

RESEARCH ARTICLE

# Long Term Outcome after Application of the Angio-Seal Vascular Closure Device in Minipigs

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## Abstract

Minipigs are frequently used in (neuro-)interventional research. Longitudinal experiments may require repeated vessel access via the femoral artery. Anticoagulation and incomppliance of the animals necessitates the use of a vascular closure device (VCD). The effects of the Angio-Seal VCD in minipigs were longitudinally assessed. Minipig (42±8.4 kg body weight) femoral arteries were sealed using the 8F (n = 6) or 6F (n = 7) Angio-Seal VCD. The pre-interventional femoral artery diameter was 5.1±0.4 mm (4.3–5.8 mm). Sealed puncture sites were analysed angiographically as well as by computed tomography angiography (CTA) for a mean period of 14.1±8.0 weeks (1–22 weeks). All animals were constantly treated with acetylsalicylic acid (ASS) (450 mg/d (n = 7) or 100 mg/d (n = 1)) and clopidogrel (75 mg/d (n = 8)). Non-instrumented (n = 2) and arteries sealed using the VCD (n = 2) were examined histologically. No postoperative hemorrhagic complications were observed. Three arteries were occluded after VCD placement (1 animal diagnosed after 4 weeks (8F), 2 animals after 1 week (6F)) and remained so until the end of the experiments after 22, 12 and 4 weeks, respectively. In one artery a 50% stenosis 8 weeks after application of a 6F Angio-Seal was detected. In 69.2% (n = 9) the VCD was applied without complications. Histopathological analysis of the sealed arterial segments showed subtotal obliteration of the vessel lumen, formation of collagenous tissue and partial damage of the internal elastic lamina. The Angio-Seal VCD prevents relevant hemorrhagic complications in minipigs treated with dual platelet inhibition, but is associated with increased vessel occlusion rates.

## Introduction

Evaluation of novel (neuro-)interventional devices and treatment modalities often necessitates longitudinal experiments with animal models. The pig is an increasingly used animal model [1,2] also in the field of interventional radiology because of its favourable size and comparable peripheral arterial diameter [3]. Additionally, there are some similarities between the pig's blood coagulation system and the human one [4–7].

If domestic pigs, like German Landrace, are used, their continuous weight gain might pose a problem relating to comparability of the experimental results besides the handling of heavy-weight animals [1]. For example at the age of 250 days domestic pigs weigh about 120 kg compared to minipigs with less than 40 kg. To avoid these problems, minipigs are increasingly being used due to their stable size and stable vessel diameter [8].

Longitudinal endovascular experiments may require repeated vessel access via the femoral artery. Pigs would not accept lengthy immobilisation without anesthesia or applying of a pressure bandage. This missing compliance as well as anticoagulation implies the necessity of a suitable and efficient VCD. Manual compression of the puncture site, especially if pigs received anticoagulation therapy, is not thought to be effective.

Since their introduction in the 1990s different types of VCDs were developed. A frequently used device is the Angio-Seal vascular closure device (St. Jude Medical, St. Paul, MN, USA) [9–11]. Angio-Seal works by compression of the puncture site in a “sandwich technique” in combination with induction of hemostasis by a collagenous sponge [12]. The system consists of three completely biodegradable components: an anchor (made from polylactic and polyglycolic acids) deployed intraarterially, a small extravascular positioned bovine collagenous sponge and a suture of polyglycolic acid, which connects the elements [13,14]. Angio-Seal is available in sizes of 6F and 8F. All components are completely absorbed within 90 days after application [15,16]. Possible adverse events described in humans are hematoma, AV fistula, pseudoaneurysm, late bleeding requiring transfusion, vessel occlusion and stenosis, allergic reaction, foreign body reaction, inflammation and edema [12–14,17–19].

There are no long term experiences regarding the application of VCDs in minipigs. Tellez et al. [20] investigated the absorption of Angio-Seal only sonographically in large domestic Yorkshire pigs. Isfort et al. [21] tested the StarClose (Abott Vascular, Santa Clara, CA, USA) in 20 German Landrace pigs over a period of 28 days. Hofmann et al. [22] examined the applicability of the Sutura SuperStitch (Sutura, Fountain Vally, CA, USA) and Perclose (Abott Vascular, Santa Clara, CA, USA) system in 8 domestic pigs over 4 weeks.

In the present study the outcome after vessel closure using the Angio-Seal VCD was assessed in minipigs up to 22 weeks. Treatment effects were analysed angiographically as well as by CTA and histologically.

## Materials and Methods

### Animals

The experiments were carried out after receiving approval of the governmental animal care office (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen, Recklinghausen, Germany). National guidelines for animal ethics, welfare and experimental conduct were followed. 8 female minipigs (Ellegard Göttingen Minipigs A/S, Dalmose, Denmark) ( $42 \pm 8.4$  kg initial body weight) were housed under controlled environmental conditions ( $20^\circ\text{C} \pm 1^\circ\text{C}$ , 12:12 h light/dark cycle). The acclimatization period before starting the experiments was 2 weeks. Apart from fasting directly before the experiments all animals received feed and water ad libitum.

### Experimental design

The animals were deployed in various interventional experiments regardless of the present study.

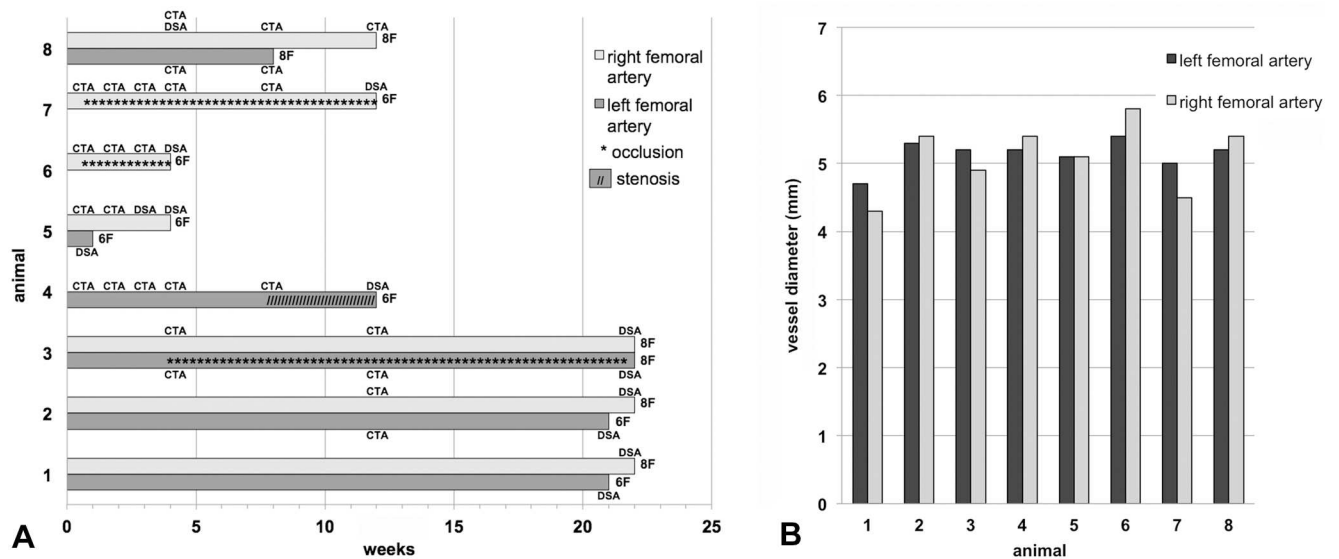
The animals received premedication with azaperone (Stresnil 40 mg ad. us. vet.; Sanochemia Pharmazeutika AG, Neufeld, Austria), atropin (Atropinsulfat, B.Braun Melsungen AG, Melsungen, Germany) and ketamine (10% Ketavet ad us. vet., Zoetis Deutschland GmbH, Berlin, Germany) followed by intubation. The animals were mechanically ventilated with an oxygen-air mixture. Anesthesia was maintained with propofol (Propofol 2% MCT Fresenius; Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). For analgesia fentanyl (Fentanyl-Janssen 0,5 mg, Janssen-Cilag GmbH, Neuss, Germany) was continuously administered. During the treatments the animals were fixed supine.

In the context of these experiments the animals were punctured at the femoral artery and a 6F or 8F sheath was inserted. The puncture site was closed by a 6F (n = 7) or 8F (n = 6) Angio-Seal VCD (Fig 1A). Application of the VCD was performed by an experienced neurointerventionalist.

Starting the day of the intervention all animals were constantly treated with ASS (Aspirin 450 mg/d (n = 7) or 100 mg/d (n = 1); Bayer Vital GmbH, Leverkusen, Germany) and clopidogrel (Iscover, 75 mg/d (n = 8); Orifarm GmbH, Leverkusen, Germany). Three of the animals were treated with 450 mg clopidogrel 24h prior treated. During the intervention animals were treated with ASS (500 mg) and heparin (3000 IU, Heparin-Natrium-5000; ratiopharm GmbH, Ulm, Germany) intravenously to prevent thrombotic events. After the intervention heparin was not received any longer. Using the Multiplate- Analyzer (Dynabyte Medical, München, Germany) the platelet function of all minipigs was verified. Decreased measured values of the ASPI- and ADP-test compared to the initial values indicated effective anticoagulation.

### Follow up imaging

To evaluate the treatment effects after application of the Angio-Seal VCD, follow up imaging of the femoral arteries was performed by CTA (Somatom AS; Siemens Healthcare, Erlangen,



**Fig 1. Experimental design.** (A) Overview of the number of animals, observation periods, imaging modality, and the condition of the femoral artery after application of an Angio-Seal VCD. (B) Porcine baseline femoral artery diameter.

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Germany) after 1 (n = 4), 2 (n = 4), 3 (n = 3), 4 (n = 6), 8 (n = 4) and 12 (n = 5) weeks (Fig 1A). The minipigs were anesthetized and fixed supine in the described manner. The tube parameters were set to 100 ml contrast agent (Solutrast 300, 300 mg iodine/ml; Altana Pharma AG, Konstanz, Germany) and 30 ml sodium chloride injection with 4 ml / sec. flow.

Treatment effects were also evaluated angiographically (Axiom; Siemens Healthcare) via contralateral vessel puncture access after 1 (n = 1), 3 (n = 1), 4 (n = 3), 12 (n = 2), 21 (n = 2) and 22 (n = 4) weeks. One artery was examined twice. The pigs were anesthetized and fixed supine in the described manner.

The outcome after application of the Angio-Seal VCD was evaluated retrospectively. For that reason, times and modalities of examination differ between some of the animals.

The data were evaluated for stenosis or vessel occlusion. In all cases the initial pre-interventional femoral artery diameter was measured angiographically (Fig 1B).

After the last follow up imaging the animals were sacrificed by intravenous injection of 0.5–1 ml/kg body weight natrium-pentobarbital (Narcoren 16 g/100ml; Merial GmbH, Hallbergmoos, Germany). The treated (n = 13) and untreated (n = 3) femoral arteries were prepared and fixed with 4% formalin.

## Histopathological analyses

The arteries of two animals euthanized at 4 (animal 6) and 12 (animal 7) weeks after instrumentation were analysed histologically. Femoral artery segments harbouring the punctured and sealed vessel region were collected as well as the contralateral non-instrumented arteries. After immersion fixation with 4% buffered formalin the arteries were sectioned at 0.4 cm intervals. Artery sections were embedded in paraffin, cut at 5 µm thickness onto slides and stained with hematoxylin and eosin, kongored, turnbull blue or van Gieson stain. Images of stained slides were captured with a Zeiss Axio Scope.A1 microscope and AxioCam MRC camera (Carl Zeiss Microscopy, Jena, Germany).

## Results

Data evaluation yielded an average pre-interventional femoral artery diameter of  $5.1 \pm 0.4$  mm (Fig 1B). The minipigs were observed for a mean period of  $14.1 \pm 8.0$  weeks (Fig 1A). All treated animals tolerated the procedure well, no postoperative haemorrhagic complications were observed. Technical success rate of the Angio-Seal VCD was 100%.

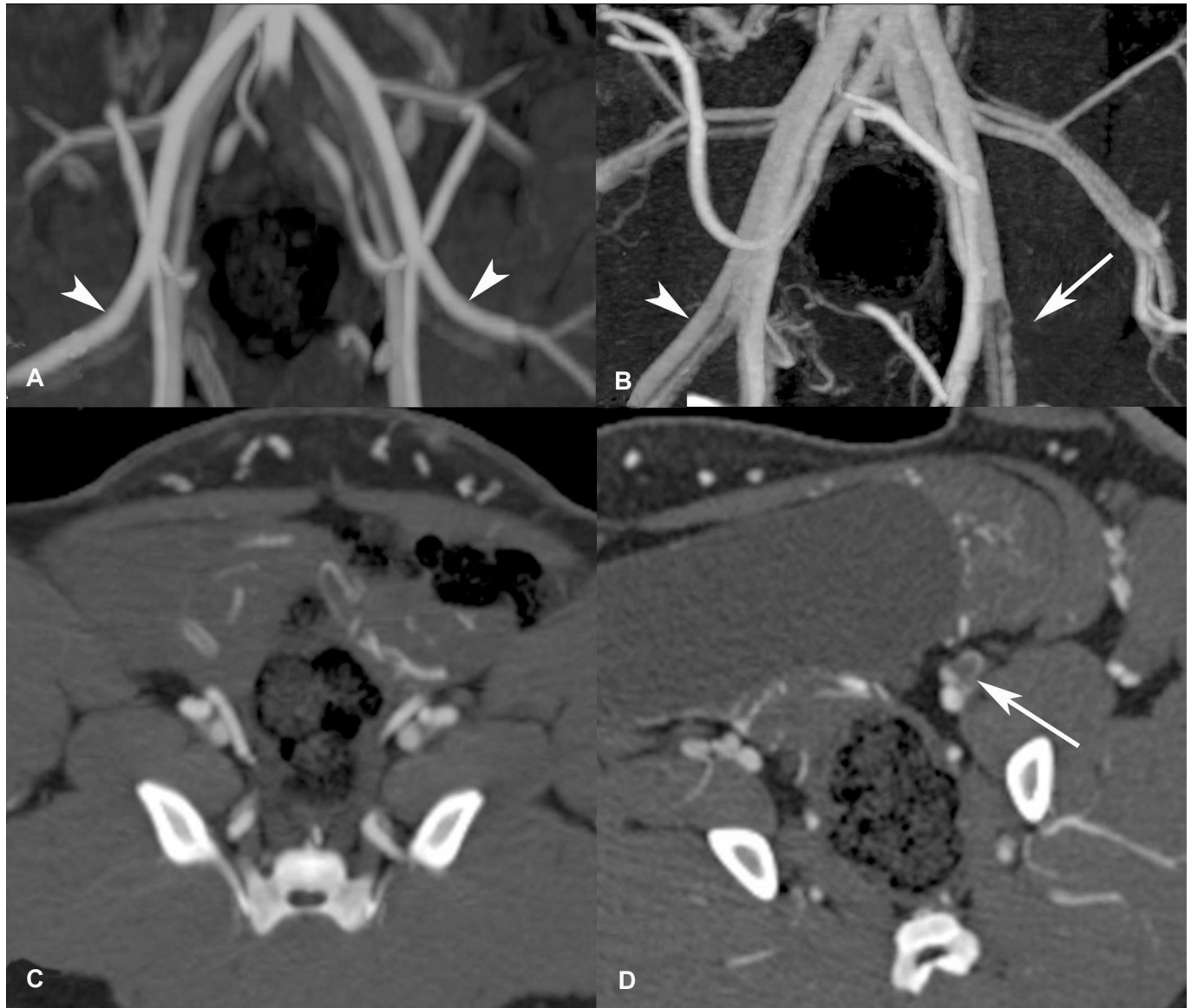
After application of the Angio-Seal VCD three arteries were found to be occluded (1 animal after 4 weeks (8F), 2 animals after 1 week (6F)) and remained occluded until the experiments were finished after 22, 12 and 4 weeks, respectively (Figs 1 and 2). As none of the animals showed any impairment, such as pain or lameness, the experiments were continued as scheduled.

8 weeks after application of a 6F Angio-Seal a 50% stenosis was detected in one artery (animal 4) by CTA and after 12 weeks by digital subtraction angiography (DSA) (Figs 1 and 3).

None of the animals showed signs of distal ischemia or any other impairments.

In the remaining 69.2% (n = 9) Angio-Seal was effectively applied without any complications.

While cross sections of arteries from the non-instrumented side showed normal arterial vessel architecture without fibrosis, calcification or inflammatory changes (Fig 4A and 4B) sections of sealed arterial segments showed an over 90% to subtotal obliteration of the vessel lumen, mainly due to mesenchymal and foreign body reaction with an excessive formation of collagenous tissue involving the intima and focally extending to the media. Multinucleated histiocytes, lymphocytes and scattered eosinophils around copolymer material also indicate a



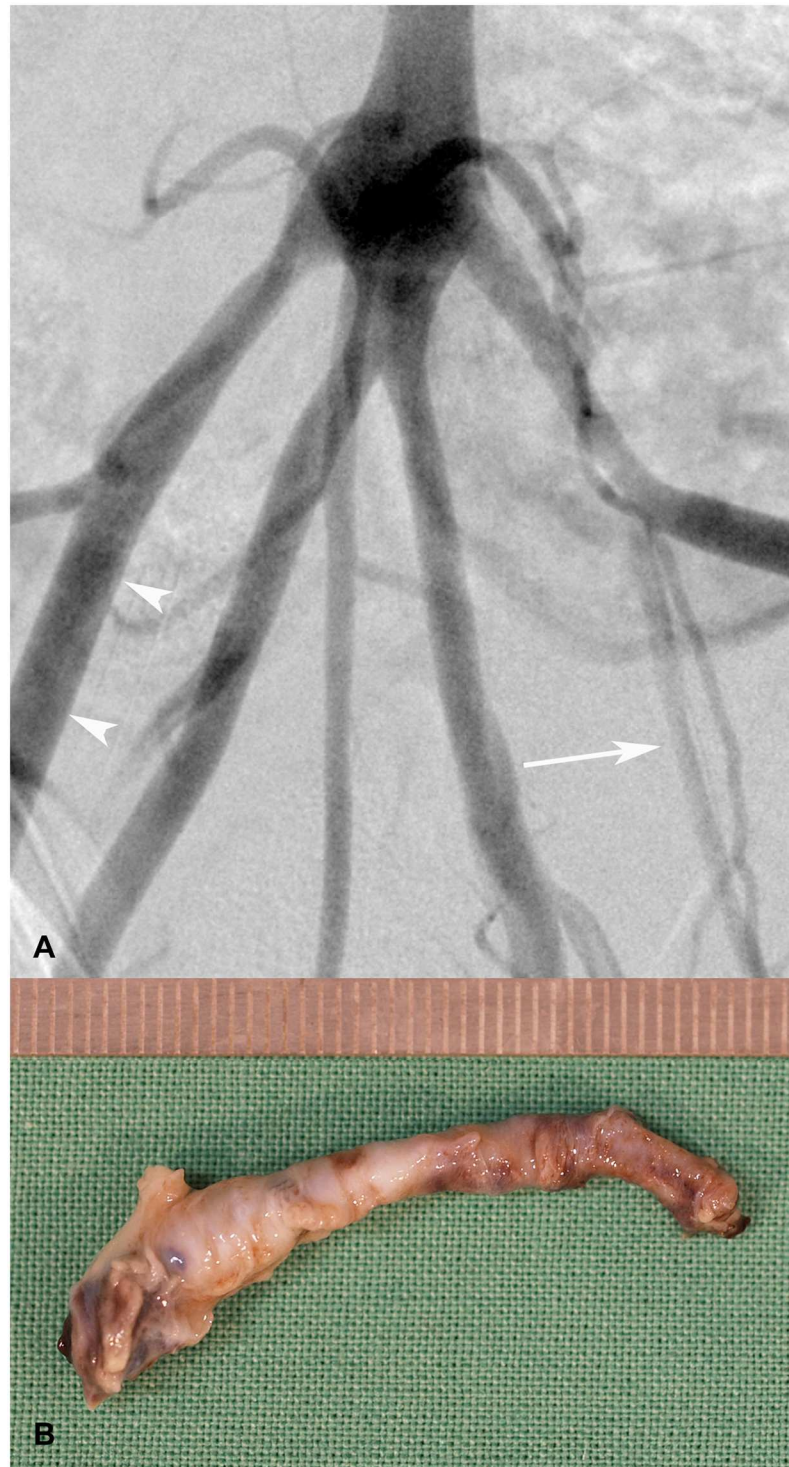
**Fig 2. Occluded left femoral artery after application of an 8F Angio-Seal vascular closure device.** (A, C) CT-angiography demonstrates the intact femoral arteries prior to arterial puncture (arrow heads in A). (B, D) Four weeks after implantation of an 8F Angio-Seal VCD CT-angiography shows occlusion of the left femoral artery of animal 3 (white arrow in B and D). The animal presented in this figure is one of 3 animals that developed vessel occlusion after application of the Angio-Seal VCD.

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florid foreign body reaction within the endovascular area. Here and there the internal elastic lamina (IEL) was destroyed with remnants of elastic material lying in fibrotic tissue adjacent to the media (Fig 4F). Hemosiderin deposits indicate hemorrhage within tissue mass at the former vessel lumen.

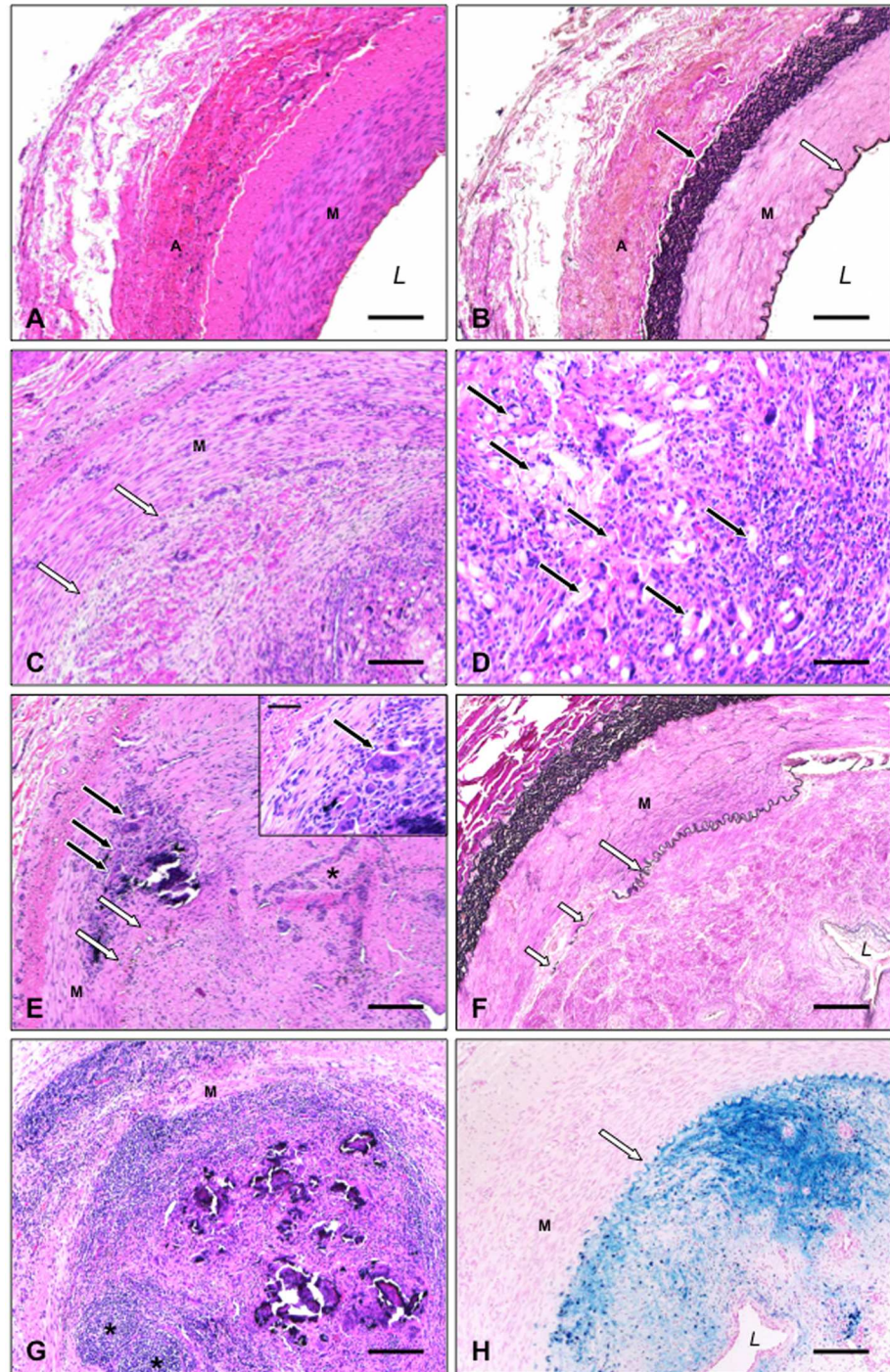
In the case of the pig finalized 4 weeks (animal 6) after Angio-Seal implantation aggregates of approximately 15  $\mu\text{m}$  in diameter measuring pale eosinophilic corpuscles were discernible in the former vessel lumen. This foreign material obviously representing remnants of the VCD's intraluminal component turned out to be partially kongophilic and birefringent and was surrounded by granulation tissue dominated by histiocytic cells, several of them being





**Fig 3. Stenosis of the left femoral artery 12 weeks after application of a 6F Angio-Seal.** (A) Digital subtraction angiography shows a local stenosis at the puncture site (white arrow). The normal contralateral artery is shown for comparison (white arrow heads). (B) Macroscopic photography of the left femoral artery shows the pathologically thickened vessel segment at the position of the applied Angio-Seal VCD.

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**Fig 4. Histopathological findings.** (A, B) Segment of normal porcine femoral artery; A adventitia (Tunica externa), M media (Tunica media), L vessel lumen, black arrow external elastic lamina, white arrow internal elastic lamina (A H&E, B van Gieson stain; scale bars = 180  $\mu$ m). (C) Femoral artery 4 weeks after intervention. Obliteration of vessel lumen; M media, arrows internal elastic lamina (H&E; scale bar = 180  $\mu$ m). (D) Multinucleated histiocytes, lymphocytes and scattered eosinophils around copolymer material (arrows), same animal as in C (H&E; scale bar = 90  $\mu$ m). (E) Advanced connective tissue formation in former intravascular space 12 weeks after endovascular instrumentation. Focal media calcification surrounded by lymphocytes and multinucleated histiocytes (black arrows). Area with prominent neovascularisation as indicated by asterisk; white arrows internal elastic lamina (H&E; scale bar = 180  $\mu$ m). Inset: Multinucleated giant cell (arrow) in partially destroyed media (H&E; scale bar = 65  $\mu$ m). (F) Subtotal obliteration of femoral artery



(same animal as in E). Segmental destruction of internal elastic lamina (arrow) with remnants of elastic material (short arrows); (van Gieson stain; scale bar = 180  $\mu$ m). (G) Prominent inflammatory response (same animal as in E and F). Follicle-like aggregation of small lymphocytes (asterisks) and calcifications embedded in a lympho-histiocytic infiltrate (H&E; scale bar = 180  $\mu$ m). (H) Considerable hemosiderin deposits (blue staining) at the former vessel lumen (same animal as in E–G); L residual artery lumen (turnbull blue; scale bar = 180  $\mu$ m).

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multinucleated (Fig 4C and 4D). Scattered lymphocytes and eosinophilic granulocytes as part of a florid foreign body reaction could also be seen.

12 weeks after instrumentation the foreign material was almost completely degraded and only patchy foci of histiocytes including multinucleated giant cells could be detected, mostly in association with dystrophic calcifications (Fig 4E). Within the soft tissue rich in collagen fibers newly formed capillaries and small vessels occurred (Fig 4E). Extensive hemosiderin deposits within the lumen obliterating fibrous tissue referred to former microbleeding during tissue maturation and neovascularisation (Fig 4H). The affected femoral artery (animal 7) showed pronounced inflammatory changes with an eccentric transmural cellular infiltration of large parts of the vessel wall, focally reaching the adventitia (Fig 4G). This infiltrate was dominated by small reactive lymphocytes which were occasionally assembled in follicular structures, and again histiocytes, granulocytes being only rarely admixed. There were no hints to arterial wall dissection or arteriovenous fistulas in the arterial specimen of any animal.

## Discussion

Since their introduction in the 1990s VCDs are used increasingly with the Angio-Seal being one of the more frequently used VCDs [9–11]. Technically, an anchor is located intraarterially, and a bovine collagenous plug is pressed against the anchor from the outside of the arterial wall. The functionality of the Angio-Seal responses predominantly on practice of the “sandwich technique” supplemented by the thrombogenic properties of the collagen [14,19].

VCDs are of relevance not only for treatment of humans, but also for vessel occlusion of laboratory animals, especially in long term experiments with repeated vessel access and anticoagulant therapy. The pig is one of the species most frequently used for endovascular experimental studies. For long term experiments minipigs should be preferred, because of their stable vessel diameters, stress resistance and suitable size [23,24]. Manual compression of a puncture site, applying of a pressure bandage and lengthy immobilisation are not suitable to occlude puncture sites in pigs without the risk of hemorrhagic complications [21], particularly in the context of anticoagulant or anti-platelet therapy. This implies the necessity of a fast, safe and efficient method of sealing the puncture site.

Hitherto, the use of VCDs has only been investigated in domestic pigs, like German Landrace [20–22]. Detailed examinations of VCDs in minipigs and their long term outcome, however, are missing. The aim of the present study was thus to examine the long term outcome after application of the Angio-Seal VCD in minipigs receiving anticoagulant therapy.

Results of our study suggest that in minipigs the components of the Angio-Seal principally are degradable in accordance with the manufacturer's data. Thus in 69.2% of cases, regardless of the size of the VCD (6F or 8F) and despite dual platelet inhibition applying ASS and clopidogrel, the application and resorption of the Angio-Seal was successful without any complications. Nevertheless, three animals developed vessel occlusion after application of the Angio-Seal VCD (8F (n = 1) and 6F (n = 2)) (Fig 1A). Furthermore, one artery showed a 50% stenosis 8 weeks after application of a 6F Angio-Seal (Fig 1A). We thus considered the reasons which may have led to these complications.



The initial vessel diameters, measured angiographically, of all femoral arteries were greater than 4 mm (Fig 1B). Thus, the conditions of the manufacturer were complied [14]. Prior to placement of the Angio-Seal, correct positioning of the catheter sheath was verified by contrast injection.

Histologic examinations figured out that despite degradation of the VCD's components in the animals with subsequent vessel occlusion at the puncture site (i.e. animal 6 and 7 in Fig 1A) mostly intravascular tissue reaction with subtotal luminal oblitative fibrosis occurred (Fig 4A–4H). Whereas Tellez et al. [20] did not report on such complications, several studies in which a polyglycolic and polylactic acid polymer was used described similar reactions after implantation of this material in pigs [25,26]. Allergic reactions due to polyglycolic and polylactic acid are known in humans [14]. It thus can not be ruled out that comparable allergic reactions may also occur in pigs.

The complication rate of approximately 30% may be ascribed to the small sample size of this study. Compared to studies of human medicine with several hundred patients, where complications after application of the Angio-Seal occur less frequently, in the present study a total of 13 arteries were analyzed in 8 pigs. Thus, data from a larger sample size might have altered the reported complication rate.

One of the limitations of the underlying study is that follow-up imaging was performed at heterogenous time points. The reason for this was that the animals were deployed in various interventional experiments regardless of the present study. The follow-up intervals were thus determined by these experiments. Nevertheless, synchronization of imaging intervals would not have relevantly affected the outcome of the study.

Another debatable limitation is the lack of a control group (i.e. manual compression of the femoral artery to achieve bleeding control). In pigs, bleeding control would have been difficult to establish due to the pigs' anatomy and due to the fact, that the animals are not compliant regarding immobilisation or bedrest.

Finally, only a relatively small number of pigs was examined, which also might have affected the reported complication rate of around 30%.

In conclusion, Angio-Seal effectively prevents relevant bleeding complications in minipigs treated with dual platelet inhibition, hereby allowing longitudinal endovascular studies. It should, however, be noted that rates of vessel occlusion or stenosis might be increased in the context of using this VCD.

## Supporting Information

**S1 Fig. Physiologically perfused femoral arteries of animal 2 (22 weeks after application of a 6F and 8F Angio-Seal VCD shown by DSA).**

(TIF)

**S2 Fig. Physiologically perfused femoral arteries of animal 2 (12 and 22 weeks after application of a 6F and 8F Angio-Seal VCD shown by CTA and DSA).**

(TIF)

**S3 Fig. Occluded left femoral artery of animal 3 (4, 12 and 22 weeks after application of a 8F Angio-Seal VCD shown by CTA and DSA).**

(TIF)

**S4 Fig. Follow-up imaging using CTA and DSA demonstrated a stenosis of the left femoral artery of animal 4 after application of a 6F Angio-Seal VCD.**

(TIF)

**S5 Fig. Physiologically perfused femoral arteries of animal 5 (1, 2, 3 and 4 weeks after application of a 6F Angio-Seal VCD shown by CTA and DSA).**

(TIF)

**S6 Fig. Occluded right femoral artery of animal 6 (1, 2, 3 and 4 weeks after application of a 6F Angio-Seal VCD shown by CTA and DSA).**

(TIF)

**S7 Fig. Occluded right femoral artery of animal 7 (1, 2, 3, 4, 8 and 12 weeks after application of a 6F Angio-Seal VCD shown by CTA and DSA).**

(TIF)

**S8 Fig. Physiologically perfused femoral arteries of animal 8 (4,8 and 12 weeks after application of a 8F Angio-Seal VCD shown by DSA and CTA).**

(TIF)

## Author Contributions

**Conceived and designed the experiments:** LK AN ON SH MAB MK AO.

**Performed the experiments:** LK AN MAB MW.

**Analyzed the data:** LK MAB KWN.

**Wrote the paper:** LK.

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