Evaluation of safety and performance of a new prototype self-expandable nitinol venous stent in an ovine model

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ABSTRACT

Objective: Our study was a prospective in vivo study performed on an animal model to evaluate the safety and performance of a novel venous stent designed specifically for venous applications.

Methods: The novel stents were implanted in the inferior vena cava of nine sheep. The stents were deployed with different distances between the closed cell rings to test for if the segments might migrate after being deployed at maximal distance. Three different total lengths were 9, 11, and 13 cm. After 1, 3, and 6 months, vascular injury, thrombus, neointima coverage, and stent migration were evaluated through computed tomography venography and histopathology. Imaging, histology, and integration data were analyzed for each group.

Results: All stents were deployed successfully, and all sheep survived until the time of harvesting. In all cases, the native blood vessel sections were intact. The segmented stent parts showed a differently pronounced tissue coverage, depending on the duration of the implantation.

Conclusions: The new nitinol stent is safe and feasible to implant in the venous system with a rapid surface coverage. Alteration of stent length did not affect the development of neointimal formation and did not cause migration. (JVS—Vascular Science 2023;4:100113.)

Clinical Relevance: The clinical relevance of our study titled "Evaluation of Safety and Performance of a New Prototype Self-Expandable Nitinol Stent in an Ovine Model" lies in its potential to advance the field of venous intervention. Stent implantation is a common procedure used to treat deep venous obstruction, and the use of self-expandable nitinol stents has been shown to be effective in improving the patency rates. However, the safety and efficacy of new stent prototypes must be evaluated thoroughly before they can be used in clinical practice. Our study contributes to the evaluation of a new prototype self-expandable nitinol stent by demonstrating its excellent mechanical properties, biocompatibility, and histopathological response in an ovine model. The results of our study may provide valuable insight for researchers and clinicians in developing and implementing new stent technologies, ultimately improving patient outcomes in the treatment of chronic venous obstruction.

Keywords: Venous obstruction; Sheep model; Skipped segment; Venous stent; Self-expandable

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Chronic venous obstruction (CVO) can cause a wide spectrum of symptoms of venous hypertension, ranging from edema of the lower extremities to venous claudication, skin changes, and venous ulcers.[1-4] Because it is minimally invasive and has a high safety profile, endovascular venous stenting is increasingly becoming the treatment of choice for patients with CEAP class 3 to 6.[5-7] According to a joint clinical practice guideline for the management of CVO published by the American Venous Forum and the Society for Vascular Surgery, stent placement is recommended for patients with symptomatic CVO owing to iliac vein compression or obstruction, with the goal of improving symptoms and preventing recurrent venous thromboembolism.[8] However, restenosis owing to neointimal proliferation and wall thickening, thrombus formation, and negative remodeling continues to be the most common cause

of stent failure, particularly in patients with extensive CVO.[9-11]

Compared with arterial stents, research on venous stents is behind. There has been a significant increase in the number of dedicated venous stents manufactured in recent years. In terms of clinical usefulness and mechanical properties, each model has some differences compared with competing models.[12,13] Despite persistent advancements in intervention techniques and stent design, there are still a noteworthy number of stent occlusions after venous interventions. The reported primary patency rates at one-year ranges from 59% to 87% in patients with post-thrombotic syndrome.[14-16]

We evaluated a new, tapered, segmented, laser-cut nitinol stent with adjustable length for more precise sizing and positioning. The more porous structure of the stent is theoretically less restrictive for the inflow through the tributaries and provides faster coverage of the stent struts. Its adjustable length and tapered design makes it suitable for use in iliofemoral lesions, in which the vessel size differs. The purpose of this study was to test the accuracy of stent release in vivo, investigate the risk of stent migration after elongation maneuver, evaluate the time needed the stent struts to be covered, and assess the safety and performance of the stent in animals, providing a reference for further clinical trials.

ARTICLE HIGHLIGHTS

- **Type of Research:** Experimental research
- **Key Findings:** The implantation of the novel stent in the venous system is safe and feasible.
- **Take Home Message:** Alteration of stent length and increasing the skipped segments did not affect the development of neointima formation and did not cause migration.

METHODS

The study was designed and performed in accordance with the Guide for the Care and Use of Laboratory Animals. Our institutional Animal Care and Use Committee and the relevant government authorities approved the experimental protocol.

Structural features of the stent and delivery system

The W-Stent is not currently available for commercial use. The stent's availability for clinical use depends on further testing, regulatory approval, and commercialization plans. The in length variable W-Stent (Venous Stent B.V., Maastricht, the Netherlands) is designed with a high porosity to improve fast coverage of the struts, decreasing the need for anticoagulation and closed cell segments to improve radial force and interconnections to improve flexibility and length adjustability. Finally, barbs prevent migration after implantation.

The self-expandable nitinol stents used have a diameter of 18 mm with a proximal closed cell segment of 4 cm long with barbs, two segments in the middle of 1 cm length, and a final segment of 2 cm with barbs again. The stent length can vary between 8 cm, intersegmental distance of 0 cm and maximum of 13 cm, with an intersegmental distance of 1.5 cm (Fig 1).

The stent is mounted in a standard delivery system that can release the stent by retracting the sheet and deploying each individual segment. In between the segments, the length can be increased by pulling and rotation. The stents are deployed with different distances between the closed cell rings to test whether the segments might migrate after being deployed at maximal distance. Three different total lengths were used—9, 11, and 13 cm—three times in nine sheep.

Animal models and experimental design

The study included nine female sheep (type swifter; mean age, 2 years) with a mean bodyweight of 44.3 kg (range, 37-52 kg) divided in three groups (n = 3 per group), all of which received a venous stent implantation in the inferior vena cava (IVC). After stent implantation the first group of three animals was followed and sacrificed at 4 weeks (G1), the second group at 12 weeks (G2), and the third group at 6 months (G3) after the intervention.

During follow-up duplex ultrasound (DUS) examination of the stent in the IVC was done at 3 days and 4 weeks after stent implantation for each group (G1, G2, and G3), at 12 weeks for G2 and G3, and at 6 months for G3. Each sheep underwent a computed tomography (CT) scan before euthanasia and autopsy. This was for G1 at 4 weeks, for G2 at 12 weeks, and for G3 at 6 months after the intervention.

Stent placement and intraoperative protocol

All stents were implanted in the IVC under general anesthesia. Intrajugular injection of ketamine (10-20 mg/kg bodyweight) and inhalation of isoflurane 5% were used for sheep sedation anesthesia. General anesthesia was maintained through inhalation of isoflurane 2.5% after insertion of an endotracheal tube. An intravenous catheter was placed at the left hind leg to provide intravenous medication during surgery. Arterial access was gained via the right ear. Additionally, a gastric tube was placed.

Buprenorphine 10 to 20 μg/kg, meloxicam 0.5 mg/kg, gentamicin 6.6 mg/kg, and penicillin 40,000 IU/kg were given intravenously during surgery. After shaving the neck region, the surgical area was scrubbed with an iodine sponge followed by disinfection with isobetadine and Braunol. The animals were draped with a sterile, impermeable covering to isolate the disinfected area. A 5F sheath was placed in the right jugular vein. Heparin (5000 IU) was administered after placement of the sheath intravenously.

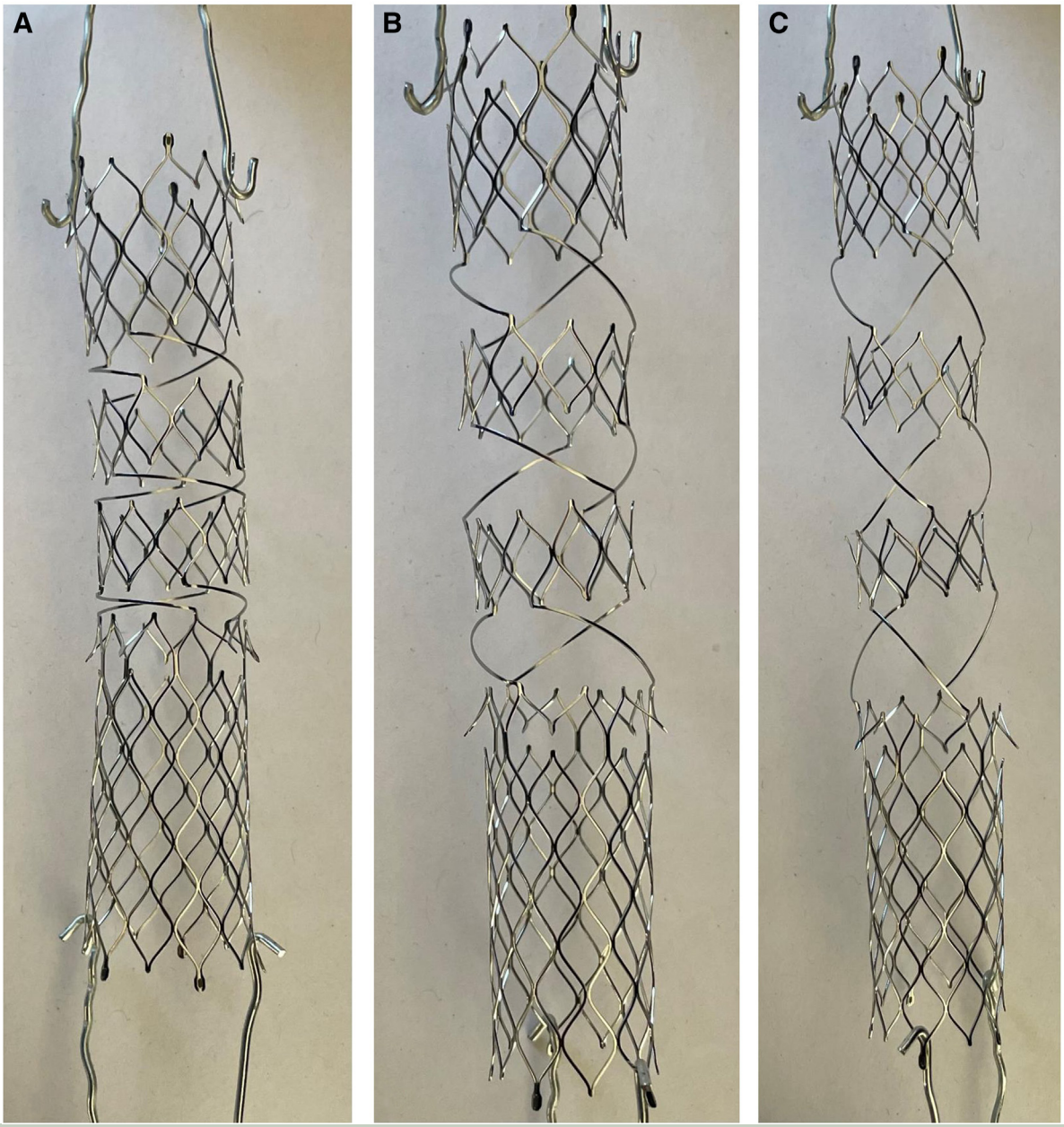

Fig 1. W-Stent design. Three different total lengths of the stent relative to the degree of rotation during implantation: **(A)** 9 cm, **(B)** 11 cm, and **(C)** 13 cm.

Phlebography was performed using a pigtail and the iliocaval confluence was visualized. Gadoteric acid (Dotarem) 0.5 mmol/mL was used as contrast solution. The sheath was upsized to 10F to facilitate stent placement. Via a stiff guidewire using the Seldinger technique, the 18 mm × 100 mm variable vein stent was positioned in the IVC initiated at the iliocaval confluence up to the suprahepatic part of the IVC and deployed under fluoroscopy by retracting the covering sheath. After stent implantation, control phlebography was obtained by using a pigtail catheter to document the patency and position of the stent. Then, the vascular sheath was removed, and hemostasis was achieved by manual compression of the puncture site for 10 minutes. After the procedure enoxaparin was given 3 mg/kg twice per day subcutaneously until termination (120-140 mg twice per day depending on the availability of enoxaparin).

Follow-up and euthanasia

The follow-up examinations at the observation points (Table I) were performed by an independent researcher who was blinded to the animal groups.

Postoperative day 3. All sheep underwent DUS examination of the stent in the IVC under sedation with ketamine (10-20 mg/kg bodyweight intravenously), and inhalation of isoflurane 5% through a mask.

Table I. Postintervention procedure

	Postoperative day 3	1 Month	3 Months	6 Months
DUS examination	9 sheep	9 sheep	6 sheep	3 sheep
CTV	0	3 sheep	3 sheep	3 sheep
Autopsy	0	3 sheep	3 sheep	3 sheep

CTV, computed tomography venography; *DUS*, duplex ultrasound.

One month postoperative. All sheep underwent DUS of the stent in the IVC under sedation with ketamine (10-20 mg/kg bodyweight, intravenously) and inhalation of isoflurane 5% through a mask. Three sheep underwent an additional CT scan under general anesthesia with ketamine (10-20 mg/kg bodyweight, intravenously, and inhalation of isoflurane 2.5%) after placing an endotracheal tube. CT scans included plain scans, as well as scans during inspiration and expiration. Afterward, these three sheep were euthanized through application of pentobarbital (Euthasol; 120 mg/kg) intravenously followed by an autopsy.

Three months postoperative. The remaining six sheep underwent DUS examination of the stent in the IVC under sedation with ketamine (10-20 mg/kg bodyweight) and inhalation of isoflurane 2.5% through a mask. Three sheep underwent a CT scan under general anesthesia according to the same protocol after placing an endotracheal tube. Afterward, these three sheep were euthanized through application of pentobarbital (120 mg/kg) intravenously, followed by an autopsy.

Six months postoperative. The last three sheep were undergoing a DUS examination of the stent in the IVC under sedation with ketamine (10-20 mg/kg bodyweight intravenously) and inhalation of isoflurane 2.5% through a mask. Afterward, a CT scan was performed under general anesthesia followed by euthanasia and an autopsy.

Autopsy and sampling. CTV were performed under general anesthesia. Biopsies were performed after humane killing by a median laparotomy (incision from the sternum to the udder, 40 cm) with exposure of the abdominal aorta and IVC. The IVC was prepared and fixed on a cork board to avoid axial shrinkage and inadvertent iatrogenic injury of the venous endothelium. The resected IVC was rinsed with a saline solution 0.9% until flushed contents become a clear solution. A total of nine slices of stented IVC were taken for each stent as well as skipped segment between the rings (Fig 2).

Pathomorphological examination. For the histological examination, the samples were processed with preparation of plastic slide stained with toluidine blue, according to a standard protocol. The toluidine blue stain serves as the standard stain for ground specimens to provide a histological overview and shows the structure of the specimen. A portion of connective tissue with fibrosis as well as intimal proliferation and tissue overgrowth of stent struts can also be visualized well. Six segment points in each section were analyzed and measured regarding the presence and thickness of the tissue proliferation and averaged, stating the minimum and maximum value (Fig 3).

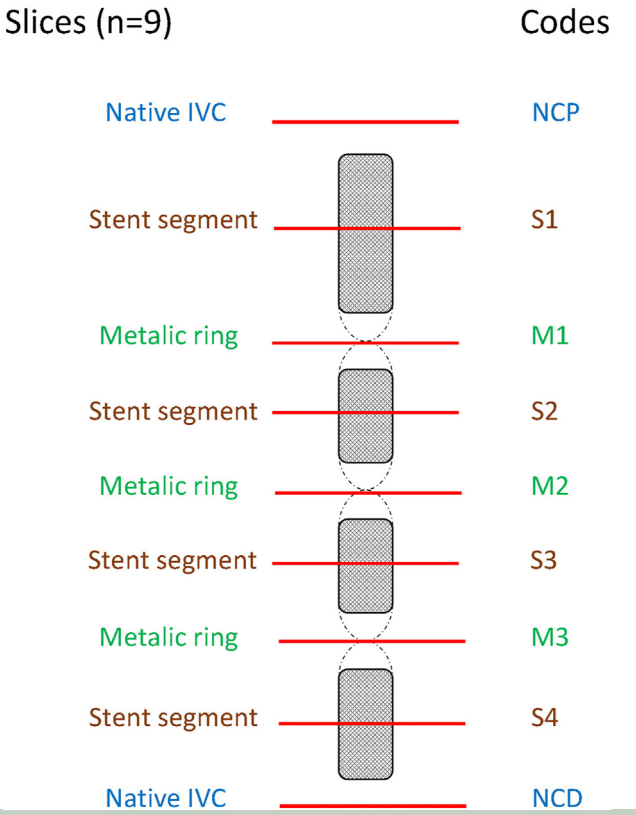

Fig 2. Schematic drawing showing the sampled segments acquired and investigated after stent explantation. *IVC*, inferior vena cava.

Digital microscopy examination. The test samples were examined with a high-resolution digital microscope with software support (Olympus digital microscope DSX-1000; Olympus, Hamburg, Germany) to assess the surface structure. The digital microscopic examination was carried out on the native, unfixed test samples without further sample processing.

Statistical analyses

Data are expressed as mean ± standard deviation. The endothelialization scores and the differences in neointimal thickness between the stents and animal groups

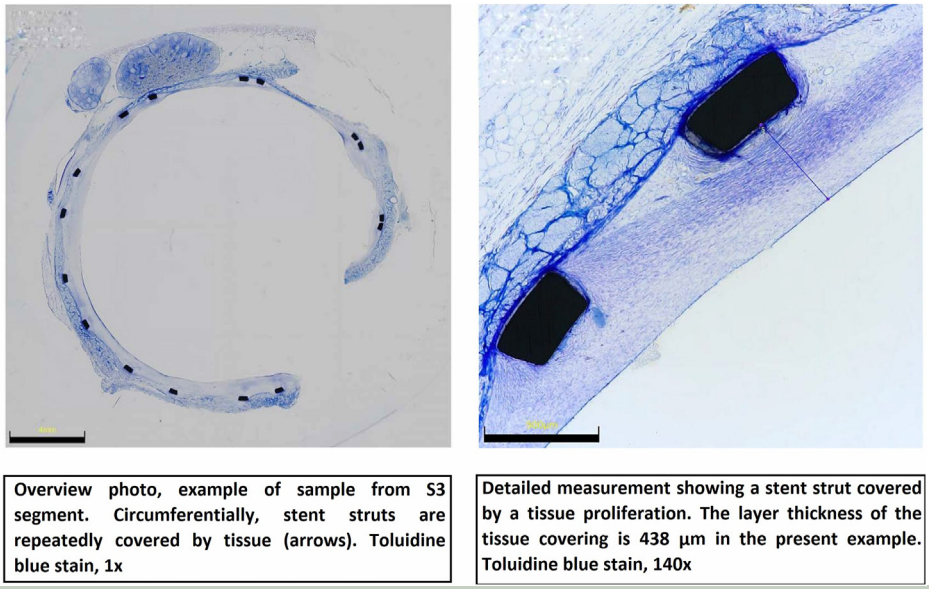

Fig 3. Histological specimens of the stented segments showing the typical neointimal pattern over the stent. **(Left)** Stain: Toluidine blue; original magnification, ×1. **(Right)** Toluidine blue; original magnification, ×140.

were compared using Mann-Whitney *U* test and one-way analysis of variance, respectively. A *P* value of $<.05$ was considered statistically significant. All statistical procedures were computed with SPSS v25.0 software (SPSS, Chicago, IL).

RESULTS

Stent implantation

Nine stents were deployed successfully in nine sheep. All animals survived until the end of the study. DUS examinations and CT scans were performed for all stents per protocol. The release compensation function of the new delivery system stabilized the tip of the stent during release. The novel stent did not exhibit obvious shortening during the release process. The operator was able to rotate the delivery system during the implantation to achieve longer skipped segments and increase the total length of the stent as intended.

DUS examination and CT scan

Follow-up investigations were performed according to the predefined timetable. All stents remained patent and were normal in shape, without fracture, distortion, or migration. The CT scan before euthanasia showed no lumen stenosis in any group (Fig 4). A review of follow-up CT scans showed stable stent diameters, with no evidence of stent migration, undersizing, or compression. Although the venous stent extended from the iliac vein confluence to the suprahepatic IVC, potentially covering the renal veins, no evidence of obstruction or compromise of the renal veins was observed in any of the animals during the study period.

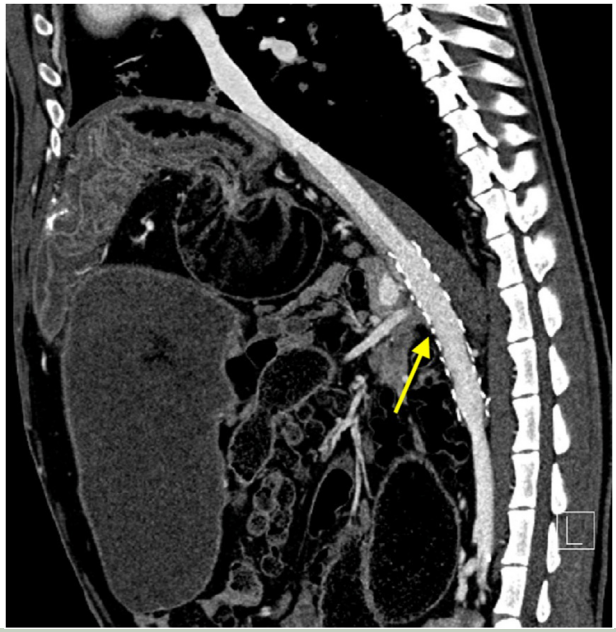

Fig 4. Representative image from computed tomography (CT) angiography of 6-month animal showing the implanted W-stent in vena cava inferior (yellow arrow).

Macroscopic and microscopic (light and digital) findings

In all cases, the native blood vessel sections were intact. The segmented stent parts showed a differently pronounced tissue coverage, depending on the duration of

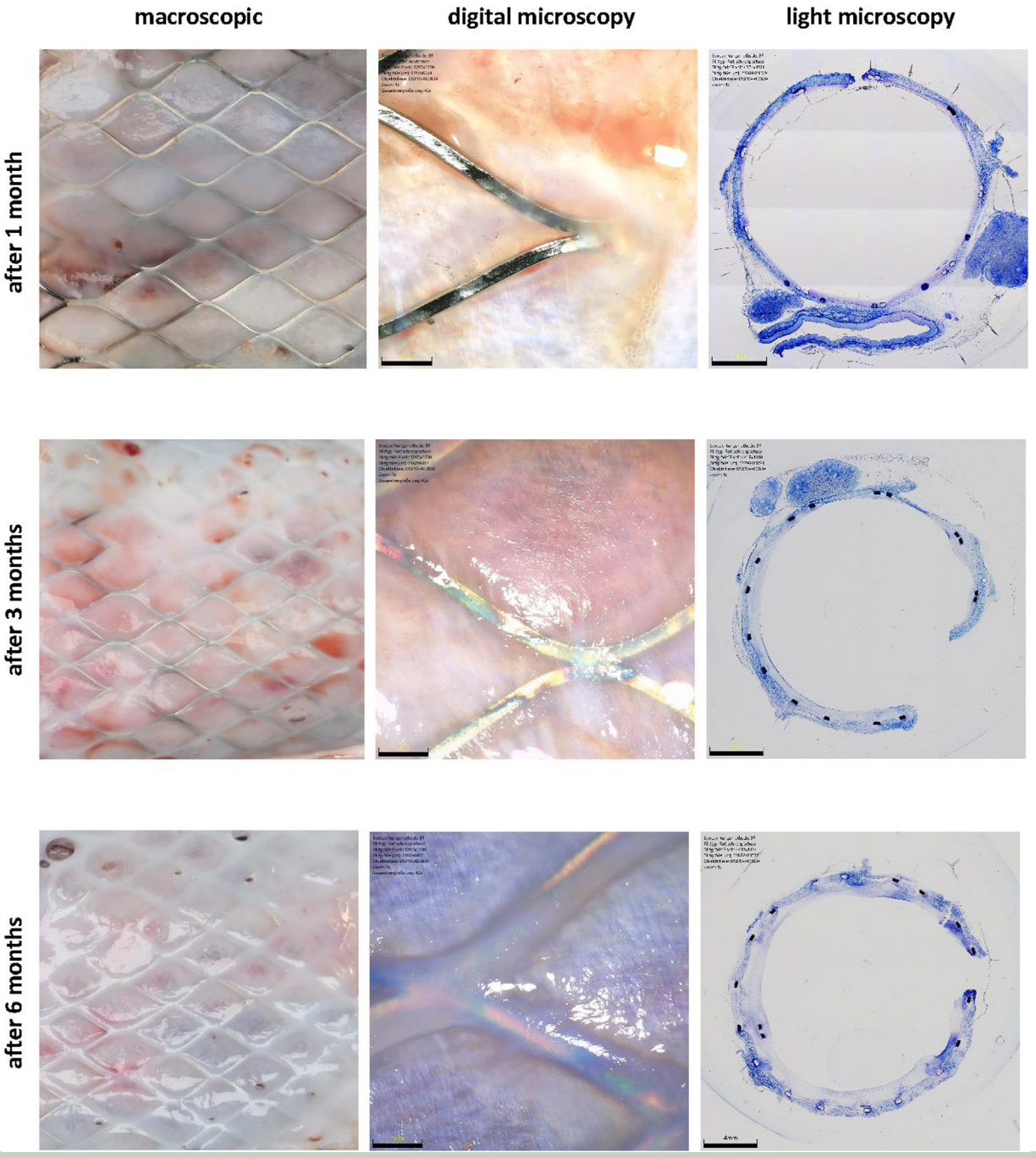

Fig 5. Representative images of macroscopic, digital microscopic, and light microscopic images of investigated segment after 1, 3, and 6 months.

the implantation. No evidence of stent fracture, corrosion or degradation could be detected during the macroscopic and microscopic evaluations (Fig 5).

One month postoperative. The tissue covering was only partially developed and often consists of only a thin layer of cells. Tissue coverage of stents tended to increase distally of ≤80%.

Three months postoperative. Compared with the results after first month, both the percentage of tissue coverage and the density of the intraluminal tissue layer increased. A tissue coverage of 80% up to 100% was seen in all samples. The tissue coverage over nitinol rings and density of layers increased distally.

Six months postoperative. The nitinol rings of the stents were almost completely covered with a dense tissue layer (100%) with minor gaps in the area of vessel branches.

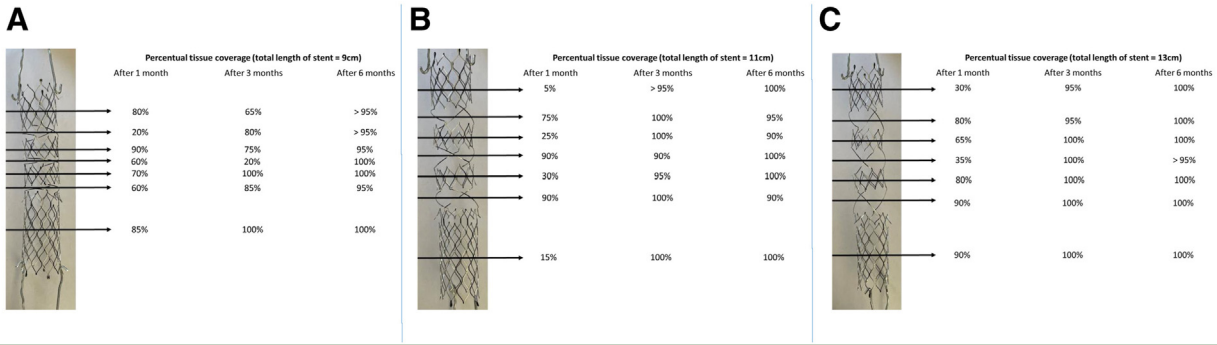

Fig 6. (A-C) Overview of tissue coverage over stents with different lengths after 1, 3, and 6 months.

Table II. Endothelialization of stents after 1 month

Segment	Total length of stent = 9 cm	Total length of stent = 11 cm	Total length of stent = 13 cm
NCP	No intimal proliferation	No intimal proliferation	No intimal proliferation
S1	127 μm	30 μm	99 μm
M1	-	419 μm	193 μm
S2	378 μm	112 μm	285 μm
M2	1125 μm	-	474 μm
S3	314 μm	160 μm	439 μm
M3	695 μm	330 μm	160 μm
S4	219 μm	89 μm	78 μm
NCD	No intimal proliferation	No intimal proliferation	No intimal proliferation
Average	476 μm	190 μm	247 μm

Analyses of endothelialization

One month postoperative. The native blood vessel wall was intact. At 1 month after implantation, there was already a thin layer of tissue over the stents. The neointimal coverage of stents essentially began at the distal segments (Fig 6, *A*). The tissue coverage tends to increase distally by ≤127 μm in S1, 378 μm in S2, and 439 μm in S3. In S4, there is less tissue coverage, with a maximum of 219 μm. The nitinol rings were covered by tissue up to a maximum of 419 μm in M1, 1125 μm in M2, and 695 μm in M3 (Table II). No significant differences were found between different lengths of stents.

Three months postoperative. At 3 months after implantation, the stents were almost completely covered by thicker and denser layer of tissue (Fig 6, *B*). A small number of wires between the stent segments (M1 and M2) were not completely endothelialized. Through the neointima, the structure of the scaffold was visible. There was a distally increasing tissue coverage of a maximum of 217 μm in S1, 653 μm in S2, and 641 μm in S3. In S4, there is a maximum tissue coverage of 721 μm. The nitinol rings were covered with tissue up to a maximum of 1176 μm in M1, 1297 μm in M2, and 1180 μm in M3 (Table III). No significant differences were found between different lengths of stents.

Six months postoperative. At 6 months after implantation, the stents were completely covered by a dense tissue layer (Fig 6, *C*) with a distally increasing tissue coverage of ≤480 μm in S1, 1129 μm in S2, and 1278 μm in S3. Circumscribed stent sections were exposed only in the area of vascular branches. In S4, there was a maximum tissue coverage of 1425 μm. The nitinol rings were covered by tissue up to a maximum of 1005 μm in M1, 1582 μm in M2, and 912 μm in M3 (Table IV). No significant differences were found between different length of stents.

DISCUSSION

Endovenous stenting is increasingly used to treat obstructive lesions of the deep venous system. These improvements are partly the result of advancements in interventional technology and a better understanding of chronic iliac vein obstruction. Moreover, venous stent placement has shown good mid-term to long-term patency rates[17-19] and significant clinical improvementd.[20,21] The European Society for Vascular Surgery

Table III. Endothelialization of stents after 3 months

Segment	Total length of stent = 9 cm	Total length of stent = 11 cm	Total length of stent = 13 cm
NCP	No intimal proliferation	No intimal proliferation	No intimal proliferation
S1	217 μm	182 μm	179 μm
M1	727 μm	1103 μm	1176 μm
S2	653 μm	155 μm	411 μm
M2	770 μm	1068 μm	1297 μm
S3	641 μm	206 μm	573 μm
M3	451 μm	621 μm	1180 μm
S4	313 μm	172 μm	721 μm
NCD	Intimal proliferation	Intimal proliferation	Intimal proliferation
Average	539 μm	501 μm	791 μm

Table IV. Endothelialization of stents after 6 months

Segment	Total length of stent = 9 cm	Total length of stent = 11 cm	Total length of stent = 13 cm
NCP	Intimal proliferation	Intimal proliferation	Intimal proliferation
S1	196 μm	480 μm	377 μm
M1	1005 μm	992 μm	793 μm
S2	1129 μm	1055 μm	600 μm
M2	913 μm	1582 μm	1134 μm
S3	1278 μm	934 μm	1064 μm
M3	701 μm	882 μm	912 μm
S4	1077 μm	1425 μm	625 μm
NCD	Intimal proliferation	No intimal proliferation	No intimal proliferation
Average	900 μm	1050 μm	786 μm

and Cardiovascular and Interventional Radiological Society of Europe guidelines recommend stenting for severe venous obstructive disease.[3,8] The new generation of dedicated venous stents have a sufficient radial force with greater flexibility than arterial stents. Nevertheless, stent deployment injures the vein wall, activating a biological response to injury.[22] The inflammation and healing responses result in two major processes including vascular remodeling and neointimal hyperplasia.[23-25] In-stent stenosis is a major drawback owing to excessive intraluminal narrowing caused by neointimal growth or thrombosis. Therefore, efforts are made to optimize the outcome of venous stenting by modifying the structural design of the stent and improving the implantation procedure. Several studies have investigated the mechanisms and factors that contribute to intimal hyperplasia in animal models. For example, a study by Kornowski et al investigated the effect of stent design on intimal hyperplasia in the coronary arteries of sheep. The authors found that stents with a greater strut thickness and a smaller stent-to-artery ratio were associated with a greater degree of intimal hyperplasia.[26] Another study that investigated the venous response to stent implantation in a sheep model found that a larger stent strut interval led to less neointima formation and better long-term patency of the venous stents.[24]

Findings from the current study show that the W-stent causes no inflammatory response or vascular injury to the native vein proximal and distal to the stent. Tissue formation is tangential, increasing from the proximal to the distal part of the stent; however, the NCP and NCD sections after 3 and 6 months, with the exception of minor intima proliferation, show no other vascular changes (Tables III and IV).

Stents with a closed cell design have a high radial force, but are less flexible compared with the open cell stents.[12,27] Despite the closed cell design of W-stent, the special high porosity configuration and greater length of its interconnecting struts provide high longitudinal and cross-sectional flexibility. A study in an ovine model investigating the neointima formation after venous stenting indicated that the longer bare areas and lower metallic burden of a stent implanted in the venous system facilitates faster and more complete endothelialization.[24]

The hypothesis is that the endothelium behind the struts die because of the mechanical pressure. The cells in between the struts stay alive and are able to cover the stent struts. Owing to the large porosity of the W-stent, the ratio between dead and living endothelial cells is more advantageous, leading to faster coverage of the struts. This effect may result in decreased time on therapeutic anticoagulation for patients.

In the current study, endothelialization was almost complete 6 months after implantation in all study groups (Fig 5). Small changes in intersegmental spaces in the W-stent did not have a significant impact on the stent endothelialization. Additionally, special attention was given to potential migration, especially in the longest configuration. However, evaluation of the stent geometry during placement and after euthanasia did not show any migration, demonstrating the efficacy of the barbs in the proximal and distal segments.

There are several limitations to this study. The sample size was small in this experiment owing to the large animal model used. Moreover, the follow-up time was relatively short; long-term studies need to be carried out. In this experiment, the stents were placed in normal veins. Hence, the effect of the novel stent in the CVO in human still needs to be verified in clinical trials.

CONCLUSIONS

This study demonstrated the feasibility and safety of implanting W-stent in the venous system with a rapid surface coverage. Alteration of stent length and increasing the skipped segments did not affect the development of neointima formation and did not cause migration.

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AUTHOR CONTRIBUTIONS

Conception and design: MB, SS, HJ
Analysis and interpretation: MB, BH, HJ
Data collection: MB, BB, ST, WC, YY, HJ
Writing the article: MB, HJ
Critical revision of the article: MB, BB, ST, BH, WC, YY, SS, HJ
Final approval of the article: MB, BB, ST, BH, WC, YY, SS, HJ
Statistical analysis: Not applicable
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Overall responsibility: MB

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