PERCUTANEOUS VENOUS VALVE IMPLANTATION IN MANAGEMENT OF CHRONIC DEEP VENOUS INSUFFICIENCY: AN OVERVIEW OF OUR EXPERIMENTAL WORK AND EARLY CLINICAL EXPERIENCE

PERKUTÁNNÍ IMPLANTACE ŽILNÍCH CHLOPNÍ V LÉČBĚ CHRONICKÉ ŽILNÍ INSUFICIENCE: PŘEHLED NAŠICH EXPERIMENTÁLNÍCH PRACÍ A PRVNÍ KLINICKÉ ZKUŠENOSTI

review

Dusan Pavcnik
Barry Uchida
John Kaufman
Frederick S. Keller
Josef Rösch

Dotter Interventional Institute
Oregon Health & Science University
3181 SW Sam Jackson Park Road,
L-342
Portland, OR 97239-3098

Accepted: 15. 4. 2007

Address for correspondence:

Dusan Pavcnik, MD, Ph.D.
Dotter Interventional Institute
Oregon Health & Sciences University
3181 SW Sam Jackson Park Road,
L-342
Portland, OR 97239-3098, USA
e-mail: pavcnikd@ohsu.edu

SUMMARY

Pavcnik D, Uchida B, Kaufman J, Keller FS, Rösch J. Percutaneous venous valve implantation in management of chronic deep venous insufficiency: An overview of our experimental work and early clinical experience

To present an overview of our 7 years of experimental work and early clinical experience with percutaneous implantation of a bioprosthetic venous valve (BVV) and our recent experimental work with percutaneous autogenous venous valve (PAVV) transplantation.
Three types of BVVs consisting of a (small) leaflet of small intestinal submucosa (SIS) attached to different types of metallic square stent frames were tested in the ovine jugular veins. Altogether 66 BVVs were tested in 32 sheep. Follow-up venograms were done from 1 to 6 months. In clinical work, 15 patients with advanced venous insufficiency were treated by placement of a single BVV into the femoral vein. PAVV transplantation with a vein segment containing a native valve attached to a stent template was explored in 9 sheep. BVVs were easy to deliver and remained in place and stable. The majority of the experimental BVVs remained competent, some up to 6 months, but demonstrated limited flexibility due to SIS remodeling. In clinical work, early

SOUHRN

Pavcnik D, Uchida B, Kaufman J, Keller FS, Rösch J. Perkutánní implantace žilních chlopní v léčbě chronické žilní insuficience: přehled našich experimentálních prací a první klinické zkušenosti

Prezentace výsledků 7leté experimentální práce a první klinické zkušenosti s perkutánní implantací bioprostetické žilní chlopně (BŽCH) a naše poslední experimentální výsledky s transplantací perkutánní autogenní žilní chlopní (PAŽCH).
V experimentu na ovčích jugulárních žilách byly testovány 3 typy BŽCH skládajících se z malých plátků submukózy tenkého střeva (STS) připevněných k různým typům kovových rámů z čtvercových stentů. Celkem bylo testováno 66 BŽCH na 32 ovcích. Kontrolní flebografie byly provedeny po 1-6 měsících. V klinické části studie bylo léčeno 15 nemocných s pokročilou žilní insuficiencí implantací jediné BŽCH do femorální žíly. Transplantace segmentu žíly s nativní chlopní připojeného ke stentu (PAŽCH) byla provedena u 9 ovcí.
BŽCH byly snadno implantovatelné a zůstaly polohově stabilní. Většina experimentálních BŽCH zůstala funkčních, některé až 6 měsíců, prokázaly však omezenou flexibilitu v důsledku remodelace STS. V klinické části studie, výsledky krátkodobého sledování byly obdobné. Později BŽCH se

follow-up studies gave similar results. Later, the BVVs became incompetent due to the leaflet thickening. Clinically, however, most patients experienced improvement of their symptoms including healing of their ulcers. PAVV transplantation gave excellent results with 3 month competency of 8 of 9 transplanted valves.
In percutaneous BVV implantation, more research needs to be done to find a valve that would keep its long-term flexibility with good function. In PAVV transplantation, long-term studies should be done prior to introduction of this method into clinical practice.
Key words: deep venous insufficiency, endovascular therapy, venous valve.

staly nefunkční v důsledku zhuštění chlopenního aparátu. Klinicky se však u většiny nemocných zlepšila symptomatologie včetně hojení vředů. PAŽCH transplantace prokázala vynikající výsledky s funkčností chlopní v 8 případech z devíti po 3 měsících.
U implantací BŽCH je třeba dalších studií a vývoje chlopně, které by udržely dlouhodobou flexibilitu a funkci. U transplantací PAŽCH by měly být provedeny nejprve experimentální studie s dlouhodobým sledováním před zavedením této metody do klinické praxe.
Klíčová slova: hluboká žilní insuficience, endovaskulární léčba, žilní chlopně.

INTRODUCTION

Chronic venous insufficiency (CVI) of lower extremities is a common medical problem. It is caused by venous valve incompetence resulting in venous reflux and distal venous hypertension. Valve incompetence can be either primary or secondary. The primary (idiopathic) valve incompetence is thought to be caused by congenital defects, weakness and abnormally distensible venous wall (1–3). As the veins and valve rings expand, separation of the valve leaflets causes poor apposition and venous reflux despite relative absence of actual leaflet damage. Primary valve incompetence often involves valves in all three venous leg systems, superficial, deep and perforator veins (2, 4). Secondary (post phlebitic) valve incompetence develops after deep venous thrombosis and involves valves of the deep venous system. As venous thrombi organize there is damage or complete destruction of the venous valves leaving them incompetent and leading to chronic deep venous insufficiency (CDVI).

Clinical symptoms of CVI depend on the degree of valve incompetence and extent of venous involvement. Symptoms can range from the minor cosmetic telangiectasia to disabling ulcerating skin conditions that may dominate individuals' way of life. If CDVI is left untreated, it results in pain, significant edema, sclerosis, and ulceration of the skin (2, 5). For a long time, CVI has been treated conservatively with use of various compression techniques and devices. Varicose veins with predominant superficial valve insufficiency (SCVI) often have been managed surgically by ligation of the saphenofemoral junction and stripping of the saphenous vein. Recently developed catheter-based percutaneous techniques including sclerotherapy and radiofrequency or laser ablation of the greater saphenous vein became very popular alternatives to surgery and are preferentially used for effective treatment of varicose veins (6–9).

The management of CDVI, however, still remains a problem. Selected patients can benefit from surgical valve repair, femoral vein transposition or venous segment transplantation (10, 11) but the majority of patients with CDVI, particularly patients with secondary valve insufficiency are not candidates for these procedures. In the last 15 years, attempts were made by interventional radiologists to develop an artificial valve based on an expandable stent that could be placed percutaneously into the femoral vein and replace the diseased or absent natural valve. In experimental work in 1993, Uflacker explored an artificial monocusp valve consisting of a thin polyether-urethane membrane in a single body Z stent (12). Thorpe et al. in 2000 explored experimentally a bicuspid venous valve made of the porcine small intestinal submucosa (SIS) mounted in a double body Z stent (13). A trimmed segment of a glutaraldehyde-fixed bovine external jugular vein sutured inside a nitinol stent was explored in animals in 2000 by Gomez-Jorge et al. (14). These valves were placed through 10F to 24F diameter sheaths and some valves remained patent up to 2 weeks. The fixed bovine valve was also placed in a few patients with CDVI, but most of them thrombosed despite adequate anticoagulation (15).

We have developed and explored in animals three types of bioprosthetic venous valves (BVV 1-3) (Fig. 1A–D). They consisted of a small leaflet of SIS (Cook Biotech, West Lafayette, IN) attached to a different types of square stent frames. SIS is a relatively acellular, non-immunogenic, biodegradable, xenogenic, collagen-based biomaterial derived from the submucosal layer of porcine small intestine. After implantation, the SIS becomes remodeled by host tissue and reabsorbs over time (16). Following successful exploration of the BVVs in animals, we used them clinically in 15 patients with advanced CDVI. We also explored experimentally percutaneous autologous venous valve transplantation. For our experimental work we used an ovine jugular vein (JV) due to anatomical and functional similarities of the sheep JV with the human femoral vein (17, 18).

VALVE IMPLANTATION – EXPERIMENTAL WORK

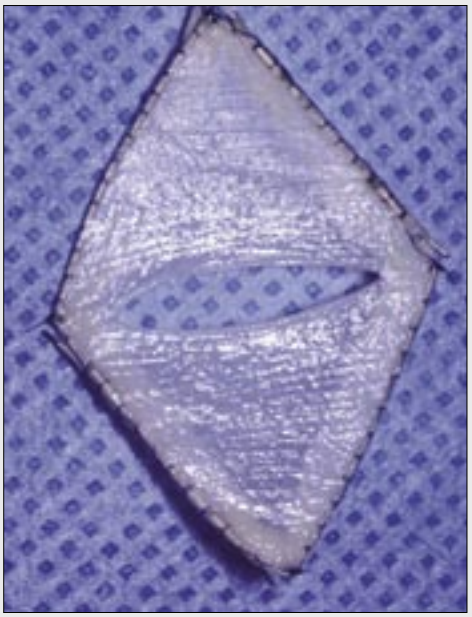
BVV1

Our original valve design, the BVV1 was developed in 1999. Its frame was formed by a single self-expandable stainless steel square stent with four barbs at its corners (Cook Inc.,

Bloomington, IN) (19). The valve leaflets were made of SIS sheets 120-180 micron thick (Cook Biotech) and were sutured with 7.0 Prolene monofilament to the stent frame (Fig. 1A, B). An 11F sheath was used for the valve placement. Of 26 BVV1s placed bilaterally into JVs of 12 sheep, 22 valves self-expanded completely and were well centered in JVs. Three valves were tilted and did not expand evenly, one valve migrated and eventually occluded a branch of the pulmonary artery (17). Immediate venograms showed uninterrupted flow in all valves. On 1, 3 and 6 months follow-up venograms, one of the three tilted valves thrombosed, the other two were incompetent exhibiting reflux. The other 22 valves were competent, but demonstrated limited cusp flexibility due to leaflet thickening (Fig. 2A, B). The gross and microscopic examination of the valve and vein specimens at one month revealed partial remodeling of SIS leaflets with host cells including fibroblasts, lymphocytes, plasma cells and histocytes. Endothelial cells were also present on both sides of the leaflets. On 3 and 6 month specimens, the completely remodeled SIS matrix was covered with neointima consisting

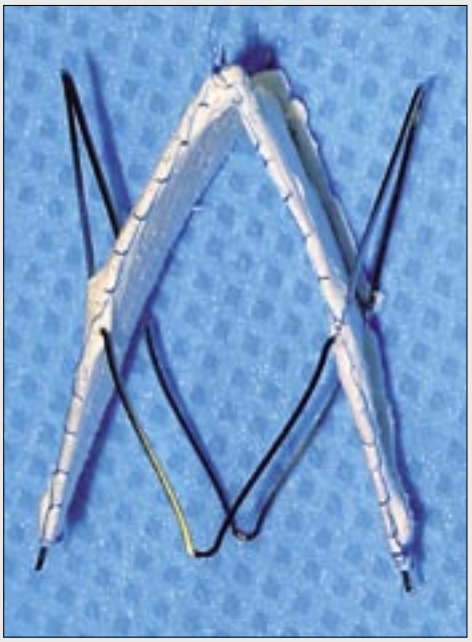
◀ Obr. 1 A

Obr. 1 B ▶



◀ Obr. 1 C

Obr. 1 D ▶



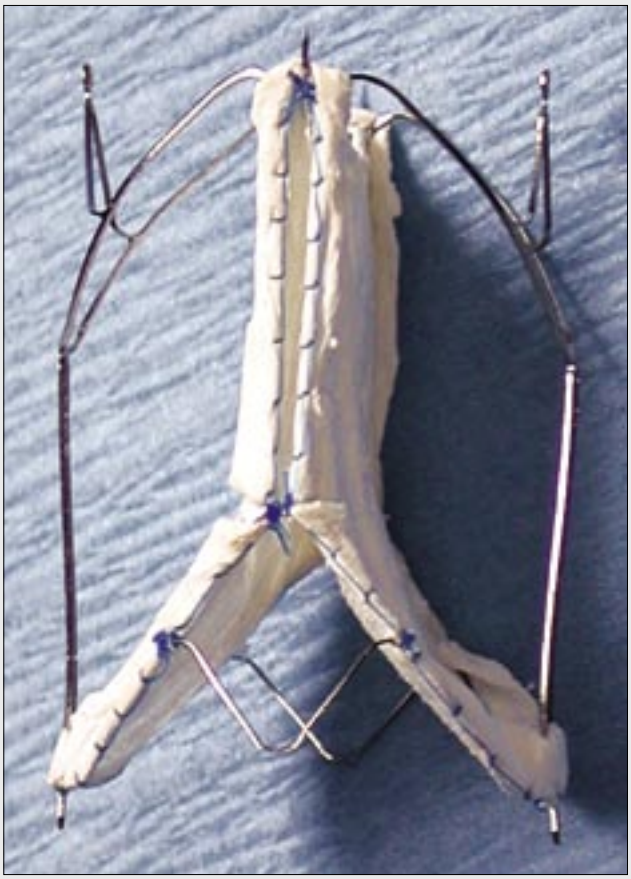


Fig. 1. ***Three types of bioprosthetic venous valves (BVV)***
A – frontal view of the original design of the square stent based BVV1; B – side view of the BVV1; C – side view of the BVV2; D – side view of the BVV3
Obr. 1. ***Tři typy bioprostetických žilních chlopní (BŽCH)***
A – čelní pohled BŽCH1 původní konstrukce založené na čtvercovém stentu; B – boční pohled na BŽCH1; C – boční pohled na BŽCH2; D – boční pohled na BŽCH3

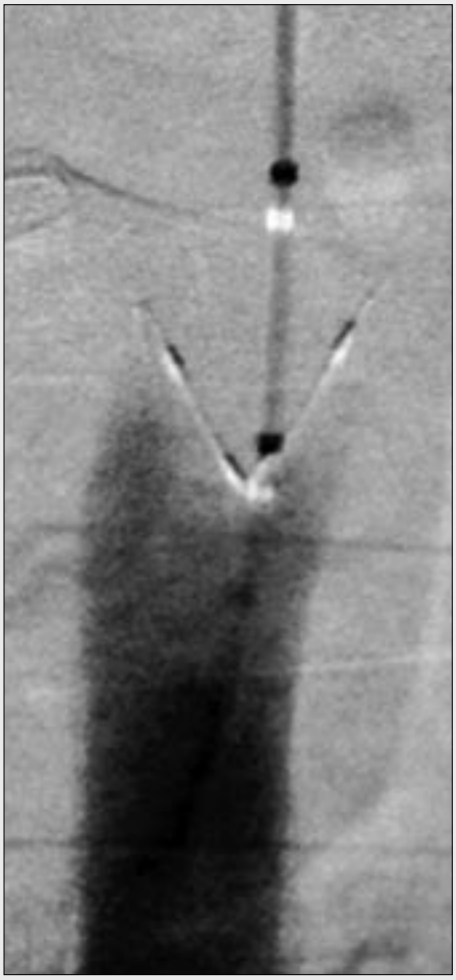
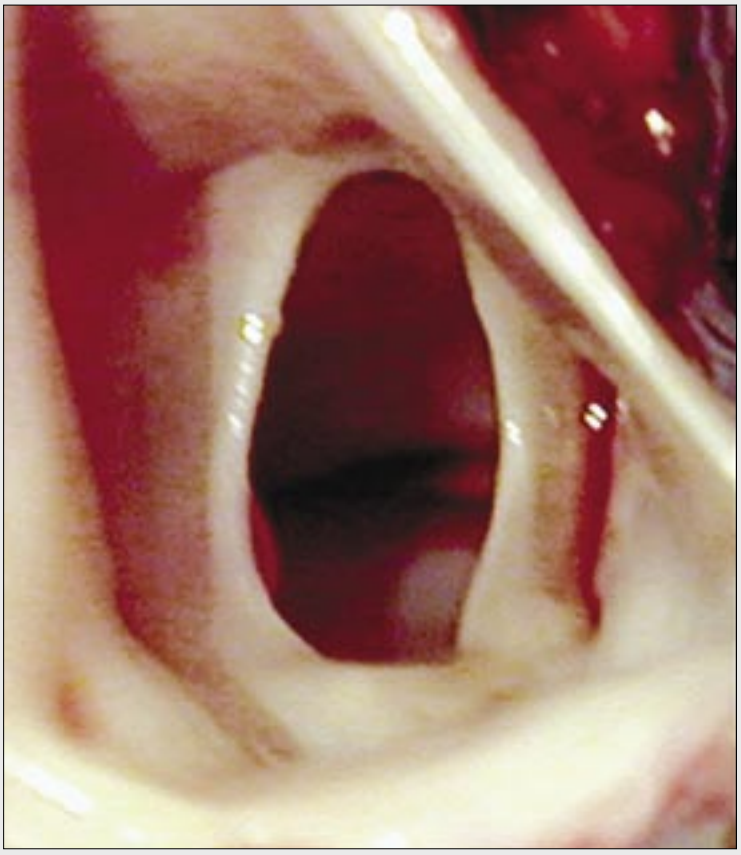


Fig. 2. ***Function of the BVV1 placed into the sheep jugular vein at 3 months***
A – jugular venogram with injection cephalad to the BVV1 demonstrates valve patency; B – venogram with injection caudal to the valve demonstrates closure of the BVVs with no reflux; C – axial view of the specimen from above shows incorporation of the BVV1 into the vein wall; D – longitudinal view of the valve opening shows thickened valve leaflets
Arrow demonstrates direction of the blood flow (H & E stain).
Obr. 2. ***Funkce BŽCH1 implantované před 3 měsíci***
A – flebografie jugulární žíly provedená vstřikem nad BŽCH1 prokazuje průchodnost chlopně; B – flebogram provedený vstřikem pod úroveň chlopně prokazující uzavření chlopně bez zřejmého refluxu; C – axiální pohled na preparát z kraniálního směru ukazuje inkorporaci chlopně do stěny žíly; D – longitudinální řez chlopní prokazující ztluštění cípů Šipka ukazuje směr toku krve (barvení hematoxylin eosin).

◀◀ *Obr. 2 A*

◀ *Obr. 2 B*



▲ *Obr. 2 C*

▲ *Obr. 2 D*

of fibroblasts with collagen deposits that caused leaflet thickening most prominent at the leaflet base (Fig. 2C, D). The leaflet bases were incorporated into the vein wall with some foreign body giant cells reaction around the sutures and wires attached to the vein (17).

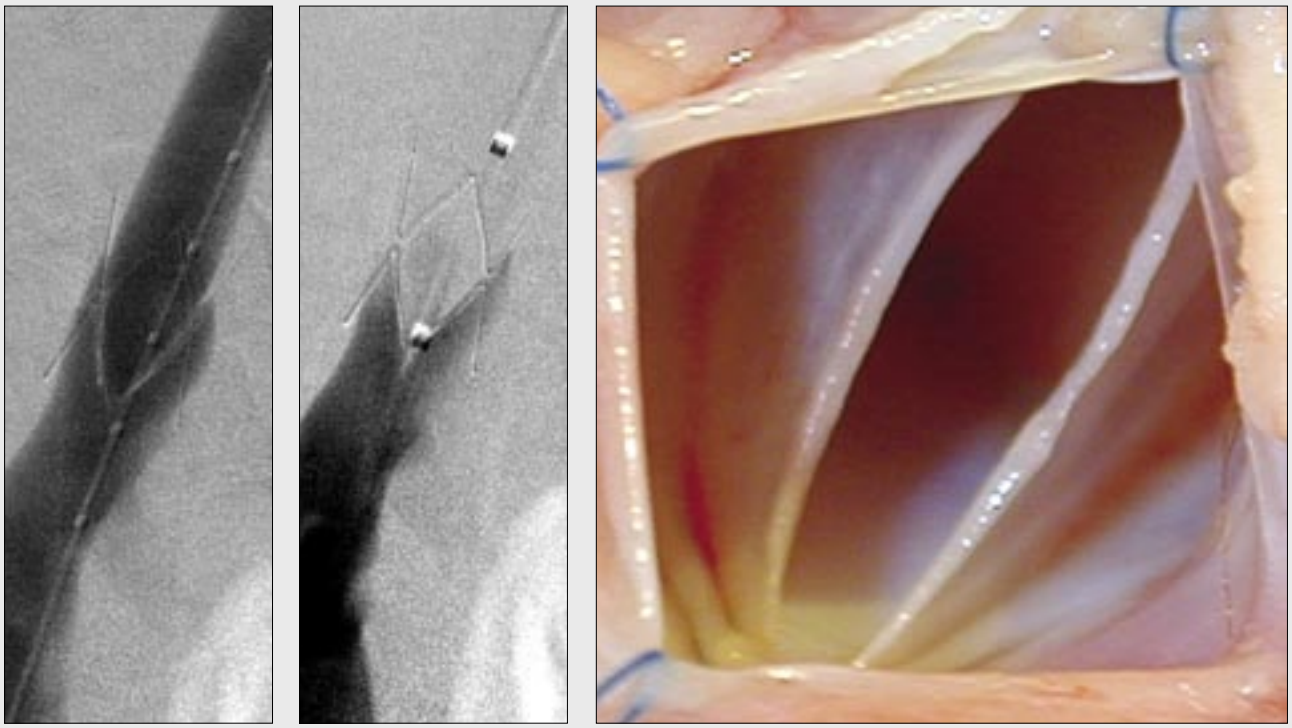
BVV2

We explored several stent frame modifications to improve valve positioning during placement and to ensure its centering in the vein without tilting. The BVV2 gave the best results. The BVV2 stent frame was made of nitinol tubing (20). It was similar to the BVV1 frame, only a second square stent without barbs was added to the midpoint of the original valve (Fig. 1C). The BVV2 was placed through a 10F sheath. Altogether, 28 BVV2 were implanted in JVs of 14 sheep. All implanted valves remained in place completely centered and well functional on immediate follow-up venograms. At 6 weeks follow-up, 26 valves remained well functional (Fig. 3A, B). Only two oversized valves were incompetent and exhibited reflux. Gross and histologic examination showed similar findings as with BVV1, partial SIS remodeling and leaflets thickening due to neointimal hyperplasia (Fig. 3C). In two incompetent oversized valves, the leaflets were either partially or completely fused with the vein wall, separated by thick neointima and unable to coapt (20).

BVV3

The third generation valve, BVV3 was designed to prevent potential contact of free leaflet portions with the venous wall and assure continued leaflet coaptation even with their possible shortening. The BVV3 frame was made of laser cut nitinol tubing and had again four barbs for valve stabilization (Fig. 1D). The round geometry of BVV3 allowed leaflets to coapt and the larger pockets of the valve improved blood flow and prevented potential thrombus formation. Two gold markers on the nitinol frame facilitated precise anatomical orientation during valve deployment. A 10F sheath was used for the valve placement and altogether 12 BVV3s were implanted into JVs of 6 sheep. Six BVV3s were oriented in the same spatial orientation as the native valves (group A) and the other six were rotated circumferentially 90° to the native valve leaflets (group B) (21). This was done to assess if different spatial orientation was important for valve implantation.

The desired special orientation was achieved after deployment in all valves and all remained stable and completely functional on venography after implantation. At 5 weeks follow-up studies, all valves in group A remained competent (Fig. 4A, B)while in group B one valve was incompetent exhibiting reflux. On gross examination, the remodeled SIS leaflets were free from the vein wall except at their distal parts



▲ Obr. 3 A ▲ Obr. 3 B ▲ Obr. 3 C

Fig. 3. ***Function and specimen of the BVV2 placed into the sheep jugular vein at 6 week follow up***
A – jugular venogram with injection cephalad to the valve demonstrates valve patency; B – a high volume injection of contrast medium caudal to the valve does not reveal any reflux and demonstrates valve closure; C – view of the valve specimen from above shows incorporation of the valve into the vein wall

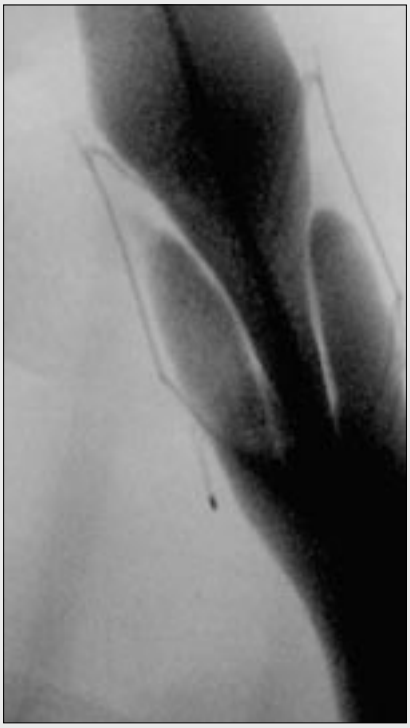
Obr. 3. ***Funkce a preparát BŽCH2 po 6 týdnech implantace do jugulární žíly ovce***
A – jugulární flebografie provedena vstřikem nad chlopeň prokazuje průchodnost chlopně; B – nástřik kaudálně od úrovně chlopně větším množstvím kontrastní látky neprokazuje reflux a demonstruje úplně uzavřené chlopně v retrográdním směru; C – pohled na preparát chlopně z kraniálního směru ukazující inkorporaci chlopně do stěny žíly

where the SIS was thickened and attached to the vein (Fig. 4C, D). Extent of the attachment was significantly smaller and the free leaflet segment was larger in the group A than in group B, underlining importance of valve placement in the same orientation as the native valve (21).

VALVE IMPLANTATION – CLINICAL PILOT STUDY

Based upon promising experimental studies, a one year clinical study was conducted in four institutions with approval of their Institutional Review Boards to determine the safety of the BVV3 implantation. Fifteen patients with advanced symptomatic CDVI including 8 patients with large venous ulcers received the valve. A single BVV3 was deployed into the femoral vein percutaneously via transjugular approach with a 12F over the wire delivery catheter system. Pre and post deployment examinations included clinical examination, intravascular ultrasound, duplex ultrasound, descending venography and air platismography at 3 and 12 months.

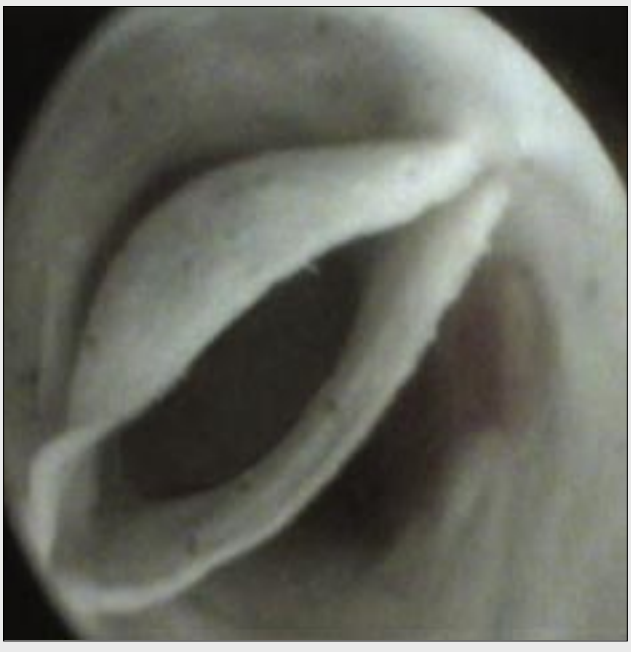
Successful placement of all 15 BVVs3 was achieved without tilting or migration, although 3 valves were oversized. Immediate valve competence was seen in 14 limbs (93 %). Follow-up studies at 3 and 12 months showed no migration



▲ Obr. 4 A

▲ Obr. 4 B

Fig. 4. ***Function and specimen of the BVV3 placed into the sheep jugular vein in the same orientation as the natural valve at 5 week follow up***
A – jugular venogram with injection cephalad to the BVV3, shows valve patency; B – subclavian venogram demonstrates valve closure with equal filling of both cusps; C, D – in vitro angioscopy of a BVV3 demonstrates valve in open and closed position
Obr. 4. ***Funkce a preparát BŽCH3 implantované do jugulární žíly ovce po 5 týdnech a ve stejné orientaci jako nativní chlopně***
A – jugulární flebografie s nástřikem kraniálně od úrovně chlopně prokazující její průchodnost; B – flebografie v. subclavia ukazující uzavření chlopně s rovnoměrným plněním obou chlopenních sinusů; C, D – ***in vitro*** *angioskopie BŽCH3 ukazující chlopeň v otevřené a zavřené poloze*



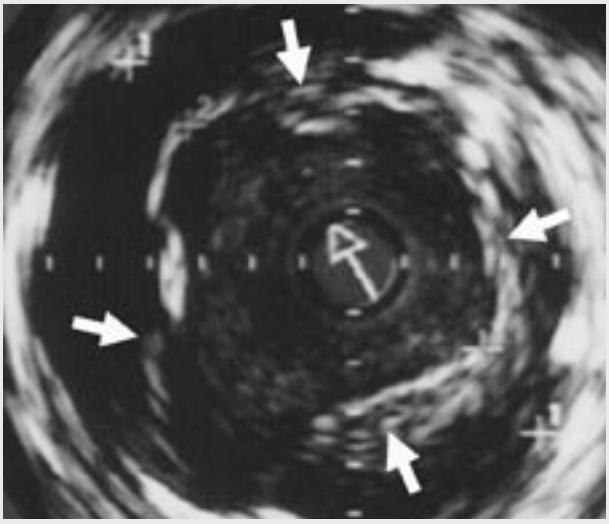
▲ Obr. 4 C

▲ Obr. 4 D

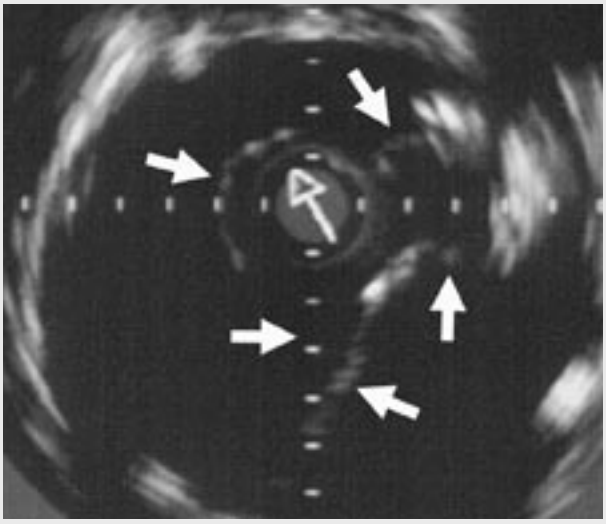
of the implanted valves. Eleven valves (73.4 % were patent and four occluded (26.6 %). Three valves occluded early (< 2 weeks), and one occluded late at 7 months. One valve occluded after placement into a duplicate femoral vein and three valves occluded in patients with low level of INR or after discontinuation of coumadin for spine surgery. At 3 months, only two valves remained fully functional. At 12 months none of the valves remained competent. Thickening and rigidity of the leaflets of the non-thrombosed valves resulted in various degrees of reflux and caused their incompetence (Fig. 5A–D). Clinically, however, valve implantation gave better results. Twelve of 15 patients (80 %) had immediate and a 3 month clinical improvement that continued in 9 patients (60 %) at 12 month follow-up. Large venous ulcers healed completely in 3 of 8 patients, improved in four and only one giant ulcer did not show improvement. None of the 15 patients' clinical symptoms worsened after valve implantation.

PERCUTANEOUS AUTOLOGOUS VENOUS VALVE TRANSPLANTATION – AN EXPERIMENTAL STUDY

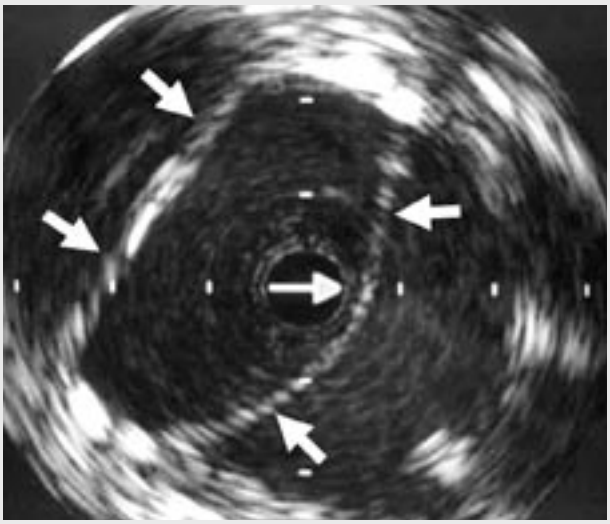
Percutaneous autogenous venous valve (PAVV) transplantation was explored in 9 sheep. PAVV consisted of a vein segment containing a native valve that was attached to a stent template designed and handmade in our research laboratory (22). The stent template consisted of two stainless steel square stents 13 or 15 mm in diameter to fit the ovine JV. A valve containing segment of the JV was surgically harvested and fixed with sutures and barbs to the inside the stent template (Fig. 6A). The valve device was then manually compressed and front loaded inside a 4 cm long chamber of the 13 F delivery sheath. This was followed by over the wire delivery into the contra lateral JV by femoral vein



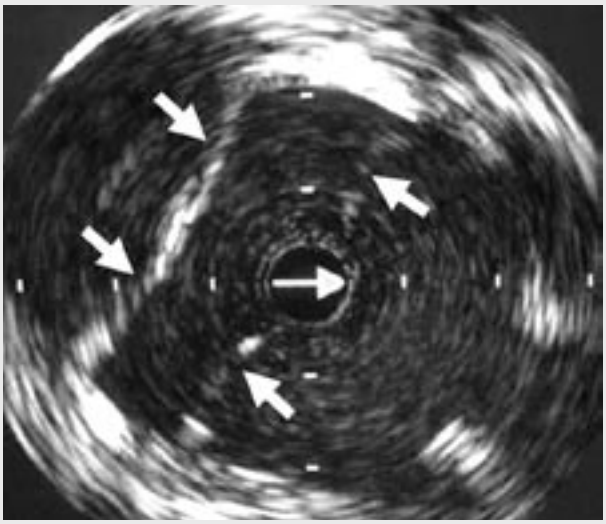
▲ *Obr. 5 A*



▲ *Obr. 5 B*



▲ *Obr. 5 C*



▲ *Obr. 5 D*

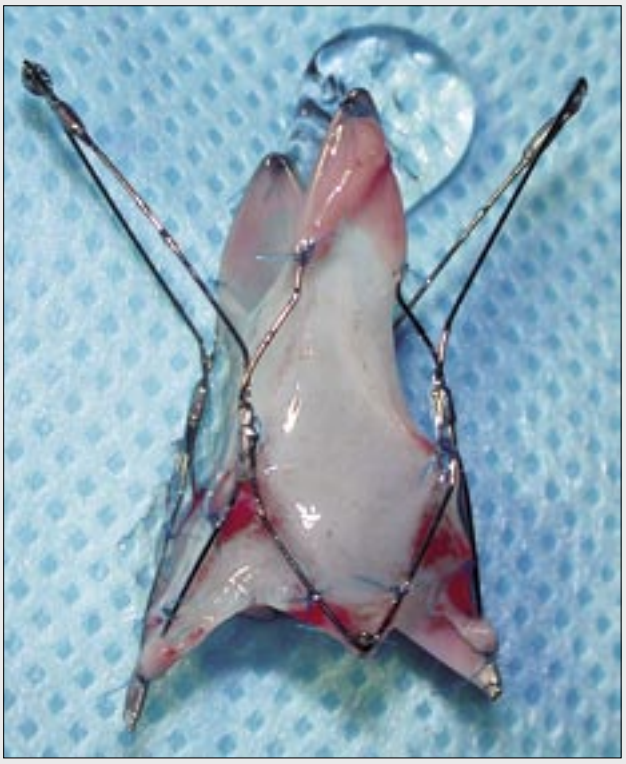
Fig. 5. ***The intravenous ultrasound studies of the BVV3 implanted into the femoral vein of a 78-year old female with advanced CDVI***
A, B – immediately after implantation the valve exhibits a good flexibility; A – in open position (arrowheads); B – in closed position (arrows); C, D – at 3 months, rigid, thickened leaflets shows limited cusp flexibility (arrows) Central arrow shows the imaging catheter.

Obr. 5. ***Zobrazení intravaskulárním ultrazvukem BŽCH3 implantovaných 78leté ženě s pokročilou hlubokou žilní insuficiencí***
A, B – bezprostředně po implantaci chlopeň prokazuje dobrou flexibilitu; A – otevřená poloha (šipky); B – v zavřené poloze (šipky); C, D – po 3 měsících rigidní, ztluštělé cípy prokazující jen omezenou flexibilitu (šipky) Centrálně uložená šipka ukazuje IVUS katétr.

approach. Transplanted PAVVs were studied by immediate and 3 months venograms when JVs were harvested for angioscopic evaluations *in vitro*. PAVV transplantation was successful in all 9 animals. Good valve function with no reflux was observed on immediate and 3 months venograms in 8 valves. Venoscopic examination at 3 months revealed intact, flexible, non-thickened valve leaflets in 8 specimens (Fig. 6B, C). One PAVV exhibited normal function of one leaflet only; the other cusp was absent, accidentally cut during the transplantation procedure. All transplanted autologous valves were free of thrombus and incorporated into the vein wall of the host vessel (22).

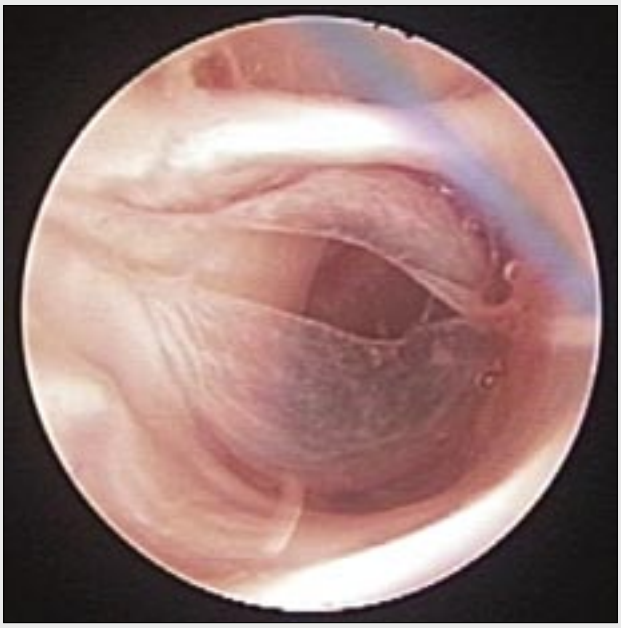
CONCLUSION

A very long path with many small steps and tedious experimental research work is usually necessary to take a new idea to a successful clinical reality. At the present time more steps are still necessary for the percutaneous BVV implantation to become clinically useful. The BVV3 stent frame is in our opinion, well suited to form a base for valve. It is easy to deliver and it self-centers and remains stable in the vein. It allows good leaflets coaptation even when the leaflets remodel and shorten and prevents their contact with venous wall. The SIS biomaterial for leaflets showed very promising early results

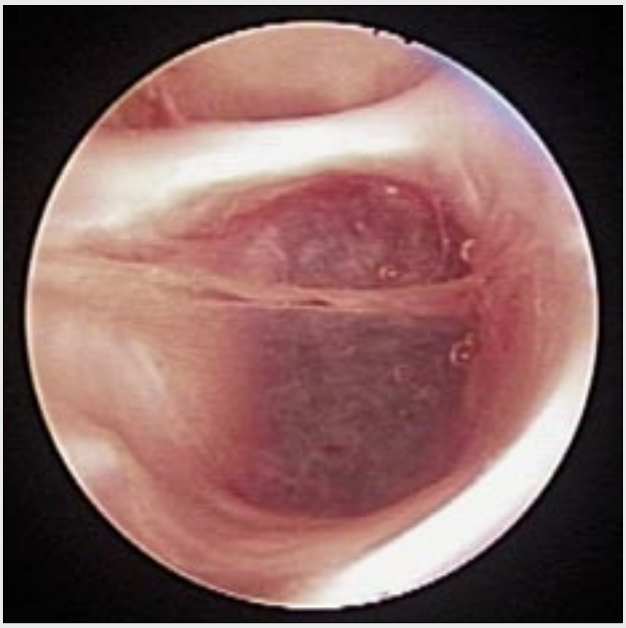


◀ *Obr. 6 A*

Fig. 6. ***Percutaneous autologous venous valve transplantation***
A – the harvested autologous venous valve attached to a stent valve template; B – venoscopy of the transplanted valve specimen at 3 months. Bicuspid valve inside a flow model demonstrates thin leaflets in open position and C – closed position.
Obr. 6. ***Perkutánní transplantace autologní žilní chlopně***
A – odebraná autologní žíla připojená ke stentu – nosiči; B – fleboskopie preparátu transplantované žilní chlopně po 3 měsících
Dvojcípá chlopeň na modelu simulujícím tok prokazuje tenké cípy v otevřené a zavřené poloze.



▲ *Obr. 6 B*



▲ *Obr. 6 C*

with pliable leaflets and good valve function. In the long--term, however, because of the scaffolding nature of SIS with fibrotic transformation and excessive neointimal formation, the SIS leaflets thickened, became rigid and caused the valves to become incompetent. In our unpublished studies, leaflets treated or coated with cytostatic chemotherapy agents and non-steroidal anti-inflammatory drugs did not give better results than leaflets with untreated SIS. Potentially, there are a couple of routes to solve this problem. The first option is to bioengineer a method to cover SIS leaflets with endothelial cells to prevent neointimal hyperplasia and enhance valve functionality. The other option is to use a more compatible biomaterial than SIS.

The percutaneous BVV implantation needs long-term studies to document the continued patency and function of the implanted valves. Research work in PAVV transplantation is close to clinical realization. A close relationship with an interested device manufacturer and endovascular surgeons would accelerate the introduction of PAVV into clinical practice.

LITERATURA

1. **Kistner RL.** Primary venous valve incompetence of the leg. Am J Surg 1980; 140: 218–224.
2. **Sumner DS.** Hemodynamic and pathophysiology of venous disease. In Vascular Surgery. Ed. Rutherford RB. Philadelphia: WB Saunders Co 1989; 1483–1504.
3. **Schmid–Schönbein GW, Takase S, Bergan JJ.** New advances in the understanding of the pathophysiology of chronic venous insufficiency. Angiology 2001; 52 Suppl 1: S27–S34.
5. **Lurie F, Kistner RL, Eklof B.** Surgical management of deep venous reflux. Semin Vasc Surg. 2002; 15: 50–56.
5. **Raju S, Fredericks RK, Hudson A, Fountain T, Neglén PN.** Venous valve station changes in "primary" and post-thrombotic reflux: an analysis of 149 cases. Ann Vasc Surg. 2000; 14: 193–199.
6. **Min RJ, Khilnani N, Zimmet SE.** Endovenous laser treatment of saphenous vein reflux: long-term results. J Vasc Interv Radiol 2003; 14: 991–996.
7. **Teruya TH, Ballard.** New approaches for the treatment of varicose veins. Surg Clin North Am 2004; 84: 1397–1417.
8. **Merchant RF, Pichot O.** Long-term outcomes of endovenous radiofrequency obliteration of saphenous reflux as a treatment for superficial venous insufficiency. J Vasc Surg 2005; 42: 502–509.
9. **Bergan JJ.** Varicose veins. Treatment by intervention including sclerotherapy. In Vascular Surgery 6th edition. Ed. Rutherford RB. Philadelphia PA: WB Elsevier Saunders Co 2005; 2251–2267.
10. **Sheridan KM, Dalsing MC.** The surgical treatment of deep venous valvular incompetence. In Vascular Surgery 6th edition. Ed. Rutherford RB. Philadelphia PA: WB Elsevier Saunders Co 2005; 2287–2302.
11. **Dalsing MC.** Surgical therapies in chronic venous insufficiency: deep venous surgery valve transplantation/SEPS. In Venous and Lymphatic Diseases. ED: Labropulos N, Stansby G. New York, London: Taylor & Frances 2006; 393–409.
12. **Uflacker R.** Percutaneously introduced artificial venous valve: experimental use in pigs. The 1993 Annual Meeting of the Western Angiographic & Interventional Society 1993, Sep 29 – Oct 3; Portland, Ore 1993: p. 30.
13. **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 2000, Feb 3–6; Phoenix, Ariz 2000: p. 82.
14. **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: 931–936.
15. **de Borst GJ, Teijink JA, Patterson M, Quijano TC, Moll F.** A percutaneous approach to deep venous valve insufficiency with a new self–expanding venous frame valve. J Endovasc Ther 2003; 10: 341–349.
16. **Badylak SF.** Small intestinal submucosa (SIS): a biomaterial conductive to smart tissue remodeling. In Bell E (ed). Tissue engineering: Current prospective. Cambridge MA: Burkhauser 1993: 179–189.
17. **Pavcnik D, Uchida BT, 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: 598–602.
18. **Wei Lu, Pavcnik D, Uchida B, Won Kyu Park, Liu L, Timmermans HA, Keller FS, Rösch J.** The ovine jugular vein as a model for prosthetic valve evaluation (Submitted to JVIR 2007).
19. **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: 207–217.
20. **Pavcnik D, Uchida B, Kaufman J, Luiz Corea, Takao Hiraki, Keller FS, Rösch J.** Second Generation Bioprosthetic Venous Valve. Short-term study in Sheep. J Vasc Surg 2004: 40: 1223–1227.
21. **Pavcnik D, Kaufman J, Uchida B, Case B, Corea OL, Hamada A, Goktay AY, Keller FS, Rösch J.** Significance of spatial orientation of percutaneously placed bioprosthetic valve in an ovine model. J Vasc Interv Radiol 2005; 16: 1511–1516.
22. **Pavcnik D, Yin Q, Uchida B, Park WK, Kim MD, Hoppe H., Keller FS, Rösch J.** Percutaneous autologous venous valve transplantation: feasibility study in and ovine model (Submitted to JVS 2007).