Acta clin Croat 2002; 41 (Suppl): 93-97 Original Scientific Paper

CHRONIC VENOUS INSUFFICIENCY AND BIOPROSTHETIC BICUSPID SQUARE STENT BASED VENOUS VALVE FOR TRANSCATHETER PLACEMENT

Dusan Pavcnik

Dotter Interventional Institute, Oregon Health Sciences University, Portland, Oregon, USA

SUMMARY – The past 25 years have witnessed experimental efforts at catheter-based management of aortic, pulmonary and venous valve regurgitation. This chapter describes the initial designs and experimental evolution of a bioprosthetic venous valve that can be implanted by using a transcatheter technique. An evaluation of a percutaneously placed bioprosthetic, bicuspid venous valve (BBVV) consisting of a square stent and small intestinal submucosa (SIS) covering was performed in 15 sheep. Of 30 BBVVs placed into the jugular veins, 28 exhibited good valve function on immediate venograms, and 25 on venograms prior to sacrifice. Gross and histologic examinations demonstrated incorporation of remodeled and endothelialized SIS BBVVs into the vein wall. Minimally invasive placed square stent based SIS valve is a promising one-way, competent valve.

Venous stasis or chronic venous insufficiency 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, redundancy or dysplasia of the valve leaflets. In PVI, valves have smooth, thin wavy leaflets in contrast to the thickened, deformed valve cusps associated with secondary valvular insufficiency (SVI). SVI is associated with a history of post-thrombotic event in etiology; valve dysfunction causing stasis may also be a predisposing factor to thrombosis[1].

Chronic venous insufficiency (CVI) is a clinical condition characterized by lower extremity venous hypertension[2]. Normal valve function and structure, combined with foot and muscle pump action, comprise a complex hemodynamic system required for efficient venous emptying of calf veins in the upright position. William Harvey initially evaluated the function of venous valves in 1628[3], however, more than 300 years had passed before Eiseman and Malette[4] reported their experimental attempt at venous valve repair. Then, 25 years ago, Kistner[5] first described venous valve repair in human beings. Internal valvuloplasty results for carefully selected patients with PVI show 70%-80% of good long term clinical and duplex follow-up, however, only 37%-100% of valve transplantation and 17%-66% of transposition procedures for CVI have good long term patency[6].

The challenge of correcting valvular incompetence has recently included application of endovascular technique. Newer approaches to restoration of valve competence include implantation of axillary vein valves or cryopreserved valves and experimental work with canine jugular vein-stent and cryopreserved vein stent combinations[7].

A percutaneous, minimally invasive, outpatient treatment of symptomatic reflux is an attractive concept. In 1981, Charles Dotter[8] suggested transcatheter venous

Correspondence to: *D. Pavcnik, M.D., Ph.D.,* Dotter Interventional Institute, Oregon Health Sciences University, L342, 3181 SW Sam Jackson Park Road, Portland, Oregon, 97201
(503) 494-8396 phone, (503) 494-4258 fax;
e-mail: pavcnikd@ohsu.edu

Acknowledgment: The author thanks Martina Basin Pavcnik, DMD, and Sheri Imai, BS, for their assistance.

valve placement: “Catheter based devices have met clinical success in the closure of patent ductus arteriosus and atrial septal defects. Why not catheter-placed prosthetic valves?” In 1993, Uflacker reported percutaneous placement in the inferior vena cava of pigs of a monocusp venous valve consisting of a single body Z stent with polyetherurethane or polytetrafluoroethylene (PTFE) membrane[9]. Two more recent experimental studies have employed catheter insertion of bovine jugular venous valves mounted within an expandable stent[10,11]. Thorpe *at al.* have also described promising short-term experimental results with catheter insertion of a bicuspid venous valve made from the porcine small intestinal submucosa (SIS) mounted on a single body Z stent base[12].

In 2000, Bonhoeffer *et al.*[13] reported first successful percutaneous valve replacement in a failed conduit from the right ventricle to the pulmonary artery in a 12-year-old boy. They used bovine jugular vein valve mounted inside stent.

Square stent based venous valve

Recently, Pavcnik *et al.* have reported results of long-term experimental study that are encouraging for the clinical application of manufactured square stent venous valve (Fig. 1). The square stent venous valves appear to undergo remodeling with recipient’s own cells and function without the need for anticoagulants. Therefore they have the potential to treat chronic venous insufficiency by replacing valves that are destroyed from thrombophlebitis or that are incompetent[14-16].

After deployment, the square stent based valve self-expanded and appeared to function in the same manner as a natural venous valve. The bioprosthetic bicuspid venous valve (BBVV) was open during continuous antegrade flow. When retrograde pressure was applied, the BBVVs closed, and the two SIS leaflets sealed against each other preventing retrograde flow through the valve (Fig. 2). BBVVs placed into jugular veins centrally (closer to heart) or across the native valve (NV) took over the function of these valves. All 16 BBVVs placed across the NVs were functional with minimally thickened leaflets after one, three and six months (Fig. 3). Twelve BBVVs placed centrally to the NV had leaflets thickened to a mean of 750 μ. This suggests that when replacing the function of the natural valve in their location, BBVVs have best chance to function.

A manufactured, percutaneously implantable, non-immunogenic venous valve that remains patent and competent over time is an attractive alternative to direct venous valvular reconstruction or transplantation. The combination of a square stent and the biomaterial SIS[14-16]. permits manufacture of a bicuspid venous valve that is anatomically and functionally similar to the NV. Attached to a square stent, SIS provides an effective bioscaffold for attraction of host cells. The BVV incorporated into a vein wall consists of two cusps, the valvular agger and the valvular sinus (Fig. 4). The cusp consists of a free border (SIS) and parietal part (vein wall). The SIS used in these experiments was 120 to 180 ì thick and was approximately 4 and 6 times thicker than the NV (30 μ)[16].

At the BBVV agger, where the SIS leaflets were attached to the vein wall, the SIS membranes were thick-

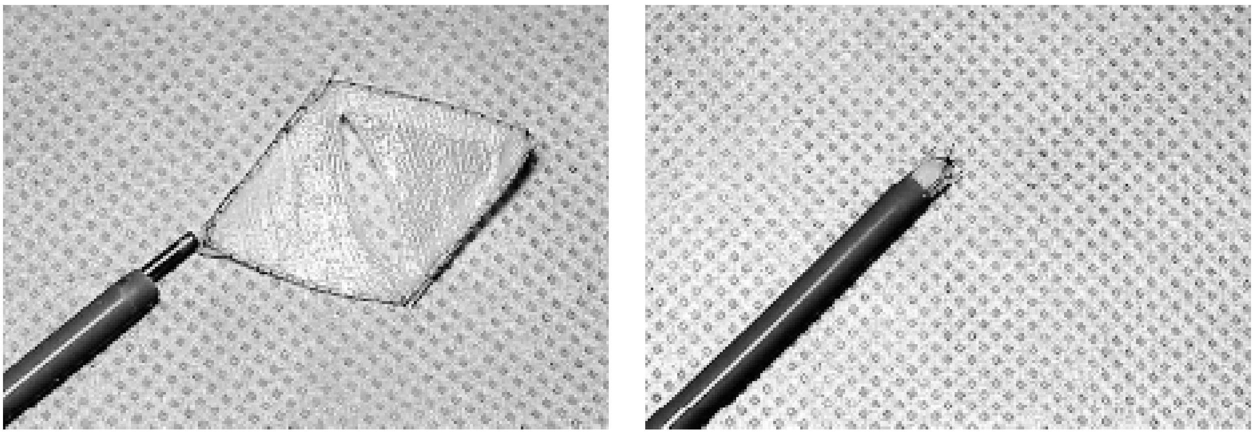

Fig. 1 Square stent based SIS venous valve. A) Non-restricted square stent based valve 20 mm long with 4 barbs for vein 14-15 mm in diameter. A retention wire pusher connected to one barb retains valve. B) Valve front loaded into a 9 Fr guiding catheter.

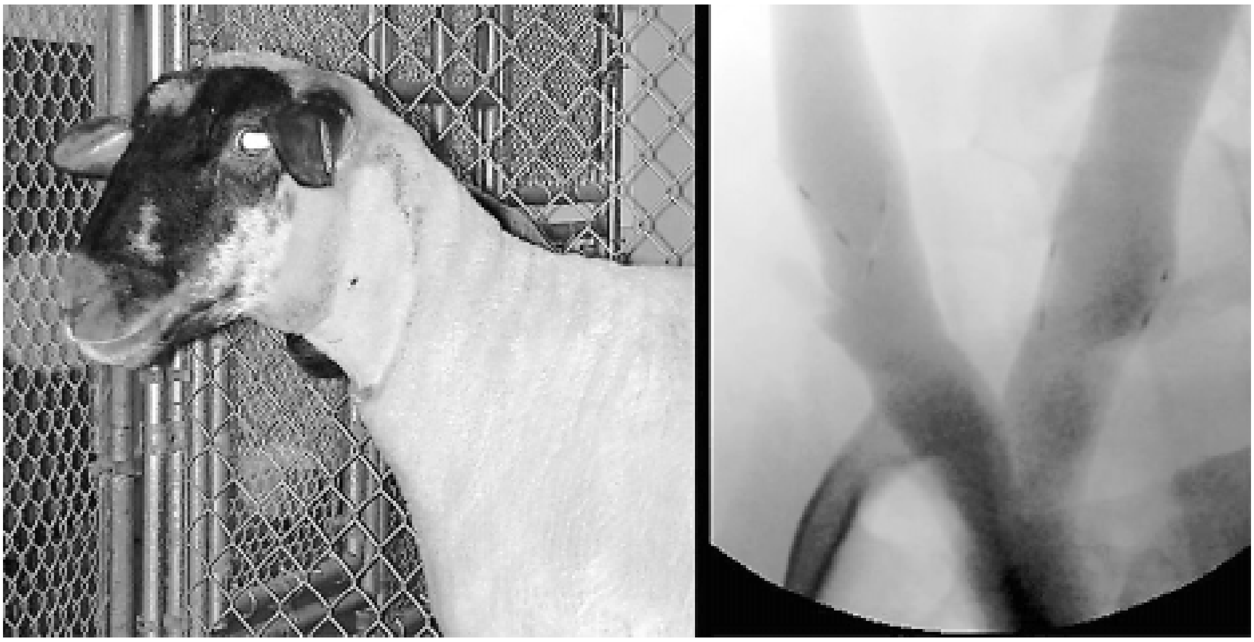

Fig. 2 Function of the square stent based SIS venous valve placed into both external jugular veins. ***A)*** *Jugular venogram with injection distal to the valve demonstrates valve patency. This is analogous to the animal standing upright.* ***B)*** *High volume injection central to the valve demonstrates closure of the valve with no leak. Valves must function in this manner to prevent cephalic reflux when the animal lowers its head to eat or drink.*

ened. This chronic inflammation and cellular ingrowth around sutures and the stent wires created a seal between the vein wall and the two valve pockets[15,16]. Parietal borders of BVV sinuses consisted of natural vein wall with intact endothelium preventing local thrombosis **(Fig. 3).** Out of 30 BVVs with 60 cusps, only one pocket of a single misaligned BVV thrombosed. This suggests the SIS valve is resistant to thrombosis. Venous endothelial cells were attached to SIS one month after implantation. As this process continued, other cells infiltrated the SIS, and the ingrowth of host cells allowed for incorporation of the valve and its borders into the vein wall[16].

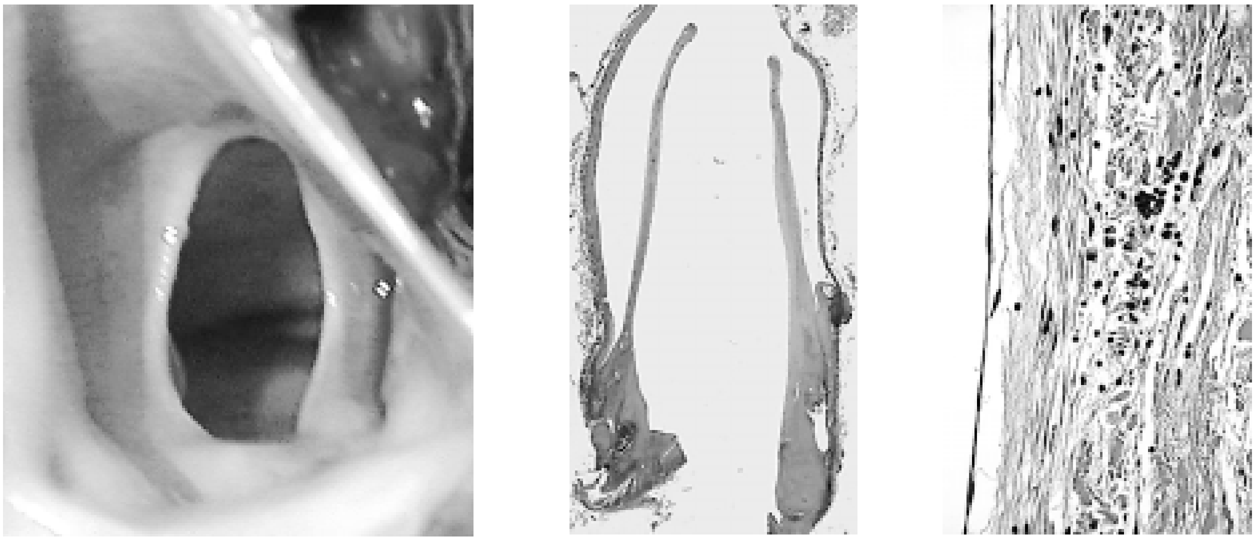

*Fig. 3 Square stent based SIS valve 3 months after implantation in animal. **A)** Axial view from above shows incorporation of the bicuspid valve into vein wall. **B)** Longitudinal microscopic view of both SIS leaflets. **C)** High magnification of the SIS leaflet shows that the membrane has been fully penetrated and reorganized by host cells, including fibrocytes, plasma cells, lymphocytes and endothelial cells. (Hematoxylin & eosin stain original magnification 400 x).*

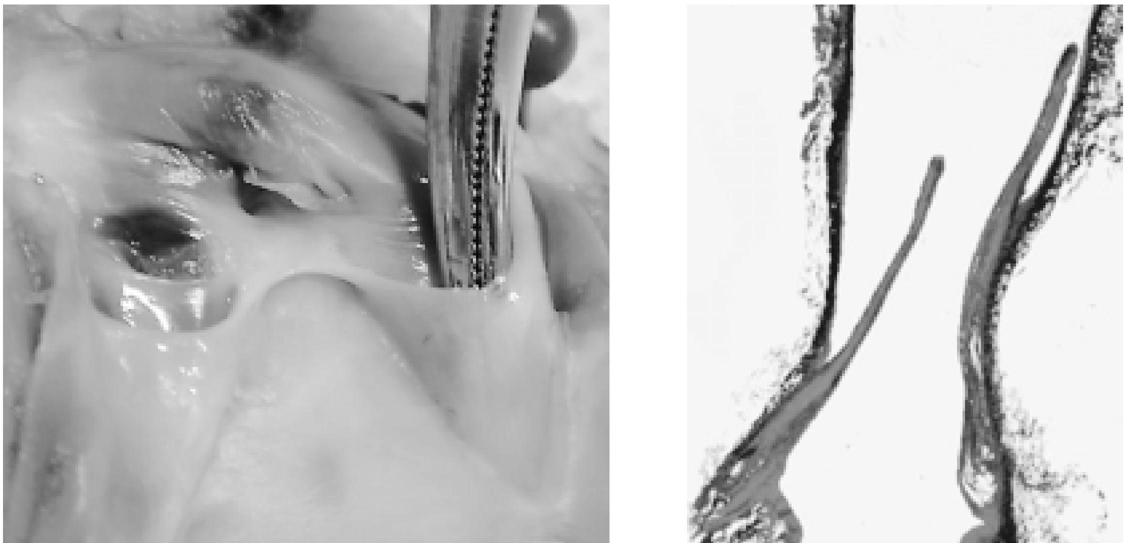

*Fig. 4 Square stent based SIS valve at 6 months. **A)** longitudinal cross-section shows an incorporated valve with two cusps and two sinuses. **B)** Longitudinal microscopic view of both remodeled SIS leaflets.*

The BBVVs described herein demonstrate several advantages over other prosthetic venous valves[9-13]. These include simple introduction with valve self-expansion and self-attachment by barbs to the vein wall. The valve appears stable and does not spontaneously migrate. The 9 Fr size of the delivery catheter for BVV is smaller than that for delivery of a monocusp valve[9]. It is, however, much smaller than the 16 Fr size for the bicuspid SIS covered Z stent valve[12] and the 18 Fr size required for insertion of a stent mounted bovine jugular vein valve[10,11,13]. Another advantage of the square stent based SIS valve is its availability in different size for various vein diameters. They may also not require anticoagulation. The results of this study are encouraging and warrant an experimental trial in humans[15,16].

Although a great deal of work remains to be done, these early results indicate that the development of a biological prosthetic, pulmonary and venous valve for transcatheter placement is more than feasible.

References

1. RAJU S. Venous insufficiency of the lower limb and stasis ulceration: changing concept and management. Ann Surg 1983:197;6:688-97.
2. SCHURR HJ, SMITH PD. Pathogenesis of venous ulceration. Phlebology 1992: (Suppl 1):13-6.
3. HARVEY W. An anatomical description concerning the movement of the heart and blood in living creatures (Whitteridge G translation). Oxford, UK: Blackwell Scientific Publications, 1976.
4. EISMAN B, MALETTE W. An operative technique for the construction of venous valve. Surg Gynecol Obstet 1953;97:731-4.
5. KISTNER RL. Surgical repair of the incompetent femoral valve. Arch Surg 1975;110:1336-42.
6. AKESSON H, RISBORG B, BJORGELL O. External support valvuloplasty in the treatment of chronic deep vein incompetence in the legs. Int Angiol 1998;18:233-8.
7. BERGAN JJ. Prospects for minimal invasion in venous disease. Vasc Surg 1999;33:247-9.
8. DOTTER ChT. Interventional radiology – review of an emerging field. Semin Radiol 1981;16:7-12.
9. UFLACKER R. Percutaneously introduced artificial venous valve: experimental use in pigs. The 1993 Annual Meeting of the Western Angiographic & Interventional Society, Portland, OR. Abstract Book 1993:30.
10. GOMEZ-JORGE J, VENBRUX AC, MAGEE C. Percutaneous development of a valved bovine jugular vein in the swine venous system: a potential treatment for venous insufficiency. J Vasc Interv Radiol 2000:11:931-6.
11. BONHOEFFER P, BOUDJEMLINE Y, SALIBA Z, HAUSSE AO, AGGOUN Y, BONNET D, SIDI D, KACHANNER J. Transcatheter implantation of a bovine valve in pulmonary position: a lamb study. Circulation 2000;102:813-6.
12. THORPE PE, OSSE FJ, CORREA LO. The valve-stent: development of a percutaneous prosthesis for treatment of valvular insufficiency. The 12th Annual Meeting of the American Venous Forum, Phoenix, Arizona. Abstract Book 2000:82.
13. BONHOEFFER P, BOUDJEMLINE Y, SALIBA Z, MERCKY J, AGGOUN Y, BONNET D, ACAR P, LE BIDOIS J, SIDI D, KACHANNER J. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403-5.
14. PAVCNIK D, UCHIDA BT, KELLER FS, CORLESS C, RÖSCH J. Retrievable IVC square stent filter: experimental study. Cardiovasc Intervent Radiol 1999;22:239-45.
15. PAVCNIK D, UCHIDA B, TIMMERMANS HA, KELLER FS, RÖSCH J. Square stent: a new self-expandable endoluminal device and its applications. Cardiovasc Intervent Radiol 2001;24:207-17.
16. PAVCNIK D, UCHIDA B, TIMMERMANS HA, CORLESS CL , O'HARA M, TOYOTA N, MONETA GL, KELLER FS, RÖSCH J. Percutaneous bioprosthetic venous valve: a long term study in sheep. J Vasc Surg 2002;35 (in press).

Sažetak

KRONIČNA VENSKA INSUFICIJENCIJA I TRANSKATETERSKO POSTAVLJANJE BIOPROTETSKE BIKUSPIDNE VENSKE VALVULE S ČETVEROKUTNIM STENTOM

D. Pavcnik

Proteklih 25 godina bili smo svjedoci eksperimentalnih pokušaja u liječenju aortne i pulmonalne regurgitacije te insuficijencije venskih zalistaka pomožu katetera. U ovom članku opisuju se početne zamisli i eksperimentalni razvoj bioprotetskih venskih valvula koje se mogu ugraditi transkateterskom metodom. Procjena perkutano postavljene bioprotetske bikuspidne venske valvule (BBVV), koja se sastoji od četverokutnog stenta i pokrova submukoze tankog crijeva (SIS), učinjena je na 15 ovaca. Od 30 BBVV-a postavljenih u jugularnu venu 28 je imalo urednu funkciju na venogramima učinjenima odmah poslije zahvata, a 25 na venogramima učinjenima prije žrtvovanja životinja. Makroskopska i histološka analiza pokazale su uklapanje remodeliranog i endoteliziranog SIS-BBVV-a u vensku stijenku. Valvula koja sadrži četverokutni stent i SIS, postavljena uz minimalnu invazivnost, jednosmjerna je valvula od koje se može očekivati uspješnost.