

RESEARCH

Open Access



Transcatheter bicuspid venous valve prostheses: fluid mechanical performance testing of artificial nonwoven leaflets

Andreas Götz^{1*}, Sabine Illner¹, Nicklas Fiedler¹, Julia Schubert¹, Jan Oldenburg², Heinz Müller³, Wolfram Schmidt¹, Klaus-Peter Schmitz², Niels Grabow¹ and Kerstin Lebahn¹

*Correspondence:
andreas.goetz@uni-rostock.de

¹ Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany

² Institute for ImplantTechnology and Biomaterials e.V.,

Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany

³ CORTRONIK GmbH, Friedrich-Barnewitz-Str. 4a, 18119 Rostock, Germany

Abstract

Background: Chronic venous insufficiency (CVI) is a common disease with a high prevalence. Incompetent venous valves are considered as one of the main causes. Besides compression therapy, various surgical therapies are practiced, whereby the reconstruction of valves is of central importance. There is an unmet clinical need, no valve prosthesis is commercially available to date. This work introduces two versions of a patented prosthetic bicuspid valve design made of electrospun thermoplastic silicone polycarbonate polyurethane (TSPCU) nanofiber leaflets attached in a nitinol stent, and their performance in static and pulsatile operation.

Results: The valves mainly fulfill the requirements widely accepted in literature. Valves of both versions were functional in the physiological pressure range up to 50 mmHg with design specific differences.

Conclusions: The here introduced design versions act as a platform technology and can be tailored for an intended implantation site. Evaluation of the original and modified valve concept demonstrated efficacy, with limitations at higher loads for original design. At the current state, the modification is preferable for fabrication, as one processing step is eliminated. Moreover, specific design recommendations could be drawn for valves of similar basic structure. Future work will focus on long-term performance and biocompatibility prior to the initiation of preclinical in vivo studies.

Keywords: CVD, CVI, Venous valve, Chronic venous disease, Valve implant, Testing, Forward flow, Reflux

Introduction

Chronic venous insufficiency (CVI), chronic venous disease (CVD), or chronic deep venous insufficiency (DVI) are often synonymously used terms, which describe principally a vascular disorder in which venous return is compromised. CVI is a persistent, progressive and often underestimated condition that is prevalent in the general population and has a huge socio-economic, physical and psychological impact.



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

The clinical presentation is accompanied by severe manifestations of edema, skin changes or leg ulcers. Prevalence data of CVI vary widely from around 1–40% in women and around 1–17% in men [1]. There are two pathogeneses universally accepted, primary valvular incompetence and primary congenital vein wall weakness [2]. Furthermore, there are numerous genetic candidate loci, but still rudimentarily understood [3].

Therapeutic methods for CVI demonstrate a wide variety. The standard initial treatment is compressing therapy, supported by medication [2]. Besides, there are several surgical treatment concepts, such as interventional therapies, occlusion, or venoplasty [2, 4]. For example, the “BlueLeaf” system is a minimally invasive technique to form fully autogenous deep endovenous valves using an expandable dissection tool [5]. The recurrence of varicose veins after surgery is a frequent phenomenon, which may be caused by the so called “hemodynamic paradox” [6, 7].

Venous valve prostheses are supposed to address the shortcomings of reconstruction surgery. In general, valve prostheses consist of a support structure, which in most cases is a stent, and the actual valve, which is designed as a single or multi leaflet. The stent is usually made of nitinol and the leaflet material can consist of natural or polymeric fiber mats. New generation of biostable medical polyurethane elastomers with favorable bio- and hemocompatibility is thermoplastic silicone polycarbonate urethanes (TSPCU), which can be additionally modified [8–12]. For example, polyhedral oligomeric silsesquioxanes–polycarbonate urethane (POSS–PCU) nanocomposites showed good biocompatibility, mechanical durability, tear resistance, and better thrombosis resistance than other common polymeric valve materials such as polytetrafluoroethylene (PTFE) [13–15]. In contrast, bioresorbable, co-growing and minimally invasive venous valve concepts with degradable polymers such as polycaprolactone (PCL), polydioxanone (PDS), polylactide (PLA) and polyglycolide (PGA) are also gaining ground [10, 16]. However, the associated research effort is considerably more complex, particularly with regard to inflammation, tissue regeneration processes and degradation rates. In general, published studies regarding artificial valve materials and designs are difficult to compare due to their individuality in terms of limits or technical parameters. Various models are being developed from concept studies [17], over animal studies (e.g. “SailValve”, “BVV1”–“BVV3”) [18–20], to clinical testing (e.g., “VenoValve”, “enVVe”, and “Inno vein”) [21–26]. In addition, there are currently limited data to support vein reconstruction and no consensus on the characteristics of an ideal prosthesis [27–30] and no international “gold standard” in terms of operating conditions and performance requirements for venous valve prostheses. Ideally, the implant should allow free blood flow towards the heart, but prevent flow in retrograde direction. However, this point of view is still controversial, as a leakage in the valve can promote the long-term patency of the design by preventing thrombosis [19, 20].

In the development of new venous valve prostheses, generally recognized requirements, especially physiological conditions and several design aspects have to be considered to ensure safe operation. Cardiac output at rest is about 5 L/min and may reach 20 L/min at strong exercise [31, 32]. Unilateral lower limb venous blood flow is in a range of 420–450 mL/min in relaxed condition [33, 34], 400–800 mL/min at normal walking [35], 1600 mL/min at standing ankle flexion [36], and 2000 or 2450 mL/min at exercise of 40 W [37, 38] or 65 W [34], respectively. The blood flow in the legs does not differ

between age groups when cycling at low intensity (20–40 W), but is significantly attenuated in older compared to younger subjects when the exercise intensity increases [39]. The anaerobic threshold describes the highest possible continuous intensity of exertion and is specified as 30–40 W for untrained older people [40].

The venous pressure at relaxed upright position depends mostly on gravitational pressure, and may reach 100 mmHg [27]. Activation of the calf muscle pump by walking removes the blood within some steps, ideally without reflux. The constantly incoming fresh blood does not fill the complete vein within one step, this creates a balance with low average pressure of 22–24 mmHg between the blood pumped out and the blood flowing in [41]. The normal operating pressure of a valve in the thigh is estimated with approximately 50 mmHg, in case no competent valve exists proximal. During coughing, sneezing, jumping or similar actions, short-term pressure surges up to 300 mmHg are transmitted from the abdomen to the legs, but in the same way to the arterial and venous system [42–45].

The vein size differs individually in a wide range as reported by various authors. Diameters of the common femoral vein are indicated with varying values of 11–12 mm [46], 6–21 mm [47], 10 mm [36], or for the proximal femoral vein of 4–16 mm [47], 8–16 mm [48], and for the distal femoral vein of 3–13 mm [47], or 3–10 mm [48]. However, vein diameters change not only due to exertion, but also with age and throughout the day. The femoral veins dilate by a few millimeters from morning to the afternoon, as indicated by 1.3–3.3 mm [49]. Suggested implant sites are 5–10 cm proximal to the saphenofemoral junction or in V. saphena parva [48]. The mid-thigh region of the femoral vein is likewise suitable [23].

From the physiological considerations further venous valve design requirements are derived. A minimal invasive surgery type is preferred and the valve design needs to ensure a blood flow similar to the native valves [29]. The orifice area should be larger than 30% of the vessel cross-sectional area [13, 50]. Leakage and reflux are controversially discussed, the valve can be considered functional when the leakage is less than 10% of the forward blood volume [51], or less than 3 mL/min [27]. Since native vein valves typically open with a pressure gradient of less than 5 mmHg, the opening pressure of prosthetic valves should be similar [27, 35, 51]. Tilting of the valve should be prevented from a fluidic perspective to keep patency and avoid thrombosis as main complication [29, 52].

Oversizing is a suitable method for secure fitting the implant in the vein, size mismatch of prostheses and vein should be less than 15% [53], which means stent oversizing in the range of 1–2 mm. A rarely specified but crucial factor is which condition was used as the basis to calculate oversizing for determining the implant diameter to take account of the varying vein diameters under different load situations. Further anti-displacement techniques such as barbs are a common and effective solution to prevent valve migration, in sheep model barb penetration through the vein wall was seen in 56% of cases [54].

Recently, our group has reported on a novel prosthetic venous valve concept [55]. Main objective of the current study is to further improve this concept regarding the prevention of tilting and downstream migration, as well as maximization of effective orifice area (EOA). As part of this approach, two valve design embodiments were systematically

assessed in vitro in an effort to establish more robust design and testing requirements for prosthetic venous valves. For the oversizing values, the inner diameters of the test attachments were applied as base value and set in relation to the uncompressed stent diameters. Systematic experimental testing is conducted to identify design strengths and weaknesses. The evaluation and comparison of valve performance is used to demonstrate the impact of design changes, to identify key elements for future implant developments.

Results

Artificial bicuspid venous valves

In both designs, the electrospun nanofiber nonwovens were assembled in the stents as an inwardly folded, double-layered sandwich. Both sandwich layers, inside and outside of the stent structure, are thermally spot welded in the center of the rhomboid stent cells allowing clearance and load distribution, thus enabling structural flexibility during the entire load history and avoiding critical load peaks. In the welding points fibers were melted together and no longer recognizable as individual fibers. Some details of manufacturing and bonding method are presented in Fig. 1. Morphologically, the TSPCU leaflets consisting of nanofiber nonwovens showed a smooth surface and slightly stucked together. The fiber diameters of the nanofibrous leaflets were 870 ± 140 nm of valve A14, 720 ± 140 nm for valve B12, and 770 ± 110 nm for valve B13. The leaflet thicknesses were 100 ± 15 μ m for valve A14, 90 ± 10 μ m for valve B12, and 146 ± 15 μ m for valve B13.

Performance in static operation

The valve performance was tested for both directions, open (forward flow) and closed valves (reflux). Water pressure equivalent to 1, 3, and 5 mmHg for forward flow, as

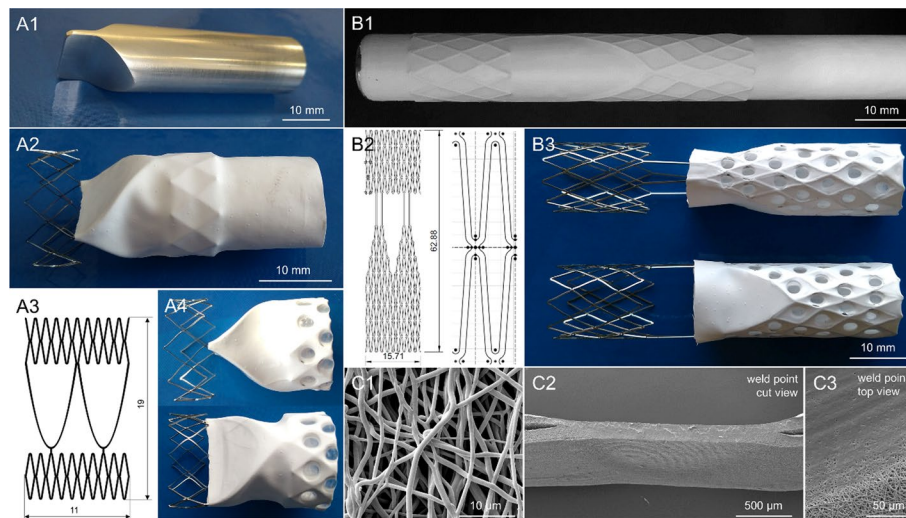


Fig. 1 Valve versions. **A1**: aluminium mold for electrospinning of version A nonwovens, **A2**: version A, stent enclosed with electrospun cover and protruding part for fixation, **A3**: sketch of version A stent, **A4**: assembled valve of version A in front and side view, **B1**: electrospun layer on version B stent mounted on metal cylinder, **B2**: sketch of version B stent as whole and a basic element, **B3**: assembled valve of version B in front and side view, **C1**: SEM image of nanofiber material, **C2**: SEM image of a cut weld point in side view, **C3**: SEM image of a weld point in top view

well as 20 up to 140 mmHg for reflux was achieved by adjusting water levels of distinct height (see Fig. 6). Maximum possible flow values were measured using attachments without valves. Valve A14–17 allowed about 1/3 of these maximum flow to pass through, with valves of version B approximately 2/3 of maximal flow values were observed, see Fig. 2A, C. The results of reflux are displayed in Fig. 2B.

Valve A14–17 revealed a reflux less than 310 mL/min for the physiological pressure range of 30–50 mmHg. Considerably increased reflux was observed at a pressure of more than 80 mmHg with a maximum of 2420 mL/min at 140 mmHg. After the experiment, the valve was found to be deformed and tilted, see Figure S16. The valves of version B12–9 and B12–20 revealed a reflux of less than 225 mL/min and 180 mL/min for the physiological pressure range, respectively. Considerably increased reflux was observed at a pressure of more than 80 mmHg (B12–9) and 100 mmHg (B12–20). A maximum reflux of 1510 mL/min (B12–9) and 890 mL/min (B12–20) resulted. The valve B13 revealed a reflux flow less than 905 mL/min (B13–8) and 290 mL/min (B13–18) for the physiological pressure range, respectively. Reflux was considerably increased at a pressure of more than 80 mmHg (B13–18). In contrast, for B13–8 a pressure proportional increase of reflux was observed with a maximum of 2635 mL/min.

Performance in pulsatile operation

To illustrate the valve performance at a representative working condition, a typical operating pressure of 50 mmHg imitating moderate physical exertion is compared here for both valve versions. The complete data series mimicking different exertions are provided in supporting information 4. Experimental results of pulse duplicator testing of valve A14–17 at 60 bpm revealed valve opening at 0.21 s, forward flow until 0.66 s, maximal flow at 0.4 s of about 3.5 L/min, and valve closing at 0.7 s with some post-pulse oscillation, see Fig. 3. A total reflux of 1.75 mL per cycle was measured. The calculated effective orifice area (EOA) was 0.27 cm², i.e. 24% of attachment cross-sectional area.

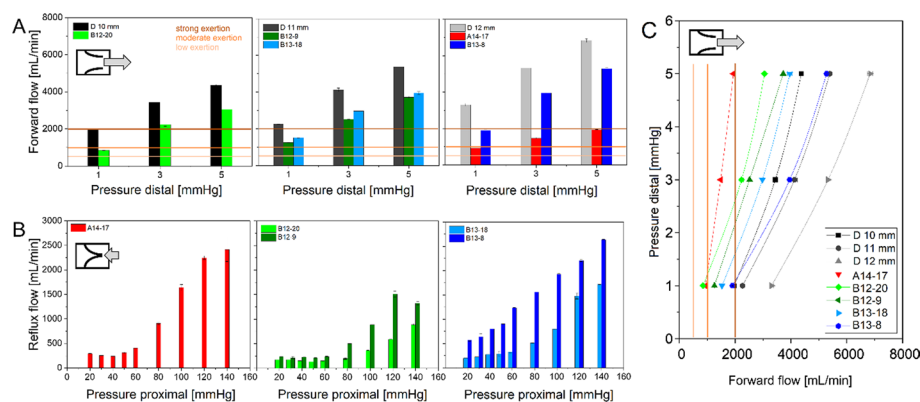


Fig. 2 Static test results. **A** Open valves (under distal pressure) with inner attachment diameter of D 10 mm (left), D 11 mm (mid), and D 12 mm (right), black/gray color: attachments without valve, red: valve version A14, green: version B12, blue: version B13, **B** closed valves (under proximal pressure), version A14 (left, red), version B12 (mid, green), version B13 (right, blue), **C** comparison of pressure-flow characteristics (under distal pressure) of valves and attachments, $n=3$ measurements each. **A**, **C** Indicator lines for low (light orange), moderate (orange) and strong exertion (dark orange)

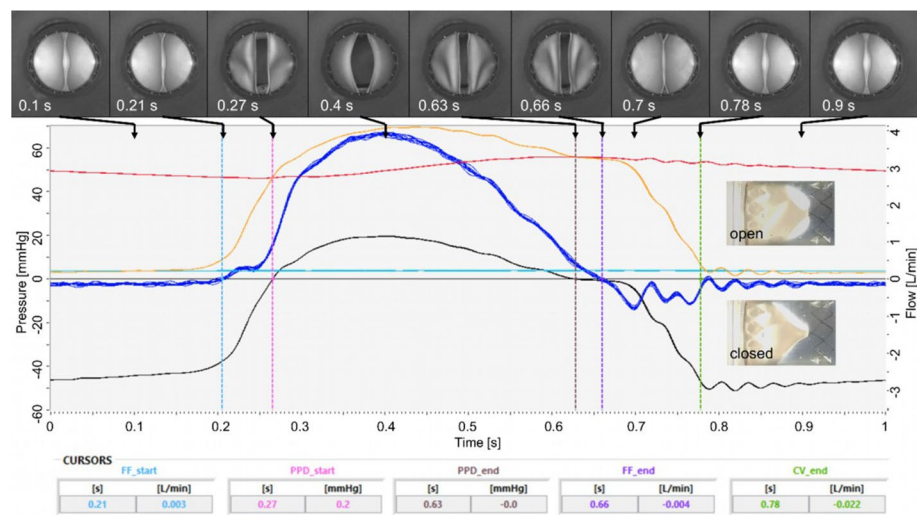


Fig. 3 Pulsatile experiment, valve version A14–17, 60 bpm, 1 L/min, 50 mmHg. Curves ($n=10$): red—pressure proximal to the valve, yellow—pressure distal to the valve, black—difference pressure, dark blue—flow, light blue—pre-pressure at water reservoir, cursors: FF—forward flow, PPD—positive pressure difference, CV—closing volume, Images: from proximal inline camera at points in time as specified, and photographs from outside of open and closed state

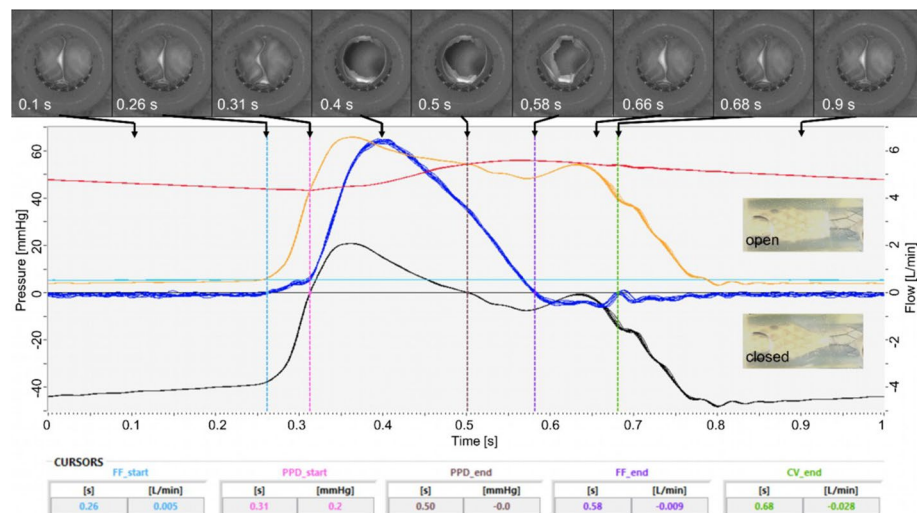


Fig. 4 Pulsatile experiment, valve version B12–9, 60 bpm, 1 L/min, 50 mmHg. Curves ($n=10$): red—pressure proximal to the valve, yellow—pressure distal to the valve, black—difference pressure, dark blue—flow, light blue—pre-pressure at water reservoir, cursors: FF—forward flow, PPD—positive pressure difference, CV—closing volume. Images: from proximal inline camera at points in time as specified, and photographs from outside of open and closed state

Pulsatile testing of valve B12–9 at 60 bpm revealed valve opening at 0.31 s, forward flow until 0.58 s, maximal flow at 0.4 s of almost 6.5 L/min, and valve closing at 0.66 s, see Fig. 4. A total reflux of 1.68 mL per cycle was measured. The calculated EOA was 0.49 cm^2 , i.e. 51% of attachment cross-sectional area.

Characteristic flow parameters and three simulated physiological conditions at operating pressure of 50 mmHg are summarized in Fig. 5. Similar PPD values were consistently

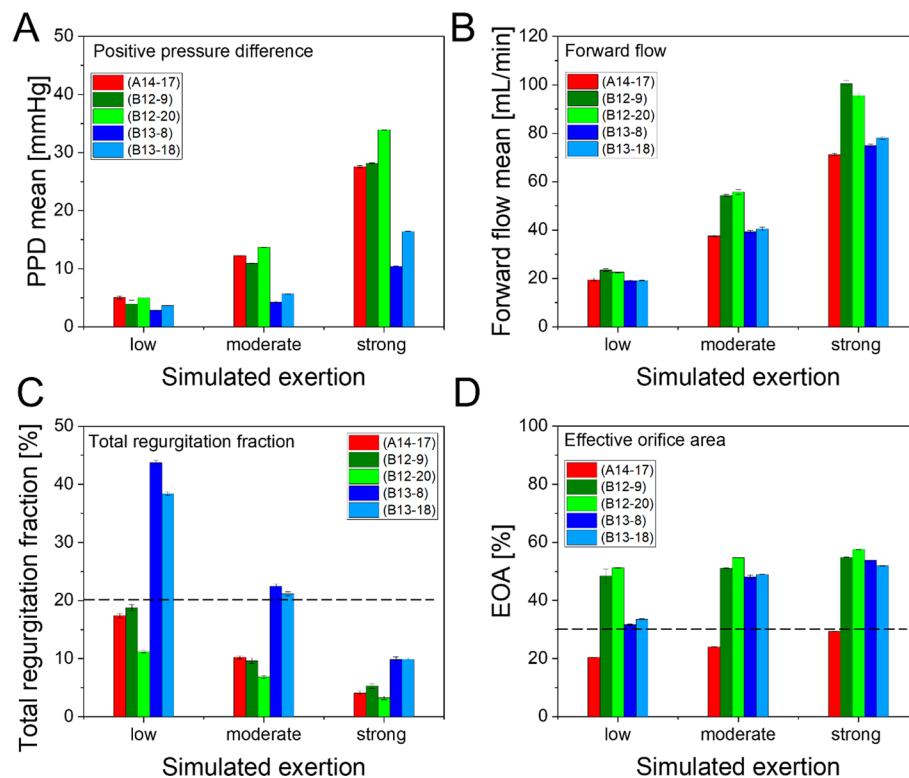


Fig. 5 Representative pulsatile performance data at operating pressure of 50 mmHg. Simulated exertion as indicated: low (0.5 L/min at 40 bpm), moderate (1 L/min at 60 bpm), strong (2 L/min at 80 bpm), tests: $n = 10$, each. **A** positive pressure difference (PPD), **B** forward flow, **C** normalized total regurgitation fraction, dashed reference line at 20% indicating acceptable reflux [56], **D**: effective orifice area (EOA) normalized to circular cross section, dashed reference line at 30% as recommended minimum value [13]

observed for versions A14 and B12 across all simulated exertions. The leaflets opened and closed simultaneously on both sides evenly and symmetrically for both versions (see supporting information 5, especially Figure S17 and Figure S18). In contrast, version B13 required approximately half pressure at simulated moderate and strong exertion. The mean forward flow of version B12 was noticeable higher than versions A14 and B13, which revealed similar values. The total regurgitation fraction decreased with increased simulated exertion, for all tested valves. A significant higher regurgitation fraction was observed for valve B13. Version A revealed an increasing EOA of about 20–30% of circular cross section with rising simulated exertion. The EOA of version B12 also slightly increased with twice as large values (compared to version A14) of 50% to almost 60%. In difference, the EOA of version B13 increased from 30% to about 50% with rising simulated exertion.

Discussion

Physiological load of standing upright is simulated by static testing

Assuming that the EOA at static flow conditions is comparable to pulsatile operation, the difference in forward flow ratios of empty and valve loaded attachments, between the valve versions can be explained. For proximal pressure up to 60 mmHg all valves (except

B13–8) revealed nearly constant reflux, over 80 mmHg the reflux considerably increased with pressure, which indicates functionality with some safety reserve. The proportionally to pressure increasing reflux of version B13–8 can be seen as hint for insufficient oversizing and leakage, despite proper valve function in pulsatile operation. Consequently, 8% oversizing revealed as insufficient sealing in this experimental setup. Hence, version B revealed functional with safety reserves in the physiological pressure range and beyond, if sufficiently oversized. A larger stent diameter allows slightly increased flow at a given vessel diameter (versions B), but the EOA has a significantly greater influence on the flow (version A vs. B).

Version A revealed limited performance due to significant higher flow resistance as a fluid dynamic deficit, which may be a potential risk factor for thrombosis. However, the static condition is more theoretical than practical, muscle activity is always necessary for upright standing. Small amounts of blood of different volumes are continuously pushed towards the heart by the muscle pump, which in reality means semi-pulsatile valve operation.

Physiological load of walking is simulated by pulsatile testing

All valves are functional in acute testing conditions showing an almost constant operating behavior over the tested pressure and flow ranges, see Figures S1–S15, there is no concerning drifting out of line. The mean PPD of version B13 at simulated moderate and strong exertion was almost half the values of versions A14 and B12 (with similar forward volume per cycle), this indicates significantly less flow resistance or longer time duration. For versions A14 and B13 similar mean forward flow was observed, but with half pressure for B13, i.e. version B13 is of less flow resistance. Due to similar PPD values (A14 and B12) the higher forward flow indicated less flow resistance of version B12. The flow resistance of A14–17 is more than double the value of B12–9, which can be explained by different EOA. If the standard for heart valves is considered as a guideline, reflux in the range of 10–20% are described as acceptable (Table S2) [56]. The tested constellations except B13–8 fulfil this requirement. For natural saphenous veins a closing pressure of 2–5 mmHg at flow of 12–32 mL/min is reported [57]. Both versions appear applicable under physiological conditions. However, without any flow or pressure, the valves of both versions are slightly open and allow slow blood flow without considerable resistance, e.g. horizontally lying person.

Risk of valve displacement

Valve migration was not observed in the experiments presented here. As the inner surface and the compliance of a real vein differ from 3D printed material, no valid statement can be drawn. Due to pressure difference within the valve, a force is generated in the axial direction, which the implant has to resist to avoid displacement. Nevertheless, rough estimation of axial force can be calculated with circular cross section area and proximal pressure for the closed valve. In forward direction, with increasing valve opening the axial forward force decreases, a suction effect due to the wake turbulence may also pull on the valve. Additionally, due to irregular leg movements, mass inertia of blood, and hydrodynamic conditions maximal axial short-term forces of about some Newton are realistic. Radial force distribution of oversized stents is not uniform due to

anatomical environment or possibly uneven calcification [58]. However, recommendations for avoiding valve displacement require complex considerations including axial force, radial force, surface properties, and the anatomical–biological environment.

In contrast to the arterial system, vein diameter is not constant in different load situations and due to postural changes of the body, causing permanent changes in hydrostatic pressure and systemic conditions. Therefore, comparably high oversizing and a high compliance is essential for venous stent-based implants, to accommodate to the vessel diameter changes and achieve secure fixation. To avoid migration of the stent in the vein, oversizing of 1–4 mm (10–20%) is recommended [19, 59]. In general, veins show lower maximum stresses and Young's moduli, but higher maximum strains compared to arteries, indicating that the thin venous wall can tolerate more extensive dilatation without rupture [60–62]. Nevertheless, permanent high overexpansion of the venous wall should be prevented, as it could affect neointimal growth [63]. High radial force can cause inflammatory response and fibrosis [59].

Implant migration or tilting can also be prevented by surgical suture or additional elastic stent elements. One further option is the utilization of barbs, which are for example used for inferior vena cava (IVC) filters [64], these are not further discussed here.

Compliance with general recommendations

Considering the general recommendations derived from literature, following respects can be stated. Both versions are designed to being crimped for minimal invasive implantation. Secure fixation should be ensured, but permanent overexpansion of the vein wall should be prevented. The bicuspid design mimics blood flow similar to natural valves, version A causes higher flow velocity and thus washout of region behind leaflets, version B allows a high orifice area with less dead space. The orifice of an open venous valve is always elliptical, never circular [57], hence, natural flow conditions are achieved when the valve is not fully open. These are theoretical considerations, monocuspid valves are also under development, which imitate natural blood flow less conforming. Tilting and deformation occurred with the valve of version A below 80 mmHg in both scenarios (static and pulsatile), which could be prevented by the double strut of version B, no displacement was observed here. Manufacturing leaflets from material of the group of polycarbonate urethane is promising to us in regard of biocompatibility and thrombosis triggering, but in vivo tests were not performed in this study. Reflux was observed in the range of 1–4 mL/min in physiological pressure range at pulsatile testing, which is less than 10% of forward flow in most cases and fits mainly the recommended range. Valves of both versions open at a pressure gradient below 5 mmHg relating to natural conditions. The ratio of implant length to diameter is controversial, a short implant is less burden for the vein wall and easier to handle, but is of increased tendency for tilting. A long implant shows less tendency for migration, but has to withstand bending [60]. That ratio is for version A 1.6, and for version B 4.6. Version can be designed differently by adapting the number of cell (rhomboid) rings and changing the length of double struts (keeping the mid part) without impairing its performance. The EOA of version A14–17 revealed less than the recommended area of 30% of vessel cross-sectional area [50], valves of version B fulfil this requirement. The long-term performance of the valves was not yet investigated, the focus was on functional testing prior enduring studies. The

long-term requirements are estimated as followed: when a hypothetical patient slowly walks 1 h a day with a cadence of 40 steps per minute, the valve performs 2400 cycles per day or 0.9 million steps per year, Sathe et al. recommend durability for at least 500.000 cycles [35].

Depending on the stage of CVI disease, the vascular situation can be diverse in terms of venous dilation and deformation. An advanced therapy concept may comprise several implantation sites for valve prostheses. A possible therapy approach that takes into account superficial and deep implantation sites, in consideration of the hemodynamic paradox [7] as an example, could work with differently designed valves that are tailored to the respective conditions. For this advanced therapy, valve prosthesis of version A (shorter, more flexible) seem to be more suitable for peripheral system, and valves of version B (longer, more sturdy) are well suited for central veins. Summing up, the intended positive effects of version B have been confirmed in the experimental findings.

Further aspects for the application of venous valve prostheses

The utilization of non-magnetic or non-metallic material is advantageous in order not to limit the spectrum of available diagnostic examinations or therapy options for a patient, e.g. MRI ("MR-safe" or "MR-conditional"), and radiotherapy. Further, a concept for diagnosing the current state of the implant itself is also recommended, regarding to wear, aging, structural failure. This can be achieved e.g. through accessibility for ultrasound, radiopaque elements, sensing wires, or microelectronic components. Sonography is limited in metallic stents, but in the here presented design the leaflets are accessible. A prospective special biologized valve that prevents both neointima and intimal hyperplasia and improves the functionality of the valves could be achieved with tissue engineering, e.g. seeding with endothelial cells [18].

In addition, durability and crimpability for minimal invasive implantation of the whole implant will be investigated in forthcoming work. Further, studies on different stent materials (stainless steel, cobalt chrome alloys, or nonmetallic or polymeric material) are intended.

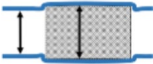
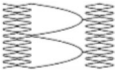
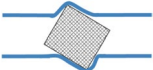
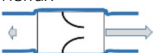
Venous valve design recommendations

Considering the testing results, also concerning to generally accepted commendations of other authors, we derive design recommendations for prosthetic venous valves as listed below, see Table 1.

Limitations

From valve version A only one size was available, due to the aforementioned deficiencies and the consequently design of version B, no further sizes of version A were manufactured. The influence of leaflet thickness cannot be clearly distinguished from other design effects, in consideration the other findings a subordinate role is presumable. In static and pulsatile conditions, the whole flow was measured, discriminating perivalvular leak fraction from the flow fraction through the valves was not possible. Based on the inline camera video recordings at high pressure levels, no gaps or incomplete radial stent apposition were apparent, so that only minor influence of perivalvular leakage was assumed. The long-term performance of the valves has yet to be investigated, as

Table 1 Recommendations for new version of bicuspid venous valve design and testing conditions

	Parameter/aspect	Recommendation	Explanation based on our test results
Advances in similar valve designs	Stent oversizing 	10–20% of vessel diameter	Vessel dilation should be considered 8% revealed as too small, 9% is the limit in tests without vessel deformation More than 20% may injure the vein wall [19, 59]
	Stent fixation	Additional elastic stent retaining structures	Prevention of dislocation E.g. hooked barbs may penetrate venous wall
	Stent structure 	2–3 cell rings (e.g. rhomboid) at the top and bottom	Acceptable implant length Sufficient stability Single rings showed tendency to rocking motion
	Cell ring connector	Double struts between leaflet and upper cell ring	Increase stability Prevention of deformation and tilting
	Stent length/diameter 	Ratio (L/D) more than 2	Prevention of tilting Shorter ring connection reduces implant length
	Stent sidewall 	Filled with cells (e.g. rhomboids)	Prevention of inward bulging of wall material Version A vs. version B, see also Fig. 1
	Effective orifice area (EOA) 	Large (maximum)	Less flow resistance Larger than 30% of the vessel cross-sectional area [13, 50]
Specific test parameters	Leaflet fixation	Fixation of leaflet in cells (rhomboids) of sidewall	Prevention of leaflet sliding down Improved sealing to vessel wall
	Leaflet material	Flexible, biocompatible, antithrombotic, long-term stable, non-biological origin	Artificial (synthetic) material has no variations in quality, texture, durability, etc. compared to natural material Less complexity in testing (in vitro, in vivo)
	Pressure range	Runing up to at least twice the physiologically expected pressure values	Discovering hidden weaknesses Safety reserve
	Opening/closing pressure	Opening and closing at low pressure difference (below 5 mmHg)	Performance close to natural valves
	Flow range for vessels (Ø > 10 mm)	Capability to operate at flow of 2 L/min	No failure under high operational load
	Frequency	60 bpm (minimum)	Simulation of realistic exertion scenario
	Reflux 	< 20% of forward flow (pulsatile operation)	Sufficient functionality

the focus of the present study was on functional testing prior to enduring studies. The crimpability of version B has not yet been investigated to determine whether the leaflet structure has been damaged, but this will be done in future work. The inner surface of a natural vein differs from attachments made of 3D-printed material, and the compliance of the vein wall depends on the tension of smooth muscles. Therefore, statements about oversizing are of limited validity.

Conclusion

In this study, a modified venous valve concept was comparatively compared to the original design by performance testing under static and pulsatile flow conditions. The valve leaflets were fabricated of electrospun TSPCU nanofiber nonwoven, due to favorable biocompatibility and simple processability. It could be shown that the ES parameters can be adapted to both setups of versions A and B, without any particular advantage of one concept over the other. However, version B is far easier to produce, eliminating the elaborate process step of nonwoven transfer from an ES mold, while also improving leaflet thickness homogeneity and maximizing EOA. Regarding stent design, version B improved stent anchoring and leaflet fixation. In terms of material selection, the approach of using low Shore hardness TSPCU material could be substantiated.

Both valve versions performed under different simulated physiological conditions, whereas version A revealed a tendency to reach its limits in the situation of higher operational loads earlier. It can be summarized that the design modifications in version B demonstrated the intended positive effects on valve performance, but the modified stent design is initially a test platform rather than a final implant, it points the way to more suitable venous valve implants. The evaluation demonstrates the impact of design changes identifying key elements for future implant developments. Specific design and testing recommendations were drawn.

Future work will focus on long-term functionality, which will be investigated by endurance testing and comprehensive biocompatibility testing of various leaflet materials in vitro and in vivo is intended.

Materials and methods

Bicuspid prosthetic venous valves designs

The initially developed design is in the following named “version A” [55], the modified design is named “version B”. In light of the aforementioned requirements, two bicuspid valve concepts with valve leaflets made of thermoplastic silicone polycarbonate urethane (TSPCU) nanofiber nonwoven material were investigated. The valve leaflets are attached to nitinol stents consisting of two cell rings (rhomboid) and a leaflet support in between the cell rings, see Fig. 1. Version A consists of two cell rings with ten rhomboid-shaped elements, which are connected by two arched struts in between. The leaflet structure is attached to the lower ring, and the commissure of the leaflet matches the support structure, so the valve remains in its shape. The results of preparatory experimental studies on version A have encouraged the development of version B, which modifications are following:

- The rhomboid rings consist of three rows each instead of one, to avoid rocking motion.
- The side walls are filled with rhomboids for three reasons: (1) fixing the leaflets to prevent migration from stent attachments, (2) prevent inward bulging, (3) improved sealing to the vessel wall.
- Double struts were added between leaflet and upper rhomboid ring to improve stability and prevent tilting. In neutral position, the valve leaflets are to be slightly open.
- Application of leaflets with a cylindrical shape and a diameter according to the stent diameter for three reasons: (1) fully open cross-sectional area with lowest possible flow resistance, (2) no mold for electrospinning is needed, (3) possibility of using simple tube-shaped wrought material valves, which are not directly electrospun on the stent.

Fabrication of testing specimens

Stent samples

Stent A was designed using the CAD software Creo Parametric 6.0.3.0 (Parametric Technology Corp., Needham, MA, USA). Stent B was designed in Fusion 360 2.0.17721 (Autodesk GmbH, München, Germany). The stents were manufactured from a nitinol tube with a diameter of 5 mm and a wall thickness of 0.24 mm (Euroflex GmbH, Pforzheim, Germany). The stents were laser cut using a StarCut Tube system (Coherent Corp., Saxonburg, PA, USA) with a pulsed laser source Monaco 1035-80-60, frequency 500 kHz, pulse duration 300 fs, pulse energy 10 μ J, argon atmosphere with supply pressure 15 bar, and cutting velocity of 1.5 mm/s. Stent A was expanded in two steps with increasing diameter to 14 mm in a convection oven KLS 05/13 (Thermconcept GmbH, Bremen, Germany) with an annealing temperature of 512 °C for 15 min at each step. The stents of version B were expanded in three steps to final diameters of 12 and 13 mm, respectively, with 8 min annealing time per step. A polishing step followed afterwards.

Valve leaflet samples

A homogenous polymer solution of 7.5wt% TSPCU (Shore 80A) was obtained by dissolving in chloroform (CHCl_3), *N,N*-dimethylformamide (DMF) and 2,2,2-trifluoroethanol (TFE), (ratio of 3/1/1). All polymers, chemicals and solvents were used as received. In brief, electrospinning was performed using an experimental spinning setup equipped with a single jet capillary emitter (G21 cannula) and a rotating mold or cylinder, see Fig. 1. Following parameters were set: working distance of 160 mm, rotation of 4000 rpm, flow of 1 mL/min, linear traversing motion, room temperature. A high voltage of 6 kV (collector) and 22 kV (emitter) was applied and processing time was fixed at 7200 s. A layer thickness of 100 μ m was targeted for both versions. For valve version A, CNC machined aluminum molds (Haas Automation, Inc—CNC Machine Tools, Oxnard, CA, USA) were coated with electrospun TSPCU nonwoven as described in [65]. The stents of version B were directly coated on the metal cylinder.

Assembly of valves

The electrospun nonwoven was removed from the mold and transferred to stent A, or removed from the cylinder with stent B. For fixing valves of both versions on the stents, the protruding part of the nonwoven was turned inwards and spot-welded in all rhomboids using an in-house developed device [66], see Fig. 1.

The nonwoven thickness ($n=10$, each) was measured using a dial gauge Mitutoyo 543–394B with associated stand (Mitutoyo Corporation, Kawasaki, Japan).

The fiber morphology of leaflet and welded points were investigated using a scanning electron microscope (SEM) QUANTA FEG 250 device (FEI Company, Dreieich, Germany) operating in high vacuum and 10 kV voltage, using an Everhart–Thornley detector (ETD) in secondary electron mode. The nonwoven samples were fixed on aluminum carriers using conductive carbon pads. Gold sputter coating was achieved using an AGAR Sputtercoater (Agar Scientific Ltd, Stansted, Essex, UK). The fiber diameters were measured for quality control applying the GIFT-method [67, 68].

Testing fixtures

Attachments, which are simplified representations of vessels for experimental tests, were designed in three sizes with inner diameters (D10 mm, D11 mm, and D12 mm) using CAD software Fusion 360. Digital light processing (DLP) technology was used to create annular attachments of photopolymeric resin Ultracur3D FL 300 (BASF 3D Printing Solutions GmbH, Heidelberg, Germany) on an Asiga Pro 4K45 printer (Asiga, Alexandria, Australia), for details see supporting information 1.

Experimental test setup for performance testing

For preconditioning and removing of potentially existing solvent residues the assembled valves were stored in ultrafiltrated water at room temperature for at least 2 days before testing. Under immersed conditions, little material shrinking was observed. Before testing, the valves were crimped by hand at 0 °C in ice water, then implanted in the attachments. The test configurations are introduced in Table 2.

The valves were oversized by 1 or 2 mm in relation to the attachment diameter, as recommended in [19]. Regarding the experimental design, valve of version A (A14–17), available from previous work with a diameter of 14 mm has only been tested in a 12 mm attachment with 2 mm oversize. Preparatory studies revealed insufficient performance of valve A with 1 mm oversizing; hence, it was not pursued further for this work. In

Table 2 Test configurations, abbreviations for tested experimental arrangements specify the valve version, stent size, and the oversize in millimeters (O.S) resulting from the attachment, and oversizing percentage in brackets

Valve version	Stent diameter	Sample abbreviation in attachment (Ø _{tube}) and oversizing (O.S)					
		Ø10 mm	O.S	Ø11 mm	O.S	Ø12 mm	O.S
A	Ø14 mm	X		X		A14–17	2 (17%)
B	Ø12 mm	B12–20	2 (20%)	B12–9	1 (9%)	X	
B	Ø13 mm	X		B13–18	2 (18%)	B13–8	1 (8%)

contrast, two version B stents (B12, B13) were tested in attachments with two different diameters each.

For performance testing of the different valves, static testing and pulsatile testing was done. An operating pressure of 50 mmHg was estimated for a valve in the thigh. In general, the tests were run up to more than double operating pressure (worst case) to be on the safe side and detect possible trends in performance.

Static testing

The valves were implanted in different attachments, and testing was performed in forward and backward direction using water. The forward flow was measured at 1 mmHg, 3 mmHg, and 5 mmHg by gravimetric measurement of water mass, which flowed through the test specimens, at room temperature for a time interval of 30 s using a scale Sartorius MSE4202-000-D0 (Sartorius AG, Göttingen, Germany). Additionally the flow through empty attachments without valves was investigated ($n=3$, each). The reflux was measured at 20–60 mmHg in 10 mmHg steps, and 80–140 mmHg in 20 mmHg steps by gravimetric measurement of water mass ($n=3$, each). The values for pressure-equalized water column were calculated using a density value for water and mercury of 998.21 kg/m³ at 20 °C [69], and the density of mercury (13,545.89 kg/m³) [70] respectively, see Fig. 6 and Table S1.

Pulsatile testing

To investigate the fluid dynamics of venous valves under pulsatile, physiological, and pathological pressure and volume flow conditions, a fluid dynamic circulation model was used, shown in Fig. 7 and Figure S16, for details see supporting information 3.

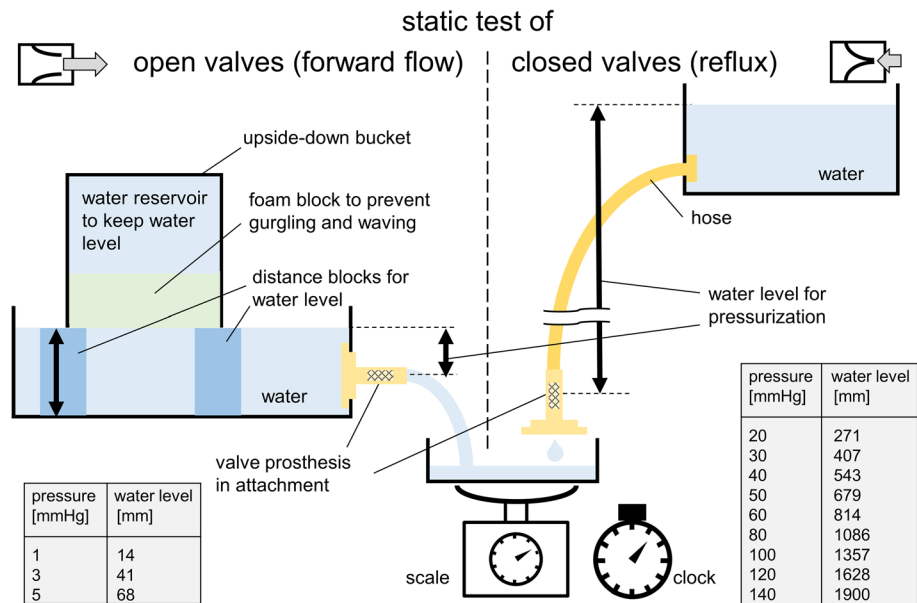


Fig. 6 Static testing. Gravimetric measurement of water mass per time interval was performed for open valves (conditions: constant water pressure was generated by distance blocks under a reservoir) and closed valves (conditions: different height levels and a flexible hose between valve and water container were utilized)

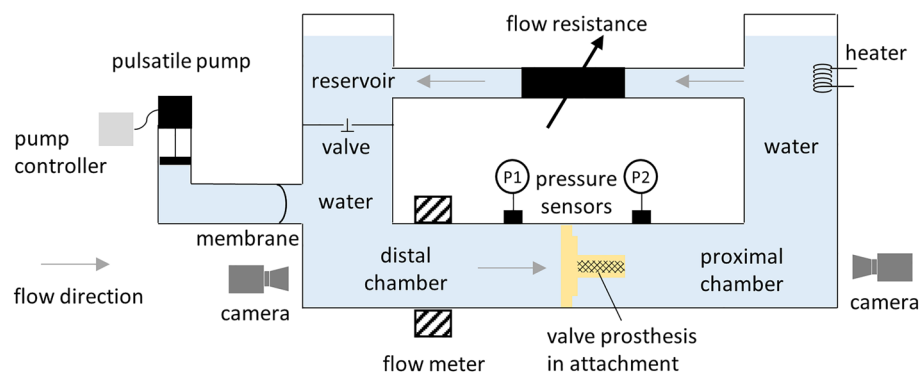


Fig. 7 Pulse duplicator system (schematic drawing)

The test series were performed with flow rates of 0.5 L/min at 40 bpm to imitate slow walking or low exertion, 1 L/min at 60 bpm for moderate exertion, and 2 L/min at 80 bpm for strong exertion. The test setup, initially designed for testing aortic and mitral valves (HDTi-6000, Biomedical Device Consultants and Laboratories, Wheat Ridge, USA), consists of two fluid compartments coupled via a flexible membrane: the pump circuit and the test circuit.

Testing was performed using 0.9% saline at 37 °C. The valves were tested with ballasting pressure in ranges of 20–60 mmHg (A14) and 20–140 mmHg (B12, B13), increased in 10 mmHg steps. For simulation of different exertion conditions, frequencies and flow parameters of 40 bpm with 0.5 L/min each, 60 bpm with 1 L/min each, and 80 bpm with 2 L/min each were adjusted. The pressures distal and proximal to the valve were measured, as well as the flow through the valve loaded testing attachment. To achieve specific flow at definite proximal pressure values, the mutually affecting parameters of displacement volume of the pulsatile pump, as well as flow resistance were controlled.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12938-024-01316-x>.

Supplementary Material 1

Acknowledgements

The authors thank Katja Hahn, Manfred Strotmeier, Babette Hummel, Falk Reinhardt, Dalibor Bajec, Eric Bohne, and Jens Großmann for their expert technical assistance and skillful work.

Author contributions

AG: Conceptualization, methodology, validation, formal analysis, investigation, writing—original draft, writing—review and editing, visualization. SI: Conceptualization, methodology, writing—original draft, writing—review and editing. NF: investigation, writing—review and editing. JS: Conceptualization, writing—review and editing. JO: Investigation, writing—review and editing. HM: Conceptualization, writing—review and editing. WS: Writing—review and editing. KS: Supervision, project administration, funding acquisition. NG: Supervision, project administration, funding acquisition, writing—review and editing. KL: Conceptualization, methodology, writing—original draft, writing—review and editing.

Funding

Open Access funding enabled and organized by Projekt DEAL. No funding.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Generative AI

Generative AI and AI-assisted technologies were only used in the writing process to improve the language and readability. Generative AI and AI-assisted tools were not used in data evaluation, images and artwork.

Received: 12 July 2024 Accepted: 15 November 2024

Published online: 29 November 2024

References

1. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol*. 2005;15:175–84. <https://doi.org/10.1016/j.annepidem.2004.05.015>.
2. Gujja K, Kayiti T, Sanina C, Wiley JM. Chronic venous insufficiency. In: Dangas GD, Di Mario C, Thiele H, Barlis P, editors. *Interventional cardiology: principles and practice*. 3rd ed. Newark: John Wiley & Sons Incorporated; 2022. p. 835–43. <https://doi.org/10.1002/9781119697367.ch87>.
3. Baylis RA, Smith NL, Klarin D, Fukaya E. Epidemiology and genetics of venous thromboembolism and chronic venous disease. *Circ Res*. 2021. <https://doi.org/10.1161/CIRCRESAHA.121.318322>.
4. Azar J, Rao A, Oropallo A. Chronic venous insufficiency: a comprehensive review of management. *J Wound Care*. 2022. <https://doi.org/10.12968/jowc.2022.31.6.510>.
5. Vasudevan T, Robinson DA, Hill AA, Ouriel K, Holden A, Gagnon J, et al. Safety and feasibility report on nonimplantable endovenous valve formation for the treatment of deep vein reflux. *J Vasc Surg Venous Lymphat Disord*. 2021;9:1200–8. <https://doi.org/10.1016/j.jvsv.2020.12.073>.
6. Recek C. The hemodynamic paradox as a phenomenon triggering recurrent reflux in varicose vein disease. *Int J Angiol*. 2012;21:181–6. <https://doi.org/10.1055/s-0032-1325168>.
7. Recek C. Calf pump activity influencing venous hemodynamics in the lower extremity. *Int J Angiol*. 2013;22:23–30. <https://doi.org/10.1055/s-0033-1334092>.
8. Liu Z, Liu B, Li C, Xiao Y, Wei H, Zhou J, Feng Z. Zwitterionic modification: a strategy to enhance the mechanical properties, lubricity and hemo- and biocompatibility of silicone poly(carbonate urethane urea). *React Funct Polym*. 2024;203: 106007. <https://doi.org/10.1016/j.reactfunctpolym.2024.106007>.
9. Wei S, Wu J, Gu X, Shen S, Ma M, Shi Y, et al. Low protein adsorption and high cellular activity of PEG-based silicone polyurethane for artificial heart valves. *Mater Today Commun*. 2024;39: 109357. <https://doi.org/10.1016/j.mtcomm.2024.109357>.
10. Wang Y, Fu Y, Wang Q, Kong D, Wang Z, Liu J. Recent advancements in polymeric heart valves: from basic research to clinical trials. *Mater Today Bio*. 2024;28: 101194. <https://doi.org/10.1016/j.mtmbio.2024.101194>.
11. Dempsey DK, Carranza C, Chawla CP, Gray P, Eoh JH, Stacy Cereceres S, Cosgriff-Hernandez EM. Comparative analysis of in vitro oxidative degradation of poly(carbonate urethanes) for biostability screening. *J Biomed Mater Res, Part A*. 2014;102:3649–65. <https://doi.org/10.1002/jbm.a.35037>.
12. Bachtar EO, Erol O, Millrod M, Tao R, Gracias DH, Romer LH, Kang SH. 3D printing and characterization of a soft and biostable elastomer with high flexibility and strength for biomedical applications. *J Mech Behav Biomed Mater*. 2020;104: 103649. <https://doi.org/10.1016/j.jmbbm.2020.103649>.
13. Zong Q, Liu J, Chen Y, Kong Y, Dang Y, Wang Z. Prosthetic venous valves for chronic venous insufficiency: advancements and future design directions. *Med Novel Technol Devices*. 2024;21: 100288. <https://doi.org/10.1016/j.medntd.2024.100288>.
14. Kidane AG, Burriesi G, Edirisinghe M, Ghanbari H, Bonhoeffer P, Seifalian AM. A novel nanocomposite polymer for development of synthetic heart valve leaflets. *Acta Biomater*. 2009;5:2409–17. <https://doi.org/10.1016/j.actbio.2009.02.025>.
15. Kannan RY, Salacinski HJ, de Groot J, Clatworthy I, Bozec L, Horton M, et al. The antithrombogenic potential of a polyhedral oligomeric silsesquioxane (POSS) nanocomposite. *Biomacromol*. 2006;7:215–23. <https://doi.org/10.1021/bm050590z>.
16. Rocco KA, Maxfield MW, Best CA, Dean EW, Breuer CK. In vivo applications of electrospun tissue-engineered vascular grafts: a review. *Tissue Eng Part B Rev*. 2014;20:628–40. <https://doi.org/10.1089/ten.TEB.2014.0123>.
17. Oberdier MT, Rittgers SE. The design, development, and evaluation of a prototypic, prosthetic venous valve. *BioMed Eng OnLine*. 2008;7:1–16. <https://doi.org/10.1186/1475-925X-7-25>.
18. Pavcnik D, Uchida B, Kaufman J, Hinds M, Keller FS, Rösch J. Percutaneous management of chronic deep venous reflux: review of experimental work and early clinical experience with bioprosthetic valve. *Vasc Med*. 2008;13:75–84. <https://doi.org/10.1177/1358863X07083474>.
19. Borst GJ, Moll FL. Percutaneous Venous Valve Designs for Treatment of Deep Venous Insufficiency. *J Endovasc Ther*. 2012;19:291–302. <https://doi.org/10.1583/11-3766R.1>.
20. Boersma D, Vink A, Moll FL, de Borst GJ. Proof-of-concept evaluation of the sailvalve self-expanding deep venous valve system in a porcine model. *J Endovasc Ther*. 2017;24:440–6. <https://doi.org/10.1177/1526602817700120>.

21. Cifuentes S, Ulloa JH, Rasmussen TE. An implantable bioprosthetic venous valve to establish deep vein competence for post-thrombotic syndrome. *JAMA Surg.* 2023;158:316–7. <https://doi.org/10.1001/jamasurg.2022.6362>.
22. Ulloa JH, Glickman M. One-year first-in-human success for veno valve in treating patients with severe deep venous insufficiency. *Vasc Endovasc Surg.* 2022;56:277–83. <https://doi.org/10.1177/15385744211073730>.
23. Ulloa JH, Glickman M. Human trial using the novel bioprosthetic Veno Valve in patients with chronic venous insufficiency. *J Vasc Surg Venous Lymphat Disord.* 2021;9:938–44. <https://doi.org/10.1016/j.jvsv.2020.10.017>.
24. enVeno Medical Corporation, Irvine, CA (US). Transcatheter valve system and method for venous insufficiency; US20230363900A1; 16.11.2023.
25. Innovein, Inc., San Carlos, CA (US). Venous valve prosthesis; US 2017/0056175 A1; 25.08.2016.
26. Innovein, Inc., San Carlos, CA (US). SBIR Phase II: Venous Valve Prosthesis as a Cure for Chronic Venous Insufficiency. 08.07.2024. <https://www.sbir.gov/sbirsearch/detail/1644629>.
27. D'Addario J, Smeds MR, Wittgen C. Surgical treatment of deep venous insufficiency and requirements for novel interventions. *JVS-Vascular Insights.* 2023;1: 100011. <https://doi.org/10.1016/j.jvsvi.2023.100011>.
28. Wilson NM, Rutt DL, Browse NL. Repair and replacement of deep vein valves in the treatment of venous insufficiency. *Br J Surg.* 1991;78:388–94. <https://doi.org/10.1002/bjs.1800780404>.
29. Zervides C, Mahdi H, Staub RA, Jouni H. Prosthetic venous valves: short history and advancements from 2012 to 2020. *Phlebology.* 2021. <https://doi.org/10.1177/0268355520962451>.
30. Zervides C, Giannoukas AD. Historical overview of venous valve prostheses for the treatment of deep venous valve insufficiency. *J Endovasc Ther.* 2012;19:281–90. <https://doi.org/10.1583/11-3594MR.1>.
31. Bombardini T. The venous contribution to cardiovascular performance: from systemic veins to left ventricular function: a review. *Scr Med.* 2021;52:299–308. <https://doi.org/10.5937/scriptamed52-35083>.
32. Brandes R, Lang F, Schmidt RF. *Physiologie des Menschen.* Berlin: Springer, Berlin Heidelberg; 2019.
33. Rudolph PB, Recke A, Langan EA, Hunold P, Kahle BK. Are sonographically measured vascular haemodynamic parameters reproducible using magnetic resonance imaging? *Eur J Vasc Endovasc Surg.* 2016;52:665–72. <https://doi.org/10.1016/j.ejvs.2016.08.004>.
34. Jorfeldt L, Wahren J. Leg blood flow during exercise in man. *Clin Sci.* 1971;41:459–73. <https://doi.org/10.1042/cs0410459>.
35. Sathe RD, Ku DN. Flexible prosthetic vein valve. *J Med Devices.* 2007;1:105–12. <https://doi.org/10.1115/1.2736393>.
36. Rittgers SE, Oberdier MT, Pottala S. Physiologically-based testing system for the mechanical characterization of prosthetic vein valves. *BioMed Eng OnLine.* 2007;6:1–12. <https://doi.org/10.1186/1475-925X-6-29>.
37. Tschakovsky ME, Saunders NR, Webb KA, O'Donnell DE. Muscle blood-flow dynamics at exercise onset: do the limbs differ? *Med Sci Sports Exerc.* 2006;38:1811–8. <https://doi.org/10.1249/01.mss.0000230341.86870.4f>.
38. MacDonald MJ, Shoemaker JK, Tschakovsky ME, Hughson RL. Alveolar oxygen uptake and femoral artery blood flow dynamics in upright and supine leg exercise in humans. *J Appl Physiol.* 1998. <https://doi.org/10.1152/jappl.1998.85.5.1622>.
39. Koch DW, Newcomer SC, Proctor DN. Blood flow to exercising limbs varies with age, gender, and training status. *Can J Appl Physiol.* 2005. <https://doi.org/10.1139/h05-141>.
40. Posner JD, Gorman KM, Klein HS, Woldow A. Exercise capacity in the elderly. *Am J Cardiol.* 1986;57:C52–8. [https://doi.org/10.1016/0002-9149\(86\)91027-1](https://doi.org/10.1016/0002-9149(86)91027-1).
41. Pollack AA, Wood E. Venous pressure in the saphenous vein at the ankle in man during exercise and changes in posture. *J Appl Physiol.* 1949. <https://doi.org/10.1152/jappl.1949.1.9.649>.
42. Iqbal A, Haider M, Stadlhuber RJ, Karu A, Corkill S, Filipi CJ. A study of intragastric and intravesicular pressure changes during rest, coughing, weight lifting, retching, and vomiting. *Surg Endosc.* 2008;22:2571–5. <https://doi.org/10.1007/s00464-008-0080-0>.
43. Cobb WS, Burns JM, Kercher KW, Matthews BD, James Norton H, Todd HB. Normal intraabdominal pressure in healthy adults. *J Surg Res.* 2005;129:231–5. <https://doi.org/10.1016/j.jss.2005.06.015>.
44. Smith JA, Aliverti A, Quaranta M, McGuinness K, Kelsall A, Earis J, Calverley PM. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol.* 2012;590:563–74. <https://doi.org/10.1113/jphysiol.2011.213157>.
45. Schattner A. The wide-ranging spectrum of cough-induced complications and patient harm. *Am J Med.* 2020;133:544–51. <https://doi.org/10.1016/j.amjmed.2019.12.044>.
46. Fronek A, Criqui MH, Denenberg J, Langer RD. Common femoral vein dimensions and hemodynamics including Valsalva response as a function of sex, age, and ethnicity in a population study. *J Vasc Surg.* 2001;33:1050–6. <https://doi.org/10.1067/mva.2001.113496>.
47. Keiler J, Seidel R, Wree A. The femoral vein diameter and its correlation with sex, age and body mass index - an anatomical parameter with clinical relevance. *Phlebology.* 2019;34:58–69. <https://doi.org/10.1177/0268355518772746>.
48. Keiler J, Schulze M, Claassen H, Wree A. Human femoral vein diameter and topography of valves and tributaries: a post mortem analysis. *Clin Anat.* 2018;31:1065–76. <https://doi.org/10.1002/ca.23224>.
49. Salles-Cunha SX, Shuman S, Beebe HG. Planning endovascular vein valve implantation: significance of vein size variability. *J Vasc Surg.* 2003;37:984–90. <https://doi.org/10.1067/mva.2003.245>.
50. Sathe RD. Design and development of a novel implantable prosthetic vein valve [master thesis]. Georgia: School of Mechanical Engineering; May 2006.
51. Fernández-Colino A, Jockenhoevel S. Advances in engineering venous valves: the pursuit of a definite solution for chronic venous disease. *Tissue Eng Part B Rev.* 2021;27:253–65. <https://doi.org/10.1089/ten.TEB.2020.0131>.
52. Pavcnik D, Kaufman J, Uchida B, Correa L, Hiraki T, Kyu SC, et al. Second-generation percutaneous bioprosthetic valve: a short-term study in sheep. *J Vasc Surg.* 2004;40:1223–7. <https://doi.org/10.1016/j.jvs.2004.08.027>.
53. Tien W-H, Zhao X, Chen HY, Berwick ZC, Krieger JF, Chambers S, et al. Role of vessel-to-prosthesis size mismatch in venous valve performance. *J Vasc Surg Venous Lymphat Disord.* 2017;5:105–113.e1. <https://doi.org/10.1016/j.jvsv.2016.08.004>.
54. Pavcnik D, Uchida BT, Timmermans HA, Corless CL, O'Hara M, Toyota N, et al. Percutaneous bioprosthetic venous valve: a long-term study in sheep. *J Vasc Surg.* 2002;35:598–602. <https://doi.org/10.1067/mva.2002.118825>.

55. Stiehm M, Schmidt W, Grabow N, Keiler J, Reumann M, Wree A, et al. Venous Valve Prosthesis, US020230372103A1; 09.04.2021.
56. DIN EN ISO 5840. DIN EN ISO 5840: 2021-05, Herz- und Gefäßimplantate- Herzklappenprothesen- Teil 1, 2, 3 2021. Berlin: Beuth Verlag GmbH. <https://doi.org/10.31030/3180290>.
57. Thubrikar MJ, Robicsek F, Fowler BL. Pressure trap created by vein valve closure and its role in graft stenosis. *J Thorac Cardiovasc Surg.* 1994;107:707–16. [https://doi.org/10.1016/s0022-5223\(94\)70326-4](https://doi.org/10.1016/s0022-5223(94)70326-4).
58. Egron S, Fujita B, Gullón L, Pott D, Schmitz-Rode T, Ensminger S, Steinseifer U. Radial Force: An Underestimated Parameter in Oversizing Transcatheter Aortic Valve Replacement Prostheses: In Vitro Analysis with Five Commercialized Valves. *ASAIO J.* 2018;64:536–43. <https://doi.org/10.1097/MAT.0000000000000659>.
59. Massi I, Zamboni P. What are the ideal characteristics of a venous stent? *Veins and Lymphatics.* 2021. <https://doi.org/10.4081/vl.2021.9739>.
60. Taha MA, Busuttill A, Bootun R, Thabet BA, Badawy AE, Hassan HA, et al. Clinical outcomes and overview of dedicated venous stents for management of chronic iliofemoral and femoral deep venous disease. *Vascular.* 2022;30:320–30. <https://doi.org/10.1177/1708538121989860>.
61. Camasão DB, Mantovani D. The mechanical characterization of blood vessels and their substitutes in the continuous quest for physiological-relevant performances. A critical review. *Mater Today Bio.* 2021;10: 100106. <https://doi.org/10.1016/j.mtbio.2021.100106>.
62. Karimi A, Navidbakhsh M. A comparative study on the uniaxial mechanical properties of the umbilical vein and umbilical artery using different stress-strain definitions. *Australas Phys Eng Sci Med.* 2014;37:645–54. <https://doi.org/10.1007/s13246-014-0294-5>.
63. Yamaguchi M, Sugimoto K, Zamora CA, Takahashi T, Hayashi Y, Sugimura K. Placement of self-expanding stents with different diameters in the porcine venous system: an experimental study. *J Vasc Interv Radiol.* 2006;17:113–9. <https://doi.org/10.1097/01.RVI.0000186951.22050.3D>.
64. Mahnken AH, Pfeffer J, Stanzel S, Mossdorf A, Günther RW, Schmitz-Rode T. In vitro evaluation of optionally retrievable and permanent IVC filters. *Invest Radiol.* 2007;42:529–35. <https://doi.org/10.1097/RLI.0b013e318036b42b>.
65. Schubert J, Arbeiter D, Götz A, Lebahn K, Schmidt W, Grabow N, Illner S. Investigations on physico-chemical properties of TSPCU nonwoven for application as prosthetic venous valve. *CDBME.* 2021;7:613–6. <https://doi.org/10.1515/cdbme-2021-2156>.
66. Tautorat C, Lebahn K, Oschatz S, Arbeiter D, Schmitz K-P, Grabow N, Schmidt W. Thermal welding of polymeric biomaterials: development of a novel device for temperature controlled local application. *CDBME.* 2021;7:660–3. <https://doi.org/10.1515/cdbme-2021-2168>.
67. Götz A, Senz V, Schmidt W, Huling J, Grabow N, Illner S. General image fiber tool: a concept for automated evaluation of fiber diameters in SEM images. *Measurement.* 2021;177: 109265. <https://doi.org/10.1016/j.measurement.2021.109265>.
68. Huling J, Götz A, Grabow N, Illner S. GIFT: an ImageJ macro for automated fiber diameter quantification. *PLoS ONE.* 2022;17: e0275528. <https://doi.org/10.1371/journal.pone.0275528>.
69. Tanaka M, Girard G, Davis R, Peuto A, Bignell N. Recommended table for the density of water between 0 C and 40 C based on recent experimental reports. *Metrologia.* 2001;38:301–9. <https://doi.org/10.1088/0026-1394/38/4/3>.
70. Cook AH, Stone NWB. Precise measurements of the density of mercury at 20°C I. Absolute displacement method. *Philos T R Soc A.* 1957;250:279–323. <https://doi.org/10.1098/rsta.1957.0022>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.