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BASIC RESEARCH STUDIES

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In vivo evaluation of safety and performance of a nitinol venous stent in an ovine iliac venous model

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Background: **Obstruction of the iliocaval venous outflow tract is a common cause of acute and chronic venous symptoms. Percutaneous stenting is now frequently performed to alleviate obstruction in the central venous system. However, currently used stents were primarily designed for biliary or arterial indications and may not be optimal for use in the venous system. This study evaluated the safety and performance of a novel venous stent (NVS) designed specifically for venous applications in an in vivo venous animal model.**
Methods: **The study evaluated vascular response and safety of the NVS compared with the Wallstent Stent (WS; Boston Scientific, Marlborough, Mass) at baseline, 56, and 180 days in adult sheep. Four sheep received a single NVS in the iliac vein for acute evaluation, and eight underwent bilateral iliac vein stenting using a single NVS on one side and a single WS on the other for longer-term follow-up. Fluoroscopy and intravascular ultrasound imaging were performed at implantation to identify iliac vein diameters at baseline and again at 56 and 180 days. Both iliac veins from all 56-day and 180-day animals (n = 16) underwent histologic examination. Three sections from each vessel were reviewed for intimal strut coverage, luminal thickening, thrombus, and evidence of venous injury. Student *t*-tests were used to compare mean iliac vein diameters for the WS and the NVS.**
Results: **Stent placement of the NVS and WS was successful to within 5 mm of the preselected location in all animals. During follow-up, no clinical evidence of stent thrombosis or obstruction >50% occurred in any limb. Sections of the stented vein at 56 and 180 days exhibited complete or nearly complete endothelial cell coverage, no or minimal luminal thrombus, and virtually complete neointimal coverage of every strut. The WS and NVS both caused an increase in iliac vein diameters immediately after stenting. At 180 days, there was no difference in iliac vein diameter or the percentage change in diameter compared with diameters immediately after stenting as measured by venography and intravascular ultrasound.**
Conclusions: **In an ovine iliac vein model, a new NVS studied to 180 days was free of thrombotic complications and significant luminal stenosis. These data support clinical evaluation of this NVS in appropriately designed human clinical trials. (J Vasc Surg: Venous and Lym Dis 2016;4:73-9.)**

Clinical Relevance: **Stents currently used for treatment of chronic obstruction of the iliocaval outflow tract were originally designed for arterial applications. The etiology of arterial obstruction is different from venous obstruction, and the characteristics of an optimal stent for the treatment of venous disease may be different. Before deploying new stent designs in humans, it is important to validate the performance of these new designs in a relevant animal model. The model described in this report allows evaluation of the response of the venous wall to novel stent designs to determine the suitability of new stent designs for clinical trials in humans.**

Lesions that cause iliocaval venous obstruction (ICVO) are a common cause of chro/nic venous insufficiency.[1-3] Of patients with class 5 and 6 chronic venous insufficiency, 37% of patients had at least 50% narrowing at some point in the iliac or caval venous systems.[4] Hemodynamically significant outflow obstruction may render compression for limb swelling ineffective due to increased discomfort with ambulation or other activity. In a series of publications, Neglen et al and Raju et al[5-7] have described the use of stenting procedures to treat obstructive lesions of the iliac veins and the inferior vena cava (IVC) with acceptable patency rates and reduction in symptoms in most the patients.

Currently, there is no commercially available stent designed specifically for use in the venous system. The most commonly used stents are the Wallstent (WS; Boston Scientific, Marlborough, Mass) and various nitinol self-expanding stents. The WS is the only self-expanding

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stent available in the United States (U.S.) with diameters >14 mm. None are approved by the U.S. Food and Drug Administration for use in the venous system. Results using these stents designed for use in the arterial system have been favorable, but it is possible that a purpose-designed venous stent would yield improvement in outcomes.[8]

A stent and delivery system offering improved strength, good flexibility, limited shortening on deployment, stability on deployment, and long stent lengths would potentially offer improved results and improved cost-efficacy in venous interventions. In this report we present the initial results of a purpose-designed venous stent for the iliac venous system tested in a large-animal model.

METHODS

The Institutional Review Board approved this study, and animal care complied with the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Washington: National Academy Press, 1996).

Stent system. A novel venous stent (NVS) specifically for use in the pelvic venous system was designed by Veniti Inc (Fremont, Calif). The NVS is a laser-cut self-expanding stent composed of a nickel titanium alloy (nitinol) with closed-cell segments and flexible interconnections designed with high crush resistance specifically for use in the central venous anatomy (Fig 1). The NVS is available in 60-mm, 90-mm, and 120-mm lengths and 12-mm, 14-mm, and 16-mm diameters. The delivery system for the NVS has a coaxial design with an exterior shaft to protect and constrain the stent before deployment. An over-the-wire system compatible with 0.035-inch (0.89-mm) guidewires and a 9F sheath introducer allows delivery via jugular, femoral, or popliteal access.

Animal model. Twelve adult sheep received general anesthesia and both femoral areas were prepared in standard sterile fashion. Each animal received intravenous heparin (100 U/kg). The proximal femoral veins were accessed bilaterally with micropuncture sets and upsized to 9F sheaths bilaterally. Through these sheaths, .035-inch guidewires were placed through the iliac veins into the IVC bilaterally. Dilute iodinated contrast boluses (Visipaque; GE Healthcare Lifesciences, Marlborough, Mass) were injected through the sheaths individually to obtain venograms of each iliac venous system in two projections. The venograms were then used to identify the iliac vein diameters and lengths. Intravascular ultrasound (IVUS) imaging was performed using a Visions .035 catheter (Volcano, San Diego, Calif). Diameter and area measurements were made at multiple locations along the iliac outflow tract to identify the minimum and maximum sizes in the segment to undergo stenting.

In four animals comprising the acute group (immediately euthanized after stent insertion for vein evaluation), unilateral iliac vein stenting was performed via a left jugular approach using a single NVS in each case (12 mm × 60 mm in two and 14 mm × 60 mm in two). Bilateral common femoral vein access was used in the other eight animals. One iliac vein was stented using a single WS endoprosthesis, and the contralateral iliac vein was stented using a single NVS. Once successful venous access was obtained, random allocation was used to assign stent to side. In the 56-day cohort, the WS was implanted on the left side in three sheep and the NVS in one sheep. In the 180-day cohort, the WS and NVS were implanted on the left side in two sheep each.

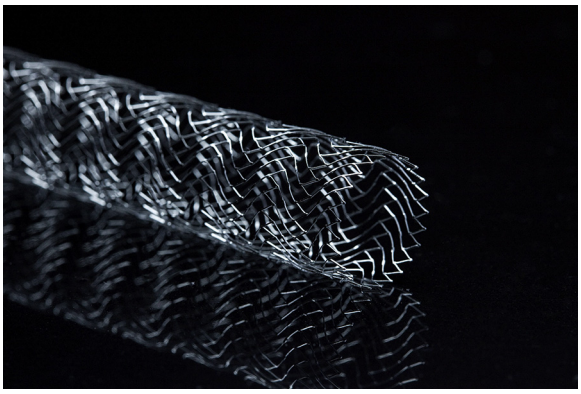

Fig 1. Novel venous stent (NVS) close-up illustrates the dense nitinol mesh with long, thin bridge members.

Stent diameter was chosen to achieve 10% to 30% oversizing wherever possible. However, the minimum iliac vein diameter in this animal model ranged from 6.5 to 12 mm, resulting in oversizing of up to 2.0 times the iliac vein size in some sheep. The same diameter WS and NVS were used in each animal (12 mm in six sheep and 14 mm in two). The length of the stent to be deployed was chosen to best match the length of the target vessel at an appropriate diameter (60 mm length in six sheep and 90 mm in two sheep). The iliac stent was positioned on each side so that the proximal end of the stent would be deployed at the confluence of the iliac veins with no extension into the IVC. Deployment of the WS was performed according to manufacturer recommendations. Deployment of the NVS into the iliac vein was performed by withdrawing the overlying sheath while pinning the stent in position.

After bilateral stent deployment, bilateral iliac venography was performed using a power injector and dilute iodinated contrast. The same two projections used before intervention were used after deployment for venography. IVUS imaging was also repeated to identify immediate postdeployment iliac diameters and to document stent apposition to the vein walls.

Follow-up study procedure. The four animals in the acute group were euthanized immediately after stent insertion. Eight weeks after stent implantation, four animals were prepared with general anesthesia, and the bilateral femoral veins were reaccessed after heparinization. Plain film X-ray images were obtained in two projections to evaluate for stent fractures. Venography was performed in two projections, and IVUS was repeated with the same protocol