Pathogenesis and etiology of recurrent varicose veins

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Background: Recurrent varicose veins (RVV) occur in 13% to 65% of patients following treatment, and remain a debilitating and costly problem. RVV were initially thought largely to be due to inadequate intervention, however, more recently neovascularization and other factors have been implicated. This review aims to provide an overview of the current understanding of the etiology and pathogenesis of RVV.

Methods: A systematic search of the PubMed database was performed using the search terms including “recurrent,” “varicose veins,” and “neovascularization.”

Results: Three types of RVV have been reported, namely residual veins, true RVV, and new varicose veins, although the definitions varied between studies. RVV are attributable to causes including inadequate treatment, disease progression, and neovascularization. Using duplex ultrasonography, neovascularization has been observed in 25% to 94% of RVV. These new vessels appear in various size, number, and tortuosity, and they reconnect previously treated diseased veins to the lower limb venous circulation. Histologically, these vessels appear primitive with incomplete vein wall formation, decreased elastic component, and lack of valves and accompanying nerves. Although the rate of RVV following open surgery and endovenous treatment appears similar, neovascularization seems less common following endothermal ablation. Other causes of RVV following endovenous treatment include recanalization and opening of collaterals.

Conclusions: Recurrence remains poorly understood following treatment of varicose veins. Neovascularization is an established and common cause of RVV, although other factors may contribute. (J Vasc Surg 2013;57:860-8.)

Open surgery remains the most common varicose vein intervention at present in the United Kingdom; approximately 24,000 operations are carried out annually. Minimally invasive treatments including endovenous thermal ablation and ultrasound-guided foam sclerotherapy (UGFS) are becoming increasingly popular. Despite advances in, and increased availability of, pre- and perioperative investigation such as duplex ultrasonography, recurrence rates following varicose veins treatment remain relatively high. Recurrent varicose veins (RVV) have been reported to occur in 7% to 65% of patients following treatment and remain a common, debilitating, complex, and costly problem. RVV were initially thought largely to be due to inadequate intervention, however, more recently other factors including neovascularization have been shown to contribute to RVV following surgery. Furthermore, the factors leading to the development of RVV following endovenous ablation and sclerotherapy may be different from those after open surgery. The aim of this review was to provide an overview of the current understanding and ongoing debate regarding the etiology and pathogenesis of RVV.

METHODS

A systematic literature search of the PubMed database was performed for articles about the etiology and pathogenesis of RVV (Fig 1). Appropriate search terms were employed, including “recurrent,” “varicose veins,” and “neovascularization.” Only articles written in English were included. Results from animal studies were excluded. The search was expanded by scrutinizing the references of articles identified for further relevant papers.

DEFINITIONS AND CLASSIFICATION OF RVV

The definitions of RVV may vary. Three types of RVV have been described. First, residual varicose veins are those which were already present in operated sites at 1-month follow-up, left as a result of tactical or technical error. Second are true RVV, which are absent at 1-month follow-up but subsequently appear either as a result of neovascularization or as a result of tactical or technical error. Third are new varicose veins, which were not present at 1-month follow-up but develop later in untreated areas due to disease progression.
RVV can also be classified into radiologic and clinical; importantly, radiologic recurrence does not necessarily translate into clinical recurrence. For example, in a prospective study of UGFS in the treatment of GSV reflux in 203 legs (146 patients), the 5-year clinical recurrence was reported to be 4%, whereas duplex ultrasound recurrence was 64%. Certain positive ultrasound findings suggest an increased risk of development of clinical RVV and reoperation in future. In one study, patients with audible reflux in the groin on a hand-held Doppler 1 year after open surgery were found to have an increased risk of clinical recurrence after 2 years.

An international consensus meeting held on ‘recurrent varices after surgery’ (REVAS) in Paris in 1998 agreed to adopt a clinical definition: the existence of varicose veins in a lower limb previously operated on for varicosities, with or without adjuvant therapies, which includes true recurrences, residual veins and new varices, as a result of disease progression. The four major causes of RVV following treatment are shown in the Table. Using the REVAS criteria, following open surgery RVV have been reported at rates ranging from 6.6% to 37% after 2 years and up to 51% after 5 years. Most patients with RVV were symptomatic, with various clinical presentations. Most had uncomplicated varicose veins and swelling (70.9%), but the remainder had skin changes (29.1%). There were multiple sources of reflux feeding the recurrence, though incompetence at the saphenofemoral junction (SFJ) was present in almost half of the patients. Ten percent had no apparent source of reflux; in 17%, it was of pelvic or abdominal origin. About 75% of legs had incompetent perforator veins. Neovascularization (20%) was as frequent as technical failure (19%) and tactical error (10%), and a combined presentation was found in 17%. In 35% of cases, the cause of reflux was uncertain. When recurrence occurred at a different site, development of reflux in new sites was found in 32% of legs.

**ETIOLOGY OF RVV**

**Tactical and technical error**

RVV caused by tactical and technical error are attributable to inappropriate or inadequate treatment, respectively. Tactical and technical errors were historically reported to be the major cause of RVV, contributing up to 80% of recurrences although this is likely to be untrue and outdated.

### Table. Four major sources of recurrence following varicose vein surgery (adapted from Kostas et al, 2004)

<table>
<thead>
<tr>
<th>Causes</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Tactical error</td>
<td>The persistence of venous reflux in a saphenous trunk resulting from erroneous or inadequate preoperative evaluation and inappropriate surgery</td>
</tr>
<tr>
<td>Technical error</td>
<td>The persistence of venous reflux due to inadequate or incomplete surgical technique</td>
</tr>
<tr>
<td>Disease progression</td>
<td>As a result of the natural history and evolution of the disease</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>The presence of reflux in previously ligated saphenofemoral junctions cause by development of thin incompetent serpentine veins linked with a thigh varicosity</td>
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Tactical error may arise from failure to identify the source of reflux or all the incompetent veins requiring treatment. Expansion of collateral veins may also contribute to recurrent junctional incompetence. The increasing use of duplex ultrasonography pre- and perioperatively during open surgery, endothermal ablation, and UGFS is likely to reduce the rate of tactical errors.

The risk of RVV may increase if the GSV is not stripped at all, or inadequately, although this remains controversial. In a randomized trial of 100 patients (133 legs) who underwent SFJ ligation with or without GSV stripping, Jones et al demonstrated a clinical recurrence rate at 2 years of 43% after surgical ligation alone and 25% after ligation and stripping, although 89% of the patients remained satisfied. Reoperation was required for 20 of 69 legs that underwent ligation only, compared with 7 of 64 legs that had additional GSV stripping (P = .012). In endovenous treatment, ablation of the GSV to the ankle opposed to above-the-knee, appears to produce more favorable clinical results, with greater improvement in quality of life, and reduced recurrence. However, treating below-knee GSV may also increase the rate of complications including paresthesia. Therefore, further studies are needed to determine which patients will benefit from full length treatment of the GSV.

In contrast to the above, there is recently some evidence to support that selective treatment of key points of venous reflux, and preservation of the saphenous vein may have a role to improve the efficacy of therapy and reduce risk of RVV. Examples of such treatment include the CHIVA (cure conservatrice et hémodynamique de l’insuffisance veineuse en ambulatoire or ambulatory conservative hemodynamic management) and ASVAL (ablation sélective des varices sous anesthésie locale or ambulatory selective varicose vein ablation under local anesthesia of varicose veins) techniques. In the CHIVA technique, following careful duplex mapping, the clinicians perform flush ligations at key points of venous reflux to decrease the hydrostatic pressure and preserve the superficial venous drainage in the saphenous veins and tributaries. There is some evidence from prospective studies including randomized trials that the CHIVA technique is efficacious with comparable, if not lower, rate of RVV. Meanwhile, the ASVAL technique involves the treatment of the refluxing epifascial veins while preserving the saphenous vein in patients whom the clinicians judge that the reflux would progress in the anterograde fashion. A retrospective study by Pittaluga and colleagues has reported good outcomes in patients with relatively less severe primary varicose veins. At present, both techniques should only be carried out on selective patients by trained specialists. Further larger randomized controlled trials are needed to confirm the efficacy and safety of these techniques.

Inexperienced surgeons. Although there is no doubt inexperienced surgeons are more prone to tactical or technical errors, and therefore increased risk of RVV, the claim that this is the main cause of RVV has been disputed. Kostas cited inadequate surgery as the least common etiology of recurrence (11%). A retrospective clinical follow-up study from Sweden examined 100 legs from 89 patients who had primary SFJ ligation and stripping of the GSV, and re-examined them after 6 to 10 years with duplex imaging and varicography in some cases. There was no significant difference in the recurrence rates related to the surgeon’s experience: surgical resident (52%), general surgeon (54%), and vascular surgeon (65%).

Recanalization and collateralization. Endovenous ablation treatment and sclerotherapy cause obliteration of the refluxing axial veins through thermal (laser or radiofrequency) energy or chemical irritation. A major cause of RVV following endovenous ablation and sclerotherapy is recanalization of the diseased veins. Although recanalization is often reported as an outcome following endovenous treatment, studies have suggested that it does not necessarily result in clinical recurrence or symptomatic reflux. The degree of damage to the vein wall required for long-term occlusion is also unknown. Recanalization can be reduced by improving the technical aspects of treatment. For example, delivering at least 70 joules per cm of laser energy to the vein wall reduces recanalization rates following thermal ablation with short wavelength laser (810 and 980 nm). Similarly, in endovenous radiofrequency ablation, adequate pullback speed to ensure proper thermal dose delivery during the procedure has been shown to reduce the rates of recanalization of saphenous veins. Recanalization is related to a number of factors, including the vein diameter in addition to the energy delivered. Similarly, in sclerotherapy, several technical factors including the use of foam rather than liquid sclerotherapy, and injecting a higher volume of foam in larger veins may reduce the rate of RVV.

Disease progression

This type of recurrence is attributable to the evolution or persistence of varicosities derived from incompetence in a remote or second saphenous system; usually the small saphenous vein (SSV) is affected following previous surgery to the GSV. The affected veins are clinically not varicose at the time of treatment but later become refluxing as a result of the natural history of the disease. It is well known that primary varicose veins progress both in severity and distribution over time. Disease progression is reported to account for 20% to 25% of recurrences. Neovascularization

Neovascularization refers to new blood vessel formation, which can occur in an abnormal tissue or position. These new vessels arise in the granulation tissue along the track of previously stripped or ligated veins. They form between the common femoral vein, the residual GSV stump, or its tributaries, and reconnect the incompetent veins to the superficial venous circulation of the leg. These new blood vessels are found relatively frequently, even after correct functional ligation. Neovascularization has been reported to account for 8% to 60% of RVV and is the most common cause of recurrence, together with the...
The mechanisms responsible for neovascularization in RVV remain unclear. It is thought that neovascularization first develops months or even years after the initial operation. It may be induced by diffusible angiogenic factors released from the surrounding tissues. Physical factors that have been implicated include the type of suture material used to ligate the GSV stump, exposure to free stump endothelium, hemodynamic effects, operative trauma, and thrombosis (Fig 2). Several hypotheses have been postulated to explain the development of neovascularization following varicose vein surgery. First, neovascularization may be a physiological response to venous disconnection. Second, it may be a manifestation of the effect of altered venous hemodynamics in a system of susceptible veins. Third, neovascularization may be part of the normal sequence of wound healing, originating from hypoxia-induced activation of endothelial cells distal to the stump ligature leading to the release of angiogenic factors. Fourth, the track of the previously stripped vein may recanalize and endothelialize. Neovascularization may be associated with hematoma formation following the initial surgery, but this has not yet been assessed.

**Imaging neovascularization.** On venography and duplex ultrasonography, neovascularization appears as a complex network of tortuous vessels (Fig 3) reconnecting the proximal or distal cut ends of the GSV or one of its tributaries to the femoral vein. The appearance is different from residual varicose veins (or non-varicose), and neovascular veins are observed after 25% to 94% of RVV. Duplex ultrasonography and venography are limited by their inability to differentiate true neovascularization from the dilatation of existing collateral veins as they appear similar. New veins seen on clinical imaging may represent adaptive dilation of pre-existing venous channels in response to abnormal hemodynamic forces, rather than true neovascularization.

**Histology and resin casting.** The morphology of neovascularization has been studied using resin casts and histologic analysis including immunohistochemistry. In
the 1980s, Glass conducted an early histologic study that found continuity of a ligated vein was restored by growth of new vessels in the surrounding tissue and vein wall.18

Resin casts clearly illustrate the tortuosity and extent of the neovascularization as well as the variation in size of the veins (Fig 4).41 The direction of the neovascularization channels from the stump is always outward toward the subcutaneous tissue.54 Some of these new vessels reconnect with the main venous tributaries and establish channels of sufficient caliber to become clinical recurrences.54

Histologically, neovascular vessels appear primitive and immature, with incomplete vein wall formation, no valves, and a lack of clearly defined tunica intima, media, and adventitia. The vessel wall appears asymmetrical and thinner than normal vein. Most of these vessels are either composed of squamous endothelium only or lined by few layers of vascular smooth muscle cells. No intimal thickening is observed and the vein wall lacks elastic fibers. In 80% no capillaries or vasa vasorum are detected in the vascular wall. Scar tissue is often seen around the vessel.58

Blood vessels generally contain nerve fibrils, which express S100 protein, particularly S100A1 and S100B. Neovascularization in RVV is characterized by an incomplete vessel wall lacking intramural nerves on S100 staining, a feature similar to the immature neovessels seen in granulation tissue and tumor.42 One study identified histologic evidence of neovascularization in 94% of RVV, all of which stained negative for S100.59 Other markers that have been used to identify neovascularization include Mib1, a monoclonal antibody that recognizes proliferating cells by binding to Ki-67.57

Although many of the features observed in histologic studies support neovascularization as an important cause of RVV, other studies have disputed this. Using immunohistochemistry, El Wajeh et al found S100 positive nerve fibrils in the majority of dilated vascular channels from both their patients having redo varicose vein surgery and control groups.57 They found little evidence of neovascularization associated with RVV and concluded that the venous channels that develop at the previously ligated SFJ may represent an adaptive dilatation of pre-existing venous channels and vascular remodelling, in response to abnormal hemodynamic forces.48

**COMPARISON OF RVV BETWEEN TREATMENT MODALITIES**

A meta-analysis of endovenous treatments for varicose veins found that endovenous laser ablation demonstrated significantly better occlusion rate, although this may not necessarily translate into clinical recurrences, than stripping, UGFS, and radiofrequency ablation.60 The 5-year vein occlusion rate for endovenous laser ablation (EVLA) was 95.4% compared with 79.9% with the original radiofrequency ablation (REFA) catheters, however, the latest radiofrequency devices deliver a higher energy and medium- and long-term outcome data for these new devices is awaited.61 Stripping and UGFS have reported 5-year success rates of 75.7% and 73.5%, respectively.60 The long-term results of all forms of treatment may depend on the rates of neovascularization.13,60 However, despite apparent reductions in neovascularization and excellent occlusion rates,
randomized clinical trials comparing EVLA and stripping have failed to show a significant advantage of laser at 2 years in terms of recurrence and quality of life outcomes.\textsuperscript{25,62} Clinical trials comparing stripping and RFA have shown advantages in quality of life for RFA at 2 years.\textsuperscript{46}

Clinical studies comparing UGFS with surgery and thermal ablation suggest that foam sclerotherapy is less effective than surgery\textsuperscript{60,63} and EVLA,\textsuperscript{60} although long-term evidence from randomized controlled trials is scarce. The VEDICO trial (Foam-Sclerotherapy, Surgery, Sclerotherapy, and Combined Treatment for Varicose Veins: A 10-Year, Prospective, Randomized, Controlled, Trial) showed that low dose sclerotherapy was less effective than high dose; results were worse with highly diluted or undiluted 3% sclerosant compared with a 1.5% concentration.\textsuperscript{63} Rates of RVV after 5 years were 44% for UGFS, rising to 56% after 10 years.

Whereas short-term data after new endothermal techniques are plentiful,\textsuperscript{56} long-term outcome data concerning recurrence and quality of life are currently awaited. A number of appropriately powered studies will report results in the next few years.\textsuperscript{25,64,65}

**DISCUSSION**

There have been a number of recent advances in the treatment of varicose veins, including the increasing use of duplex ultrasonography, treatment by specialists, and new endovenous therapies. Yet, the recurrence rates after treatment remain a challenge, at least partly because of a lack of understanding of the pathogenesis and etiology of RVV. The definition of RVV often varies in studies. In some, residual veins are included as RVV whereas others consider them not strictly RVV. Understanding the mechanisms of recurrence is essential for the development of preventative and therapeutic strategies.

SFJ reflux is caused by incompetence of one or more of the axial veins or tributaries arising from it. Therefore, during treatment of varicose veins, regardless of technique, all tributaries of the SFJ or proximal GSV with demonstrated reflux require obliteration to prevent recurrence. Most patients (85%) with SFJ incompetence only have GSV reflux.\textsuperscript{56} Traditional teaching suggests all tributaries or axial veins arising from the SFJ should be ligated at open surgery, despite the lack of evidence that this reduces recurrence and neovascularization. Endovenous thermal ablation techniques obliterate axial vein reflux but do not specifically interrupt the proximal SFJ tributaries. Theivacumar and colleagues assessed 81 legs (70 patients) 12 months after EVLA of the GSV and found that none of the legs showed SFJ reflux, although one or more patent tributaries were visible in 48 (59%) patients. The authors concluded that persistent nonrefluxing GSV tributaries at the SFJ did not appear to have an adverse effect on clinical outcome 1 year after successful EVLA of the GSV.\textsuperscript{66} However, in another study, several cases of new reflux in the anterior accessory vein were found 2 years after EVLA.\textsuperscript{25} The observation time in randomized trials comparing RVV after endovenous treatment vs surgery is still relatively short, therefore, no firm conclusion can be drawn regarding differences in RVV and neovascularization.

Meanwhile, the treatment of the competent GSV in patients with an isolated refluxing anterior accessory great saphenous vein (AAGSV), which may occur in 10% of patients with SFJ reflux, is also unclear. Theivacumar and colleagues studied 30 patients who underwent AAGSV laser ablation alone and 38 age/sex-matched controls undergoing GSV laser ablation. The authors concluded that GSV-sparing laser ablation of the AAGSV abolishes SFJ reflux associated with isolated SFJ/AAGSV reflux and improves symptom scores and patient satisfaction to a similar extent as GSV laser ablation, with no evidence of new GSV reflux or recurrent varicosities at 1-year follow-up.\textsuperscript{67} Because of lack of long-term data, the optimal treatment of AAGSV remains unclear. Some clinicians advocate for primary ablation of the AAGSV even if it is competent at the initial treatment because of potentially relatively high incidence of late reflux in this vein.\textsuperscript{25} However, some clinicians have suggested avoiding ablation of this vein at the initial operation\textsuperscript{66,68} because it can be treated at a later stage should it become incompetent, resulting in the development of RVV.\textsuperscript{25}

Neovascularization is accepted by most vascular surgeons as an established cause of RVV, especially following open surgery. Despite this, several problems remain including the lack of a unifying definition which makes assessment and reporting difficult. It is difficult to be confident that all the neovascularization described in the literature was true neovascularization, which may explain some of the conflicting results reported by various studies. For example, one study considered all veins joining the GSV stump or junctional area as missed tributaries,\textsuperscript{40} whereas other studies considered stump tributaries as substantial as 3 mm in diameter to be consistent with neovascularization. Another problem is that few studies have correlated imaging findings to histologic evidence, thereby making the interpretation of neovascularization more variable and less convincing. There is a lack of knowledge pertaining to the molecular biology of neovascularization despite the advancement in this area in other clinical contexts.

Increasingly, research is being undertaken to develop effective strategies to prevent and treat RVV; neovascularization, therefore, is an important target. Various surgical techniques have been compared with elucidate which have more favorable outcomes, including lower rates of recurrence and neovascularization.\textsuperscript{69} One important study compared the long-term clinical advantages of ligation of SFJ with and without GSV stripping during routine primary varicose vein surgery.\textsuperscript{70} Although neovascularization was present in both groups, stripping reduced the need for reoperation by two-thirds at 5 years.\textsuperscript{70} Another study compared traditional surgical treatment for varicose vein recurrence, which involved removing all sources of reflux from the deep venous network with the superficial venous network, with a less aggressive surgical approach focusing on treatment of the varicose reservoir and avoiding redo surgery at the groin. Postoperative complications
were 6.7% and 0.5%, respectively. After 3-year follow-up, traditional surgery had a recurrence rate of 9.2%, whereas recurrence in the second group was 7.1%.

The conservative approach to surgical varicose vein treatment, the CHIVA and ASVAL methods, show that selective surgical treatment may be a viable option. Studies have shown that RVV occur more frequently following saphenous stripping than after CHIVA treatment. One study showed that recurrence rates are halved at 10 years following CHIVA, with 35% recurrence after stripping and 18% recurrence after CHIVA. Equally, ASVAL showed good results with regard to neovascularization, which was only seen in 0.9% of cases, and recurrence, which was present in 6.3%.

Other strategies to prevent neovascularization that have been described include the use of a synthetic physical barrier. These barriers include polytetrafluoroethylene and silicone patch saphenoplasty, which involves suturing a polytetrafluoroethylene and silicone patch, respectively, over the saphenous opening after flush saphenofemoral ligation. This method has been deemed safe and a studies have reported an approximately 50% reduction in neovascularization, although further studies are needed to confirm this before it can be used routinely. Studies comparing endovenous treatment and open surgery have already reported a reduction in neovascularization despite the overall RVV rate remaining similar in both treatment arms, likely attributable to recanalization and opening of collaterals. It is unclear why collaterals do not open up after surgery as well as after endovenous therapies. One possible explanation for this is that there are still microchannels between the collaterals and the treated veins, whereas in open surgery, the connections between them are completely removed by either vein stripping or avulsion. Therefore, improving our understanding of RVV following endovenous therapies and refining the technology including optimizing the efficiency of energy delivery and targeting the right varicosites may have the potential to reduce the overall rate of RVV.

In addition to applying and improving the currently established treatment of varicose veins, the application of pharmacologic agents that prevent neovascularization may have a role in the future. For example, the local application of inhibitors of angiogenesis during varicose vein treatment is an attractive putative approach to prevent or limit neovascularization. There are commercially available angiogenesis inhibitors such as bevacizumab, an anti-vascular endothelial growth factor biologic available for the treatment of cancer. More selective angiogenesis inhibitors are also being developed to reduce the side effects and to improve the specificity of the treatment.

CONCLUSIONS

RVV remains a poorly understood pathology following treatment of varicose veins. Several etiologic factors including tactical and technical error, disease progression, and neovascularization contribute to the development of RVV. The factors contributing to the development may also vary with the type of varicose vein treatment. Additional molecular and clinical studies are required to understand the pathophysiology of RVV further in the development of more effective preventative and treatment strategies.

AUTHOR CONTRIBUTIONS

Conception and design: MB, CL, JS, AS, AD Analysis and interpretation: MB, CL, JS, AS, AD Data collection: MB, CL, JS, AS, AD Writing the article: MB, CL, JS, AS, AD Critical revision of the article: MB, CL, JS, AS, AD Final approval of the article: MB, CL, JS, AS, AD Statistical analysis: Not applicable Obtained funding: Not applicable Overall responsibility: MB, CL, JS, AS, AD

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