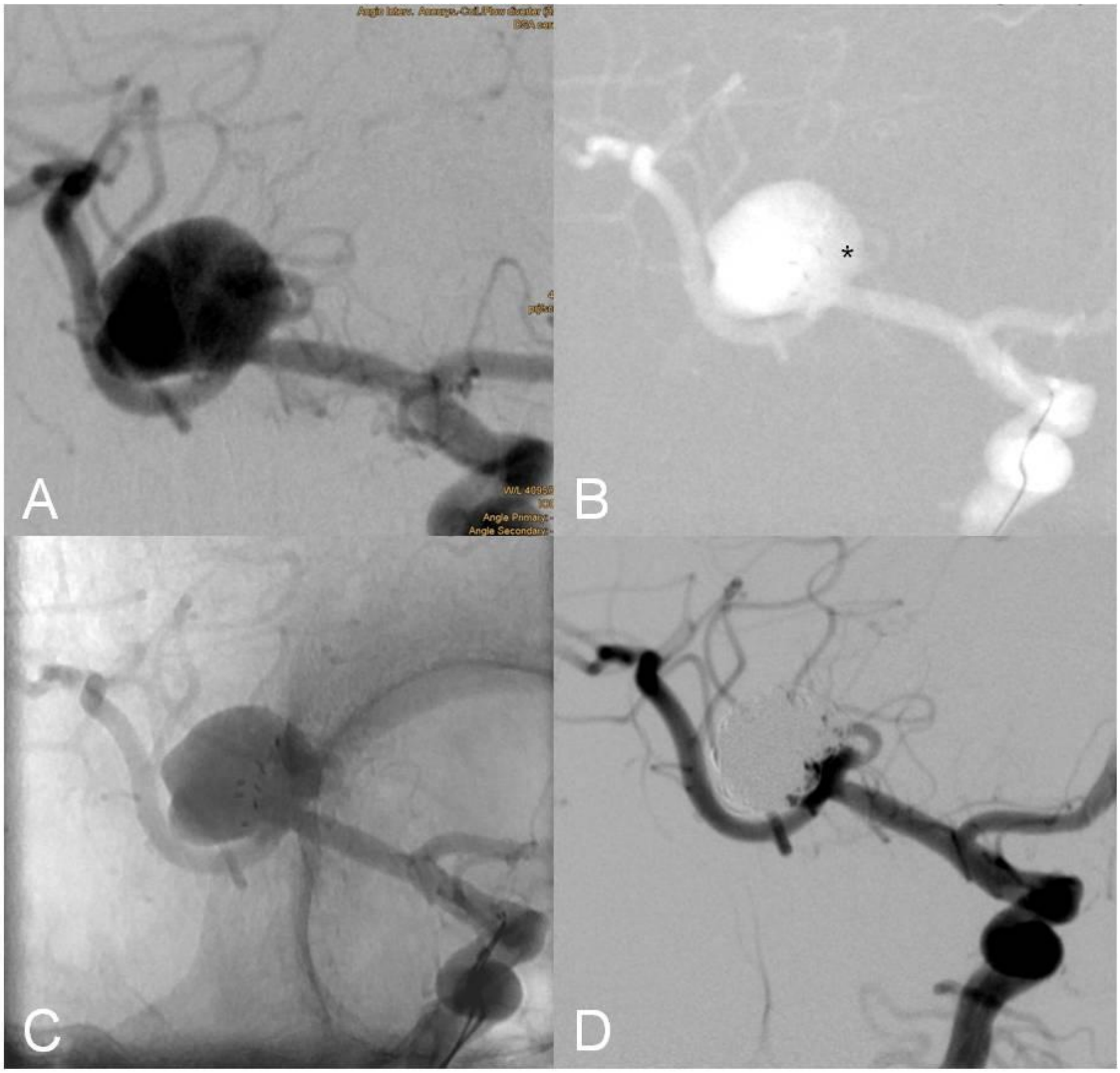


Figure 15: Patient No. 19: 51 year old male with a large unruptured symptomatic (seizure) MCA-aneurysm on the right side. (A) Right carotid artery injection showing the aneurysm. (B) Axial T2WI showing a large thrombosed compartment. (C) Right carotid artery injection after TriSpan and pCONus® assisted coil occlusion.

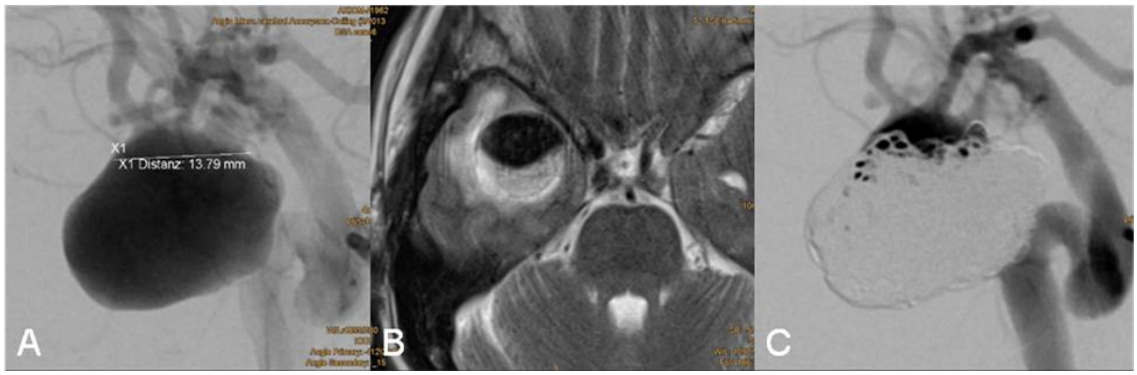
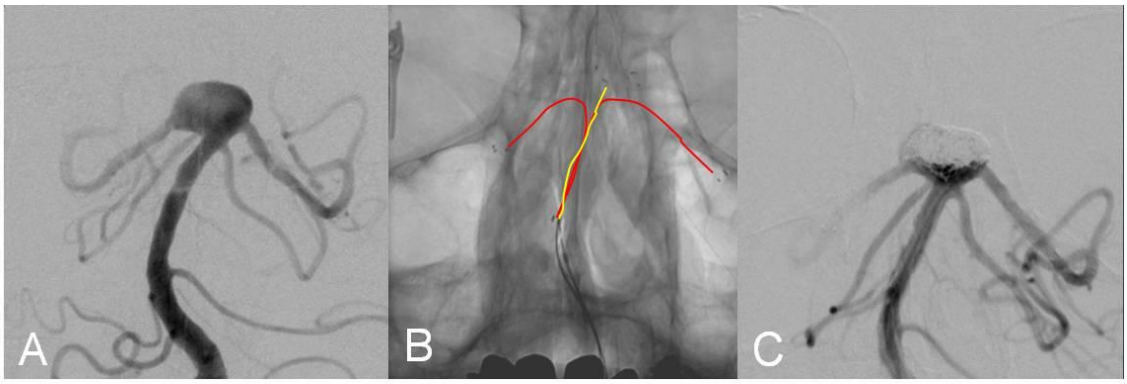


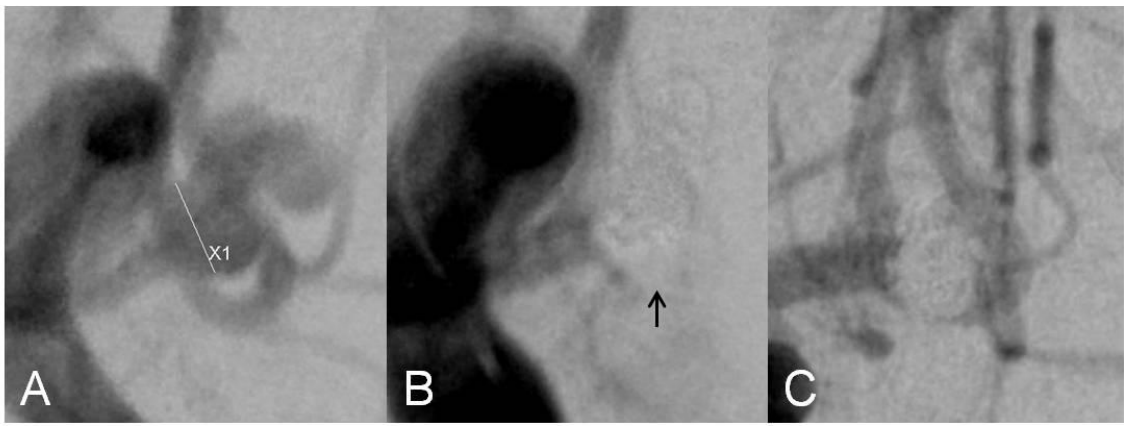
Figure 16: Patient No. 23: 62 year old female with a large unruptured basilar tip aneurysm on the right side. (A) Left vertebral artery injection showing the aneurysm, which incorporates the right SCA and both PCAs. (B) Unsubtracted view demonstrates the pCONus® (dotted yellow line) and the Y-configuration of the 2 Solitaire stents (dotted red lines) extending into both posterior cerebral arteries from the basilar trunk. (C) Left vertebral artery injection after coiling.



Insertion and controlled deployment of pCONus® was possible in all cases (100% technical success). Neither access failure nor aneurysm or vessel perforation were encountered. Catheterization of the aneurysms through the shaft of the deployed pCONus® was possible in all cases and did not cause any difficulty. No coil loop protrusion between the petals of the pCONus® was encountered.

In only 1 patient (Patient No. 17) a local thrombus formation was observed during the procedure, which resolved with a body weight adapted bolus dose of Eptifibatide (Figure 17). No another complication was observed during the treatment.

Figure 17: Patient No. 17: 34 year old female with a ruptured AcomA aneurysm on the right side. (A) Right carotid artery injection showing the aneurysm. (B) Occlusion of the left ACA after pCONus® assisted coil occlusion (black arrow). (C) Complete recanalization after intravenous administration of a body weight adapted bolus dose of eptifibatide.



The 3-points Raymond scale (Raymond et al. 2003) was used to evaluate the initial occlusion rate. In 22/50 aneurysms (44%) the occlusion rate was graded as class 1 (“complete”), 15/50 aneurysms (30%) were graded as class 2 (“neck remnant”) and 13/50 aneurysms (20%) as class 3 (“residual fundus perfusion”). In patients 3 and 18 an early second treatment within

the first week was necessary to achieve the occlusion of the aneurysm (Table 14).

Table 14: Initial angiographic results in 50 intracranial aneurysms after pCONus® assisted coil occlusion using the 3-points Raymond scale.

Initial occlusion rates	n	%
1 – complete	22	44
2 - neck remnant	15	30
3 - residual fundus perfusion	13	26

Fourty-one patients (82%) underwent either CT (n = 11) or MRI (n = 30) examination within a few days after the procedure (Table 15).

New DWI lesions on MRI occurred in 18/30 patients (60%) and remained clinically silent in all except 4 patients. Four out of 50 patients (8%) showed transient focal neurological symptoms after the treatment, which resolved within one week. No clinically evident complications with permanent neurological deficit or death related to the pCONus® deployment or coil occlusion occurred.

Of the 50 patients treated, 5 patients died. Death of patients No. 2, 4 and 20 was due to a severe SAH; patient No. 11 recovered from her SAH and died due to another disease; patient No. 29 died due to concomitant disease (Table 16).

Table 15: Post-procedure imaging in 50 patients after the pCONus® assisted coil occlusion of intracranial aneurysms.

Imaging	n	%
None	9	18
MRI	30	60
CT scan	11	22

Table 16: Clinical outcome of 50 patients after the treatment of intracranial aneurysms with pCONus® assisted coil occlusion.

Clinical outcome	n	%
New DWI lesions	18	60
TIAs	4	8
Permanent neurological deficit related to treatment	0	0
Previous neurological deficit	5	10
Death related to the endovascular treatment	0	0
Death related to the SAH	3	6
Death related to other diseases	2	4

Angiographic follow-up was available in 40/50 patients (80%). The first follow-up examination was carried out after 104 days (median). The last follow-up examination was performed after 276 days (median) (Table 17).

The first angiographic follow-up showed complete occlusion in 23/40 aneurysms (57.5%), a neck remnant in 8/40 aneurysms (20%), and an aneurysm remnant in 9/40 aneurysms (22.2%).

Of these 40 aneurysms, the angiographic follow-up showed an improvement of the degree of occlusion of at least 1 point on the Raymond grading scale in 12 aneurysms (30%), while 23 aneurysms (57.5%) remained unchanged. A reduced degree of occlusion was observed in 5 aneurysms (12.5%) (Table 18).

Amongst the 9 aneurysms with Raymond 3 at follow-up, five of them were deteriorated from a previous aneurysm remnant. Most of them were large or giant, partially thrombosed aneurysms after initial partial occlusion.

Table 17: Occlusion rate (Raymond scale) of 40 intracranial aneurysms at 276 days (median) after pCONus® assisted coil occlusion.

Occlusion rates at FU (Raymond-Scale)	n	%
1 - complete	23	57.5
2 - neck remnant	8	20
3 - residual fundus perfusion	9	22.2

Table 18: Evolution of the occlusion rate of 40 intracranial aneurysms during the angiographic follow-up at 276 days (median) after the pCONus® assisted coil occlusion.

	Raymond 1 (n = 23)	Raymond 2 (n = 8)	Raymond 3 (n = 9)
From initial 1	13	1	2
From initial 2	7	5	2
From initial 3	3	2	5

At follow-up no intimal hyperplasia inside the pCONus® shaft was observed. Coil-migration was observed in one patient, who remained asymptomatic (Figure 18).

Eight out of 9 aneurysms with reperfusion were re-treated by coiling and one is still scheduled (Table 19). In these retreated aneurysms, microcatheter access to the aneurysm through the implanted pCONus® was again possible without any difficulty. The coil retention by the pCONus® was as reliable as during the initial procedure (Figure 19).

Table 19: Aneurysms with reperfusion.

Patient No.	Location	initial RS	Time to FU (months)	RS prior / after re-treatment
No. 10	RPCA	1	12 months	3 / 1
No. 13	RMCA	3	10 months	3 / 3
No. 16	LMCA	2	4 months	3 / 1
No. 19	RMCA	3	6 months	3 / 3
No. 21	RMCA	2	13 months	3 / 2
No. 23	BA	3	10 months	3 / 2
No. 25	RMCA	3	10 months	3 / scheduled
No. 26	BA	3	12 months	3 / 3
No. 39	AcomA	1	4 months	3 / 2

Figure 18: Patient No. 7: 66 year old male with a reperfusion of a previously ruptured AcomA aneurysm. (A) Left carotid artery injection showing the aneurysm before intervention. (B) Final run after treatment with pCONus® (Raymond 3). (C) Angiographic follow-up after 3 months shows the complete occlusion of the aneurysm (Raymond 1) as well as a partial migration of a coil into the A1-segment of the left side. Vessel occlusion was not observed. The patient is asymptomatic.

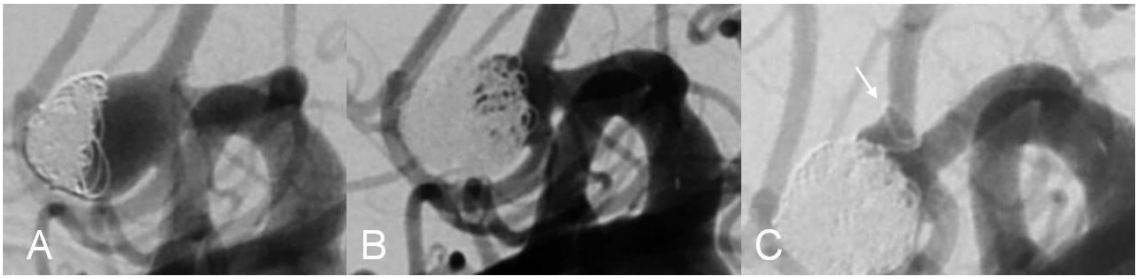
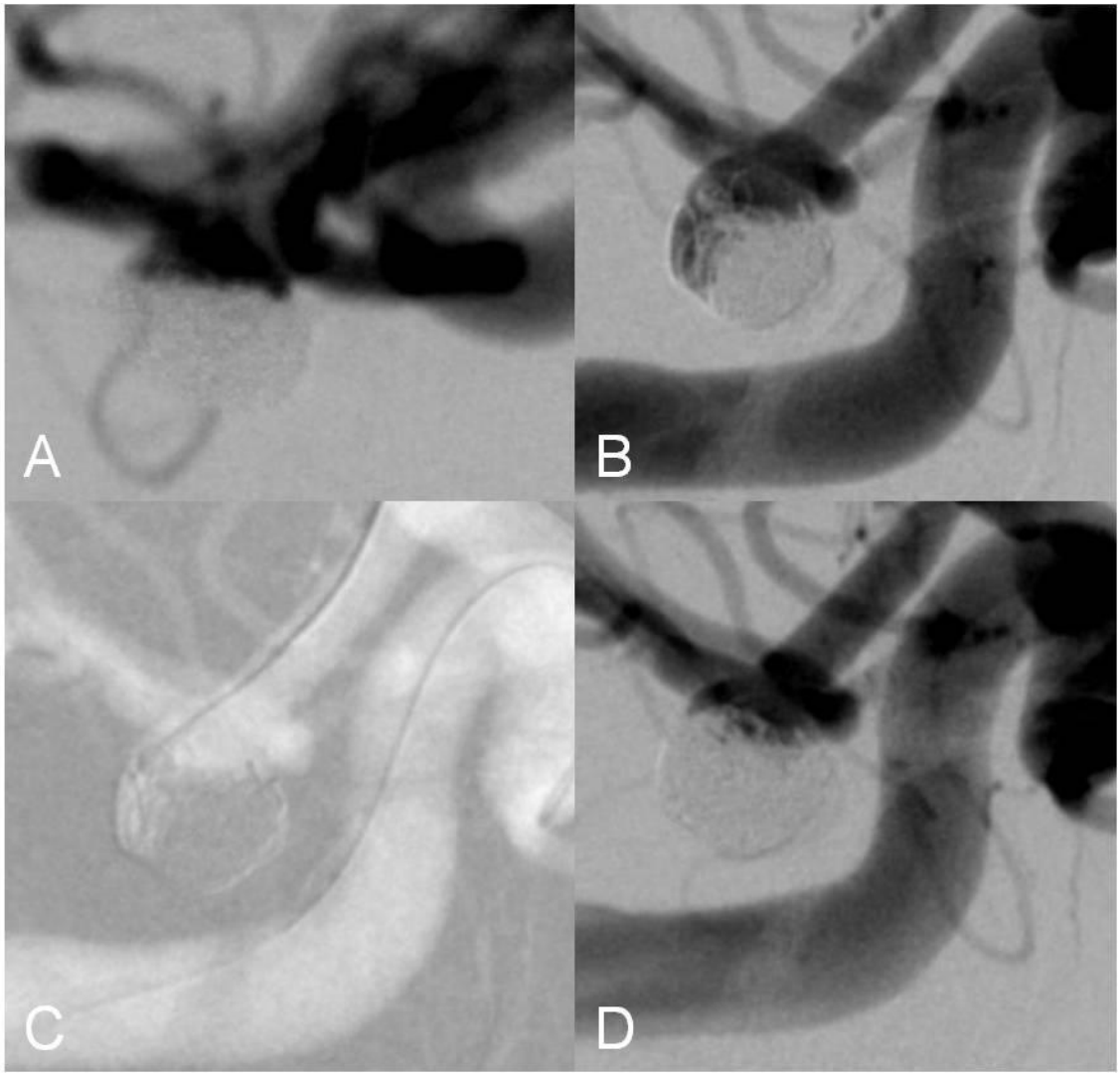


Figure 19: Patient No. 21: 62 year old male with an unruptured MCA-aneurysm on the right side. (A) Right carotid artery injection showing the final run after treatment of the aneurysm with pCONus® (Raymond 2). (B) Angiographic follow-up after 12 months shows a major reperfusion (Raymond 3). (C) Road-map picture showing the access of the microcatheter into the aneurysm through the implanted pCONus®. (D) Final run after re-coiling (Raymond 2).



7. Discussion

Early experience has shown that unassisted coiling works best in aneurysms with a well-defined neck, ideally not wider than 3 mm.

Coiling of intracranial aneurysms is a useful alternative to surgical clipping. Complex wide-necked bifurcation aneurysms, however, present a difficult challenge to neurointerventionalists because of their anatomic features.

7.1. 3D Coils

Three-dimensional coils were an early and a relatively easy-to-use solution for all wide neck aneurysms (Cloft et al. 200, Vallée et al. 2005). 3D coils alone work best in long aneurysms, but frequently do not find enough stability in shallow aneurysms and in those without any neck.

During pCONus® procedures, the first coil should be a solid 3D coil with an appropriate diameter, which might be intermingled with the petals of the pCONus®.

7.2. "Dual-catheter" technique

The "dual-catheter" technique is a straightforward and inexpensive strategy for the treatment of WNBAs (Baxter et al. 1998). A first catheter is used to deploy a framing coil (e.g., a 3D coil). This coil will, however, not be detached immediately. Subsequent coils will be inserted via a second microcatheter. A known risk of the "dual catheter technique" is related to the phenomenon that the first coil may not entirely protect the vessel bifurcation. While the first coil and subsequent coils remain controllable until they are detached, displacement of already detached coils by subsequent coils remains a serious issue. Good results with the dual or multiple microcatheter technique were reported by Kwon et al. but it is not perfect for WNBAs whenever the framing coil(s) provide insufficient neck protection.

A better protection of the aneurysm neck/parent vessel region might be provided by pCONus® but also with this device the use of small and short

coils adjacent to the aneurysm neck carries a potencial risk of coil displacement into the parent vessel.

7.3. "Balloon-remodeling" technique

The "balloon-remodeling" technique was initially advocated for sidewall aneurysms (Moret et al. 1997). The development of more flexible and atraumatic compliant balloon catheters allows today for the simultaneous use of multiples balloons (Baldi et al. 2003, Lubicz et al. 2004, Arat et al. 2005). However, risks of this technique are well known. Catheterization of the efferent vessels of a bifurcation can be very difficult and the presence of two or three catheters in the parent vessel unavoidably causes a temporary interruption of the cerebral blood flow and may cause hemodynamic compromises and/or thromboembolic events. The coverage of the aneurysm neck, once the balloons are inflated, is solid, but overinflation may cause vessel dissection or even rupture, and the risk of aneurysm rupture due to coil-induced pressure on the aneurysm wall may be increased (Spiotta et al 2001). Besides, the balloon coverage is temporary. If the coils, introduced under balloon protection, do not stabilize each other, balloon deflation may be followed by collapse of the coils out of the aneurysm into the parent vessel.

In the available literature, positive reports for balloon remodeling can be found (Lubicz et al. 2004, Spiotta et al. 2011, Gallas et al. 2005, Layton et al. 2007). Serious warnings were also brought forward. Sluzewski et al. (Sluzewski et al. 2006) reported on the basis of 71 procedures a morbidity and mortality for balloon remodeled aneurysm coiling of 14%, without improved stabilization of the coil occlusion during the subsequent course. In a small series of 43 aneurysms reported by Cronqvist et al. (Cronqvist et al. 2005), 5 major complications occurred among 11 balloon remodeling procedures. Pierot et al. (Pierot et al. 2012) recently published a review in favor of balloon remodeling. However in other studies, follow-up occlusion rates post stenting are consistently better than after balloon remodeling

(Chalouhi et al. 2013).

In our practice, we use balloon remodeling for proximal sidewall aneurysms (e.g., in cavernous and paraophthalmic location). We consider the use of multiple balloons as risky in general and often not justified.

In comparison with balloon remodeling in WNBAs, the use of pCONus® is easier and more controllable, without interruption of the blood flow and without the need to catheterize the efferent vessels. The need for dual medical antiaggregation for pCONus® is certainly a drawback, especially in ruptured aneurysms.

7.4. "Stent-remodeling" technique

Neuroform (Stryker), Enterprise (Codman), Leo+ (Balt), Solitaire (ev3/Covidien) and LVIS (MicroVention) are self-expanding stents for the treatment of WNBAs. These stents show significantly different features, including stent design, cell size, radial force and thrombogenicity (Krischek et al. 2011). Placing a stent over an aneurysm orifice may cause a neck diameter reduction (Adel et al. 2010). Stenting also improves and stabilizes the occlusion rate of wide neck aneurysms after coil treatment (Lubicz et al. 2009, Piotin et al. 2010). Stent assisted coiling can, however, be technically demanding (Henkes et al. 2004) and may result in severe complications.

In a retrospective analysis of a large series with 216 stented (predominantly with Neuroform) and coiled aneurysms, Piotin et al. (Piotin et al. 2010) found rates for procedure related permanent neurological morbidity and mortality of 7.4% and 6%, respectively. Stent deployment in a vessel bifurcation will straighten the vessels. This effect is not the same for all stents. Closed-cell stents straighten more than open-cell stents (Gao et al. 2012). In general this phenomenon may improve the hemodynamic situation in bifurcation aneurysms. In their literature survey on stent-assisted aneurysm coiling Shapiro et al. evaluated data from 39 articles with 1517 patients (Shapiro et al. 2012). They found a 9% rate of stent-related technical issues, 4% failure of stent deployment, 19% overall procedure complication rate, and 2.1%

periprocedural mortality.

The bridging of a vessel bifurcation by a single stent may provide insufficient coil retention. A more robust vessel reconstruction can be achieved, if stents are deployed in both branching vessels (“Y-stenting”). These stent reconstructions are mostly to be followed by coil occlusion of the aneurysm.

Sani et al. report on the Y-stenting of a MCA aneurysm using Neuroform (Sani et al. 2005). Chow et al. and Thorell et al., as well as, Perez-Arjona et al. and Lozen et al. focused on Y-stenting and coiling for the treatment of basilar bifurcation aneurysms (Chow et al. 2004, Thorell et al. 2005, Cho et al. 2007, Perez-Arjona et al. 2004, Lozen et al. 2009). Rohde et al. used Enterprise stents for this procedure (Rohde et al. 2010).

For the combined use of different stents (e.g., Neuroform and Enterprise), the term “hybrid Y-configured stenting” was coined (Akgul et al. 2011). Alurkar et al. and Lee et al. used Y-stenting (Neuroform or Enterprise) for ruptured aneurysms in the acute phase after SAH without complications (Alurkar et al. 2012, Lee et al. 2012).

The inherent risks of Y-stenting become obvious from the retrospective analysis of a small series of 19 patients who underwent Y-stent assisted coiling of their aneurysms (Spiotta et al. 2011). The incidence of complications at the initial treatment was 31.6%. Delayed thromboembolic complications were encountered in 10.5%. In a recently published multicenter trial, Fargen et al. reported on 45 (mostly basilar apex) aneurysms treated by Y-stenting and coiling with a rate of 84% of complete occlusion or neck remnant and an 11% procedural complication rate (Fargen et al. 2013).

Cekirge et al. were the first to emphasize the hemodynamic effect of Y-stenting with Enterprise (Cekirge et al. 2011). They observed reduced perfusion and final thrombosis of WNBAs after Y-stenting with Enterprise without coiling. One of the reasons why stents such as Enterprise with relatively large cells become hemodynamically active once they are used in crossing fashion is the compression and deformation of the stents at their

intersection (Zhao et al. 2012). If there is no jailed catheter inside the aneurysm, catheterization for coiling through crossing Enterprise stents can be very difficult.

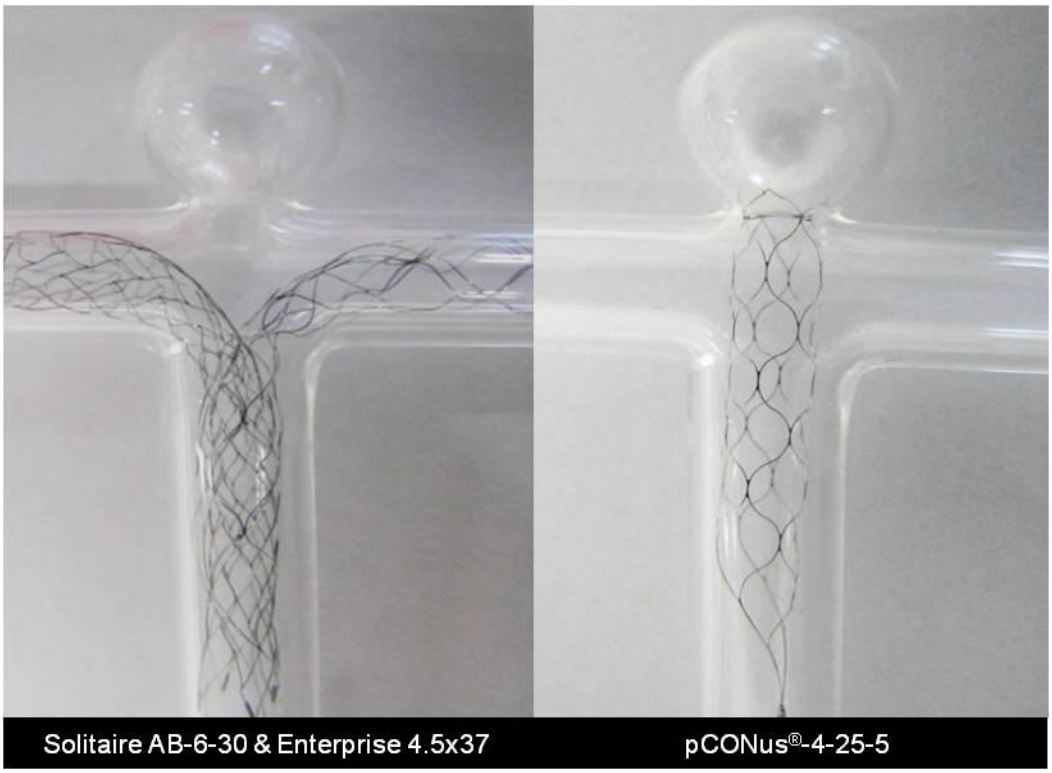
If the mutual compression of the crossing stents could be avoided, one stent can be completely deployed in one of the two efferent vessels and the second one is then deployed in a way that its proximal end is immediately adjacent to but not crossing the first stent (“non overlapping Y-configuration stenting”) (Cho et al. 2012).

For Y-stenting, hemodynamic effects are related to the metal construct in the parent artery and the alteration of the geometry of the efferent vessels. The formation of neointima over crossing stents appears at least unlikely.

If an aneurysm has afferent and efferent vessels on both sides (e.g., AcomA aneurysms with bilaterally patent A1 segments), two stents can be deployed without direct contact, protecting the bifurcation on either side (“parallel stenting”, “opposite L configuration”).

An even denser coverage of the aneurysm neck is achieved, if the stents cross each other (“X-stenting”). Saatci et al. report a series of 5 patients with ACA aneurysms, treated with X-crossing stent assisted coiling (Saatci et al. 2011). Stents were deployed from one A1 segment to the contralateral A2, crossing each other in front of the aneurysm orifice. They used the “jailed catheter” technique for the coil catheter and, despite loose initial packing, found complete occlusion at 6 months follow-up DSA without in-stent stenoses. Patients received dual medical platelet inhibition for 6 months. Similar procedures with X-crossing stents were described by other authors (Lazzaro et al. 2011, ZeleŇák et al. 2011). With Y- or X-crossing stents, significantly more stent material is placed in the blood stream than a pCONus® deployment (Sychra et al. 2011) (Figure 20). However, the advantage of permanently modifying the angulation of the vessel bifurcation observed after stenting, cannot be expected from a pCONus® treatment.

Figure 20: Comparison between pCONus® and Y-crossing stent. pCONus® provides significantly less device material in bifurcation and especially in outflowing vessels.



7.5. TriSpan neck-bridging device

The TriSpan neck-bridging device (Boston Scientific) was made of 3 nitinol loops (“petals”). These loops were coated with polyxylylene. Both ends of each petal were fixed to a central platinum coil (“umbilicus”, “stem”). This “umbilicus” was attached to a stainless steel insertion wire. Detachment of the TriSpan from the wire was possible using the GDC method of direct current induced rapid corrosion. The compressed device was accepted by a 0.021 inch inner diameter microcatheter. It was positioned just beyond the level of the neck of the target aneurysm. Upon withdrawal of the microcatheter, the petals of the TriSpan opened similar to a flower blossom. The device was kept in this position but change or correction of the position and even withdrawal was possible. Once the device was properly placed, a second microcatheter was inserted into the aneurysm fundus between the TriSpan petals and used for subsequent coil occlusion. The electrolytical detachment of the device was mostly kept as the

last step of the procedure.

Experimental (Turk et al. 2002, Raymond et al. 2002) and early clinical results (Chan et al. 2004) were promising. Raymond et al. treated 25 aneurysm patients, and TriSpan deployment failed in only 2. Complete occlusion was achieved in 3/25, a neck remnant was found in 13/25 and a residual aneurysm perfusion in 7/25. Two patients had device related ischemic complications. DSA follow-up in 16 patients showed only 4 completely obliterated aneurysms and 12 residual or recurrent aneurysm perfusions (Raymond et al. 2001). De Keukeleire et al. reported on 14 patients treated with this device with a complication rate of 37.5%, associated with a low primary complete occlusion rate (12.5%) and a high recurrence rate. A specific concern was thromboembolic events, presumably related to the large foreign body surface in conjunction with inconsistent medical antiaggregation (De Keukeleire et al. 2008).

The issues with TriSpan were multifold. Physician inexperience, lack of adequate training and proctoring contributed to the known issues. The aneurysms TriSpan was made and used for were anatomically difficult lesions. The procedures frequently gained an unusual complexity (Henkes et al. 2004). The proper deployment of the TriSpan was critical in aneurysms with a significant asymmetry or in the case of a steep angle between the longitudinal axis of the parent vessel and the aneurysm fundus. The TriSpan, once detached, had no further fixation. It was therefore necessary to either stabilize the device at the aneurysm wall or to intermingle coils and TriSpan petals in order to create a self-stabilizing conglomerate. The producing company (Boston Scientific) never gained FDA approval for this device, which certainly was useful but was too difficult for widespread acceptance. In 2007, the production of TriSpan was terminated.

pCONus® adopts functional features of the TriSpan through its distal petals. Similar to TriSpan, pCONus® can be repositioned and/or withdrawn. The positions of the four pCONus® petals (instead of 3 TriSpan loops) are, however, more stable due to their connection with the shaft. While TriSpan procedures were mostly carried out without medical antiaggregation, pCONus® should only

be implanted under dual antiaggregation. Aneurysm asymmetry is of less concern. Due to the firm connection between distal petals and proximal shaft, the device shows a tendency to center itself in asymmetric aneurysms. Similar to the behavior of TriSpan, the ability of pCONus® to retain small coils (i.e., ≤2 mm diameter) inside an aneurysm is poor. The coil occlusion of an aneurysm after pCONus® deployment should be started with at least one 3D coil and should be completed with long and soft coils with a diameter of no less than 3 mm – just as previously with TriSpan. In the case of reperfusion of an aneurysm and endovascular retreatment, a previously detached TriSpan did not provide stability for further coils. Using another TriSpan sometimes solved this. In aneurysms treated with pCONus® assisted coiling, it can be expected that the petals of the first pCONus® remain in the same position, and again prevent coils from displacement in the parent vessel(s).

7.6. "Waffle cone" technique

The term "waffle cone" technique refers to a situation in which a self-expanding stent is deployed with its distal end inside an aneurysm instead of bridging the aneurysm neck.

Neuroform (Horowitz et al. 2006, Yang et al. 2008, Huang et al. 2009, Xu et al. 2011), Solitaire AB (Synchra et al. 2011, Park et al. 2012), Leo+ (Yang et al. 2010) and Enterprise (Gruber et al. 2010) have been used for this purpose.

The "waffle cone" stent deployment may be combined with a dual catheter technique (Park et al. 2012, Gordhan et al. 2010) or with a)-configuration stenting (Cho et al. 2011). In this case, one stent is deployed in the accessible efferent vessel and a second crossing stent is deployed inside the aneurysm.

Conventional stents may have features, which are far from ideal for this purpose. Enterprise for instance has a smaller cell size and less radial force than Solitaire and pCONus® (Krischek et al. 2011). Stent migration has been observed with Enterprise if deployed in the parent vessel (Kelly et al. 2008). The risk of migration is even higher if the distal end of the Enterprise stent is placed inside an aneurysm, with an axial outward force exerted by the coils. The intended use of pCONus® is similar to the "waffle cone" deployment of the

above-mentioned stents, with the difference that pCONus® is made and optimized for this purpose.

The “waffle cone” and pCONus® technique is superior to crossing stents since less material is deployed inside the blood stream (Synchra et al. 2011). The difference between “waffle cone” deployment of conventional stents and the pCONus® is related to the distal embodiment of the devices. The Enterprise stent has flared distal ends. The Solitaire AB has 4 sharp ends with radiopaque markers. Both are potentially more traumatic to the wall of the aneurysm than the wings of the pCONus®. In any case a wide neck aneurysm considered for “waffle cone” stenting or pCONus® reconstruction should have a longitudinal fundus diameter of ≥ 4mm (Huang et al. 2009). Even more important, however, is the fact that pCONus® exerts a more stable coil retention inside the aneurysm than conventional self- expanding stents. Horowitz et al. reported on 6 WNBAs treated with “waffle cone” technique using Neuroform stents (Horowitz et al. 2006). Sychra et al. used Solitaire AB in 6 wide neck bifurcation aneurysms for “waffle-cone” technique (Sychra et al. 2011). The procedure was successful in all patients, but the occlusion rate was limited to Raymond class 2 in all 6 aneurysms. Four patients underwent angiographic follow-up, all showing asymptomatic reperfusion that required retreatment. This retreatment was possible without other remodeling devices since the “waffle cone” Solitaire stents were still in the proper positions. The antiaggregation with Clopidogrel was stopped after 8 weeks without thromboembolic complications.

It has been suggested that “waffle cone” deployment and pCONus® device can worsen the hemodynamic situation by directing the blood stream towards the aneurysm instead of blood flow diverting away from it (Gao et al. 2012, Sychra et al. 2011, Huang et al. 2009). At this moment this is an unjustified concern, which is not supported by experimental or clinical data. Furthermore the results of our in vitro study showed that the intra aneurismal flow remains unchanged after pCONus® implantation. Liu et al. report good results from 10 aneurysm patients who underwent a “waffle cone” stent implantation to assist coil occlusion (Liu et al. 2012). The initial rate of occlusion was adequate in all aneurysms and, as in our series. Angiographic follow-up showed a stable

degree or improvement of occlusion in most aneurysms. An impared occlusion at follow-up was mainly observed in large and giant partially thrombosed aneurysms. None of the aneurysms treated in the acute phase after SAH rebled.

7.7. Intraaneurysmal flow diversion

The concept of intraaneurysmal flow diversion has prompted the development of two similar devices: Woven EndoBridge (WEB) (Sequent Medical) and Luna (nFocus/Covidien). Both devices are spherical implants, made from braided nitinol wires. They are introduced into the aneurysm fundus via a microcatheter and deployed by a slow withdraw of this microcatheter. Due to the shape-memory properties of the nitinol wires, a self-expansion of the device takes place. The structure of the WEB is denser than that of LUNA. Therefore more hemodynamic effect is expected from the WEB device. Both devices can be either pulled back into the microcatheter or detached from their insertion wire.

The WEB was evaluated in an animal model, which confirmed the intended function of the device (Ding et al. 2011). Promising initial clinical results with WEB have been published (Klisch et al. 2011, Pierot et al. 2012).

Intraaneurysmal flow diversion or disruption will most likely play a role in the future practice of the endovascular treatment of WNBAs. There are, however, certain apparent issues with this device. The device itself is more rigid than conventional stents or flow diverters. This can cause friction-related difficulties during the insertion. Sizing of these devices is critical. Therefore, a variety of different sizes and shapes have to be available in order to match all possible anatomic situations. Both devices are less suitable for very large aneurysms and those with irregular shape. As it is mostly the case with the mechanism of flow diversion, the exclusion of an aneurysm from blood circulation is less predictable than after dense coil occlusion. Little is known about the mid- and long-term results with this device and aneurysm regrowth after WEB occlusion has been reported (Wallner et al. 2012). In the case of recurrent or persistent perfusion of an aneurysm treated with these devices, re-treatment can be difficult.

7.8. Pulsar Vascular Aneurysm Neck Reconstruction Device

The “Pulsar Vascular Aneurysm Neck Reconstruction Device” (PVANRD), previously named “PulseRider Neck Reconstruction Device” (Pulsar Vascular) is a bifurcation stent that can be implanted in intracranial vessel bifurcations in front of wide neck aneurysms. The device is used outside the aneurysm sac and should support coil occlusion. The implant is attached to wires that provide stability in the vessel. Turk et al. (Turk et al. 2012) report a good performance of the device in an animal model. Clinical data is not yet available. The main issue of this device is the control of orientation and position in the parent vessel bifurcation and in relation to the aneurysm neck. Safety and efficacy of this device are currently not known, but it has CE mark.

8. Summary

This study reports the *in vitro* study of the pCONus® device, its use in 9 New Zealand rabbits as well as the retrospective evaluation of 50 intracranial aneurysms treated with pCONus® between February 2012 and April 2014 in the Department of Neuroradiology of the Katharinenhospital in Stuttgart.

In our experience, pCONus® significantly facilitates the endovascular coil occlusion of bifurcation aneurysms. Its use is safe and well controllable.

pCONus® combines functional features of extrasaccular implants (for example, self-expanding stents) and intrasaccular implants (for example, TriSpan). The specific advantages of this new device are related to the facts that pCONus® does not cause an interruption of the blood flow in the target vessel, is deployed without catheterizing the efferent vessels and can be withdrawn or corrected after complete deployment if necessary.

pCONus® provides a tissue compatible stenting procedure covering the inner vessel wall of the artery without stenosis and without thrombus formation and has excellent biocompatibility and haemocompatibility with no or only minimal foreign body reaction in the interface and with an overall low neointima formation.

pCONus® provides a stable and permanent scaffold for the coils inside the aneurysm and has, quantitatively, no influence on the aneurysm flow.

The device is certainly not suitable for all aneurysms. We expect limitations if the aneurysm fundus is < 5 mm and if the relation depth/width is >2. For aneurysms with a neck diameter > 15 mm, the 15 mm pCONus® may not provide sufficient coil retention. The additional use of a second pCONus® or of a device with a function similar to TriSpan may add safety under these rare circumstances.

Recurrent perfusion of an aneurysm fundus after coil occlusion may be an indication for microsurgical clipping. Following pCONus® implantation and if the position of the device is unchanged, the aneurysm neck will remain bridged by the struts of the pCONus®, which will most likely interfere with the proper closure of an aneurysm clip.

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10. Abbreviations

AcomA	anterior communicating artery
ASA	acetylsalicylic acid
BA	basilar artery
CA	contrast agent
DSA	digital subtraction angiography
DWI	diffusion weighted imaging
F	female
FU	follow-up
IV	intravenous
L	left
M	male
MCA	middle cerebral artery
mRS	modified Rankin scale
NA	not available
PCA	posterior cerebral artery
p.o.	per os
pCONus®	phenox bifurcation aneurysm Implant
R	right
RS	Raymond scale
SAH	subarachnoid hemorrhage
SCA	superior cerebellar artery
SOP	standard of practice
TIA	transient ischemic attack
WNBAs	wide-necked bifurcation aneurysms

11. Figures

12. Tables

13. Acknowledgements

This work was made possible through the continuous support of Professor Hans Henkes, who became my academic and medical mentor. He introduced me to the practice of Interventional Neuroradiology, proposed the topic of this thesis and organized just everything necessary. The pCONus® device was only one of his many ideas.

Priv. Doz. Dr. Camillo Sherif, Neurosurgeon in Vienna, created the experimental aneurysms and guided me through the entire phase of animal experiments.

Professor Vitor Mendes-Pereira, director of the unit of Interventional Neuroradiology in the University Hospital of Geneva made possible the study of the device in a silicon flow model.

Ralf Hannes, R&D director at phenox GmbH Bochum, engineered the pCONus® device, provided all technical details and spent many hours with me in the animal laboratory in Vienna. The discussions with him allowed me to understand the potential and the limits of the device.

Dr. Ing. Hermann Monstadt, CEO of phenox GmbH, funded this research project way beyond the immediate interests of his company.

The continued and daily support of Professor Hansjörg Bäzner (Medical Director of the Neurological Clinic) and Professor Oliver Ganslandt (Medical Director of the Neurosurgical Clinic, both at the “Neurozentrum, Klinikum Stuttgart) is highly appreciated.

James Lago performed the language correction of the entire manuscript. He knows so much more than just English grammar and orthographics.