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Advances in the diagnosis and treatment of primary deep venous valve insufficiency

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Abstract
Primary deep venous valve insufficiency (PDVVI) is a common lower extremity venous disease in vascular surgery, distinguished from simple lower extremity varicose veins and lower extremity thrombotic diseases, and requires clinical management as a separate disease. Surgical procedures alone in the superficial venous system cannot completely correct valve reflux and venous hypertension and require surgical valve repair. In addition, the development of non-autologous prosthetic valve transplantation provides a new breakthrough point. This article summarizes the diagnostic and therapeutic advances in PDVVI for discussion.

Keywords Primary deep venous valve insufficiency, Deep venous valve repair, Artificial valve

Introduction

Primary deep venous valve insufficiency (PDVVI) arises from the inability of venous valves to close effectively, thereby leading to enduring venous hypertension and consequent manifestations of pain, pruritus, swelling, and chronic ulcers in the lower extremities. PDVVI stands as a prevalent vascular surgical ailment, encompasses 20% of the population with a recurrence rate of 40% of venous diseases affecting the lower extremities. Regrettably, the present dearth of clinical recognition of PDVVI as an autonomous malady has contributed to a substantial misdiagnosis rate.

With the advancement of knowledge and investigation into PDVVI disease, the imperative for prompt treatment of PDVVI has been elucidated. Following surgical intervention, patients exhibit a long-term ulcer-free rate varying between 54 and 100% [1], experience notable alleviation of leg pain and swelling symptoms, and demonstrate a significant enhancement in their quality of life. In recent times, there has been a continuous enhancement and modernization of diagnostic and therapeutic approaches pertaining to PDVVI. Surgical intervention has emerged as a dependable approach for managing primary lower extremity deep venous valve insufficiency, while the advent of novel valve prosthesis technology has significantly expedited advancements in clinical treatment.

Etiology and pathogenesis

The pathological alternations in PDVVI encompass two primary components, namely venous valve modifications and venous lumen enlargement. The former is induced by prolonged venous hypertension and gravitational forces, which subsequently lead to degenerative alternations in the valve structure, characterized by elongation, flaccidity, and sagging of the valve leaflets [2]. On the other hand, the latter is attributed to venous hypertension and inadequate blood return, resulting in the dilation and tortuosity of the superficial veins. In recent times, a majority of scholars have come to acknowledge that the enlargement of the venous lumen plays a crucial role in the pathogenesis of PDVVI [3, 4]. The expansion of the venous diameter hinders the efficient closure of the

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valve by increasing the distance between the leaflets. The enlargement of the vessel diameter can be attributed to long-term blood return overload to the heart, while the weakening of the vein wall may be influenced by the reduced elasticity and muscle head contraction forces as internal factors.

The existing body of research on risk factors presents inconclusive findings, encompassing obesity, smoking, pregnancy, heavy physical labor, and congenital or acquired iliac vein stenosis [5]. Both being overweight and engaging in sedentary standing contribute to blood stasis, resulting in elevated venous pressure in the lower extremities and compromised muscle pump function, thereby impacting valve functionality [6, 7]. Furthermore, the presence of heightened circulating hormones during pregnancy induces valve vasodilation [8].

The maintenance of unidirectional venous blood flow is achieved through the coordinated action of stable valve closure and muscle pumps. Damage to the venous valves, resulting from various factors, can directly result in venous reflux and venous hypertension. The venous valve is a crucial physiological component within the venous system. Its unique leaflet-like structure and opening and closing mechanism significantly alter the hemodynamics when venous blood passes through the valve, leading to the formation of vortices within the valve pocket; and substantial variations in shear stress on the vessel wall [9]. Research has indicated that interference with vascular flow diminishes the integrity of endothelial function, resulting in endothelial dysfunction, and the initiation of endothelial–mesenchymal transition [10]. Additionally, the muscle pump has the capacity to modify hemodynamics at the valve. In instances where the muscle pump's efficacy is compromised or absent, blood stasis within the valve pocket becomes evident, leading to the formation of conspicuous thrombus, which subsequently impairs the valve structure and consequently affects its functionality [11].

Numerous studies have demonstrated that the elimination of certain genes during the process of growth and development plays an important role in the occurrence of congenital venous valve closure insufficiency [12–14]. Vascular ultrasonography has unveiled that a considerable number of individuals with EPHB4 mutations exhibit venous valve hypoplasia and deep venous reflux. Additionally, the removal of ephrinB2 in mice leads to impairments in the extension, orientation, and proliferation of valve-forming cells, while EphB4 is an indispensable gene for the preservation of valve shape and the growth of leaflets [12]. Miguel A. Ortega conducted a study wherein he gathered excised great saphenous veins from patients diagnosed with chronic venous insufficiency (CVI). Through his investigation, Ortega discovered a notable increase in the PI3 K/Akt/mTOR signaling pathway within valve tissue exhibiting severe reflux. This elevation was accompanied by the presence of HIF-1a, CD4+, CD8+, and CD19+ positive cells. Consequently, it is postulated that hypoxia and inflammatory stimuli may serve as predisposing factors for valve injury and venous reflux [15]. Furthermore, patients with valvular dysfunction exhibit elevated levels of lipid peroxidation and oxidative stress in their serum, as indicated by the heightened expression of associated factors including iNOS, NOX1, NOX2, and the lipid peroxide (MDA) [16]. Additionally, aging serves as a risk factor for PDVVI, and the connective tissue of the venous wall progressively increases with age in valves that are functioning normally. Research has demonstrated an upregulation of DNA damage-related proteins in the venous wall of individuals afflicted with venous valve incompetence. This condition significantly affects the functionality of both the venous wall and valve tissue over an extended duration. Consequently, these findings suggest that such protein overexpression may potentially contribute to the development of primary deep venous valve insufficiency in younger patients [17].

Diagnosis of PDVVI

Despite the presence of lower extremity superficial venous system issues and other clinical manifestations in patients with PDVVI, the diagnosis of PDVVI necessitates the utilization of diverse supplementary assessments. Nevertheless, there is currently no examination technique available that enables direct visualization of venous valve structure or closure status. Retrograde venography can reveal bamboo-like alterations in well-functioning venous valves [18], wherein the valve opens to permit blood passage during centripetal blood flow and closes to prevent reflux when the blood flows in the opposite direction. The occurrence of valve damage leads to valve reflux, necessitating the utilization of diverse technical approaches to assess the extent of valve impairment [2].

Non-invasive testing methods include venous ultrasound and air plethysmography. The stability of ultrasound examination in assessing venous reflux in the lower extremities remains unaffected by variables such as examination time, patient positioning, or the technique employed to provoke reflux (whether manual or automatic inflation–deflation) [19]. Moreover, quantitative ultrasound findings, such as the venous arterial flow index (VAFI), recirculation index (RCI), venous filling index (VFI), and the postural diameter change of the saphenous trunk (PDC), have the potential to distinguish patients with and without reflux [20, 21]. However, it is necessary to establish objective reference values to accurately quantify the various degrees of PDVVI in patients. The presence of venous wall compressibility contributes to the vein's distinctive flow–pressure relationship. Air plethysmography is used to assess the venous reflux by monitoring volume changes of the airbag surrounding the calf, which result from variations in the volume of the calf vein. Moreover, this technique enables the evaluation of the efficacy of the muscle pump through the measurement of parameters such as the ejection fraction (EF) and the residual volume fraction (RVF) [22].

Invasive testing relies on retrograde angiography, a widely acknowledge method for diagnosing vascular disease. The patient underwent Valsalva breathing to elevate abdominal pressure, and femoral vein catheterization was conducted to assess venous valve reflux. The Kistner classification categorizes the degree and site of contrast reflux, enabling its classification into five grades [22, 23].

Kistner classification

Class	Description	
	Quantity	Location
0	None	None
I	Small	The highest pair of valves
II	Medium	The popliteal fossa
III	Large	The lower leg
IV	Large	The ankle

Treatment of PDVVI

Historically, owing to limited comprehension of venous pathophysiology, it has been widely accepted that the use of graduated compression stockings (GCS) and the provision of localized wound care constitute rational therapeutic approaches for the majority of patients [24]. However, this approach frequently proves inadequate in effectively managing the advancement of the disease, resulting in recurrent and persistent leg ulcers stemming from venous valve insufficiency. In this particular instance, there has been a gradual shift in perspective regarding the management of PDVVI, with the current consensus being that timely surgical intervention, primarily through open surgery, is essential when significant venous dysfunction is present.

Typically, surgeons opt for simple superficial venous system surgery to address deep venous reflux in approximately 90% of patients [25]. While this approach yields short-term improvement in clinical symptoms, the persistence of reflux due to the lack of deep venous valve repair results in persistence condition of chronic venous insufficiency. A retrospective analysis indicated a potential association between the inability to correct primary deep venous reflux through superficial venous ablation and valve asymmetry in patients. In case where the valves exhibit symmetry, it is advisable to prioritize treatment the superficial venous system with the purpose to reduce the deep overload obtaining a valve competence. Conversely, valvuloplasty and variceal ablation are necessary if asymmetry is present [26]. Nevertheless, the assessment of deep venous valve symmetry prior to surgery remains challenging, impeding the determination of the appropriate surgical approach.

The surgical interventions for PDVVI primarily consist of venous valvuloplasty, which includes internal valvuloplasty, external valvuloplasty, as well as venous valve grafting, including autologous valve grafting and non-autologous artificial valve grafting, which are still in experimental phase. Generally, endovascular venous valvuloplasty is a meticulous and time-consuming procedure with stringent technical demands. However, it exhibits a low long-term postoperative valve degradation and decay rate, making it suitable for the creation of a single pair of valves. Conversely, extravascular venous valve repair can be performed simultaneously on multiple pairs of valves [27]. Venous valvuloplasty is primarily recommended for patients with severe valve damage requiring intravascular valve repair. Following the procedure, the long-term healing rate of postoperative ulcers ranged from 60 to 76%. Additionally, there was significant relief in leg pain and swelling, with a majority of patients no longer requiring compression stockings post-surgery. Furthermore, significant improvements were observed in hemodynamics and venous manometry [28].

There are two primary types of venous valvuloplasty: internal and external valvuloplasty. Internal valvuloplasty involves the dissection and repair of the valve leaflet defect within the vascular system, with direct visualization. The approach offers the advantage of complete exposure of the valve, facilitating the adjustment of any asymmetry in the valve cusps. However, there is a risk of damaging the valve during the anatomical procedure, and the assessment of the complete closure of the two free valve edges can only be made after the completion of the valvuloplasty.

External valvuloplasty is a surgical procedure that involves the use of sutures or bands to narrow the lumen of a vein without cutting it. This procedure can be performed with or without endoscopic supervision, and is primarily used for patients with enlarged venous lumens. The narrowing of the enlarged lumen is achieved by either constricting at the cusp of the vein valve with a suture needle, or by directly wrapping the enlarged vein vessel with a valve banding material such as Dacron cuff, Venocuff I, Venocuff II, polytetrafluoroethylene, or bovine pericardium [29, 30]. The procedure exhibits a notable degree of surgical safety and operability, as it does not require incision of the vein wall. However, it is important to acknowledge the potential risk of vein lumen stenosis, which may arise. Additionally, it is worth noting that the overall success rate of this procedure ranges from 40 to 50%, which is comparatively lower than that of internal valvuloplasty.

Autologous venous valve grafting is primarily recommended for patients presenting with severe valve damage that poses challenges for repair. Successful execution of this procedure necessitates the availability of a donor venous valve that aligns the lumen diameter of the graft vessels. The donor vein, comprising axillary and brachial veins, is constrained by the lumen diameter [31, 32]. Specially, the axillary vein is deemed suitable for grafting at the femoral level, whereas the brachial vein is deemed appropriate for small-caliber popliteal veins. One advantage of venous valve grafting lies in its ability to selectively graft the distal segment of the regurgitant vessel, bypassing the non-functional segment of the vein. However, it is crucial for the procedure to be executed with precision to avoid any form of distortion, narrowing, or improper tension at the graft junction. Furthermore, the distal end of the great saphenous vein can be used to selectively slice, shape, and insert veins to serve as valve substitutes. This technique is suitable in case where there are limitations in autologous venous valve transplantation alternatives. Nevertheless, it is important to acknowledge that this technique lacks standardized procedures and requires frequent incisions.

To date, only four randomized controlled trials (RCTs) have reported the long-term outcomes of surgical treatment of primary deep venous valve insufficiency [33–36]. Earlier studies from Belcaro reported no significant complications of surgery and incidence of deep venous thrombosis [34, 35]. In 2001, Makarova compared the treatment effects of superficial vein ligation alone with intra-femoral vein valvuloplasty in PDVVI patients, evaluating the improvement of clinical symptoms by changes in venous reflux and CEAP grades. The results showed that patients who underwent femoral venous valvuloplasty compared with simple superficial vein ligation achieved a more significant postoperative improvement in clinical symptoms (86% vs 65%, $P < 0.05$). Further studies found that patients with more severe preoperative symptoms (altered CEAP grade) who underwent valvuloplasty compared with simple superficial vein surgery achieved significant improvement in clinical symptoms at 7 years (81% vs 51%, $P < 0.05$), and when the disease was stable before surgery, the clinical improvement was nearly the same in both groups (96% vs 90%, respectively). $P > 0.01$) [33]. Wang reported in 2006 that femoral vein valvuloplasty combined with superficial venous system repair could improve lower limb hemodynamics better than superficial venous system repair alone [36].

Lasted development

Existing surgical procedures for valve reconstructive surgery require skillful surgery and have the potential to cause serious complications, such as deep vein thrombosis and pulmonary embolism [37]. There is also a risk of dilation of the venous lumen at the site of valve implantation in the medium to long term, resulting in loss of function of the reconstructed valve [38]. Autologous venous valve transplantation has high requirements on the size of donor valve and recipient vein, and may destroy the normal tissue structure of donor valve area, so the application range is limited. In this case, non-autologous artificial venous valve transplantation is a new breakthrough point to seek surgical treatment. The designs of artificial venous valves include single, double or tricuspid leaflets, and the material sources are mainly allografts, xenografts and synthetic materials attached to a frame or carrier.

Artificial venous valves have been investigated as an alternative therapy since the mid-twentieth century. As early as 1985, Gerlock et al. transplanted a biological trilobular heart valve made of glutaraldehyde-fixed pericardium and polyester grafts into the inferior vena cava of dogs, and the valve functioned and survived for 6–8 months [39]. Subsequently, in 1987, Hill transplanted an artificial bilobed valve made of a polyethane polymer into the jugular vein of dogs, and all animals developed thrombosis in the vein within 8 days after the procedure in the presence of anticoagulation [40], possibly due to the prothrombotic effect of glutaraldehyde in slow blood flow.

A technical breakthrough in the development of new venous valve grafts was achieved in 2003. Using a homogeneous allogeneic sheep vein as the donor matrix, Teebken co-cultured 24 valves with recipient myofibroblasts and endothelial cells and implanted them into the external jugular vein. All but two valves functioned well during a 12-week follow-up period [41]. In 2004, Pavcnik designed a bilobed valve with a nickel titanium stent as the main body, loaded with a sheep autologous jugular vein valve. The stent has a 15-mm inflow tract and the valve was partially adjacent to the endothelial cell layer of the host vein. This design enhanced the flexibility and compliance of the valve to aid the formation of a vortex of blood flow, thus removing stagnation within the valve pocket and reducing the risk of thrombosis. During the 3-month follow-up time, all nine implanted venous valves showed unobstructed flow with only one case of reflux observed. Anatomical results showed complete integration of the valves into the host vein wall and no thrombosis was observed [42].

In pursuit of venous valves with regenerative capacity, novel tissue-engineered venous valves offer new directions [43]. The tissue-engineered transcatheter vein valve (TEVV), a tissue-engineered transcatheter vein valve formed by covering a fibrin and collagen matrix of bovine and sheep origin overlaid on a nitinol scaffold, has excellent hemodynamic properties and durability, exhibiting recellularization of the valve root in an animal model without stenosis or reflux [44]. In order to obtain better biocompatibility and good reendothelialization of valve leaflets, the biohybrid elastin-like venous valve (EVV) has characteristics similar to natural bovine venous valves, and have demonstrated excellent reendothelialization, hemocompatibility, and non-thrombogenic in vitro experiments [45].

A team of surgeons in Turkey have experimentally used internal compression therapy (ICT) to treat lower limb deep venous reflux, including in patients with primary deep venous valve insufficiency, by injecting a combination of hyaluronic acid and n-butyl-l cyanoacrylate hard gel between the deep venous valve and the muscular fascia, thereby narrowing the gap where the venous valve is not closing properly and allowing it to function properly. All one-year follow-up of 286 patients showed a 92% success rate of the technique (any reflux over 1 s was considered a technique failure) [46]. This ultrasound-guided gel injection technique provides an effective, comfortable, and long-lasting solution to venous compression, while at the same time, this technology needs to be analyzed in more centers and larger samples.

Although various prosthetic valve designs and animal experiments continue to emerge, more data are needed to apply the results to clinical patients. Up to now, only VenoValve by Universidad de Los Andes and Hancock Jaffe Laboratories has been used in humans, with subsequent 30-month follow-up showing sustained clinical improvement (healing of ulcers and reduction in swelling), high patency rates, and no thrombosis [47, 48]. However, the implantation of VenoValve needs to be performed by incision and suture of vascular vessels. In the future, it is expected to use endovascular technology to implant artificial valves to reduce surgical trauma.

Comments

Challenges remain in the treatment of patients with PDVVI. In addition to the selection of different surgical approach, the current clinical treatment also includes the selection of the number and location of reconstructed valves. Studies have shown that the ulcer healing rates of internal and external valvuloplasty, respectively, are 89% and 79% while the ulcer recurrence rates are 7% and 19%. Multiple valve reconstruction procedures improved ulcer healing to 94%, however, the valve patency rate was lower than that of the above two surgical methods [49]. At the same time, the choice of location also affects the prognosis, with implantation effect of the common femoral vein or the end of the superficial femoral vein is better than that of other sites.

The ideal prosthetic venous valve should also have the function of preventing thrombosis and avoiding the use of thrombus-prone substances, while the size of the valve should match the size of the host's vein to optimize hemodynamics. Studies have shown that prosthetic valves should be less than 15% of the maximum vein diameter of the host transplanted vein to optimize hemodynamics at the valve and reduce wall pressure [50]. Percutaneous graft should be used to reduce surgical injury and prevent turbulence caused by tilt of the valve stent or carrier. Finally, the service life of the artificial valve should have a certain length of time, the extension of life will reduce the number of surgeries required and reduce the economic cost of patients and improve quality of life. In the future, more comprehensive and long-term follow-up trials are needed to investigate the recovery of valve function in PDVVI patients after receiving different treatment strategies, in order to provide standard surgical treatment for PDVVI patients and improve the treatment effect, especially valve replacement surgery.

Author contributions

Chuang Wang and Nan Hu wrote the main manuscript. Wen-Dong Li, Xiao-Long Du and Li-Li Sun critical reviewed and revised the article. Lun Xiao and Xiao-Qiang Li provided the guidance and fund support for this paper.

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Availability of data and materials

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Declarations

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Competing interests

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