Percutaneous Therapy for Deep Vein Reflux

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ABSTRACT

At present, there are no widely accepted surgical or percutaneous treatment options for chronic venous insufficiency of the deep venous system. The small intestinal submucosa square stent bicuspid venous valve (BVV) has shown the most promising results of artificial venous valves developed to date. In experimental long-term studies in sheep jugular veins, 88% of implanted valves exhibited good function; 12% had decreased function related to valve tilting, of which only 4% had partial thrombosis. BVVs were also placed in three patients and have remained patent without thrombosis or other complications since 2002. At present, 3 years after BVV placement, symptoms in two patients are decreased. Proper sizing and proper placement of the valves were critical to their function. To eliminate occasional tilting of the original BVV, a second-generation BVV has been developed and tested.

KEYWORDS: Venous valve, deep venous insufficiency, stents and prostheses, biomaterial, interventional procedures, experimental

Objectives: Upon completion of this article, the reader should be able to (1) describe research for transcatheter valve replacement in animals, (2) understand the different treatment options available to patients with chronic deep venous reflux, and (3) understand percutaneous therapy for deep venous insufficiency.

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Although the development of percutaneously implantable devices began in the 1960s and 1970s, it was not until 1981 that Dotter noted that "Catheter based devices have met clinical success in the closure of patent ductus arteriosus and atrial septal defects. Why not catheter-placed prosthetic valves? Femoral vein valve incompetence might offer a reasonable initial target."¹ That idea has led to further refinements of the technology, which in turn led to new inventions. Several percutaneously implanted prosthetic valves for replacement of diseased or absent venous valves have been

experimentally developed over the past 12 years.²⁻⁷ Most devices were tested initially in animal models, and the tests with two different artificial valves were followed by initial clinical trials in humans.⁸ This emerging technology will be of great interest to interventional radiologists, vascular surgeons, and other physicians who care for patients with advanced chronic venous disease.

Artificial venous valves constructed from either synthetic material or biomaterial should be low in profile, easy to place percutaneously, durable, stable,

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nonthrombogenic, and functionally reliable and should prevent reflux. Biological materials have potential advantages over synthetic materials as coverings for intravenous valve devices; these include rapid and complete endothelialization, reduced immunologic response, easier incorporation into the vessel wall, and higher resistance to infection.^{6,9,10}

Since 1999, we have been working on a square stent-based bicuspid venous valve (BVV). The valve cusps are constructed of porcine small intestinal submucosa (SIS) (Cook Biotech, West Lafayette, IN), a material that is marketed in the United States as a surgical mesh to reinforce soft tissue. The SIS is sewn to the stainless steel valve frame (Cook, Bloomington, IN).^{4,6,11} We completed a long-term study in sheep with BVV placement in jugular veins, studied its endothelialization, and then placed it in three patients to evaluate its safety.^{4,6,8,11} To eliminate occasional tilting of the original venous valve, a second-generation nitinol BVV has been developed and tested in sheep.¹² We found it very promising.

THE VALVE AND ITS MODIFICATIONS

First-Generation Bioprosthetic Venous Valve

The original valve is a prosthetic, bicuspid valve consisting of three major components: a valve frame, valve cusps, and a delivery system. The stainless steel square stent with four barbs becomes a venous valve when two pieces of SIS are sutured to a stent frame (Fig. 1A).^{4,6,11} BVVs were manufactured in sizes from 8 to 19 mm in diameter in 2-mm increments (Cook, Inc.). They are deployed with an over-the-wire delivery catheter system (Cook, Inc.) consisting of an 11 Fr (outer diameter) guiding catheter with distal marker and coupled with a 9 Fr dilator. The dilator has a round indentation ~6 cm from its tip to nest the folded valve. The valve is front loaded inside the guiding catheter (Fig. 1A).

The method of valve deployment is similar to that of deploying self-expandable stents. Typically, the BVV should be oversized 1–2 mm to the vein maximal diameter. After deployment, the BVV self-expands and appears to function in the same manner as a native venous valve. The BVV is open during continuous antegrade flow. When retrograde pressure is applied, the BVV closes, the two SIS leaflets forming a seal preventing retrograde flow through the valve. The BVV incorporated into a vein wall consists of two cusps, the valvular agger distal and the valvular sinus proximal. The cusp consists of a free border (SIS) and parietal part (vein wall). Square stent barbs engage into the vessel wall and ensure proper position of the BVV and prevent its displacement by blood flow. In vitro and in vivo testing proved that the valve is competent and able to withstand

retrograde hydrostatic pressures. BVV is anatomically and functionally similar to the native valve.^{4,6,11} The lyophilized and the hydrated BVVs used in these experiments were about four and six times thicker than a natural valve (30 μ m).^{6,10} BVV placed in a reverse position into vessels such as the inferior vena cava or aorta is effective enough to become a vascular occluder.^{8,11} The SIS valve acts as a scaffold for tissue ingrowth. Brountzos and associates demonstrated that recruitment of circulating cells could initiate in vivo remodeling of an SIS venous valve independent of cell wall contact.¹⁰

EXPERIMENTAL LONG-TERM STUDY IN SHEEP

In 2001, Pavcnik and colleagues reported on 6-month experimental studies that were encouraging for the clinical application of a prosthetic venous valve made from SIS.¹¹ Twenty-five BVVs were placed into the jugular veins in 12 sheep. Eighty-eight percent of the implanted valves exhibited good function; 12% had decreased function related to valve tilting, of which only 4% had partial thrombosis. This study demonstrated that the SIS valve is nonthrombogenic, a great advantage in the venous circulation, where, in contrast to the arterial circulation, hardly any thrombogenic surface is tolerated. The parietal borders of BVV sinuses consist of native vein wall with intact endothelium, which was thought to help in preventing local thrombosis. In addition, after implantation, venous endothelial cells quickly attached to the SIS. Endothelialization of both surfaces of the valve leaflets was complete in approximately 1 month.^{11,12} Gross and histologic examinations demonstrated incorporation of remodeled and endothelialized SIS of BVVs into the vein wall. SIS valves were remodeled with newly formed collagen fibers, endothelial cells, variable fibrocytes, capillaries, and some inflammatory cells. As this process continued, other cells infiltrated and multiplied, completely enveloping the SIS bioscaffold in about 3 months. Slight to moderate leaflet thickening was found mostly at their base. Chronic inflammation and cellular ingrowth around sutures and the stent wires created a seal between the vein wall and the two valve pockets. The SIS was gradually reabsorbed and replaced by the host's own cells. The results of this study were encouraging for the clinical application of a prosthetic venous valve.

POSSIBLE CLINICAL APPLICATIONS

The BVV is intended for use as a treatment for incompetent venous valves in patients with chronic venous insufficiency of the lower limbs, patients with valve damage secondary to thrombosis, and patients with valvular aplasia or dysplasia.

Possible clinical applications include chronic venous insufficiency, varicoceles in males, pelvic venous congestion in females, and failed conduits from the right ventricle to the pulmonary artery.

Advanced Deep Chronic Venous Insufficiency Deep chronic valvular insufficiency (CVI) is a central feature in the natural history of primary venous disease, and it plays an important role in post-thrombotic disease. Deep CVI is a clinical condition characterized by lower extremity venous hypertension. Venous stasis is the result of valvular reflux, obstruction, or both. Reflux in the venous system is due to incompetent or destroyed valves. Primary valvular incompetence (PVI) is the result of a dilated valvular ring or redundancy or dysplasia of the valve leaflets. SVI is associated with a history of post-thrombotic etiology; valve dysfunction causing stasis

may also be a predisposing factor to thrombosis.¹³ In PVI, valves have smooth, thin wavy leaflets, in contrast to the thickened, deformed valve cusps associated with secondary valvular insufficiency (SVI).

Pelvic Venous Congestion and Varicoceles Pelvic venous congestion in females and varicoceles in males present a complex problem. In most cases, these conditions are related to valvular incompetence of gonadal veins. Both populations of patients may present with chronic pain (in the pelvis for women, in the scrotum for men), and male patients may also manifest decreased

Figure 1 Percutaneous therapy for deep vein reflux in a 39-year-old male. Patient with post-thrombotic syndrome had severe venous claudication with an active venous ulcer. (A) First-generation venous valve and radiographic image of the front-loaded valve inside the delivery sheath (arrows). (B) Descending venogram in upright position, showing grade 4 reflux at the left common femoral vein, with contrast flowing retrograde into the profunda femoral vein and valveless femoral vein all the way into the calf. (C) Valve placed into cranial aspect of femoral vein.

Figure 1 (continued) (D) Follow-up descending venogram in upright position 2 months after valve placement demonstrates no reflux through the valve into femoral vein (arrows). (E) Active ulcer before artificial valve placement. (F) Healed ulcer at 1-month follow-up. (Reprinted from Pavcnik D, Machan L, Uchida B, et al. Percutaneous prosthetic venous valves: current state and possible applications. *Tech Vasc Interv Radiol* 2003;6:140, with permission from Elsevier.)

fertility. An estimated 10 million women are affected by pelvic pain, but a clear etiology is often elusive. It has been postulated that the pain in many such cases is secondary to gonadal reflux and secondary pelvic venous congestion. The standard treatment for gonadal reflux has been surgical ligation or percutaneous transcatheter embolization with sclerosing agents and coils.¹⁴⁻¹⁶ Patients presenting with these syndromes might instead benefit from treatment with BVV.

Percutaneous Implantation of a Valve in the Pulmonary Position Extracardiac conduits for the establishment of right ventricular to pulmonary artery continuity are constructed with xenograft, pericardial, or homograft valves. In the event that the conduit becomes stenotic and requires stent placement during percutaneous catheterization, the valve in conduit must be sacrificed. Boudjemline and Bonhoeffer¹⁷ have reported successful percutaneous valve replacement in failed conduits using a bovine jugular vein valve mounted inside a stent. A long-term feasibility study has been done by C.E. Ruiz to evaluate BVV in swine pulmonary artery (personal communications).

CASE REPORTS

A pilot clinical trial using the first-generation bioprosthetic venous valve (Cook) has been completed (but not yet published). Three patients with established symptomatic deep CVI were treated with square stent-based SIS BVVs as part of a safety trial. Patients began warfarin (Coumadin) therapy 2 days prior to the BVV implantation at 5 mg/day to achieve a therapeutic international normalized ratio (INR) of 2.0–3.0 and were kept on a dose appropriate to maintain this level for 6 months. Prior to BVV implantation, patients received 5000 units of heparin. The valves were implanted percutaneously by a right internal jugular approach using a delivery system consisting of an 11 Fr guiding catheter and 9 Fr dilator. Descending venograms of the involved limb were done first in the upright position without and with a Valsalva maneuver (Fig. 1B). The proximal and distal femoral vein (FV) diameter was measured in two projections in the location of the intended vein implantation using a 0.035 graduate measuring guidewire (Cook Inc.).

The valve was selected using a size similar to the vein diameter measured with a Valsalva maneuver, ~1–2 mm larger than the vein diameter without increased pressure. The selected lyophilized BVV was rehydrated with injection of 10 mL of heparinized saline through the side arm of the 11 Fr guide catheter 15 minutes before valve delivery. The BVV was implanted into the proximal FV just below the confluence of the deep FV. Delivery of the BVV was accomplished by withdrawing the guiding catheter while holding the 9 Fr dilator. As the self-expanding BVV was deployed, it

opened to make contact with the vein wall. The retention dilator and the 9 Fr (internal diameter) guiding catheter were removed, leaving the 11 Fr sheaths in the internal jugular vein for the follow-up venograms. The BVVs were studied for function and stability in the upright position by injecting contrast medium above the BVV. Follow-up descending venograms were done at 2 months and then the patients were observed by duplex ultrasonography.

Patient 1 A 38-year-old man with post-thrombotic syndrome had severe venous claudication with a CEAP C-6 (active ulcer) secondary to valve insufficiency of the deep veins of the left limb. The disease involved mainly deep veins, with descending venograms showing severe (grade IV) reflux at the left common FV, which extended into the profunda FV and valve-less FV all the way into the calf (Fig. 1B). There was no significant reflux into the greater saphenous vein and only grade I reflux into the lesser saphenous vein. After a 15-mm BVV was deployed, descending venography demonstrated only minimal reflux (Fig. 1C). Follow-up descending venograms at 2 months and duplex ultrasonography at 1, 3, 6, and 12 months demonstrated no spontaneous reflux through the valve into the FV (Fig. 1D). A significant grade III leak between vein wall and valve frame was seen, although only when a Valsalva maneuver was performed. Clinically, edema of the left leg improved, and the left thigh circumference decreased from 63.8 cm before valve placement to 58.5 cm at 1-year follow-up. The patient's active ulcer was found healed at 1 month after BVV implantation and had not recurred at 1 and 3 years follow-up (CEAP C-5) (Fig. 1E and 1F).

Patient 2 A 64-year-old man had skin changes, edema, and pain of the left leg related to severe PVI at the left femoral and popliteal vein. Placement of an 18- to 19-mm BVV was technically successful, but it was placed 8–10 mm lower in the FV than had been intended. This resulted in a vein-valve size mismatch and a BVV with a significant valve leak. During the 3-year follow-up the BVV stayed patent and did not cause any complication, but there was no change in the patient's clinical symptoms.

Patient 3 A 40-year-old man with deep CVI syndrome related to post-traumatic, post-thrombotic syndrome had severe venous claudication with CEAP C-4 (skin changes, edema, and pain) in his left leg. These symptoms were due to severe reflux in the left femoral and valve-less popliteal veins. An 11-mm BVV placed into the distal left FV resulted in ~30% valve tilting. An immediate follow-up venogram showed good valve function with minimal leak. The patient had immediate clinical improvement of his symptoms, mainly a decrease of edema and pain in his leg. At present, 3 years after

Figure 2 Second-generation valve at 6 weeks follow-up. (A) Non-restricted lyophilized bicuspid venous valve with four barbs. (B) Radiographic image of the valve with barbs front loaded into an over-the-wire 10 Fr delivery system (arrows). (C) Jugular venogram with injection above the valve demonstrates valve patency (unrestricted antegrade flow).

Figure 2 (continued) (D) An injection of contrast medium below the valve demonstrates closure of the valve and does not reveal any reflux. (E) Explanted specimen shows smooth incorporation of the bioprosthetic valve into the vein wall in sheep jugular vein at 6 weeks.

BVV placement, the patient's symptoms are significantly decreased and the BVV is functioning well with minimal leak as a monocusp valve (because of tilting).

Second-Generation Bioprosthetic Venous Valve

DEVICE

To eliminate occasional tilting of the original bioprosthetic venous valve, a second-generation BVV (SG-BVV) has been developed. The new valve is a sturdier version of the device described previously. It now has two overlapping stents made from nitinol, providing four extra points at which the device makes contact with the inner wall of the vessel. Two sizes of SG-BVV were tested in veins with diameters of 10 to 12 mm and 12 to 14 mm (Fig. 2A).

DELIVERY SYSTEM

The 110-cm-long 10 Fr delivery system consists of an introducer sheath with a radiopaque marker tip and Tuohy-Borst adapter (Cook) and dilator with a cutout

where the SG-BVV is loaded (Fig. 2B). The lyophilized SG-BVV with approximately the same diameter as the target vein should be selected and rehydrated at least 10 minute before implantation by injecting 10 mL of heparinized saline through the side arm of the sheath.

SHORT-TERM STUDY IN SHEEP

The SG-BVV was evaluated for 6 weeks in 13 sheep. All the SG-BVVs self-centered in the veins and no tilting was seen in 26 jugular veins. The expanded SG-BVVs, with their two pockets, were anatomically and functionally similar to the natural valves. On venograms immediately after placement, all 26 valves were competent except for minimal reflux at the unincorporated attachment sites. This minimal leak was corrected when remodeling by host cells from the venous wall and circulating cells fused the SIS membrane to the wall. Venograms at 6 weeks follow-up demonstrated no reflux in 24 (92.3%) valves (Fig. 2C, 2D, 2E). Incompetence in two valves was related to oversized valves.¹²

Selecting the proper valve size—matching the valve size to the vein diameter—is essential for good valve function. The vein at the site of intended valve

placement should be measured in maximal distention in two projections. We measured the sheep jugular veins in the Trendelenburg position. In human subjects, an up-right position during venography or intravascular ultrasonography will be necessary to measure accurately maximum FV diameters. We believe that the optimal site for SG-BVV placement is the location of the failed natural valve, usually caudal to the entrance of a venous tributary, where the vein is larger.

SUMMARY

At present, there are no widely accepted surgical or percutaneous treatment options for deep chronic venous insufficiency. A percutaneously implantable, nonimmunogenic and nonthrombogenic bioprosthetic venous valve that remains patent and competent over time is an attractive alternative to direct venous valvular reconstruction or transplantation. Our results demonstrate the potential for effective treatment with bioprosthetic venous valves and warrant additional research in carefully selected patients that may lead to an effective, minimally invasive treatment for deep chronic venous insufficiency. More recently, the second-generation BVV has been further modified. At the time of this writing, a modified SG-BVV has been in clinical trials outside the United States.

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